Drug Delivery Technology®

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NANO-SCALED CARRIERS

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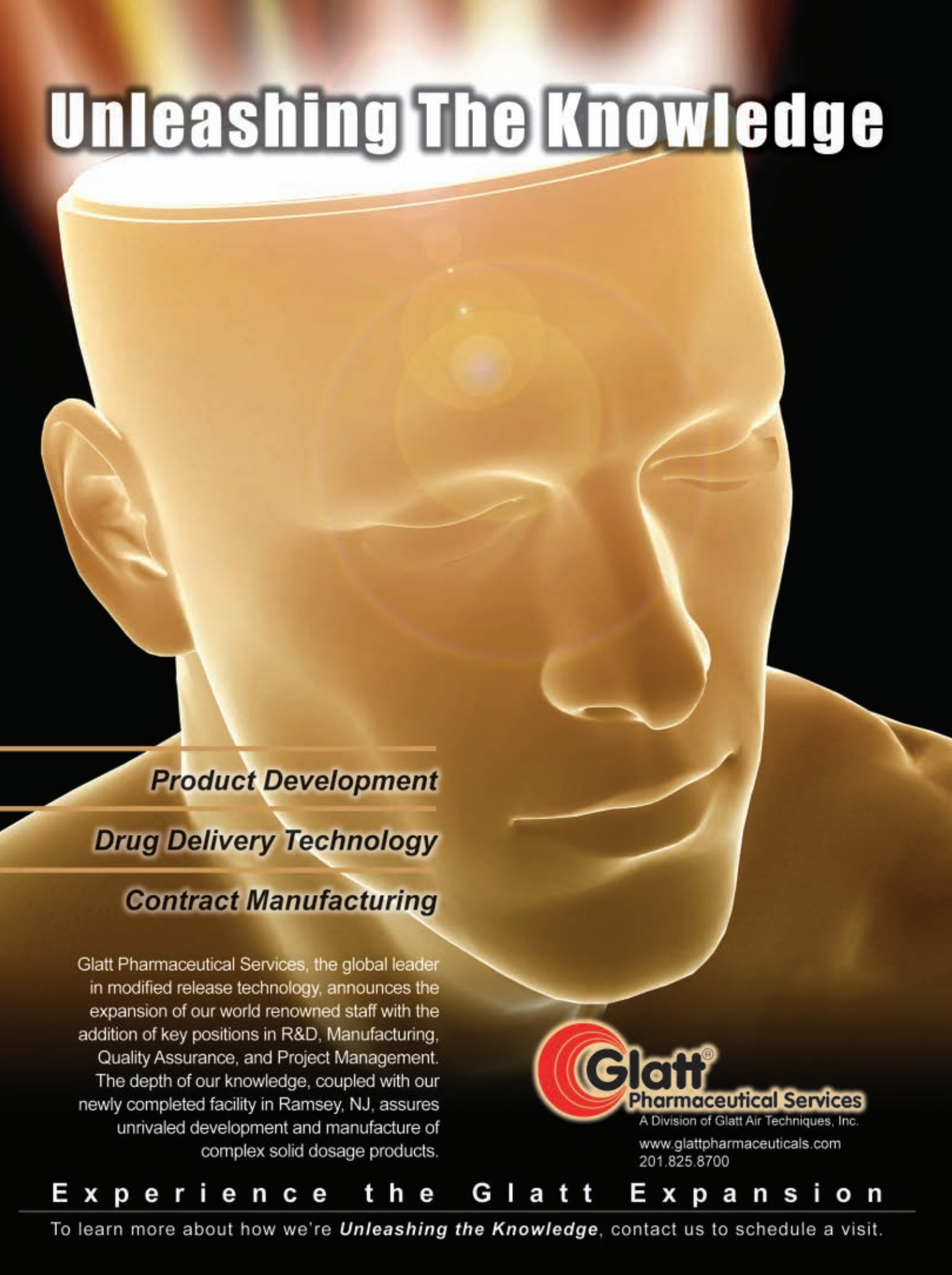
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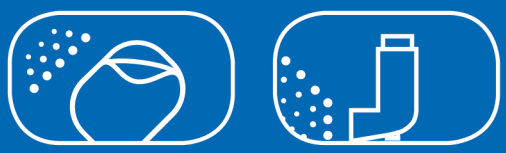

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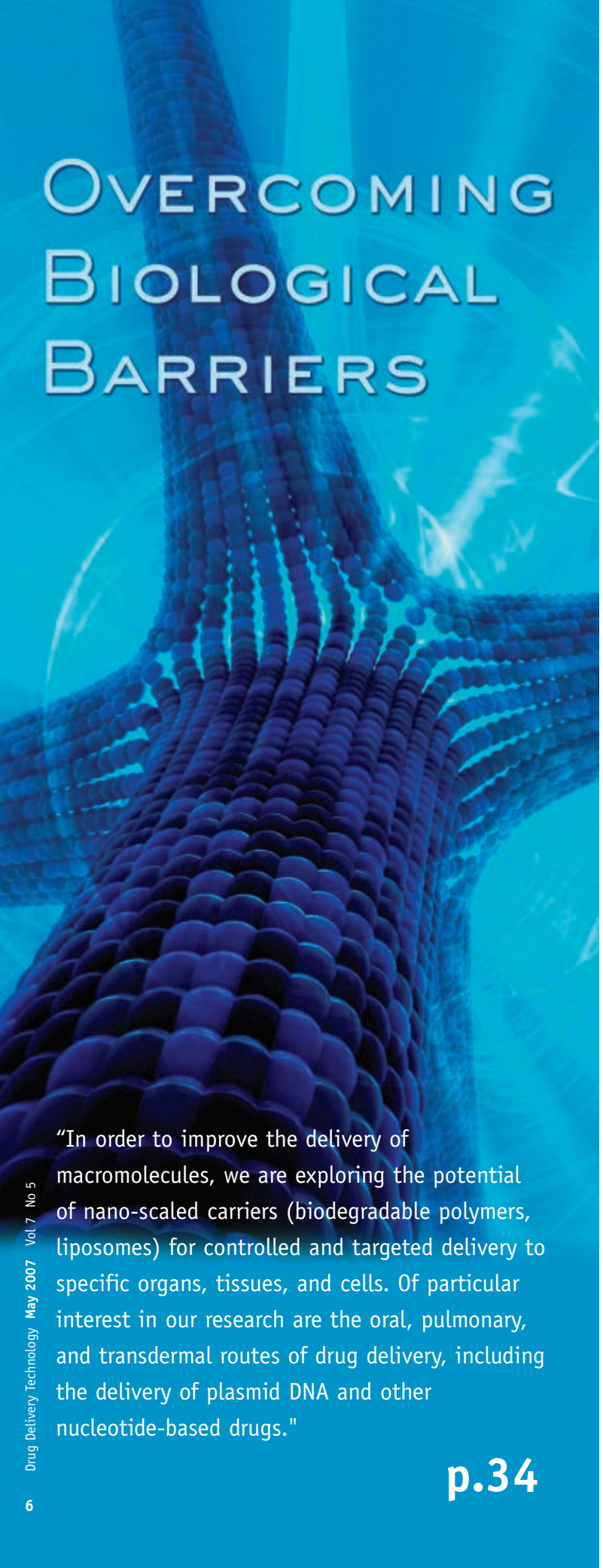

"In order to improve the delivery of macromolecules, we are exploring the potential of nano-scaled carriers (biodegradable polymers, liposomes) for controlled and targeted delivery to specific organs, tissues, and cells. Of particular interest in our research are the oral, pulmonary, and transdermal routes of drug delivery, including the delivery of plasmid DNA and other nucleotide-based drugs."

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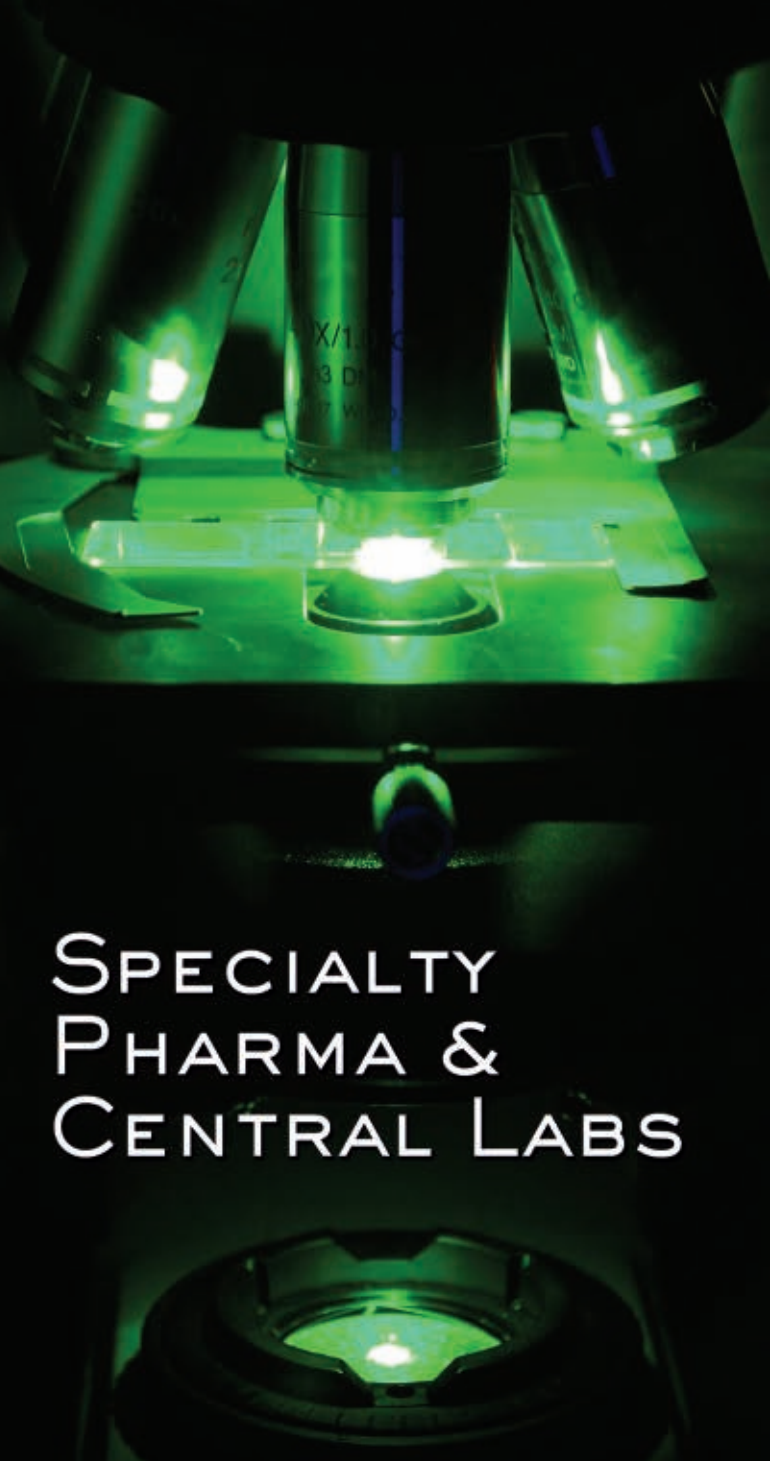

Specialty Pharma & Central Labs

"With R&D spending expected to reach $140 billion by 2009, the CL industry is poised for continued growth. Generating $1.8 billion dollars in 2006, the industry is expected to grow an average of 12% to 13% a year over the next 4 years, reaching $2.9 billion by 2009. How much of this growth is dependent on the relationships CLs forge with Specialty Pharma?"

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Market News and Trends

Innovative Pulmonary & PEGylation-Based Therapeutic Product Development Drives Nektar

Innovative pulmonary and PEGylation-based therapeutic product development is the focus of two new business units recently created at Nektar Therapeutics, the company recently announced. Nektar also announced the creation of a new global communications team to expand and fortify investor and analyst relations.

"We have focused our strongest leaders on our core technologies to accelerate the development of breakthrough pulmonary and PEGylation-based therapeutics to help patient and medical professionals," said Nektar President and Chief Executive Officer Howard W. Robin. "And we have hired two experienced communications professionals, who have strong ties with the investment, analyst, medical, and media communities, which will not only improve transparency with these stakeholders but also enable us to better articulate our value proposition and corporate developments."

Nektar PEGylation technology can enhance the properties of therapeutic agents by increasing drug circulation time in the bloodstream, decreasing immunogenicity and dosing frequency, increasing bioavailability and improving drug solubility and stability. It is a technique in which non-toxic polyethylene glycol (PEG) polymers are attached to therapeutic agents, and it is applicable to most major drug classes, including proteins, peptides, antibody fragments, small molecules, and other drugs.

Nektar is pioneering new applications for its PEGylation platform technology, including the PEGylation of small molecules to reduce blood brain barrier penetration. The first product that the company is developing using this platform is NKTR-118 (PEG-naloxol oral), which applies the company's advanced PEGylation technology to address opioid-induced constipation, a debilitating side effect of opioid treatments. NKTR-118 combines Nektar's Advanced PEGylation technology with naloxol, a derivative of the opioid-antagonist drug naloxone. A Phase I study indicates that NKTR-118 may have the potential to mitigate the constipation side effect from opioid use, without hampering the painkilling properties of opioid drugs in the central nervous system by reducing blood brain barrier penetration.

In addition, Nektar is developing NKTR-102 (PEG-irinotecan), a PEGylated small molecule invented by Nektar using its leading PEGylation technology. It is a PEGylated form of irinotecan, a chemotherapeutic agent used for the treatment of solid tumors. In preclinical studies in tumor-bearing mice, NKTR-102 resulted in significantly higher reduction in tumor growth than irinotecan in colon, lung, and breast tumors. Furthermore, preclinical studies revealed that NKTR-102 was well-tolerated with significant reduction of neutropenia and diarrhea, two debilitating side effects of non-PEGylated irinotecan. Nektar PEGylation Technology is also currently used in eight additional approved partnered products in the US or Europe, including Roche's PEGASYS for hepatitis C and Amgen's Neulasta for neutropenia.

Nektar Pulmonary Technology uses innovative molecular formulations and novel delivery devices designed for ease-of-use to improve or enable administration of medicines to and through the lungs for both lung diseases and systemic conditions. The cornerstone of the pulmonary technology is the development of fine, aerodynamic drug particles for efficient dispersibility and reproducible delivery. As a non-invasive alternative to injection, the pulmonary delivery route offers opportunities for improved and innovative drug delivery and greater patient compliance. In addition, pulmonary delivery offers rapid onset of action and more efficient and targeted treatment of lung disorders. Partnered with Pfizer, Nektar developed the core technologies used for Exubera (insulin human [rDNA origin]) Inhalation Powder, including the formulation and particle engineering for the insulin powder, the filling and packaging techniques for the insulin blister, and the Exubera Inhaler with its components. Exubera is the first approved inhaled insulin and is considered an important advancement in the treatment of diabetes that could help adult patients manage their disease. Nektar manufactures the Exubera Inhalers and supports the manufacturing of the powder processing for the insulin powder. The company also has a proprietary inhaled anti-infective product currently in clinical development and four additional pulmonary products in the clinic with strategic partners, including tobramycin inhalation powder in Phase III trials for lung infections in cystic fibrosis patients by Novartis AG. In addition, Nektar is developing NKTR-061 (inhaled amikacin) for patients with hospital-acquired pneumonia that need mechanical ventilation or patients on ventilators who contract ventilator-associated pneumonia who have high morbidity and mortality rates, in spite of available broad spectrum intravenous antibiotics to treat these infections. This anti-infective platform is designed to treat pneumonias in this difficult-to-treat ventilated patient population.

Greystone Pharmaceuticals & 3M Health Care Announce Supply & Distribution Agreement

Greystone Pharmaceuticals, Inc. recently announced it has signed an agreement with 3M Health Care Limited of Loughborough, England, for the supply and distribution of Greystone's advanced wound care dressing, DerMax, in the UK. Under the agreement, 3M Health Care Limited will brand and distribute DerMax in the UK. Greystone's European wound care products subsidiary, Dermagenics Europe, BV, will manufacture the product for 3M.

The product covered by the agreement is currently marketed throughout the European Union by Dermagenics Europe under the trade name DerMax. 3M will market the product under its own brand name, which has not yet been announced.

DerMax is indicated for use as a wound dressing to manage pressure ulcers (stages I-IV), stasis ulcers, diabetic skin ulcers, skin irritations, cuts, and abrasions. It is the first wound care product allowed to claim the ability to down regulate the production of certain protein enzymes called Matrix Metallo-Proteinases (MMPs). Reducing the production of elevated MMPs is believed to be important to the healing of many chronic and acute wounds.

"Greystone is thrilled to be involved with 3M in this venture, to deliver our product to patients with hard to heal wounds in the UK," said Greg Pilant, Greystone's Chairman. "Greystone continues to grow as an international company, and our success is solidified through this relationship with a first-class company like 3M."

Gary Stapleton, Director, 3M Health Care, commented, "3M welcomes the addition of this innovative dressing to our advanced skin care and wound management portfolio. It offers another exciting solution for our customers to manage their most complex wounds and to deliver optimum patient care."

Founded in 1996, and currently headquartered in Fort Myers, Florida, with additional offices in Memphis, Tennessee, and Kaatshevall, the Netherlands, Greystone Pharmaceuticals is a medical products research and development company that has developed a proprietary advanced chronic wound care technology for the treatment of non-responsive wounds, particularly in diabetic patients.

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Market News and Trends

Access Pharmaceuticals Signs Definitive Merger Agreement With Somanta Pharmaceuticals

Access Pharmaceuticals, Inc. and Somanta Pharmaceuticals, Inc. recently announced they have signed a definitive merger agreement by which Access will acquire Somanta. The companies had previously announced the execution of a non-binding Letter of Intent regarding the merger. Under the terms of the merger agreement, Access will issue 1.5 million shares of common stock to Somanta stockholders in exchange for all the outstanding capital stock of Somanta. The merger agreement has been approved by the boards of both companies. In addition, Access has received voting agreements from certain Somanta shareholders representing approximately 81% of Somanta's outstanding common shares and approximately 60% of its outstanding preferred shares under which the parties, subject to certain limited exceptions, have granted an irrevocable proxy to vote their Somanta shares in favor of the merger. The closing of the merger is subject to the fulfillment of certain conditions contained in the merger agreement. The parties expect the transaction to be completed during the summer.

With the proposed acquisition of Somanta, Access will acquire four novel anti-cancer compounds in development, one of which is currently in Phase II clinical trials. Each of the drug candidates acts by a unique mechanism of action and has the potential to target a wide range of cancer types.

"We believe this transaction will immediately strengthen our drug pipeline, enhancing Access' franchise value within the oncology space," said Stephen R. Seiler, Access' President and CEO. "In addition to offering a clinical-stage drug candidate, Somanta's preclinical pipeline is highly diversified with each anti-cancer compound having its own novel mode of action, which can be applied to a wide range of cancer types."

Somanta Pharmaceuticals is a company focused on the development of novel oncology compounds and anti-cancer agents. Somanta's lead clinical product Sodium Phenylbutyrate (PB) is currently in Phase II development and is being developed with its partner, Virium Pharmaceuticals. In National Institute of Health sponsored trials, PB has demonstrated the greatest activity in CNS cancers, several of which are "orphan" indications, such as Glioblastoma Multiforme. Moreover, promising data has also emerged, which suggests PB may be an effective therapy for certain blood cancers and other solid tumors. PB has been well tolerated; its safety profile has generally been established due to its many years of clinical use in pediatrics for inherited urea cycle disorders. Somanta's preclinical drug candidates include Angiolix, Prodrax, and Alchemix. Angiolix is a humanized monoclonal antibody that appears to induce cell death selectively to tumor blood vessels using a different mode of action than VEGF- oriented therapies. Prodrax is a novel family of prodrugs that enables compounds to remain inert until they reach the hypoxic region of tumors where they become toxic, thus targeting tumor cells that are typically difficult to kill. Alchemix is a pan-target inhibitor that is effective in tumor cells resistant to conventional chemotherapy by targeting and irreversibly binding to DNA. Somanta believes Prodrax and Alchemix have the ability to overcome many different pathways of drug resistance, and will be studied in a broad range of cancers, including lung, colon, ovarian, and renal. Proof-of-principle preclinical studies have been completed in both of these compounds, and Phase I dose escalation trials are being planned. Somanta has prepared clinical development plans for all preclinical projects.

Access Pharmaceuticals, Inc. is an emerging biopharmaceutical company that develops and commercializes propriety products for the treatment and supportive care of cancer patients. Access' products include ProLindac, currently in Phase II clinical testing of patients with ovarian cancer, and MuGard for the management of patients with mucositis. The company also has other advanced drug delivery technologies, including Cobalamin-mediated targeted delivery and oral drug delivery.

Emisphere Appoints New President & Chief Executive Officer

The Board of Directors of Emisphere Technologies, Inc. recently announced it has appointed Michael V. Novinski to the position of President and Chief Executive Officer, effective immediately. Previously, Mr. Novinski was President of Organon USA Inc., a business unit of Organon BioSciences Inc, for the past 4 years. During his tenure as President, Organon USA received FDA approval for a number of ethical pharmaceutical products in the areas of Women's Healthcare, Fertility, Neuroscience, Anti-thrombotics, and Anesthesia.

Mr. Novinski, who will assume his duties at the company beginning this May, replaces Mr. Lewis Bender, who was appointed interim Chief Executive Officer on January 16, 2007. Mr. Bender will continue in the role of acting CEO until that time. Mr. Novinski brings to Emisphere a significant level of leadership and experience in the development of pharmaceutical products. He has over 28 years of industry and specialty product experience, which is critical to the company as it moves to late-stage product development. Mr. Novinski held several senior executive positions within Organon BioSciences prior to becoming President of Organon USA, and served on its board for the past 4 years. On March 12, 2007, Akzo Nobel announced the intended sale of Organon BioSciences to Schering-Plough for $14.4 billion.

"I am very excited about this opportunity to join Emisphere," said Mr. Novinski. "The company's technology is exciting and well advanced, and I believe it will yield important improvements in healthcare. Many key Emisphere programs have the potential to create brands with substantial value and unique profiles and benefits for both prescribers and patients."

Mr. Novinski was appointed Director of Marketing in 1992 at Organon and later became the Vice President of the Department. For 10 years, he led the company's marketing efforts and directed the launch of eight new brands in the US market. In addition, from June 2000 through December 2001, he was General Manager for Organon Sanofi-Synthelabo LLC. In 2002, he became Executive Vice President of Operations and Marketing for Organon International. At the same time, he was elected as a Board Member for Organon International. In February 2003, Mr. Novinski was named President of Organon USA. In June 2003, he assumed responsibility for Worldwide Business Development and Lifecycle Management and led collaborative agreements with a number of pharmaceutical companies, including Pfizer, Sanofi-Aventis, and Ligand Pharmaceuticals. Mr. Novinski earned his BS with a major in Biology from Washington and Jefferson College in Washington, PA. He also studied under fellowship at the University of Pittsburgh Medical School, Department of Microbiology.

Emisphere Technologies, Inc. is a biopharmaceutical company pioneering the oral delivery of otherwise injectable drugs. Emisphere's business strategy is to develop oral forms of injectable drugs, either alone or with corporate partners, by applying its proprietary eligen technology to those drugs or licensing its eligen technology to partners who typically apply it directly to their marketed drugs. Emisphere's eligen technology has enabled the oral delivery of proteins, peptides, macromolecules, and charged organics. Emisphere and its partners have advanced oral formulations or prototypes of salmon calcitonin, heparin, insulin, parathyroid hormone, human growth hormone, and cromolyn sodium into clinical trials. Emisphere has strategic alliances with world-leading pharmaceutical companies.

Market News and Trends

Eurand Announces Positive Phase III Clinical Study Results for Pancreatic Enzyme Replacement Therapy

Eurand, a global specialty pharmaceutical company, recently unveiled data from two Phase III clinical trials on its lead product candidate, Zentase, formerly EUR-1008, for the treatment of Exocrine Pancreatic Insufficiency (EPI). The US FDA granted fast track status for Zentase for the treatment of EPI. The company intends to file for FDA approval during the second quarter of 2007 for this potentially first-in-class pancreatic enzyme replacement therapy.

Zentase is a zero-overfill, highly-stable, porcine-derived pancreatic enzyme replacement therapy used to treat EPI and was designed to meet FDA guidelines for pancreatic enzyme replacement products. According to the FDA, no currently marketed pancreatic enzyme product (PEP) has been shown to demonstrate consistent enzyme bioactivity that results in predictable safety and effectiveness. Many of the current enzyme products contain overfill to compensate for product instability during shelf-life, which can lead to variability in dosing. As a highly-stable product, Zentase does not require overfill. Currently, there are no FDA-approved PEPs for the treatment of EPI on the market in the US.

"We are excited to present the results of our Phase III studies supporting Zentase for the full spectrum of cystic fibrosis patients suffering from EPI, including those needing limited supplementation to those with very aggressive enzyme deficiency," said Gearoid Faherty, Eurand Chairman and CEO.

Zentase met all primary and secondary endpoints in two Phase III clinical trials. The studies were designed to determine whether the product candidate could alleviate serious malabsorption associated with EPI in both a pediatric (younger than 7 years) and an older patient population.

Study results showed a clinically and statistically significant increase in the coefficient of fat absorption (CFA) in patients treated with Zentase. The mean percentage of CFA in patients receiving Zentase was 88.3% versus 62.8% in patients receiving placebo ($p < 0.001$). Treatment guidelines suggest that the CFA should be at least 85% in cystic fibrosis (CF) patients.

"The protocols for these trials were reviewed by the FDA and developed in collaboration with the Cystic Fibrosis Foundation (CFF). We want to thank the CFF for their support," added Mr. Faherty.

This randomized, double-blind, placebo-controlled, cross-over study evaluated CF patients with EPI aged 7 years and older. Patients treated with Zentase showed a statistically significant increase in the coefficient of fat absorption and coefficient of nitrogen absorption (CNA) as compared to those receiving a placebo. They also had fewer symptoms associated with impaired absorption, such as bloating, flatulence, pain, and evidence of fat in stools.

Moreover, in all study patients, regardless of starting levels while taking placebo, Zentase returned CFA and CNA absorption levels to ranges considered normal in healthy patients. Eurand believes this suggests Zentase can provide the level of enzyme supplementation required by cystic fibrosis patients with different levels of EPI.

"I believe the results of this successful trial demonstrated the efficacy and safety of Zentase," said James E. Heubi, MD, Professor and Associate Chair for Clinical Research of Pediatrics at Children's Hospital Medical Center in Cincinnati, OH. "During the study, the level of fat absorption achieved with Zentase was very high and close to levels seen in healthy patients, even without the use of proton pump inhibitors (PPIs). This high fat absorption, without relying on PPIs, could significantly reduce the number of pills patients take each day."

This open-label study in CF patients under the age of 7 involved a 7-day dose-stabilization period followed by a 7-day treatment period. The study evaluated the percentage of "responders," or those patients without excess fat in stools and without signs and symptoms of malabsorption after 1 and 2 weeks of treatment. Secondary endpoints included weight change, nutritional status, stool frequency and consistency, incidences of bloating, pain, and flatulence as well as physician and parent or guardian judgment of clinical symptoms improvement. In the study, malabsorption symptoms were significantly lower at the end of treatment than at screening, consistent with control of malabsorption symptoms with Zentase in the pivotal Phase III trial.

Market News and Trends

Sciele Pharma, Inc. to Acquire Alliant Pharmaceuticals $122 Million

Sciele Pharma, Inc. recently announced it has reached an agreement to acquire Alliant Pharmaceuticals, Inc., a privately held pediatric specialty pharmaceutical company headquartered in Alpharetta, Georgia. Sciele will pay $122 million in cash for Alliant, which includes approximately $12 million in indebtedness to be paid at closing. The agreement also includes potential payments of up to $55 million based on meeting certain profit targets and product development targets for Alliant's products. The agreement was unanimously approved by each company's Board of Directors. This transaction is subject to approval under the Hart-Scott-Rodino Antitrust Improvement Act as well as other customary closing conditions, which is expected to be completed during the second quarter of 2007.

Alliant Pharmaceuticals is expected to generate revenues of approximately $50 million to $60 million for the full-year 2007. Alliant has a field force of approximately 85 people, who will be retained by Sciele and will form Sciele's new Pediatric sales division. Alliant's pediatric product portfolio under promotion includes Orapred and Orapred ODT for asthma; Allegra Oral Suspension for allergies; Methylin Oral Solution and Methylin Chewable Tablets for ADHD; Lindane for head lice and scabies; and Rondec Syrup and Rondec DM Oral Drops for allergies, coughs, and colds.

Sciele expects the acquisition of Alliant to provide diversification and strategic expansion into pediatrics; well-recognized branded pediatric prescription products with growth potential; a solid base of unique or patent-protected products; product pipeline opportunities through life-cycle management, particularly with Rondec; and similar pay-for-performance business model with platform for potential acquisitions.

Patrick Fourteau, Sciele's Chief Executive Officer and President, said, "The acquisition of Alliant gives Sciele a much larger presence in pediatrics, a therapeutic area in which we are involved with our Furadantin product, and will enable us to maximize the potential of glycopyrrolate, a Sciele product that is in pivotal Phase III clinical trials for pediatric chronic, moderate-to-severe drooling. We have known Alliant since its inception, and we believe the integration between the two companies will be straightforward as we both have similar pay-for-performance models with an emphasis on speed of execution." Mr. Fourteau also noted, "This acquisition should be an excellent revenue and earnings growth opportunity for Sciele, and meets our disciplined investment parameters of doing acquisitions that are accretive to earnings in the near-term."

Mark Pugh, Chief Executive Officer and President of Alliant, added, "We have successfully grown our company by focusing on marketing innovative products for children. We have significantly increased sales in 2006 to more than $40 million from less than $1 million when the company was founded in 2004. We believe that combining the strengths of Alliant and Sciele will enable us to accelerate growth of our existing product line and enable us to more rapidly pursue product development opportunities, utilizing the financial strength of Sciele."

Alliant Pharmaceuticals, Inc. is a specialty pharmaceutical company focused on acquiring, developing, and commercializing proprietary products for the pediatric and pediatric specialty markets. While a unique niche, the pediatric market is one of the fastest-growing pharmaceutical sectors. Alliant's product focus includes the sub-specialties of allergy and immunology, psychiatry, neurology, dermatology, urology, and infectious diseases.

Sciele Pharma, Inc. is a pharmaceutical company specializing in sales, marketing, and development of branded prescription products focused on cardiovascular/diabetes and women's health. The company's cardiovascular/diabetes products treat patients with high cholesterol, hypertension, high triglycerides, unstable angina, and type 2 diabetes, and its women's health products are designed to improve the health and well-being of women and mothers and their babies.

BDSI Announces Positive Phase III Clinical Trial Results for BEMA™ Fentanyl

BioDelivery Sciences International, Inc. (BDSI) recently announced statistically significant results with BEMA Fentanyl in cancer patients with breakthrough pain in its pivotal Phase III efficacy clinical trial for the product. The results are based on achievement of the primary efficacy endpoint of the trial, Summary of Pain Intensity Difference (SPID), compared to placebo. The results demonstrated that patients treated with BEMA Fentanyl showed a statistically significant improvement on the primary efficacy endpoint at 30 minutes (SPID 30) compared to placebo ($p < 0.004$), meaning a greater reduction in pain. Eighty (80) patients participated in the double-blind, placebo-controlled portion of the study.

BEMA Fentanyl consists of a small, dissolvable polymer disc formulated with the opioid narcotic fentanyl for application to the buccal membranes. Upon administration, BEMA Fentanyl is designed to deliver a rapid, reliable dose of drug across mucous membranes.

Dr. Andrew Finn, BDSI's Executive Vice President of Product Development, said, "We are obviously very pleased with these efficacy results. Only five patients (approximately 3% of those patients entering the initial titration phase of the study) were unable to achieve adequate pain relief. We believe this high level of pain control is attributable to the efficient, reliable absorption from the buccal mucosa, the ease of application of the BEMA Fentanyl product, and the ability to titrate across a wide range of doses up to and including our 1200-mcg dose. Importantly, the results also demonstrated that BEMA Fentanyl was well-tolerated by patients in the trial, with no reported drug-related changes to the oral mucosa, which is important for cancer patients who may also have oral ulcerations as a result of a weakened immune system."

"Once we have the remainder of the data analyzed, including the secondary efficacy parameters, our plan will be to submit the data to a scientific conference for presentation. We will do that at the first available opportunity and at the most appropriate forum. However, we wanted to be able to share the news that we have achieved the most important endpoint, namely the SPID 30, at this time," concluded Dr. Finn.

