Drug Delivery® Technology

March 2007 Vol 7 No 3 www.drugdeliverytech.com

Drug Delivery: *Exploiting Growth Potential*

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

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MR. PAUL JOHNSON

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Drug Delivery Technology

March 2007 Vol 7 No 3

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 Drug Delivery Technology (ISSN 1537-2898) is published 10 times in 2007, January, February, March, April, May, June, July/August, September, October, and November/December by Drug Delivery Technology LLC, 219 Changebridge Road, Montville NJ 07045. Subscription rates: $99.00 for 1 year in the United States, Canada, and Mexico. $153.00 for 1 year outside the United States, Canada, and Mexico. All subscriptions are payable in US funds, drawn on US banks. Send payment to: Drug Delivery Technology LLC subscription Department, 219 Changebridge Road, Montville NJ 07045. Single copies (prepaid) $15.00, US, Canada, and Mexico; $24.00 in all other countries. Add $5.00 per order for shipping and handling. ***Periodicals Postage Paid at Montville, NJ 07045-9998 and additional mailing offices. Postmaster:*** *please send address changes to Drug Delivery Technology, 219 Changebridge Road, Montville NJ 07045.*

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Focusing on Drug Delivery

"Drug Delivery companies are likely to enable pharmaceutical companies to revive late-stage products by using drug delivery platforms and re-branding products. As a result, Drug Delivery companies are likely to remain the focus of attention of big pharma and specialty pharmaceutical companies as acquisition targets or licensing partners."

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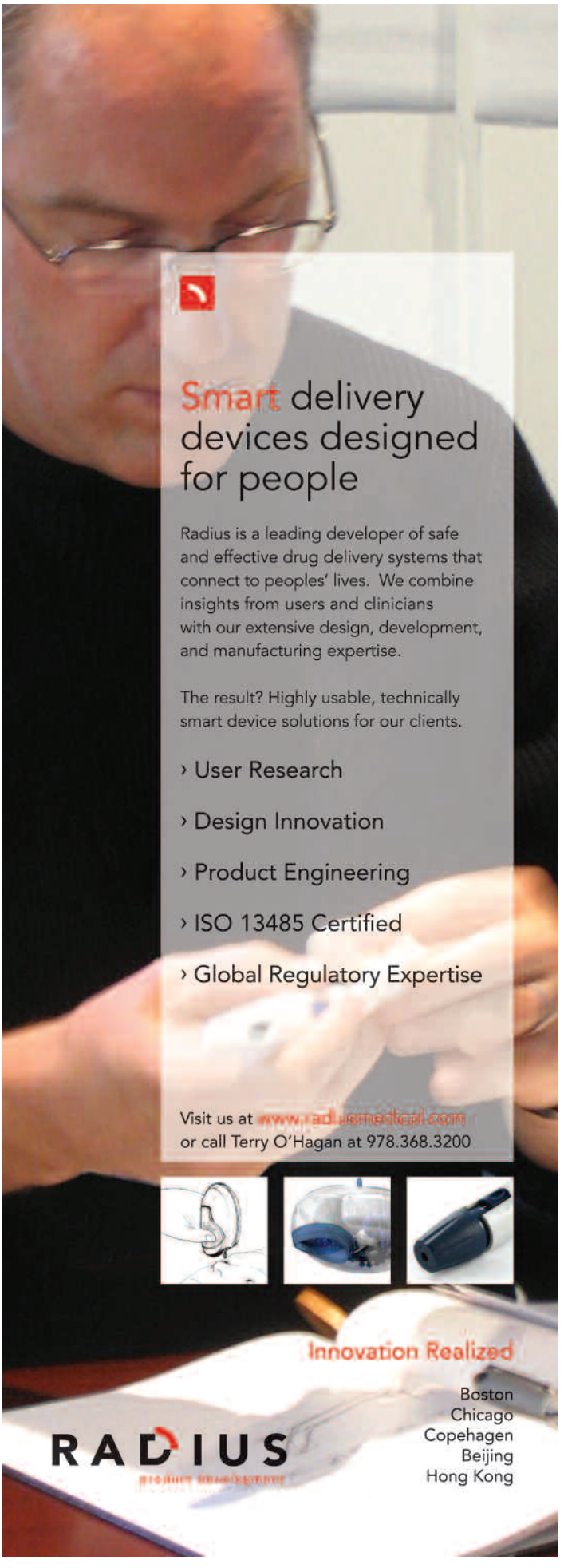

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[1] Graff MR, McClanahan MA. Assessment by patients with diabetes mellitus of two insulin pen delivery systems versus a vial and syringe. Clin Ther. 1998;20(3):486-496.
[2] Weiss, P.M., http://www.femalepatient.com/html/arc/sig/pharma/articles/028_07_031.asp

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Market News and Trends

BDSI Announces FDA Acceptance of Bioral® Amphotericin IND: First IND for Cochleate Drug Delivery Technology

BioDelivery Sciences International, Inc. recently reported the filing and acceptance by the US FDA of BDSI's first IND for the company's Bioral cochleate drug delivery technology. The lead Bioral product for which the IND was filed is an enchocleated version of Amphotericin B (CAMB), a potent, broadly active antifungicidal agent for treating infections, such as esophageal candidiasis, an infection prevalent in HIV patients and many patients who are receiving cancer chemotherapy.

In addition to the treatment of such infections as esophageal candidiasis, Amphotericin B is also an important drug for treating Leishmaniasis, a parasitic disease that affects an estimated 2 million people worldwide, according to the Centers for Disease Control and Prevention. While highly effective, the use of the currently available Amphotericin B products on the market is limited by the requirement for intravenous administration, toxicity, and cost.

"CAMB would be the first broadly effective oral antifungicidal agent available in the world, if clinical trials are successful and the product achieves marketing approval," said Dr. Mark Sirgo, President and CEO of BDSI. "As such, it could have a major impact on the treatment and prophylaxis of fungal infections."

Dr. Sirgo continued, "Although we continue to spend the vast majority of our financial and other resources on our Phase III BEMA® Fentanyl product, we are encouraged by the potential formulations for the Bioral technology and indications for Amphotericin B."

The patented Bioral cochleate technology has the potential to transform drugs, such as Amphotericin B, which are currently available only by injection, into patient friendly, orally available products. Cochleates are made of naturally occurring substances and are designed to encapsulate, protect, and deliver certain drug molecules that are either broken down by gastrointestinal enzymes and acids, or cannot be absorbed through the gastrointestinal tract.

"CAMB consistently showed significant efficacy against systemic fungal infections and substantial safety levels throughout the preclinical development period using animal models," stated Dr. Raphael Mannino, BDSI's Founder and Chief Scientific Officer. "In addition, we believe we have developed a highly cost-competitive manufacturing protocol that we expect will be advantageous as we move through the next stage of clinical testing and potential partnering discussions."

Dr. Mannino continued, "The FDA's acceptance of this IND is a major accomplishment for the Bioral cochleate technology and our company. We are now in a position to potentially broaden our product offerings and move into normal volunteers to determine the distribution and safety of CAMB in our first Phase I evaluation. In addition, we believe positive clinical trials of CAMB could support the extension of the Bioral technology to a large number of additional existing injectable, difficult-to-formulate, and toxic drugs."

The development of Bioral CAMB for fungal infections has been supported in part by the Division of AIDS, National Institutes of Allergy and Infectious Diseases, and National Institutes of Health (NIH).

Depomed & Biovail Sign License Agreement for AcuForm™ Drug Delivery Technology

Depomed, Inc. and Biovail Corporation recently announced that the companies have entered into an agreement that provides Biovail with access to Depomed's proprietary AcuForm drug delivery technology for the development of up to two Biovail products.

Under the terms of the agreement, Depomed has granted Biovail Laboratories International SRL, a subsidiary of Biovail, an option to license Depomed's AcuForm technology to develop and commercialize up to two pharmaceutical products. Biovail may select these products from an agreed-upon list of compounds at any time over the next 18 months. Depomed will have no development obligations under the agreement.

In return, Biovail has paid Depomed an up-front fee of $500K and is contingently obligated to pay Depomed additional fees related to the exercise of the license option, the initiation of the first Phase III trial for each product, and upon receipt of US regulatory approval for each product. The agreement also stipulates that Biovail make royalty payments to Depomed on net commercial sales of any product developed under the agreement.

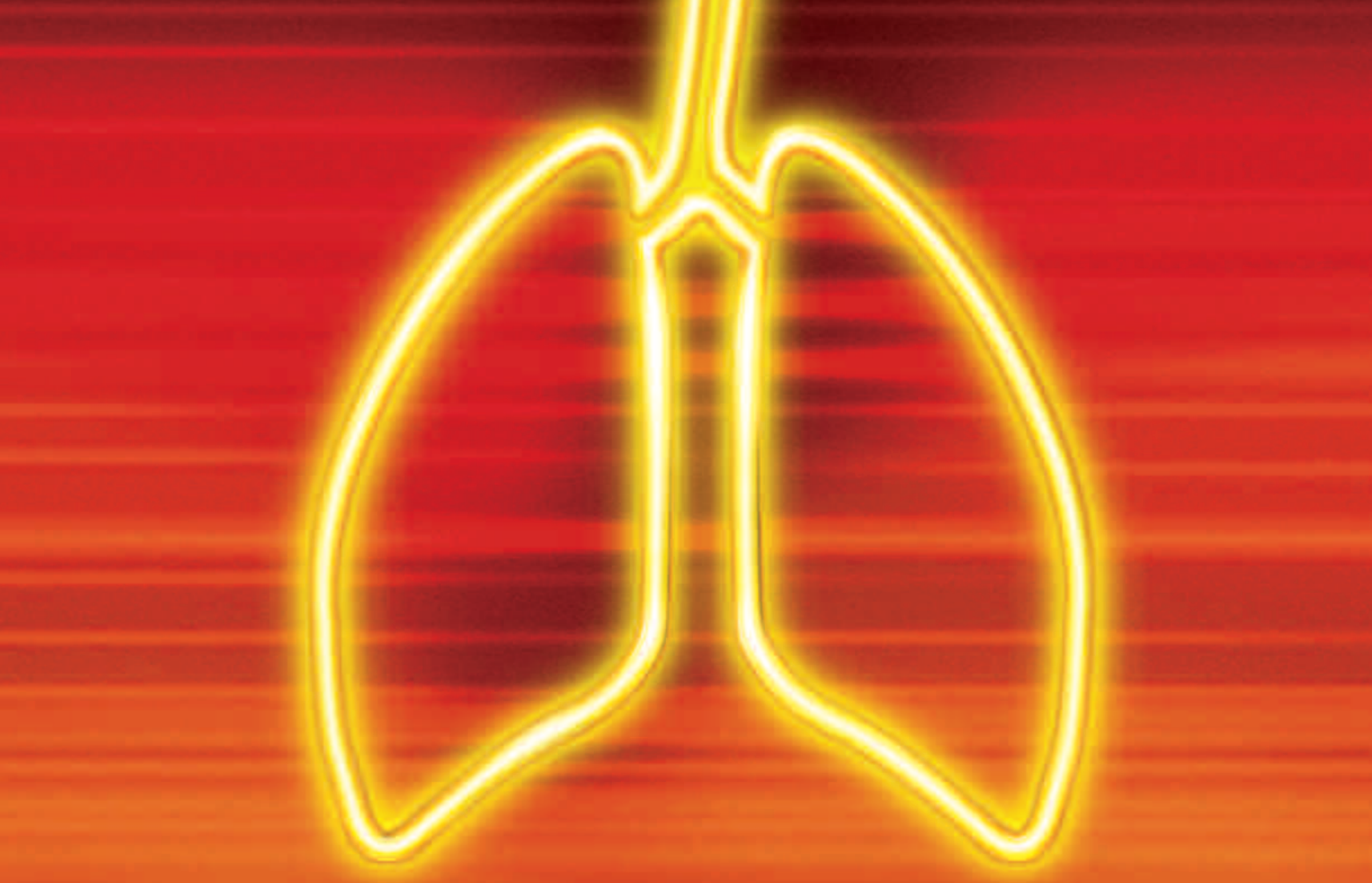
"We are very pleased to have entered into this agreement with Biovail for our AcuForm technology, further validating the potential for its broad utility," said John Fara, PhD, Depomed's Chairman, President, and CEO. "Given Biovail's in-depth familiarity with the AcuForm platform, we are confident they have the know-how to develop additional products without any diversion of our resources from current projects."

Dr. Douglas Squires, CEO of Biovail, added, "This agreement with Depomed is another example of Biovail leveraging strategic partners with complementary drug delivery technologies to further deepen its drug-development pipeline."

In addition, Depomed and Biovail have amended their May 2002 Security Purchase Agreement to eliminate Biovail's Board observer rights and right of first negotiation related to any Depomed acquisition transactions.

Depomed, Inc. is a specialty pharmaceutical company utilizing its innovative AcuForm drug delivery technology to develop novel oral products and improved, extended-release formulations of existing oral drugs. AcuForm-based products are designed to provide once-daily administration and reduced side effects, improving patient convenience, compliance, and pharmacokinetic profiles. ProQuin XR (ciprofloxacin hydrochloride) extended-release tablets have been approved by the FDA for the once-daily treatment of uncomplicated urinary tract infections and are currently being marketed in the US. In addition, once-daily Glumetza (metformin hydrochloride extended-release tablets) has been approved for use in adults with type 2 diabetes and is currently being marketed in the US and Canada. The company is conducting a Phase III trial in postherpetic neuralgia and has completed a Phase II trial in diabetic peripheral neuropathy with its product candidate, Gabapentin GR.

Biovail Corporation is a specialty pharmaceutical company engaged in the formulation, clinical testing, registration, manufacture, and commercialization of pharmaceutical products utilizing advanced drug delivery technologies.



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Nitto Denko Subsidiary Develops Novel Drug Delivery Technology Platform

Japan's leading diversified materials company Nitto Denko Corporation has developed, at its wholly owned US R&D subsidiary Nitto Denko Technical Corporation (NDT), a platform technology for a novel drug delivery system (DDS) using a biodegradable polymer material, the company announced recently, adding that the development has been conducted in collaboration with University of California, San Diego (UCSD).

Located in Oceanside, California, NDT is engaged in high-tech research in various fields, including biomedical materials. It is a member of Nitto Denko Group comprising Nitto Denko and its 117 subsidiaries in 24 countries around the world.

The technology NDT developed this time together with the Moores Cancer Center of UCSD takes advantage of a biodegradable and biocompatible polymer material which, when linked to certain therapeutic agents, can greatly enhance the drug's solubility and act as a "carrier" with promising potential to deliver such agents to the target tissue with high efficiency.

While not possessing any therapeutic properties per se, the polymer-based carrier has shown the potential to increase therapeutic efficacy and offer the benefit of reduced side effects when conjugated to existing drugs. In addition, it has the potential to serve as a carrier for a large number of compounds in a range of therapeutic classes, for treating a wide variety of diseases.

Nitto Denko possesses a strong portfolio of transdermal drug delivery technology, including asthma patches as well as patches for ischemic heart disease, with a large share in the Japanese market. Having added to its Medical Division a US company (Aveva Drug Delivery Systems)" in Florida in 2003, Nitto Denko Group is actively engaged in further expanding the business of manufacturing and selling transdermal drug delivery patches.

The technology developed by NDT is consistent with Nitto Denko's plan to increase their profit-margins by leveraging their expertise in polymer synthesis to increase their business in the lucrative drug delivery industry. Aside from this new technology, NDT has also been engaged in extensive research into biomedical materials applications by leveraging Nitto Denko's polymer synthesis capabilities, to develop a gene delivery reagent based on a biodegradable cationic polymer, as well as a polymeric solid support for oligonucleotide synthesis and biomedical-related technologies.

Showing great promise to expand the Group's Medical business, this new technology is expected to become the core of a new technological platform, in addition to the Group's existing transdermal DDS assets, and is being earmarked for further R&D from hereon.

It is envisaged that successful completion of the development of this technology would result in achievement of increased efficacy and reduced side effects of existing drug classes, such as cancer chemotherapy; improved therapeutic efficacy of existing drugs that exhibit high toxicity (side-effects) or poor solubility; and renewed commitment to promising drugs whose development was halted due to high toxicity or poor solubility.

Market News and Trends

IOMED Introduces Hybresis™ System at American Physical Therapy Association's CSM

IOMED, Inc., a leader in the development of active drug delivery systems using iontophoresis, recently introduced the new Hybresis System, a first-of-its-kind integrated mini-controller and patch system that uses no lead wires and can deliver in-clinic treatment in as little as 3 minutes. The product was showcased to attendees of the American Physical Therapy Association's Combined Section Meeting this past February in Boston.

The Hybresis System consists of a wireless, miniaturized, rechargeable controller that connects directly to an iontophoresis patch and a charging station with four controller bays. The product combines leading-edge design and function with the efficacy, safety, and quality that embody IOMED products.

"The Hybresis System is a quantum leap in iontophoresis technology," said Robert J. Lollini, IOMED's President and CEO. "For the first time, clinicians have access to a wireless system that offers precise dose control, alternative treatment modes, is easy to set up, and can significantly increase patient throughput due to shortened in-clinic treatment times. Patients who use iontophoresis now have access to a discreet, comfortable system that does not require long wear times."

Mr. Lollini said the Hybresis System could also lend itself to applications in new markets outside of physical and occupational therapy and sports medicine markets, which have long used iontophoresis delivery systems. IOMED, currently awaiting 510(k) clearance for the Hybresis System from the US FDA, expects to ship the new product within the next several months pending regulatory approval.

IOMED is a leader in developing, manufacturing, and marketing active drug delivery systems used primarily to treat acute local inflammation in the physical and occupational therapy and sports medicine markets. The company is pursuing opportunities to advance its position as a provider of quality, innovative non-invasive medical products that improve patient healthcare. IOMED seeks to accomplish this by expanding its product line, distributing new products, developing strategic partnerships, and through acquisitions.

InSite Vision & Inspire Pharmaceuticals in $32-Million Licensing Deal on AzaSite™

Inspire Pharmaceuticals, Inc. recently announced the signing of an exclusive licensing agreement with InSite Vision Incorporated for the US and Canadian commercialization of AzaSite (1.0% azithromycin ophthalmic solution), a topical anti-infective product currently under review by the US FDA for the treatment of bacterial conjunctivitis.

Under the terms of the agreement, Inspire has acquired from InSite Vision exclusive rights to commercialize AzaSite for ocular infections in the US and Canada. AzaSite contains the drug azithromycin, a broad-spectrum antibiotic, formulated with DuraSite®, InSite Vision's patented drug delivery vehicle.

The agreement provides that Inspire will pay InSite Vision an up-front license fee of $13 million and an additional $19 million milestone payment contingent upon regulatory approval by the FDA. Inspire will also pay a royalty on net sales of AzaSite for ocular infections in the US and Canada, if approved by regulatory authorities. The royalty rate will be 20% on net sales of AzaSite in the first 2 years of commercialization and 25% thereafter. Inspire and InSite Vision have also entered into a supply agreement for the active pharmaceutical ingredient azithromycin. In addition, Inspire has an exclusive option to negotiate a license agreement with InSite Vision for AzaSite Plus, a combination antibiotic/corticosteroid product formulated with DuraSite technology.

Christy L. Shaffer, PhD, President and CEO of Inspire, commented, "The addition of AzaSite to our late-stage product portfolio leverages our therapeutic focus in ophthalmology, builds on the capabilities of our commercial organization, and provides a sizable near-term revenue opportunity. We believe AzaSite, if approved, could capture a meaningful share of the growing ophthalmic anti-infective US prescription market, which exceeds $600 million for both single-entity and combination products."

"We look forward to the completion of the FDA's review of the AzaSite NDA by the end of April 2007, as determined by the Prescription Drug User Fee Act (PDUFA). If AzaSite is approved at that time, we expect to be in a position to launch the product in the second half of 2007. Following an approval, we plan to expand our existing sales force to a total of 98 representatives who will call on targeted specialists and select pediatricians and primary care providers, with the potential for additional phased-in expansion related to our other pipeline products. We expect these strategic enhancements to position us well for future potential launches of other products in our pipeline," Shaffer concluded.

Terrence P. O'Brien, MD, Professor of Ophthalmology and Charlotte Breyer Rodgers Distinguished Chair in Ophthalmology, Bascom Palmer Eye Institute of the University of Miami, addeded, "AzaSite represents an exciting new potential treatment option for external ocular infections, including bacterial conjunctivitis. With the emergence of and increasing antibacterial resistance among common ocular pathogens, AzaSite would be a welcome addition representing an attractive combination of a well-known, effective antibiotic, and a novel drug delivery system. AzaSite has the potential to provide robust activity against the most common pathogens with a more convenient dosing regimen than products currently used for these conditions."

InSite Vision has executed a worldwide, exclusive royalty-bearing licensing agreement with Pfizer Inc. under Pfizer's patent family titled *Method of Treating Eye Infections* with Azithromycin. Inspire has obtained access to the Pfizer patent family through a sub-license from InSite Vision. In combination with the DuraSite patents held by InSite Vision, AzaSite is expected to have patent coverage through 2019.

New Pharmaceutical Services Company – Senopsys – Makes Pharmaceuticals More Palatable

Jeff Worthington, a noted expert in pharmaceutical sensory analysis and formulation development, recently announced the launch of Senopsys LLC, a specialty services company that partners with pharmaceutical, biotechnology, and drug delivery companies and their CROs to improve the palatability of pharmaceuticals.

Headquartered in Massachusetts, Senopsys uses proprietary sensory assessment tools to identify the critical sensory attributes of drug substances, quantify taste-masking challenges, measure the flavor quality or palatability of drug prototypes and competing products, and develop target sensory profiles that result in patient-acceptable pharmaceuticals. The company also works with drug developers to assess the suitability of novel dosage forms for specific drug substances and develop new formulation systems for investigational and approved drugs.

"The simple truth is if patients don't like a medication, they just won't take it, which can have far-reaching implications on patient health and the widespread acceptance of a drug product," said Mr. Worthington, Founder of Senopsys. "Many will point to a product's flavor (orange, grape, chocolate) as the key determinant of patient acceptance; but a drug's palatability is much more complicated than its flavor. The key to developing palatable pharmaceuticals lies beneath the surface and includes factors, such as balancing the four basic tastes (sweet, sour, salty, and bitter) building blend and body, extending the aftertaste duration, and adding beneficial mouth feel factors."

"Unfortunately, few drug developers have the expertise to effectively evaluate or optimize these factors, which can have such a significant impact on acceptability and sales," he continued. "This is where Senopsys steps in. We help reduce technical and market risks associated with a product's aesthetics so that developers can concentrate on other technical aspects of clinical and commercial development."

Senopsys is an independent and objective partner that does not license technology or sell ingredients. The results of the company's work are custom formulations that meet the needs of diverse patient populations. Drug manufacturers continue to introduce new dosage forms, such as fast-dissolving tablets, oral films, and soft chews, that are more convenient, portable, and easier for children, the elderly, and impaired patients to swallow. Most of these dosage forms are based on food technology and each has its own set of unique challenges, such as taste-masking, hardness, texture, stickiness, and ease-of-swallowing, that developers must address to create a product patients will find acceptable. Senopsys applies its knowledge of flavor construction, excipient functionality, and processing technology to develop formulations for both traditional and novel dosage forms of investigational and approved drugs that meet the needs of specific patient populations.

"Developing palatable drug formulations for specific patient groups can be a daunting challenge," explained Mr. Worthington. "The pediatric market, for example, is particularly tricky and likely the reason that drug developers have not introduced more pediatric medications despite regulatory requirements and incentives to do so. Many of the dosage forms that work for adults, such as tablets and capsules that bypass taste receptors, simply are not age appropriate for children. Senopsys has the expertise to develop palatable dosage formulations that are acceptable to any patient group."

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Market News and Trends

Halozyme & Baxter Present Promising Results for the Use of Hylenex From the Infuse-Morphine Study

Halozyme Therapeutics, Inc. and Baxter Healthcare recently announced the presentation of results of a Phase IIIB clinical trial showing that subcutaneous administration of morphine with Hylenex recombinant (hyaluronidase human injection) accelerated the time to maximal blood levels of morphine by 33% versus morphine with placebo, and appeared safe and well-tolerated.

