Drug Delivery® Technology

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INTRODUCING PAINLESS LASER INTRAEPIDERMAL DELIVERY

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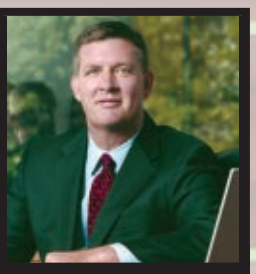

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PUBLISHER/PRESIDENT
Ralph Vitaro

EXECUTIVE EDITORIAL DIRECTOR
Dan Marino, MSc
dmarino@drugdeliverytech.com

CREATIVE DIRECTOR
Shalamar Q. Eagel

CONTROLLER
Debbie Carrillo

CONTRIBUTING EDITORS
Cindy H. Dubin
Debra Bingham
Jason McKinnie
Malcolm A. Teasdale

TECHNICAL OPERATIONS
Mark Newland

EDITORIAL SUPPORT
Nicholas D. Vitaro

ADMINISTRATIVE SUPPORT
Kathleen Kenny

Corporate/Editorial Office
219 Changebridge Road, Montville, NJ 07045
Tel: (973)299-1200
Fax: (973) 299-7937
www.drugdeliverytech.com

Advertising Sales Offices

East & Midwest
Victoria Geis - Account Executive
Cheryl S. Stratos - Account Executive
103 Oronoco Street, Suite 200
Alexandria, VA 22314
Tel: (703) 212-7735
Fax: (703) 548-3733
E-mail: vgeis@drugdeliverytech.com
E-mail: cstratos@drugdeliverytech.com

West Coast
Warren De Graff
Western Regional Manager
818 5th Avenue, Suite 301
San Rafael, CA 94901
Tel: (415) 721-0644
Fax: (415) 721-0665
E-mail: wjdegraff@drugdeliverytech.com

International
Ralph Vitaro
219 Changebridge Road
Montville, NJ 07045
Tel: (973) 299-1200
Fax: (973) 299-7937
E-mail: rvitaro@drugdeliverytech.com

Mailing List Rental
Candy Brecht
Tel: (703) 706-0383
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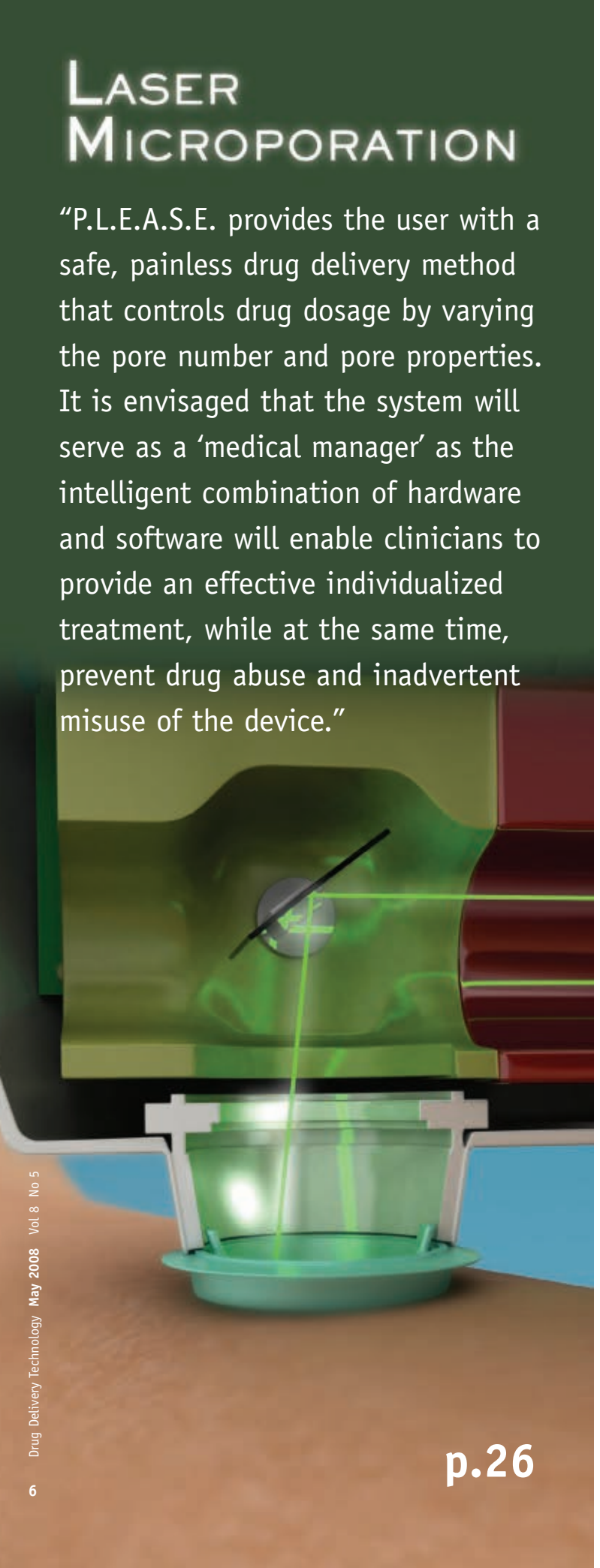