Dr. Mark Sirgo, President and CEO of BDSI, added, "These Phase III results demonstrate that the BEMA delivery system is effective in delivering a significant level of fentanyl over a range of doses to manage the breakthrough cancer pain that occurred in these patients. The results also demonstrated that the dosage form was convenient and comfortable to use. Importantly, we believe that the dose linearity (ie, double the dose and double the plasma concentration of the drug) demonstrated in our previously announced pharmacokinetic studies up to the 1200-mcg dose provide the ability to relieve breakthrough cancer pain in a higher percentage of patients. This was demonstrated by the fact that only 3% of patients who entered the titration phase did not proceed to the double-blind, placebo-controlled phase of the study because they could not achieve adequate pain control. Overall, given the efficacy profile of BEMA Fentanyl as demonstrated during this Phase III study, along with the apparent ease of use and comfort of the BEMA disc, we remain confident that BEMA Fentanyl has the potential to play an important role in the future treatment of breakthrough cancer pain."

Tepha Receives FDA Clearance for First Medical Device Derived From New Class of Biopolymers

Tepha, Inc., a privately held medical device company, recently announced the FDA has cleared its TephaFLEX Absorbable Suture product for marketing in the US. The TephaFLEX Absorbable Suture is the first medical device derived from a new class of biopolymers that is the product of patented recombinant DNA technology developed by Tepha and licensed from the Massachusetts Institute of Technology (MIT). The TephaFLEX material has biological and mechanical properties that are uniquely suited for implantable medical devices. Tepha and its corporate partners are pursuing a wide array of medical device applications for the TephaFLEX technology.

Dr. Simon Williams, President and CEO of Tepha, said, "We are delighted the FDA has cleared the TephaFLEX Absorbable Suture and determined that devices of this type will be regulated as class II (510k) devices. The company's novel biopolymer technology can now be further applied to the development of a range of medical devices to meet unmet clinical needs."

TephaFLEX polymer is a member of a new class of biopolymers with mechanical and biological properties that are uniquely applicable to implantable medical devices when compared to conventional synthetic and biologically derived polymers. Compared to synthetic polymers, such as polylactic acid (PLA) and polyglycolic acid (PGA), TephaFLEX material is tougher and more flexible with an absorption rate and degradation profile that are compatible with human tissue repair and replacement applications. However, unlike other biopolymers, such as collagen and hyaluronate, TephaFLEX polymer is a thermoplastic and can be fabricated into virtually any shape or form, including fibers, films, tubes, foams, textiles, microspheres, and molded constructs, using a wide range of conventional melt and solvent processing techniques.

The TephaFLEX Absorbable Suture is engineered to be one of the strongest absorbable fibers known, offering up to 50% greater tensile strength than currently marketed monofilament absorbable sutures. In addition to high strength, the TephaFLEX Absorbable Suture also offers surgeons improved flexibility, good knot security, and prolonged strength retention when implanted.

The new class of biopolymers to which the TephaFLEX polymer belongs is a product of Tepha's patented recombinant DNA technology. This technology allows the company to engineer materials with a range of biological and mechanical properties for specific tissue repair and replacement applications. After the repair process, the biopolymers degrade in the body to natural metabolites in a biocompatible, cell-friendly manner.

Professor Anthony Sinskey of the MIT Department of Biology, and a co-inventor of the recombinant DNA technology, added, "This breakthrough technology will allow Tepha and its partners to progress beyond the constraints of traditional medical device materials to offer new solutions for the unmet needs of physicians and their patients."

Several leading medical device companies have recognized the unique properties profile of TephaFLEX material for human tissue repair and replacement applications. Tepha's current corporate partners are pursuing a wide array of products, including sutures, surgical meshes for orthopedic and hernia repair, anti-adhesion films, hemostats, intra-cardiac devices, absorbable stents, ligament and tendon repair and replacement devices, embolization agents, and drug delivery systems. Tepha's current partners include Aesculap AG, HemCon Medical Technologies, LifeCell Corporation, NMT Medical, and Tornier, Inc.

Tepha was formed as a sister company to Metabolix, Inc. Both companies are engaged in commercializing new polymers derived from recombinant DNA technology licensed from the Massachusetts Institute of Technology. Tepha is focused specifically on in vivo medical applications of the technology. Metabolix, which recently had its initial public offering, is focused on using the technology in the development of environmentally sustainable alternatives to petrochemical-based plastics, fuels, and chemicals.

Market News and Trends

Disposable Insulin Nanopump Marks Major Breakthrough in Diabetes Treatment

Debiotech and STMicroelectronics recently announced a strategic cooperation agreement aimed at manufacturing and delivering to the market a unique miniaturized insulin-delivery pump. The Nanopump, which relies on microfluidic MEMS (Micro-Electro-Mechanical System) technology, is a breakthrough concept that allows a tiny pump to be mounted on a disposable skin patch to provide continuous insulin infusion. The Nanopump will enable substantial advancements in the availability, treatment efficiency, and the quality of life of diabetes patients. The original technology was awarded the Swiss Technology Award in 2006, and this agreement brings it closer to the market.

Insulin pump therapy, or Continuous Subcutaneous Insulin Infusion (CSII), is an increasingly attractive alternative to individual insulin injections that must be administered several times a day. With CSII, the patient is connected to a programmable pump attached to a storage reservoir, from which insulin is infused into the tissue under the skin. Continuous delivery throughout the day more closely mimics the natural secretion of insulin from the pancreas.

The highly miniaturized disposable insulin pump combines Debiotech's expertise in insulin delivery with ST's strengths in manufacturing high-volume silicon-based microfluidic devices. Microfluidic technology allows the flow of very small amounts of fluids to be electronically controlled. This pump represents a significant step in the development and adoption of CSII therapy, and the leading-edge technology will also find applications in many other biomedical applications.

Currently, existing insulin pumps are about the size of a pager. The new ST- enabled Debiotech miniaturized MEMS device is about one quarter the size of these existing pumps and can be worn as a nearly invisible patch on the skin. The small size frees the patient from concerns with holding the pump in place and concealing it under clothing.

The MEMS-based Nanopump also provides better control of the administered insulin doses. Dosing precision is a critical factor in treatment efficacy and contributes to reducing adverse long-term consequences. The Nanopump is able to control delivery at the nanoliter level, very close to the physiological delivery of insulin. The device prevents over-dosing and detects under-delivery, occlusion, air bubbles, and other potential malfunctions in the pump to further protect patients. As a disposable device, manufactured using high-volume semiconductor processing technologies, the MEMS-based Nanopump will also be much more affordable, allowing the patient or the health system to avoid the typical up-front investment associated with current pump solutions.

The insulin Nanopump, developed by Debiotech and industrialized by ST, represents the first use of microfluidic MEMS technology in diabetes treatment. Functional samples have already been produced, and the two partners expect that a fully industrialized product, in the form of a disposable cartridge, will be available in selected markets in 2008. Debiotech will remain responsible for the commercialization of the product through its licenses with major players in the medical device market.

The industrialization efforts will leverage STMicroelectronics' growing experience in the biomedical market. Other biotech programs within ST's Microfluidic Division include the In-Check Lab-on-Chip platform, currently being applied to the detection of sepsis and Avian flu.

"ST's increasing focus on applying its semiconductor manufacturing processes and growing experience in microfluidic biotech applications affords us the potential to improve lives for millions of people around the world," said Anton Hofmeister, Group Vice President and General Manager of ST's Microfluidic Division. "Working with Debiotech, a leading developer of innovative biomedical applications, we are committed to the industrialization of the insulin Nanopump that aspires to push the boundaries of diabetes treatment."

Baxter Healthcare Presents Phase I Inhaled Insulin Study Results

Baxter Healthcare Corporation recently announced results of a Phase I study that evaluated pulmonary insulin produced with Baxter's PROMAXX microsphere technology and administered using a small, standard dry powder inhaler. Baxter presented the Phase I data at the Respiratory Drug Delivery Europe 2007 Conference in Paris.

The study demonstrates that the insulin powder can be effectively administered to the deep lung using an off-the-shelf dry powder inhaler designed for upper airway drug delivery. A total of 30 subjects participated in the randomized, two-way crossover study conducted in Germany. Each subject received in randomized fashion a single dose of 10 International Units of insulin through subcutaneous injection (SC) in one period, and 6.5 mg of the inhaled insulin microspheres, called recombinant human insulin inhalation powder (RHIIP) in the other period.

RHIIP is made using Baxter's proprietary PROMAXX formulation technology. Unlike other dry powder formulations of insulin, RHIIP is 95% insulin and does not rely on the use of inactive ingredients to facilitate delivery to the deep lung. In this study, no serious adverse events were reported and no subjects withdrew from the study due to an adverse event. All adverse events were mild in severity. The most common reported treatment-emergent adverse event was phlebitis. There were no reported episodes of cough or shortness of breath in this study.

Study data show that RHIIP had a faster onset of action than SC (time to reach 10 percent of total area under the glucose infusion rate (GIR) curve 73 vs 95 min.; GIR-tmax 173 versus 218 min., $p < 0.0001$). Duration of action (371 vs 366 min.) and total metabolic effect (GIR-AUC0-10 h of 2,734 vs 2,482 mg/kg) were comparable. Pharmacokinetic results were in accordance with these findings: RHIIP was absorbed faster (time to reach 10% of total area under the insulin curves 44 vs 66 min., $p < 0.0001$), and maximum insulin levels were reached earlier (86 vs 141 min., $p = 0.002$). The bioavailability of RHIIP relative to SC was more than 12%.

"These encouraging results show the bioavailability of RHIIP compare favorably with that observed for many other inhaled insulin preparations, even though the standard type of inhaler used in this study was not optimized for delivery of insulin to the deep lung," said Dr. Tim Heise, Profil Institut fur Stoffwechselforschung GmbH in Neuss, Germany, and Principal Investigator for the study. "RHIIP may have the potential to achieve even higher bioavailability through further improvements in the insulin delivery technique, and this will be the subject of further studies."

"We are very excited to share these results that illustrate the strong potential of PROMAXX technology," said Peter J. Arduini, Corporate Vice President and President of Baxter's Medication Delivery business. "We look forward to working with partners to apply this technology broadly to the formulation of therapeutic proteins and peptides."

Boston Scientific to Buy Celsion's Prolieve Assets for $60 Million

Celsion Corporation recently announced it has entered into an Asset Purchase Agreement under which Boston Scientific Corporation will purchase the company's Prolieve assets for $60 million, subject to reduction under certain circumstances. The Asset Purchase Agreement contains customary terms and conditions, including approval by Celsion's stockholders.

The Asset Purchase Agreement is different in certain key aspects from the Transaction Agreement entered into between Celsion and Boston Scientific in January 2003, as amended in August 2005. In particular, instead of paying $60 million for the Prolieve assets on the date of closing, Boston Scientific will pay $30 million at closing, $15 million on the first anniversary of the closing, and up to $15 million on the second anniversary of the closing. The $30 million payable at closing will be reduced by approximately $17 million, representing the principal and accrued interest due on three promissory notes previously issued by Celsion to Boston Scientific. The Asset Purchase Agreement also contains customary indemnification provisions, including for breaches of representations, warranties, and covenants contained in the Asset Purchase Agreement.

Stockholders will be asked to approve the transaction at the company's annual meeting of stockholders currently scheduled in June 2007.

"We are pleased that Boston Scientific has decided to exercise its option to purchase our Prolieve assets earlier than required, well in advance of the expiration of the option, under its original agreement with Celsion," said Michael H. Tardugno, Celsion's President and Chief Executive Officer. "The sale of the Prolieve assets will complete Celsion's transition to an oncology-focused drug company, enabling us to fully focus our resources on the development of our lead drug ThermoDox. The installment-based payout will provide immediate non-dilutive funding sufficient for us to initiate and make substantial progress with our lead Phase III and II clinical trials for primary liver and recurrent chest wall breast cancers, respectively."

Mr. Tardugno went on to say, "We believe the company's heat-activated liposome technology platform holds great promise of future value creation for our stockholders. The gain generated by the asset sale will result in a significant increase in stockholder equity and put us on schedule to fully comply with the AMEX listing criteria within the timeframe agreed upon with the exchange."

Celsion is dedicated to the development and commercialization of oncology drugs, including tumor-targeting treatments using focused heat energy in combination with heat-activated drug delivery systems. Celsion has research, license, or commercialization agreements with leading institutions, such as the National Institutes of Health; Duke University Medical Center; Massachusetts Institute of Technology; Harbor UCLA Medical Center; Montefiore Medical Center; and Memorial Sloan-Kettering Cancer Center in New York City; Roswell Park Cancer Institute in Buffalo, New York; and Duke University.

Celsion has also developed a microwave-based system, the Prolieve Thermodilatation system, for the treatment of benign prostatic hyperplasia, which is marketed in the US under an exclusive distribution agreement with Boston Scientific Corporation.

Market News and Trends

Halozyme Announces $32.1 Million Private Financing

Halozyme Therapeutics, Inc., a biopharmaceutical company developing and commercializing recombinant human enzymes, recently announced it has entered into a definitive stock purchase agreement with New River Management V, LP for a $32.1 million private placement of newly issued shares of Halozyme common stock. The financing is subject to customary closing conditions, including the receipt of anti-trust clearance, and is not subject to shareholder approval. Upon the satisfaction of the closing conditions, Halozyme will issue 3,500,000 shares of common stock to New River at a price of $9.17 per share. This sale price represents a $0.22 per share premium to the closing price of Halozyme common stock on the date that the parties executed the definitive stock purchase agreement relating to the sale of the shares.

New River is a private investment fund affiliated with Halozyme's largest stockholder, Randal J. Kirk. Halozyme's Board of Directors specifically approved the sale of shares to New River, and the increase in Mr. Kirk's beneficial ownership is not expected to trigger the anti-takeover provisions of Halozyme's existing Stockholder Rights Plan.

The shares of common stock to be sold in the private placement will not be immediately registered under the Securities Act of 1933, as amended, or state securities laws and may not be offered or sold in the United States absent registration with the Securities and Exchange Commission (SEC) or an applicable exemption from the registration requirements. The shares will only be offered and sold to New River, which is an accredited investor pursuant to the rules and regulations of the SEC. The company has agreed to file a registration statement with the SEC on or before November 1, 2007, covering the resale of the shares of common stock to be issued in this private placement.

Halozyme is a biopharmaceutical company developing and commercializing recombinant human enzymes for the drug delivery, palliative care, oncology, and infertility markets. The company's portfolio of products is based on intellectual property covering the family of human enzymes known as hyaluronidases. The company's Enhanze Technology is a novel drug delivery platform designed to increase the absorption and dispersion of biologics. In addition, the company has received FDA approval for two products: Cumulase and Hylenex, for use as an adjuvant to increase the absorption and dispersion of other injected drugs and fluids. The company also has a number of different enzymes in its portfolio that are targeting significant areas of unmet need.

Indevus Pharmaceuticals & Valera Pharmaceuticals Announce Completion of Merger

Indevus Pharmaceuticals, Inc. and Valera Pharmaceuticals, Inc. recently announced the completion of their previously announced merger, which became effective April 18, 2007. Trading in Valera common stock has been discontinued. The merger, which was announced in December 2006, was approved by the stockholders of both companies at meetings held this past April. In addition, Indevus stockholders approved each of the other proposals presented at its meeting.

"We are very pleased with the strategic acquisition of Valera and believe this transaction will be a strong driver of growth for us in the coming years," said Glenn L. Cooper, MD, Chairman and Chief Executive Officer of Indevus. "The completion of the merger firmly establishes Indevus as an emerging leader in the specialty areas of urology and endocrinology and fully leverages our national sales force. We are very excited about our expanded product portfolio and anticipate five new product launches within 2 years, including three products from Valera."

"This is an exciting day for Valera," said David S. Tierney, MD, Chief Executive Officer of Valera. "Becoming part of Indevus creates considerable opportunities for our shareholders, our customers, and our employees."

Under the terms of the merger agreement, each holder of Valera's common stock issued and outstanding immediately prior to the effective time, other than dissenting shares, will receive 1.1337 shares of Indevus common stock for each share of Valera common stock. In addition, these Valera stockholders will receive three contingent stock rights for each of their shares of Valera common stock. The contingent stock rights will become convertible into $1.00, $1.00 and $1.50, respectively, worth of Indevus common stock upon the achievement of particular milestones with respect to three Valera product candidates in development - Supprelin-LA, ureteral stent, and VP003 (Octreotide implant).

Indevus also announced that James C. Gale, formerly Chairman of the Board of Directors of Valera, has been elected as a member of the Board of Directors of Indevus. Mr. Gale, who served as a Valera Director since 2001, is a Managing Director of SMH Capital Inc., a national investment management and investment banking company, and serves as Chief Investment Officer of the Corporate Opportunities Funds and Life Sciences Opportunities Fund, affiliates of SMH Capital.

Indevus is a specialty pharmaceutical company engaged in the acquisition, development, and commercialization of products to treat conditions in urology and endocrinology. The company's marketed products include Sanctura for overactive bladder, which it co-promotes with its partner Esprit Pharma, Inc., and Delatestryl to treat male hypogonadism. The compounds in development include Sanctura XR, the once-daily formulation of Sanctura, Nebido for male hypogonadism, PRO 2000 for the prevention of infection by HIV and other sexually-transmitted pathogens, pagoclone for stuttering, and aminocandin for serious fungal infections, for which the company recently licensed worldwide rights to Novexel S.A.

Valera Pharmaceuticals is a specialty pharmaceutical company focused on developing, acquiring, and commercializing products to treat urology and endocrinology diseases and disorders. Utilizing its innovative Hydron technology, Valera is developing soft, compact, and flexible hydrogel-based implants, which can be designed to release therapeutic agents at a controlled rate for up to 12 months. Vantas, a patent-protected once-per-year implant currently marketed by Valera for the palliative treatment of advanced prostate cancer, employs this drug delivery technology.

Neuromed Licenses Phase III Chronic Pain Product From ALZA; Neuromed to Make Up-Front Payment of $30 Million

Neuromed Pharmaceuticals Ltd., a biopharmaceutical company developing next-generation chronic pain drugs, recently announced it has licensed from ALZA Corporation the exclusive US rights to develop and commercialize OROS Hydromorphone, an extended-release formulation of a potent opioid analgesic in Phase III clinical development.

Under the terms of the agreement, Neuromed will make an up-front payment of $30 million, additional regulatory milestone payments, and will pay royalties based on commercial sales of the product. Neuromed will develop and market the product in the US, while ALZA will retain the rights to develop and market the product in other countries. ALZA will manufacture the product for Neuromed as well as for other markets in which the product is sold.

OROS Hydromorphone was developed by ALZA and uses the OROS PUSH-PULL delivery system to release the opioid at a controlled rate. OROS Hydromorphone has been approved in Germany and other European countries and is marketed by Janssen-Cilag under the name JURNISTA. The product received an Approvable Letter from the US FDA in October 2000. Neuromed anticipates that one successful adequate and well-controlled clinical trial will be needed to support approval of OROS Hydromorphone in the US.

"Our licensing of the US rights to OROS Hydromorphone from ALZA is an excellent fit with Neuromed's strategy to address the significant need for alternative chronic pain treatments," said Dr. Christopher Gallen, President and CEO of Neuromed. "Hydromorphone is an effective and well-known pain reliever, and we believe a once-daily version can provide a significant benefit for the large number of patients with moderate-to-severe pain that require pain relief around the clock."

"OROS Hydromorphone is a perfect fit with our existing programs, including our partnered N-type calcium channel program and our own T-type calcium channel blocker program," Dr. Gallen added. "Neuromed will develop a specialized sales force to market OROS Hydromorphone in the US upon FDA approval. The addition of a commercial presence in the US will allow Neuromed to market niche products while continuing its dedication to the research and discovery of novel, breakthrough analgesics."

Hydromorphone is a Schedule II opioid that has been widely used for many years under the brand name DILAUDID and is also available from various generic manufacturers. Current formulations of hydromorphone marketed in the US are immediate release, requiring dosing several times per day.

OROS Hydromorphone employs the OROS osmotic drug delivery technology, which provides controlled drug release over an extended period and has been employed as a sustained-release formulation for many successful products, including CONCERTA, DITROPAN XL, COVERA-HS, and PROCARDIA XL. Four dosage strengths of OROS Hydromorphone (8 mg, 16 mg, 32 mg, and 64 mg) are currently marketed in Europe, with an additional lower strength (4 mg) in development.

Managing a Successful Buy-Side Acquisition

By: Debra Bingham and Tim Howard, MBA

Whether you are a member of a large publicly traded organization or a small privately held organization, an acquisition strategy on the buy-side is very much the same. The major difference is typically the size of the assets considered. There are many reasons why an executive management team decides to acquire. The main considerations typically are to expand a portfolio, build critical mass, leapfrog to a superior competitive market position, and add manufacturing capacity.

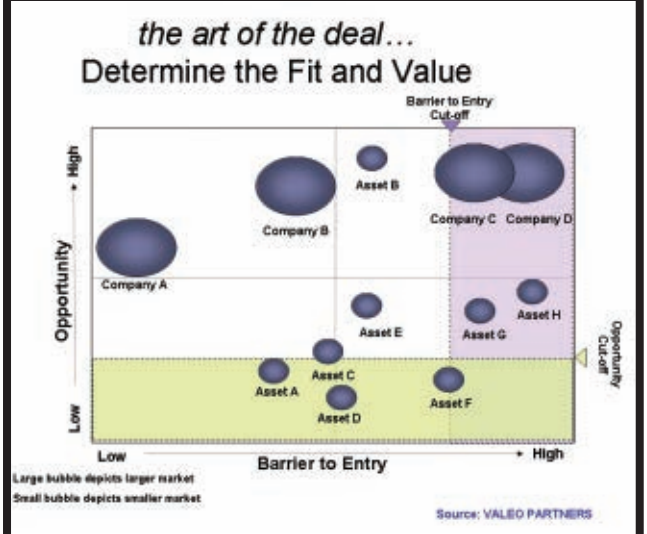
In the increasingly competitive atmosphere facing management teams today, it is critical to develop a sharp, well-thought-out strategy for a buy-side acquisition. When the strategy is established, it is important for it to be well synchronized among the team members who are tasked with the execution. The way in which the strategy is carried out will highlight the acquirer's strengths and weaknesses. The target being evaluated for acquisition will take notice. In most cases, the process is a competitive one in which there are more than two companies interested. Professionalism and clear messaging can go a very long way in a competitive situation. If the asset is highly sought after, the selling company will have the luxury of choosing the best fit from an economic and a cultural standpoint. At the end of the day, the selling company is interested in becoming part of a winning organization.

A strong buy-side acquisition will follow a clear overriding growth initiative. The strategy will be focused and will prevent distraction when the target company scouting begins. Assuming there is a clear expansion plan into a specific sector in the industry, the acquisition strategy is not difficult to develop. The plan will include but is not limited to the following:

- Therapeutic or technical focus (important considerations include synergies, marketing strength, competition, etc)
- Stage of development of asset or maturity of portfolio
- Actual and projected sales of each asset in portfolio
- Pipeline depth and robustness
- Regulatory strategy of company
- Valuation range
- Territory considerations
- Timing preferences

When the plan is outlined and agreed upon, it is time to begin the process. The labor involved is quite extensive. A buy-side acquisition can easily become a full time job. In larger organizations, it is the sole job function for a number of professionals. In a small organization, it can pull key executive team members away from important daily responsibilities. In these situations, many companies choose to use a third party to build strategy and to execute on the most labor-intense aspects of the exercise. There is nothing particularly glamorous or magical about the work involved in the scouting portion of an acquisition plan. The plan is the same regardless of who is doing it, and the following should be noted:

FIGURE 1



Opportunity (y-axis): Subjectively captures the overall opportunity, which includes market size, predicted market potential, and fit. Large bubbles constitute large market sizes when compared to those with small bubbles. Barrier to Entry (x-axis): Subjective interpretation of multiple factors, such as regulatory risk/hurdles, patent issues, competitive positioning, technology development stage, and fit with internal expertise. The "cut-off" is subjective and reflects the overall investment required to obtain the technology and/or company.

- Build a database of opportunities
- Qualify the opportunities
- Rank the opportunities
- Contact the companies
- Exchange non-confidential information
- Establish confidential management presentations
- Elevate the best candidate to executive management for approval
- Extend an offer
- Negotiate the offer
- Start over

The "art of the deal" comes in when the team is sorting and ranking opportunities. Going after the right asset for the right reason can make all of the difference. It is great to read a press release after an acquisition and think, "Wow…those guys are smart, what a great strategy!"

Managing a buy-side acquisition requires first, a clear strategy regarding the asset to be acquired and a clear understanding of the value proposition of the asset. Usually, the executive management team of a company decides that as an important growth initiative, the company will begin a plan to acquire particular product assets either through strategic licensure or through complete acquisition of the property holder. Using an organized process for acquisition will yield the best results.

As drug delivery companies take more risk with in-house products, they will become more attractive acquisition targets. Also, as some of these companies experience success with both partnered and proprietary products, they will in-turn look to grow through acquisition. The drug delivery sector will experience more acquisition activity throughout the next 3 years. It is therefore important, as members of the drug delivery sector, to understand the buy-side strategy to take advantage of it as a growth or as an exit opportunity.

Acquisitions offer a powerful business propulsion for both the acquiring and the acquired – the distance with which it can take a company is completely dependant on the strategy as well as the level of precision in which the strategy is executed. ◆

Biographies

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.

Mr. Tim Howard leads the Life Science practice with Stonecroft Capital and has extensive transaction and management experience in the Healthcare and Life Science sectors. Stonecroft Capital is an investment bank dedicated to providing the highest quality strategic advice to growth companies with high potential. Prior to joining Stonecroft, Mr. Howard was Founder and CEO of Galt Associates, Inc., a bioinformatics firm providing solutions to leading biopharmaceutical and medical device companies worldwide. Mr. Howard has twice been selected as an Ernst & Young Entrepreneur of the Year Finalist in the life sciences sector, and led his company to positions in the Deloitte & Touche National Fast 500, and Virginia Fast 50. He has led venture financing, partnering, and acquisition activities and negotiated strategic transactions with 8% of the top 20 global pharmaceutical companies. Mr. Howard currently serves as a Board Member and Advisor to numerous life science companies. His education includes a BS in Physics and Mathematics from Ursinus College, and an MBA from The Wharton School of the University of Pennsylvania.

Slouching Toward a Cure?: Court, FDA Ponder Expanded Patient Access to Investigational Drugs, Raising Constitutional & Commercial Issues

By: James N. Czaban, Esq., Wilmer Cutler Pickering Hale & Dorr LLP

On December 11, 2006, the FDA proposed two rules designed to expand early access by patients to investigational drugs during clinical development phases, and to further facilitate sponsors' ability to charge for both investigational and approved drugs used in clinical trials. And, in March 2007, a federal appeals court heard re-argument in Abigail Alliance v. von Eschenbach, a case that could establish a much broader legal right for patients to gain access to unapproved investigational drugs. The FDA proposals, if finalized, and the Abigail Alliance case, have the potential to benefit both patients and pharmaceutical companies, and particularly Specialty Pharma companies whose only products are still in the investigational phase, but also pose difficult challenges to FDA's ability to thoroughly review the safety and efficacy of new drugs prior to their widespread use in patients.

BACKGROUND

Under the Federal Food, Drug, and Cosmetic Act (FDCA), "new drugs" may not be commercially marketed before receiving FDA approval, and even then, they may not be promoted for uses beyond those specifically approved by the FDA. During clinical trials on new drugs, however, some patients are given the test drug, while others in the study receive a placebo or some other approved active-control drug. For serious or life-threatening diseases, there is often no adequate approved drug treatment available, and thus use of an experimental drug sometimes offers the only hope for improvement or even survival. But given the length of the investigational and FDA review processes, drugs that show promise for serious diseases often are not available to dying patients for many years after the potential benefit has been identified. This has long created pressure on the FDA and pharmaceutical companies to make promising experimental drugs available to patients other than those enrolled in clinical trials for the drug, and more recently has generated constitutional litigation challenging the fundamental principle of the Federal Food, Drug, and Cosmetic Act that drugs must receive FDA approval prior to being made available to patients outside of regulated clinical trials.

A related issue under consideration by FDA is whether, and to what extent, drug companies should be allowed to charge patients for the drugs they receive in clinical trials. Drug companies may not commercialize unapproved drugs, meaning that in most cases, they may not charge for drugs in clinical development. Given the tremendous expense of drug development, the ability to recoup some of the costs incurred during drug testing is of particular interest to early stage and Specialty Pharma companies, as well as academic research institutions, which may be operating on small budgets and uncertain future financing.

Inadequacy of Current Access & Charging Policies

The FDA has long recognized the forgoing concerns and has had policies and regulations that, in a limited way, allowed early access to investigational drugs, and in some circumstances, permitted sponsors to charge for investigational drugs. However, the FDA believes that the existing policies have limitations that now need modernization. In announcing the proposed rules, the FDA stated that "the existing regulations did not adequately describe the full range of [expanded access] programs available," and noted concern that "the lack of specific criteria and submission requirements results in disparate access to treatment use for different types of patients and diseases." With respect to charging for investigational drugs, the FDA has found that few requests have been made to charge for investigational drugs, but that more commonly, sponsors request permission to charge for approved drugs used as comparators in clinical trials, or used in third-party studies seeking new indications of approved drugs. Moreover, the agency believes that "the current charging rule is not very specific and does not provide sufficient guidance to sponsors on the costs that

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In response to FDA's earlier refusal to grant its petition seeking the adoption of a broad early access policy, the Abigail Alliance sued FDA challenging the constitutionality of FDA's general refusal to allow dying patients to obtain and use investigational drugs that have successfully completed Phase I clinical studies and have been shown to be sufficiently safe to be further tested in larger Phase II studies. In 2006, the U.S. Court of Appeals for the D.C. Circuit issued a controversial 2-1 decision holding "that where there are no alternative government-approved treatment options, a terminally ill, mentally competent adult patient's informed access to potentially life-saving investigational new drugs determined by the FDA after Phase I trials to be sufficiently safe for expanded human trials, warrants protection under the Due Process Clause." That decision was later vacated and the case was re-argued en banc before ten judges of the D.C. Circuit on March 1, 2007. A ruling is expected later this year.

THE PROPOSED RULES

Expanded Treatment Access

The expanded access proposed rule seeks to make it easier for patients with serious or life-threatening diseases or conditions to gain access to experimental drugs. It does so in part by proposing explicit criteria for access by individual patients and by intermediate-size patient populations, in addition to the larger-size patient populations for which treatment INDs have historically been available. The baseline criteria for allowing treatment access to investigational drugs in all scenarios are: 1) that the drug is intended to treat a "serious or immediately life-threatening disease or condition" for which there is "no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;" 2) that the potential patient benefit outweighs the potential risks; and 3) that providing the drug for treatment uses will not interfere with the clinical investigations that could support marketing approval. Although the first criterion is essentially unchanged from current regulations, in proposing to codify the second and third criteria, the FDA hopes to clarify and expand the circumstances that can support treatment use of investigational drugs.

Of particular interest, the FDA recognizes that "the evidence needed to demonstrate the safety and potential benefit of a proposed use varies with the size of the population to be treated and the relative seriousness of the disease or condition to be treated." Thus, the proposed rule would create a sliding scale for the required levels of evidence of safety and potential benefit needed to allow early access, depending on the seriousness of the disease and the size of the proposed patient treatment population. With respect to the safety/benefit/seriousness evaluation, the FDA explains that "as the seriousness of the disease increases, it may be appropriate to authorize expanded access use based on less data, still taking the size of the patient population into account."

At one end of the spectrum, to support expanded access for large patient populations, the FDA would generally require safety and effectiveness data from Phase III clinical trials, or in cases of immediately life-threatening diseases, compelling data from Phase II trials. At the other end of the spectrum, for single-patient access requests, where the patient has an immediately life-threatening disease and has not responded to available therapy, "the evidentiary burden could be very low" and early access may be allowed based on Phase I safety data (using doses similar to those to be used in the patient) and some appropriate data to suggest potential effectiveness. And, when a patient's condition is immediately life-threatening, the FDA may allow access based only on preclinical data and/or evidence as to the mechanism of action of the drug.

The safety/potential benefit considerations with respect to intermediate-size patient populations are, unsurprisingly, somewhere between those to be applied for single-patient access and large-scale treatment INDs. As the FDA explains, the criteria for intermediate-size populations, "there must be at least some preliminary clinical evidence of effectiveness of the drug or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population."

The proposal's approach to intermediate-size patient populations is perhaps the most potentially useful aspect of the proposed rule because it may fill a gap in current practice between large-scale treatment INDs and single-patient compassionate-use exceptions. The FDA contemplates that this approach may be used in several circumstances not adequately addressed under current policy.