"The observed shortening of the time to maximal concentration for a co-administered morphine with Hylenex recombinant implies that clinical effects, such as analgesia, may be achieved more rapidly by subcutaneous injection, without the need for intravenous infusion," said Jay Thomas, MD, PhD, Clinical Medical Director at San Diego Hospice and Palliative Care, an affiliate of the University of California, San Diego School of Medicine and Principal Investigator for the trial. "Further testing is warranted to fully determine the promising indication of clinical utility observed in this study."

Hylenex recombinant is a liquid injectable formulation that includes the active pharmaceutical ingredient, recombinant human hyaluronidase (rHuPH20), which is approved by the US FDA for use as a spreading agent to increase the absorption and dispersion of other injected drugs and for subcutaneous (SC) hydration. Morphine is a widely used drug for pain management and is currently approved for both intravenous and subcutaneous administration.

The double-blind, randomized, crossover, placebo-controlled, INcreased Flow Utilizing Subcutaneously-Enabled Morphine clinical trial, or INFUSE-Morphine study, was designed to determine the time to maximal blood levels of morphine after subcutaneous administration with and without Hylenex recombinant, to determine the time to maximal blood levels after intravenous administration of morphine, and to assess safety and tolerability.

Key results from analysis of the 12 evaluable hospice and palliative care patients in the trial include: the validation of the hypothesis was achieved by demonstrating a statistically significant acceleration in the average time to maximal plasma concentration (Tmax) of morphine; Tmax was reduced from 13.8 minutes when injected subcutaneously with the saline placebo to 9.2 minutes when injected with Hylenex recombinant, a 33% reduction in the time to maximal plasma concentration ($p<0.05$); SC administration of morphine with Hylenex recombinant provided total drug exposure (4-hour area under the concentration-time curve, AUC) of morphine and its active metabolite that was comparable to IV morphine administration, as calculated based on the sampling timepoints for measuring absorption; and the most commonly reported adverse events were mild injection site redness, rash, swelling, and itching (however, no Hylenex recombinant-related toxicity was apparent based on a comparison of adverse events for SC injections with Hylenex recombinant versus saline placebo).

These results suggest that SC morphine plus Hylenex recombinant provides pharmacokinetic characteristics that are superior to SC morphine alone and closer to IV morphine. The INFUSE-Morphine trial follows the INFUSE-Lactated Ringers (LR) trial, which showed that the use of Hylenex recombinant preceding subcutaneous LR infusion accelerated the flow rate of LR by approximately four-fold versus the subcutaneous infusion preceded by placebo. The infusion preceded by Hylenex recombinant also caused less edema and was preferred by both investigator (for 92% of subjects) and study subjects (92%).

New Ways to Partner With the Federal Government: Insights From King Pharmaceuticals

By: Christopher Robinson, MBA, PhD, and Debra Bingham

Following such infamous events as 9-11, the anthrax scare, hurricane Katrina, and the fear of a pandemic flu, the US government has significantly stepped up its efforts to address the nation's vulnerability to biological, chemical, or other threats to public health. For the pharmaceutical and biotechnology industry, this has led to a resurgence of new opportunities to partner with the government. In this month's forum, we investigate the opportunities for the drug delivery industry.

To explore this topic, Valeo Partners spoke with a team of experts at King Pharmaceuticals. Through its acquisition of Meridian Medical Technologies, Inc. in 2003, King established itself as a world leader in the development and manufacture of autoinjector drug delivery systems with specific applications to military and emergency medical needs. This company has been a critical supplier to the US Department of Defense for more than 50 years, and remains the only approved supplier of autoinjector nerve agent antidotes. Valeo will summarize the key points and insights from our conversation with these executives.

Q: What are King's autoinjector products and technologies?

A: King's autoinjector products (Figure 1) can generally be defined as acute-care products. Unlike a traditional syringe, which can be cumbersome, time-consuming, and intimidating for the untrained, autoinjectors provide a compact and portable delivery system to meet the demanding operational needs of the US armed forces, emergency responders, and patients requiring acute/chronic injection of medications.

EpiPen®, containing epinephrine, is an autoinjector for the emergency treatment of life-threatening allergic reactions. AtroPen®, containing atropine, is used to counter the effects of organophosphorus or nerve agent poisoning. The company also produces a Pralidoxime Chloride autoinjector, which is an adjunct treatment for nerve agent poisoning. Soldiers will carry 3 "Mark 1" kits of Atropine/Pralidoxime autoinjectors into combat. The Mark I kit is being phased out. King's new dual-chambered technology, which sequentially delivers the two critical nerve agent antidotes from one injection, will replace the Mark I kit. This new technology is known as ATNAA (Antidote Treatment Nerve Agent Autoinjector) by the military and Duodote (atropine and pralidoxime injection) by emergency responders. Another autoinjector product contains diazepam, an anti-convulsant, used to alleviate convulsions resulting from poisoning by nerve agent and one that contains morphine for pain management. Trainers, or units that contain neither a drug nor needle, assist soldiers in learning to use these products.

Q: From a historical perspective, how did Meridian get its start in working with the government?

A: Over 50 years ago, one of Meridian's founders responded to a key unmet technology need that was a subject of debate at a military conference he attended. The objective was to replace an existing technology called a "syrette" for administration of atropine. This delivery system was designed in the early days of Word War II. The syrette product was contained in a small aluminum tube similar to that used for applying topical ointments or toothpaste. The tube had a tiny cap that is removed to expose a needle through which the drug solution containing atropine is squeezed. Soldiers exposed to nerve agents would understandably have difficulty using the syrette. The product worked well in a controlled setting, but it was not ideal for battlefield use. Meridian was able to work with the government to design an autoinjector that was a vast improvement over the syrette (Figure 2).

Q: How are pharmaceutical products for the Government unique?

A: Perhaps the greatest difference is that the chance of these products being used is probably low. However, it is important to have these products available in case of exposure. A good analogy is that of a fire extinguisher, which no one thinks about until one is needed.

A second difference is that there are many unique delivery requirements that are not typical of normal pharmaceutical products administered in a controlled setting. These products must satisfy tough military field standards for ruggedness to ensure that they can perform under severe conditions. As an example, one of King's devices is specifically designed to penetrate through seven layers of clothing and still deliver an intramuscular injection. Special packaging design features allow a soldier to be able to identify the drug contents of an autoinjector by feel, instead of by sight, which

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FIGURE 1

might be compromised in a combat situation (eg, darkness, smoke). Prolonged stability is important, as the environment in a military or emergency setting is not ideal for this purpose.

When considering the government customer, a drug delivery system must be able to withstand the practical realities on the ground. Take the original syrette example. Now imagine for a moment a scared soldier, in the field with thick heavy gloves, a mask, and body armor, trying to squeeze the contents of a small toothpaste-like tube through several layers of clothing, all the while suffering the initial effect of a nerve agent. An autoinjector is the best solution. Technologies, such as these, adapted to emergency use will always be attractive to the government.

Lastly, the government has a range of needs, depending on the agency and the product. Biodefense agents (eg, antibiotics, vaccines) are well-suited for stockpile because you have some time to administer treatment once those who have been exposed have been identified. However, victims of nerve agent exposure need to be treated immediately, as they only have minutes to survive. It is important that local EMS arrives with antidotes already on board their vehicles.

The national stockpile is designed to deliver supplies anywhere in the United States within 8 hours. For biodefense agents, this makes perfect sense, but not for chemical agents. In order to help address this need, the government developed the CHEMPACK program, which places forward deployments of the national stockpile into key metropolitan areas. Even these inventories are considered a second line of defense. The public still relies on local first responders to have access to antidotes in emergency settings, so the buyers and distributors may be different depending on the product.

Drug delivery technologies play a critical role in addressing the government's unique needs. Using the chemical defense arena as an example, the major changes in the past 50 years have primarily been in the delivery systems, not the medicines. Atropine has been around for a long time. However, the delivery systems for it and other treatments will continue to evolve.

Q: How has the marketplace changed since 9-11?

A: The community has changed considerably since 9-11. There is a far greater focus on preparedness and self-sufficiency. In major metropolitan areas, there are now vehicles that move around the city day and night that have King's nerve agent antidotes in them. So, if there is an attack on the subway in the city, these antidotes are going to show up on the scene.

Bioshield and BARDA (Biodefense Advanced Research & Development Agency) legislation was just signed into law. The government is investing heavily in research and development to address gaps in our current capabilities to protect not only the warfighter, but also the civilian, against certain threats. There are now many more development opportunities that have gone beyond bioterrorism agents to other health threats, such as pandemic flu. As a result of the broadened scope and increased availability of development funding, the overall environment could not be more favorable to drug delivery companies with innovative technologies and products.

Funding and distribution channels for EMS products have also changed significantly. The Department of Homeland Security (DHS) now allocates funds to the cities and states that can purchase at the local level. Now a firehouse in any metropolitan area can apply for funding to purchase supplies for first line of defense products and likely not be turned down if they can justify their need. Because this is a local decision, one fire station may have an entire system in place to obtain multiple sources of preparedness funds, while another may not even be aware that funding is available. Companies must understand everyone who might buy their product at all levels of government.

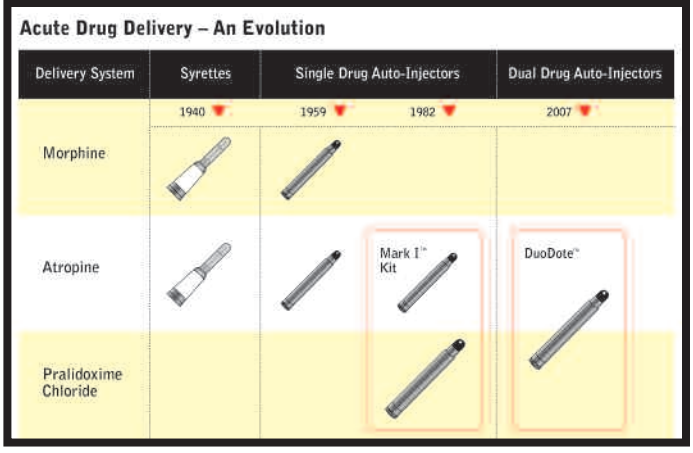
Q: What are the challenges in working with the Government as a development partner?

A: There are many challenging aspects of partnering with the government that differ from the typical experience in the commercial sector. Generally, a company can expect much longer development timelines to get products to market. If you look at some of the more recent Requests for Proposals (RFPs), they are calling for products to be available in 5 to 15 years. This might be discouraging to emerging or start-up drug delivery companies ready to commercialize their technologies.

The second key issue is that the developer has no influence over Federal funding priorities. If the political system decided to shift funding priorities, or if a new substitute technology were to be invented, there is no guarantee of continued funding. For this reason, managing the inevitable starts and stops of government contracting can be precarious for a small technology company. You will essentially have to figure out how to manage the burn, and losses might never be recovered.

Lastly, doing business with the government has rules that are unfamiliar to most pharmaceutical companies. King's autoinjector business has unique cost accounting and compliance systems required

FIGURE 2



by the government. This is a substantial hurdle for small companies. While the government is willing to allow some flexibility for emerging products that fill urgent needs, long-term relationships with the government will require adoption of these standards. One should expect the government to routinely audit these systems to ensure compliance.

On the flip side, working with the government can be quite beneficial. The main benefits include a unique opportunity for funded research and development and the creation of company-owned intellectual property. Longer timelines and more government rules are often outweighed by the potential to receive development funds for technologies, personnel, and intellectual property associated with government projects.

Q: How can companies address these unique challenges?

A: A company is advised to work with another company familiar with government contracting or hire such expertise. You need someone who can walk you through the process from start to finish, as you can stub your toe easily if you are not careful. The right organizational mindset is essential. When a company contracts with a commercial partner, the goal is almost always the commercialization of the technology. In the case of the government, successfully completing each phase or deliverable by the date specified in the contract requires a different discipline. While the objective might eventually be deployment, the completion of any given phase of a project cannot be overlooked. The lesson is to approach each government opportunity as a clearly defined, incremental scope of work and focus your company's development around achieving each contract milestone.

In adopting this mindset, it is important to recognize that the government, in essence, has one of the most sophisticated project management systems in use today. A successful partnership with the government will require integrating the development plan for your technology with the government's project management milestones. King has been so successful throughout the years because its leadership understands both sides of the table and how to synchronize its efforts with those of its government customers.

Q: Does the amount of money a company receives for a development contract compensate for the fact there may not be a buyer of the products at the end of the contract?

A: Yes, in many cases you can build in a certain level of profit margin into a contract. Throughout the past several years, agencies such as the Department of Defense and the Department of Homeland Security have gained a deeper appreciation for the complexities of the drug discovery and development process. People in the government are better trained to recognize the profit-making needs of their commercial partners in the pharmaceutical industry. The government has also started to integrate the knowledge housed in its different agencies and departments. Every year, the government has become a more educated buyer tuned to the needs of the pharmaceutical industry.

It is probably best to remember that accomplishing the scope of work is the goal. The smart way to do business with the government is to properly align the scope, milestones, and development plan. If you try to scope out too much, the unknowns in drug development will cripple the program.

The potential for keeping all of the intellectual property arising from a government grant is an enormous benefit to the commercial enterprise. So, not only is research and development funded, but the intellectual property is usually available for commercial use.

Lastly, after a company develops a unique product, the government may be able to provide ongoing support in other ways. King is one of the few companies in the pharmaceutical industry to receive an IBMC (Industrial Base Maintenance Contract) with the military. The IBMC came out of operation Desert Storm and Desert Shield, where the military recognized the need to support its industrial partners so they can always be ready to respond to spikes in demand. The contract supports a warm base of readiness, where appropriate inventory levels are maintained; trained personnel are available; and manufacturing is available on demand. Thus, this type of program can keep a pharmaceutical company engaged, after development is completed and production requirements are met.

Q: Who defines the requirements for the Government's needs?

A: Most of the time, the government determines product or technology requirements. As an example, King's ATNAA/Duodote was a result of the military's request for smaller, simpler designs and fewer steps. The

government defined the basic requirements and then bid out the contract in a very public and structured manner where there were multiple competitors. This public RFP process is managed through their acquisition/procurement site, Federal Business Opportunities (FedBizOpps).

However, there are other instances in which the government identifies a technology or product that stands on its own merits. King's AtroPen® product was originally developed for insecticide poisoning for field workers. When the military saw it, they concluded that it was a better mousetrap. The technology was drafted by the military so to speak.

In general, it is very difficult to market products to the government. Most contracts are awarded under competitive circumstances. While there is some negotiation room in the RFP process, the rules governing a competitive bidding and award process can never be circumvented.

Q: Who are the key government buyers?

A: There are many potential buyers for drug delivery-based products. Roughly half of King's autoinjector business is from international or US government supply of nerve agent antidotes and other products for emergency preparedness. The domestic government revenue comes from more than 30 unique customers, including the Department of Defense, CDC's national strategic stockpile (and forward stockpiles), the Department of State (to supply embassies around the world), Health and Human Services for the Metropolitan Medical Response System, and other federal security agencies. King also sells to local stockpiles, which are cities/municipalities that desire stockpiles for their local first responders as well as replenishment inventory. Many state, county, and public health agencies also purchase products for stockpiling and deployment to EMS personnel.

Q: What advice could you give to companies regarding government marketing efforts?

A: A company might approach the government opportunity like any new area in which unique expertise is required to effectively compete. In this case, in addition to the prerequisite knowledge of the FDA regulations, it is important for a company to have ready access to people who have a working knowledge of the federal acquisition system and government contracting process. To attempt to win government business without this second skill set would be the equivalent of attempting to develop a novel therapeutic without a sufficient working knowledge of the FDA! Ultimately, companies will need to learn the language of the federal acquisition process to be successful.

To this point, King's organization includes a dedicated manager for international and Department of Defense relationships. Moreover, King's managers have significant knowledge of government needs and the acquisition and procurement process. Dr. Jim Stewart, who leads research and development for King's autoinjector business, is a retired US Army Colonel who worked on a number of programs focused on pharmacology, development of chemical defense systems, and homeland security planning. Dr. Jerry Wannarka, a retired US Army Colonel, also has both pharmaceutical and government experience. As former customers, they understand the issues on both sides of the fence. Having this type of experience on board facilitates doing business with the government.

If this type of expertise is not feasible to have in-house, an excellent way to approach the issue is to identify a company with expertise in the area that is willing to team on a specific government opportunity. Relying on a proven partner alleviates much of the learning curve and resource commitment required to compete.

Q: What should a pharmaceutical/biotechnology company look for in a partner to help win and do business with the Government?

A: Obviously the most critical component is a successful track record in working with the government. A second critical success factor is landing a partner who can provide value in all phases of a contract. To understand this second point, it is helpful to look through the eyes of the government procurement agent. That is, each new player in a proposal constitutes a new risk and another party to track. An established company such as King can do everything (eg, technology, contracting, manufacturing, clinical development, regulatory filing). The government will find the one-stop approach with a known supplier easier and less risky to manage. For any company seeking to do business with the government for the first time, getting a partner who is established and experienced in dealing with the government is probably the best way to start.

Q: How does a company do business with King?

A: For King's government business, those products that are (1) suitable to self-administration or (2) essential in time-sensitive medical situations will fit well. In general, we target products and technologies that may also have civilian use. Due to the nature of our government business, King will only license or acquire products from companies who respect intellectual property rights and can legally conduct business with the US.

King offers its partners a well-established track record of supplying products and services to the US government. King has expertise and capabilities in pharmaceutical development, manufacturing, and commercialization, including drug delivery

systems. King is an excellent partner for doing business with the government or for commercializing products outside the government in therapeutic areas such as cardiovascular/metabolics, acute care, and neuroscience, which may require a large sales force. If interested in discussing partnering or other business development opportunities, please contact Ted Marcuccio, King's Vice President of Business Development and Strategic Planning at ted.marcuccio@kingpharm.com.

Q: Putting it all together, would you see this as an attractive area for a drug delivery company?

A: Absolutely. While a new company may not want to focus exclusively on the government, it can approach the opportunity as it would approach any new therapeutic area. There is certainly a need within the government and a role for drug delivery technologies. While each company's situation will be different, the potential for government support for research and development funding, and the creation of intellectual property rights cannot be overlooked. Simply view this as an opportunity to build your platform, improve your technology and capabilities, and satisfy a new customer. ◆

ACKNOWLEDGEMENTS

Valeo Partners would like to extend a special thanks to the team at King Pharmaceuticals that contributed to this discussion. Without their insight, this article would not have been possible: Dennis O'Brien, Executive Vice President and President, Meridian Medical Technologies; Cristina Derasmo, Vice President, Government Programs; Tom Handel, Vice President, Commercial Pharmaceuticals and Alliance Management; Ted Marcuccio, Vice President, Business Development and Strategic Planning; David Robinson, Senior Director, Corporate Affairs; James Stewart, PhD, DVM, (Colonel, US Army Retired), Senior Director, Research and Development; Jerry Wannarka, PhD, RPh, (Colonel, US Army Retired), Formerly, Sr. Vice President, Technology

* Meridian Medical Technologies owns the U.S. NDA for EpiPen, but the trademark name EpiPen is owned by EMD Chemicals under license to Dey LP. Trademarks Duodote and AtroPen are owned by Meridian Medical Technologies.

BIOGRAPHIES

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

Ms. Debra Bingham is a Partner of Valeo Partners. She brings clients over a decade of specialized expertise in the pharmaceutical and biotech industries. At Valeo, her primary focus is in helping clients in the areas of business strategy, business development, growth opportunity assessment, and strategic partnering. Ms. Bingham leads Valeo's strategic partnering offering in affiliation with Stonecroft Capital, a DC-based investment bank, which provides full-service transactional capabilities from licensing to M&A. She spent the majority of the past 10 years working in the pharmaceutical industry assisting companies with strategic business assessment and business development. Ms. Bingham has authored many drug delivery business articles and technology reviews and is a featured speaker at industry trade conferences.

LICENSING STRATEGIES

Drug Delivery's Increasing Importance to Big Pharma & Specialty Pharma

By: Barath Shankar, Research Analyst, Pharmaceuticals & Biotechnology, Frost & Sullivan

INTRODUCTION

The drug delivery (DD) market, valued at over $55 billion in 2006, is poised to witness rapid expansion owing to major patent expiries, generic competition, increasing focus on life-cycle management, and tightening FDA regulations. DD companies are likely to enable pharmaceutical companies to revive late-stage products by using drug delivery platforms and re-branding products. As a result, DD companies are likely to remain the focus of attention of big pharma and specialty pharmaceutical companies as acquisition targets or licensing partners.

Big pharma pipelines are continuing to shrink, while patent expiries continue to threaten the multi-billion dollar blockbuster business model. DD companies are thus perceived as natural partners to big pharma companies and thus an increase in partnerships between pharma and DD companies is already being witnessed.

SPECIALTY PHARMA & DRUG DELIVERY

Specialty pharmaceutical companies focus on different stages and aspects of drug development and marketing in addition to partnering with large pharmaceutical companies in the life-cycle management of their products. The areas of expertise for these companies include drug delivery, clinical development, generic drugs, and sales and marketing.

Specialty pharmaceutical companies typically focus on one or two of these areas, leveraging their expertise and positioning themselves in a niche pharmaceutical market. The business models of specialty pharmaceutical companies can be broadly classified into the following four types:

- Strategy 1: Acquire low sales-generating inline branded products and market them;
- Strategy 2: In-license and develop the market for products;
- Strategy 3: Develop drug delivery technologies for existing and new products; and
- Strategy 4: Develop and market generic pharmaceuticals.

Figure 1 shows the business model adoption by the top specialty pharmaceutical companies in 2005-2006. The figure also clearly points out that the adoption of in-house drug delivery technologies has been minimal compared to other strategic options that are pursued by top specialty pharma companies, opening up the potential for specialized DD companies to take advantage of the market potential. Because these specialty pharma companies tend to operate in non-blockbuster product areas, the addition of DD could enable them to position their products in a better and effective manner without incurring the cost and risk of extended clinical development.

LICENSING STRATEGIES

Expiring patents have always been a problem in the branded pharmaceutical segment, and especially the big pharma companies. The next 5 years are going to be tougher with more than $70 billion worth of key branded drugs expected to go off-patent.

DD companies have before them several options to decide on the strategic direction they need to adopt with a therapeutic line/company portfolio or dosage type. DD platforms tend to remain highly customizable and hence offer pharmaceutical companies flexibility. However, revenue or profit share of DD companies have remained lower than expected owing to the lesser risk that they have tended to take. With the pharmaceutical industry expected to witness lower margin and revenue

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FIGURE 1

Top Specialty Pharmaceutical Companies: Business Model Adoption (U.S.), 2005-06

Company	Model 1	Model 2	Model 3	Model 4
Teva Pharmaceutical Industries Ltd.	Medium	Medium	Low	High
Forest Laboratories Inc	High	High	Low	Low
Allergan Inc	Low	High	Medium	Low
Watson Pharmaceuticals Inc	High	High	Low	High
King Pharmaceuticals Inc	High	High	High	Low
Barr Laboratories Inc	Low	High	Medium	High
Cephalon Inc	Medium	Medium	Low	Low
Endo Pharmaceuticals	Low	Medium	Medium	Medium

Key:
Model 1: Acquire "low sales generating" inline branded products and market them
Model 2: In-license and develop the market for products
Model 3: Develop drug delivery technologies for existing and new products
Model 4: Develop and market generic pharmaceuticals

Source: Frost & Sullivan

growth compared to the first half of the decade, DD companies will have to be more aggressive and retain a higher share of risk to exploit the growth potential the market offers.

It is not unlikely that DD companies with sufficient cash or financial backing could acquire specialty or niche pharma companies to develop and market their own product line. Several large mergers and acquisitions amongst big pharma have also resulted in products being out-licensed or sold off to specialty pharma companies, as they did not fit into the strategic direction of the larger company.

Specialty pharma companies adopt a combination of licensing and acquisition strategies that include single product acquisition/licensing, franchise acquisition, or corporate acquisition. The top specialty pharma companies have been successful in implementing these strategies in a robust manner. Hence, a DD-specialty pharma merger or acquisition is likely to set the ball rolling for a new generation of companies that are likely to drive the growth of the market at the tier 2 level.