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"We are seeing significantly more complex peptides entering clinical trials. Peptides with sequence lengths exceeding 40 amino acids or with multimeric structures are becoming quite common. Without an appreciation of the analytical and manufacturing issues associated with such structures, it is easy to overlook issues that need addressing whilst the project is in its development stage."

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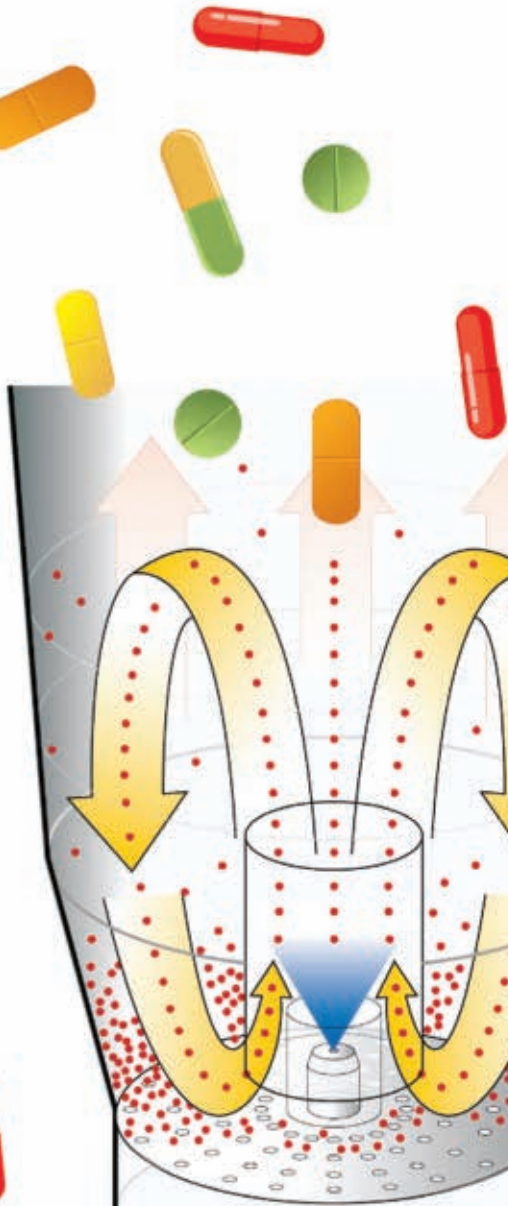

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Market News and Trends

Zelos Therapeutics & Aegis Therapeutics Announce Collaboration for Intranasal Delivery of ZT-031

Zelos Therapeutics, Inc. and Aegis Therapeutics LLC recently announced the signing of a collaboration agreement for the development of an intranasal spray formulation of the proprietary parathyroid hormone (PTH) analog ZT-031 [Ostabolin-C, cyclic PTH-(1-31)]. Under the collaboration, which is exclusive across the PTH field, Zelos will utilize Aegis' patented Intravail permeation enhancer technology to develop an intranasal version of ZT-031 for the treatment of osteoporosis and other bone diseases. A subcutaneous formulation of ZT-031 has already successfully completed a 12-month Phase II clinical trial in the treatment of osteoporosis.