Specifically, intermediate-size population expanded access may be possible for drugs that are not being developed because, for example, the disease or condition is too rare to enable the sponsor to adequately recruit patients for clinical trials. In


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addition, such access programs may be approved where the drug is being actively developed, but patients requesting the drug are unable, or ineligible, to participate in the clinical trials. Similarly, expanded access may be granted for approved drugs that are no longer being marketed, due to safety reasons or because of unresolved non-compliance with current Good Manufacturing Practices requirements (as long as the safety or manufacturing issues do not pose a risk that is unreasonable in comparison to the risks of the disease being treated).

Charging for Drugs in Clinical Trials

Like the expanded access proposed rule, the FDA's proposed rule for charging for drugs in clinical trials does not present an entirely new concept as the FDA's policy has previously provided for potential charging in limited circumstances. However, the FDA has identified aspects of its policy that require clarification and limited expansion, as proposed in the new rule and described further on. The charging rule would clarify the circumstances in which patients can be charged for drugs (both experimental and approved) used in clinical trials. The rule would permit charging for the sponsor's own drug if the drug, a new indication for the drug, or new safety data might not otherwise be developed, the trial is essential to the development of a new drug or would support a significant labeling change for an approved drug, and the charging is necessary to conduct the trial. Sponsors would also be able to charge for use of another company's approved drug when co-administered with, or used as a comparator to, an investigational drug, or in trials evaluating a new use for an approved drug.

As a baseline matter, however, the FDA makes clear that charging for investigational drugs will not become the norm, explaining that "[g]enerally, the costs of conducting a clinical trial are costs that the sponsor should bear. Conducting a clinical trial is part of the drug development process, and drug development is an ordinary business expense for a commercial sponsor. If the investigational drug proves successful in clinical trials, the sponsor will recoup its development costs by marketing the drug for its approved indication." Moreover, as the FDA notes, clinical trial subjects put themselves at risk, in part for the benefit of the sponsor, and in most cases, subjects are compensated by the sponsor for their participation, rather than being charged for the drugs used in the study.

Importantly, the FDA cautions that sponsors have sometimes interpreted existing regulations too broadly in the past. For example, sponsors have sought charges intended to cover multiple types of costs associated with the research, development, and handling of the drug, or even costs of facilities used to commercially manufacture the drug. Thus, the agency makes clear that the intent of its current and proposed charging policies is not to allow recovery of the costs of research and development of a drug before marketing.

Specifically, the FDA states that the "purpose of permitting charging for an investigational drug in a clinical trial is to permit a sponsor to recover the costs of a drug when the drug is extraordinarily expensive. Thus, [the proposal] would limit cost recovery to the direct costs of making the investigational drug available in these situations. Indirect costs could not be recovered."

Direct costs that may be recoverable would include, on a per-unit basis, costs of manufacturing (materials, labor, non-reusable supplies), and costs to acquire the drug from another source, including direct shipping, handling, and storage costs. Non-recoverable indirect costs include physical plant and equipment intended for commercial-scale manufacturing, and research, development, administrative, labor, and other costs that would be incurred even without the clinical trials under which cost recovery is sought.

One circumstance in which the FDA has always recognized a legitimate basis for charging for investigational drugs is in the treatment IND context, because the use of a drug in this context does not benefit the sponsor by generating significant useful safety and efficacy data to support FDA approval. Rather, these programs are designed to treat patients, just as in the post-approval commercial context. Thus, the agency proposes to retain its current regulations, in expanded form, to facilitate charging in the newly defined expanded access categories (single-patient access, and intermediate-size patient populations). Recoverable costs for expanded access treatment uses would also include the costs of administering the drug in such programs, monitoring the expanded access use, complying with IND reporting requirements, and other administrative costs incurred in an expanded access program.

Finally, when an approved drug is being studied by an

entity other than the sponsor/manufacturer — such as active-drug controls in a trial of a sponsor's investigational drug, or in third-party trials studying a new indication for the approved drug — the FDA intends to set a lower threshold for allowing charging for the approved drug. This approach may prove especially beneficial to academic institutions, or smaller independent research organizations.

IMPLICATIONS

The Constitutional reasoning of the D.C. Circuit's original decision in Abigail Alliance sent shock waves through FDA, the pharmaceutical industry, and patient advocacy groups. Although Abigail Alliance is itself a patient advocacy group, several other patient groups sided with FDA in opposition to the original appeals court's decision, arguing among other things, that the type of expanded access endorsed by the court would lead to fewer patients enrolling in the pivotal clinical trials necessary to definitively establish whether a new treatment does in fact work, and thus could cause a long-term reduction in treatment options for the seriously ill and dying.

Pharmaceutical companies may be concerned about product liability implications, charging limitations, and the possibility that any broad early access rule could lead FDA to require even more data at the earliest stages of drug development, further escalating the cost and time required to bring new drugs to market. Regardless of the outcome of the court's re-review, it is expected that the losing side will seek a final ruling from the Supreme Court.

Although the concerns raised in opposition to the Abigail Alliance case have also been raised by some in the context of FDA's proposed rules, Specialty Pharma companies should carefully evaluate their clinical programs in the context of the FDA's proposed rules, as there may be unrealized opportunities for wider distribution and cost recovery during the critical clinical evaluation period. For some companies in tight financial circumstances, even the relatively incremental benefits of the expanded access and charging proposals could make a material difference in a company's ability to reach the finish line of FDA approval without additional venture (or other) funding, or further dilution of ownership/control of the company. ◆

BIOGRAPHY

Mr. James N. Czaban, Esq.
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Mr. James Czaban is a Partner in the Washington, DC, office of Wilmer Cutler Pickering Hale & Dorr LLP (WilmerHale), where he leads the firm's FDA Department. In addition to his nearly 15 years of private practice in Food & Drug law, Mr. Czaban has lectured widely on topics of FDA regulation of pharmaceuticals, including at Harvard University, Fordham Law School, Seton Hall Law School, Hastings College of Law, the American Bar Association, the Food & Drug Law Institute (FDLI), the Biotechnology Industry Organization (BIO), the Regulatory Affairs Professionals Society (RAPS), the Drug Information Association (DIA), and numerous other pharmaceutical industry symposia. He is the author of chapters in three legal treatises on Food & Drug law, writes regular legal columns for various trade publications, and is a member of the Editorial Advisory Boards of *Specialty Pharma* and *Drug Delivery Technology* magazines. He was recognized as a "Top Lawyer" in Food & Drug Law by *Washingtonian Magazine*. Sponsors who have questions about the proposed rules, the *Abigail Alliance* case, or other pharmaceutical regulatory issues can contact Jim at (202) 663-6292, or james.czaban@wilmerhale.com.

CONTROLLED RELEASE

High Drug-Load Controlled-Release Dosage Forms for the OTC Market

By: Michael Hite (candidate)

INTRODUCTION

Many APIs are only pharmacologically useful at relatively high dosages (>500 mg). Developing these products as controlled-release dosage forms presents multiple obstacles, including achieving release-profile performance, optimizing manufacturability, and minimizing physical size. Product performance over 12 to 24 hours requires employing drug delivery systems capable of controlling the release of the active compound with a minimum of controlling excipients. Moreover, these formulation excipients must often improve the manufacturability of the dosage form by simultaneously acting as binders, compression aids, and flow modifiers to compensate for often poor physiochemical properties of the APIs themselves. To be successful in the Over-the-Counter (OTC) marketplace, high-load controlled-release products must be cost-effective to manufacture and provide the customer with demonstrable value superior to that of immediate-release products, which may be priced at a substantial discount.

RELEASE-PROFILE PERFORMANCE

Product efficacy often requires a bimodal extended-release profile. Such profiles typically feature a combination of an immediate-release loading dose of the drug to induce onset of efficacy and a controlled-release dose of the drug to maintain therapeutic efficacy until the next dose is administered. The most common means of achieving such performance for high drug-load products is through bi-layer dosage forms. Employed in both tablet and caplet embodiments, these bi-layer systems typically contain the immediate-release component in one layer and the extended-release component in the other layer. This separation of the layers allows the immediate- and extended-release profiles to be formulated independently; dividing the drug load in such a manner is particularly advantageous for high-drug-load products because of the relatively low volume for controlling excipients and tableting aids available in the dosage form.

One example of an extremely successful high-drug-load product launched in recent years is Adams Respiratory Therapeutics's Mucinex® line of guaifenesin products. Guaifenesin is water-soluble and readily lends itself to formulation within the immediate-release portion of the tablet, but effectively controlling the release of the drug over 12 hours is more challenging. Adams chose to use a drug delivery system comprising hypermellose, a cellulose ether, and Carbomer 934P, a high molecular weight polymer of acrylic acid cross-linked with allyl ethers of sucrose or pentaerythritol. Mucinex contains 600 mg of guaifenesin delivered in a bi-layer tablet, with approximately 150 to 200 mg formulated for immediate-release and approximately 400 to 450 mg formulated for controlled-release over 12 hours. Adams has also adapted its delivery technology to accommodate combination products of pseudoephedrine (Mucinex-D®) and dextromethorphan (Mucinex-DM®) in addition to the guaifenesin-only formulation. In vitro release profiles of guaifenesin from Mucinex, Mucinex-D and Mucinex-DM are shown in Figure 1.

Another example of a well-formulated bi-layer product is Tylenol Arthritis Pain®, an extended-release acetaminophen product developed by McNeil Consumer Healthcare (a Johnson & Johnson company). Like guaifenesin, acetaminophen is water soluble and similarly well-suited to immediate-release preparations. Tylenol Arthritis Pain contains 1350 mg of acetaminophen in each dose and employs a combination of hydroxyethyl cellulose and hypermellose to control the release of the drug. Due to the high-drug load required to achieve efficacy over 8 hours, McNeil divided the dose between two caplets or gelcaps.

A novel alternative to bi-layer dosage forms has been developed by SCOLR Pharma, Inc. Using its CDT® delivery system platform, SCOLR has developed an extended-release formulation for ibuprofen that mimics the release performance of a bi-layer

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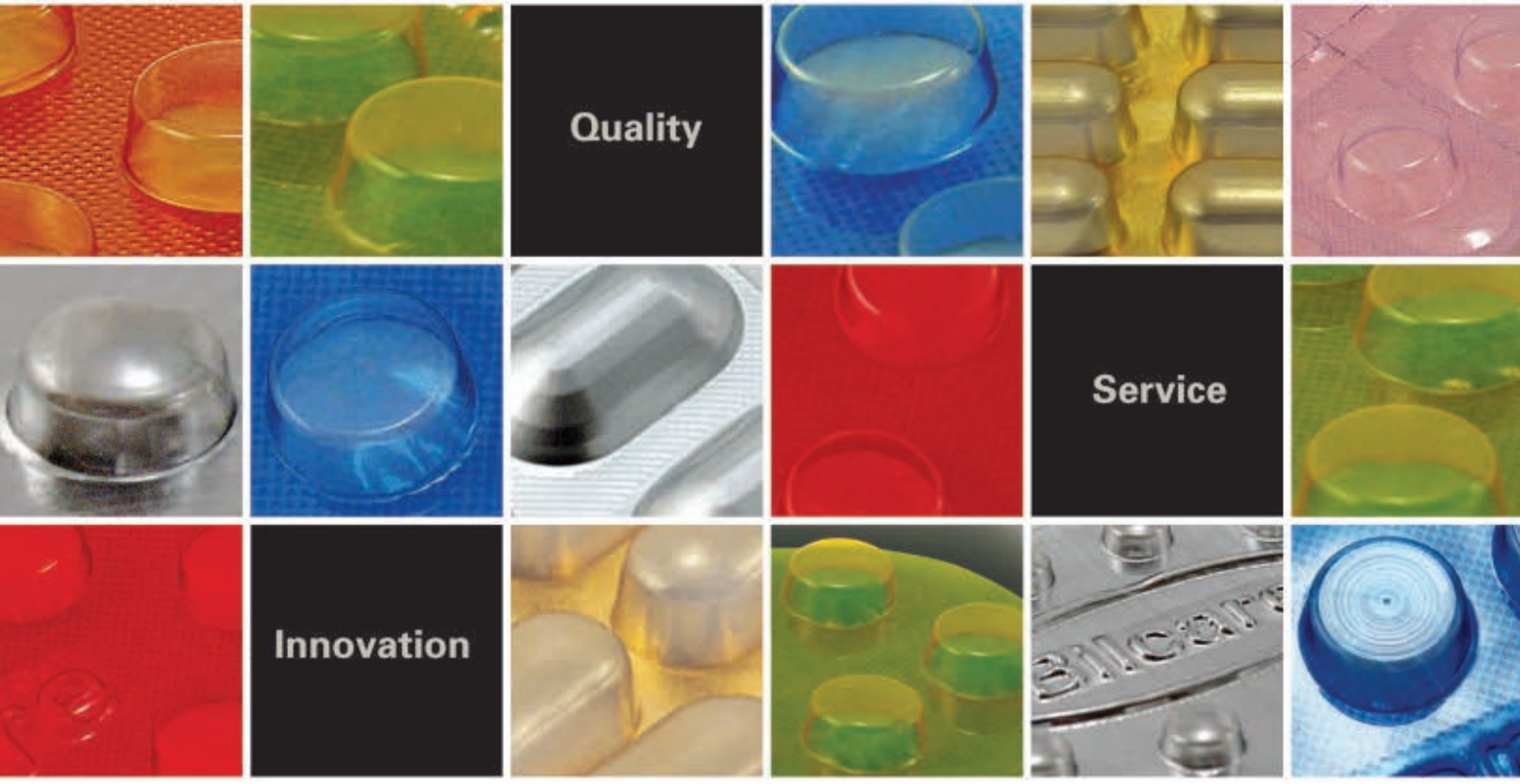

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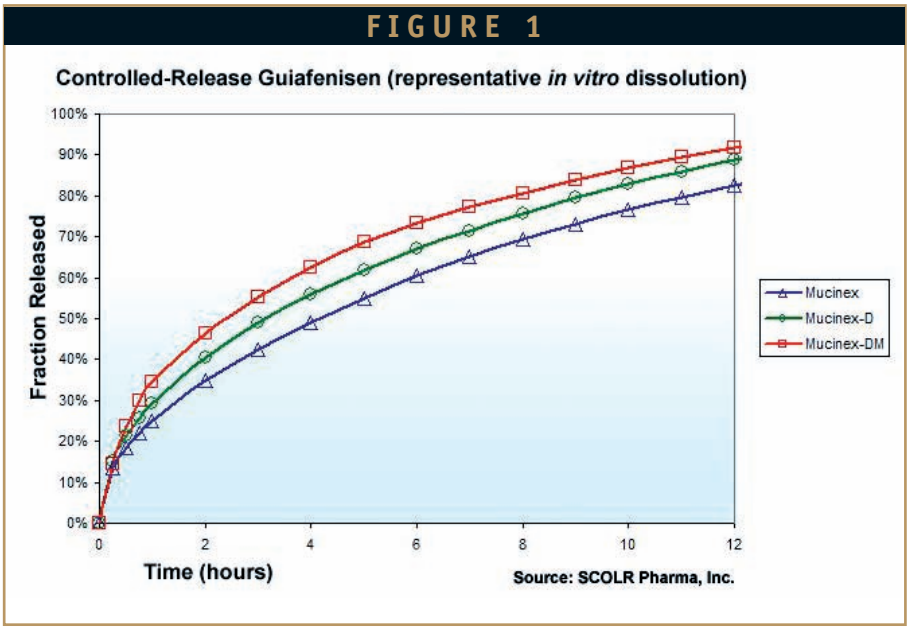
system, but does so within the embodiment of a monolithic tablet. Ibuprofen displays pH-dependent solubility (ibuprofen is only sparingly soluble at low pH, but readily soluble at higher pH), creating dissolution characteristics that are markedly different from those of acetaminophen or guaifenesin. Ibuprofen's dissolution behavior under low pH conditions is a substantial obstacle to creating a therapeutically effective loading dose. Immediate-release ibuprofen tablets overcome this low-pH solubility limitation through disintegration of the entire dosage form. Within a monolithic tablet, replicating such a disintegration process is not possible using traditional matrix technologies. SCOLR employed its CDT platform to create a hydrogel matrix that upon hydration, rapidly swells and creates a pronounced gel strength differential between the exterior and the core of the tablet. This difference in gel strength allows for a therapeutically efficacious amount of initial drug release to occur via erosion of the less-viscous exterior of the tablet, while the release of the remaining drug-load is controlled via diffusion from the more viscous tablet core. The in vivo release profile reflects this bimodal drug release, as presented in Figure 2.

MANUFACTURABILITY

The physical properties of high-load APIs are not always conducive to simple and manufacturable formulations. Acetaminophen, for example, possesses very poor compression characteristics, requiring a precursor step in manufacturing (such as granulation) or the use of substantial volumes of excipients to render the material manufacturable in tablet form. Ibuprofen and guaifenesin, by contrast, are more readily compressible, but feature exceptionally low-melting points (75°C to 77°C and 78.5°C to 79°C, respectively), often manifested by the compressed formulation sticking and picking to the punch faces of a tablet press.

Bi-layer tablet formulations are one means of addressing issues surrounding APIs with negative physical properties. By isolating the immediate-release and extended-release components in separate compression cycles of the tablet press, tableting aids, such as binders and fillers, may be used in differing volumes that may be optimized for the individual layer formulations without impacting the performance of the other tablet layers. Multiple-layer tablet presses have become more standard pharmaceutical equipment in recent years, but throughput is still limited in most cases by the design of press itself. In contrast, compression of monolithic tablet formulation on a dual-sided press can demonstrate a production throughput two or more times above that of a bi-layer tablet formulation on a similar press. If a two-stage dry-blend and direct compression process can be substituted for a more complex multiple-stage granulation and bi-layer compression process, significant cost-savings can result from the resulting improvement in production efficiency.

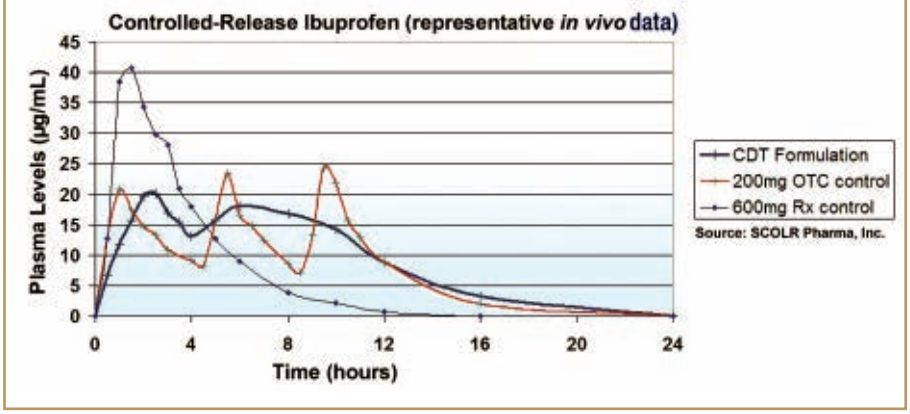
FIGURE 1



MARKET ACCEPTANCE

Within the OTC and generic pharmaceutical markets, cost is one of the most significant factors driving product success. Although controlled-release products provide significant added value, retail consumers will not support a significant price premium. Thus, the cost-of-manufacture for OTC controlled-release products cannot contain significant pricing increases over that of immediate-release products. This cost limitation effectively eliminates from consideration many delivery technologies that require inherently complex manufacturing processes (such as multiparticulate and osmotic pump systems) and those technologies that employ specialized

FIGURE 2



excipients (such as novel hydrophilic polymers).

Currently, Adams Mucinex products do not face any generic competition within the OTC market because of FDA exclusivity and protection garnered from its patent estate. McNeil's Tylenol Arthritis Pain loses patent protection in 2007, and a generic competitor has already been approved by the FDA. Although both companies possess excellent brand strength, significant pressure may be placed upon the pricing advantage that their products have possessed once generic competition commences.

The inevitability of generic competition was acknowledged by SCOLR Pharma during the development of the 12-hour controlled-release ibuprofen product. By starting with a dry-blend direct-compression formulation, the ability of generic competitors to undercut the innovator product has been reduced substantially. SCOLR has entered the nutraceutical market in partnership with Perrigo, the world's largest manufacturer of OTC and nutritional supplement products for the store brand market. The nutraceutical market is even more price sensitive than the OTC market. SCOLR's experience in designing cost-effective, high-load formulations of Niacin (1000 mg), Glucosamine (500 mg), and Glucosamine-Chondroitin (500- to 400-mg combination) for Perrigo was applied to the dosage form design of its CDT ibuprofen product.

One means of preventing price erosion by generic competition is to develop a more complex branded product that is less susceptible to simple reformulation. Adams' guaifenesin combination products are an excellent example of this strategy. Mucinex D and Mucinex DM have demonstrated the effectiveness of employing combination therapies in conjunction with high-drug-load controlled-release products. Another such area within the OTC space that has yet to be addressed is the need for a controlled-release analgesic product (such as ibuprofen, acetaminophen, or naproxen) available in combination with controlled-release cough-cold products (such as pseudoephedrine and dextromethorophan). Such combination products, especially if developed within a branded franchise capable of garnering some duration of market exclusivity, may have a substantial impact on the cough-cold market.

SUMMARY

The development of high-drug-load controlled-release products for the OTC market has seen major advances in recent years. Bi-layer formulations of guaifenesin and acetaminophen have become well-established products, attesting to the increased value consumers place upon the convenience and improved performance of controlled-release products. With the development of a novel monolithic controlled-release tablet formulation for ibuprofen, a significant technological barrier to delivering cost-effective controlled-release products to the OTC consumer has been removed. As the demand for controlled-release products increases, applications of cost-effective controlled-release technology will expand proportionally and allow new combination products and Rx-to-OTC switchover products to be developed.

BIOGRAPHY

Mr. Michael Hite is a Market Research and Technical Assessment Analyst with SCOLR Pharma, Inc. He joined the company in 2000 as a formulator and is one of the founding members of the company's product development group. Mr. Hite is a graduate of Amherst College and is currently pursuing his MBA at the University Of Washington School of Business. He is also a member of the American Association of Pharmaceutical Scientists (AAPS), the Controlled Release Society (CRS), and the American Chemical Society (ACS). He has published multiple articles in peer-reviewed journals, presented numerous poster presentations at the AAPS and CRS national conferences, and is a frequent editorial contributor to numerous pharmaceutical industry publications.

NANO-SCALED CARRIERS

Nanomedicines for the Improved Delivery of Drugs Across Biological Barriers

By: Claus-Michael Lehr, PhD

ABSTRACT

Pharmaceutical nano-biotechnology has an enormous potential to improve the delivery of drugs across biological barriers, both for local as well as for systemic application. This holds in particular for macromolecular biopharmaceuticals (peptides, proteins, antisense agents, gene vectors) as well as for conventional small organic molecules. In order to improve the delivery of macromolecules, we are exploring the potential of nano-scaled carriers (biodegradable polymers, liposomes) for controlled and targeted delivery to specific organs, tissues, and cells. Of particular interest in our research are the oral, pulmonary, and transdermal routes of drug delivery, including the delivery of plasmid DNA and other nucleotide-based drugs.

INTRODUCTION

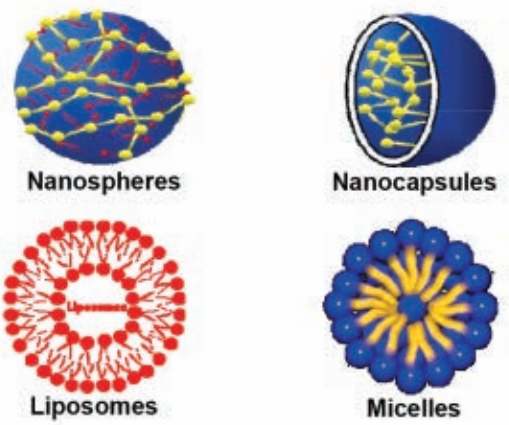
According to a recent definition elaborated by a working group of the European Science Foundation in 2004, "Nanomedicine" is built on complex systems of nanometer-scale size consisting of at least two components, one of which is an active pharmacological ingredient and the whole system leading to a special function related to the diagnosis, treatment, or prevention of disease.[1] In this context, nano-scale should be taken to include active components or objects in the size range from 1 nanometer to hundreds of nanometres. Nanomedicines in the form of drug carriers (eg, particles, liposomes, dendrimers, etc) play an important role to warrant safe and efficient delivery of active compounds to their intended site of action. The major challenges here are 1) to target specific cell tissue or organs, and 2) to overcome biological barriers, such as the skin, the intestinal or respiratory mucosa, or the so- called blood-brain-barrier, which is represented by the tight brain microvascular endothelium.

Nanoparticles as drug carriers were first described by Speiser and co-workers in the 1970s.[2] Since then, a considerable amount of work on nanoparticles has been and is still being carried out around the world in the field of drug/gene delivery, and some of these nanomedicines have already entered clinical trials or even reached regulatory approval as a drug product. Drugs or other biologically active molecules are dissolved, entrapped, or encapsulated in the nanoparticles or are chemically attached to the polymers or adsorbed to their surface.

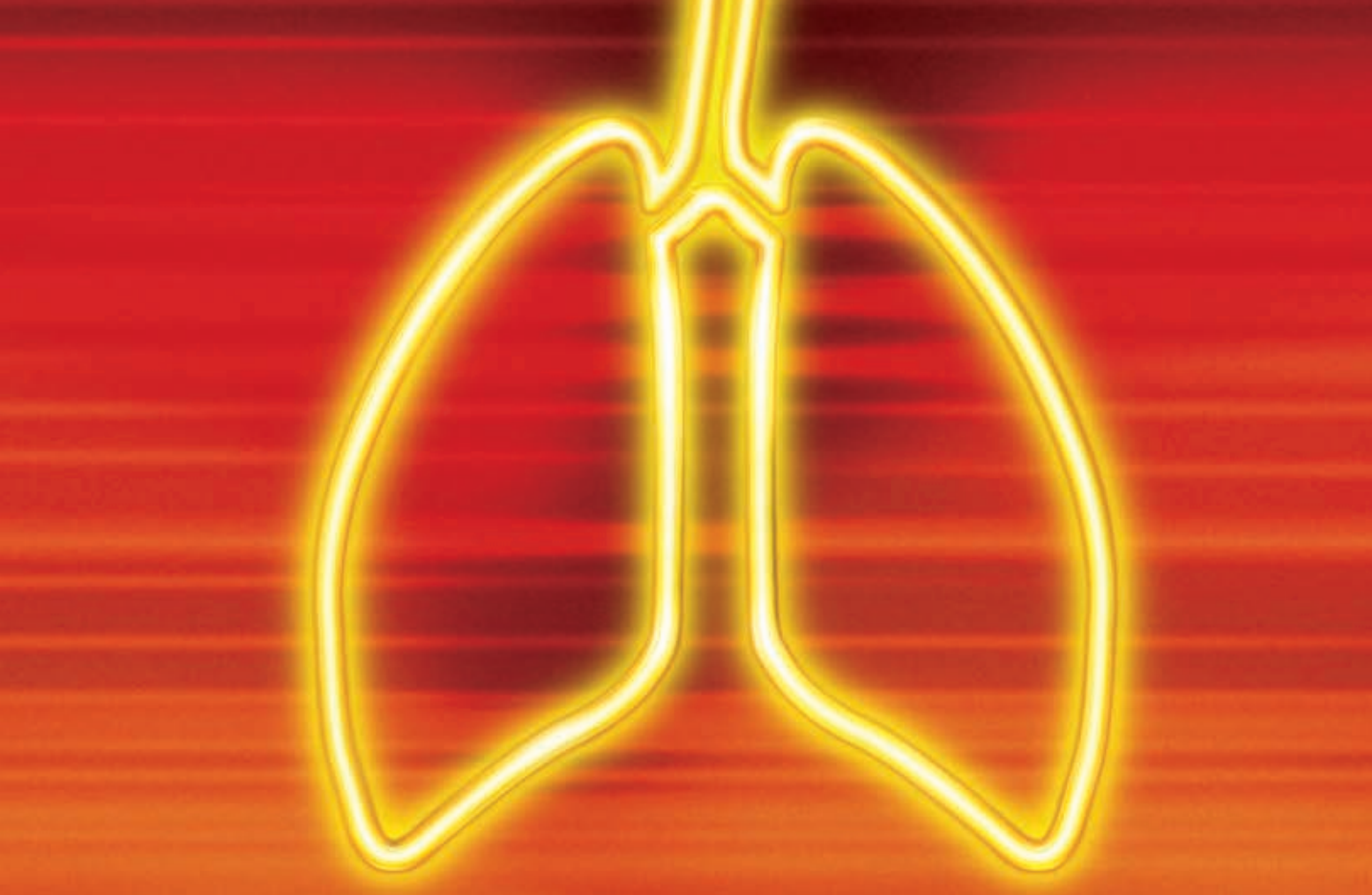
The selection of the appropriate method for preparing drug-loaded nanoparticles depends on the physico-chemical properties of the polymer and the drug. On the other hand, the procedure and the formulation conditions will determine the inner structure of these polymeric colloidal systems. Two types of systems with different inner structures are possible: 1) a matrix-type system composed of an entanglement of oligomer or polymer units, defined here as a nanoparticle or nanosphere; and 2) a reservoir-type system, consisting of an oily core surrounded by a polymer wall, defined here as a nanocapsule. Various colloidal nanoparticulate systems in use for drug/gene delivery are shown in Figure 1.

For a recent and rather comprehensive review on the preparation and characterization of nanoparticulate drug carriers, the reader is referred to Kumar et al.[3] For the purpose of this short paper, the potential of pharmaceutical

FIGURE 1



Various Concepts of Nanoparticulate Carriers for Pharmaceutical Applications[4] (Kumar RM, Sameti M, et al. Polymeric nanoparticles for drug and gene delivery. In: Encyclopedia of Nanoscience & Nanotechnology. Nalwa HS, ed. American Scientific Publishers;2003:1-19.)



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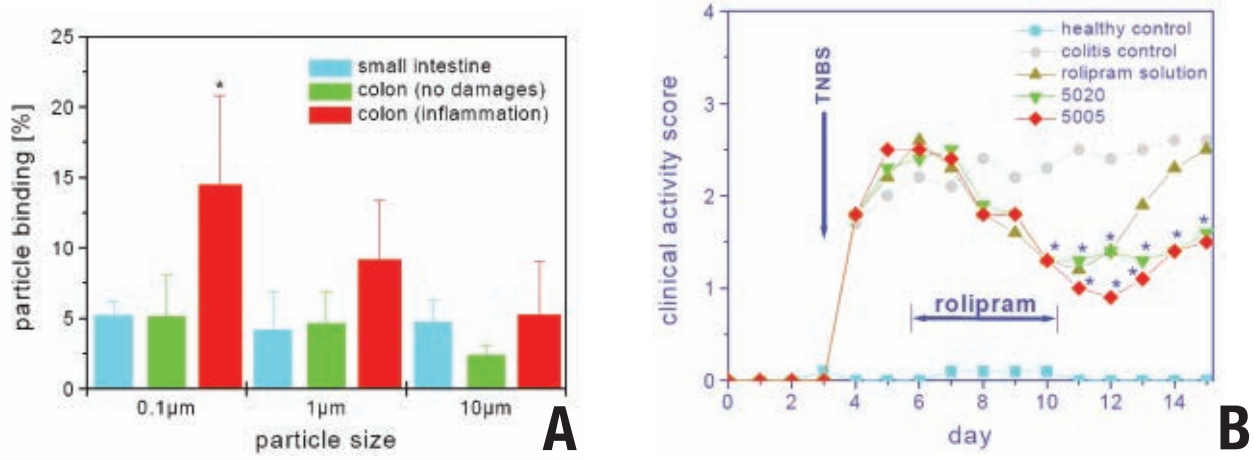
NANO-SCALED CARRIERS

FIGURE 2



(A) Quantitative determination of particle deposition in the colitis group comparing different colon regions on day 9 after colitis induction. Results are shown in percent of administered particle mass as mean values ± SD. *P <0.05 compared with colon deposition in colitis rats given 10-micron particles.[3] (Lamprecht A, Schäfer UF, et al. Size dependent bioadhesion of micro- and nanoparticulate carriers to the inflamed colonic mucosa. Pharm Res. 2001;18:788-793.) **(B) Clinical activity score during the whole experimental period always determined for n = 6 animals.[5]** (Lamprecht A, Ubrich N, et al. Biodegradable nanoparticles for the targeted drug delivery in treatment of inflammatory bowel disease. J Pharmacol Experimental Therapeut. 2001;299(2):775-781.)

nanocarriers shall be illustrated by some selected examples of published data from the author's own lab.