CONSOLIDATION TO CONTINUE

Big pharma has been facing increasing pressure with thinning potential blockbuster pipelines, the pull out of several key products, and falling margins. Hence, it is expected that 2007 is likely to witness significant market consolidation with several niche biotech, specialty pharma, and drug discovery companies likely to be acquired by big pharma companies.

Licensing or acquisition of product(s) involves understanding the clinical and market potential in order to have an understanding of the company's theoretical return on investment. The rapid growth of tier 1 and tier 2 pharmaceutical and biotech companies has resulted in increased competition from several companies targeting corporate and product acquisition. Hence, there is significant pressure on companies to pay a premium, which often results in dependence on a single product, or technology and subsequently increased risk in the case of failure.

The mix of business models and licensing strategies adopted by DD companies enables them to limit clinical risk and absorb commercial risk to a greater extent. In-licensing and out-

licensing are likely to remain important concepts in determining the future direction of the industry based on current trends, and DD technologies are likely to complement these decisions to a large extent.

LIFE-CYCLE MANAGEMENT & OUTSOURCING

As DD companies continue to exhibit rapid growth, they tend to compete more directly with pharmaceutical companies. However, the DD business offers the advantage of carrying lesser risk compared to its pharmaceutical counterparts owing to its customizable nature – in other words, the failure of a DD technology on a product A does not limit its application in product B or C.

With several major products reaching the end of their patent life recently, there is an increased interest in product life-cycle management. Life-cycle management has always been a buzz word in the pharmaceutical industry, but seems to have found increasing focus amongst the specialty pharma group. Drug delivery technology platforms are widely used by specialty pharma companies for LCM of their products.

There is a large complementary potential between biotechs (which are typically innovation engines), DD, and specialty pharma companies that focus on sales and marketing. The combination of the three could create an integrated entity that could leverage the strengths from all sides and complement it further with outsourced activities, such as research and manufacturing. This entity would thus achieve critical mass at a significantly lower cost compared to the big pharma business model.

Overall, the DD business continues to be driven predominantly by investor interest in the perceived robustness of the business model and the business development strategies adopted by companies. With the industry moving forward into a phase of intense competition and consolidation, we are likely to witness a more synergistic and proactive approach by DD companies, which is likely to augur well for the market.

BIOGRAPHY

Mr. Barath Shankar is a Research Analyst with the Frost & Sullivan North American Healthcare Practice. He focuses on monitoring and analyzing emerging trends, technologies, and market behavior in the pharmaceuticals and biotechnology industries in North America. Since joining Frost & Sullivan in October 2004, Mr. Shankar has completed several research studies and consulting projects on Pharmaceuticals and Biotechnology. Prior to this, Mr. Shankar was a Research & Development intern at IPCA Laboratories Ltd., Mumbai, India. He brings with him considerable analytical and quantitative experience, giving him a keen perception into the functioning of technology in the healthcare industry. Mr. Shankar has received acclaim for his research through articles and quotes published in various magazines, including *Specialty Pharma* and *Drug Delivery Technology*.

OCULAR DELIVERY

In Situ Gel Systems for Ocular Drug Delivery: A Review

By: Mitan R. Gokulgandhi, BPharm; Dharmesh M. Modi, MPharm; Jolly R. Parikh, PhD

INTRODUCTION

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing pharmaceutical scientists. The anatomy, physiology, and biochemistry of the eye render this organ exquisitely impervious to foreign substances. The challenge to the formulation is to circumvent the protective barriers of the eye without causing permanent tissue damage. The primitive ophthalmic solution, suspension, and ointment dosage forms are clearly no longer sufficient to combat some present virulent diseases.[1]

In spite of active and continued research and frequent introduction of novel ophthalmic drugs, ocular drug delivery does not seem to progress at the lively pace typical of oral, transdermal, or transmucosal delivery. The vast majority of existing ocular delivery systems are still fairly primitive and inefficient.[2] Successful delivery of drugs into the eye is extremely complicated because the eye is protected by a series of complex defense mechanisms, which make it difficult to achieve an effective concentration of the drug within the target area of the eye.[3] Poor bioavailability of drugs from ocular dosage forms is mainly due to the tear production, non-productive absorption, transient residence time, and impermeability of corneal epithelium.[4]

The drainage of the topically administered dose via the nasolacrimal system into the nasopharynx and the gastrointestinal tract takes place when the volume of fluid exceeds lachrymal fluid (lachrymal fluid 7 to 10 µl). Thus, the contact time of the drug with ocular tissue is relatively short (1 to 2 min), mainly due to the spillage of the instilled solution from the precorneal area. As a consequence of these mechanisms and factors, the rate of the loss of drug from the eye can be 500 to 700 times greater than the rate of absorption in to the anterior chamber, and 1% to 5% or less of the drug applied topically as a solution reaches the inner part of eye. Thus, it may be concluded that both transconjuctival and transnasal absorption after drainage via the nasolacrimal duct are generally undesirable, not only because of the loss of active ingredient into the systemic circulation, but also because of possible side-effect.[5,6] Therefore, to optimize topical ocular drug delivery systems, prolonged contact time with the cornea surface and better penetration through the cornea are necessary.[7]

ANATOMY & PHYSIOLOGY OF THE EYE

Lachrimal Apparatus

The lachrymal apparatus is a group of structures that produce and drain lachrymal fluid or tears. The lachrymal glands, each about the size and shape of an almond, secrete lachrymal fluid, drain in to 6 to 12 excretory lachrymal ducts that empty tears into the surface of eyelid. Lachrymal fluid is a watery solution, containing salts, some mucus, and lysozyme, a protective bacterial enzyme. After being secreted, lachrymal fluid is spread medially over the surface of the eyeball by blinking of the eyelid. Each gland produces about 1 ml of lachrymal fluid.

Lachrimal System

The lachrimal system consists of secretary glandular and excretory ductal elements. A thin fluid film (the so-called preocular tear film, which is formed and maintained by the lachrymal apparatus) covers the conjuctive and cornea. The lachrymal gland and the accessory gland contribute to the formation of the aqueous layer, containing inorganic salts, glucose, and urea as well as retinal, ascorbic acid, various proteins lipocalins, immunoglobulins, lysozyme, lactoferrin, and glycoproteins.[8-10]

Conjuctiva

The conjuctiva is a transparent mucus membrane. The ocular conjunctiva is very thin, and blood vessels are clearly visible beneath it. When the eye is closed, a slit-like space occurs between the conjuctiva-covered eyeball and eyelid. This so-called conjuctival sac is where a contact lens lies, and eye medications are often administered in to its interior recess. Although the conjuctiva protects the eye by preventing foreign objects from penetrating beyond the confines of the conjuctival sac, its major function is to produce lubricating mucus that prevents the eyes from drying out.[8]

Eyelid

The eyelid serves a variety of special functions, including protection of the eye from mechanical and chemical injuries. In human beings, the average blink rate is 15 to 20 times per minute, which has great influence on the bioavailability of drug. The osmolality of the tear film equals 310 to 350 mosm/kg in normal eyes and is adjusted by principal inorganic ions Na^+, K^-, Cl^-, HCO_3^-, and protein. The mean pH value of normal tears is about 7.4. The buffer capacity of the tear is determined by bicarbonate ions, protein, and mucin.[8,11]

Mucus Layer

The mucus layer is secreted in to the eye surface by goblet cells, intimately associated with glycocalyx of the corneal/conjuctival epithelial cell. The mucus layer can form a diffusion barrier to macromolecules depending on the degree

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AMEX: IOX

of network entanglement on the other hand; mucus can bind cationic substance because of the negative change of mucin.

In 1992, Prydal et al suggested that the human tear film is composed substantially of mucus instead of fluid. A film composed largely of mucus (40 microns in thickness), mucus consists of glyco protein, protein lipid, electrolyte, enzyme, mucopolysachhride, and water.[12-14]

TRADITIONAL OPHTHALMIC DOSAGE FORMS

Traditional ophthalmic dosage forms include solutions, suspensions, and ointments. Solutions, in spite of their limitations (ie, quick elimination from the precorneal area resulting in poor bioavailability), are still given top priority by formulators because they are relatively simple to prepare, filter, sterilize, and are cost effective. Suspensions, while not as common as solutions, are widely used for formulations involving poorly soluble drugs, such as anti-inflammatory steroids.

Ocular suspensions, however, have several disadvantages. Proper shaking is required, which if not done can lead to inconsistency in the administered dose. A fine sediment may form that can be difficult to disperse with gentle shaking. And seldom occurring, but of serious consequences, is a polymorphic change in the suspended drug to form a less soluble or insoluble form of the drug. An important feature of the ointment is that it remains in the conjuctival cul-de sac, forming a reservoir of the drug. Moreover, the disappearance from the precorneal area of a drug administered in an ointment vehicle is very slow (0.5% per min) when compared with the elimination by the normal lachrymal turnover (about 16 per min). These preparations, however, occupy a position of minor importance because they are ill accepted on account of their greasiness, vision blurring effects, etc, and are generally used as night medications.[15]

VARIOUS FORMULATION APPROCHES TO IMPROVE OCULAR BIOAVAILABILITY

A typical time course of drug release in the eye from conventional ophthalmic solutions follows a pulsed entry, ie, peak and valley patterns. It initially shows a very high drug concentration followed by rapid decline. Various approaches that have been attempted to increase the bioavailability and the duration of therapeutic action of ocular drugs can be divided into two following categories:

1. Maximizing corneal drug absorption and minimizing precorneal drug loss.

2. Drug delivery system to provide the controlled and continuously delivery of ophthalmic drug to the pre- and intra-ocular tissue.

Several new preparations have been developed for ophthalmic use, not only to prolong the contact time of the vehicle on the ocular surface but also slow down drug elimination. Successful results were obtained with inserts and collagen shields, although preparation involves some disadvantages, such as non-compliance, especially by elderly people, and many patients sometimes lose the device without noticing it.[16] A more desirable dosage form would be one that can be delivered in a drop form, create little to no refractive index problem for vision, and dosed no more frequently then once or twice daily.[17] This can be achieved by using an in situ gel-forming ophthalmic drug delivery system prepared from polymers that exhibit reversible phase transition (sol-gel-sol) and pseudo-plastic behavior to minimize interference with blinking, increase pre-corneal residence of the delivery system, and enhance ocular bioavailability.

Because much has already been published about the use of viscosity-enhancing agents, penetration enhancers, use of cyclodextrins, prodrug approaches, ocular inserts, and the ready-existing drug carrier systems, along with their application to ophthalmic delivery, the main focus of this review will be on the phase transition system (ie, in situ activated gel-forming systems) to improve ocular bioavailability to a sufficient extent that an ocularly delivered drug can elicit its biological action. The aim of this article is to provide an insight into the potential applications of the phase transition system for the conception of innovative ophthalmic delivery approaches, to decrease systemic side effects, and to create a more pronounced effect, which may be achieved with lower doses of the drug.

IN SITU ACTIVATED GEL-FORMING SYSTEM

A gel is a soft, solid, or solid-like material consisting of two or more components, one of which is a liquid, present in substantial quantity. A gel should, in a time scale of seconds, not flow under the influence of its own weight. The solid-like characteristic of gel can be defined in terms of two dynamic mechanical properties, an elastic modules, G '(w), which exhibit a pronounced plateau extending to time at least of the order of second; and a viscous modules, G"(w), which is considerably smaller than G' (w).[18] Gelation occurs via the cross-linking of polymer chains, something that can be achieved by the following:

1. Covalent bond formation (chemical cross-linking)

2. Non-covalent bond formation (physical cross-linking[19]

The progress that has been made in gel technology is in the development of a droppable gel. In situ gel-forming systems can be described as low-viscosity solutions

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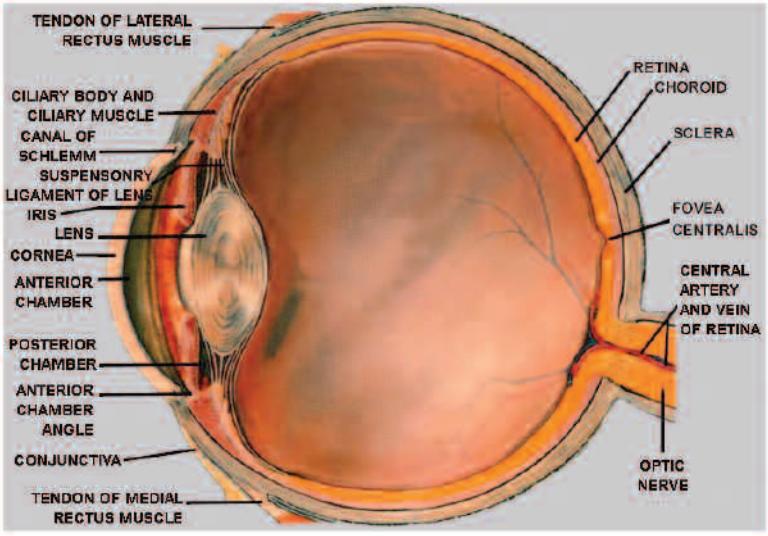
FIGURE 1



that undergo phase transition in the ocular cul-de-sac to form viscoelastic gels due to conformational changes of polymers in response to the physiological environment.[20,21,22]

The rate of in situ gel formation is important because between instillation in the eye, and before a strong gel is formed, the solution or weak gel is produced by the fluid mechanism of the eye. Hence, contact times in humans were measured for a salt-free solution of Gelrite® preparation with varying osmolality. The hypotonic samples were non-irritating whereas the isotonic and hypertonic solution caused an increase in lachrymation and blurred vision. The high tolerance of the hypotonic sample is due to the rapid formation of a gel residing in the conjuctival sac, thus avoiding any solution spreading over the sensitive cornea.[23]

Advantages

The principal advantage of this formulation is the possibility of administering accurate and reproducible quantities in contrast to already gelled formulations. This type of gel combines the advantage of a solution because these are conveniently dropped as a solution into the conjuctival sac, making it patient convenient and minimizing interference with blinking.[24] Gel formulation with suitable rheological properties increases the contact time with the mucus at the site of absorption. The increased contact time is caused by the mucoadhesive properties of the polymer in the gel and by the rheological properties of the ocular protective mechanism and hence better bioavailability. [25,26]

This new concept of producing a gel in situ was suggested for the first time in the early 1980s. These methods have been employed to cause phase transition on the eye surface. Change in viscosity can be triggered by change in temperature, change in pH, and change in ionic or electrolyte composition.

Temperature

Gelling of the solution is triggered by change in temperature, and sustained drug delivery can be achieved by the use of a polymer that changes from solution to gel at the temperature of the eye (37°C).[27] Poloxamers are thermoreversible gels that seem to fulfill the aforementioned conditions. Poloxamers are a broad group of compounds that were introduced commercially in the early 1950s as food additives and for pharmaceutical preparations. These water-soluble inert surfactants are triblock co-polymers with a central hydrophobic part (Polyoxypropylene) and two identical lateral hydrophilic parts (Polyoxyethyler).[28] Poloxamers were employed as solubilizers and proposed as artificial tears. Pluronic® F127 is no more damaging to the mouse or rabbit cornea than a physiological saline.[29] The poloxamers are reported to be well tolerated and non-toxic even though large amounts (20% to 30%) of polymers are required to obtained a suitable gel.

At concentrations of 20% w/v and higher, aqueous solutions of Poloxamer-407 remain as a liquid at low temperatures [< 15°C] and yield a highly viscous semisolid gel upon instillation into the cul-de-sac. At low temperatures, the poloxamer forms micellar subunits in solution, and swelling gives rise to large micellar subunits and the creation of cross-linked networks. The result of this phenomenon is a sharp increase in viscosity upon heating.[30] Miller et al examined a temperature-sensitive solution of poloxamer used to deliver the miotic pilocarpin.[31]

An alternative in situ gelling material of natural origin for ocular drug delivery is xyloglucan, a polysaccharide derived from Tamarind seeds. When partially degraded by Beta-galactosidase, this gelling material exhibits thermally reversible gelation in dilute aqueous solutions, and varying sol-gel transition temperatures upon degree of galactose elimination.

Attwood et al has reported enhancement of the miotic response following sustained release of Pilocarpin from the 1.5% w/w xyloglucan gel. In order to develop a thermosetting gel with a suitable phase transition temperature, Wei et al combined poloxamer (Pluronic F127 and F68) and sodium hyaluronan. Gamma scintigraphy demonstrated that the clearance of an optimized formulation containing 21% F127

and 10% F68 was significantly delayed with respect to a phosphate buffer solution. A three-fold increase of the corneal residence time was achieved in the rabbits.[32]

pH

Gelling of the solution is triggered by a change in the pH. Cellulose acetate phthalate (CAP) latex, cross-linked poly acrylic, and derivatives such as carbomers are used.[33] Cellulose acetate derivatives are the only polymer known to have a buffer capacity that is low enough to gel effectively in the cul-de-sac of the eye. The pH change of about 2.8 units after instillation of the native formulation (pH 4.4) into the tear film leads to an almost instantaneous transformation of the highly fluid latex into viscous gel.[34,35,36] Cellulose acetate phthalate latex is a polymer with potentially useful properties for sustained drug delivery to the eye because latex is a free-running solution at a pH of 4.4, which undergoes coagulation when the pH is raised by the tear fluid to pH 7.4. The use of pH-sensitive latex nanoparticles has been described by Gurny.[37] But the low pH of the preparation can elicit discomfort in some patients.[38] The poly acrylic acid and its lightly cross-linked commercial forms (Polycarbophil® and Carbopol®) exhibit the strongest mucoadhesion. In the pioneering paper, Hui and Robinson demonstrated that the use of acrylates for ocular delivery of progesterone was based not only on viscosifying but also on bioadhesion properties.[39] Carbopol is a polyacrylic acid (PAA) polymer, which shows a sol-to-gel transition in aqueous solution as the pH is raised above its pka of about 5.5.[40] Different grades of Carbopol are available. The manufacturer states that Carbopol 934 gel has the lowest cross-linking density, while Carbopol 981 intermediate and Carbopol 940 have the highest.

Polycarbophil-based in situ gelling systems were developed by Robinson and Mlynek.[41] Polycarbophil is insoluble in water, but its high swelling capacity in a neutral medium permits the entanglement of the polymer chains with the mucus layer. The non-ionized carboxylic acid group binds to the mucin by means of hydrogen bonds.[41,42]

Ionic Strength

Gelling of the instilled solution is also triggered by change in ionic strength. It is assumed that the rate at which electrolytes from the tear fluid is adsorbed by the polymer will depend on the osmotic gradient across the surface of the gel. It is therefore likely that the osmolality of the solution might have an influence on the rate of the sol-gel transition occurring in the eye. One example is Gelrite®, an anionic extracellular polysaccharide, low acetyl gellan gum secreted by pseudomonas elodia. Gelrite formulations in aqueous solutions form a clear gel in the presence of the mono or divalent cations typically found in the tear fluids. The electrolyte of the tear fluid and especially Na^{+}, Ca^{+}, and Mg^{+2} cations are particularly suited to initiate gelation of the polymer when instilled as a liquid solution in to the cul-de-sac. The concentration of sodium ion in human tears is 2.6 gm/l, which is particularly suitable to cause gelation of Gelrite when topically instilled in to conjuctival sac. Gelrite has been the most widely studied and seems to be preferred compared to the pH-sensitive or temperature-setting systems. The polymeric concentration is much lower compared to previously described systems.[43]

Rozier et al found an improvement in the ocular absorption of timolol in albino rabbits when administered in Gelrite when compared with an equiviscous solution of hydroxyl-ethyl cellulose.[44]

Sanzgiri et al compared various systems of Methyl prednisalone (MP): esters of MP with Gelrite eye drops, gellan-MP film, and gellan film with dispersed MP. Gellan eye drops provided better performance because they afforded the advantage of faster gelation over a higher surface area in eye, whereas the results obtained with the gellan-MP film seemed to indicate that the gelation at the surface of the film occurred very slowly, and the surface of release was not controlled.[45] Maurice and srinivas measured a two-fold increase in the permeation of the fluoroscein in humans when using gellan gum compared to isotonic buffer solution.[46]

Schenker et al compared the commercial product Timoptic XE® 0.5% with a timolol maleate gel-forming solution with xanthan gum as the gelling polymer (Timolol GFS® 0.5% Alcon Research). The xanthan gum preparation was developed for once-daily dosing. The reported data indicated equivalent efficacy in the reduction of intraocular pressure (a maintained reduction during long-term use) and consequently therapeutic equivalence.[47]

Hartmann and Keipert reported that the increase in therapeutic effects (eg, miosis) in rabbits could be due to a permeation-enhancing effect of gellan gum comparable to EDTA. Apart from its in situ gelling property, gellan gum diminishes drainage after instillation.

The commercial product Timoptol XE® preparation containing Gelrite remains for a longer period at the eye surface when compared to conventional timolol maleate eye drops. This resulted in an enhanced drug transfer sufficient enough to obtain an intra-ocular pressure reduction after a once-daily topical instillation.[48-50]

COMBINATION OF DIFFERENT APPROACHES

Most of the systems require the use of a high concentration of polymers. In order to reduce the total polymer content and improve the gelling properties, Joshi et al first used a combination of polymers in an ocular drug

delivery system. Several researchers explored the advantage of using various in situ gelling polymers with different phase transition mechanisms in ophthalmic drug delivery. The main idea is that aqueous composition reversibly gelled in response to simultaneous variation in at least two physical parameters, such as pH, temperature, and ionic strength, can be formed by using a combination of polymers that exhibit reversible gelation properties. Due to rapid release of hydrophilic drug out of the poloxamer network, Desai and Blanchard added metylcellulose and hydroxypropylmethyl cellulose to Pluronic F127 solution. This slowed down the gel dissolution rate and pilocarpin release, thereby modulating the therapeutic response.[51]

A physical combination of methylcellulose (a thermally induced gelling material) and carbomer (pH-induced gelling polymer), which are able to achieve a desired viscosity at lower polymer concentration, were investigated.[52] Srividya et al used a non-irritating system based on Carbopol 940 and hydroxypropyl methylcellulose (Methocel E50) and obtained a sustained-release system for Ofloxacin over an 8-hour period.[53]

Kumar et al expanded on the invention of Joshi et al who developed an ocular drug delivery system based on a combination of Carbopol and methylcellulose. Kumar et al developed a similar delivery system using a combination of Carbopol and hydroxypropylmethyl cellulose. For both systems, it was found that reduction in the Carbopol concentration without compromising the in situ gelling properties as well as overall rheological behaviors can be achieved by adding a suitable viscosity-enhancing polymer.[54,55]

Kumar and Himmelstan combined pH and thermosensitive properties of both polyacrylic acid and hydroxypropylmethyl cellulose (HPMC), respectively, to be used as an in situ gelling ophthalmic drug delivery system. This HPMC-PAA combination showed slow in vitro release of incorporated timolol maleate.[56]

El-Kamel attempted to reduce the poloxamer concentration without compromising the in situ gelling capacity by adding viscosifying agents, such as methylcellulose and hydroxypropylmethyl cellulose. The slowest drug release was obtained from a 15% Pluronic F127 solution with 3% methylcellulose. The ocular bioavailability in rabbits increased by 2.5- and 2.4-fold for 25% Pluronic F127 gel formulation and 3% MC/15% F127, respectively, compared with an aqueous timolol solution.[57,58]

Miyazaki et al evaluated xyloglucan and Pluronic F127 as sustained drug release vehicles for pilocarpin hydrochloride in rabbits. A similar miotic response was observed for a 1.5% xyloglucan gel and a 25% Pluronic F127 gel.[59]

Lin and Sung studied the influence exerted by an aqueous solution containing Carbopol 934P, poloxamer (Pluronic F127), and Carbopol/poloxamer mixture on the bioavailability of pilocarpin. The combined 0.3% Carbopol/14% (w/w) Pluronic solution exhibits a better ability to retain the drug than the individual polymer solutions. Pilocarpin did not disrupt the stronger three-dimensional network formed at the physiological condition. After instillation as an eye drop, a strong gel was formed following the phase transition, which withstood the shear force during blinking.[60] The use of the bipolymer system (PAA/PVP) was proposed as a formulation strategy to overcome problems associated with the use of highly viscous materials. The PAA/PVP system exhibits a low viscosity while keeping mucoadhesive properties intact.[61]

CONCLUSION

Drug delivery as it pertains to the eye is a generic term, which is defined broadly as representing an approach to controlling and ultimately optimizing delivery of the drug to its target tissue in the eye. In liquid dosage form, such as viscous eye drops in which polymer solution is fully hydrated before instillation, the mucoadhesive performance is limited. Mucoadhesion is based on entanglement or non-covalent bonds between polymer and mucus, thus, mucoadhesion as the whole factor responsible for an improvement in bioavailability is questionable. Interaction with corneal/conjuctival epithelium could play a role. The in situ gelling system seems promising because as with non-viscous eye drops, accurate and precise sustained-release properties with little or no eye irritation is possible.