"The improved biochemical and clinical profile of our subcutaneous formulation of ZT-031 over existing, marketed PTH therapeutics creates the potential for an important new anabolic therapy for osteoporosis and other bone diseases with commercial potential that we estimate to be in excess of $1 billion dollars," said Dr. Brian MacDonald, CEO of Zelos. "We anticipate that an intranasal formulation of ZT-031 may substantially expand the market for bone formation agents by improving patient acceptance and compliance and represents a potential commercial opportunity that may be comparable in size to the market leading bisphosphonates, currently the mainstay of osteoporosis treatment. The ease of formulation of ZT-031 with Intravail, by providing the opportunity for rapid development, was also an important consideration for Zelos. We are pleased that, in preliminary studies, Intravail has already proven capable of significantly enhancing the pharmacokinetic profile of nasally administered ZT-031 and look forward to moving intranasal ZT-031 into clinical studies as quickly as possible."

"Aegis looks forward to collaborating with Zelos on the development of intranasal ZT-031. The unique and differentiated product profile and strong clinical results for ZT-031 are impressive, and we believe this PTH analog is an ideal match for our Intravail technology," added Dr. Edward Maggio, Aegis' CEO. "Our work alongside Zelos' highly capable team serves to advance a new and potentially advantageous dosing formulation that may bring significant benefit to those suffering from osteoporosis and other bone diseases."

ZT-031 is a proprietary cyclic 31-amino acid parathyroid hormone (PTH) analog. In a 12-month Phase II study in postmenopausal women with low bone mass, a subcutaneous formulation of ZT-031 was demonstrated to be a powerful bone formation agent with a rapid onset of effect, leading to clinically important increases in bone mineral density (BMD) at doses with low potential for calcium related toxicity. ZT-031 is expected to enter Phase III trials in osteoporosis this year, and clinical programs in fracture repair and renal bone disease indications are planned to begin over the next year.

Zelos Therapeutics specializes in the development of innovative treatments for bone disorders and related indications in large, underserved markets. Led by an experienced team of biopharmaceutical executives and funded by leading healthcare investors, Zelos is advancing a portfolio of product opportunities into late-stage clinical trials.

Intravail allows the intranasal delivery of a growing number of peptide or protein drugs used to treat a wide range of human diseases. Examples include insulin, growth hormone, parathyroid hormone, GLP-1, and interferon, among many others. Unlike dry powder inhalable systems for pulmonary delivery of peptide drugs to the lungs that require specialized and expensive controlled-particle-size manufacturing technology, Aegis' Intravail intranasal formulations use standard and comparatively inexpensive homogeneous liquid formulation and fill technology and are administrable using simple "off-the-shelf" metered nasal spray devices that avoid the possibility of lung exposure.

Aegis Therapeutics LLC is a drug delivery technology company commercializing its patented or proprietary drug delivery and drug formulation technologies through product specific licenses. In addition to its Intravail drug delivery technology, Aegis offers its ProTek technology to allow for the creation of proprietary, easily manufacturable, and stable aqueous or lyophilized dosage forms that maintain the integrity and physiological activity of many protein and peptide therapeutics. ProTek technology is applicable to injectable, intranasal, and other dosage forms of peptide or protein therapeutics.