EXAMPLES FOR SPECIFIC APPLICATIONS OF PHARMACEUTICAL NANOPARTICLES

Targeting of Nanoparticles to Inflamed Areas of the Intestinal Mucosa

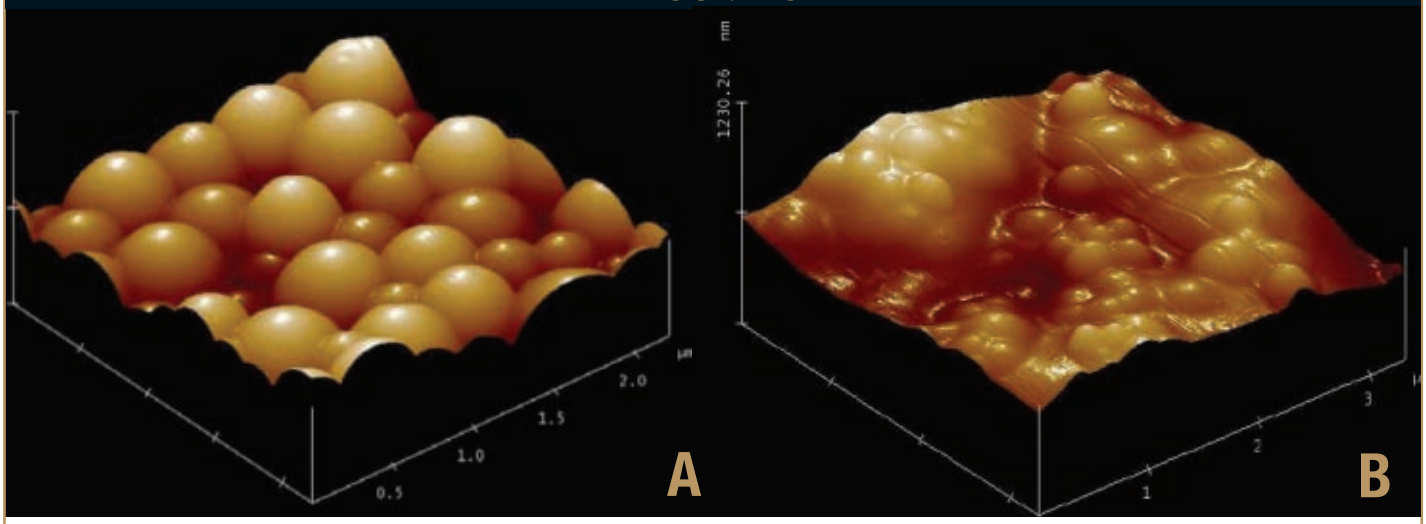
The use of polymeric nanoparticles based of poly (lactic acid-co-glycolic acid) (PLGA) for targeted oral drug delivery to the inflamed gut tissue in inflammatory bowel disease was examined.[4,5] Such a strategy of local drug delivery would be a distinct improvement compared with existing colon delivery devices for this disease. An experimental colitis was induced by trinitrobenzenesulfonicacid (TNBS) to male Wistar rats. Rolipram, an anti-inflammatory model drug, was incorporated within PLGA nanoparticles, which were administered once a day orally for 5 consecutive days. A clinical activity score and myeloperoxidase activity were determined to assess the inflammation, whereas an adverse effect index reflected the remaining neurotropic effect of rolipram resulting from its systemic absorption. All nanoparticle formulations proved to be as efficient as the drug in solution in mitigating the experimental colitis. The clinical activity score and myeloperoxidase activity decreased significantly following the oral administration of rolipram nanoparticles or solution. During the next 5 days when animals were kept without drug treatment, the drug solution group displayed a strong relapse, whereas the nanoparticle groups continued to show reduced inflammation levels. The rolipram solution group had a high adverse effect index, whereas the rolipram nanoparticle groups proved their potential to retain the drug from systemic absorption as evidenced by a significantly reduced index. This new delivery system enabled the drug to accumulate in the inflamed tissue with higher efficiency than when given as solution. The nanoparticle deposition in the inflamed tissue should be given particular consideration in the design of new carrier systems for the treatment of inflammatory bowel disease.

Nanoparticles for Transdermal Drug Delivery

The effect of the inclusion of flufenamic acid in PLGA nanoparticles on the transport of flufenamic acid into excised human skin was investigated.[6,7] Penetration and permeation data were acquired using two different in vitro test systems: the Saarbruecken penetration model (SB-M), where the skin acts as its own receptor medium, and the Franz diffusion cell (FD-C), where the receptor medium is a buffer solution. For the stratum corneum, no

NANO-SCALED CARRIERS

FIGURE 3



AFM Images of Flufenamic Acid Containing NP6 (A) Aqueous suspension (B) Incorporated into Natrosol.[6] (Luengo J, Weiss B, et al. Influence of nanoencapsulation on human skin transport of flufenamic acid. Skin Pharmacol Physiol. 2006;19(4):190-197.)

differences were found between nano-encapsulated and free drug. Drug accumulation in the deeper skin layers and drug transport across human skin was slightly delayed for the nano-encapsulated drug compared to the free drug after shorter incubation times (< 12 hours). In contrast, after longer incubation times (> 12 hours), the nano-encapsulated drug showed a statistically significant enhanced transport and accumulation ($P < 0.05$). Additional nano-encapsulated flufenamic acid was visualized by multiphoton fluorescence microscopy. Particles were found homogeneously distributed on the skin surface and within the dermatoglyphs, but no nanoparticles were detected within or between the corneocytes.

Nanoparticles for the Delivery of Plasmid DNA

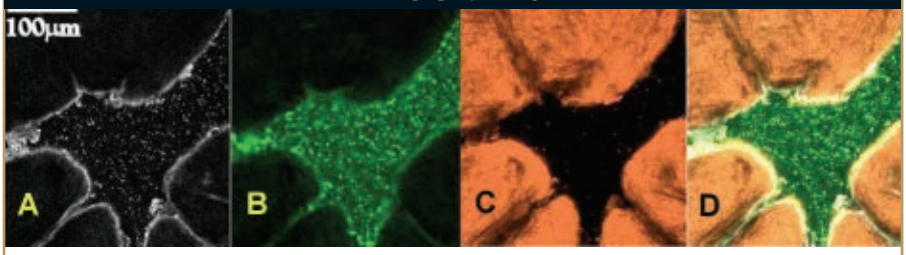
Diverse polycationic polymers have been used as non-viral transfection agents. As an alternative technology, we reported the ability of nano-sized silica particles with covalently attached cationic surface modifications to transfect plasmid DNA in vitro and make an attempt to describe the structure of the resulting transfection complexes, referred to as *nanoplexes*.[8,9]

Furthermore, the ability of these particles to transfect pCMVβ, reporter genes was tested in Cos-1 cells, and optimum results were obtained in the presence of fetal calf serum and chloroquine at a particle ratio of 80. These nanoparticles were tested for their ability to transfer genes in vivo in the mouse lung, and a two times increase in the expression levels was found with silica particles in comparison to the plasmid DNA alone. A very low or no cell toxicity was observed, suggesting silica nanoparticles as potential alternatives for gene transfection.[10]

As an alternative to silica, we also investigated in technologies to prepare positively charged nanoparticles based on biodegradable polymers, such as poly(lactic acid) (PLA) and poly(lactide-co-glycolide) (PLGA).[11,12]

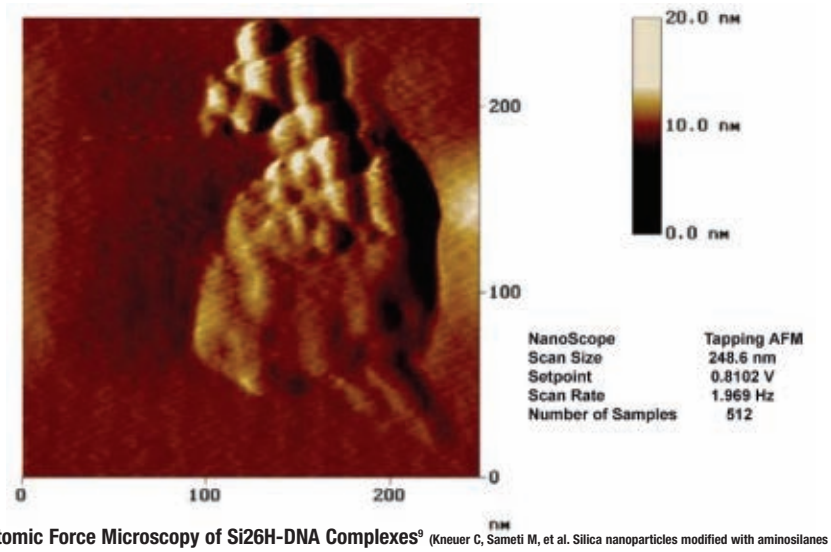
An emulsion-diffusion-evaporation technique to make cationic nanospheres composed of biodegradable and biocompatible co-polyester PLGA has been developed. PVA-chitosan blend was used to stabilize the PLGA nanospheres. The nanospheres were characterized by Atomic Force Microscopy (AFM), Photon-Correlation Spectroscopy (PCS), and Fourier Transform Infrared Spectroscopy (FTIR). Zeta potential and gel electrophoresis studies were also performed to understand the surface properties of nanospheres and their ability to condense negatively charged DNA. The designed nanospheres have a zeta potential of 10 mV at pH 7.4 and size under 200 nm. From the gel electrophoresis studies, we found that the charge on the nanospheres is sufficient to efficiently bind the negatively charged DNA electrostatically. These cationic PLGA nanospheres could serve as potential alternatives of the existing negatively charged nanoparticles.

FIGURE 4



Multiphoton Microscopy for the Investigation of Dermal Penetration of Nanoparticle-Borne Drugs[7] (A) gray scale, predominantly keratin autofluorescence and fluorescein (B) 488-nm excited image, green scale – Fluoresceine covalently linked to NP polymer (C) 543-nm excited image, orange scale – Texas Red nano-encapsulated in polymer NPs (D) overlay of all 3 images. (Stracke F, Weiss B, et al. Multiphoton microscopy for the investigation of dermal penetration of nanoparticle-borne drugs. J Investigat Dermatol. 2006; 126(10):2224-2233.)

FIGURE 5



Atomic Force Microscopy of Si26H-DNA Complexes[9] (Kneuer C, Sameti M, et al. Silica nanoparticles modified with aminosilanes as carriers for plasmid DNA. Int J Pharm. 2000;196:257-261.)

Pulmonary Drug Delivery & Novel In Vitro Models of the Air-Blood Barrier for the Assessment of Aerosolized Nanomedicines

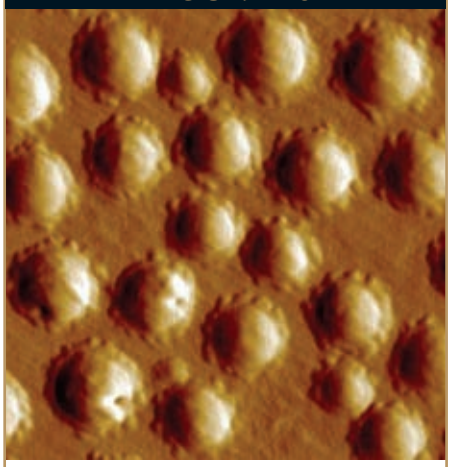
The pulmonary route is of increasing interest for the development of new medicines, not only for the treatment of lung diseases (eg, asthma, COPD) but also for the fast and efficient delivery of drugs into the systemic blood circulation. Advanced drug carriers, such as nanoparticles or liposomes, however, require the use of polymers and other excipients, the effects of which on the airway and respiratory epithelia are still relatively unknown, especially with regard to their safety.

While the safety and efficacy of new drugs and delivery technologies can only be judged by clinical studies in man, such tests are usually preceded by preclinical tests on animals. Still, however, animals by their nature are rather complex systems and do not easily allow to obtain detailed information on the mechanisms of drug absorption at a given biological barrier, such as the air-blood-barrier of the lung. Therefore, in vitro models of biological barriers are extremely useful because they allow for the studying of biological processes at such barriers under controlled conditions. Apart from the possibility to use such systems for absorption/safety screening among larger amounts of candidates, studies at the cellular level provide a better understanding of critical factors and therefore to optimize formulations accordingly.

The surface area of the alveolar epithelium is estimated at 100 to 145 m^2, which is rather large and comparable to that of the intestinal mucosa. Also, the high blood perfusion rate and the very small alveolar fluid volume of 7 to 20 ml are in favor of the lung as a novel route for the application of medicines. The alveolar epithelium in the deep lung is one of the thinnest barriers in the human body. The distance between airspace and the capillary blood is only about 1 micron thick and can supposedly be passed also by relatively large molecules.

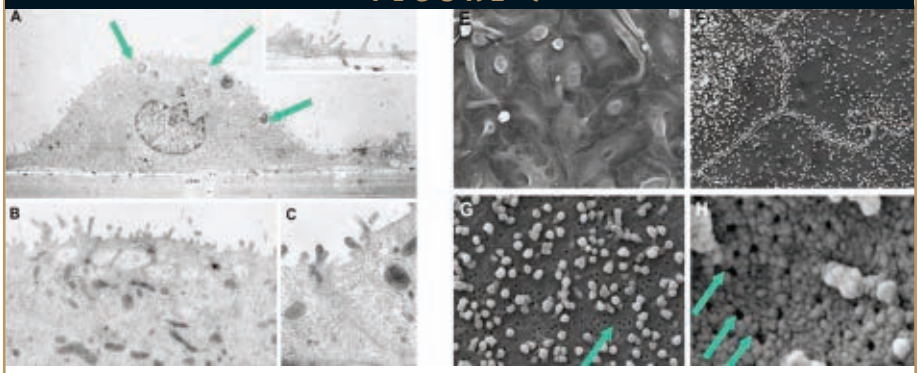
Lung alveolar epithelium in vivo is composed of two specialized epithelial cell types, the squamous alveolar epithelial type I (ATI) cell, which constitutes more than 90% of the alveolar epithelial surface area, and the surfactant-producing cuboidal alveolar epithelial type II (ATII) cell. The isolation of ATII cells predominantly from rat and rabbit lung tissue, and their culture over time leading to a primary culture of ATI-like cells is now an established technique for different purposes. The isolation of human alveolar type II epithelial cells (HAEpC) and their primary culture was described first by Elbert et al, which results in confluent monolayers capable of generating tight junctional complexes and high transepithelial electrical resistance.[13] The morphological cell change from an ATII phenotype to an ATI-like cell phenotype over time of culture was described by Fuchs et al.[14] Moreover, the

FIGURE 6



AFM Picture of DNA-Nanopshere Complex[12] (Kumar RM, Bakowsky U, et al. Preparation and characterization of cationic PLGA nanospheres as DNA carriers. Biomaterials. 2004;25(10):1771-1777.)

FIGURE 7



Evidence For Nanometric Vesicles & Pores (Arrows) in Human Alveolar Epithelial Cells in Primary Culture (HAEpC)[14] (Fuchs SA, et al. Differentiation of human alveolar epithelial cells in primary culture: morphological characterization and synthesis of caveolin-1 and surfactant protein-C. Cell & Tissue Research. 2003;311(1):31-45.)

formation of characteristic plasma membrane structures termed caveolae and the synthesis of their major structural protein, caveolin-1, was observed in these cells. The caveolae system is of interest because of its potentially important role in macromolecule transport across the air-blood-barrier of the lung, possibly also relevant to the transport of nanoparticles.

SUMMARY & OUTLOOK

Nanoparticles were demonstrated to have an excellent potential as advanced drug carrier systems. Their advantage compared to other formulation approaches relies on the following: 1) protection and controlled release of the active compound, 2) size-dependent accumulation to inflamed mucosal areas, and c) enhanced cellular binding and uptake, eventually mediated by surface modification with receptor-specific ligands.

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BIOGRAPHY

Dr. Claus-Michael Lehr is head of the Department of Biopharmaceutics and Pharmaceutical Technology at Saarland University, Germany. He earned his PhD in 1991 from Leiden University, the Netherlands and was a Post-doc at the University of Soiuthern California, Los Angeles. The central theme of his research includes biological barriers, in particular those of the lungs, the GI tract, and the skin. A first line of his research focuses cell culture based in vitro models, a second line with advanced drug carrier systems, in particular nanomedicines, to overcome these barriers. His work was recently recognized by the APV Research Award 2006 for Outstanding Achievements in the Pharmaceutical Sciences. Dr. Lehr is European Editor of the *European Journal of Pharmaceutics and Biopharmaceutics* and member of the editorial boards of several other peer-reviewed international journals in the Pharmaceutical Sciences. He coordinates the EU-funded GALENOS network (www.galenos.net) with currently more than 50 academic and several industrial member institutions. The networks' program *Euro-PhD in Advanced Drug Delivery* aims to promote and to recognize in-depth scientific training and international mobility of young pharmaceutical scientists across Europe and worldwide.

EXTENDED RELEASE

Oral Extended Release: Snapshots & Benefits

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

INTRODUCTION

How a drug is going to be delivered to a patient is a concern for pharmaceutical and biotechnology companies for every project from the point of R&D conception. Even though oral delivery is often the preferred choice of developers for many applications, within that realm, there are a variety of release formulation approaches and technologies available. Extended release is an oral delivery approach that in many cases can bring benefits to companies from both a product performance and business standpoint. This can apply to both new products and existing products currently in the marketplace.

Within the area of drug delivery, oral products tend to get a great deal of focus in drug development due to the obvious ease-of-use-factor for patients. Additionally, however, within the realm of oral delivery, there are a variety of different aspects that contribute to the therapeutic performance and systemic exposure properties of the drug in vivo. How the drug substance is released over time plays an important role in that. Often, companies can also take existing oral products, and for lifecycle or innovation purposes, change the release form, thereby potentially improving therapeutic performance as well as revenue and growth potential.

Not all products can benefit from a transition to an extended-release form. However, for those in which this delivery modification can bring added benefits, it is worthwhile for pharmaceutical companies to consider this change. Often, one factor that comes about from an extended-release version is the reduction of adverse side effects. For a product that has good therapeutic efficacy, but is limited in use by uncomfortable or inconvenient side effects, this can be an important factor to increase product penetration in the marketplace. Other benefits include reduced dose frequency due to the product's ability to obtain a longer sustained level in the blood. The patient can also receive benefit from reduced fluctuation of the product over time, a point especially relevant to compounds with short half-lives. This can also benefit patients by reducing the number of daily pills if the drug requires multiple from a conventional formulation version.

PRODUCT PROFILE: NIASPAN (NIACIN EXTENDED RELEASE)

An example of the product benefits that can occur from an extended-release formulation can be found in the cholesterol drug, Niaspan (niacin extended release). Niacin has been utilized as a drug to modulate lipid levels since the 1950s and is the oldest pharmacotherapy used in the treatment of cholesterol disorders. However, use of niacin has been limited due to adverse side effects, most notably cutaneous flushing of the facial and truncal regions of the body. In order to potentially improve upon this, sustained-release niacin was developed to attempt to reduce the flushing side effect. The reduction of flushing did occur with this change, however, sustained-release niacin gained in the adverse point of the potential for hepatotoxicity, as well as liver failure.

Launched by Kos Pharmaceuticals (now a subsidiary of Abbott Laboratories) in the US in 1997, Niaspan is currently the best option for patients looking to utilize a niacin-based approached to cholesterol therapy. Kos Pharmaceuticals utilized its proprietary HydroGel drug delivery technology in the extended-release formulation of the product. This delivery technology is based on a superporous hydrogel. The extended-release formulation of niacin in Niaspan has enabled the product to have a variety of superior product characteristics over other types of immediate- or sustained-release niacin formulations in the market. Due to the mechanism obtained through this extended-release formulation, the product resulted in a reduced flushing profile without an increase risk for hepatotoxicity. The differentiation and subsequent patient benefits through this has also enabled the product to become the leading revenue niacin product in the market. Kos Pharmaceuticals expanded its product line past Niaspan by incorporating the drug in its single pill combination product, Advicor (niacin extended-release/lovastatin).

TECHNOLOGY PROFILE: SODAS — ELAN CORPORATION

The Spheroidal Oral Drug Absorption System (SODAS) from Elan Corporation is a flexible dosage technology that allows for customization of the dosage form for a variety of dosage profiles. This technology is based on spherical beads that contain the drug compound and excipients coated with a polymer that provides customized dissolution rate control. The beads are placed in a hard gelatin capsule for the final product, depending upon the desired

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FIGURE 1

Product	Delivery Company	Technology	Drug Company	Therapeutic Area
Niaspan	Kos Pharmaceuticals	Hydrogel	Abbott (Kos Pharmaceuticals)	Cholesterol Management
Avinza	Elan	SODAS	King Pharmaceuticals	Pain Management
Glumetza	Depomed	AcuForm	King Pharmaceuticals	Diabetes
Glucotrol XL	ALZA	OROS	Pfizer	Diabetes
Ditropan XL	ALZA	OROS	Ortho-McNeil	Overactive Bladder
Ultram ER	Biovail	Smartcoat	Ortho-McNeil	Pain Management
Opana ER	Penwest Pharmaceuticals	TIMERx	Endo Pharmaceuticals	Pain Management

Selected Marketed Products Utilizing Extended-Release Formulations

release profile. This technology is used in several marketed products, including Avinza (morphine sulfate extended-release capsules), currently marketed by King Pharmaceuticals. In Avinza, extended-release properties obtained from using Elan's SODAS technology resulted in positive product properties, such as less peak-to-trough plasma concentration fluctuations and improved quality of sleep versus other competing products with different formulation types.

TECHNOLOGY PROFILE: OROS – ALZA CORPORATION

The OROS technology from ALZA Corporation is utilized in the extended-release formulation of multiple products currently in the global market. In OROS, ALZA offers a variety of drug-performance technological alternatives and is highly customizable. OROS is an osmotic technology that provides precision delivery control for up to 24 hours and can be utilized with both highly soluble and poorly soluble compounds. This technology is currently used in a number of commercial products to achieve an extended-release profile. These include both OTC and prescription drug products utilized in diverse areas, including cardiovascular, diabetes, allergy, and ADHD.

WHAT'S THE IMPACT

For pharmaceutical companies, the availability of extended-release technologies is something that can benefit them in a variety of ways. For products that have suboptimal product profile characteristics, or other factors that may limit usage, an investigation into whether a new formulation approach could improve upon that may be warranted. Also, the changing of a product to an extended release-version could benefit the company from the aspect of lifecycle management. This is achieved by attempting to move the patient population on the product to the newer extended-release type, which would have a longer period of IP protection. For example, Novartis introduced an extended-release version of Lescol (fluvastatin) in 2000 named Lescol XL. The US patent on Lescol expires in 2011, while the patent on Lescol XL expires in 2019. It is estimated that the majority of patients on Lescol had moved to the XL version by 2004. If the formulation technology is something that is developed in-house, in addition to utilization in the company's own product line, they could also look to partner with other companies in order to reap further gains from their intellectual property. Through extended-release formulations, the benefit to patients in many cases can be significant. This in turn can create new market opportunities, as in the case of Niaspan.

For drug delivery companies, developing oral technologies that are highly adaptable to client needs are the ones that could have a higher potential in terms of the number of partnership arrangements. Because products throughout the industry have diverse requirements in terms of product performance, those technologies with the largest amount of design capabilities in terms of achieving an extended-release drug could have the broadest appeal to companies looking for a technology partner. Even though some pharmaceutical companies may attempt to go-it-alone in terms of the development of both formulation and drug in-house, the expertise that drug delivery companies can offer should be carefully evaluated in order to ensure the development of the best product possible.

BIOGRAPHY

Mr. Daniel Ruppar is the Industry Manager of Frost & Sullivan's North American Pharmaceutical & Biotechnology analyst team. He focuses on monitoring and analyzing emerging trends, technologies, and market dynamics in the Pharmaceutical and Biotechnology Industry in North America. Since joining Frost & Sullivan, Mr. Ruppar has assumed primary coverage of the cardiovascular sector. His recent work has focused on cholesterol therapy, thrombosis, diabetes, and colorectal cancer. He also has performed consulting duties for the Venture Capital industry. Prior to this, Mr. Ruppar spent 9 years in the pharmaceutical industry as a Medicinal Chemist. Additionally, he is a co-author of multiple scientific publications in peer-reviewed journals for his work in chemistry, has authored multiple articles in *Drug Delivery Technology*, and is a co-inventor on four patents for his work in drug discovery. He earned his BS in Biochemistry with a minor in Economics from Trinity University.

A pH-Triggered In Situ Gel-Forming Ophthalmic Drug Delivery System for Tropicamide

By: Mitan R. Gokulgandhi, (MPharm); Jolly R. Parikh, PhD; Megha Barot, MPharm; and Dharmesh M. Modi, MPharm

ABSTRACT

A major problem in ocular therapeutics is the attainment of optimal drug concentration at the site of action, which is compromised mainly due to precorneal loss factors resulting in only a small fraction of the drug being ocularly absorbed. The effective dose administered ophthalmically may be altered by increasing the retention time of medication into the eye by using an in situ gel-forming system. The aim of this work was to prepare and evaluate an ophthalmic delivery system of a model drug (tropicamide) based on the concept of pH-triggered in situ gelation. Polyacrylic acid (Carbopol® 940 0.4% to 0.5% w/v) was used as the gelling agent in combination with HPMC K15M (0.3% to 0.5% w/v) as a viscosity-enhancing agent. Suitable concentration of mannitol and benzalkonium chloride were used as an isotonicity-adjusting agent and a preservative, respectively. All the formulations were sterilized in an autoclave at 121°C and 15 psi for 20 mins. The aforementioned formulations were evaluated for in vitro gelling capacity, rehological behaviors, and % drug release. The in vitro gelling capacity was carried out using simulated tear fluid showing a higher gelling capacity for Carbopol 940 (0.4% to 0.5% w/v) formulation containing higher concentration of HPMC K15M. All the formulations were found to exhibit pseudoplastic behavior for both the solution and gel. The developed formulation provides sustained release of drug from formulation at the site of action over an 8-hr drug release with increased time of residence of the formulation in the precornea. The selected formulation was tested in albino rabbits (male) using the Draize test protocol with cross-over studies and found to be non-irritant to the rabbit eye. Thus, the developed system may be a valuable alternative to the conventional system.

INTRODUCTION

The available ocular drug delivery systems are fairly primitive and inefficient. Medication is applied to the surface of the eye for two purposes: to treat the outside of the eye for infection (such as conjunctivitis, blepharitis, and keratitis) or to provide intraocular treatment through the cornea for diseases (such as glaucoma or uveitis). Most ocular diseases are treated with a topical application of solution administered as eye drops. But these preparations, when instilled in to the cul-de-sac, are rapidly drained away from ocular cavity due to tear flow and lachrymal nasal drainage. Only a small amount is available for its therapeutic effect resulting in infrequent dosing, an due to naso-lacrimal drainage, other systemic toxicity can occur.[1] Thus, inefficient drug delivery into the eye occurs due to rapid tear turn over, lachrymal drainage, and drug dilution by tear fluid.[2]

Eye drops used for soluble drug require frequent instillation of highly concentrated solution. The practical reasons for selecting a solution is the generally favorable cost advantage, the greater simplicity of formulation development and production, and the good acceptance by patient despite a little blurring.[3] Despite the excellent acceptance by patients, one of the major problems encountered is rapid precorneal drug loss. To improve ocular drug bioavailability, there is a significant effort directed toward new delivery systems for ophthalmic administration.

Several new preparations have been developed for ophthalmic use, not only to prolong the contact time of the vehicle at the ocular surface, but at the same time slow down the elimination of drug from the eye.[4] Successful results were obtained with inserts and collagen shields, although these preparations present some disadvantages, such as patient non-compliance (especially by elderly people) and people who lose the device (sometimes without becoming aware of it).[5,6] Based on this, liquid dosage forms are preferable.

The aforementioned problems can be overcome by using in situ gel-forming ophthalmic drug delivery systems prepared from polymers that exhibit reversible phase transition and pseudoplastic behavior to minimize interference with blinking. These kinds of systems can be formulated as a drug containing a liquid dosage form suitable for administration by instillation in

TABLE 1

Formulation	Polymer Concentration (% w/v) in Ultrapure Water	
	Carbopol® 940	HPMC K15 M
CH1	0.4	0.3
CH2	0.4	0.4
CH3	0.4	0.5
CH4	0.5	0.3
CH5	0.5	0.4
CH6	0.5	0.5

Various Formulations of an In Situ Gelling System for Carbopol

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to the eye, which upon exposure to physiological conditions of the eye, will shift to the gel phase (semi-solid phase) from the liquid phase, thus increasing precorneal residence of the delivery system and enhancing ocular bioavailability. The following three methods have been employed to cause phase transition on the eye surface (change in viscosity):

- Change in ionic concentration or electrolyte composition[7]
- Change in pH[8]
- Change in temperature[9]

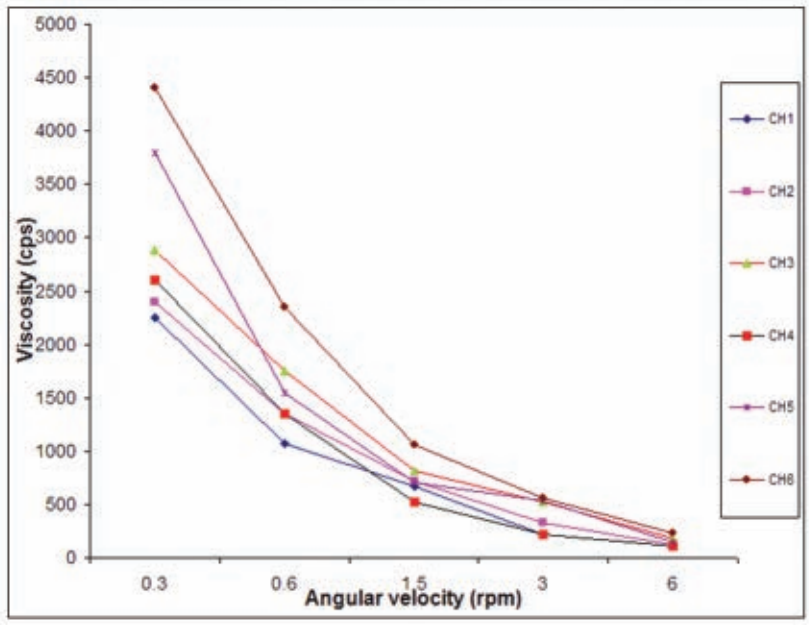
Sustained drug delivery can be achieved using a polymer that changes from sol to gel by change in pH of the formulation due to presence of simulated tear fluid. Carbopol, a Polyacrylic Acid (PAA), is a polymer that exhibits a sol-gel phase transition by change in pH of the formulation. It shows a sol-gel transition as the pH is increased above its pKa value.[10]

Different grades of Carbopol are available, but the manufacturer states that Carbopol 934 gel has the lowest cross-linking density, while Carbopol 981 has intermediate, and Carbopol 940 has the highest cross-linking density. The objective of the present work was to develop a pH-triggered in situ gelling ophthalmic delivery system of tropicamide, a mydriatic agent used to produce mydriasis and cycloplegia in the eye. A combination of Carbopol and hydroxypropyl methyl cellulose (HPMC) was investigated as a vehicle for the formulation of eye drops of tropicamide (0.5% w/v), which would gel when instilled into the eye and provide a sustained release of drug at the site of action.

MATERIALS

Tropicamide was obtained as a gift sample from Allargan. Carbopol 940 was obtained as gift sample from Arihant Trading Co. (Noveon). HPMC K15M was a gift sample from Zydus Cadila. All the other ingredients and reagents were of AR grade.

FIGURE 1



Comparison of Viscosity (CPS) of Various Formulations

METHODS

Selection of Vehicles

The solubility of tropicamide was tested in Acetate buffer (pH 5.0) and Phosphate buffer (pH 7.4). Solubility of tropicamide was evaluated using a U.V. Spectrophotometer (Shimadzu 1601) at 252.5 nm.

Preparation of In Situ Gelling System

Aqueous solutions of varying concentrations of Carbopol 940 and HPMC K15M were prepared (Table 1) and evaluated for gelling capacity and viscosity in order to identify the composition suitable for use as an in situ gelling system.