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COX-II Inhibitor-Loaded Microspheres for Familial Adenomatous Polyposis: Characterization, In Vitro Release & Stability Studies

By: Madhumathi Seshadri and Lakshmi Sivasubramanian

ABSTRACT

Familial Adenomatous Polyposis (FAP) is a colon cancer predisposition syndrome in which hundreds to thousands of precancerous colonic polyps develop. FAP is an inherited condition caused by a mutation in the APC gene that is inherited in an autosomal dominant way. The condition is characterized by the formation of polyps also known as Adenomas (because they are at a precancerous stage where they may or may not develop into cancerous cells). The usual adopted treatment is surgery, which may or may not offer good results. The only other possibility (and a far better option in the authors' opinion) is chemotherapy. This is achieved by the use of COX-II inhibitors to reduce the recurrence of polyps. But this syndrome requires the release of a drug for a prolonged time. Therefore the formulation of COX-II inhibitors as microspheres was studied. Because COX-II inhibitors are hydrophobic drugs, the best method for the preparation of microspheres was Emulsification-Solvent Evaporation, which produced a better yield in less time, microspheres with good drug content, and high microencapsulation efficiency. In this method, the authors used three different polymers (ethyl cellulose, sodium carboxymethylcellulose, hydroxypropyl methyl cellulose) and various characterization like drug content, microencapsulation efficiency, *in vitro* release studies, flow property, scanning electron microscopy, and stability studies to prove the best of the three polymers used.

INTRODUCTION

There are many methods for the treatment of FAP, with surgery being the oldest.[1-3] Genetic counseling and radiation therapy are also provided to patients with FAP, but there is no relief to the development of polyps in the colon as it keeps recurring. The only long-term treatment for this is chemotherapy and particularly use of NSAIDs (ie, COX-II inhibitors like Celecoxib, Rofecoxib, Valdecoxib to name a few).

FAP requires the use of drug treatment for more than 24 hours in a single dose. There has already been lot of research in this area to formulate a drug for the treatment of this syndrome on a long-term basis. This is the reason to formulate the COX-II inhibitors (Valdecoxib and Rofecoxib) as microspheres in this study. Microencapsulation is one of the most intriguing fields in the area of drug delivery systems.[4,5,6] It requires the knowledge of pure polymer science, emulsion technology (it being an interdisciplinary field), and an understanding of drug and protein stabilization.

Microencapsulation is a process by which solids, liquids, or even gases may be encapsulated into microscopic size particles through the formation of a thin coating of "wall materials" around the substance being encapsulated. A solvent evaporation process may result in a microsphere or a microcapsule, depending on the amount of loading. The main purpose of encapsulating is for protection and increasing its stability. Its release was triggered by major environmental changes as going from a dry to wet environment or by a physical trauma caused by chewing or grinding of capsules

To date, there has been a study using Celecoxib, another COX-II inhibitor, which was prepared as microspheres in the treatment of FAP. Various biodegradable polymers like ethyl cellulose, sodium carboxy methyl cellulose, and hydroxy propylmethyl cellulose were used for the study.

The characterization to check

LONG BEACH

CALIFORNIA

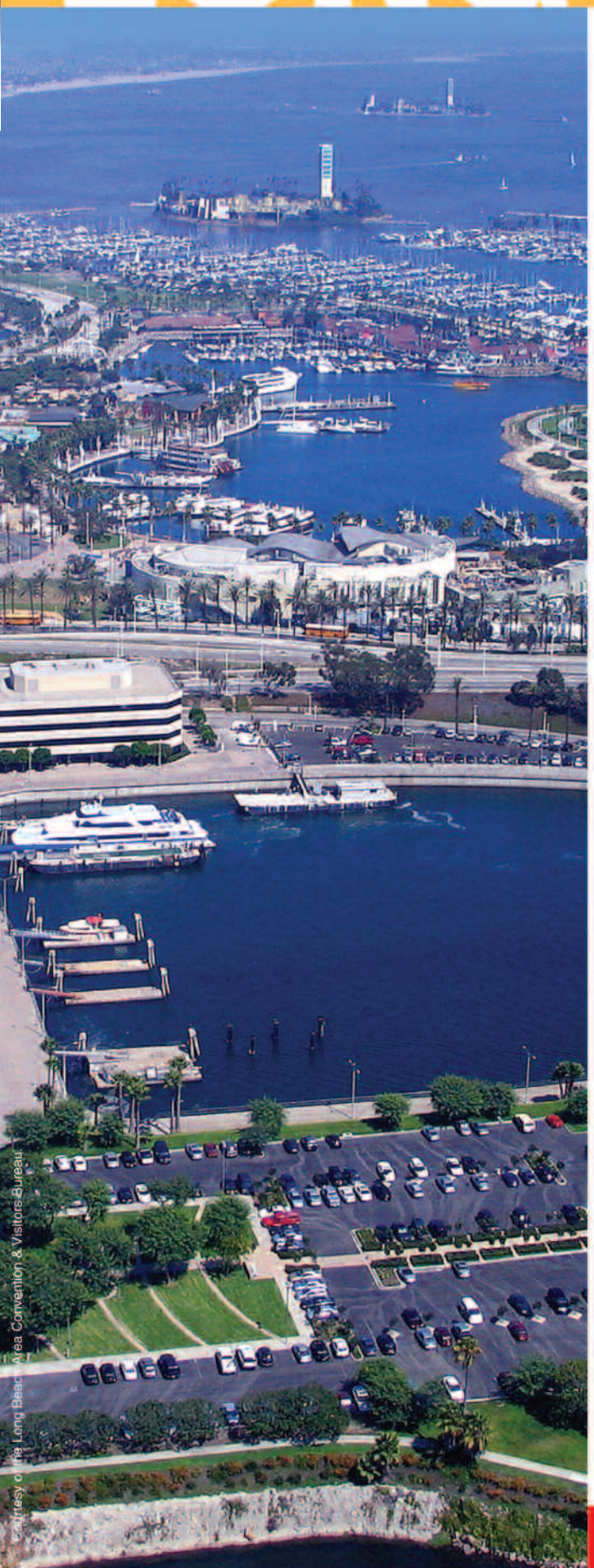

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TABLE 1

Microsphere Sample (100 mg)	Drug Content in mcg/ml		
	EC	SCMC	HPMC
Rofecoxib	0.0219	0.04629	0.03169
Valdecoxib	0.0284	0.0485	0.038

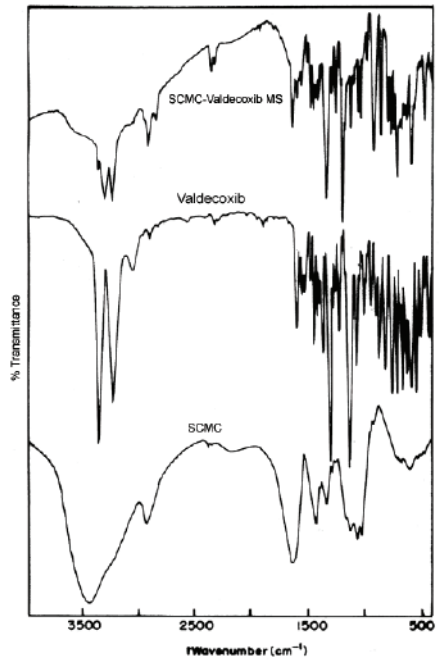
The drug content in the prepared microspheres after a specified time interval

TABLE 2

Microsphere Sample (100 mg)	Microencapsulation Efficiency(%)		
	EC	SCMC	HPMC
Rofecoxib	43.8	92.6	63.4
Valdecoxib	56.8	97	76

The microencapsulation efficiency in the prepared microspheres after a specified time interval.

FIGURE 1



FTIR overlay spectrum of SCMC loaded with Valdecoxib microspheres.

microsphere formation was done by checking for its release profile, drug content, and microencapsulation efficiency. The scanning electron microscopy Figure 2a and 2b also proves that microspheres were formed. Various tests to check for such things like flow properties were also performed, which showed the efficiency of formed microspheres. The stability studies were also performed, further strengthening the result of the best of the three polymers used for the microencapsulation of drugs.

MATERIALS & METHODS

Materials

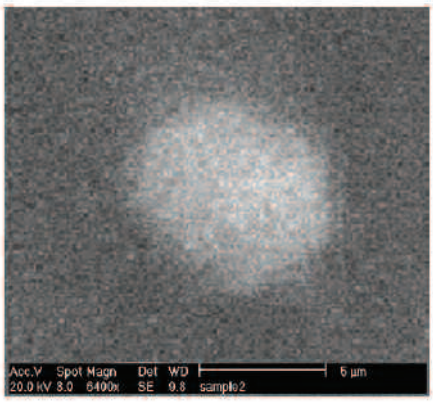
Polymers used in the preparation of microspheres included sodium caroboxymethyl cellulose (MW 162.14), hydroxy propyl methyl cellulose (MW 162.14), and ethyl cellulose, which were obtained from CEEAL Analytical Labs, Chennai, India, as gift samples. Solvents used in the preparation of microspheres included chloroform and 1,2 dichloroethane, which were purchased from SDFINE Chem. Ltd, Mumbai, India. Liquid paraffin (used as an emulsifying agent) was purchased from CDH, Mumbai, India. Petroleum ether, used for removing the stickiness from the microspheres, was purchased from SDFINE Chem. Ltd, Mumbai, India.

Methods

Method A (Preparation of SCMC Microspheres): In this method, an equal amount of the drug and polymer (1:1) was used. First, the polymer was dissolved in solvent 1,2 dichloroethane 50 ml and allowed to stir for sometime until the entire polymer dissolved. Then liquid paraffin was added for emulsification to set in, thus forming microspheres by slowly allowing the solvent to evaporate and the newly formed microspheres to settle. The liquid paraffin was decanted, and the "stickiness" of the microspheres was washed off repeatedly with the help of petroleum ether. The microspheres were then air dried and stored in airtight containers.

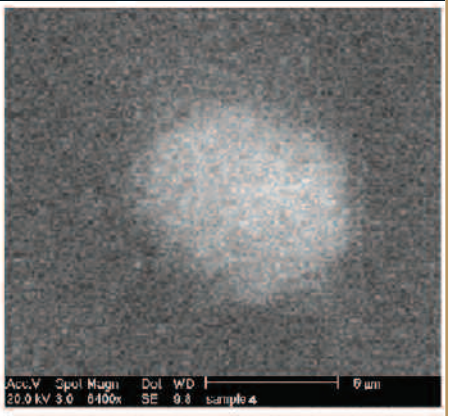
Method B (Preparation of HPMC & EC Microspheres): All steps for this method were the same, but a small change was made in the use of the solvent. In this method, chloroform was used. There was no change in the rest of the steps.

FIGURE 2A



Scanning Electron Microscopy (SEM) of SCMC loaded with Valdecoxib microspheres.

FIGURE 2B



Scanning Electron Microscopy (SEM) of SCMC loaded with Rpfecoxib microspheres.

CHARACTERIZATION[7,8]

Determination of Drug Content

About 100 mg of the prepared drug-loaded microspheres were treated with 100 ml of phosphate buffer saline (pH 6.8) in a clean conical flask and kept in an incubator with shaker (50 rpm) at 40°C for 24 hours [Orbit Shaker Incubator (OSI) 264]. Then it was filtered and analyzed spectrophotometrically at 241 nm for Valdecoxib and at 230 nm for Rofecoxib (Shimadzu – UV Double Beam Spectrophotometer).[9-12] The corresponding drug concentrations were calculated from a calibration plot generated by regression. The results are shown in Table 1.

Determination of Microencapsulation Efficiency

Microencapsulation efficiency was calculated using the following formula: Microencapsulation Efficiency = [Estimated Drug Content/Theoretical Drug Content] X 100. The results of the analysis are shown in Table 2.

Assessment of Flow Properties

A funnel was fixed in a stand in which the tip of the funnel was about 6 cm from the surface. Then the microspheres of 30/40-sieve size were allowed to flow through the funnel so that they form a conical heap on the surface. The height (h) and radius (r) of the heap were measured, and the repose angle was determined by the following formula: $\tan\theta = h/r$. Where; θ = repose angle, h = height of the heap, and r = radius of the heap. The results are shown in Table 3.

INFRARED SPECTROSCOPY

Infrared spectra of Valdecoxib, Rofecoxib, EC, SCMC, HPMC, and microspheres loaded with Valdecoxib and Rofecoxib were taken separately by preparing KBr pellets, which were then recorded on a ThermoNicolet 330 FT-IR spectrometer. The spectra are shown in Figure 1, and the values are shown in Tables 4 through 6.

SCANNING ELECTRON MICROSCOPY

The sample for SEM analysis was prepared by sprinkling the prepared microspheres on one side of an adhesive stub. The stub was then coated with gold using Jeolifine coat ion sputter fc 1100. The microspheres were viewed at an accelerating voltage of 20 kV. The results are shown in Figures 2a and 2b.

TABLE 3

Microsphere Sample (100 mg)	Angle of Repose (θ)		
	EC	SCMC	HPMC
Rofecoxib	47.2	39.8	56.3
Valdecoxib	42.5	36.9	53.1

The flow properties in the prepared microspheres after a specified time interval.

IN VITRO RELEASE STUDIES

Release of Valdecoxib and Rofecoxib from the prepared microspheres was studied in phosphate buffer saline pH 6.8 (900 ml) using a USP Tablet Dissolution Apparatus with a basket stirred at a constant rpm of 100 and at a temperature maintained at 37 ± 1°C as prescribed for Valdecoxib and Rofecoxib tablets in USP XXIV.

A preweighed amount of microspheres equivalent to 50 mg of Valdecoxib and Rofecoxib was put to use in each test. Exactly 1 ml of the samples were withdrawn every 0.5 hours for the first 5 hours and the rest at every hour, which were then assayed at 241 nm for Valdecoxib and 230 nm for Rofecoxib using a Shimadzu UV-1601 Spectrophotometer. The same volume of fresh dissolution medium was replenished after each sampling, and the sample was withdrawn until there was a decrease in absorbance value. The results are shown in Table 7. The release profile is shown in Figures 3 and 4.

STABILITY STUDIES

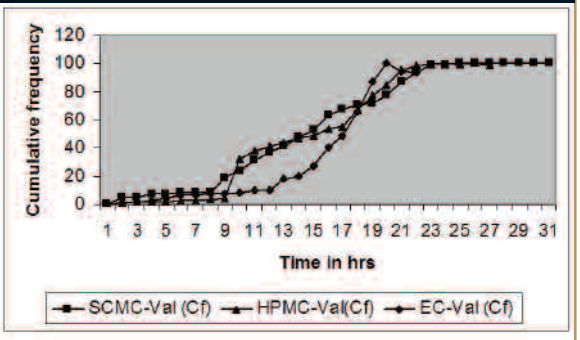
At Different Temperatures

A preweighed amount (300 mg) of prepared microspheres was taken in amber-colored bottles or vials and was placed at various temperatures from room temperature (37°C), 50°C, and 60°C for a period of 21 days. During this period, an equivalent amount of samples (about 100 mg) was withdrawn at a regular period of 7 days.

The sample was then mixed in 100 ml of phosphate buffer pH 6.8 for 24 hours in a rotary shaker at a constant rpm of 50, and then filtered and analyzed spectrophotometrically at 241 nm for Valdecoxib and 230 nm for Rofecoxib in a Shimadzu UV-1601 Spectrophotometer.

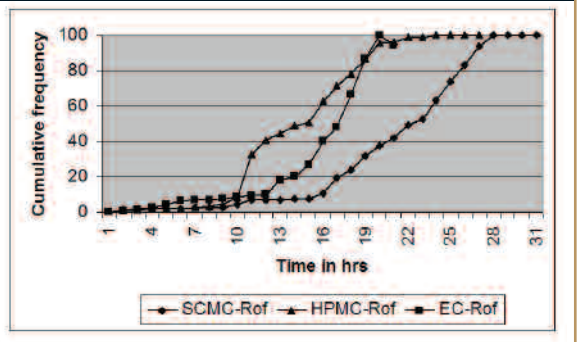
Similarly, it was done for samples at 50°C and 60°C, and values were recorded for EC, SCMC, and HPMC with drug-loaded microspheres. Further calculations for drug content after storing at different temperatures and the results are shown in Table 8a and further in Figure 5. Also, the percentage decrease in the amount of drug

FIGURE 3



Comparative cumulative drug release profile of Valdecoxib-loaded microspheres.

FIGURE 4



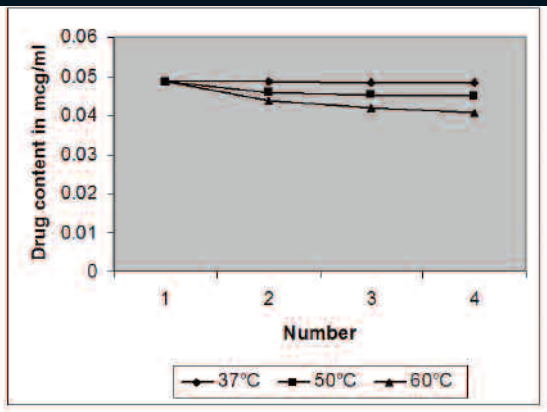
Comparative cumulative drug release profile of Rofecoxib-loaded microspheres.

TABLE 4

FTIR peaks	Rofecoxib	Valdecoxib
-N-H stretch	-	3376.34 cm^{-1}
Aromatic stretch	3092.36 cm^{-1}	3070.52 cm^{-1}
-C=N stretch	-	1621.15 cm^{-1}
-C=O stretch	1747.70 cm^{-1}	-
-S=O stretch	1089.67 cm^{-1}	1073.68 cm^{-1}
-C-O stretch	1035.37 cm^{-1}	1027.63 cm^{-1}

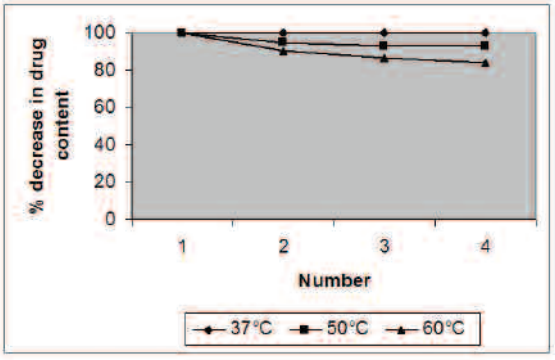
The characteristic peaks of drugs.

FIGURE 5



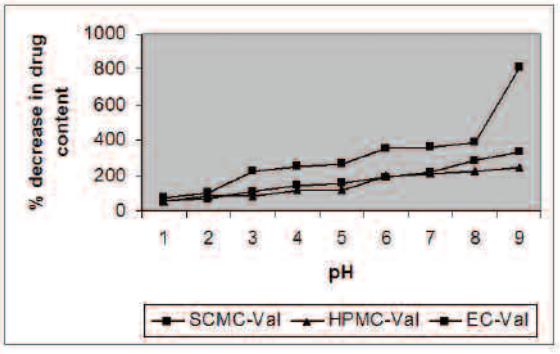
The decrease in drug content of SCMC Valdecoxib-loaded microspheres at various temperatures.

FIGURE 6



The percentage decrease in drug content of SCMC Valdecoxib-loaded microspheres at various temperatures.

FIGURE 7



The decrease in drug content of Valdecoxib-loaded microspheres at various pH levels.

TABLE 5

FTIR peaks	EC	SCMC	HPMC
-OH stretch	3485.23 cm^{-1}	3440.76 cm^{-1}	3452.81 cm^{-1}
-CH3 stretch	2976.92 cm^{-1}	2923.48 cm^{-1}	2927.45 cm^{-1}
-CH2 stretch	2930.58 cm^{-1}	2155.79 cm^{-1}	-
-C=O stretch	-	1630.98 cm^{-1}	-
-C-O stretch	-	1115.13 cm^{-1}	-

The characteristic peaks of polymers

present was also calculated, and the results are shown in Table 8b and further in Figure 6.

At Different pH

Buffers of varying pH from 1 to 10 were prepared as per the IP-Appendix and then stored. Accurately, 100 mg of weighed microsphere samples were taken and placed in 100 ml of phosphate buffer pH 1 to 10 and kept in a rotary shaker for 24 hours. They were then filtered and analyzed spectrophotometrically at 241 nm for Valdecoxib and 230 nm for Rofecoxib in a Shimadzu UV-1601 Spectrophotometer.

This was similarly done for both drug-loaded microspheres with SCMC, EC, and HPMC. The percentage decrease in drug amount in different pH was also calculated, and the results are shown in Tables 9a and 9b and further in Figures 7 and 8.

RESULTS & DISCUSSION

Drug Content

The study revealed that SCMC drug-loaded microspheres have a drug content of 0.0485 (Valdecoxib) and 0.04629 (Rofecoxib), which is greater than those of EC and HPMC drug-loaded microspheres (Table 1).

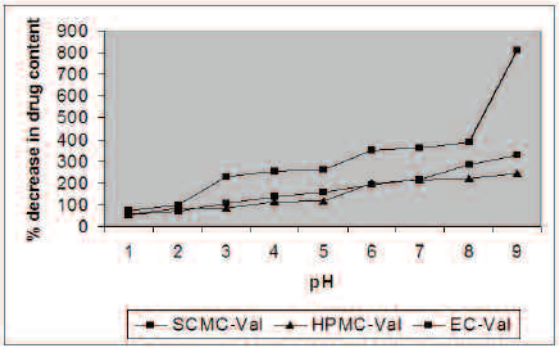
Microencapsulation Efficiency

SCMC drug-loaded microspheres have a microencapsulation efficiency of 97% (Valdecoxib) and 92.6% (Rofecoxib), greater than those of EC and HPMC drug-loaded microspheres.

Angle of Repose

The SCMC drug-loaded microspheres were found to have a lesser angle of 36.9 degrees (Valdecoxib) and 39.8 degrees (Rofecoxib), showing better flow property than the HPMC and EC drug-loaded microspheres having a larger angle of repose.

FIGURE 8



The percentage decrease in drug content of Valdecoxib-loaded microspheres at various pH levels.

FTIR Studies[13]

The FTIR spectrum was interpreted, and there was no chemical interaction taking place between polymer and drug in the drug-loaded microspheres. The various characteristic peaks of polymers and drug were discovered. The result is shown in Figure 1, showing FTIR overlay spectrum of SCMC loaded with Valdecoxib microspheres.

Scanning Electron Microscopy (SEM)

Morphological examination using SEM showed spherical Valdecoxib loaded in SCMC microspheres with a main diameter of 3 to 5 µm (Figure 2a) and spherical Rofecoxib loaded in SCMC microspheres with a main diameter of 3 to 5 µm (Figure 2b). There was no significant differences between the lot.

TABLE 6

FTIR Spectrum	Peaks cm^{-1}					
	EC-R	SCMC-R	HPMC-R	EC-V	SCMC-V	HPMC-V
-OH stretch	3730.34	3654.35	3624.75	3475.61	3376.26	3317.13
-NH stretch	-	-	-	3322.95	3317.32	3317.13
Ar stretch	3091.97	3092.12	3092.74	3251.76	3248.78	3249.13
=CH of alkyl stretch	2929.71	2926.25	2924.78	3042.94	2924.62	2924.08
-S-H stretch	2394.50	2360.07	2359.84	-	-	-
-C=O stretch	1747.49	1747.68	1747.69	-	-	-
-S=O stretch	1148.71	1089.38	1089.44	1098.41	1096.95	1097.23
-C-O stretch	1035.24	1035.09	1035.11	1238.65	1240.19	1239.60
Ar C=C stretch	1595.02	1594.70	1594.80	1595.41	1594.38	1594.60
-C=N stretch	-	-	-	1547.85	1547.97	1547.85
-C-S stretch	552.96	553.09	553.11	571.55	572.28	572.41
-C-N stretch	847.30	847.50	847.08	842.38	842.87	842.74

The characteristic peaks of drug-loaded microspheres.