Market News and Trends

Stromedix Raises $25 Million Series B for Fibrosis Programs, Begins Clinical Trial

Stromedix, Inc., a biotechnology company focused on innovative therapies for fibrosis, recently announced it has raised $25 million in a Series B financing round led by New Leaf Venture Partners. Other new investors are Bessemer Venture Partners and Red Abbey Venture Partners. Series A investors Atlas Venture and Frazier Healthcare Ventures also participated in the round. In connection with the financing, Ron Hunt, a Managing Director of New Leaf Venture Partners, and Chris Gabrieli, a Partner of Bessemer Venture Partners, will join Stromedix's board of directors.

Earlier this year, Stromedix initiated a Phase I clinical trial of STX-100, the company's lead drug candidate. STX-100 is a novel humanized monoclonal antibody licensed in 2007 from Biogen Idec, which is also a shareholder in the company. STX-100 targets integrin av(beta)6 and exhibits significant antifibrotic activity in preclinical animal models of lung, kidney, and liver disease. As a first indication, Stromedix is developing STX-100 for treatment of chronic allograft dysfunction, a fibrotic condition that is a leading cause of graft loss in kidney transplant patients and for which there are no approved therapies. Stromedix believes that STX-100 may have broad therapeutic utility in settings where there is significant unmet medical need, such as idiopathic pulmonary fibrosis, chronic kidney and liver disease, and cancer.

"Fibrosis is an important medical problem in many different diseases, and there are no current therapies to prevent, slow, or reverse the course of its progression," said Mr. Hunt. "Although the biology of fibrosis is increasingly well understood, this knowledge has not yet been translated into clinical benefit for patients. Stromedix is putting the pieces in place do this, acquiring an exciting molecule from a leading biotech company, designing and implementing a creative clinical trial strategy to evaluate its therapeutic utility and assembling an outstanding management team to execute its plan."

Stromedix is led by one of its founders, Michael Gilman, PhD, who was formerly Executive Vice President of Research at Biogen Idec. The company's senior management team also includes Daniel Lynch, Executive Chairman; Neil Kirby, PhD, Chief Development Officer; and Bradley Maroni, MD, Chief Medical Officer. Together the team brings many years of innovative biotechnology development experience from companies, such as Biogen Idec, Amgen, Vertex, ImClone Systems, TKT, and Genetics Institute.

"Stromedix has put together a fantastic team," said Bessemer Venture Partners' Chris Gabrieli. "They are experienced, thoughtful, and focused on addressing a problem that affects a huge number of lives. I am excited to be able to participate in building this program and this company."

"Stromedix is targeting a very exciting market opportunity for new therapeutics. It is one of the few disease areas with multibillion dollar market potential that has no existing approved products and very few products in clinical development. We believe Stromedix will be a leader in this important field" added Peter Barrett, who represents Atlas Venture as board member and founding investor of Stromedix.

"We are excited to welcome a high-quality group of new investors to the strong investors who were involved in founding Stromedix," said Michael Gilman. "We look forward to working with this outstanding syndicate to bring powerful new treatments to patients suffering from fibrotic organ failure."

Market News and Trends

Aradigm Initiates Trial of Lung Rx's Inhaled Treprostinil

Aradigm Corporation recently announced it initiated a bridging clinical trial of inhaled treprostinil utilizing its AERx Essence pulmonary delivery system. The trial in healthy volunteers is being conducted in the United Kingdom to evaluate aerosol delivery by assessing lung distribution, pharmacokinetics, and safety of inhaled treprostinil delivered by the AERx Essence system versus delivery with the Nebu-Tec OPTINEB-ir nebulizer. The latter device was used by Lung Rx, Inc., a wholly owned subsidiary of United Therapeutics Corporation, in the recently concluded TRIUMPH (TReprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension) study of inhaled treprostinil in patients with Pulmonary Arterial Hypertension (PAH).

The Company was granted authorization to proceed with the clinical trial by the UK Medicinal Health Care products Regulatory Agency (MHRA) as required under the European Union Clinical Trials Directive.