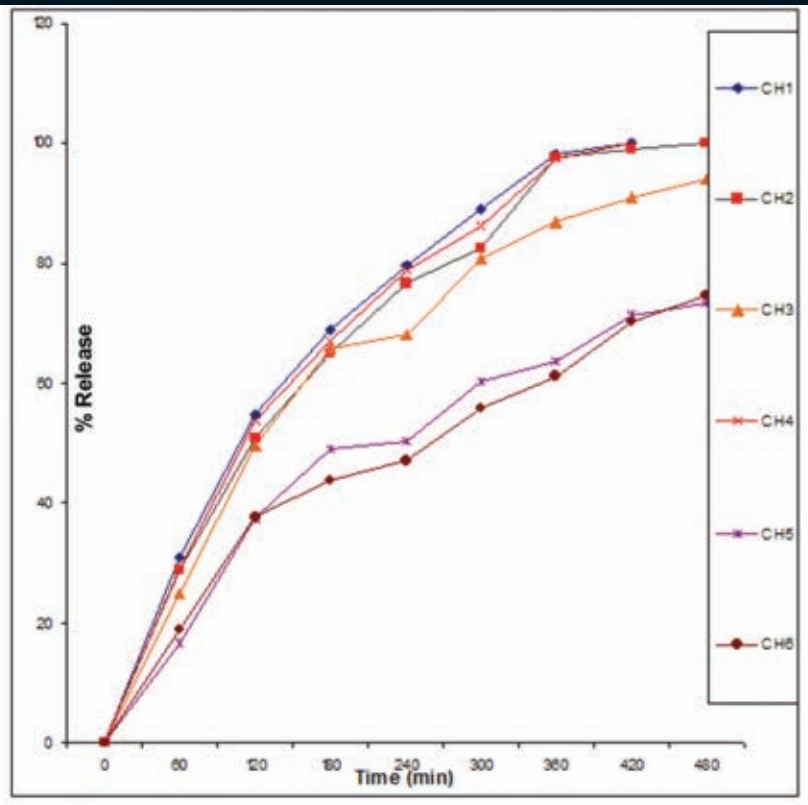
The details of the formulation ingredients for preparing the in situ gel-forming systems of tropicamide are shown in Table 2. The buffer salt potassium dihydrogen phosphate was dissolved in 50 ml of ultrapure water. HPMC K15M was added and allowed to hydrate. Carbopol 940 was sprinkled over the solution and stirred until it dissolved. Appropriate amount of 0.2 M NaOH was added into that solution. Tropicamide (0.5% w/v) was added to the solution as well. Mannitol and benzalkonium chloride (0.01% w/v) were added as an isotonicity-adjusting agent and preservative, respectively. The ultrapure water was then added to make up the volume to 100 ml. The developed formulations were then sterilized by autoclaving at 121°C and 15 psi for 20 mins. Formulations were preserved in a tightly close container.

Isotonicity Adjustment

Carbopol 940 and HPMC K15M combination formulations were made isotonic using an isotonicity-adjusting agent. Mannitol was used as a non-electrolyte isotonicity-adjusting agent. The quantity required for adjustment was calculated from the following equation:

[(Gram/L)/Mol Wt)]*100 = mosmol/L
(Molecular weight of mannitol = 182.17)

FIGURE 2



Comparison of % Release of Drug for Different Formulations

EVALUATION PARAMETERS

In Vitro Gelling Capacity

The gelling capacity of the prepared formulations was determined by placing a drop of the formulations in a test tube containing 2 ml of freshly prepared simulated tear fluid. The composition of the tear fluid was NaCl (0.670 g), Na_2CO_3 (0.200 g), $CaCl_2$ (0.008 g), and ultrapure water (100 ml), which equilibrates at 37°C ± 0.5°C. The gel formation was then visually observed, noticing the time for the gel to form and the time taken for the gel to dissolve.

Rheological Studies

Rheological properties of the gels were measured with a Brookfield viscometer (LV-II + PRO). The samples were thermostated at 37°C ± 0.5°C by a circulating bath connected to the viscometer adaptor prior to each measurement. The angular velocity of the spindle was increased from 0.3, 0.6, 1.5, 3, 6 rpm, and the viscosity of the formulations was measured. The hierarchy of the angular velocity was reversed, and the average two reading was used to calculate the viscosity.

In Vitro Release of In Situ Gel-Forming System

In vitro release of tropicamide was carried out in formulations with different concentrations of Carbopol 940 with different concentrations of HPMC K15M using a dialysis membrane. The diffusion medium was taken as 500 ml of simulated tear fluid composition-I and stirred at 50 rpm at 37°C ± 0.5°C. One end of the basket (USP type-II) was covered by a dialysis membrane, and the remaining portion was covered by suitable material. The formulation was kept in that basket, and the basket was kept in the diffusion medium so as the formulation came in contact with the simulated tear fluid. The drug samples were withdrawn at the interval of 30 mins from diffusion medium and analyzed by a U.V. spectrophotometer [Shimadzu 1601] at 252.5 nm using simulated tear fluid as a blank.

Ocular Irritancy

In 1999, Draize, who was at that time a member of the FDA staff, and his co-workers published the first standardize method that formed the basis of the most widely used system for studying in vivo eye irritation. The original method has undergone sudden changes in order to incorporate the ability to test eye irritation with different types of chemicals.[11] All these techniques were designed for the ocular irritation potential of the ophthalmic product prior to marketing. According to the Draize test, the amount of test substance applied to the eye is normally 100 microliters (or 100 micrograms for solid) placed into the lower cul-de-sac with observation of the various criteria made at a designated required time interval of 1 hr, 24 hrs, 48 hrs, 72 hrs, and 1 week after administration. Approval of the Institutional Animal Ethic Committee was obtained prior to the commencing of the study. A total six albino rabbits (male) weighing 1.5 to 2 kg were used for the present study. The sterile formulation was instilled twice a day for a period of 7 days, and a cross-over study was carried out (a 3-day washing period with saline was carried out before the cross-over study). Rabbits were observed periodically for redness, swelling, watering of the eye. The evaluation was made according to the Draize test protocol.

RESULT & DISCUSSION

Selection of Vehicle

Buffers play a vital role in formulating ophthalmic drug delivery systems. They contribute significantly to the chemical stability and clinical response and influence the comfort and safety of the product, hence

the importance of selecting a suitable buffer that ensures product stability and desired drug solubility. The studies in buffer solutions indicate that drug was soluble in Acetate buffer pH 5.0 and Phosphate buffer pH 7.4 at the dosage level desired (0.5% w/v). The marketed eye drops were found to have pH of 6.8. Phosphate buffer pH 7.4 was therefore selected as the vehicle for the formulated eye drops.

Preparation of Formulation

The use of Carbopol 940 (Polyacrylic acid, PAA) in in situ gel-forming systems was substianted by its ability to transform from an aqueous property into stiff gels when the pH is raised. However, the concentration of PAA required to form stiff gels results in highly acidic solutions, which are not easily neutralized by the buffering action of the tear fluid. A reduction of Carbopol 940 concentration without compromising the gelling capacity and rheological properties of the delivery system may be achieved by the addition of a viscosity-enhancing polymer, such as HPMC K15M.

In Situ Gelling Capacity

The two main prerequisites of an in situ gelling system are viscosity and gelling capacity. The formulation should have an optimum viscosity that will allow for easy instillation into the eye as a liquid (drops), which would undergo a rapid sol-to-gel transition (triggered by increased pH). Additionally, the gel formed in situ should preserve its integrity without dissolving or eroding for a prolonged period. Table 3 shows the gelling capacity of the different formulation combination of Carbopol 940 and HPMC K15M.

Rheology Studies

Formulations with a combination of Carbopol 940 and HPMC K15M were found to be shear thinning, and increase in shear stress was observed with increase in angular velocity. The administration of an ophthalmic preparation should influence as little as possible the pseudoplastic character of the precorneal tear film. Because the ocular shear rate is very large, ranging from 0.03 S^{-1} during interblinking period to 4250-28500 S^{-1} during blinking. An increase in pH to 7.4 (the pH of tear fluid) caused the solution to transform into gels with high viscosity. Viscosities of the different formulations at pH 7.4 are shown in Table 4. As the angular velocity increases, the viscosity of the formulation decreases (Pseudoplastic rheology) (Figure 1). The rank order of viscosity of different formulations of Carbopol 940 and HPMC K15M combinations are as follows: CH6> CH5> CH3> CH2> CH4> CH1.

TABLE 2

Ingredients	Quantity Required (g)
Tropicamide	0.5
Carbopol® 940	0.4,0.5
HPMC K15 M	0.3,0.4,0.5
NaOH I.P	0.117
Mannitol	5.0
Benzalkonium Chloride	0.01% w/v
Potassium dihydrogen phosphate	0.6804
Ultra pure water	Up to 100 mL

Ingredients of the Developed Formulation

TABLE 3

Formulation	Polymer Concentration (% w/v) in Ultrapure Water		Gelation Capacity
	Carbopol® 940	HPMC K15M	
CH1	0.4	0.3	+
CH2	0.4	0.4	++
CH3	0.4	0.5	+++
CH4	0.5	0.3	+
CH5	0.5	0.4	+++
CH6	0.5	0.5	+++

+ Low-gelling capacity, ++ Intermediate gelling capacity, +++ High-gelling capacity

In Situ Gelation Capacity for Various Formulations

In Vitro Release Studies

The % drug release of the formulations CH1, CH2, CH3, CH4, CH5, and CH6 were found to be 100%, 99.10%, 93.47%,74.58%, 73.37%, and 69.85%, respectively. Cellulose derivatives like HPMC K15M with a higher molecular weight dissolve in water and yield much more viscous solution compared to Carbopol 940 solution. Thus, the increase in viscosity might have contributed to the decrease in rate of drug release from these formulations. The % release of tropicamide as a function of time is shown in Figure 2. The in vitro drug release condition may be very different from those likely to be encountered in the eye. However, the results clearly show that the gels have the ability to retain tropicamide and that premature drug release will not occur. In the cul-de-sac, the gels will probably undergo faster dissolution due to the shearing action of the eyelid and eyeball movement. So from the data of % release and viscosity profile, formulation CH5 was selected for its ocular irritancy study.

Ocular Irritancy

The formulation (CH5) was found to be non-irritating with no ocular damage or abnormal clinical signs to the cornea, iris, or conjunctivae observed. The result of ocular irritancy studies are shown in Table 4.

CONCLUSION

Tropicamide, a mydriatic agent used to produce mydriasis and cycloplegia, was successfully formulated as pH-triggered in situ gel-forming eye drops (0.5% w/v) using Carbopol 940 as a gelling agent in combination with HPMC as a viscosity-

TABLE 4

Angular Velocity (rpm)	Formulation Batch					
	CH1	CH2	CH3	CH4	CH5	CH6
0.3	2250	2400	2600	2850	3800	4400
0.6	1075	1350	1350	1750	1550	2350
1.5	670	720	520	820	700	1060
3	220	325	220	525	540	560
6	110	125	115	180	150	235

Comparison of Viscosity (CPS) for Different Formulations of Carbopol With HPMC K15 M

TABLE 5

Eye Part	Cornea	Iris	Conjunctiva	Total
Score point	1.5	1	1.5	4

Ocular Irritancy Study as per the Draize Test Protocol

enhancing agent. Formulation CH5 was liquid at the formulated pH and underwent rapid gelation upon raising the pH to 7.4. Also, the formulation was found to be clear, having highest in situ geltion capacity and sustained drug release over an 8-hr period, and non-irritant as per the Draize test protocol. Upon regression analysis of % release as a function of square root of time, r^2 was found to be 0.9787. So from the different model for kinetics of drug dissolution, the prepared formulation follows the Higuchi model.[12,13] The developed formulation is a viable alternative to conventional eye drops by virtue of its ability to enhance bioavailability through its longer precorneal residence time and ability to sustain drug release. Also important is the ease of administration afforded and decreased frequency of administration, resulting in better patient acceptance.

ACKNOWLEDGEMENTS

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INCLUSION COMPLEXION

Physico-Chemical Characterization & In Vitro Dissolution Behavior of Simvastatin-Cyclodextrin Inclusion Compounds

By: R.P. Patel, MPharm, and M.M. Patel, PhD

ABSTRACT

The objectives of this research were to prepare and characterize inclusion complexes of simvastatin with β-cyclodextrin and hydroxypropyl-β-cyclodextrin and to study the effect of complexation on the dissolution rate of simvastatin, a water-insoluble lipid-lowering drug. The phase solubility profiles with both cyclodextrins were classified as A_L-type, indicating the formation of 1:1 stoichiometric inclusion complexes. Gibbs free energy (ΔGtr°) values were all negative, indicating the spontaneous nature of simvastatin solubilization, and they decreased with increase in the cyclodextrins concentration, demonstrating that the reaction conditions became more favorable as the concentration of cyclodextrins increased. Complexes of simvastatin were prepared with cyclodextrins using various methods, such as kneading, coevaporation, and physical mixing. The complexes were characterized by Fourier-transform infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC) studies. These studies indicated complex prepared kneading and coevaporation methods showed successful inclusion of the simvastatin molecule into the cyclodextrins cavity. The complexation resulted in a marked improvement in the solubility and wettability of simvastatin. The complexes exhibited faster and higher rates of dissolution compared to that of simvastatin alone. The complex prepared with hydroxypropyl-β-cyclodextrin using the kneading method exhibited the fastest and highest in vitro dissolution rate when compared to the tablets of pure simvastatin. Physical mixture of cyclodextrin/simvastatin also showed significant improvement in the dissolution rate compared to pure simvastatin. Mean dissolution time of simvastatin decreased significantly after preparation of complexes and physical mixture of simvastatin with cyclodextrins. Similarity factor (f_2) indicated significant difference between the release profiles of simvastatin from complexes and physical mixture and from pure simvastatin.

TABLE 1

Type of CDs	Method of Preparation	Name of Sample
β-CD	Physical Mixture	PMB
β-CD	Coevaporation	CCB
β-CD	Kneading	CKB
HPβ-CD	Physical Mixture	PMH
HPβ-CD	Coevaporation	CCH
HPβ-CD	Kneading	CKH

Abbreviations used to designate samples of SIM prepared with β-CD and HPβ-CD by different methods

INTRODUCTION

Simvastatin (SIM) is a lipid-lowering agent derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, SIM, an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is a principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase, the enzyme that catalyses an early and rate-limiting step in the biosynthesis of cholesterol.[1] SIM is a white, crystalline, non-hygroscopic powder that is insoluble in water and 0.1 N HCl (30 µg/ml and 60 µg/ml, respectively). At room temperature, the partition coefficient of SIM between octanol and either pH 4 acetate or pH 7.2 acetate is > 1995.[2] It is generally considered that compounds with very low aqueous solubility will show dissolution rate-limited absorption and hence poor absorption, distribution, and targeted organ delivery.[3] Improvement of aqueous solubility in such a case is a valuable goal to improve therapeutic efficacy.

Cyclodextrins (CDs) form a group of structurally related oligosaccharides with cylinder-shape cavities that have the capacity to form inclusion complexes with many drugs by taking a whole drug molecule, or a part of it, into the cavity.[4,5] Because of the large number of hydroxyl groups on CDs, they are water soluble. They are known for their ability to molecularly encapsulate a wide variety of drugs into their hydrophobic cavity without the formation of any covalent bonds. CDs have widespread pharmaceutical applications mainly because of their effect on enhancing the solubility and bioavailability of many drug formulations. Complexation with cyclodextrins has been reported to enhance the solubility, dissolution rate, and bioavailability of poorly water-soluble drugs.[6-9] CDs first came to the fore in marketed products as drug delivery technologies that enabled the development of various prostaglandins.[10]

β-cyclodextrin (β-CD) has ideal dimensions to complex a range of commonly used drugs. Unfortunately, it has a limitation of high affinity for cholesterol, which may lead to crystallization of poorly water-soluble β-CD-cholesterol complex in the kidney and hence causing nephrotoxicity. Hydroxypropyl-β-cyclodextrin (HPβ-CD), a chemical derivative of β-CD, similarly improves the aqueous solubility of many drugs, but it is more hydrophilic than the β-CD, forms a less stable complex with cholesterol, and is therefore less toxic.[11] HPβ-CD is more water-soluble than the parent molecule and

has hydroxypropylester groups attached to the hydroxyl groups in position 2. Mass spectrometry and molecular modeling studies on the inclusion complexes between α, β-cyclodextrins and simvastatin were performed.[12] Inclusion complex of Rofecoxib/HPβ-CD (1:1 molar ratio) has been prepared using the kneading method with a subsequent improvement in dissolution due to amorphization.[13] Many other drugs, such as ibuprofen, tolbutamide, ganciclovir, nimesulide, itraconazole, etc have been tested to determine the effect of CD inclusion on enhanced solubility.[14-18]

In vitro dissolution testing provides an easy and convenient means to evaluate the performance of pharmaceutical preparations. The in vitro dissolution profile is a reliable index to accurately predict the in vivo performance. In this study, an attempt was made to compare the similarity between in vitro dissolution profiles of SIM from complexes, physical mixture, and pure SIM. Dissolution profiles can be compared by calculating similarity factor (f_2 values). The method was first reported by Moore and Flanner.[19] It has also been adopted by the Center for Drug Evaluation and Research (US FDA, 1997) and by the Human Medicines Evaluation Unit of The European Agency for the Evaluation of Medicinal Products (EMEA, 1999) as a criteria for the assessment of similarity between two dissolution profiles. The similarity equation is given in the US FDA guidelines for industry for dissolution testing of immediate-release products.[20,21] A value of 100% for the similarity factor (f_2) suggests that the test and reference profiles are identical. Values between 50 and 100 indicate that the dissolution profiles are similar, whilst smaller values imply an increase in dissimilarity between release profiles.[19]

Mean dissolution time (MDT) reflects the time for the drug to dissolve and is the first statistical moment for the cumulative dissolution process that provides an accurate drug release rate.[22] It is an accurate expression for drug release rates. A higher MDT value indicates greater drug-retarding ability.[23]

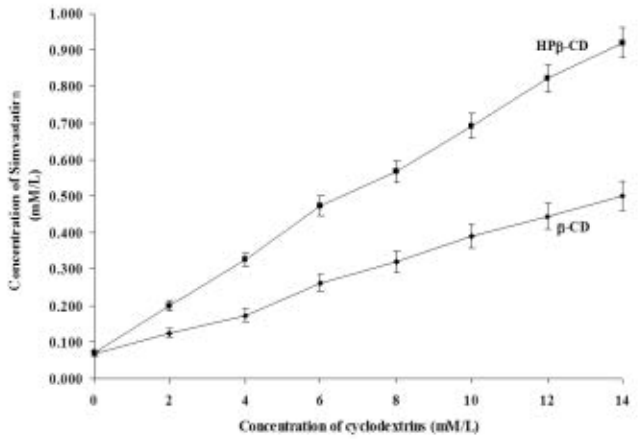
The objective of the present study was to prepare inclusion complexes of SIM with β-CD and HPβ-CD using various methods, such as kneading, coevaporation, and physical mixing to improve its aqueous solubility and dissolution rate. The study was further aimed to characterizations of prepared inclusion complexes by methods such as Fourier Transform Infra Red (FTIR) and Differential Scanning Calorimetry (DSC) studies.

MATERIALS & METHODS

Materials

HPβ-CD and β-CD were a generous gift from Roquette Frères, France. Simvastatin was received as a gift sample from Lincoln Pharmaceuticals Ltd, (Ahmedabad, India). The sample sodium lauryl sulfate (SLS) was procured from S.D. Fine Chemicals, (Vadodadra, India). Directly compressible lactose, maize starch, sodium starch glycollate, colloidal silicon dioxide, and magnesium stearate were received as gift samples from Maan Pharmaceuticals Ltd., (Ahmedabad, India). All chemicals and solvents used in this study were of analytical reagent grade. Freshly distilled water was used throughout the work.

FIGURE 1



Phase Solubility Curve of SIM in Aqueous Solution of CDs at 37°C

Phase-Solubility Studies

Phase-solubility studies were performed according to the method reported by Higuchi and Connors.[24] SIM, in amounts that exceeded its solubility, were transferred to screw-capped vials containing 25 ml of aqueous solution of β-CD (molecular weight = 1135) or HPβ-CD (molecular weight = 1500) in various molar concentrations (0, 2.0, 4.0, 6.0, 8.0, 10.0, 12.0, and 14.0 mM/L, each for β-CD and HPβ-CD). The contents were stirred on electromagnetic stirrer (Remi, India) for 36 hrs at 37°C ± 0.1°C and 350 rpm (this duration was previously tested to be sufficient to reach equilibrium). After reaching equilibrium, samples were filtered through a 0.22-m membrane filter, suitably diluted and analyzed spectrophotometrically for drug content at the wavelength of 238 nm using a spectrophotometer (Shimazdu-1601, UV/Vis Spectrophotometer, Shimadzu Corp, Kyoto, Japan). Solubility studies were performed in triplicate (n = 3). The apparent stability constant (Ks), according to the hypothesis of 1:1 stoichiometric ratio of complexes, was calculated from the phase-solubility diagrams using the following equation:

$$K_{1:1} = \frac{\text{slope}}{S_o(1 - \text{slope})}$$

Where slope is obtained from the initial straight-line portion of the plot of SIM concentration against CDs concentration, and S_0 is the equilibrium solubility of SIM in water.

Preparation of Inclusion Complexes

Complexes of β-CD and HPβ-CD with SIM were prepared in the molar ratio of 1:1 (on the basis of phase solubility study) by different methods like physical mixture, coevaporation, and kneading. For ease in discussion, the samples are designated with different abbreviations shown in Table 1.

Physical Mixture

Physical mixture (PM) of CDs and SIM were prepared by simply mixing powders with a spatula for 15 mins.

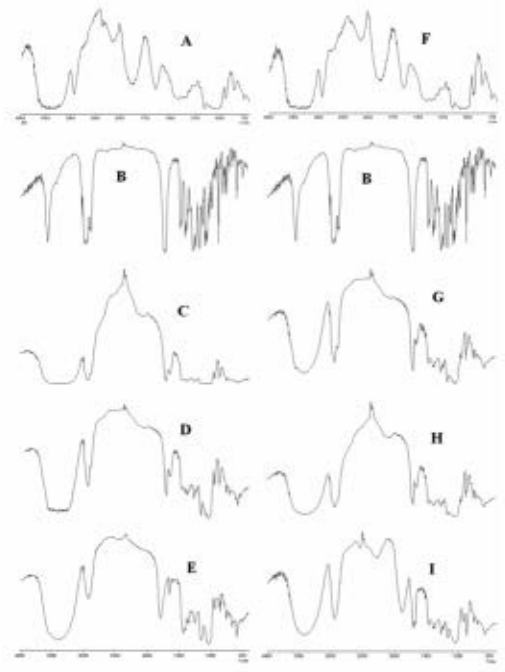
Coevaporation Method

For preparation of complexes using the coevaporation method, methanol and water were used as solvents. The required quantities of SIM and CDs were dissolved in the same quantities of methanol and water, respectively. Both the solutions were mixed, and the solvents were evaporated by controlled heating at 45°C to 50°C. The resultant solids were pulverized and then sieved through No. 120.

Kneading Method

For preparation of complexes using the kneading method, the required quantities of CDs and distilled water were mixed together in a motor so as to obtain a homogeneous paste. SIM was then added slowly, and while grinding, a small quantity of methanol was added to assist the dissolution of SIM. The mixtures were then ground for 1 hour. During this process, an appropriate quantity of water was added to the mixture to maintain a suitable consistency. The pastes were dried in an oven at 45°C to 50°C for 24 hrs. The dried complexes were pulverized and then sieved through No. 120.

FIGURE 2



FTIR Spectras of βCD(A), SIM(B), PMB(C), CCB(D), CKB(E), HPβCD(F), PMH(G), CCH(H), and CKH(I)

TABLE 2

Concentration of CDs in water (mM/L)	$\Delta G_{tr}°$ (Cal/mol)[a]	
	β-CD	HPβ-CD
2	-370	-656
4	-575	-955
6	-831	-1186
8	-954	-1298
10	-1076	-1420
12	-1156	-1526
14	-1229	-1596

[a](n=3)

Gibbs free energy of transfer (ΔGtr°) for solubilization process of SIM in aqueous solutions of βCD and HPβCD at 37ºC.

Drug Content

The complexes prepared by the kneading, coevaporation, and physical mixture methods were assayed for SIM content by dissolving a specific amount of the complexes in methanol and analyzing for the SIM content spectrophotometrically at 238 nm on a spectrophotometer.

Characterization of Complexes

Fourier Transform Infrared (FTIR) Spectroscopic Analysis: FTIR spectrums of moisture-free powdered samples of SIM, CDs, their PMs, and complexes with β-CD and HPβ-CD were obtained using a spectrometer (FTIR-8300, Shimadzu Co., Kyoto, Japan) using the potassium bromide (KBr) pellet method.

Differential Scanning Calorimetry (DSC) Analysis: DSC scans of the powdered sample of SIM, CDs, their PMs, and complexes with β-CD and HPβ-CD were recorded using a DSC-Shimadzu 60 with TDA trend line software. The samples (6 to 7 mg) were accurately weighed in crimped aluminum pans and heated from 50°C to 300°C, at a scanning rate of 10°C /min under air flow (100 ml/min).

Wettability & Dissolution Studies

Wettability studies were performed using open tubes containing SIM, CDs, their PMs, and complexes with β-CD and HPβ-CD and were placed with their lower capillary ends dipped into colored water (0.01% eosin in water). The upward migration of the colored front was registered as a function of time. Dissolution studies of SIM in powder form, its PM, and complexes with β-CD and HPβ-CD were performed to evaluate in vitro drug-release profiles. Dissolution studies were carried out using USP dissolution apparatus type II with 500-ml dissolution medium at 37°C ± 0.5°C and 50 rpm for 3 hrs. 0.1 N HCl and distilled water containing 0.25 % (w/v) of sodium lauryl sulfate (SLS) were used as different dissolution mediums. At fixed time intervals, 5-ml aliquots were withdrawn, filtered, suitably diluted, and assayed for SIM content by measuring the absorbance at 238 nm using a spectrophotometer. Equal volume of fresh medium at the same temperature was replaced in to the dissolution medium after each sampling to maintain its constant volume throughout the test. Pure drug, its PM, and complexes with β-CD and HPβ-CD were evaluated for dissolution rate studies. Dissolution studies were performed in triplicates (n = 3), and calculated mean values of cumulative drug release were used while plotting the release curves. MDT values and f_2 values were calculated to compare the extent of improvement in the dissolution rate of SIM from pure drug, its PM, and complexes with β-CD and HPβ-CD. Preliminary tests demonstrated that there was no change in the λmax of SIM due to the presence of CDs dissolved in the dissolution medium.

Formulation Studies

Formulation excipients were selected on the basis of preliminary tests, which demonstrated no interference of these excipients with the λmax of SIM. Tablets containing 10 mg of SIM were made by direct compression using different formulation excipients, such as directly compressible lactose, colloidal silicon dioxide, and magnesium stearate. Tablets containing complexes prepared using the kneading method equivalent to 10 mg SIM were made similarly but using less quantity of lactose. The blend was compressed on an eight-station single rotary machine (Cadmach, India) using round-shape, flat punches to obtain tablets of 4 to 6-kg/cm^2 hardness and 3.5 to 3.7-mm thickness. For the assay, three tablets were crushed, and a blend equivalent to 10 mg of SIM was weighed and dissolved in dissolution mediums. The tablets were studied in triplicates (n = 3) for release profile of drug using the same methodology as described in in vitro dissolution studies.

Statistical Analysis

The model-independent mathematical approach proposed by Moore and Flanner for calculating a similarity factor f_2 was used for comparison between dissolution profiles of different samples. The similarity factor f_2 is a measure of similarity in the percentage dissolution between two dissolution curves and is defined by the following equation:[19]

$$f_2 = 50 \text{ X } \log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t\left(R_t - T_t\right)^2\right]^{-0.5} \text{ X } 100\right\}$$

Where n is the number of withdrawal points, R_t is the percentage dissolved of reference at the time point t, and T_t is the percentage dissolved of test at the time point t.

A value of 100% for the similarity factor (f_2) suggests that the test and reference profiles are identical. Values between 50 and 100 indicate that the dissolution profiles are similar, whilst smaller values imply an increase in dissimilarity between release profiles.[19]

RESULTS & DISCUSSION

Phase Solubility Study

Phase solubility analysis has been among the preliminary requirements toward the optimization of the development into inclusion complexes of the drugs as it permits the evaluation of the affinity between cyclodextrin

and drug molecule in water. This process has been used by many researchers for the determination of the exact molar ratios in which the drugs could make complexes with CDs.[25,26]

The phase solubility curve of SIM in the presence of CDs is shown in Figure 1. From this curve, it can be seen that the apparent solubility of SIM increases due to the formation of an inclusion complex between SIM and CDs. A linear increase of solubility of SIM was observed with an increase in concentration of CDs in water. Increasing amounts of CDs increased the amount of SIM going into water, improving the aqueous solubility of SIM. Solubility of SIM is increased by 7.35-fold and 13.3-fold at 14 mM/L concentration of β-CD and HPβ-CD, respectively. Increased solubility may be due to improved dissolution of SIM particles in water by CDs.

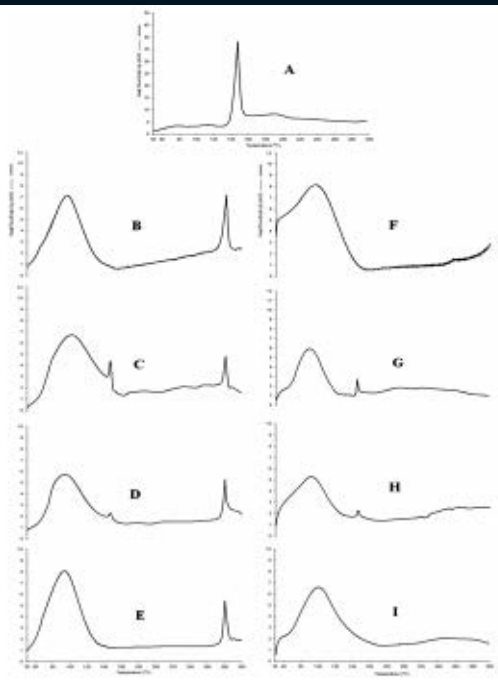
An indication of the process of transfer of SIM from pure water to aqueous solution of CDs was obtained from the values of Gibbs free energy change. The Gibbs free energy of transfer (ΔG_{tr}°) of SIM from pure water to aqueous solutions of CDs was calculated using the following equation:[27]

$$\Delta G_{tr}^{\circ} = -2.303RT\log\left(\frac{S_o}{S_s}\right)$$

Where S_o/S_s = the ratio of molar solubility of SIM in aqueous solution of CDs to that of the pure water. The obtained values of Gibbs free energy are shown in Table 2. This data provide the information regarding the increased solubility of SIM in the presence of CDs. In other words, the Gibbs free energy values provide the information as to whether the reaction condition is favorable or unfavorable for drug solubilization in the aqueous carrier solution. Negative Gibbs free energy values indicate favorable conditions. ΔG_{tr}° values were all negative for CDs at various concentrations, indicating the spontaneous nature of SIM solubilization, and it decreased with an increase in its concentration, demonstrating that the reaction became more favorable as the concentration of CDs increased. These values also indicated that the extent of improvement in solubility was more with HPβ-CD as compared to β-CD.

The stoichiometric ratio at which optimum complexation occurs was confirmed by the phase solubility analysis. The phase solubility plot showed an A_L type solubility curve for both CDs, which indicates that 1:1 β-CD-SIM and HPβ-CD-SIM inclusion complex was formed in solution. Furthermore, the slope values (0.0611 and 0.0317) were lower than 1.0, indicating that inclusion complexes in a molar ratio of 1:1 were formed between the guest (SIM) and host (β-CD and HPβ-CD, respectively) molecules. The values of stability constants (Ks) for the complexes at 37°C, assuming a 1:1 stoichiometry, calculated from the slope of the initial straight portion of the solubility diagram were 520.47 M^{-1} for β-CD: SIM and 804.40 M^{-1} for HPβ-CD:SIM, which indicated a suitable and stable complex formation. It is reported that cyclodextrin-drug complexes with the values of Ks in the range of 200 to 5000 M^{-1} show improved dissolution properties and hence better bioavailability.[24]

FIGURE 3



DSC Thermograms of SIM(A), βCD(B), PMB(C), CCB(D), CKB(E), HPβCD(F), PMH(G), CCH(H), and CKH(I)

TABLE 3

	% SIM release[a]					
	Distilled water			0.1 N HCl		
Sample	$Q_{30\ min}$	$Q_{60\ min}$	$Q_{120\ min}$	$Q_{30\ min}$	$Q_{60\ min}$	$Q_{120\ min}$
Pure SIM	12.6±0.31	18.6±0.43	28.8±0.56	12.8±0.54	20.5±0.68	32.0±0.82
PMB	29.2±1.58	42.0±2.63	58.9±3.04	26.0±1.41	38.0±1.96	58.0±3.37
CCB	43.7±0.61	69.0±0.73	83.2±1.05	52.0±1.33	70.6±1.69	84.8±1.70
CKB	53.6±0.58	78.6±0.99	93.2±1.19	60.5±1.63	79.7±1.83	92.3±1.93
PMH	29.1±1.46	39.2±1.57	53.4±2.98	32.8±1.89	48.9±2.85	64.0±3.96
CCH	55.4±0.82	69.6±0.89	82.8±1.07	55.5±0.68	75.2±1.33	85.0±1.58
CKH	65.5±0.71	81.1±1.01	90.9±1.22	74.5±0.84	89.8±1.09	96.4±1.49

[a]Mean ± SD, n = 5

Percentage of drug dissolved within 30, 60, & 120 minutes.