TABLE 7		
Polymer + Drug in Microspheres	**Time (hrs)**	**Type**
SCMC	30	Slow & Extended
HPMC	26-27	Fast
EC	20-21	Fast & Short

The *in vitro* release profile in the prepared microspheres after a specified time interval.

In Vitro Release Studies

The studies showed that drug release was 30 hours (slow and extended) from SCMC drug-loaded microspheres. In contrast, the HPMC and EC drug-loaded microspheres showed two extremes of release. Thus, SCMC drug-loaded microspheres are found to be more suitable for controlled-release formulations. The results are further shown in Figures 3 and 4.

Stability Studies

In Varying Temperature: There was no significant change in the drug content in SCMC drug-loaded microspheres at 37°C for a period of 21 days, but there was a gradual decrease in drug content at 50°C and 60°C, whereas a steep fall in drug content in HPMC and EC drug-loaded microspheres was observed as shown in Figure 5. Also there was no significant change in the percentage decrease in drug content in SCMC drug-loaded microspheres at 37°C for a period of 21 days, but there was a gradual decrease in percentage decrease in drug content at 50°C and 60°C, whereas a steep fall in percentage decrease in drug content in HPMC and EC drug-loaded microspheres was observed as shown in Figure 6.

In Varying pH: The drug-loaded microspheres were found to be stable in the acidic pH (1 to 7) than in the alkaline pH (7 to 10). The drug content was found to decrease slowly in the acidic pH, showing that the polymer degrades lesser in the acidic pH (not releasing drug all at once), rather releasing it gradually at pH 7. And in highly alkaline pH, it releases drug even more slowly and gradually, thus prolonging the release even more as shown in Figures 7 and 8.

CONCLUSION

This work investigated the use of three different polymers (ethyl cellulose, sodium carboxy methylcellulose, and hydroxy propyl methylcellulose), which were used as a coating material for COX-II inhibitors (Rofecoxib and Valdecoxib). These drugs and various other NSAIDs are used to treat Familial Adenomatous Polyposis, which is known to produce polyps or adenomas in the colon, and chemotherapy is the best way for its treatment to avoid the recurrence of polyps in colon. This disease requires the prolonged administration of drug, hence this work aimed at producing effective and ideal microspheres of these two drugs. The use of these two drugs was decided based on the fact they obey Beer's concentration of linearity by showing a correlation coefficient almost equal to 1. A comparitive study was done between them. The Emulsification-Solvent Evaporation method was used in the production of the microspheres, which was decided after optimizing the method because of its high yield, ease of the procedure, and is less time consuming.

These microspheres were further characterized for their drug content, microencapsulation efficiency, *in vitro* release studies, repose angle, FTIR studies, and SEM, DSC, and stability studies. All these showed that the microspheres coated with sodium carboxymethylcellulose showed good morphological character, high percentage of yield, good drug content, high microencapsulation efficiency, good flow property, and a slow and extended release. Thus, they were found to be suitable for controlled release. The stability studies were also carried out in various pH and different temperatures, and the results were shown to favor sodium carboxymethylcellulose because there was only a slight decrease in the drug content. So it is conclude that SCMC is one of the best choices of polymers to make microspheres and obtain sustained release for the COX-II inhibitors studied.

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TABLE 8A

At 37°C						
	Drug Content in mcg/ml					
Days	EC-R	SCMC-R	HPMC-R	EC-V	SCMC-V	HPMC-V
7	0.02187	0.04629	0.03169	0.02836	0.0485	0.0379
14	0.02160	0.04623	0.03165	0.02160	0.04843	0.03788
21	0.02160	0.04623	0.03165	0.02160	0.04843	0.03788
At 50°C						
7	0.01988	0.0441	0.02878	0.02231	0.03354	0.046
14	0.01972	0.0440	0.02806	0.02189	0.04519	0.0321
21	0.0179	0.04215	0.0591	0.01935	0.0450	0.02908
At 60°C						
7	0.01646	0.04088	0.02309	0.01796	0.0438	0.02789
14	0.01486	0.03906	0.02187	0.01595	0.04189	0.02527
21	0.01187	0.0385	0.01784	0.01252	0.04061	0.02116

The drug content in the prepared microspheres after a specified time interval.

TABLE 8B

At 37°C						
	Drug Content in mcg/ml					
Days	EC-R	SCMC-R	HPMC-R	EC-V	SCMC-V	HPMC-V
7	99.68	100	100	99.85	100	99.71
14	98.6	99.8	99.87	99.68	99.8	99.68
21	98.6	99.8	99.87	99.68	99.8	99.68
At 50°C						
7	90.8	95.3	90.8	78.5	94.8	88.3
14	90.0	95	88.5	77	93.1	84.5
21	81.7	91	81.8	68.1	92.8	76.5
At 60°C						
7	75.2	88.5	72.9	63.2	90.30	73.4
14	67.8	84.4	69	56.2	86.4	66.5
21	54.2	83.2	56.3	44.1	83.7	55.7

The percentage decrease in drug content in the prepared microspheres after a specified time interval at various temperatures.

TABLE 9A

	Drug Content in mcg/ml					
pH	EC-R	SCMC-R	HPMC-R	EC-V	SCMC-V	HPMC-V
1.2	0.07237	0.1570	0.08011	0.09370	0.392	0.0934
2	0.05723	-	0.07911	0.08025	0.1892	0.08570
4	0.03828	0.07077	0.07723	0.06271	0.1760	0.08140
5	0.03574	0.06165	0.06419	0.05489	0.1711	0.07510
6	0.03154	0.05386	0.06232	0.04512	0.1287	0.04461
7	0.01895	0.03508	0.04762	0.04003	0.1222	0.04312
8	0.01729	0.02944	0.04486	0.03077	0.1102	0.03144
9	0.01342	0.02911	0.03121	0.01992	0.04914	0.03130
10	0.00878	0.02790	0.02220	0.01548	0.03673	0.02032

The drug content in the prepared microspheres after a specified time interval at various pH.

TABLE 9B

	% Decrease in Drug Content					
pH	EC-R	SCMC-R	HPMC-R	EC-V	SCMC-V	HPMC-V
1.2	40.1	60.3	70	54.5	75.7	53.5
2	61.3	62.8	82.1	70.1	101.3	82.4
4	78.9	63.6	141.6	108.3	227.2	82.7
5	86.5	75.8	150.3	140.9	251.9	113.5
6	144	116.35	196.7	158.9	265.3	117.4
7	163.2	133.1	202.6	193.3	352.8	197.6
8	174.8	152.9	243.7	220.8	362.9	214.2
9	261.3	166	249.6	282.6	390.1	225.5
10	330.4	339.1	252.8	330	808.2	245.8

The percentage decrease in drug content in the prepared microspheres after a specified time interval at various pH.

BIOGRAPHIES

Lakshmi Sivasubramanian has 6 years of teaching experience. Her research interest includes analytical method development for single and combined dosage forms using various analytical tools as well as synthesis and characterization of targeted drug delivery systems. She is a member of the Indian Pharmaceutical Association and Association for Pharmacy Teachers of India. She has published 12 articles in national and international journals and more than 20 articles at national and international conferences.

Madhumathi Seshadri has just completed her PG in Pharmacy and is planning to move to Australia to begin her PhD Programme. She has authored an estimated 8 e-articles at pharmainfo.net. She has also presented 4 articles at national and international conferences.

NON-INVASIVE INSULIN UPDATE

Current Status of Non-Invasive Insulin Delivery Technologies

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

ABSTRACT

The discovery of insulin is one of the greatest milestones in medical history that revolutionized the use of peptides and proteins as therapeutic agents. Patients with Insulin-Dependent Diabetes Mellitus need to use insulin in the form of multiple subcutaneous injections to achieve adequate glycemic control. This is a heavy burden for them and it involves a lot of discomfort. Significant efforts are currently focused toward developing non-invasive insulin delivery systems, and there are several competing technologies at different stages of development. Innovative, non-invasive methods to deliver insulin are poised to transform diabetes management. Major breakthroughs have been observed regarding the pulmonary/inhaled insulins with the FDA approval and launch of the first inhaled insulin Exubera® by Pfizer and Netkar in 2006. Novo Nordisk is also in the final stages of clinical studies on AERx, and it may be launched by 2008. This article is an update to review the current status of the various non-invasive insulin technologies. Review on the market and research status of inhaled and oral insulin has been provided. Current developments in alternative routes of insulin delivery have also been appraised.

INTRODUCTION

The discovery of insulin is one of the greatest milestones in medical history that revolutionized the use of peptides and proteins as therapeutic agents. In the past several decades, insulin from different animal sources was used, until the breakthrough in biotechnology made it possible to produce human insulin. Insulin, a pancreatic hormone, helps to lower the blood sugar levels. An intensive treatment that mimics the physiologic secretion of insulin secretions would be ideal. Patients with Insulin-Dependent Diabetes Mellitus need to use insulin in the form of multiple subcutaneous injections to achieve adequate glycemic control. Significant efforts are currently focused toward developing non-invasive insulin delivery systems, and there are several competing technologies at different stages of development. Innovative, non-invasive methods to deliver insulin are poised to transform diabetes management. Investigators have contemplated every possible route of drug delivery for insulin. The non-invasive methods in insulin therapy include oral, pulmonary, transmucosal, buccal, nasal, transdermal, rectal, ocular, vaginal, gene therapy, islet cell transplantation, and diabetes vaccine.[1] An article has been presented earlier by us on the *Non-Invasive Insulin Delivery Technologies*, which gives a detailed description about the various routes of insulin.[2] In the near future, several novel approaches that mimic the endogenous release and kinetics of insulin shall be designed to achieve better control and effective treatment of diabetes.[3]

The aim of this update is to review the current status of the various non-invasive technologies for insulin. As previously stated, major breakthroughs have been observed regarding pulmonary/inhaled insulins with the FDA approval and launch of the first inhaled insulin (Exubera) in 2006. Novo Nordisk is also in the final stages of clinical studies on its AERx. Numerous developments have also been observed for oral insulin with Biocon being the brand leader in the supply of oral insulin. Current developments in alternative routes of insulin delivery (buccal, ocular, nasal, colon, vaginal, and transdermal) have also been appraised. In addition, application of nanotechnology for designing insulin drug delivery systems has also been reviewed.[4]

The combined type 1 and type 2 diabetes mellitus population worldwide is projected to grow from 39.4 to 49.4 million from 2003 to 2010. With the aforementioned new treatments in late-stage development, diabetes disease management is on the brink of a therapeutic revolution. In the $4-billion insulin market, the arrival of inhaled and oral insulins will offer greater flexibility and options for both type 1 and type 2 patients.[5-7]

PULMONARY ROUTE

Pulmonary insulin delivery is the most promising alternative with several inhaled insulin systems in the process of development and approval for the treatment of adult patients with type 1 or type 2 diabetes.[8] They deliver insulin into the lungs, which can be a powder formulation or a solution. The first inhaled human insulin, a product of a joint development program initially between Aventis, Pfizer, and Nektar (Exubera), was approved in the United States and the European Union on January 27, 2006, for the treatment of adult patients with type 1 or type 2 diabetes. Exubera is a rapid-acting, fine powder form of insulin. This system delivers a fine dry-powder formulation (< 5 microns) in

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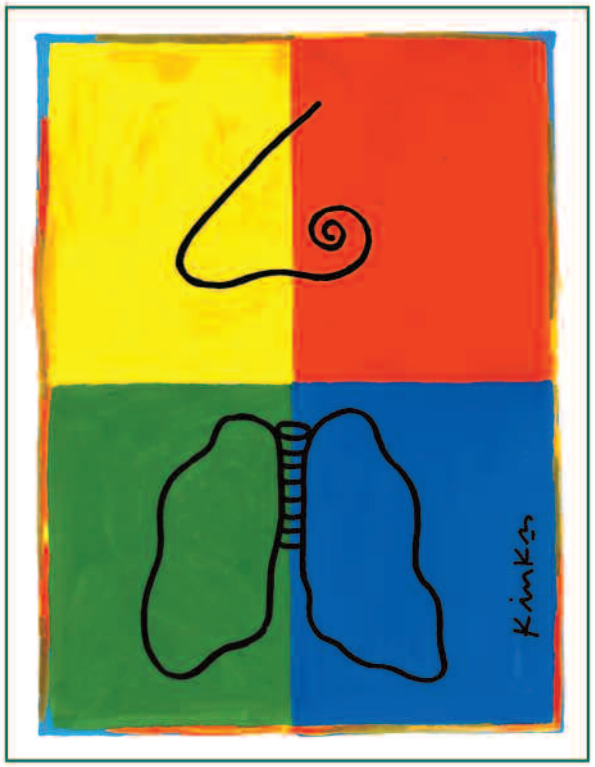

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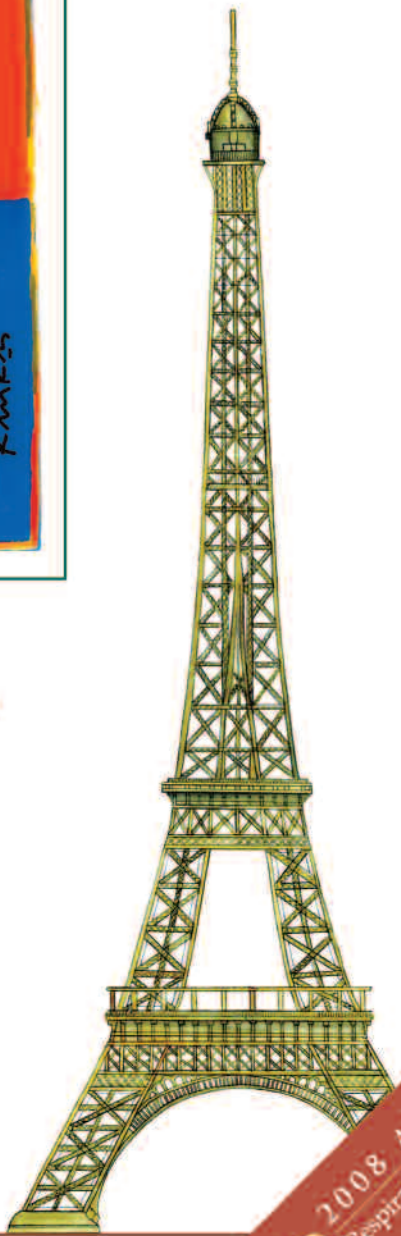

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diameter of regular short-acting human insulin to the deep lung in a reproducible and efficient manner. The number of individual blister packs inhaled controls the dose. The insulin dry powder is packaged into a single-dose blister containing 1 or 3 mg, with a 1-mg blister corresponding to ~3 units of insulin.[9] The bioavailability of this product is about 10% compared to regular human insulin given by subcutaneous route.[10] The safety and efficacy of Exubera have been studied in about 2,500 adult patients with type 1 and type 2 diabetes. In clinical studies, Exubera reached peak insulin concentrations more quickly than regular insulin, administered by an injection. Peak insulin levels were achieved in about 50 minutes (range 30 to 90 minutes) with Exubera inhaled insulin compared with 105 minutes (range 60 to 240 minutes) with regular insulin. For patients with type 1 diabetes, inhaled insulin can be added to longer-acting insulin taken with meals. Whereas for patients with type 2 diabetes, inhaled insulin can be used alone, along with oral medication that controls blood sugar, or with longer-acting insulins.

The major problems with the inhaled insulin are loss of drug within the inhaler and mouth during inhalation, variations in absorption due to age-related differences, respiratory tract infections, and smoking. The long-term effects of the inhaled insulin deposited in the lungs are not known. There is also the risk of production of anti-insulin antibodies against inhaled insulin. Because the bioavailability of inhaled insulin is relatively low, very high doses of insulin (about 8 times that of subcutaneous dose) may be needed to achieve the same glycemic control, which can increase the financial burden on patients.[10]

Some of the reported side effects associated with Exubera therapy are low blood sugar, cough, shortness of breath, sore throat, and dry mouth. Exubera is not recommended for active smokers or by those who have quit smoking within the past 6 months. Exubera is contraindicated for patients with asthma, bronchitis, or emphysema. Baseline lung function tests are recommended before starting the treatment and should be repeated every 6 to 12 months thereafter.[11]

TABLE 1

Serial No.	Product Name	Pharmaceutical Company	Regulatory Status	Year
1	Exubera	Pfizer Inc.	Approved	Jan. 2006*
2	AERx (iDMS)	Novo-Nordisk & Aradigm	Phase III	2002**
3	AIR (HIIP)	Eli Lilly & Alkermes	Phase III	July 2005
4	Technosphere	Mannkind	Phase III	2004
5	BAI	KOS Pharmaceuticals	Phase II	2004

Regulatory Status of Various Inhaled Insulin Delivery Devices
*** USA and European Union**
**** Put on hold in 2005 for examination of its dosing issues.**

The traditional study designs cannot provide answers to important and practical questions regarding real-world effectiveness, which is influenced by psychological or other access barriers. To overcome these limitations, a real-world randomized clinical trial has been undertaken (protocol No. A21710187, registered with Clinicaltrials.gov, Registration ID. NCT00134147) with approximately 700 patients from Canada, France, Germany, Italy, Spain, United Kingdom, and the United States with type 2 diabetes mellitus poorly controlled by oral agent therapy. This trial has been designed to estimate the effect of the availability of Exubera as a treatment option for glycemic control in the global population.[12]

The other pulmonary insulin delivery systems under investigation are ProMaxx, AIR, Spiros, and Technosphere. However, much information is not available on their status. The AERx (iDMS) is the only inhaled insulin system currently in clinical trials to investigate the use of a liquid (water-based) insulin formulation. The AERx (iDMS) device creates an inhalable aerosol of liquid insulin droplets (1 to 3 microns) by compressing the liquid insulin formulation through an array of hundreds of precisely laser-drilled holes. In this, single-use insulin strips are combined with a hand-held, breath-activated, microprocessor-controlled device to guide the correct rate and depth of breathing for triggering insulin at the optimum movement in the inspiration-expiration cycle. This aims at consistent delivery of insulin, regardless of a patient's breathing ability. However, liquid formulations carry the risk of microbial growth and thus require refrigeration.[13] The bioavailability of this liquid formulation is shown to be about 13% to 17%.[10]

Compared to Exubera, the dry-powder AIR-(HIIP) (Human Insulin Inhalation Powder) formulation developed by Lilly and Alkermes apparently has much larger individual particles (10 to 20 microns) that contain both insulin and excipients. Despite larger geometric diameter of the particles, the company claims that the mass mean aerodynamic diameter remains within the range (ie, < 5μm) for optimal delivery to the deep lung because of the particle's porous, low-density properties.[13]

The dry-powder insulin utilized by Mannkind is the microencapsulated form of insulin entrapped within a small (2 microns) organic particle known as Technosphere, which self-assembles around insulin during the manufacturing process.[13] The Technosphere contains 90% excipient and hence may constitute an increased powder burden for the lungs of patients compared with other insulin delivery systems.

The KOS insulin is an excipient-free

TABLE 2

Name of Agent	Type	DosageForm/ Delivery of Insulin	Reference
BBI (Bowman-Birk-Inhibitor)	Protease Inhibitor	Thiolated chitosan-insulin tablets	18
Ovomucoid- glycoprotein inhibitor	Protease Inhibitor	Polymeric hydrogel	19
Wheat germ agglutinin	Protease Inhibitor	Liposomes and solid-lipid Nanoparticles	20
Camostat mesilate	Protease Inhibitor	Azopolymer-coated pellets for colon targeting	21
Eudragit S-100	Protease Inhibitor	Eudragit Micropsheres	22
Sodium salicylate	Permeation Enhancer	Eudragit S100-coated insulin HGC	23
2,6-di-O-methyl-beta-cyclodextrin (DM-beta-CyD), lauric acid (C12), or the sodium salt of C12 (C12Na)	Absorption Enhancers	Acrylic hydrogel of insulin	24
Lysalbinic acid	Absorption Promoters	Buccal	25
Sodium glycocholate	Absorption Promoters	Colon targeted	26
Capric acid, glycyrrhizic acid, deoxycholic acid, hydroxypropyl-beta-cyclodextrin (HPbetaCD) cholic acid	Absorption Enhancers	Insulin-loaded poly (ethylcyano acrylate) nanospheres	27
Hydroxylpropyl-beta-cyclodextrin (HP-beta-CD), chitosan, polyethylene-polypropylene glycol, polyoxyethylene lauryl ether, polysorbate 80, egg lecithin, or oleic acid	Absorption Enhancers	Sublingual insulin	28
Methyl cellulose	Mucoadhesive Agent	Liposomal insulin	29
Cross-linked poly(methacrylic acid) and poly(ethylene glycol)	Complexing Agent	Microparticles	30

Various Types of Agents Used in Insulin Drug Delivery

crystalline recombinant human insulin delivered by the company's BAI (Breath Actuated Inhaler) device. The bioavailability of the KOS formulation has been found to range from 10% to 15% of subcutaneous regular insulin.

The following are advantages of dry-powder insulin formulations and delivery devices:

- Reusable, durable, and simple for the patients to use.
- Convenient to store, carry, and use by the patients.
- Works without the use of electronics, batteries, and microchips.
- Formulation is stable at room temperature, less susceptible to microbial growth, and environmental degradation.
- Long-term chemical stability (prepared by glass stabilization process).
- Available as individual unit-dose packaging in aluminium foil blister packs, which provides strong barrier against moisture.
- No chemical propellant to dispense the insulin. Instead, it uses patient-activated pressurized air as the energy source.

The regulatory status of various inhaled insulin delivery devices has been summarized in Table 1.

ORAL ROUTE

Considerable research efforts have also been devoted to the development of oral forms of insulin that can be delivered safely and effectively without the need for injection. In contrast to the inconvenient and potentially problematic method of parenteral insulin administration, the oral route offers the advantages of self-administration with a high degree of patient acceptability and compliance. This route also closely replicates the natural secretion pathway of insulin from the pancreas to the liver. Due to the directness of this route, many of the major insulin-related side effects that diabetics suffer from could possibly be avoided. However, there are several limitations of the oral route. These include low oral

bioavailability due to degradation in the stomach, inactivation and digestion by proteolytic enzymes in the luminal cavity, poor permeability across intestinal epithelium because of its high molecular weight, and lack of lipophilicity.[14] Scientists developed various approaches to overcome these enzymatic and diffusional barriers. Furthermore, the results of *in vivo* studies on different animals in the past decade have suggested that protection of insulin by adopting a suitable means improve the absorption. These include enteric polymer coatings to protect the drug as well as carrier systems from digestion in the stomach, incorporation of penetration enhancers, use of protease inhibitors in the system to prevent insulin from intestinal enzymatic digestion, incorporation of insulin into bioadhesive polymeric carriers, or a combination of these approaches for increasing bioavailability. The agents used for increasing bioavailability of insulin formulations can be classified as the following:

- Enzyme inhibitory agents
- Inhibitors that are not based on amino acids, such as p-aminobenzamidine, FK-448, and camostat mesilate
- Amino acids and modified amino acids, such as acid derivatives
- Peptides and modified peptides (eg, bacitracin, antipain, chymostatin, and amastatin)
- Polypeptide protease inhibitors (eg, aprotinin, Bowman-Birk inhibitor, and chymotrypsin inhibitor, soybean trypsin inhibitor, chicken, and duck ovomucoid
- Absorption enhancers and promoters (eg, bile salts, sodium cholate, long-chain fatty acids, salicylates, cyclodextrins, chelating agents, and surfactants)
- Mucoadhesive polymers
- Natural polymers (eg, alginate, pectin, chitosan, lectin, and gelatin)
- Synthetic polymers (eg, sodiumcarboxymethylcellulose, hydroxypropylmethylcellulose, polyacrylic acid)

Complexing agents also display enzyme inhibitory activity. Drawbacks of these agents, such as risk of toxic side effects or high production costs, might be excluded by the development of advanced drug delivery systems.[15-17] Various types of agents used by scientists in insulin formulations are shown in Table 2.