"We are delighted that we are making good progress with Aradigm toward providing PAH patients with ever more convenient ways to treat their condition using the palm-sized AERx Essence inhaler," said Martine Rothblatt, PhD, Chairman and CEO of Lung Rx and United Therapeutics Corporation.

"This clinical trial is an important milestone for our company," said Igor Gonda, PhD, President and CEO of Aradigm. "First and foremost, it is a key step in our collaboration with Lung Rx. Second, it is another opportunity to demonstrate the value of the AERx technology for the development of important new therapeutic products administered by inhalation."

Aradigm is an emerging specialty pharmaceutical company focused on the development and commercialization of a portfolio of drugs delivered by inhalation for the treatment of severe respiratory diseases by pulmonologists. Current activities include partnered and self-initiated development programs addressing the treatment of cystic fibrosis, bronchiectasis, pulmonary hypertension, asthma and bronchitis, inhalation anthrax infections, and smoking cessation. Lung Rx, Inc. is a biotechnology company focused on unmet medical needs in pulmonary medicine and pulmonary delivery of innovative therapeutic products.

Market News and Trends

Calando Pharmaceuticals Receives FDA Approval for Phase I Clinical Trial Using a Targeted siRNA Nanoparticle Therapeutic

Calando Pharmaceuticals, a majority owned subsidiary of Arrowhead Research Corporation, recently announced that the US FDA has approved its IND for its lead anti-cancer compound, CALAA-01. The drug candidate is a targeted nanoparticle composed of a proprietary, non-chemically modified siRNA against the M2 subunit of ribonucleotide reductase (a clinically validated cancer target) formulated with Calando's proprietary RONDEL (RNAi/Oligonucleotide Nanoparticle Delivery) polymer delivery system. The FDA approval allows the initiation of a Phase I trial that will be conducted at the UCLA Jonsson Cancer Center (UCLA) in Los Angeles, and the South Texas Accelerated Research Therapeutics (START) clinic in San Antonio. It will be led by Drs. Antoni Ribas (UCLA) and Anthony Tolcher (START).

"We are pleased to have received FDA approval of our IND application for CALAA-01," said Jeremy Heidel, CSO of Calando. "We look forward to initiating a Phase I clinical trial with CALAA-01 that we believe will be the first clinical study using targeted, systemic delivery of siRNA in an oncology setting. The entire Calando team is excited to be at the forefront of this new area for therapeutic development."

RNA interference, or RNAi, is a naturally occurring mechanism within cells for selectively silencing and regulating specific genes. Because many diseases are caused by the inappropriate activity of specific genes, the ability to silence genes selectively through RNAi could provide a new class of medicines to treat a wide range of human diseases. RNAi is induced by small, double-stranded RNA molecules. One method to activate RNAi is with chemically synthesized small interfering RNAs, or siRNAs, which are double-stranded RNAs that are targeted to a specific disease-associated gene. The siRNA molecules are used by the natural RNAi machinery in cells to cause highly targeted gene silencing.

Calando Pharmaceuticals Inc. is a biopharmaceuticals company using proprietary technologies developed at Caltech to create targeted siRNA-based therapeutics. Calando combines its innovative RONDEL system of polymeric delivery with siRNA to solve the long-standing obstacle of effective delivery and targeting for this revolutionary new field of medicine using RNA interference, or RNAi. Based upon the innovative breakthrough in siRNA delivery enabled by the RONDEL system, the promise of using siRNA in new systemic therapies may finally be realized.

Calando's RONDEL technology involves the use of cyclodextrin-containing polymers that form the foundation for its two-part siRNA delivery system. The first component is a linear, cyclodextrin-containing polycation that, when mixed with small interfering RNA (siRNA), binds to the anionic "backbone" of the siRNA. The polymer and siRNA self-assemble into nanoparticles smaller than 100 nm in diameter that fully protect the siRNA from nuclease degradation in serum. The siRNA delivery system has been designed to allow for intravenous injection. Upon delivery to the target cell, the targeting ligand binds to membrane receptors on the cell surface and the RNA-containing nanoparticle is taken into the cell by endocytosis. There, chemistry built into the polymer functions to unpackage the siRNA from the delivery vehicle. In addition to targeting tumors, the targeting of liver cells has also been accomplished in vivo.