Drug Content

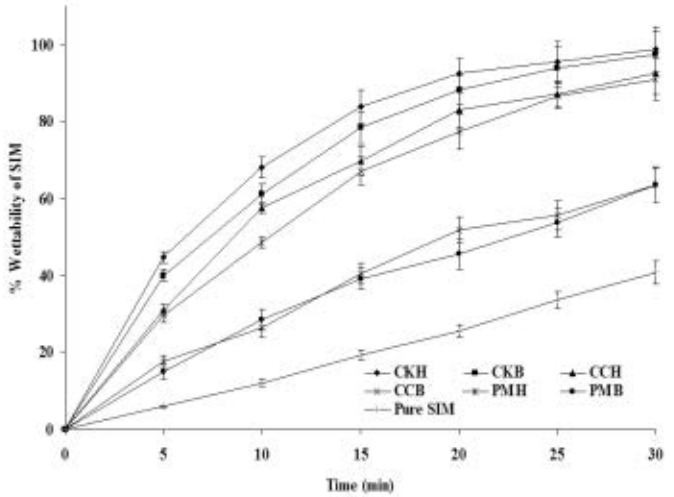
The drug content of the CKB, CCB, PMB, CKH, CCH, and PMH were found to be 99(± 3.54)%, 99(± 3.38)%, and 95(± 7.43)%, 100(± 4.02)%, 99(± 3.12)%, and 96(± 8.06)%, respectively, which approximately correspond to the stoichiometric ratio of the complex and indicate chemical stability and content uniformity of SIM in its complex form.

Characterization of Complexes

Infrared (IR) Spectroscopic Analysis: Fourier transform infrared spectroscopy (FT-IR) has been used to assess the interaction between β-CD and guest molecules in the solid state. The chemical interaction between the drug and the carrier often leads to identifiable changes in the infrared (IR) profile of complexes. However, some of the changes are very subtle, requiring careful interpretation of the spectrum.[28]

The IR spectras of PMB, CCB, CKB, PMH, CCH, and CKH were compared with spectrum of β-CD, HPβ-CD, and SIM (Figure 2). The spectrum of pure SIM presented characteristic peaks at 3553 cm^{-1} (alcohol O-H stretching vibration); 3011 cm^{-1} (olefinic C-H stretching vibration); 2957 and 2878 cm^{-1} (methyl and methylene C-H asymmetric and symmetric stretching vibration); 1701 cm^{-1} and 1719 cm^{-1} (lactone C = O and ester C = O stretch); 1453, 1406, and 1383 cm^{-1} (methyl and methylene bending vibration); 1267, 1222, 1178, and 1080 cm^{-1} (lactone and ester C-O-C bending vibration); 1060 cm^{-1} (secondary alcohol C-O stretching vibration);

FIGURE 4



Wettability Study of Pure SIM, PMB, PMH, CCB, CCH, CKB, and CKH in Water (n=3)

TABLE 4

	MDT (min)[a]	
Sample	**Distilled Water**	**0.1 N HCl**
Pure SIM	75	68
PMB	63	64
CCB	44	36
CKB	36	31
PMH	61	57
CCH	42	37
CKH	33	28

[a]Data are obtained by taking mean of cumulative drug release, n = 5

Mean dissolution time (MDT) values for pure SIM, its physical mixtures, and complexes with CDs in distilled water and 0.1 N HCl.

and 879 cm^{-1} (trisubstituted olefinic C-H wag), respectively. The presence or absence of characteristic peaks associated with specific structural groups of the drug molecule was noted. The IR spectrums of the β-CD and HPβ-CD are characterized by intense bands at 3300 to 3500 cm^{-1} due to O-H stretching vibrations. The vibration of the -CH and CH_2 groups appears in the 2800 to 3000 cm^{-1} region. Any sign of interaction would be reflected by changes in the characteristic peaks of SIM, depending on the extent of interaction.

The IR spectras of PMB, CCB, CKB, PMH, CCH, and CKH were equivalent to the addition spectrum of CDs and SIM. These results indicate absence of well-defined chemical interaction between CDs and SIM during mixing, coevaporation, and kneading. The IR spectras of PMB, CCB, CKB, PMH, CCH, and CKH showed most of characteristic peaks similar to that of CDs, except one peak at 1700 cm^{-1} for lactone and ester carbonyl stretching vibration (hydrogen bonded for 1711 and 1700 cm^{-1}), which is characteristic of SIM. The assumption for this is that pyrol part of the SIM may remain outside the CDs, whereas the remaining part fit inside the cavities of CDs.

Differential Scanning Calorimetry (DSC) Analysis: Differential scanning calorimetry enables the quantitative detection of all processes in which energy is required or produced (ie, endothermic or exothermic phase transformations). The thermograms for pure SIM, CDs, their PM, and complexes with β-CD and HPβ-CD are presented in Figure 3. The SIM showed a melting peak at 143.5°C with enthalpy of fusion (ΔH) 76.379 J/g. In the thermogram of the β-CD and HPβ-CD, two peaks were present. Peak at 100°C was due to loss of water from CDs molecules, and a peak at 300°C indicates the melting or thermal decomposition of CD.

In the thermogram of PMB and PMH, a sharp peak was observed at the same position to that of SIM, indicating the presence of untrapped SIM. A characteristic sharp endothermic peak of SIM in the range of 140°C to 150°C was absent in the thermograms of CCB, CKB, CCH, and CKH, indicating partial amorphization of the drug and trapping of SIM inside the CD's cavity.

Wettability & Dissolution Studies: Solubility of SIM in water was found to be 30 µg (± 0.523)/100 ml. PMB, CCB, CKB, PMH, CCH, and CKH improved the solubility of SIM to 219 µg (± 17.321)/100 ml, 278 µg (± 19.783)/100 ml, 313 µg (± 21.803)/100 ml, 248 µg (± 16.233)/100 ml, 303 µg (± 20.085)/100 ml, 339 µg (± 25.607)/100ml, respectively. Thus, upon complexation of SIM with β-CD and HPβ-CD using the physical mixing, coevaporation, and kneading method, the solubility of SIM was improved by 7.3-fold, 9.2-fold, 10.43-fold, 8.2-fold, 10.1-fold, and 11.3-fold, respectively.

The improvement in wettability of SIM by physical mixing and complexation with CDs is presented in Figure 4. CKB and CKH showed the highest wettability in water (97.6% and 98.8%, respectively), as compared to pure SIM (40.8%) at 30 mins. Even PM of CDs with SIM enhances wettability of SIM in water significantly. Thus, the results of wettability studies indicate that both CDs improve wettability of SIM in water both in PM as well as in complex form due to its hydrophilicity.

The dissolution of poorly soluble drugs requires dissolution media that are different from those normally used for water-soluble drugs. One of the techniques that have been used is the incorporation of a small amount of surfactant in the dissolution medium.[29] The use of surfactants in the dissolution systems may be physiologically more relevant, due to presence of natural surfactants like bile salts in the gastrointestinal tract. The mechanisms of surfactants to enhance the in vitro dissolution of poorly water-soluble drugs may be wetting, micellar solubilization, and/or deflocculation. It is necessary that a biorelevant medium will require similar surface activity as bio-fluids. Studies on sodium lauryl sulfate (SLS) solutions indicate that surface tension of SLS solutions decreased significantly above the critical micelle concentration (0.023%), and it reached a minimum surface tension at 0.2% with no significant change at higher concentrations.[30,31] This suggested that a biocomparable surface activity can be achieved at low surfactant concentrations (0.2%). SLS was selected as a suitable surfactant in the present dissolution studies because preliminary experiments confirmed that SLS exhibited higher solubilization for SIM than other surfactants. Based upon these findings, dissolution of pure SIM and all other prepared systems (complexes and physical mixture) was carried out in aqueous SLS solution (0.25% w/v). When the SIM was dispersed on the surface of the aqueous surfactant solution, SIM rapidly left the surface and was dispersed in the bulk of solution, which clearly indicate wetting of SIM, unlike pure water. Because the principal objective of this work was to improve the dissolution rate of SIM, dissolution studies were carried out for initially 3 hrs.

$Q_{30\ min}$, $Q_{60\ min}$, and $Q_{120\ min}$ values (percent drug dissolved within 30, 60, & 120 mins) in 0.1 N HCl and distilled water are reported in Table 3. From this data, it is evident that onset of dissolution of pure SIM is very low in both dissolution medium (32.0% and 28.8% within 120 mins, respectively). CCB, CKB, CCH, and CKH considerably enhanced dissolution rates within 120 mins compared to pure SIM, PMB, and PMH. The graphical presentation of the dissolution profile of pure SIM, its PM, and

complexes with β-CD and HPβ-CD samples in 0.1 N HCl and distilled water over a period of 3 hrs is shown in Figures 5A and 5B. It is evident that the dissolution rate of pure SIM is very low in both 0.1 N HCl and distilled water, about 40.4% and 39.6% of the drug being dissolved in 3 hrs, respectively. CCB, CKB, CCH, and CKH enhanced the dissolution rate of SIM significantly (91% to 100% in 0.1 N HCl and 88% to 96% in distilled water) within 3 hrs. Possible mechanisms of improved dissolution rates of complexes include reduction of crystallite size, a solubilization effect of carrier, absence of aggregation of drug crystallites, improved wettability, dispersibility of a drug from dispersion, dissolution of the hydrophilic carrier, conversion of drug to amorphous state, and finally, the combination of the aforementioned methods.[32]

The dissolution rate of SIM from PMB and PMH was higher (71% to 75% in 0.1 N HCl and 65% to 73% in distilled water) than that of pure SIM (40.4% in 0.1 N HCl and 39.6% in phosphate buffer) within 3 hrs. Physical mixing of SIM with CDs brings the drug in close contact with CDs. The increased dissolution rate observed in the case of PM can be attributed to several factors, such as a solubilization effect of CDs, improved wettability of drug, and prevention of particle aggregation.

In order to understand the extent of improvement in dissolution rate of SIM from its complexes and physical mixture, the obtained dissolution data of pure SIM, its PM, and complexes with CDs were fitted into the following equation:

$$MDT_{\text{in vitro}} = \frac{\sum_{i=1}^{n} t_{mid}\,\Delta M}{\sum_{i=1}^{n} \Delta M}$$

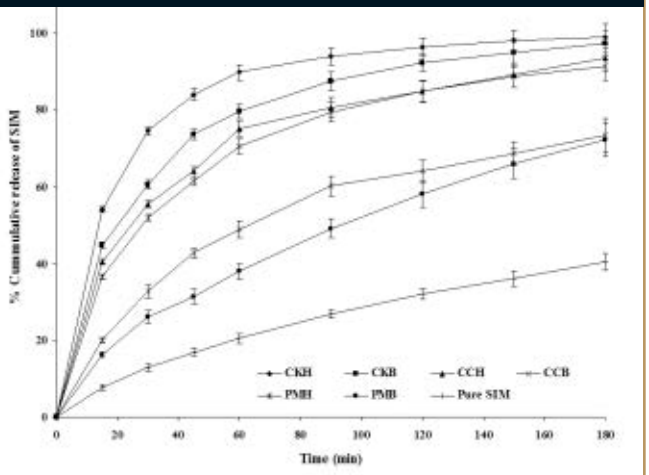
Where, i is dissolution sample number, n is number of dissolution times, t_{mid} is time at the midpoint between times t_i and t_{i-1}, and M is the amount of SIM dissolved (g) between times t_i and t_{i-1}. MDT reflects the time for the drug to dissolve and is the first statistical moment for the cumulative dissolution process that provides an accurate drug release rate.[22] It is an accurate expression for drug release rate. A higher MDT value indicates greater drug retarding ability.[23] In order to calculate mean dissolution time (MDT) of pure SIM, its PM, and complexes with β-CD and HPβ-CD, the mean (n = 3) of cumulative drug release (µg) was used. The obtained values of MDT for pure SIM, PMB, CCB, CKB, PMH, CCH, and CKH are presented in Table 4. The MDTs of SIM are 68.47 mins in 0.1 N HCl and 75.02 mins in distilled water. These values decreased to greater extent after preparing complex of SIM with CDs, ie, 34 and 40 mins for CCB and CKB, and 29 and 37 mins for CCH and CKH in 0.1 N HCl, and 36 and 44 mins for CCB and CKB, and 33 and 42 mins for CCH and CKH in distilled water. Even MDT values of PMB and PMH are sufficiently lower than pure SIM. Complexes prepared using the kneading method, which exhibited the best dissolution profile and lowest MDT values, were used for the formulation studies.

A value of 100% for the similarity factor (f_2) suggests that the test and reference profiles are identical. Values between 50 and 100 indicate that the dissolution profiles are similar, whilst smaller values imply an increase in dissimilarity between release profiles.[19] Calculated f_2 values are presented in Table 5. From this Table, it is evident that the release profile of SIM from CKB and CKH is highly different from pure SIM in both dissolution medium (f_2 values 14.30 and 13.19 in 0.1 N HCl and 14.15 and 11.49 in distilled water, respectively). Even release profiles of SIM from CCB, CCH, PMB, and PMH are also significantly different from pure SIM in both dissolution mediums. The release profile of SIM from CCB, CKB, CCH, and CKH were similar in both the dissolution medium as the f_2 values for these profiles are greater than 50.

Formulation Studies: The complexes prepared by the kneading method (CKB and CKH) were studied for physical properties to judge their tableting ability. In general, compressibility index values up to 15% and angle of repose between 25 to 30 results in good to excellent flow properties.[33] Percent compressibility and angle of repose were 14.11% and 29.3° for CKB and 11.03% and 26.3° for CKH, respectively. These values indicate good compressibility and flow properties, making it suitable for tableting.

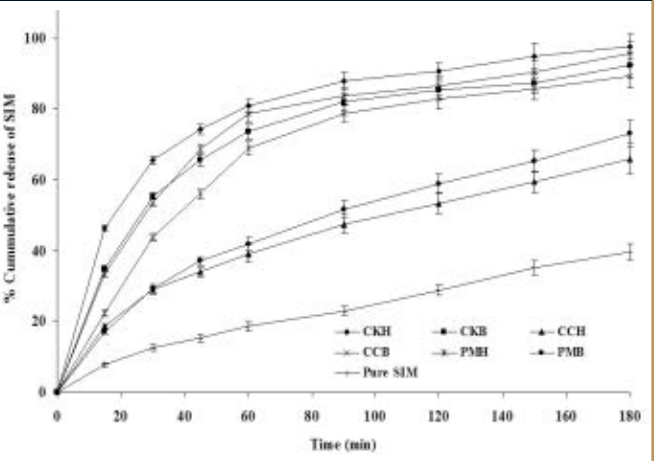
During in vitro dissolution studies, CKB and CKH exhibited more than 80% and 78%, 81%, and 89% drug release within 60 mins from 0.1 N HCl and distilled water, respectively, whereas tablets prepared by compressing CKB and CKH provided the same drug release within 150 and 120 mins with $T_{50\%}$ value of 50 and 75 mins, respectively. Disintegration of tablets (disintegration time 7 to 8 mins) was the step that delayed the drug release slightly in comparison with complex in powder form. However, these tablets showed faster and reproducible release as compared to the tablets containing pure SIM and no CDs, which showed 64.2% and 60.0% release in 4 hrs with $T_{50\%}$ of 167 and 182 mins in 0.1 N

FIGURE 5A



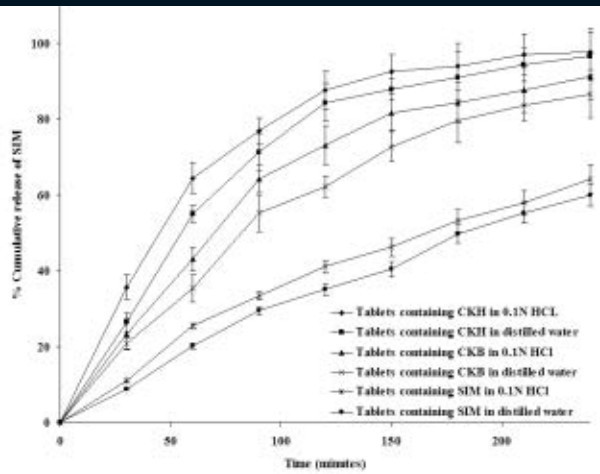
In Vitro Dissolution Profiles of Pure SIM and its Physical Mixture and Complexes in 0.1 N HCl (n=5)

FIGURE 5B



In Vitro Dissolution Profiles of Pure SIM, and its Physical Mixture and Complexes in Distilled Water (n=5)

FIGURE 6



Release Profiles of SIM From Conventional Tablets Containing SIM and Tablets Containing CPK and CPH in 0.1N HCl and Distilled Water (n=3)

TABLE 5

(A) β-CD

Release Profile in 0.1 N HCL →

Release Profile in Distilled Water ↓

Sample	SIM	PMB	CCB	CKB
SIM	83.58	31.07	18.39	14.30
PMB	34.18	76.76	35.67	27.40
CCB	17.58	30.17	61.09	51.08
CKB	14.15	24.21	54.78	49.96

(B) HPβ-CD

Release Profile in 0.1 N HCL →

Release Profile in Distilled Water ↓

Sample	SIM	PMH	CCH	CKH
SIM	83.58	34.74	16.53	13.19
PMH	28.82	54.35	28.67	23.03
CCH	16.62	34.45	75.94	53.71
CKH	11.49	23.85	43.84	58.92

Similarity factor ($f2$) for release profiles of SIM in 0.1 N HCl and distilled water.

HCl and distilled water, respectively (Figure 6). This confirmed the advantage of improved aqueous solubility of SIM in its complex form, which can be formulated as tablets with better dissolution characteristics. Release profiles of SIM from conventional tablets containing SIM alone are significantly different from tablets containing CKB and CKH as the f_2 values are 31.36, 33.61, 23.44, and 23.74 in 0.1 N HCl and distilled water, respectively. MDT values of SIM from tablets containing CKH and CKB in both dissolution medium (56.87 and 74.70 mins in 0.1 N HCl and 66.46 and 83.18 mins in distilled water) are significantly lower than that of conventional tablets containing only SIM and no CDs (99.71 mins in 0.1 N HCl and 105.65 mins in distilled water).

CONCLUSION

Solubility studies showed a significant, linear increase in the aqueous solubility of simvastatin with increasing concentration of β-CD and HPβ-CD. At maximum studied concentration of β-CD and HPβ-CD (14 mM/L) resulted in 7.35-fold and 13.3-fold improvement in the saturation solubility of simvastatin. An inclusion complex of simvastatin with β-CD and HPβ-CD was prepared successfully by the kneading and coevaporation method in a molar ratio of 1:1. This was confirmed by FTIR and DSC studies. The highest improvement in solubility and in vitro drug release were observed in inclusion complex prepared with HPβ-CD by the kneading method. More improvement in solubility and in vitro drug release of simvastatin was observed with HPβ-CD as compared to β-CD. The solubility and in vitro drug release of the physical mixture, when compared to that of the complexes prepared by the kneading and coevaporation method, was improved to a lesser degree. These findings are extremely important from a commercial point of view as the prepared complex removes drawback of a poor dissolution profile of simvastatin.

ACKNOWLEDGEMENTS

We are thankful to Roquette Frères, France for a generous gift of HPβ-CD and β-CD. We would like to thank Lincoln Pharmaceuticals Ltd. for donating simvastatin. We would also like to thank Maan Pharmaceuticals Ltd. for providing formulation excipients. We are also grateful to the Department of Pharmacy, M.S. University, India for conducting DSC studies of the samples.

REFERENCES

References available upon request. Contact Dan Marino at DMarino@drugdeliverytech.com

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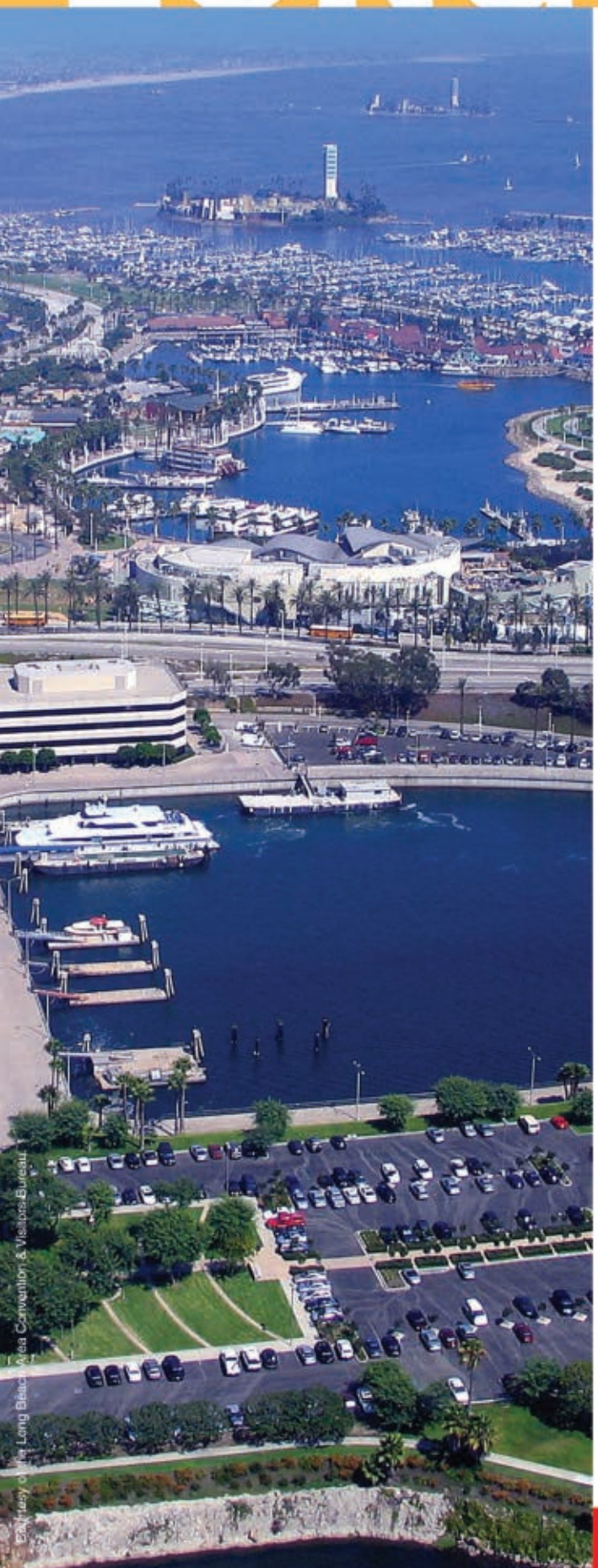

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MINERAL OIL EMULSIONS

Mineral Oil Emulsion Preparation with Acacia

By: Antoine Al-Achi, PhD; Anita Mosley, PhD; and Ishwin S. Dembla, BS

ABSTRACT

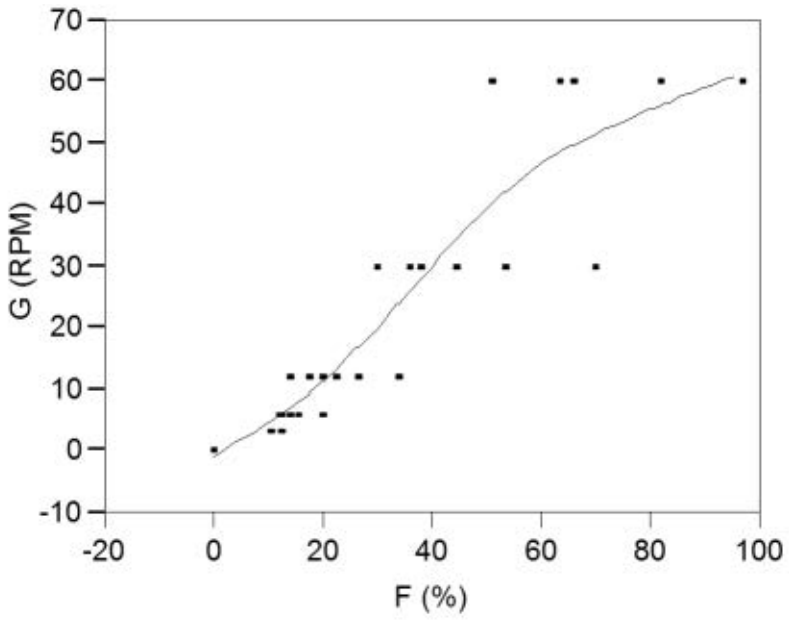
The use of mineral oil emulsions (MOEs) is well documented. In this study, we compared the physical characteristics of MOEs prepared with Acacia NF or Acacia Spray-dried (SD). Emulsions with Acacia NF were compounded by the English method and the Continental method, whereas those prepared with Acacia SD were made only by the English method. All emulsions showed an acidic pH close to pH 4.0. The specific gravity of all emulsions was slightly less than 1.0. The surface tension was about 30 dynes/cm for all the emulsions tested. The emulsions exhibited pseudoplastic flow with their characteristic shear-thinning profiles. The creaming rate was the slowest for emulsions prepared with Acacia NF using the Continental method. Overall, MOEs prepared by the Continental method using Acacia NF had the best physical stability.

INTRODUCTION

Mineral oil emulsions (MOEs) are commonly used internally as laxatives and externally for their emollient hydrating effect. Acacia NF is the emulsifying agent found in the official NF emulsion.[1] The preparation is made by the Continental method (also known as the dry gum method) using the traditional 4:2:1 ratio for making the primary emulsion. We recently reported that Acacia SD was not a good alternative for Acacia NF in this formulation.[2] Using the Continental method, Acacia SD does not produce a stable acceptable primary emulsion. However, the use of the English method (also known as the wet gum method) results in a stable primary emulsion with Acacia SD.

Acacia is commonly known as Gum Arabic. It is a natural product obtained from the dry gummy exudate of the Acacia senegal tree.[3] A 5% solution of Acacia has a pH between 4.5 and 5.0 at room temperature.[3] In this study, we compared MOEs prepared using both types of Acacia with regard to their physical characteristics. Specifically, we measured the specific gravity, pH, surface tension, creaming rate, and rheological profile of the compounded emulsions. All measurements were obtained under ambient temperature (room temperature).

FIGURE 1



Rheologic profile of mineral oil emulsion prepared by the English method using Acacia NF. The rheogram shows a pseudoplastic flow between the shearing force (%) and the rate of shear (G, rpm). Data points are actual observations.

MATERIALS

Mineral oil light NF was purchased from EMD Chemicals Inc. (lot No. A51680-D). Acacia NF (lot No. 23-6114 OA) was purchased from EMD Chemicals

Inc., and Acacia, SD (lot No. ND H6344) was obtained from Spectrum Chemicals Mfg. Corp. De-ionized water was used in all the preparations.

METHODS

Preparation of the Emulsions: Six different emulsions were made of each of the following formulations: 1) mineral oil 50 ml, Acacia NF 12.5 g, de-ionized water enough to make 100 ml, and 2) mineral oil 50 ml, Acacia SD 12.5 g, de-ionized water enough to make 100 ml. Preparation (1) was made by the English and the Continental methods, whereas preparation (2) was made by the English method only because the Continental method does not form an acceptable primary emulsion.[2]

Specific Gravity Measurement: Using a grease pycnometer (Catalogue No. 3-247, Fisher Scientific), the weight of the empty pycnometer (A), the weight of the pycnometer containing de-ionized water (B), and the weight of the pycnometer containing the tested emulsion (C) was determined. The specific gravity was then estimated from the following equation: Specific gravity = (C – A)/(B – A).

pH Measurement: Accumet Basic AB 15 pH Meter (Fisher Scientific) was used for these measurements. The meter was standardized using standard solutions of pH 4.0 and pH 7.0.

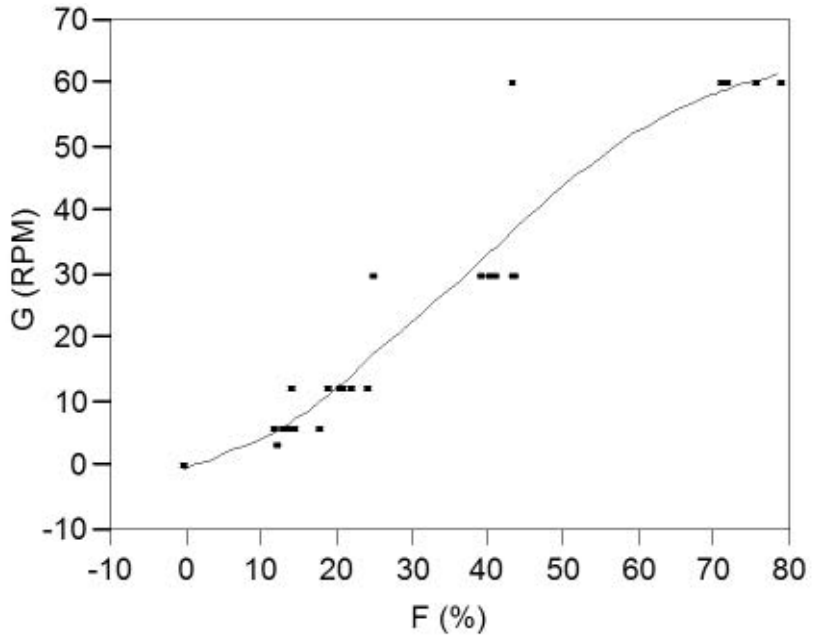
Determination of the Surface Tension: A capillary glass tube was immersed into a 60-ml emulsion held in a 100-ml glass beaker. Four measurements were performed on each emulsion at the 12, 3, 6, and 9 o'clock marks. De-ionized water was used as a reference liquid (surface tension 72.8 dynes/cm). The rise of the liquid inside the capillary tube from the surface of the liquid (h) was measured with a ruler. The surface tension was determined using the following equation: $\gamma_1 = (\gamma_2\, d_1\, h_1)/(d_2\, h_2)$.[4]

In which γ is the surface tension, d is the density of the liquid, and h is the height of the liquid inside the capillary tube from the surface of the liquid; subscripts 1 and 2 refer to the tested emulsion and to water, respectively.

Rate of Creaming Determination: Emulsions were prepared and immediately placed inside a 100-ml graduate cylinder. The rate of creaming over 72 hours was determined by observing the rise of the droplets of the internal phase. An average creaming rate (ml/hr) was calculated by dividing the volume separated (ml) by time (hours).

Rheologic Profile: Brookfield viscometer (Model LVDI+; Serial No. AE42476) was used to generate the rheogram between the shearing force (F%) and the rate of shear (G, rpm). Also, the viscometer was employed to determine the change of viscosity (viscosity coefficient) of

FIGURE 2



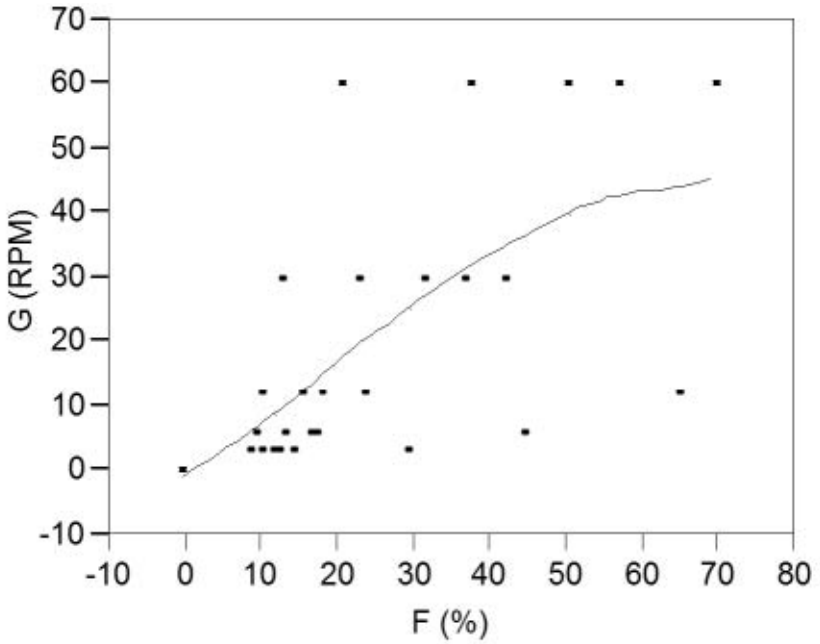
Rheologic profile of mineral oil emulsion prepared by the English method using Acacia SD. The rheogram shows a pseudoplastic flow between the shearing force (%) and the rate of shear (G, rpm). Data points are actual observations.