Several companies across the globe are solely concerned with the creation of effective oral insulin delivery in the form of buccal sprays, enteric-coated tablets, gel capsules, etc. Some companies are market leaders in the field of oral insulin, including Biocon in India (which acquired the IP rights to its collaborator Nobex in 2006), Emisphere Technologies in the United States, Generex in South America, and numerous other companies throughout the world. These companies are at various stages of putting oral insulin through clinical trials.

Biocon completed Phase-IV trials for insulin and marketed it as Insugen in the Indian market. Biocon plans to launch Insugen in Europe in 2007 and in the US some time in 2008. Under development by the Canadian company Generex Biotechnology, Oral-Lyn is developed. It is a liquid formulation of human insulin that is sprayed into the mouth using its proprietary RapidMist device. The liquid spray is absorbed by the buccal mucosa. It is approved for use in Ecuador.[31] NIN-058 (oral insulin analogue) is a GlaxoSmithKline/Nobex product that is a pill form of insulin. The product has completed Phase-I trials. This milestone is important in the development of oral insulin. However, major pharmaceutical companies are in mid stage of clinical development.

In October 2006, Emisphere announced results of a 90-day, Phase II multi-center, randomized trial for its oral insulin tablet using its propriety (eligen®) technology. The four-arm study evaluated the safety and efficacy of low and high fixed doses of oral insulin tablets versus placebo in patients with type 2 diabetes mellitus on existing oral metformin monotherapy. One focus of the trial was to confirm that insulin delivered orally could be administered as a fixed-dose product without the need to conduct glucose monitoring or titrate the insulin dose. Emisphere is currently putting together a Scientific Advisory Board (SAB), composed of leading clinicians, endocrine, and metabolic experts. With the SAB, Emisphere will be in a strong position to continue and move its oral insulin program ahead.

Apollo Life Sciences announced the successful completion of data gathering in independent Phase I toxicology trials for oral insulin and its oral delivery device, Oradel, in December 2006. Oramed Pharmaceuticals is focused on the development of oral delivery solutions based on proprietary technology. Oramed is currently developing an orally ingestible soft gel insulin capsule for the treatment of type 1 and 2 diabetes. The preclinical studies were completed and presently it is under Phase I trials.[32] Diabetology, a UK clinical research and development company, has an oral insulin capsule (Capsulin), which is currently in Phase II).[33] However, extensive studies of insulin products on humans are necessary. The results of such clinical trials can only predict the future of oral insulin drug delivery.

NANOPARTICLES FOR INSULIN DELIVERY

Nanoparticles can be used as carriers for delivering proteins and peptides and thus have enormous significance in insulin drug delivery. Li MG, Lu WL, and co-workers investigated distribution, transition, bioadhesion, and release behaviors of insulin-loaded pH-sensitive nanoparticles in the gut of rats, as well as the effects of viscosity agents on them. It was observed that the release profile of insulin from the nanoparticles was S-shaped, and addition of HPMC was found to be favorable to the absorption of the drug loaded.[34]

Attivi et al formulated insulin-loaded polymeric nanoparticles using response surface methodology. The nanoparticles were prepared by water-in-oil-in-water emulsification and evaporation methods using blends of biodegradable poly-epsilon-caprolactone (PCL) and positively charged, nonbiodegradable polymers (Eudragit RS). An interesting formulation exhibited 25 IU/100 mg of polymer entrapment, 350 nm particle size, +44 mV zeta potential with a

polydispersity of 0.21, and 4.8 IU/100 mg of insulin release after 7 hours.[35]

Lectin-modified solid lipid nanoparticles (SLN) containing insulin were designed and characterized for oral drug delivery by Zhang and co-workers. Some insulin-loaded SLNs were modified using wheat germ agglutinin (WGA)-N-glutaryl-phosphatidylethanolamine. *In vivo* studies indicated greater stabilizing effect of WGA-modified SLNs than SLNs alone. However, the higher bioavailability observed in SLNs and WGA-modified SLNs demonstrated increase in oral absorption of insulin.[36] An oral insulin delivery system based on hydroxypropyl beta cyclodextrin-insulin (HpbetaCD-I) complex encapsulated in polymethacrylic acid-chitosan-polyether (polyethylene glycol-polypropylene glycol copolymer, PMCP) nanoparticles have also been developed. PMCP nanoparticles displayed good insulin encapsulation efficiency, and release profile was greatly dependent on the pH of the medium.[37]

Zhang and co-workers also evaluated the transport characteristics of wheat-germ agglutinin (WGA)-modified insulin-liposomes and SLNs in a perfused rat intestinal model. Formulations containing 100 IU/kg insulin were administered to the duodenum, jejunum, and ileum on fasted rats. Insulin concentration was found to be decreased for the formulations in different absorption sites in the following order: duodenum > ileum > jejunum for WGA-modified liposomes and duodenum > jejunum > ileum for WGA-modified insulin containing SLNs; ileum > jejunum > duodenum for insulin containing liposomes and duodenum > ileum > jejunum for aqueous solution of insulin. This indicated that nanoparticle type and delivery site were important factors for intestinal mucosal absorption.[20]

Nanoparticles composed of chitosan and poly(&ggr;-glutamic acid) were prepared and characterized by Lin et al for oral insulin delivery. Nanoparticles remained spherical even after loading with insulin, and the release profiles were significantly affected by their stability in distinct pH environments. The study indicated reduction in blood glucose level in a diabetic rat model.[38]

Cui FD and co-workers investigated the potential of PLGA nanoparticles (PNP) and PLGA-Hp55 nanoparticles (PHNP) as carriers for oral insulin delivery. Use of insulin-loaded PHNP was found as an effective method for reducing blood glucose levels.[39]

Nanoparticles have also found application in delivering insulin through other routes. In a recent finding, nanoparticles prepared using mucoadhesive polymers have proved a promising drug delivery system for delivering insulin through the transmucosal routes (ie, pulmonary, nasal, and oral). Cui and workers have prepared mucoadhesive polymer-coated nanoparticles colloidal carriers. These nanocarriers were prepared using the emulsion polymerization process using chitosan, poly(acrylic acid) and carbopol. They were found to be stable under physiological pH conditions. The amount of mucoadhesive polymers and concentration of the radical initiator affected the performance of the carriers. These nanoparticles were found to be suitable for carrying protein or peptide drugs like insulin.[40]

In another latest discovery reported by Joshi et al, gold nanoparticles were prepared as carriers for transmucosal delivery of insulin. Insulin was loaded into bare and aspartic-acid-capped gold nanoparticles and administered orally and intranasally to rats. A significant reduction of blood glucose levels (postprandial hyperglycemia) was observed when insulin was delivered using the gold nanoparticles. Furthermore, the intranasal administration showed control of postprandial hyperglycemia comparable to that achieved using the standard subcutaneous administration used for type I diabetes mellitus. Thus, it could be observed that use of nanoparticles through the transmucosal route might show considerable potential for further developments.[41]

Nanoparticles have also been used for delivering insulin transdermally using novel $CaCo_3$ nanoparticles. A study conducted in animals using the transdermal nanoinsulin demonstrated significant decrease in the blood glucose levels in diabetic mice. The results have opened new avenues for the feasibility of developing nanoparticles transdermally for human applications.[42]

ALTERNATIVE ROUTES FOR INSULIN DELIVERY

Buccal

The buccal route for the delivery of insulin has also sighted many new approaches. In a biokinetic study conducted by Pozzilli and co-workers, the metabolic effect of a buccal insulin spray was compared with subcutaneous regular insulin in patients with type 1 diabetes. No statistically significant difference in glucose, insulin, or C-peptide levels was measured after administration of subcutaneous versus buccal spray insulin. It was concluded that insulin administered via the buccal spray formulation was as effective as the subcutaneous route in lowering blood glucose levels.[43]

Zhu and his research team have prepared soybean lecithin-based vesicles to improve the permeation-enhancing effect of insulin through the buccal route. The vesicles were prepared by ultrasonic, high-speed shear and high-pressure homogenization methods. The particle size and the method of preparation were found to have a significant effect on the buccal delivery of insulin.[44]

A new absorption promoter, lysalbinic acid, was used for improving the buccal delivery of insulin by Starokadomskyy and Dubey. They have reported that the new promoter was free from any irritant effects and also showed improvement in taste along with improved delivery of insulin through the buccal route.[25]

Nasal

In addition to pulmonary insulin administration, the nasal route seems to be the next route that provides a wide array of opportunities for the delivery of insulin. The large surface area and the high vascularity of the nasal mucosa favor the fast absorption of insulin. In a study conducted by Reger and Craft, they have demonstrated the superiority of transport of insulin through the nasal route as compared to peripheral insulin administration. Intranasal insulin administration resulted in direct insulin transport from the nasal cavity to the central nervous system via intraneuronal and

extraneuronal pathways and suggests that the intranasal insulin administration is safe in humans. Thus, they have concluded that intranasal insulin administration offers a novel treatment strategy for disorders associated with central insulin abnormalities, such as diabetes and neurodegenerative diseases.[45]

Chitosan as a polymer for nasal delivery: To increase the nasal absorption of insulin, permeation enhancers or mucoadhesive polymers are used in the drug delivery systems. Chitosan represents a multifunctional polymer possessing both mucoadhesive and permeation-enhancing properties. It is thus a promising polymer for nasal delivery of insulin. Thiolated chitosan has been used by Krauland et al for the preparation of insulin microparticles that were evaluated *in vivo*. They reported that the thiolated chitosan microparticles demonstrated better glucose reduction capacity and pharmacological effect than the unmodified chitosan.[46] In another study conducted by Varshosaz and co-workers, chitosan was used as a bioadhesive gel. The authors reported that the use of permeation enhancers, such as saponins, sodiume decxycholate, EDTA, and lecithin, improved the nasal absorption of insulin. They also concluded that the *in vivo* studies of the EDTA-chitosan gels showed reduction of glucose levels as much as 46% as compared to the intravenous route.[47] Yu et al have studied the delivery of insulin through the nasal route using chitosan solution. Chitosan solutions containing absorption enhancers, such as Tween 80, EDTA, beta cyclodextrin, and hydroxylpropyl betacyclodextrin, have been studied to improve the nasal delivery of insulin.[48]

Vaginal/Uterine Route

The polypeptide insulin, which is extensively degraded by proteolytic enzymes of the gut, can be alternatively administered by vaginal or uterine modes due to the associated advantages like painless self-administration, prolonged retention, and avoidance of hepatic first-pass elimination. Degim et al showed that chitosan gel (CH-gel) could be used for effective administration of insulin. The penetration of insulin through the rectal and vaginal mucosa was found to increase further with the incorporation of dimethyl-beta-cyclodextrin (DM-betaCD) as a penetration enhancer.[49]

Ning et al have encapsulated insulin in niosomes using Span 60 and Span 40 for the penetration of the vaginally administered niosomes. Insulin-sorbitan monoester niosomes were therapeutically effective on vaginal administration. This study opens up avenues for the use of niosomes as carriers of proteinaceous drugs for vaginal delivery.[50]

Ocular Route

The ocular route has also been suggested as an alternative to subcutaneous administration of insulin using polymeric systems, such as nanoparticles, liposomes, ocular inserts, gels, etc. However, its use is limited due to the amount of insulin absorbed systemically via eyes. Xuan et al used insulin eye drops and studied the effects of pH and absorption enhancers, such as glycocholate and fusidic acid in rabbits. Systemic absorption was higher at increased pH (8.0), and both the absorption enhancers further increased the insulin absorption.[51]

Transdermal Route

The human skin presents itself as a rather thick barrier to allow permeation of large molecules like insulin. However, the significant advantage offered by transdermal delivery of drugs is the complete lack of degrading enzymes, which has attracted a good amount of investigations for this alternative route. Iontophoresis increases the transdermal permeation of charged and neutral compounds by the process of electro-migration and electro-osmosis. Tokumoto et al reported from their *in vivo* study on percutaneous absorption of human insulin in rats that synergistic application of electroporation (EP) and iontophoresis (IP) enhanced the percutaneous absorption.[52] Rapid progress in the fields of microelctronics, nanotechnology, and miniaturization of devices allow for improved designs with better control of drug delivery.[53]

Murthy and co-workers suggest the use of electro-osmosis (anodal iontophoresis) subsequent to electroporation in the presence of 1,2-dimyristoylphosphatidylserine or other anionic lipids to achieve therapeutic levels through the epidermis.[54] Rastogi and Singh have investigated the effect of various chemical enhancers, such as fatty acids and limonene and cathodal iontophoresis, on percutaneous absorption of insulin. It has been reported that linolenic acid produced greater permeability of insulin when compared with other fatty acids.[55]

Recent studies have also demonstrated the use of ultrasound-mediated transdermal insulin delivery with the use of cymbal array.[56] An Erbium:yttrium-aluminium-garnet (Er:YAG) laser can be effectively utilized for transdermal delivery of macromolecules and protein-based drugs like insulin.[57]

SUMMARY

Non-invasive insulin delivery technologies are poised to change the status of disease management. Much progress has been made since several decades in the development of non-invasive techniques. Various delivery strategies and specialized companies have evolved throughout the past few years to improve the delivery of insulin. Among all the approaches, pulmonary administration of insulin has achieved much clinical significance. The oral route is also booming to enter the market and has undergone considerable market research, and other delivery routes are chasing closely behind. However, delivery via the non-invasive route yet remains a challenge due to poor absorption and enzymatic instability. Long-term studies to ensure the safety of the alternative routes of insulin are yet necessary before recommending its extended use. Although as these technologies become feasible in the near future, they could offer non-invasive, efficacious, and a more physiological way of insulin administration to patients with diabetes.

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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.

Ms. Tejal Shah is currently working as an Assistant Professor in Pharmaceutics, Nirma University of Science & Technology. Ms. Shah has 8 years of teaching experience. She has 5 publications and a chapter written by her in a multi-authored book on Novel Drug Delivery Systems. She earned her MPharm in Pharmaceutics and is actively working toward her PhD at Sardar Patel University.

Dr. Jagruti A. Patel is currently working as an Assistant Professor in Pharmacology, Nirma University of Science & Technology. Dr. Patel has more than 14 years of experience of which 6 years of regular teaching and 7 years of professional and research experience. She has published 10 research papers and review articles in Indian and international journals. She has also been awarded the C.L. Malhotra prize of the Association of Physiologists and Pharmacologists of India, the Hari Om Ashram Prize of Sardar Patel University, and several other prizes for her research publications. She earned her MPharm and PhD in Pharmacology.

Ms. Anuradha Gajjar is currently working as an Assistant Professor in Pharmaceutical Chemistry, Nirma University of Science & Technology. Ms. Gajjar has 9 years experience teaching. She earned her MPharm in Pharmaceutical Chemistry and has submitted her PhD thesis at the Hem. North Gujarat University.

Technology Showcase

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Abeille Pharmaceuticals, Inc., is a pharmaceutical product development company with a mission to develop pharmaceutical products that focus on improving a drug's administration to enhance convenience, improve compliance, and/or ameliorate side-effects. The company's initial focus is on developing products in oncology supportive care, diabetes, and related metabolic disorders based on transdermal delivery and oral controlled-release systems. Abeille creates a strong proprietary position around each of the products it pursues, which is achieved through internal efforts and is further complimented through the acquisition and/or in-licensing of intellectual property rights related to the pipeline products. The products being developed by Abeille seek to fill market niches that account for several tens of millions of dollars in potential sales. For more information, contact Abeille Pharmaceuticals at (609) 951-2204 or visit **www.abeillepharma.com.**

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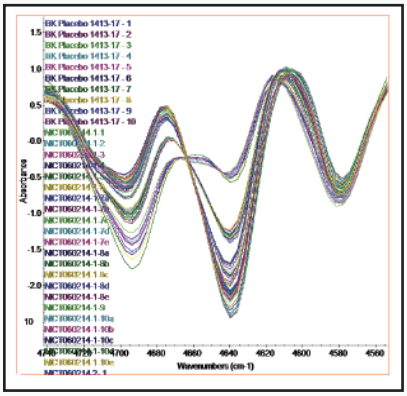

Process Analytical Technology (PAT) is a system for designing, analyzing, and controlling manufacturing through timely measurements of critical quality and performance attributes with the goal of ensuring final product quality. The concept is embraced by the FDA and regulatory agencies worldwide to improve product quality in the 21st century. Aveva DDS is applying PAT, such as near infrared red detection, with on-line, real-time process analyzers in its manufacturing of transdermal systems, increasing efficiency for process development, optimization, scale-up, technology transfer, and ultimate final product control. Aveva's quality monitoring, using in-process PAT technology, streamlines its ability to meet R&D timelines and lower production costs. Aveva DDS is based in Miramar, FL, where it uses its proprietary drug-enabling technologies to develop and commercialize innovative transdermal products. For more information, visit Aveva DDS at **www.avevadds.com.**

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Addressing Unmet Needs in Management of Parkinson's Disease

By: **Steven Damon**,
Vice President, Business Development, and
Yogi R. Patel,
Manager, Business Development,
Altea Therapeutics

Altea Therapeutics is currently in clinical development of a transdermal patch designed to address a major unmet need by preventing "off" periods and provide an improved therapeutic option for managing Parkinson's disease.

Introduction

Parkinson's disease is a progressive neurodegenerative disorder of the central nervous system that has a terrible impact on the quality of life of many of the 4 million sufferers worldwide. The disease tends to affect both genders equally, and the initial symptoms typically appear when people are in their late 50s or early 60s. Because there is no cure for the disease, patients are prescribed medications mainly to alleviate their symptoms, which is difficult to accomplish in later stages.

Parkinson's disease is associated with the part of the brain responsible for coordinated movements and is caused by a loss of dopamine-producing cells in these areas. Often, the first symptom of Parkinson's disease is tremor (trembling or shaking) of the hands, arms, legs, jaw, and/or face. Other common symptoms include rigidity or stiffness of the limbs and trunk, bradykinesia or slowness of movement, and postural instability or impaired balance and coordination. In severe cases, Parkinson's can lead to dementia, memory loss, and other cognitive disturbances. Common complications of the disease include depression, difficulty chewing and swallowing, urinary problems, sleeplessness, injuries from falls, side effects of medications, and difficulty performing general activities of daily living. Medications for Parkinson's disease may also cause a number of complications, including involuntary twitching or jerking movements of the arms or legs (dyskinesia), hallucinations, sleepiness, and a drop in blood pressure when standing up (orthostatic hypotension).

Parkinson's disease causes a severe burden not only on the patients, but also on their family and loved ones. Patients often suffer disrupted family and personal relationships, withdraw from social activities, and frequently suffer from depression (even from the earliest stages of the disorder). As the disease progresses and deterioration increases, it usually has a negative impact on the entire family's quality of life and financial status.

In the United States alone, combined direct and indirect costs for Parkinson's disease is estimated to exceed $5.6 billion per year. Medication costs for an individual patient average $2,500 a year, and therapeutic surgery can cost up to $100,000 per patient. The greatest financial costs associated with Parkinson's disease can be attributed to loss of productivity followed closely by homecare and direct healthcare costs.

Current Treatments

Currently, no treatment has been shown to slow or stop the progression of Parkinson's disease. Instead, therapy is directed at treating the symptoms that are most troublesome to a patient. Treatment approaches include medication and surgical therapy. Surgery is an option for patients who have severe, fast-progressing disease and have failed on other therapies. Other treatment approaches include general lifestyle modifications, physical therapy, and speech therapy.

The most effective therapy currently available for Parkinson's is levodopa, which remains the cornerstone of Parkinson's treatment. Nevertheless, the effectiveness of levodopa tends to diminish over time. After 2 to 5 years, 60% to 80% of Parkinson's disease patients on levodopa experience fluctuations in response to their therapy. Also, the most common side effect of levodopa is dyskinesias, which are abnormal and involuntary muscle movements.

Other common drugs used to manage the symptoms of Parkinson's disease include Catechol-O-methyl transferase (COMT) inhibitors, anticholinergic agents, and monoamine oxidase (MAO-B) inhibitors.

Another class of drugs, known as dopamine receptor agonists, mimic the

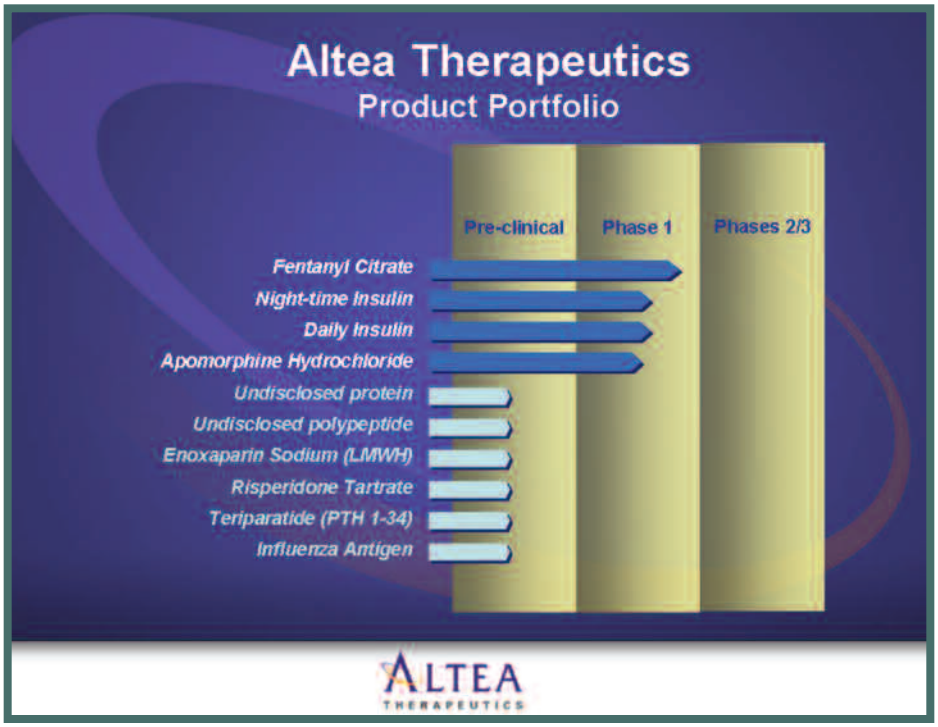

Figure 1. *The Company's Development Pipeline Attests to the Ability of the PassPort™ System to Deliver a Wide Variety of Drugs and Vaccines Transdermally*

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Figure 2. *The PassPort™ System is simple and easy to use.*

action of dopamine in the body.

Dopamine agonists currently dominate the Parkinson's disease market due to the lack of efficacy of marketed brands from other drug classes, which fail to provide long-lasting symptomatic relief. In addition, although levodopa (and other dopaminergics) have been widely used, recent studies suggest that dopamine agonists are a useful symptomatic long-term treatment for Parkinson's disease and that the early use of dopamine agonists reduces the incidence of motor complications as compared to levodopa.

The various dopamine agonists differ in several respects, including chemical structure, duration of action, and side effects. The response to a particular dopamine agonist varies considerably between individuals, so that if one dopamine agonist does not offer benefit or causes bothersome side effects, another agonist may be tried.

Emerging Treatments

Despite the enormous efforts toward finding a cure, symptomatic relief using various drugs remains the therapeutic cornerstone. These drugs, although effective, do not provide complete resolution of symptoms. In fact, some medications result in side effects that are further debilitating for patients. The major unmet need in the treatment of advanced Parkinson's disease is the reduction of "off" periods — frequent, prolonged, and/or unpredictable periods of hypomobility. Novel drug delivery mechanisms and formulations will become an increasingly important product-differentiating strategy.

Using its proprietary PassPort™ System, Altea Therapeutics is developing a transdermal skin patch to provide continuous delivery of apomorphine for the prevention of "off" periods and provide an improved option for the symptomatic management of Parkinson's disease.