Market News and Trends

Pantec Biosolutions Unveils Preclinical Data for Novel Transdermal Delivery Platform

Pantec Biosolutions AG, a privately owned company developing innovative technologies for transdermal drug delivery, recently reported promising preclinical in vitro data in support of the company's novel P.L.E.A.S.E.® (Painless Laser Epidermal System) intraepidermal drug delivery platform.

Pantec Biosolutions has achieved further important milestones in the replacement of injection-based therapies with painless needle-free transdermal systems. In vitro permeation proof-of-principle studies with a series of small and large molecular weight therapeutics demonstrate that P.L.E.A.S.E. significantly increases drug transport of poorly and non-permeating therapeutic agents.

"Proof-of-principle means cumulative drug permeation that is at least equivalent to delivery from the existing dosage form, eg, by subcutaneous injection," according to Dr. Yogeshvar Kalia of the School of Pharmaceutical Sciences, University of Geneva and Scientific Advisor to Pantec Biosolutions.

The company has completed in vitro permeation studies with several key hormones in its primary focus area of In Vitro Fertilisation (IVF). The results formed the basis of collaboration agreements with a pharmaceuticals company and a patch development and manufacturing company. Development of transdermal patch systems, optimized for use with the P.L.E.A.S.E. technology, is underway with clinical results expected in 2009. At present, Pantec Biosolutions is financing the entire project and, in line with its business strategy, is open to licensing both its P.L.E.A.S.E. technology and the transdermal patches in a one stop shop concept.

In the area of pain management, Pantec Biosolutions has completed investigations with diclofenac (a nonsteroidal anti-inflammatory) and lidocaine (a topical anaesthetic).

The diclofenac results indicate that significantly more drug can be administered topically using P.L.E.A.S.E., providing real scope for increasing the current range of indications. Furthermore, topical administration will alleviate the risk of gastrointestinal and other systemic side effects.

Lidocaine is a topical anaesthetic used to numb the skin and underlying tissue before needle-stick procedures and at present, the slow onset of effect limits its wider use. Microporation prior to lidocaine application results in substantially faster action and enables the needle procedure to be performed minutes after applying the anaesthetic.

Pantec Biosolutions also reported initial in vitro results with a large protein, showing significant delivery, in the double digit microgram range, within 24 hours.

"We are very pleased to present such proof-of-principle data in the field of IVF, our lead therapeutic area, to our partners and investors," said Dr. Christof Boehler, Pantec Biosolutions' CEO. "The IVF results together with the data in other therapeutic areas represent a further important milestone on our way to building partnerships with pharmaceutical and biotechnology companies."

Genta Receives Key Patent Related to Oral Gallium; Seeks Buyer for Marketed Parenteral Product

Genta Incorporated recently announced it has received notice that its patent application covering novel pharmaceutical gallium compositions and complexes has been allowed by the US Patent Office. Issued US Patent No. 7,354,952 extends the intellectual property surrounding the company's franchise of oral gallium-containing products that are intended as potential treatment for diseases associated with accelerated bone loss. The lead compound in this investigational pipeline, G4544, was developed in collaboration with Emisphere Technologies, Inc. and has completed its initial Phase I dose-ranging study. Results of this study will be presented at the Annual Meeting of the American Society of Clinical Oncology in Chicago from May 30 to June 3, 2008.

With continued progress in the oral formulation program, the company has elected to seek a buyer for the intravenous formulation of its on-market product from this franchise, Ganite (gallium nitrate injection). The active ingredient in both Ganite and G4544 is ionic gallium, which is reversibly incorporated into bone where its acts as a potent inhibitor of bone resorption and possibly as a mild anabolic agent to enhance bone formation. Ganite is approved by the US FDA for treatment of patients with cancer-related hypercalcemia that is resistant to hydration. Ganite is exclusively marketed in the US by Genta and is available to patients outside the US on a named-patient basis.