TABLE 1 - Specific Gravity of Mineral Oil Preparations

Type of Acacia	Method of Preparation	Specific Gravity[a]
Acacia NF	English	0.9704 ± 0.0004 (6)
Acacia NF	Continental	0.9427 ± 0.0269 (6)
Acacia SD	English	0.9702 ± 0.0004 (6)

[a] Acacia NF/Continental method is significantly different from the other two groups ($p = 0.0102$)

FIGURE 3



Rheologic profile of mineral oil emulsion prepared by the Continental method using Acacia NF. The rheogram shows a pseudoplastic flow between the shearing force (%) and the rate of shear (G, rpm). Data points are actual observations.

TABLE 2 - pH of Mineral Oil Preparations

Type of Acacia	Method of Preparation	pH[a]
Acacia NF	English	4.49 ± 0.083 (6)
Acacia NF	Continental	4.23 ± 0.060 (6)
Acacia SD	English	4.09 ± 0.029 (6)

[a] Significantly different from each other ($p < 0.0001$)

the emulsion with changing the shearing rate (G).

Statistical Analysis: Results were reported as mean ± standard deviation. An Analysis of Variance test (ANOVA) or a t-test was used to compare groups. The Tukey Kramer HSD test was used as a post-hoc test whenever ANOVA was significant. All comparisons were two-sided. A p value of 0.05 or less was considered significant. JMP® Statistical Discovery Software (SAS Institute) was used for the statistical analysis.

RESULTS & DISCUSSION

Compounding pharmacists prepare emulsions using different techniques, including the Continental method and the English method.[5] However, the use of the Continental method with Acacia SD is not practical because it does not produce a stable primary emulsion.[2] This may be explained in part by its high affinity to water (spray drying technique enhances the dissolution of the material in water).[6] During the preparation of the emulsion by the Continental method, Acacia SD absorbs all the water added and prevents it from dispersing with the oil. We observed the formation of very large "globules" produced by the hydrated acacia in oil. All the added water was entrapped inside the "globules," preventing them from forming the primary emulsion. The English method does not suffer from this difficulty because Acacia is dispersed first in water, and oil is added in small portions to form the primary emulsion.

The specific gravity of the compounded emulsions are shown in Table 1. Although the Continental method with Acacia NF produced statistically ($p = 0.0102$) lower specific gravity for the emulsions, this difference is not practically significant. All emulsions had a specific gravity value slightly less than 1.0. The pH of the emulsions was acidic and was slightly higher than 4.0 (Table 2). The English method with Acacia SD produced the lowest pH ($p < 0.0001$). The surface tension (dynes/cm) is shown in Table 3. There was no statistical difference among the preparations ($p = 0.3715$). On average, the surface tension for the formulations was 30.36 dynes/cm, which is significantly lower than water (72.8 dynes/cm) ($p < 0.0001$; one-sample t-test; two-sided test). Using the Continental method for emulsions preparation with Acacia NF produced the greatest physical stability with respect to creaming rate. Acacia NF with the English method produced a creaming rate similar to that of Acacia SD prepared by the English method [0.399 (± 0.230) ml/hr vs. 0.352 (± 0.095) ml/hr, respectively]. The rate of creaming obtained from the Continental method with Acacia NF was 0.0764 (± 0.138) ml/hr, which was statistically significantly different from that obtained from Acacia NF or Acacia SD with the English method ($p < 0.0001$). Thus, the rate of creaming may be related to the method of preparation and not to the type of Acacia used in the formulation.

Figures 1 through 3 show the various rheograms obtained from the preparations. MOEs had pseudoplastic flow with a characteristic shear-thinning property. From the practical point of view, a decrease in the viscosity with increasing shearing rate is a highly desirable property in formulations; shaking the bottle containing the emulsion (ie, increasing the shearing rate) by the patient prior to pouring would greatly facilitate its delivery from the bottle, due to a decrease in the emulsion's viscosity (Figures 4 through 6).

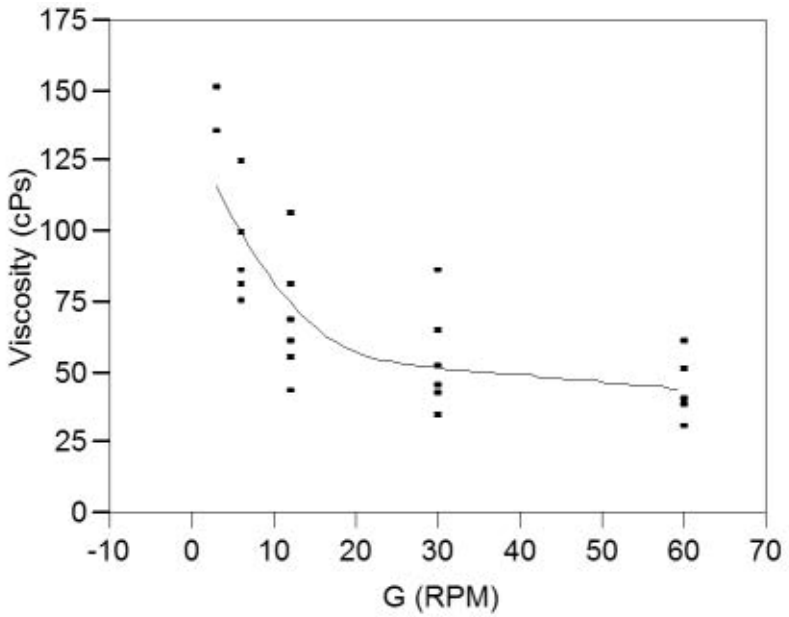
CONCLUSION

Mineral oil emulsions NF contain Acacia as an emulsifying agent. This study demonstrated that Acacia SD may not be a good alternative to Acacia NF in this formulation. Preparations made by the SD variety do not produce a stable primary emulsion by the Continental method. When the English method is used with Acacia SD, stable emulsions were formed. However, their rate of creaming is significantly higher than those prepared by the Continental method and Acacia NF, and similar to those prepared by the English method/Acacia NF. All emulsions showed a pseudoplastic flow with their characteristic shear-thinning profiles. We recommend that compounding pharmacists not use Acacia NF and Acacia SD interchangeably in emulsion formulations, unless there is evidence to the contrary.

ACKNOWLEDGEMENT

The authors would like to acknowledge the excellent technical help provided by Mr. Christian Griggs in performing some of the experiments in this study.

FIGURE 4



Acacia NF (English method): The viscosity of the emulsion decreases as the shearing rate increases. Data points are actual observations.

TABLE 3 - Surface Tension of Mineral Oil Preparations

Type of Acacia	Method of Preparation	Surface Tension (dynes/cm)[a]
Acacia NF	English	29.11 ± 9.81 (6)
Acacia NF	Continental	34.50 ± 7.86 (6)
Acacia SD	English	27.47 ± 8.51 (6)

[a] No significant difference in the surface tension among the three groups ($p = 0.3715$)

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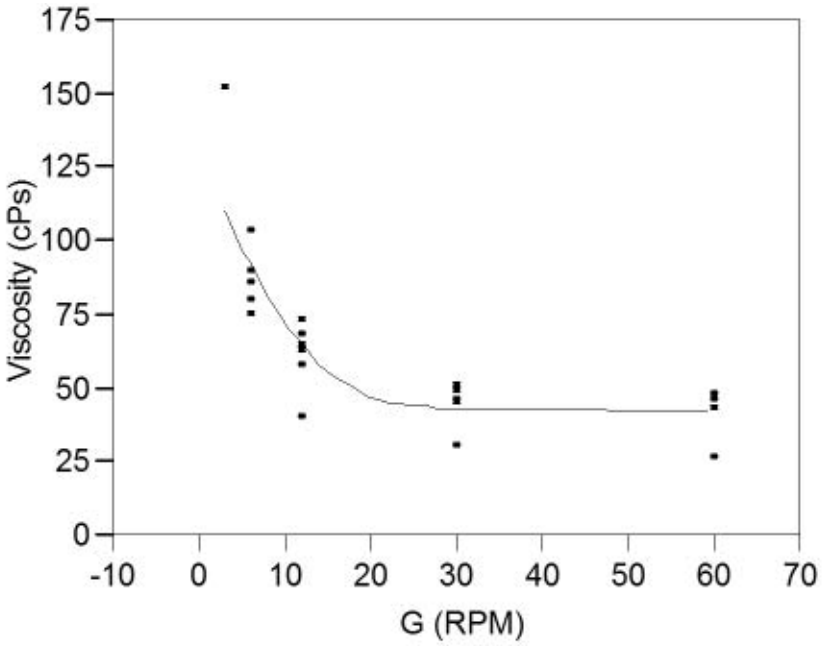
6. Kim CK, Yoon YS. Development of digoxin dry elixir as a novel dosage form using a spray-drying technique. J Microencapsul. 1995;12(5):547-556.

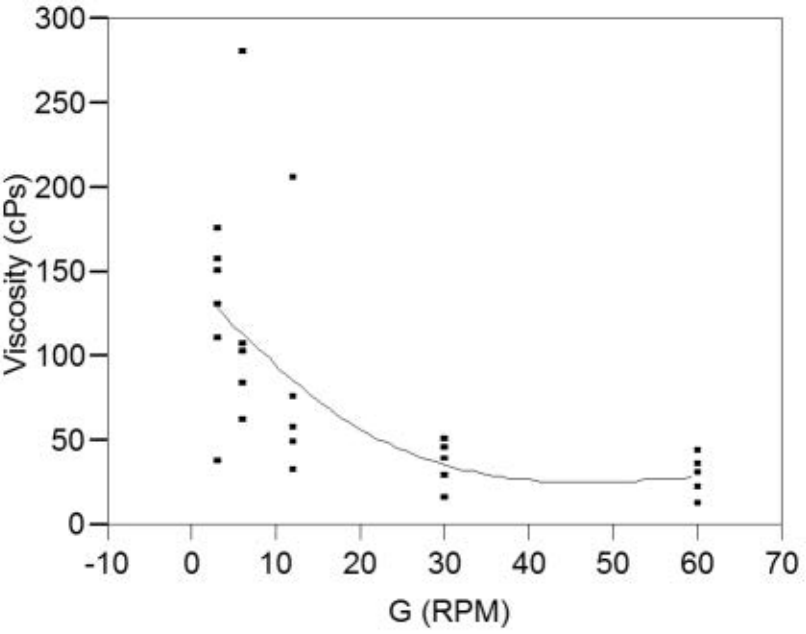
MINERAL OIL EMULSIONS

FIGURE 5



Acacia SD: The viscosity of the emulsion decreases as the shearing rate increases. Data points are actual observations.

FIGURE 6



Acacia NF (Continental method): The viscosity of the emulsion decreases as the shearing rate increases. Data points are actual observations.

BIOGRAPHIES

Dr. Antoine Al-Achi is Associate Professor of Pharmaceutical Sciences at Campbell University School of Pharmacy. Dr. Al-Achi earned his PhD in Biomedical Sciences from Northeastern University in 1988. Since then, he worked on several projects, including solid tumors pharmacology, pharmacokinetics studies, and dosage forms design. His research interest focuses on oral drug delivery systems of peptides and proteins. Dr. Al-Achi has published in *Cancer Research, Drug Development and Industrial Pharmacy, JAMA, and Drug Delivery Technology*.

Dr. Anita Mosley is an Assistant Professor of Pharmaceutics at the Feik School of Pharmacy at the University of the Incarnate Word in San Antonio, Texas. Areas of interest include drug solubilization, nanoparticle technology, dosage form design, and drug delivery. Dr. Mosley is a member of the American Association of Pharmaceutical Scientists, the American Chemical Society, the American Society of Health System Pharmacists, the American Pharmacists Association, and the American Association of Colleges of Pharmacy. Dr. Mosley has published in the *International Journal of Pharmaceutical Compounding and the Journal of Pharmaceutical and Biomedical Analysis*.

Mr. Ishwin S Dembla is currently a graduate student majoring in Industrial Pharmacy at Campbell University School of Pharmacy. He graduated with a BS (BSPS) from Campbell University in 2006. During his undergraduate studies, he conducted research on the diffusion of Morphine Sulfate and did a study on the physical properties of various commercially available over-the-counter products. Mr. Dembla is a student member of ISPE.

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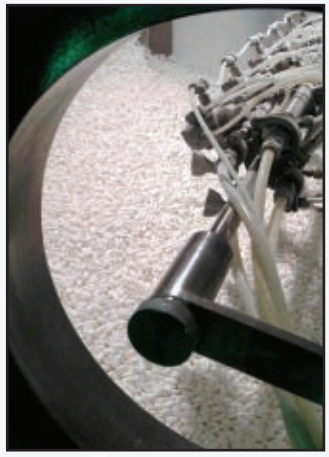

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SPECIALTY PHARMA
Strategies For Business Development

Central Lab Partnering

Specialty Pharma & Central Labs

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

Introduction

Today, the concept of centralized laboratory services is well accepted, but that was not always the case, according to Applied Clinical Trials. Two decades ago, the Central Laboratory (CL) industry was born out of a need for a more accurate way to collect and report clinical trials data. Since that time, the industry has grown into a billion-dollar market that is now a critical component in more than 70% of all clinical trials worldwide. The year 2006 marked the 20th anniversary of the CL industry. CLs analyze blood, tissue, urine, and other specimens through biochemical assays, providing nearly 90% of all data that comprise a new drug application. As biopharmaceutical companies are under continued pressure to provide enhanced therapies that help improve and lengthen human life, reduce drug development costs, and speed drug development cycle times, the CL industry is becoming more important than ever. With R&D spending expected to reach $140 billion by 2009, the CL industry is poised for continued growth, according to Applied Clinical Trials. Generating $1.8 billion dollars in 2006, the industry is expected to grow an average of 12% to 13% a year over the next 4 years, reaching $2.9 billion by 2009. How much of this growth is dependent on the relationships CLs forge with Specialty Pharma? We asked some of the leading central laboratories about the importance of their partnerships with the Specialty Pharma industry.

Q: How do companies quantify their CL's performance?

Dr. Agostino Fede: Historically, the performance of a CL was measured by surveys, with some quantitative indicators included for satisfaction and perceived service levels. This approach was more subjective and obviously qualitative, serving the partnership fairly well over time, especially across the continuum of the relationship to measure trends. Today, a more analytical or mechanical approach seems to prevail where certain metrics are requested from a CL to try to objectivize the performance. The challenges for the industry are that there is no standard set of metrics, although some efforts are underway, and that there is not a standard understanding of what and how these indicators should be delivered and then used. We favor a balanced approach, using both surveys and a limited set of metrics in which definitions/collections are discussed and agreed upfront for mutual and maximal leverage.

Mr. Jeff Mayhew: Measurement really starts before the study does. We're measured on the timeliness of our proposal response and of course our cost effectiveness. Other areas that we know are important to our clients — and therefore LabConnect — are how quickly we fulfill kit supply requests, data transfers, turnaround time for results, etc. One area that is unique to LabConnect is that we measure our performance not only from the sponsor perspective but also from the investigator sites' perspective. We have always believed that site satisfaction will equate to sponsor satisfaction. Toward that end, we have set up our systems to evaluate our performance and provide compensation to our operations team based on our survey results.

Mr. John Schultz: In our experience, our sponsor's use quantitative performance metrics measured from study launch through final data transfer. Typical performance metrics fall into a number of categories including analytical, logistics, data management, and client/site support services. These performance metrics allow our sponsors to track progress and serve as early detectors of bottlenecks and potential obstacles. This is of particular importance for Specialty Pharma companies, as quick identification and resolution of issues can save considerable time and expense. Examples of performance metrics in some of these areas include time to resolution for site data clarifications (which is a measure of the communication process between the CL and the investigative sites), call hold time/dropped calls for client services (which is a measure of the CL's responsiveness to the investigative sites' needs), average turnaround time (TAT) for kit resupply (which is critical to study success because the lack of laboratory kits could limit the site's ability to perform protocol-specific procedures or to screen potential subjects), percentage of unacceptable proficiency testing results (which is a measure of quality in the laboratory), and timeframe for implementation of amendments to lab service specifications (which could affect the quality of the laboratory database because the CL must be able to implement an amendment as soon as each individual site has IRB approval for the amendment). Our sponsors expect a CL to have a well-established quality program with quality and performance metrics supported and routinely monitored by operations and senior management.

Mr. David Spaight: There are a number of key ways to quantify CL performance. Metrics have become an integral part of evaluating performance, enabling a sponsor to monitor many factors throughout trials and programs. Metrics can tell you if the lab hit the critical milestones for turnaround time, study start-up, kit shipment, transport, re-supply for investigators, data delivery, database lock, etc. In addition, evaluating data from key metrics enables the lab to continuously improve and identify areas where processes and systems could be enhanced. Price, of course, is a major consideration for every sponsor, and often sponsors use price to qualify their CL partners. But it would be a mistake to select a lab partner based solely on price when there are many other important factors that should be taken into consideration. Not all labs are the same. MDS Pharma Services Global Central Lab business is part of a full-service CRO, which can be a great advantage to a sponsor. We are the market leader in Phase I testing. In addition to discovery and preclinical cardiac safety assessment of a compound, we offer centralized cardiac safety assessment from Phase I through Phase IV, and if needed, can bring your protocol all the way into Phase IV. Certifications are another way to quantify CL performance. MDS Pharma Services' fully owned central labs have CAP and NGSP accreditations as well as all relevant regional certifications, and we hold our affiliate labs to the same demanding standards. Finally, while effective communication is less quantifiable, it is

nonetheless an important measure of CL performance, and is especially important in the extremely complex "machine" of a clinical trial with its many moving parts. Sponsors understand that in such an environment, there will be challenges and delays. Keeping people informed about those issues, as well as their resolution, will help reduce frustration and improve efficiency.

Q: Can you please discuss how important it is to know all the services a potential lab partner provides?

Dr. Agostino Fede: The success of the trial from a CL perspective goes above and beyond the quality lab results. It is key to obtain and understand the data delivered during a flawless experience. It is about supplies management, investigator site support, reporting and data transfer, overall management of the project, and relation with your team. A thorough understanding of all non-analytical services will ensure that the logistics elements are well embedded with the other activities of the SP and/or its other service providers are well in sync so that execution is not only optimal time- and money-wise but also easy on the sites, your team, and your provider. You may also want to ask for service that goes above and beyond the lab and logistics provision and include services like protocol consultation/design, data analysis, performance metrics, and management report — or any type of flexible approach to meet your specific needs.

Ms. Lisa Hanges: Over the past 20 years, routine clinical laboratories have been replaced by CLs to support clinical trials. This is driven by the fact that the CL provides a much wider array of services customized to meet the unique needs of the biopharmaceutical industry than the analytical services a clinical laboratory provides to physician offices and hospitals. These services are designed to fulfill medical, scientific, and regulatory requirements, standardize data across multiple investigative sites, as well as provide electronic data in a manner and format required for analysis and submission. CL services are not limited to reporting results — they must include design, implementation, logistics, site and client support, and project management to ensure the success of each sponsor's studies. When choosing a laboratory, it is critical for the sponsor to know all of the available services provided by a potential laboratory partner, in order to maximize the benefit and value that the laboratory can provide. Most CLs have developed their capabilities in response to sponsor needs and regulatory requirements. We continually review and enhance our service offerings based on feedback received from working with sponsors and our review of the literature and marketplace. By learning about the laboratory's services, a sponsor can consider all of the options available and can work with the laboratory to customize the program to meet the study's specific needs. In addition to understanding the services provided, a sponsor must thoroughly assess a potential laboratory partner in essential areas, such as 21 CFR Part 11 compliance, system validation, quality systems, project management, geographical reach and experience, and capabilities and security. A laboratory partner needs to show how uniquely it can provide these services to the sponsor upfront so that both parties can maximize the benefits of the relationship. This is of particular importance to a Specialty Pharma company since oftentimes the support infrastructure is not present in-house.

Mr. Jeff Mayhew: Certainly, it is important for sponsors to understand in detail the capabilities that apply to their specific needs, but not necessarily the entire scope of services. Part of our business development team's job is to gain an understanding of how and when the company utilizes laboratory services across the organization (preclinical, clinical) and ensure that potential partners are fully appraised of the services that match their needs.

Mr. David Spaight: It is always useful for a sponsor to have a good understanding of all the services available from a potential lab partner. This allows the potential to minimize the number of vendors involved in a trial and simplify the communication processes. Most companies will look for efficiencies when offering multiple services, and this can also result in clear cost-savings — both direct and indirect — for the sponsor. For example, MDS Pharma Services offers a full spectrum of resources to meet drug discovery and development needs. We apply advanced scientific knowledge and technological expertise throughout the drug discovery and development process from lead optimization, pre-IND research, early clinical research (bioequivalence, Phases I–IIa), and bioanalysis, to global clinical development (Phases IIb–IV), central lab, and centralized cardiac services.

Q: When is it ideal to work with a lab that provides several other types of services? When is it not?

Dr. Agostino Fede: It depends on how much each SP company is really able and willing to do by itself or in combination with other resources. There are clear benefits to using CL services in conjunction with its own clinical and data management services for time considerations and resource optimization. The one-stop-shop approach fits certain SP organization and resource levels. Sometimes it is better to use only the pure analytical capabilities of a special lab in a certain country for critical care-type studies where turnaround time is more important than data centralization, although there is limited use of this for SP. In other situations, you may use the CL's logistics-only capabilities as your existing local and hospital labs relationships seem to do the work you need. The trade-offs are around the overhead and time impact an SP has to manage a non-central, full-fledge service as well as data quality and usability outcomes.

Mr. John Schultz: As many Specialty Pharma companies outsource the entire range of clinical development services, it is crucial that the selected outsource providers can integrate service delivery for a seamless support network for the investigative sites and data management team. Our past project management activities indicate that the primary

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Bougival, France	T, S
Idstein, Germany	T, S
Gallarate, Italy	T, S
Budapest, Hungary	T, S
Istanbul, Turkey	T, S
Barcelona, Spain	T, S
Moscow, Russia	T, S
Asia-Pacific	
Singapore	D, S
Fuji-Gun, Shizuoka, Japan	M, D, S
Shanghai, China	M, D, T, S
Goa, India	M, D, T, S
Seoul, Korea	T, S
Latin America	
Buenos Aires, Argentina	D, T, S
Cotia, Brasil	M, D, T, S
Bogota, Colombia	D, T, S
Caracas, Venezuela	D, S
Santa Fe, Mexico	D, T, S

Key:
M Manufacturing
D Distribution
T Technical Service Laboratory
S Sales

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factor for success is the ability of the combined project team to integrate communication and support. We find that for large, multinational trials, it often works best when the CL provider also can coordinate other biomarkers and ancillary services. Although most of the large CROs have CL divisions, it is rare to find one that has integrated its laboratory systems into its clinical systems — they operate as separate entities and work together very much in the same way as with non-related providers. We gain many efficiencies in our integrated operations that could be realized by the entire industry through better integration within this sector. Early development studies, particularly Phase I and II, greatly benefit from the use of a CL that provides a broader array of services. We have five clinical sites in the US and Canada within our family of companies that perform Phase II trials. By using our CL across our sites for all of the biomarkers and clinical labs in the Phase II study, we provide greater data consistency often more cost effectively while saving time in the reporting and interpretation of the clinical results.

Mr. David Spaight: Working with a full-service provider, such as MDS Pharma Services, can allow a pharmaceutical or biotechnology company to limit the number of providers and thereby achieve efficiency, cost and quality benefits. Advantages can be derived from contracting with a single provider for biomarker development and cardiac safety monitoring, clinical trial management, and CL safety testing. MDS offers a full spectrum of services to support every stage of drug discovery and development, as well as complete program management through our Development and Regulatory Services group, and required services can often be incorporated into a single Master Service Agreement or contract to simplify the process. Working with a full-service CRO can have a beneficial cost implication and improve the quality of data — two key factors during the clinical trial. For example, if the same provider is used for both CL safety testing and esoteric biomarker analysis, samples need not be shipped between numerous laboratories. This results in both lower shipment costs and less data integration — and therefore inquiries — at the end of the trial. Finally, providers that offer multiple services have working relationships with other suppliers. A sponsor can capitalize on these established relationships and well-defined communication structures in place to support them.

Mr. Jeff Mayhew: Many of LabConnect's clients tend to require a high level of specialized services and project management support. This is especially true when a protocol may require a broad range of testing services. For example, in a number of our current projects, we are providing safety testing, therapeutic drug level monitoring, and esoteric assays. Our clients prefer to have a single project manager as their one lab contact to manage everything from simple safety tests to highly complex esoteric assays to centralized pathology work, and at the same time, to ensure that all this is coordinated with investigator manuals, lab collection kits, and reports. However, if by "other types of services" you're referring to functions like EDC, monitoring, etc., that's not what we do. We believe in focusing on doing one thing well — CL services — which translates to our not being a CRO. Full-service CROs certainly have their place for certain clients. However, most clients tend to view a CL as somewhat of a stand-alone function.

Q: When is the right time to add a CL partner to the clinical research team?

Dr. Agostino Fede: As early as possible. We see a tendency for CL decisions to be made very late in the outsourcing process, usually at the last moment after all other decisions are made, as if CL services are "ancillary." Clearly this is not the case as CL data constitute the bulk of the content for your approval, and as such, are your most important assets for a development project. Another more practical consideration is that there is always potential for optimization in CL study design, be it the scheduling and exact definition of assays to be performed (for cost and time considerations) or the optimal use of logistics resources, which play a major role in the budget of CL services and can impact the overall feasibility of a study.

Ms. Lisa Hanges: In order to maximize the value the CL partner can provide, a Specialty Pharma company should select a CL partner before Phase I. By choosing a CL early in the clinical development process, the sponsor can better integrate the Phase I, II, and III studies. The biomarkers and laboratory data will be more consistent. Ideally, the selection process should occur during development of the program and/or study protocols. By partnering with a laboratory early in the product development lifecycle, a Specialty Pharma company can save time and money by establishing reporting and data formats for use throughout the clinical development program. In addition, the CL can provide services that will enhance the productivity and ease of conducting the study — not just for the Specialty Pharma but also for the investigative sites — an often overlooked, but critical component for a successful clinical trial. As Laboratory Medicine is constantly evolving, the laboratory partner can provide valuable input during protocol development to ensure the most appropriate biomarkers are utilized to measure safety and key efficacy parameters; input also can be provided on inclusion/exclusion parameters as they relate to laboratory measures. Bringing a CL partner into the clinical research team late in the process greatly reduces the value the laboratory can provide. From a time and resource perspective, there is no good reason not to partner with the laboratory from the beginning.

Mr. Jeff Mayhew: This will vary depending upon the complexity and scope of the project. If you are planning a project that will require specialized assay validation and an extensive number of unique site visits, you should plan on a minimum of 3 to 4 months lead time. Projects that are more straightforward in nature can generally be set up in 2 months or less.

Mr. David Spaight: The earlier a CL is involved in the clinical trial process, the more added value it can provide. Often, a CL will

not be brought in until the protocol is almost final and most key analytical and country details are confirmed. However, the laboratory partner has a great deal of knowledge and could serve as a valuable consultant. New technologies and assays are constantly being added to a CL's repertoire of available tests, and most labs would be happy to share their expertise that relates to specific therapeutic areas. For instance, a specific assay with limited stability may be included in a protocol, and this could influence the countries or cities that should be used for the trial. A CL's experience and geographic presence can be a big advantage to sponsors. With more company-owned labs than other CL providers, MDS Pharma Services offers sponsors access to local investigators and diverse patient populations. We have had a CL in China for more than 10 years — longer than any other CRO — so we understand the regulations and have the right relationships with the regulatory bodies. MDS is also one of the few companies with a strong presence and network in Latin America. Involving a CL as early as possible in the planning process will help sponsors to choose the most effective and appropriate assays, countries, and logistics.

Q: What are some of the most important considerations for SPs (whose resources are generally tighter than Big Pharma) when outsourcing a CL partner?

Dr. Agostino Fede: We suggest looking at the overall value proposition from a potential CL partner. What is it the SP looking for? Is it time gains, service levels, or costs? One of our competitive edges is shortening development time to accelerate market access. It is appealing to look at costs and try to make apple-to-apple comparisons, but it is also risky and potentially wrong as there are so many other things above and beyond the seemingly simple provision of test results. Quality of analysis is expected — a must have as long as you work with labs with recognized accreditation and appropriate QMS, you should count on it. The difference is in the setup and conduct of the study, in its overall logistics, and how your CL goes about it. Will it be easy and painless? If there are issues, do I trust the team to be proactive and avoid any effects? Or do I risk major delays and additional cost down the road if I buy a service from a provider that does have good results but lacks infrastructure and process to deliver?

Mr. Jeff Mayhew: Since Specialty Pharma companies tend to have limited in-house project support resources, it is important to select laboratory services partners that are able to provide a high level of personalized support and guidance. In our experience, we find that our SP clients depend heavily on our project managers' support and guidance.

Ms. Lisa Hanges: Although laboratory data can be over 50% of the final data submission, the laboratory budget is usually small relative to the overall trial cost. Since Specialty Pharma companies often have tight resources, the laboratory must be flexible in its pricing schedule and service offerings to allow the Specialty Pharma to select only the services required for their study. A lab with a "one-size-fits-all" approach is generally focused on big pharma and may not be the best partner for Specialty Pharma. The laboratory partner should be just that — a partner who can help the Specialty Pharma develop the best and most efficient trial or program relative to the sponsor's needs and resource — not just a vendor producing laboratory data. Areas to consider include efficiency of logistics, negotiated rates with courier companies, history of change orders relative to the overall budget, "just-in-time" kit re-supply, and project management processes. As we mentioned previously, a CL that is integrated with the Phase I and II clinics provides value early in the process, which can be extended to Phase III studies and beyond.

Mr. David Spaight: A multi-service vendor is an attractive option for a Specialty Pharma company because they enable efficiencies at many levels, resulting in savings of internal time and external spend. Because there are so many aspects of a study to be managed, building a relationship with a CL partner with the expertise and capabilities to manage them all will be a great advantage. For example, a full-service CRO, such as MDS Pharma Services, can be directly responsible for the CL, cardiac safety core labs, imaging labs, IVRS, and data management. This provides a central point of contact for the SP. Specialty Pharma companies whose compounds make it into the later phases of development (Phases II-IV) will need help with managing these larger and more complex trials. SPs are less likely to have the in-house capabilities of Big Pharma, and are therefore more likely to outsource entire development programs. It is important that they not only select a partner that will be able to meet their immediate needs, but one that fits into their longer-term plans.

Q: How can a CL partner help with key decisions within the company?

Dr. Agostino Fede: On many levels, if a SP engages its CL early in its process, it can gain immense insight into its own process and protocol development. One example is consulting on protocol design and test requirements (what and when). Often, the SP can amplify its own therapeutic area expertise with the CL that brings a wealth of experience in these areas. We have helped clients add specific tests that were absolutely key for a successful submission and removed others that were superfluous and costly. In other instances, we were able to adapt the scheduling of tests to meet certain budget constraints, offering economies of scale without jeopardizing the overall timelines. A CL can also help point to hot beds of recruitments and experience with selected sites and countries.

Mr. John Schultz: In addition to supporting the medical and scientific team with expertise during protocol development, we are integral to key decisions during the course of the trial. For example, our CL provides the entire clinical team with a view of near real-time activities at each investigative site through the use of secure

Internet tools. These tools may allow earlier "go/no-go" decisions and can provide insight into performance of each site to determine if individual sites are not delivering to their enrollment commitment, have higher than expected screen failure rates, or excessive data clarifications. The sites' interaction with the laboratory is often an indicator of their overall performance.

Mr. David Spaight: A CL can be an invaluable partner, offering expertise and advice, and will be more valuable when brought into the project as early as possible. Establishing a strong relationship with your lab partner early on will enable you to develop an efficient, effective process for your trial and capitalize on their experience: they can help you design your study protocol, help you successfully choose the appropriate assays, assist with biomarker selection and design, and geographic considerations. In addition, tools and processes — from set-up to invoicing — can be customized, with key input from the lab.