The PassPort™ System

Altea Therapeutics new transdermal technology enables the sustained transdermal delivery of water-soluble drugs, peptides, proteins, and nucleotides from a painless and cost-effective skin patch. The PassPort System enables the affordable, non-invasive, painless, and controllable delivery of a wide range of drugs (Figure 1) via the skin that cannot be delivered using conventional patches. In addition to PassPort™ Apomorphine, Altea Therapeutics is developing a fentanyl citrate patch for management of moderate-to-severe pain. The fentanyl citrate patch is designed to incorporate layers of potential deterrents against product abuse, misuse, and diversion, and provides rapid and sustained delivery of a highly effective opioid. The company is also developing a basal insulin patch for treatment of diabetes, a low molecular weight heparin patch for prevention and acute treatment of thrombosis, an atypical antipsychotic

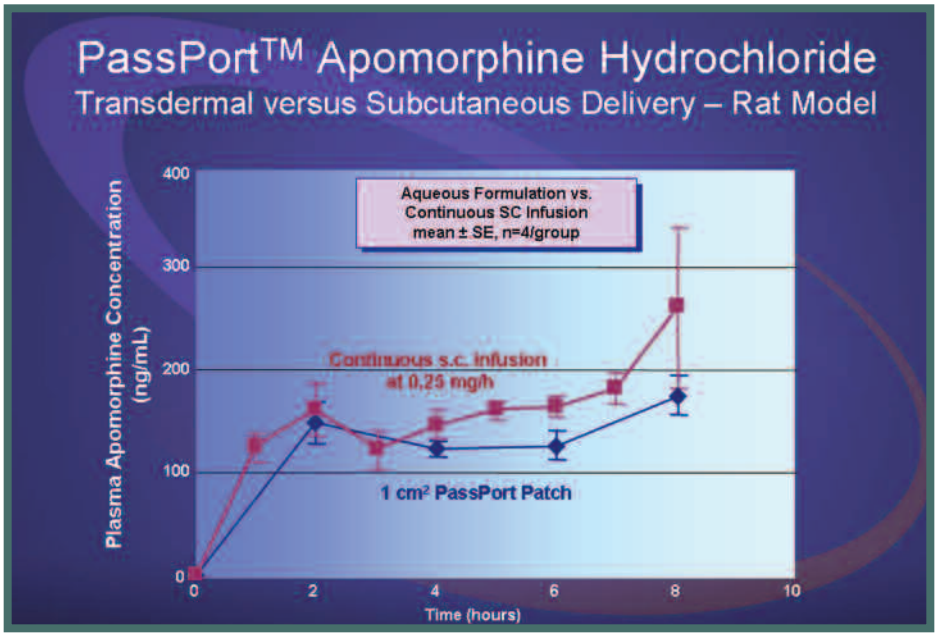

Figure 3. *Apomorphine Concentration (Plasma) Versus Time in Hairless Rats by (i) Transdermal Administration Using the PassPort™ System and (ii) Subcutaneous Infusion*

patch for schizophrenia and related disorders, and an influenza vaccine patch.

The PassPort System (Figure 2) is painless and easy to use: Step 1: Clip a PassPort Patch into the applicator and place against the skin. Step 2: Press the activation button of the applicator. Step 3: Remove the applicator, thereby leaving the drug patch on the skin. Secure patch and commence drug delivery.

PassPort Apomorphine is designed to deliver continuous levels of apomorphine over a sustained period of time from a skin patch ranging from 2 cm^2 to 8 cm^2. Currently, the PassPort Apomorphine Patch is undergoing Phase I clinical development. An initial Phase I pharmacokinetic study has demonstrated steady delivery of apomorphine over an 8-hour application period with rapid rise to steady plasma levels and rapid elimination after patch removal. Preclinical studies have demonstrated transdermal delivery of apomorphine in hairless rats comparable to subcutaneous infusion (Figure 3). The patch provides constant therapeutic effect without interruption and thereby serves to completely replace injections.

The applicator facilitates intuitive, accurate, and easy patch application. In addition, the applicator stores verifiable dosing information, including a record of time and date for each successful patch application by the patient. This information may be accessed by the physician to monitor compliance — a critical tool in the management of Parkinson's disease since only 10% of all patients are fully compliant with their prescribed therapy.

Market Potential & Partnership Opportunity

Altea Therapeutics PassPort Apomorphine represents an important opportunity in the management of Parkinson's Disease as it addresses the most significant unmet market need in managing the symptoms — the prevention of "off" periods by a small, painless, and convenient skin patch. With the potential to provide a major increase in the quality of life of Parkinson patients, Altea expects to grow and capture a significant share of the market for Parkinson's disease therapy. The market for drugs for the treatment of Parkinson's disease was $2.7 billion in 2005. Throughout the previous 5 years, the market has reported a growth rate of 12.9%. Dopamine agonists currently dominate the Parkinson's market; six out of the top nine marketed brands are dopamine agonists.

Altea is actively looking for a development and commercialization partner who has the capability to support development and effectively market this exciting new therapy in the CNS/Parkinson's market. ■

Steven Damon

Vice President, Business Development
Altea Therapeutics

Mr. Steven Damon leads the Business Development Team for Altea Therapeutics and has over 17 years of experience with various business roles in the medical and pharmaceutical industries. His experience includes business development, commercial development, and mergers and acquisitions. Prior to joining Altea Therapeutics, Mr. Damon was at Durect Corporation, where, as Executive Director, he completed several product partnership agreements with major pharmaceutical companies, was responsible for other commercial activities (including the Alzet brand drug delivery pumps for animal research), and was President of a wholly owned subsidiary - Absorbable Polymers International. He was previously at Kimberly-Clark Professional Healthcare with lead responsibilities for commercial development of the healthcare business in Europe and key responsibilities for a number of major acquisition deals.

Yogi R. Patel, PharmD

Manager, Business Development
Altea Therapeutics

Mr. Yogi R. Patel is currently the Manager of Business Development for Altea Therapeutics. His experience at the company also includes supportive roles working in pharmaceutical research and development. Prior to joining Altea Therapeutics, Mr. Patel completed a Medical Information Residency with AstraZeneca Pharmaceuticals in Wilmington, DE. He earned his PharmD from Mercer University in 2003.

Facts & Figures

Bionumbers: A Resource for Plans, Forecasts & Budgets

Specialty Pharma Index Trends

Both markets seem to have reversed themselves in the early part of 2007 (www.bionumbers.com). Following a strong 2006 (up 22%), the Emerging Stage Specialty Pharma Index (ESPI) has given back a large part of its gains (down 6%) through the end of January 2007. The Commercial Stage Specialty Pharma Index (CSPI) in contrast was up nicely, a little more than 5% in January 2007 after posting only a 4% increase in all of 2006. The largest fluctuations in valuations through January are to be found in the smaller members of the two indexes. With share prices in the single digits and teens, even a $1 change in price can cause a large percentage change.

Commercial Stage Index Trends

The CSP Index moved up on good gains by the larger market cap companies. While Shire was up a solid 3% for the month, it was King, Hospira, and Endo all up by double digits that drove the index growth. It's not clear whether this is an indication of renewed strength in the market or whether it is a rebound from 2006 where these companies all showed cumulative losses in market capitalization. Among the market cap leaders only Abraxis was down, continuing its slide of 2006. Among the five leading laggards, there was a mixture of trends. Several companies showed big losses in January 2007 after strong gains in 2006 (Advancis +118%, Santarus +60%, and Columbia +30% in 2006), while for the other companies, it was more of 2006 (Encysive -46% and Bentley -11% in 2006). Overall, the index capitalization was up only $500 million despite a 5% index growth because of the departure of Kos from the index following its year-end acquisition by Abbott.

Emerging Stage Index Trends

The ESP Index showed a significant reversal in growth following a very good 2006 (up 22%). Almost all of the larger cap companies (larger being strictly relative) showed a major drop in January 2007 that weighed heavily on the index. The exception was New River, which basically held it's own with a 2% increase in January. (Since then, New River has agreed to be acquired by Shire at a premium of 14.4% over its closing price; about the same premium relative to its end of January 2007 close). Only four companies in this 20-company index showed an increase for the month. The laggards were led by Nektar, Alexza, and Penwest, among the biggest market cap contributors to the index. Capitalization for the index dropped to $6.9 billion from $7.3 billion at the end of December 2006. Only a little more than one-tenth the size of the Commercial Stage Index, the Emerging Stage Index capitalization will take a huge hit later in the year when the New River acquisition is completed. ■

Editor's Note: These indices are intended to provide information on the macro trends within each covered sector. These indices have no value for investment purposes. Given the fluid nature of market prices, public company information updates, and a once-monthly index revision, the information will at best be of historical value.

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Bionumbers Commercial Stage Specialty Pharma Index

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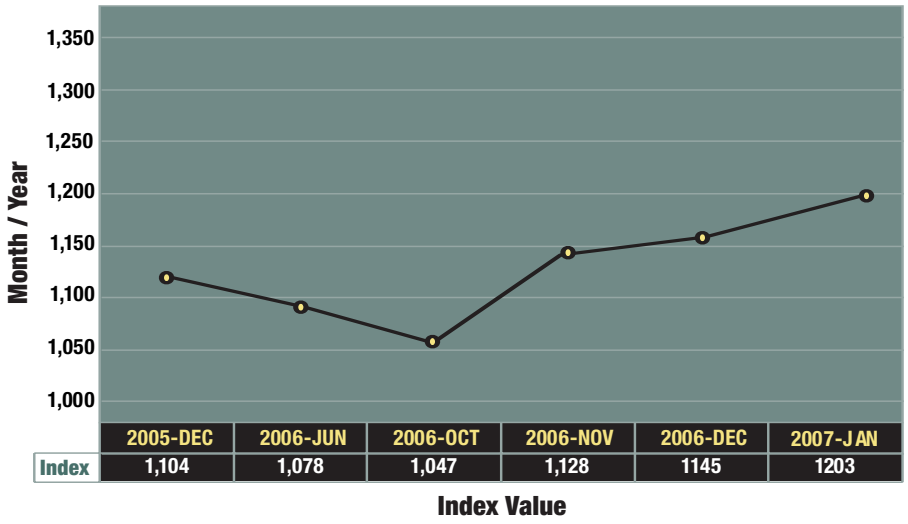


Key Figures January 2007
Index Value: 1203
Change YTD: +5.1%
Total Index Capitalization: -$59.7 Billion

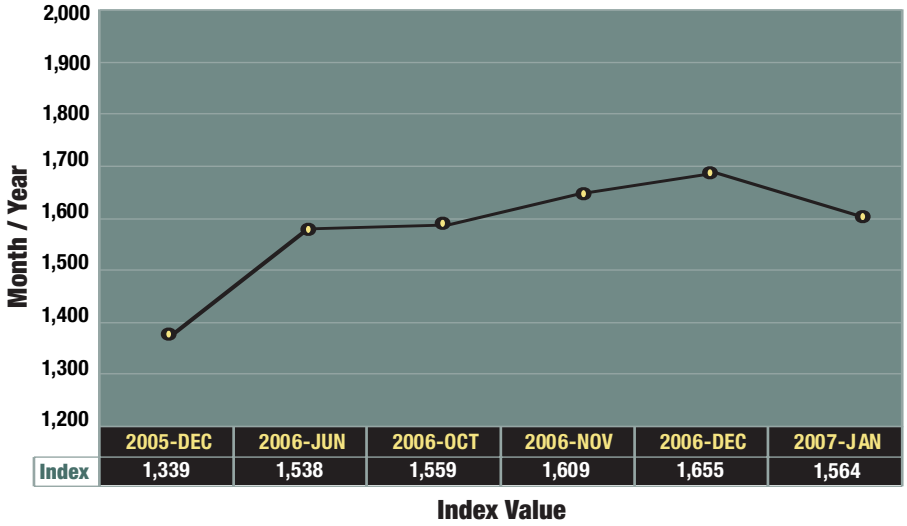
Top 5 Gainers YTD Change	
Savient	+33%
Pharmion	+24%
Vivus	+22%
Salix	+17%
InterMune	+14%

Top 5 Laggards YTD Change	
Advancis	-25%
Encysive	-20%
Santarus	-11%
Bentley	-11%
Columbia Labs	-9%

Top 5 Capitalizations YTD Change		
Shire	$10.8 Billion	3%
Hospira	$5.8 Billion	10%
King	$4.4 Billion	12%
Abraxis	$4.2 Billion	-4%
Endo	$4.1 Billion	11%

Bionumbers Emerging Specialty Pharma Index

JANUARY 2007



Key Figures January 2007
Index Value: 1564
Change YTD: -5.5%
Total Index Capitalization: $6.9 Billion

Top 5 Gainers YTD Change	
Catalyst	+32%
Spectrum	+16%
Acusphere	+11%
New River	+2%
All Others -ve	

Top 5 Laggards YTD Change	
Nektar	-16%
Alexza	-15%
Penwest	-14%
Keryx	-14%
Scolr	-12%

Top 5 Capitalizations YTD Change		
New River	$2002 Million	2%
Nektar	$1143 Million	-16%
Aspreva	$716 Million	-3%
Keryx	$493 Million	-14%
Cadence	$343 Million	-1%

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Clinical Trials

Conducting Clinical Trials in Asia

By: Ames Gross, MBA, President & Founder; and
Momoko Hirose, Associate, Pacific Bridge Medical

Introduction

With steadily increasing drug development costs and significant time spent on clinical trials, outsourcing clinical trials in Asia has rapidly become an appealing option for many firms (Figure 1). As developing a single drug can cost more than $200 million and take at least 10 years, Asia (except Japan) offers a less expensive, less time-consuming process for clinical trials. Simultaneously, increased demand and awareness for various medical drugs and health services (Tables 1 and 2) have encouraged many of these countries to develop their own Contract Research Organizations (CROs), and many US firms have eagerly turned to these options to survive in a growing competitive global market.

Why Go to Asian CROs?

The major incentive for moving clinical trials overseas is cost. Often, the cost of the hospitals, clinical evaluations, and data analysis are cheaper in Asia than in the US or Europe. One of the main factors contributing to lower costs with outsourcing clinical trials in Asia is that patient recruitment is generally easier and faster. Recruitment is a time-consuming task and sometimes accounts for about half of the time required for the clinical trial. In fact, almost 90% of clinical trials experience an unexpected delay of some sort, and problems with recruiting patients are generally the number one reason for these delays.

Other incentives include lower costs due to looser regulations in some of the Asian countries, excluding Japan. For example, governments in some Asian countries may have a less conservative stance on what population segments or parts of the body are permitted for testing. Some countries may also have less complicated regulatory regimes, allowing for faster approval times.

Asia also boasts a genetically diverse population with more than 4 billion people, many of whom have never received medication to treat their conditions. With such large numbers of new candidates, pharmaceutical companies can assess the success of their drug more accurately.

Finally, many of these Asian people may be willing to undergo testing for the access to medication and care they otherwise would not be able to afford. For example, India provides free medication and, in many cases, better

Table 1.

Country	Pharmaceutical Market Size
China	$20 billion
Hong Kong	$1.5 billion
Philippines	$300 million
Indonesia	$350 million
Japan	$60 billion
Malaysia	$210 million
Singapore	$400 million
Korea	$6.5 billion
Taiwan	$2.5 billion
India	$6 billion
Thailand	$1.5 billion

Source: Pacific Bridge Medical

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medical attention to clinical trial patients than the average Indian hospital would provide.

What to Watch Out For

Despite all of the advantages of outsourcing clinical trials, there are also concerns and potential pitfalls that should be addressed. One concern is the lax enforcement of intellectual property laws or complete lack of intellectual property laws at all. For example, it may be difficult for a foreign pharmaceutical company doing trials in China to ensure that the formula for its new drug will be kept strictly confidential when utilized by a Chinese CRO. Confidentiality agreements, which in theory are binding in the West, may not be so "confidential" in Asia. In addition, enforcement of intellectual property is not uniform throughout the Asian region.

Measures have been taken to address such concerns. Now, with the World Trade Organization's agreement on Trade Related Aspects of Intellectual Property Rights, member countries are required to establish minimum standards concerning the scope and use of IP rights and the procedures for enforcing them. Contract research organizations in Asia are also enforcing stricter IP procedures. At WuXi PharmaTech in Shanghai, China, workers who fail to follow IP protection procedures are fired after two warnings. Of course, by then it may be too late.

Another concern of pharmaceutical companies working with foreign CROs is that the research and clinical trial data will be of low quality. This is certainly a legitimate issue as in some developing countries, the quality of facilities, infrastructure, and data collection may not be as high as one might expect in a typically modern, high-tech hospital in the US, Europe, or Japan. However, quality is constantly improving, and in places like Singapore and Hong Kong, the facilities and quality control of the trials are comparable to Western standards.

There is also concern about unethical treatment of patients in countries without specific laws protecting participants. Some countries may not get the "informed consent" of the subjects in the trial beforehand. Also, many CROs purport to run facilities that are compliant with the International Committee on Harmonization (ICH) standards of Good Clinical Practice (GCP), but in practice they do not do so.

How to Choose a CRO

Understandably, it can be daunting to find an appropriate, qualified CRO in an Asian (or any foreign) country. The conventional choice is to pick one of the large global CROs that has offices around the world and an excellent reputation. However, this may not always be the best choice for every company. A CRO may have done excellent work in the US or Europe, but its offices in farther-off locales like Asia may not be staffed with the same quality of personnel as its headquarters. A local CRO may be better suited for certain clinical studies because it can devote more attention to smaller projects, and because it may value that client more than a large global CRO would. Local CROs may also have more expertise on the local regulations, as well as closer ties to the local regulatory authorities. In addition, a global CRO may be more concerned about keeping its large pharmaceutical clients, with their large, multi-site studies with hundreds of patients, happy.

Once a CRO is chosen, it may also be a good idea to have a local

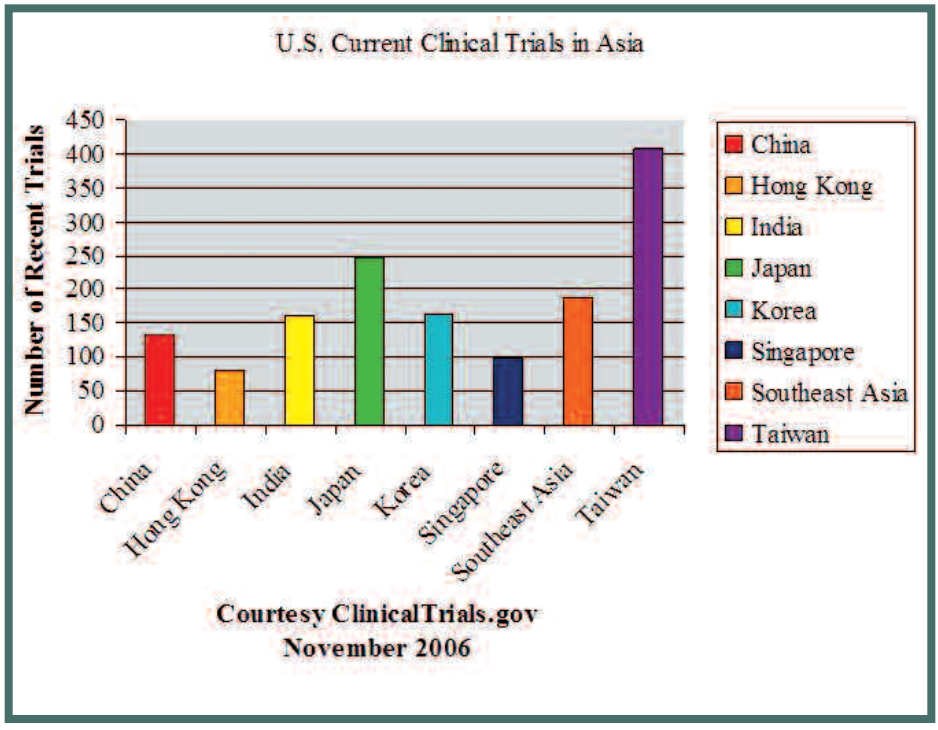

Figure 1.

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Table 2.

Country	Health Expenditure Per Capita	Health Expenditure as % of GDP	Physicians Per 1,000 People	Hospital Beds Per 1,000 People
China	$61	5.60%	1.6	2.5
India	$27	4.80%	0.6	0.9
Indonesia	$30	3.10%	0.1	6
Japan	$2,662	7.90%	2	14.3
Korea	$705	5.60%	1.6	7.1
Malaysia	$163	3.80%	0.7	1.9
Philippines	$31	3.20%	1.2	1
Singapore	$964	4.50%	1.4	2.9
Thailand	$76	3.30%	0.4	2.2
Taiwan	$743	5.60%	7.4	5.7
Vietnam	$26	5.40%	0.5	2.4

Source: World Bank, World Development Indicators 2006.

independent regulatory person or one of your employees move abroad to help oversee the trials. CROs that are monitored locally often provide their services in a timelier manner and at a higher level of quality.

Which Countries?

Aside from differences in cost, one should look at other attributes, such as each country's regulatory and healthcare environment. Ease of regulatory approval can vary significantly depending on each government's regulations and laws on drugs and clinical research. Some countries may be able to provide large numbers of patients that suffer from a particular disease or illness, while other countries may not have such patient populations. Sometimes you may be willing to do the trials in a foreign language, while in other cases, English is required.

Clinical trial locations in Asia can be divided into three tiers. The first tier is Japan, which has a very high-quality, very conservative medical community. Clinical trials in Japan are normally more expensive than comparable trials in the West, and the quality of the clinical research is generally just as high. As more medical companies enter Japan, the need for at least some local clinical trials has increased.

The second tier includes Taiwan, Korea, Singapore, and Hong Kong. These countries provide clinical trial services at a relatively high level of quality and generally at lower cost than in Japan or the West.

The third tier includes India, China, and Southeast Asian countries, such as Indonesia, Malaysia, the Philippines, and Thailand. Clinical trials in these countries can be of decent quality and normally offer significantly lower costs than places like Taiwan, Singapore, and Hong Kong. However, issues such as the quality of the trials and intellectual property protection are generally real concerns in these locations. The information below gives some background on most of these Asian countries and outlines how to get started with clinical trials.

Tier 1: Japan

Japan's medical business is very sophisticated and comparable to Western standards. Western companies looking to outsource clinical trials to save money and time should NOT go to Japan. However, in almost all cases, Western companies that wish to sell drugs or more risky medical devices in the Japanese market will need to do at least some clinical trials in Japan in order to get product approval.

In Japan, the Ministry of Health, Labor, and Welfare (MHLW) oversees the regulation and safety of pharmaceuticals, medical devices, cosmetics, and food. It is comparable to the US FDA. The Pharmaceuticals and Medical Devices Agency (PMDA), established in April 2004 under the revised Pharmaceutical Affairs Law (PAL) in 2002, oversees regulatory affairs for drugs and medical devices. Though both have websites in English (www.mhlw.go.jp/english/index.html and www.pmda.go.jp/index-e.html), they are not updated as regularly as the Japanese sites.

Currently, there are no base guidelines or specific laws about what types of foreign clinical data are acceptable for each product. In many cases, the PMDA must work on a case-by-case basis for each medical product with independent Japanese experts to determine specific logistical issues, such as number of participants, what data is required, and how the study should be conducted. However, the PMDA is currently working with experts in specific fields to establish clinical trial guidelines for different product types.

Before making a clinical trial request, an applicant submits a Clinical

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Trial Notification (CTN) to the PMDA. The notification mainly consists of description and product summary, pre-clinical data, clinical trial protocol, analysis plan, SOPs, contact person, and appropriate research institution. Also, compliance with Good Clinical Practice (GCP) often requires an Institutional Review Board (IRB) to review the clinical trial protocol, written informed consent forms for participants, and adverse event reporting. For those who require further specific guidance on their product, the PMDA also provides more in-depth consultation sessions.

Tier Two: Taiwan, Singapore, Hong Kong, Korea

Taiwan: Taiwan is a country in which CROs are already very active. Quality standards for clinical trials in Taiwan adhere to the accepted international standards of ICH GCP. GCP guidelines were implemented by the Department of Health (DOH; www.doh.gov.tw/EN/Webpage/index.aspx) in 1997 and then further revised in 2002 to be consistent with ICH standards. The DOH conducts GCP inspections on nearly all clinical trials to ensure their quality and credibility and is equivalent to the US FDA.

Before a clinical trial in Taiwan can begin, approval of the clinical trial protocol must be obtained from both the IRB and the DOH. The IRB or ethics committee of the individual hospitals will review the protocol for any ethics concerns. Approval takes about 2 to 3 months.