Genta Incorporated is a biopharmaceutical company with a diversified product portfolio that is focused on delivering innovative products for the treatment of patients with cancer. Two major programs anchor the company's research platform: DNA/RNA-based Medicines and Small Molecules. Genasense (oblimersen sodium) Injection is the company's lead compound from its DNA/RNA Medicines program. Genta is currently recruiting patients to the AGENDA Trial, a global Phase III trial of Genasense in patients with advanced melanoma. The leading drug in Genta's Small Molecule program is Ganite (gallium nitrate injection), which the company is exclusively marketing in the US for treatment of symptomatic patients with cancer-related hypercalcemia that is resistant to hydration. The company has developed G4544, an oral formulation of the active ingredient in Ganite, that has recently entered clinical trials as a potential treatment for diseases associated with accelerated bone loss. The company is also developing tesetaxel, a novel, orally absorbed, semi-synthetic taxane that is in the same class of drugs as paclitaxel and docetaxel. Ganite and Genasense are available on a named-patient basis in countries outside the US.

Transdel Pharmaceuticals Advances Lead Topical Pain Drug Into Phase III Program

Transdel Pharmaceuticals, Inc. recently announced that based on the US FDA review of its Phase III submission, the company can initiate its Phase III clinical program for its novel topical cream-based non-steroidal anti-inflammatory drug (NSAID), Ketotransdel. Transdel Pharmaceuticals is a specialty pharmaceutical company pursuing the development and commercialization of non-invasive topically administered medications.

"I am pleased to announce that the FDA has reviewed our February 7, 2008, FDA submission and has stated that it is safe to proceed with the Phase III program. The FDA also noted that there are no clinical hold issues and provided comments regarding the registration requirements of our lead drug. We will continue our discussions with the FDA regarding the final product approval requirements," said Dr. Juliet Singh, President and Chief Executive Officer of Transdel Pharmaceuticals.

Dr. Singh continued, "Advancing into Phase III clinical studies for Ketotransdel marks a significant milestone for the company. Our dedicated and committed team is focused on successfully advancing our topical drug to FDA approval."

Based on industry estimates, the market for NSAIDs and Cox-2 inhibitors exceeds $6 billion per year; more than 30 million people worldwide use NSAIDs daily. Due to the recognition of known risks associated with orally administered NSAIDs, including cardiovascular, gastrointestinal, and other medical complications, and the decline in the use of Cox-2 inhibitors because of safety concerns, Transdel believes there is a significant demand for topical pain management products, such as Ketotransdel. Moreover, the company expects that Ketotransdel, if approved by the FDA, could become the first topical NSAID cream product in the US for acute pain management. The drug could address a significant unmet medical need for patients with medical conditions and those patients seeking safer alternatives to the standard pain management approaches.

In the second quarter of 2008, the company intends to initiate the randomized, double-blind, placebo-controlled Phase III program to evaluate the efficacy and safety of Ketotransdel in acute pain care management. The company also stated that in the near term it will be announcing organizational changes as the company transitions into late-stage clinical phase.

Transdel Pharmaceuticals, Inc. is a specialty pharmaceutical company pursuing the development and commercialization of non-invasive topically delivered medications. The company's lead topical drug, Ketotransdel, utilizes the company's innovative patented Transdel cream formulation technology to facilitate the passage of ketoprofen, an NSAID, through the skin barrier to reach targeted underlying tissue where the drug can exert its prolonged localized anti-inflammatory and analgesic effect. The company is also investigating other drug candidates and treatments for transdermal delivery using the patented Transdel platform technology for products in pain management and other therapeutic areas.