Mr. Jeff Mayhew: A good example of this type of support would be instances where we are asked to prepare draft laboratory services budgets during the protocol development stage. Sponsors use this information not only to evaluate our pricing and services but also to prioritize assays to be included in the final protocol. In other instances, sponsors draw upon the expertise of our scientific team in order to determine the most appropriate and cost-effective assays for safety or endpoint measurement.

Q: How can a company best manage its CL partner, especially when the lab needs to interact with other vendors?

Ms. Lisa Hanges: The keys here are partnership, flexibility, and communication. By nature of the laboratory's role in a clinical trial, multiple vendor relationships are required. It is critical that a full communication plan be established to ensure seamless services across multiple vendors, including key contacts. The SP should include in the plan a Senior Management contact as a means of escalating issues and creating management buy-in for the services provided. Specialty Pharma companies may have up to 15 vendors involved in a study — the best means of managing this is to ensure that written responsibilities are in place for the vendors to work from. Without this, the investigative site can be burdened with communicating to each vendor individually. Specialty Pharma should insist on a primary contact at the CL to streamline communication and avoid costly misunderstandings, as well as maintain routine teleconferences with all vendors throughout the program. A primary contact at the CL will lessen the workload of the Specialty Pharma team, enhance overall communications, and help ensure a more efficient and cost-effective trial or program.

Mr. David Spaight: Strong study management at all levels is always essential to a successful trial. A lab partner can be primarily managed by the Pharma/Biotech company, or via the CRO. Certainly, the more vendors that are involved, the more complex the communications become, and we have experienced that first-hand. MDS Pharma Services has been in the position of working as a subcontractor or general contractor with other CROs and other labs, and our experience has shown that the keys to success are having a central point of contact in the sponsor company, clear communication, and well-defined processes. As long as each player understands their role, vendors are usually able to interact well to achieve client objectives.

Mr. Jeff Mayhew: We appreciate it when our sponsor's conduct regularly scheduled team meetings, including all key project participants. This process helps establish camaraderie and open communication between the vendors and keeps everyone on the same page throughout the study. ■

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PPD, Inc.

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Managing Director of Miami Operations
Allied Research International – Cetero Research

Mr. Jeff Mayhew

Chief Operating Officer
LabConnect

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Mr. David Spaight

President
MDS Pharma Services

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Executive Summary

Mr. Paul Bleicher
Chairman & Founder, Phase Forward

Phase Forward: Revolutionizing Integrated Data Management Solutions for Clinical Trials & Drug Safety

By: Cindy H. Dubin, Contributor

Prior to starting Phase Forward, Mr. Paul Bleicher worked in various roles in clinical development — first as a clinical investigator at Harvard Medical School, then as a medical monitor at a contract research organization (CRO), and finally as the head of clinical development in a biotechnology company. In each of these settings, he experienced first-hand the challenges and complexities of conducting multi-center clinical trials using traditional paper-based case report forms (CRFs). The inefficiency of the process, and its manual nature simply astounded him. More importantly, he saw that key information about the clinical trial — both the data and the operations — was not readily available to the people responsible for patient safety and trial conduct. Technology seemed like the solution to the problems inherent in data collection in clinical research, but in those days (pre-1995), computer-aided data collection was cumbersome and difficult to use. When he first saw a web browser, he knew immediately that it could revolutionize the process of clinical trials. Mr. Bleicher co-founded Phase Forward in 1997 to capitalize on this observation, creating a web browser-based application for more efficient and cost-effective data collection that also provided access to the data and operations of a clinical trial. Phase Forward's solutions now facilitate end-to-end clinical data management for multi-center and multi-continent clinical trials across thousands of sites worldwide. He says the pharmaceutical industry has the capability to save lives with necessary medicines, drugs, and devices, and his company's mission is to help these companies get products to market faster — with improved safety and reduced costs — through technology-enabled process change.

Q: ***What services/technologies does the company provide to the Specialty Pharma sector?***

A: Phase Forward provides award-winning technology products, coupled with global services, to automate and integrate the entire life cycle of the clinical development process. Our end-to-end solutions are designed to provide customers with the necessary means to track and monitor product efficacy and safety, while building their trials more efficiently and cost effectively. These solutions are practical and are used by Specialty Pharmaceutical companies of many types and sizes. Phase Forward clinical data solutions include Electronic Data Capture (InForm™), Clinical Data Management (Clintrial™), and Applied Data Standards (WebSDM™). Phase Forward safety solutions include Clinical Trials Signal Detection (CTSD™), Strategic Pharmacovigilance (WebVDME™) and Signal Management, and Adverse Event Reporting (Clintrace™).

Q: ***How does your software work? Is this something clients purchase and use themselves or do they outsource the work to you?***

A: InForm ITM (Integrated Trial Management) is an Internet-based EDC (electronic data capture) software used to collect and manage typical case report form data in clinical trials. The product provides near real-time access to both clinical and operational data. It helps to ensure data accessibility and quality through automated data checking and comprehensive reporting and analysis capabilities.

Our Clintrial Clinical Data Management system consolidates all clinical data management information (both traditional, paper-based, and EDC) into one system to facilitate data collection, review, and analysis. Built-in features automate data entry control and tracking, check for errors, and support industry-standard clinical codes.

WebSDM Applied Data Standards is a review tool that allows users to test whether their FDA submission is compliant with the latest (CDISC-SDTM format) clinical trial data, an FDA-accepted standard. Users can easily

navigate through standards and upload data via a variety of graphical formats.

CTSD Clinical Trials Signal Detection provides clinicians, medical monitors, and clinical safety scientists with a set of powerful graphical and analytical tools to assess clinical trial drug safety and detect potential adverse problems early on.

Clintrace Adverse Event Reporting is a web-based product that helps companies identify, analyze, and report adverse events, as well as meet regulatory reporting deadlines and global requirements.

WebVDME Visual Data Mining Environment and Signal Management works by applying classical and Bayesian data mining techniques against in-house or publicly available adverse event databases (e.g. AERS), and this data mining solution allows users to detect safety signals in databases of adverse event reports.

Our customers use a combination of in-house installation and outsourcing to accomplish their goals using Phase Forward products. We license our software for enterprise installations and deliver services directly to pharmaceutical, biotechnology, and medical device manufacturers, as well as public health organizations and contract research organizations. We also make our clinical trial data management applications available via a Software as a Service (SaaS) hosting model, so that organizations have the flexibility to access our technology without investing in an IT infrastructure of their own. Our technology is also available through CROs and academic research organizations (AROs), which offer our products to customers on a trial-by-trial basis along with their own value-added clinical services.

Q: ***What needs do Specialty Pharma customers typically have that bring them to Phase Forward?***

A: For Specialty Pharma companies, managing their product development life cycle is becoming increasingly complex as issues surrounding drug safety join the traditional issues involving drug efficacy. Relying on paper-based data management processes in this rapidly changing environment is becoming counterproductive. Using Internet-based electronic data capture (EDC) and safety solutions can make product development more efficient and cost-effective, while accelerating time-to-market. In addition, EDC and safety solutions provide near real-time data visibility for earlier decision-making. For Specialty Pharma companies working on in-licensing, alliances, or acquisitions, our safety signal detection software can provide detailed, rapidly available analysis of safety data relating to a compound, helping identify and quantify safety risks early on. We believe our customers frequently evaluate and select Phase Forward over our competitors for three reasons.

First, we provide industry-leading technology. Our customers need real-world solutions to their data management needs with comprehensive functionality and assurance that their clinical trial management tools will allow compliance with industry regulations. They require system automation and integration to promote team collaboration and to achieve greater operational efficiency.

The second reason is our exceptional services and support. Product innovation is invaluable, but at the end of the day, our customers require clinical trial proficiency and field-proven experience. Often, customers need customized support and integration with other clinical systems as well as ongoing process improvement assistance. Drug safety offerings include both installed software and consulting offerings, so customers can integrate with their existing solutions and create a workflow to meet their needs, whatever in-house resources they have available.

Third is our market leadership and financial stability. Choosing a solution provider for clinical trial management is a long-term commitment. Our customers are looking for experts with in-depth industry knowledge and a proven track record in clinical trial management. They want a leader in the industry with financial strength and stability that will be there for the entire life cycle of their trial and clinical development plan.

Q: ***What makes your company unique?***

A: We provide industry-leading data collection and data management solutions for clinical trials and drug safety. Our award-winning product offerings and field expertise provide our clients with the proven solutions they need to manage trials efficiently and cost-effectively — while delivering products to market faster and safer. We bring a depth and breadth of clinical data management knowledge and domain expertise to every client engagement. Our end-to-end solutions are highly scalable and can support all clinical trial phases. Our products and services have been used in more than 10,000 clinical trials involving more than 1,000,000 trial study participants at over 260 life sciences companies, medical device firms, regulatory agencies, and public health organizations. It's difficult to match the breadth of our product offerings and depth of our service experience.

Q: ***What do you believe is the key to a successful clinical trial, and what is the biggest mistake that companies make during this time?***

A: Clinical trials are successful because of clear thinking and planning in two key areas: clinical science and clinical operations. Clear thinking in planning and implementing clinical trial operations requires a proper understanding of the three factors, namely people, process, and technology. Starting with technology, today's clinical trial requires immediate accessibility of data, and a detailed and complete understanding of clinical operations. EDC technology can satisfy this need while providing the capability of incorporating adaptive clinical trial methodologies into the clinical science planning. EDC speeds the resolution of data discrepancies and allows clinical data management to minimize the time from data entry to database lock and statistical analysis. Companies should choose an EDC solution that is easy to use, built on a scalable architecture, and supports the levels of integration and data sharing required by today's enterprise organizations. When choosing an EDC vendor, companies should look for a vendor with strong global presence, clinical experience, skilled around-the-clock support resources, and financial stability.

Technology must be implemented with process change. Simply overlaying a technology solution on a manual process is worse than inefficient; it is a recipe for disaster. In fact, it is THE biggest mistake that companies frequently make when conducting EDC-based clinical trials for the first time. With EDC, the clinical data management process should be changed to incorporate the

many benefits it can bring, such as simultaneous and immediate data review. An EDC vendor with substantial expertise in clinical operations and a methodology for business process optimization can help guide companies to avoid the mistakes and get the most from EDC.

Finally, EDC and EDC-enabled processes will only work when the people involved in those processes have been properly trained. Today, training may be group training at an investigator's meeting, one-on-one at a clinical site, or through the use of web-based training modules. Again, an EDC vendor with experience will have the materials and knowledge to implement the right kind of training for each situation.

Q: ***Can you share with our readers some of the drugs that you helped conduct clinical trials and safety management tests for and their current phase of development, or if those drugs are currently on the market?***

A: Pharmaceutical companies are typically reluctant to discuss the specific technologies used in clinical development. As we have a growing number of top pharmaceutical and biotechnology companies who are using our EDC technology in virtually all of their clinical trials, we are already aware of drugs approved using data obtained with our technology, and we anticipate many more. In one non-commercial setting, our EDC technology is being used by the Aurum Institute to support a paperless study of tuberculosis and AIDS in 60,000 gold miners in South Africa; this study is being funded by the Bill and Melinda Gates Foundation.

Another example comes from a very current situation in which the FDA used our technology to evaluate the safety of a marketed drug. On February 12, 2007, the FDA announced a "black box" warning for Ketek, the Sanofi-Aventis antibiotic. The warning eliminated two of the three previously approved indications — acute bacterial sinusitis and chronic bronchitis and limiting current indications to the treatment of community-acquired pneumonia.

This announcement came following an advisory committee meeting on December 14, and 15, 2006, at which an FDA Medical Officer and Statistician presented the results of a data mining analysis conducted on Ketek, as part of the agenda for the 2-day meeting. The FDA report refers to Dr. William DuMouchel's Multi-item Gamma Poisson Shrinker (MGPS) method, used to evaluate the safety data. This technology is at the heart of Phase Forward's WebVDME product, and Dr. DuMouchel is the Chief Scientist in Phase Forward's Lincoln Technologies safety division.

This scenario is an example where precision data mining identified safety signals that resulted in significant new label warnings and changes in the populations for which the drug is helpful, allowing a labeling change in place of pulling a useful drug from the market. While the labeling was modified, the drug is still available as an option in situations where the benefits outweigh the risks. Data mining conducted at the FDA using WebVDME played an important role in helping regulators and the company to quantify these risks.

Q: ***What do you envision will be the future of clinical trial management and drug safety?***

A: On the clinical side of the equation, we predict that clinical trial management will grow and increasingly become automated. Technologies like EDC, and approaches involving adaptive trials and other innovative approaches, will be used increasingly to accelerate development timelines, drive down costs, and improve the evaluation of drug safety. Regulatory issues serve as the major driver on the drug safety side. In the US, there is a great potential for major changes in the approach to drug safety. The September 2006 Institute of Medicine (IOM) report, *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, calls for changes in drug approvals and post-approval monitoring, which could significantly modify the current approach to drug approval. The IOM report further recognizes the very important role for technology in safety signal detection, which may lead to increased adoption of these technologies. Risk management will also likely be a critical issue in clinical trial management.

Q: ***What are your thoughts on what will spur AND stifle the Specialty Pharma industry in the next 5 to 10 years?***

A: The current R&D productivity crisis, and the accompanying slowdown in NDA submissions, has even the largest pharmaceutical companies considering new strategies for preserving profitability. We believe some companies will start investing more heavily in specialty products, while others will divest small-market products to focus on their core research areas. The high volume of licensing, M&A, partnerships, and alliances in the pharma space, including Specialty Pharma, will likely continue.

As promising compounds become fewer and farther between, Specialty Pharmas will have fewer development candidates to choose from and will need to do even more homework before acquiring new compounds. Having full and accurate information about potential compounds and their safety risks will be critical for facilitating this activity. We can foresee a time when scanning a prospect's safety database using data mining will be a routine part of due diligence for acquisitions and development partnerships. At the same time, the standardization of clinical trial data in the CDISC format will facilitate safety screening activities in Phase II and III.

As drugs reach smaller markets with corresponding limitations on pharma revenues, the cost of R&D will need to be controlled wherever possible. Pharmaceutical companies will need to leverage the efficiencies of information technology to reduce the cost per clinical trial and per subject. Technologies like EDC will provide early access to safety data and enable adaptive trials, allowing for the early identification of failed clinical candidates. Conducting high-productivity, low-cost trials will be critical to getting future products to market.

New technologies, such as nanotechnology, gene therapy, and RNAi therapeutics, may well be amongst the drivers of future success in the Specialty Pharma industry. However, new technologies come with new risks, and the FDA has already sent signals to the industry that it will carefully evaluate the unique safety potential for these, and other future technologies. ■

Facts & Figures

Bionumbers: Specialty Pharma Market Indices Through March 2007

Index Trends

The overall US equity markets mostly headed sideways in March, and this was reflected in the two Specialty Pharma indexes. The Commercial Stage Specialty Pharma Index (CSPI) was down about 1% for the month but still up a little more than 4% for the year. March changes for the Emerging Stage Specialty Pharma (ESPI) index were negligible, but this index is still down about 1.6% year-to-date. April has provided a big bounce for both indexes through the 26th; the CSPI was up about 8% for the month and 13% year-to-date. The ESPI is showing a similar jump in April, and is up a bit more than 3% year-to-date.

Commercial Stage Index Trends (CSPI)

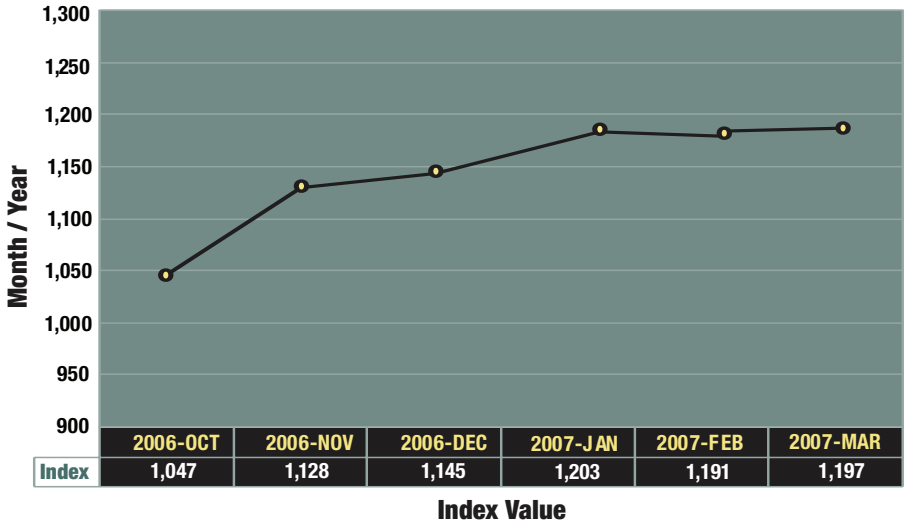
Among the Big Boys, Hospira and King were up double digits, while Endo, Shire ,and Abraxis were all up by only single digits. Among the smaller members, Vivus, Draxis, Ista, and MGI Pharma all had substantial year-to-date increases. A number of companies are experiencing double-digit bleeding. Angiotech in particular seems to have lost about a third of its market valuation through March due perhaps to concerns about the safety of coated stents.

Emerging Stage Index Trends (ESPI)

The New River acquisition was effectively closed in March, so the index will not have this valuation driver for the rest of the year. Nektar, Keryx, and Penwest continue to be the biggest contributors to the index softness through the end of March. Their drag has been largely countered by the strong performances of New River and Cadence. A number of companies, including Spectrum, Epicept, and Javelin have also taken the edge off these losses. End of March capitalization for the index was $7.4 billion, about where it was at the start of the year. ■

Bionumbers Commercial-Stage Specialty Pharma Index

MARCH 2007



Key Figures March 2007
Index Value: 1197
Change YTD: +4.5%
Total Index Capitalization: -$59.4 Billion

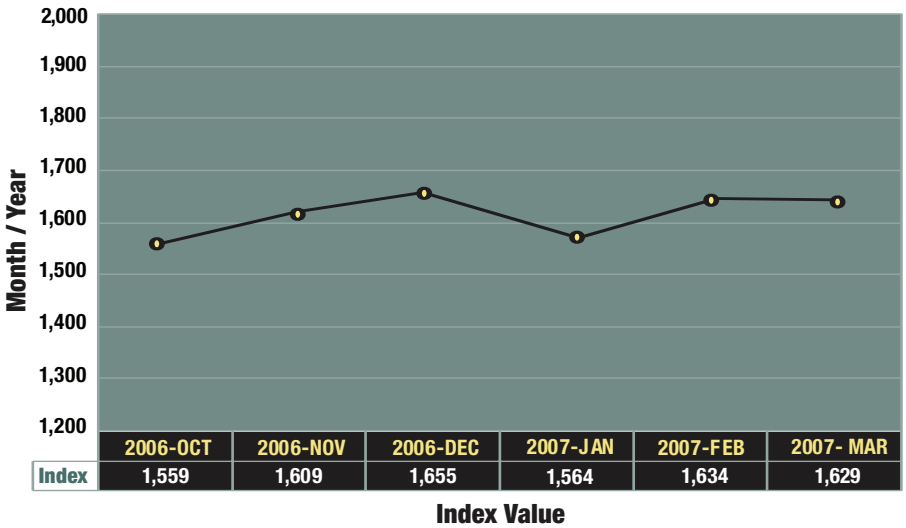
Top 5 Gainers YTD Change	
Vivus	+71%
Draxis	+34%
King	+24%
Ista	+20%
MGI Pharma	+20%

Top 5 Laggards YTD Change	
Columbia Labs	-74%
Avanir	-47%
Novavax	-36%
Angiotech	-34%
Advancis	-32%

Top 5 Capitalizations YTD Change		
Shire	$11.4 Billion	8%
Hospira	$6.4 Billion	19%
King	$4.8 Billion	24%
Abraxis	$4.4 Billion	2%
Endo	$3.9 Billion	6%

Bionumbers Emerging-Stage Specialty Pharma Index

MARCH 2007



Key Figures March 2007
Index Value: 1629
Change YTD: -1.6%
Total Index Capitalization: $7.4 Billion

Top 5 Gainers YTD Change	
Cadence	+24%
Spectrum	+22%
Epicept	+21%
New River	+20%
Javelin	+15%

Top 5 Laggards YTD Change	
Scolr	-48%
Penwest	-39%
AP Pharma	-24%
NovaDel	-21%
Sonus	-18%

Top 5 Capitalizations YTD Change		
New River	$2358 Million	+20%
Nektar	$1194 Million	-13%
Aspreva	$758 Million	+3%
Keryx	$458 Million	-20%
Cadence	$429 Million	+24%

Human Growth Hormone – A Multifaceted Paradigm for Specialty Pharma

By: Usman Qazi, PhD, Principal Consultant, Healthcare & Life Sciences, Frost & Sullivan

Introduction

Human growth hormone (hGH; somatotropin) provides a relevant paradigm for many business aspects of Specialty Pharma. In 2006, global manufacturer sales of hGH were estimated at $2.5 billion, having grown from $1.5 billion in 2000. The North American market represents nearly half of the global revenues.

Recombinant hGH represents a major initial leap for genetic engineering, and its clinical development has targeted relatively rare indications, even to the extent of influencing their medical definition. Significant regulatory and ethical issues have surrounded hGH, including the question of biosimilarity and the justification of its expense for several therapeutic applications. A section of the public regards hGH with considerable fascination, leading to restrictions on its off-label use, which in-turn hampers genuine investigative clinical work.

Recombinant hGH: A Landmark in Genetic Engineering

Initially, hGH obtained from pituitary glands of cadavers was administered to children under a US government program for more than 20 years until 1985, when its distribution was ended following reports of patient deaths from Creutzfeldt Jakob Disease. Recombinant hGH was among the first products to be produced via microbial genetic engineering by Genentech in the early 1980s. Under the brand-name Protropin, it received FDA approval in 1985 as an orphan drug. Eli Lilly followed suit by genetically engineering Humatrope (which differed from Protropin in missing just one methionine amino acid), and successfully received FDA approval despite Genentech's opposition.

Protropin was subsequently phased out by Genentech and replaced by Nutropin (also lacking the extra methionine). Today, the US hGH market includes seven companies marketing 10 FDA-approved products (see Table).

Developing Markets Based on Rare Indications

The availability of recombinant hGH spurred its use in children having Growth Hormone Deficiency (GHD), with some diagnostic definitions getting broadened and creating clinical controversy. Manufacturers were also able to demonstrate the efficacy of hGH therapy in adults with GHD. They won approvals for rare genetic

Table 1. Human Growth Hormone Brands; US.

COMPANY	PRODUCTS (US LAUNCH BY YEAR)
Eli Lilly	Humatrope (1987)
Genentech	Protropin (1985) Nutropin Depot (1999) – Discontinued Nutropin (1993) Nutropin AQ (1995)
Novo Nordisk	Norditropin (1997)
Pfizer	Genotropin (1995)
Sandoz	Omnitrope (2006)
Serono	Saizen (1996) Serostim (1996) Zorbtive (2004)
Teva	Tev-Tropin (2005)

disorders, such as Praeder-Willi's and Turner's syndromes. Other approved indications are for other relatively rare childhood disorders, such as chronic renal insufficiency and for children diagnosed as small for gestational age.

Defining More Widespread Indications

In 2003, Eli Lilly gained approval for another clinical application of its hGH product by effectively defining Idiopathic Short Stature (ISS; cause clinically unknown) as a height beyond 2.25 standard deviations below the population mean, effectively covering the shortest 1% of US children. While children with ISS are considered healthy, increasing their height was shown to provide a significant improvement in their quality of life. While other approved indications for hGH have targeted relatively small populations, the number of US children with ISS is estimated to be over a million. In contrast, the number of children and adults with GHD is estimated to be nearly tenfold less.

The social cost of hGH treatment for ISS has been the subject of a significant controversy in clinical literature and focusing on factors other than height has been proposed to offer psychosocial adjustment to short children.

Same Thing But Different?

For what is arguably the same product, differentiation is created in several ways. Every manufacturer has a product approved for GHD-Children, and nearly all for GHD-Adults. However, Serono has chosen a clear strategy in creating distinct brands for three different indications. While Saizen is approved for GHD in both children and adults, Zorbtive is uniquely approved for short bowel syndrome, which affects perhaps a little more than 1,000 patients in the US. Serostim is FDA-approved only for AIDS-related wasting. In terms of their price per mg, the latter two products are more than twice as expensive as Saizen.

Another product distinction is created among patients by delivery devices that provide advantages over injections. Eli Lilly — an insulin manufacturer — was the first to gain approval for a cartridge allowing the reconstitution of injectable hGH, with other companies following suit. Novo Nordisk has also applied its prowess with insulin delivery to a premixed pen offering multiple doses with an ultra-sharp, retractable needle. Serono offers needle-free injection devices to both patients with GHD and AIDS-wasting.

Pricing is beginning to emerge as a differentiating factor. With the annual cost of growth hormone therapy approaching $20,000 per patient, Teva, a recent hGH market entrant, has positioned itself by being considerably cheaper than competitors. Biosimilar products could further lower prices.

A Paradigm for the Biosimilar Controversy

Following a long controversy, the FDA approved Omnitrope (Sandoz) in 2006, on the basis of its demonstrated equivalence to Pfizer's Genotropin. The FDA refused to accept it as a therapeutic equivalent (or generic), but rather labeled it a "follow-on protein product," sufficiently similar to an approved product to warrant its own approval. Earlier in 2004, the FDA had responded to Sandoz's NDA by saying that it lacked an adequate legal framework to make a decision. Omnitrope's approval followed an order by a federal court requiring the

"Human growth hormone (hGH; somatotropin) provides a relevant paradigm for many business aspects of Specialty Pharma. In 2006, global manufacturer sales of hGH were estimated at $2.5 billion, having grown from $1.5 billion in 2000. The North American market represents nearly half of the global revenues."

FDA to act. The FDA noted that its decision did not make it any easier for other follow-on biologics to get approval, given that hGH products have only one active ingredient, are not glycosylated, and are extensively characterized.

The European Medications Agency (EMEA) has approved two biosimilars: Omnitrope from Sandoz and Valtropin from BioPartners. Several other companies, including the Korean LG Life Sciences and the Chinese Anke Bio, have hGH products in other markets. However, as biologicals are expensive to manufacture, it is not apparent whether follow-on products can seriously undercut existing products.

Restraining the Use of hGH as an Elixir

The illicit growth hormone market is a subject of considerable interest. In a manner analogous to anabolic steroids, US public law forbids the use of hGH for other than specifically approved indications. Back in 1990, Genentech agreed to pay $50 million in fines for aggressively marketing Protropin for indications beyond GHD-Children that were unapproved. However, there is considerable speculation on the size of the illicit market for hGH, for targeting users seeking muscle growth and rejuvenation. Researchers have noted that growth hormone prescriptions for adults have been twice those for children, suggesting a significant use for unapproved indications. The Federal Trade Commission has targeted several advertisers of illicit hGH-related products. In a particular case in 2005, the accused agreed to pay up to $20 million in consumer redress.

Regulatory agencies and government auditors are also particularly sensitive to the unnecessary expense of hGH. As a case in point, the EMEA refused to approve Serono's Serostim for AIDS-related wasting, even after giving it an orphan drug status. In 2005, Serono was prosecuted by the US Department of Justice and fined $706 million for an aggressive promotion of Serostim to doctors. Pfizer also came under media spotlight for a whistle-blowing lawsuit (which it won) regarding the alleged off-label promotion of its hGH product. The legal tussle appears to be still not quite over.

Future Growth

Currently, there is interest in hGH analogs as well as next-generation products. Human Genome Sciences has reported clinical studies on Albutropin, a longer-acting version of hGH. Other niche markets have also sprung from the decades of clinical characterization of hGH. Manufacturers, such as Insmed and Tercica, have received FDA approvals for Insulin-like Growth Factors, targeting patients who do not respond to hGH.

While new entrants have historically grown the overall hGH market, healthy growth is also foreseen among underdiagnosed adult populations with GHD. Restrictions on hGH prescription also curtail its investigative use. However, hGH is considered to potentially benefit patients suffering from severe burns to diabetes (and its side effects) to several types of cancers. If a significant decline in prices occurs with biosimilar products impacting the North American and Western Europe, increasingly prosperous middle-income nations could also offer significant opportunities to hGH manufacturers.

Summary

hGH is distinct in being relevant to patients with both clinical and psychosocial symptoms. While public concerns over hGH have restrained its

promotion by reputable manufacturers, its almost magical appeal has also created a large underground market. However, legitimate manufacturers have argued with tremendous success on the cost-benefit of their hGH products, which figure prominently among their top-selling brands.

Recombinant hGH had a trailblazing effect for subsequent genetically engineered biologics. Thus, leading companies capitalized on clinical knowledge by influencing medical paradigms, while improved delivery devices created distinct brand awareness. Significant competition appears to be occurring away from the public eye, with manufacturers forging privileged relationships with managed care.

The biosimilar controversy has also established hGH as a benchmark for follow-on products. The FDA has clearly stated that it will require a level of product characterization, safety, and efficacy comparable to what exists for hGH for any follow-on biologics. hGh holds a promising future, with considerable opportunity in expanding product labels particularly those applicable to adults. ■

Usman Qazi, Principal Consultant, Healthcare & Life Sciences

Frost & Sullivan

Dr. Usman Qazi joined Frost & Sullivan in 2002. Since then, he has worked in a variety of consulting engagements across healthcare and life sciences. In the specialty pharmaceuticals and biotechnology market, he has provided strategic insights to clients in a variety of disease areas, including arthritis, endocrinology, hematology, and infectious diseases. His projects have included new product feasibility studies and competitive intelligence in established markets. He has modeled specific segments within the clinical diagnosis and drug discovery markets, and carried out opportunity assessments in medical imaging and patient monitoring. Previously, Dr. Qazi was a biophysics post-doctoral fellow at Lawrence Berkeley National Lab. He earned his doctorate at the University of Texas, Houston Health Science Center. He came into biomedicine with an MS in Physics from the University of Nevada, Las Vegas, and previously earned a BS in Physics from Université de Franche-Comté, France.

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EXTERNAL DELIVERY

What The World Needs Is More People Like Charles Park!

By: John A. Bermingham

I have always disliked consultants. Like lawyers, they are rainmakers who waste a lot of your time and charge you a lot of money. In particular, AT&T had more consultants than any one company deserved. When I was with them, we had consultants for everything.

There was a reason though. It was because no one at AT&T ever wanted to be accountable for anything, so they had consultants everywhere. Thus, if a mistake was made, they could blame the consultant. AT&T consultants, knowing how badly they were required at AT&T, took months to accomplish what should have been accomplished in weeks. The crowning achievement was AT&T/Lucent's $1 million retainer to a consultant to develop their logo: a paint brush "swoosh" effect of a red circle. Come on! The red circle wasn't even a complete circle! I won't even start with some of the McKinsie reports that I have inherited.

When I joined Lang Holdings last August to turn it around, there were many areas to address, but one of the major problems was with their operations and supply chain. I looked at the situation and realized that it would take too much of my time to fix it, and I had too many other areas that also required immediate attention. My Board recommended that I retain a consultant to reorganize and repair our operations and supply chain, while I focused on the rest of the company. Gads! Not a consultant. Anything but a consultant! But with great reluctance, I began interviewing consulting firms to help our operations and supply chain.

After several interviews, I selected TRG, a turnaround consulting firm that would begin the day after New Year's Day. Enter Charles Park from TRG. Charles is a combat experienced ex-Army Airborne Ranger officer, a Columbia University MBA, and has a vocabulary that causes me to have to consult my dictionary after every meeting. Charles is a no nonsense guy. He tells it like it is, never plays politics, and has accomplished in weeks what should have taken months.

Lang Holdings has five entities. Two of them were recent acquisitions. The other three had their own problems. So we are a fairly complex organization. Charles Park has integrated these five entities' operations and supply chains into a structured, process-oriented, organization in half the time I thought that it would. I made Charles the interim VP of Operations after a few weeks on the job because I needed him in that role. He has taken that responsibility in our company to a new level of greatness. He has also been accepted as one of us by our people because of his constant and positive interaction with all constituents. Charles, while filing a weekly written update report with our Board and me, has yet to develop a consultant's 3" binder of information, complete with Power Point slides. He just gets the job done every day and keeps making progress. He is a daily communicator to me on what is happening ,and I am always informed.

More than anything, Charles has made me believe in the following:

1. That there are great consultants who can be of tremendous service and benefit to a company and that there are straight-ahead people who you can trust in this world.
2. That he is an integral part of our turnaround and that the company may have failed without his involvement and expertise.
3. I now believe in consultants.

Oh yeah. Did I mention that he is a great guy to be around and enjoys a "brew review" after work on occasion? Thanks Charles! ◆

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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