Taiwan also offers the option of joint IRB (JIRB) approval, which allows for multi-center approval as opposed to individual IRB approval from each hospital. More than 40 hospitals have participated in the joint IRB, and JIRB has helped Taiwan attract more multi-center trials.

In addition to IRB approval, the clinical trial protocol must also be reviewed and approved by the Bureau of Pharmaceutical Affairs at the DOH. The Center for Drug Evaluation (CDE), a non-governmental, non-profit organization, assists in reviewing all clinical trial protocols submitted to the DOH. In addition, it also provides regulatory consultation, reviews informed consent documents, and facilitates the drug development process in Taiwan. Regulatory approval to start clinical trials also takes 2 to 3 months.

Singapore: Singapore is a good location for conducting clinical trials because it boasts the second-best healthcare system in Asia (after Japan). Singapore has 4.3 million people, high-quality facilities, and highly educated doctors, many of whom went to school in the US or Europe (especially England). However, one of the drawbacks of doing clinical trials there is its small population; sometimes trials in Singapore can encounter difficulty recruiting enough patients.

Singapore is also strong in intellectual property (IP) protection, being ranked the top Asian country for IP protection for 3 years (2002-2004) by the Institute for Management Development (IMD), the World Economic Forum (WEF), and the Political Economic Risk Consultancy (PERC).

The Health Sciences Authority (HSA) (www.has.gov.sg/), established in 2001, is generally responsible for the quality, safety, and efficacy of drugs and devices. The Centre for Drug Administration (CDA), a division of the HSA, regulates and evaluates drugs and medical devices, including clinical trials. All clinical drug trials in Singapore require regulatory approval in the form of a Clinical Trial Certificate (CTC), granted by the CDA before the trial can proceed.

The Medical Clinical Research Committee (MCRC) reviews applications for CTCs, in addition to conducting continuing reviews of the clinical trial and monitoring adverse events. The entire approval process to start clinical trials takes about 2 to 3 months, including IRB/EC approval. All clinical trials conducted in Singapore must comply with the Singapore Guidelines for Good Clinical Practice (GCP), which were adapted from ICH-GCP standards and implemented in 1998.

Hong Kong: This country is an emerging market for clinical trials. The country has advanced medical care, along with developed infrastructure, strong presence of academic institutions, and high-quality investigators. Doctors are highly educated and have studied abroad, particularly in the US and Europe (ie, England). The majority of clinical trials conducted in Hong Kong are in Phases II to IV, and clinical trials are regulated by the Department of Health (www.dh.gov.hk/eindex.html).

Under Regulation 36B of the Pharmacy and Poisons Regulations, a certificate for Clinical Trial/Medicinal Test (CTC) is required before conducting a clinical trial. Before applying for a CTC, an applicant should first receive approval from the hospital's Ethics Committee (EC). Obtaining EC approval generally takes 4 to 6 weeks.

The CTC submission will include the protocol, investigator's brochure, pre-clinical study results, drug samples, the EC approval letter, an informed consent form, and an endorsement letter from the principal investigator. The CTC is granted to the principal investigator, and usually takes an additional 4 to 6 weeks.

The sponsor must also apply for an import license at the Trade and Industry Department for permission to import samples of the drug for the purpose of obtaining the CTC. This will generally be available within a week. A copy of the CTC will be required when the drugs are actually imported for clinical testing. The total approval time will be about 2 to 4 months.

Korea: The Korea Food and Drug Administration (KFDA; www.kfda.go.kr/), established in 1996, is the main regulatory body for drugs, medical devices, food, and cosmetic products. To conduct a clinical trial in Korea, the sponsor must obtain both regulatory approval and IRB approval. The KFDA provides optional pre-IND (Investigational New Drug) consultation services, and it is generally recommended that the sponsor engage in these consultations. The sponsor will then submit the clinical trial application dossier with the appropriate supporting documents (such as the protocol, Chemistry, Manufacturing and Control data, etc.) to the KFDA. The full clinical trial application must be translated into Korean. All trials must follow KGCP (which was revised in 2001 to harmonize with ICH guidelines) and can only take place at accredited sites. The KFDA will consult with the Central Pharmaceutical Affairs Committee in making its decision on approving the clinical trial. Regulatory approval takes about 30 days while the IRB approval also takes about 30 days. Both these processes can be done in parallel.

Tier Three: India, China, Southeast Asia

The third tier of clinical research includes countries whose healthcare infrastructures may not be as highly developed as in wealthier Asian countries. However, clinical trial services offered here are often significantly less expensive than in the second-tier countries and can be of decent quality. Even amongst these countries there is some variation. For example, India has a highly educated human resource pool and existing infrastructure for drug production, which has made it easier for Indian companies to transition into clinical research. There are many local CROs that are headquartered in India, along with many satellite offices of global CROs. Recently, China too has become a target location for many clinical trials. In the Southeast Asian countries, however, there are not many local "homegrown" CROs and only a few branch offices of large global or regional CROs. As of today, not many foreign medical companies focus on Southeast Asia (Malaysia, Philippines, Indonesia, and Thailand) when looking to do clinical trials in the region.

India: For a number of reasons, India's clinical trial business has grown rapidly throughout the past few years. Perhaps the major factor for such growth is the fact that clinical trials in India are significantly cheaper than in the West. Another factor spurring growth in the Indian market is the large, already-existing presence of pharmaceutical know-how and capacity. Add to that the tremendous diversity of its population, huge geographic expanse, the number of foreign-educated doctors, and the fact that English is a spoken language; it is no surprise, then, that India has become a prime spot for clinical research activity.

India's recent changes in patent regulations have also encouraged more international business in the past 10 years. The Indian Patents Act (1970) did not recognize pharmaceutical product patents as only manufacturing process patents were recognized. However, in 1995, India agreed to uphold the WTO Trade-Related Intellectual Property Rights (TRIPS) in which India would recognize and enforce pharmaceutical product patents, in addition to other product patents.

Drug registrations and approvals fall under the responsibility of the Central Drug Standards Control Organization (CDSCO). A key official within this organization is the Drug Controller General India (DCGI), and both work together on regulations for clinical trials. Legislative requirements on clinical trials are guided by specifications of Schedule Y of the Drug & Cosmetics Act, 1940. Schedule Y contains detailed information for each trial phase, including requirements for Ethics Committees, informed consent, animal pharmacology, and other details.

The CDSCO has recently passed new regulations on global clinical trials based on a meeting held in October 2006. For the purpose of granting permission, clinical trials are to be classified into Category A and B. Category A will include those trials whose protocols are approved by the US, UK, Switzerland, Australia, Canada, Germany, South Africa, Japan, and

EMEA (European Medicines Agency). Because permission will be granted accepting the approvals of the protocols from these countries, the CDSCO estimates that approval time for clinical trials will take 2 to 4 weeks. However, all other applicants will fall under Category B, which will require protocol verification and take 3 to 4 months approval time.

The CDSCO (http://cdsco.nic.in/index.html) has also categorized protocol amendments into three groups: those not requiring any notification or permission, those that require notification but no permission, and those requiring prior permission from the CDSCO before implementation of clinical trial protocol amendments.

China: The State Food and Drug Administration (SFDA; www.sfda.gov/cn/eng/) is the Chinese equivalent of the US FDA and is the national authority that approves and reviews clinical research. The regulation of drugs and clinical trials is outlined by the Drug Administration Law of the People's Republic of China, which went into effect in December 2001, and the Drug Registration Regulation of 2002.

Before a clinical trial may be carried out in China, it must first be approved by the SFDA. The sponsor should prepare and submit the dossier and drug samples to the SFDA, which will consult with the Center for Drug Evaluation before issuing a clinical trial approval letter. Other drug institutes, such as the National Institute for the Control of Pharmaceutical and Biological Products, will also aide the SFDA in screening applications. The entire process for clinical trial approval takes approximately 7 to 9 months. Fast-track review is available for clinical trials of drugs that treat serious or life-threatening illness, or for drugs that are the same kind of drug as one that has already been approved.

Southeast Asia: Each country has a specific governmental health organization that oversees clinical trials and pharmaceutical regulations. Approval processes can be relatively quick in these countries, taking only 3 to 4 months. The most popular location for clinical trials in Southeast Asia (not including Singapore) is Malaysia for its relatively developed hospital infrastructure and advanced regulatory environment for drugs.

Summary

Outsourcing clinical trials in Asia provides a way for US and European medical companies to reduce cost and increase productivity and efficiency. Currently, about 25% of US medical companies outsource overseas to some extent. Although IP protection issues still linger, some US companies are now outsourcing all phases of product development, including drug discovery, research and development, clinical trials, and manufacturing. American companies will continue to outsource in Asia as the medical communities in Asian countries continue to become more sophisticated and cost reduction can be more clearly defined. ■

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Mr. Ames Gross, MBA

President & Founder
Pacific Bridge Medical

Mr. Ames Gross is President and Founder of Pacific Bridge Medical (PBM), and is recognized nationally and internationally as a leader in the Asian medical markets. Established in 1988, PBM is a consulting firm that assists medical companies with business development and regulatory issues in Asia. PBM has helped more than 200 medical companies over the years. Mr. Gross earned his BA, Phi Beta Kappa, from the University of Pennsylvania and his MBA from Columbia University.

Ms. Momoko Hirose

Associate
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Ms. Momoko Hirose is an Associate of PBM. She works on research, writing, and consulting projects and is a graduate of Brown University.

Executive Summary

Paul Johnson
President,
DPT Laboratories, Ltd.

R&D Takes Center Stage at DPT

By: Cindy H. Dubin, Contributor

DPT Laboratories, Ltd. is a contract development and manufacturing organization (CDMO), specializing in semi-solid and liquid dosage forms. Recognized globally for technical expertise and manufacturing capabilities, the company is turning its attention to R&D, while still maintaining its focus on dosage forms. Paul Johnson, President, tells Specialty Pharma that this is done to help the company differentiate itself in the market. He also shares with SP readers about the company's desire to remain privately held and its success in Texas.

Q: ***Why does DPT invest in research and development?***

A: While maintaining our focus on semi-solids and liquids, we are spending more in research and development, especially in drug delivery technology. It is an essential part of our emphasis on being a contract development and manufacturing organization, or CDMO. A lot of companies strictly do work for hire. We take a certain amount of our profit and invest it in research. It's done primarily because there is tremendous market need for companies to differentiate themselves. We can add value to our customers through novel drug delivery or package and delivery systems. We are investing more and more into those areas as a way to continue bringing greater value to our customers. For example, some time ago, we launched MVE technology (Multi-Vesicular Emulsion) system, which we patented. We offer this technology to our customers as a potential way of maintaining efficacy but decreasing irritation of actives that have a tendency to be irritating. In addition, we built continuous spray system capability at DPT with the help of a customer. Using this system, we recently launched a prescription wound care product that was only available in a tube. This spray system makes the product easier to use for caregivers.

Q: ***What is the value of being and remaining privately held?***

A: We've been private since 1990. I think that has allowed us to focus on mid- to long-term and not quarter-to-quarter results, allowing us to make investments that do not have an immediate payoff. We can also make quicker decisions, there are fewer people to get buy-in from, and, ultimately, our ability to adapt is better so we can adjust to changing market dynamics that may come at us. In many ways, we have always operated with the financial discipline of a publicly held company. However, being privately held allows us to make decisions that are not based on quarter-to-quarter results, but decisions that are based on whether they are right for the business.

Q: ***Why have you kept DPT in San Antonio all these years instead of moving it to the northeastern United States?***

A: We certainly have a very strong northeast presence, and it's important to note that we have 1 million square feet of infrastructure between San Antonio and our Lakewood, New Jersey, site. We now have sites

that give customers the confidence — the assurance — that they have a back-up plant versus a single-source site. That being said, San Antonio offers a great quality of life to a great number of people, and we have no difficulty attracting top talent — and customers — to the site. San Antonio is also becoming better known for its biotech emphasis, and this city has a very strong commitment to the biotech industry. There are very good resources and synergies that we utilize in San Antonio, where, if necessary, we can draw on their expertise. We also receive very strong support from the city of San Antonio, which considers DPT a preferred employer. And Texas is, on the whole, friendly to business.

Q: ***What makes the company's business model unique?***

A: It is the concept of a CDMO. Often in our industry, you're either known for your development or you're known for your manufacturing. So a customer might source from a development organization and separate manufacturing organization. We put equal emphasis on both of those capabilities so that we can get involved very early in the development process, from preformulation all the way through FDA approval. Once the product is approved, we have excellence and strength in the manufacturing and supply chain piece, as well. And very, very few could ever make that claim. I think DPT is in a unique position to be able to claim that we have strength in both of those domains. The reason that we execute the CDMO concept very well is our emphasis on semi-solids and liquids. We're focused. We're not trying to be all things to all people. Our expertise in semi-solids and liquids gives us the ability to excel in both development and manufacturing.

Q: ***What makes the company attractive as a partner to pharma companies?***

A: I think the first thing a pharma company looks for is a stellar regulatory compliance record. Our size and critical mass are also keys. This is a very fragmented industry and for our area of specialty, we really are the leader. We are the industry choice when it comes to outsourcing services for semi-solid and liquid dosage products. I believe our expertise is another area that makes us attractive. And ultimately, our track record, the number of products that we have successfully launched for our customers. I think those are all things that a pharma company would look at in selecting someone for the first time. We are not so big that our customers get lost in trying to do business with us; nor do we have the limitations of a one-person shop. We have enough infrastructure and enough talent that we can do multiple projects at the same time. That infrastructure encompasses everything from quality to research and development, to engineering. We have the balance and the flexibility with the critical mass. Customers first want to make sure of your regulatory compliance. Once they have that, they want to know that you can deliver a product on time, every time. Thirdly, they're going to find out if you are competitive price-wise. But if you don't get No. 1, then you don't really get to talk about No. 2 or No. 3. Once we get past those three, I think the value-added proposition that we provide is comprehensive services for our focus, and our market segment, from early development through commercialization. Customers need to have confidence in the people they will be working with. They are handing off, in many ways, their baby, to someone. And they have to have the trust and confidence that you are going to nurture and take care of that child and bring it to fruition and growth. They'll talk to your quality people. They'll talk to your R&D people, operations people, and engineering. And it's really an entire team approach to get comfortable with the company before the customer makes that decision. The customer's career depends on your ability to do what you say you're going to do. In the case of Specialty Pharma or virtual pharma, it may not just be their career, but their whole company. A lot of trust is required in this business. We have some customers with whom we have such a strategic relationship that if we don't deliver, they cease to be. They are 100% dependent on us for their entire supply chain.

Q: ***How is your work today different from in years past?***

A: We are finding ourselves doing earlier and earlier development work, a greater need for Phase II and Phase III development work. That whole CDMO concept, we're seeing more and more of our work shifting to development services. That is becoming a larger percentage of the overall scope of the company. The need to launch new products has never been greater for most of our customers, and they just don't have the internal resources to do it, so they are seeking companies that can fulfill that need for them. For these customers, it used to be all in-house, so that's a huge shift. A lot of products are coming off patent, and we're finding that we can go to our customers and give them suggestions on how to differentiate their product and possibly extend its life cycle. We recently met with one that has a several-hundred-million-dollar brand coming off patent in a couple of years. We have no problem getting meetings with top executives when we can talk about that. The majority of work we are doing today is assisting clients with their development programs, but also taking it and launching it into a commercial, viable product, which is different from what we did in the past. In the past, it was more opportunistic: "I don't have enough capacity in my plant. I'll give you my leftovers." Or tactical: "I have a surge in demand. Can you handle that for me?" The industry has now recognized that what pharma does particularly well is research, and what they do particularly well is sales and marketing. They also don't want to tie their money up in the development, manufacturing piece. They prefer to spend their money on research and on sales and marketing. Therefore, you better find the right partner, because this is a strategic decision. It's not only this one opportunity, but making sure their partner can handle opportunity two, three, four, or five. So that's the shift that we're seeing in the industry, and I think the pendulum is still shifting. What used to happen, too, is they'd go out and find a development company, do formulation development, find a method development company, and then they'd find a clinical trial manufacturer, and then they would transfer it to a contract manufacturing organization. Today, as a world-class CDMO, we have the expertise to offer all of those services together to our customers.

Q: ***What are some of the business strategies that have contributed to your success?***

A: The first would be our proactive approach to extend product life cycles. We've focused on new technologies and innovation, with more emphasis on development to bring continued value to our customers. Number two is operational excellence. There is huge pressure in the marketplace to lower costs. So we're expending a lot of effort in our strategy to achieve operational excellence, and taking non-value-added steps out of the process to become more competitive than our customers could be within their own facilities. The third contribution to our success that I believe is really key is that we have been very successful in recruiting and retaining top talent. It is amazing the transition throughout the past 4 years if you look at the management team and the individuals we've been able to bring on board, not only from a technical standpoint, but also our emphasis on our value system. We have a huge initiative to continue focusing on our value system, so we really believe that it is not only what you get done, but how you go about doing it that's really a sustainable model for the long haul. That is really the differentiating point with pharmaceutical companies. They want to know who the people are, and that they have a common, shared value system. Overall, the pharmaceutical industry is a very ethical industry, and it attracts individuals of like mind. The talent that we've brought to DPT has a strong value system.

Q: ***What was one thing that happened in the past year that you were not expecting?***

A: In March 2006, a strategic partner and Specialty Pharma organization asked us to take over the management of its entire supply chain for an acquisition that had just taken place. That included the active pharmaceutical ingredient, or API, through processing of the API, to the manufacture of that product. We not only had supply chain issues associated with it, but also had some serious regulatory issues. We were given very little notice. We met and agreed to this, and here we are now, and the supply services are excellent, and the regulatory issues have been dealt with, all in a very timely manner. That really speaks to the talent and the depth we have in our organization because the API part of the supply chain was an area that wasn't particularly in our core. But it demonstrates that customers are looking at us in a very different light and trust us to bring the expertise to handle difficult projects. This company didn't have the expertise or the resources to resolve its compliance issues and supply chain issues. Therefore, it sought out a strategic partner. DPT is the partner that has resolved those issues, and the client now can focus its expertise, generating more sales. Because we've helped resolve these issues, the customer generated more sales and the price it paid for this acquisition compared to what it is worth today is astounding. We think there's going to be more of this, where companies will say, "You guys are good at running plants and factories. Can you take over the management of our plant?" Or, "We have three plants, but we only need two. Can you take that project on for us?" We probably couldn't have pulled this off 3 or 4 years ago, but now we can look at the world a little differently. With the vast number of products that we handle, we are in a unique position. Sometimes plants are running only run a few products at a time — two, three, four. We run hundreds of product formulas and have seen hundreds, so we have a unique way of looking at the world because of what we've been exposed to. So when we take on that assignment, we can say, "Why are you doing things this way? Why is it being done this way?" We can incorporate our experience and expertise and change things when it makes sense. We're able to learn best practices from the amount of projects we do and then we're able to apply those practices to certain situations.

Q: ***What's the mistake you have to avoid going forward?***

A: We can't allow complacency to creep in. We have an outstanding, stellar regulatory compliance record, and our service levels are very good. We've had strong growth, but this is an extremely challenging business and you're only as good as the last product you helped bring to market, last order you shipped, and last audit. We can never allow ourselves to be satisfied or complacent because this market is a tough market and it's ever-changing. So, we can't make the mistake of resting on our past success, because it does not guarantee your future success.

Q: ***What are the goals and objectives going forward for the company in the next 5 years?***

A: Our vision is to focus on service, innovation, and technology. We'll have tremendous focus on our core business, which is semi-solids and liquids, in both development and manufacturing. We'll also be expanding into what we call adjacent technologies that we'll bring to our customers. Our strategy isn't necessarily to become the biggest, but our goal is to be the best at whatever we take on.

Q: ***What keeps you awake at night?***

A: Finding and retaining the talent to execute DPT's vision. I'm convinced the market dynamics are there. The industry trend is there. The only thing that's going to stop us from getting there is being able to bring the talent to sustain this growth throughout the next 5 years. We plan to double in size, so every hire is key to us. DPT has a very rigorous interview process, and it's not just with the hiring manager. It is a cross-functional team that has to agree on this individual, not only the experience and technical expertise, but the shared values, as well, that allow this person the opportunity to be successful in this organization. We have found that if you don't have the right fit, it doesn't matter if that individual is good or bad. It's not a good fit if you don't share the same values. We call our values system "IDPT," for "Integrity, Dignity, Perseverance, Trust," and we really try to live by it. I believe if you model those values at the top, then you have a right to expect it at the director level, the managerial level, the supervisory level, and on the production line. Come to think of it, our success in finding talented employees who share our core values is helping me sleep pretty well these days. ■

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On Guard….or is it En Guard?

By: John A. Bermingham

I couldn't figure out exactly what to name this article, so I went for two names, one defensive and one offensive. The reason is that all people who work with others have to remain "on guard" at all times and "en guard" when necessary. What is this guy talking about, you ask?

I'm talking about those people around you that continually undermine you and stab you in the back. Even CEOs have to constantly watch out for this. So you always have to play defense and sometimes offense. The following is one example that happened to me.

Prior to my taking over a previous company to turn it around, the CEO in place before me had led the company downward in revenue and profit for 3 straight years. During that time, the CEO was not necessarily giving the Private Equity firm that owned the company accurate information, or he was promising things that he absolutely could not deliver. Two senior executives in this company took it upon themselves to back channel information to the Private Equity firm around the CEO with the "real truth," which differed completely from what the CEO was reporting. So the Private Equity firm's management chose to believe the two back-channeling executives due to the credibility issue they had with the CEO. The back channelers cost the CEO his job. Enter me as the new CEO.

So these two executives decided that because they had ingratiated themselves so well with the Private Equity firm's management, they would continue on doing it to me so as to strengthen their position even more so with the Private Equity firm's management. Once I found out that this was happening, I did what any CEO would do. I spoke to them individually and reconfirmed to them the new ground rules, making certain that there was no confusion on their part. I explained that undermining anyone in the company was a real no-no, particularly the CEO, and that it would not be tolerated going forward. I also told them that if it happened again, it would be dealt with quickly and severely. I wanted them to understand the disruption and harm they were causing the company.

They both continued on so I did what any CEO would do. I pulled a Tony Soprano. I whacked the weaker of the two of them (fired for insubordinate conduct) and let the stronger one make his/her own decision as to how to act going forward. The other one quickly saw the light and conformed Thanks Tony!

So what if you are not the CEO? Well, the very first time it happens to you, do not ever ignore it. When you discover a back-channeling, back-stabbing, lying, low life reprobate doing this to you, it probably has been going on for some time. I suggest that you confront the person with the facts or suspicion and let them know in no uncertain terms that you will not tolerate this conduct. I would then bring your boss into the loop quickly. If it happens again, file a complaint with human resources, your boss, and the person's boss.

I have always believed that there are two types of people in a company; those who are competent and compete fairly for advancement, and those who are incompetent and compete in an underground behind your back manner. You cannot escape the second type of person, so you must deal with them like Tony Soprano would: quickly, directly, and aggressively.

So I always try to keep in mind that I have to be on guard all of the time and resort to en guard whenever it becomes necessary. And just like in the en guard fencing move, hesitation means defeat. ◆

BIOGRAPHY

John A. Bermingham is currently the CEO of The Lang Companies, an innovative leader in the social sentiment and home décor industries. He was previously the President, Chairman, and CEO during the successful turnaround and sale of Ampad, a leading manufacturer and distributor of office products. With more than 20 years of experience in guiding enterprises to new levels of performance, Mr. Bermingham also held the positions of Chairman, President, and CEO of Centis, Inc., a diverse multinational manufacturer and marketer of office, storage, and human resources products. Among many career highlights in the role of President and CEO, he also successfully reorganized Smith Corona Corporation and refocused operations and a strategic vision for a dramatic turnaround for Rolodex Corporation. Mr. Bermingham's expertise 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, earned his BA in Business Administration from Saint Leo University, and completed the Harvard University Graduate School of Business Advanced Management Program.


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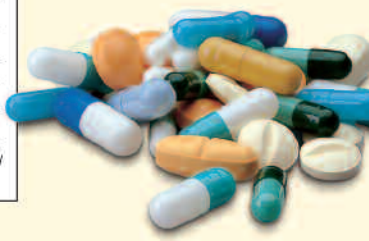

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