Echo Therapeutics & Cato BioVentures Sign Agreement for Dermatology Products & Transdermal Delivery Technologies

Echo Therapeutics recently announced it has signed a dermatology product and transdermal drug delivery technology right-of-first-offer-agreement with Cato BioVentures, the venture capital affiliate of Cato Research, a global contract research and development organization. The agreement grants Echo exclusive rights of first negotiation to all dermatology product and transdermal drug delivery technology opportunities identified or acquired by Cato BioVentures.

"This agreement expands our long-standing strategic relationship with Cato BioVentures and Cato Research and enables us to leverage their deep industry access to a wide range of business development opportunities in our core focus areas," said Patrick Mooney, MD, Echo's Chairman and CEO. "Cato is familiar with our core transdermal platforms (AzoneTS for drug reformulation and the Symphony tCGM System for non-invasive continuous glucose monitoring) and understands our model to leverage those platforms internally and with product and technology acquisition opportunities that fit our model."

"As a 20-year-old company with a broad network of industry and regulatory contacts worldwide, we have access to dozens of high-quality drug and technology development opportunities each year, many of which could be commercially relevant to Echo's strategic plan," added Allen Cato, MD, PhD, Principal of Cato BioVentures and Co-founder and CEO of Cato Research. "This agreement allows us to leverage the expertise of Echo's management team and its market resources to assess and potentially access efficiently and cost-effectively select drug and technology development opportunities that could add value to our companies."

Echo Therapeutics is focused on transdermal medical devices and specialty pharmaceuticals. Echo is developing a non-invasive (needle-free), wireless, transdermal continuous glucose monitoring (tCGM) system for people with diabetes and for use in hospital critical care units. Echo is also developing a wide range of proprietary transdermal reformulations of FDA-approved pharmaceutical products.

Cato BioVentures is the venture capital affiliate of Cato Research Ltd., a global contract research and development organization. For 20 years, Cato BioVentures has assisted entrepreneurs and established management teams in building successful pharmaceutical and biotechnology companies. Through strategic CRO service agreements with Cato Research, Cato BioVentures invests its in-kind CRO Service Capital in innovative products and technologies, giving promising companies immediate access to a broad range of essential CRO services on a noncash basis.

Founded in 1988 by Dr. Allen Cato and Lynda Sutton and headquartered near Research Triangle Park, Cato Research is a global full-service contract research and development organization (CRO) providing strategic and tactical support for clients in the pharmaceutical, biotechnology, and medical device industries. Cato Research has a staff of over 300 located in offices in the US, European Union, Canada, Israel, and South Africa.

Intelgenx Forms Strategic Alliance With Dava Pharmaceuticals to Develop Cardiovascular Product; Market Worth $1 Billion

IntelGenx Corp. has formed a strategic alliance with DAVA Pharmaceuticals, Inc. to develop and commercialize a generic equivalent to a major cardiovascular product using IntelGenx's proprietary Versatab delivery technology.

"This alliance illustrates IntelGenx's business strategy whereby we seek out key commercialization partners for development of products with significant potential using our drug delivery technologies," said Horst G. Zerbe, President & CEO of IntelGenx.

Under the strategic alliance, the companies expect to launch the product in the fourth quarter of 2010. IntelGenx will complete the development of the product, using its patented proprietary delivery technologies. IntelGenx will be entitled to fees for the development of the product as well as recurring revenue through a share of DAVA's US gross profit. DAVA will be responsible for commercialization and marketing activities in the US.

According to Datamonitor's Pharmaceuticals and Healthcare Knowledge Center, the peak US sales for the brand exceeded $1 billion annually. IntelGenx management anticipates rapid penetration of the market, achieving significant sales over the first 5 years of commercialization.

"We are indeed pleased to partner with DAVA, a rapidly growing generic company noted for its strong strategic collaborations with leading API suppliers, branded pharmaceutical companies, and generic product developers and manufacturers," said Dr. Zerbe. "Our innovative oral, immediate-release and controlled-release delivery technologies add important new options to their portfolio."

Intelgenx now has nine products in development with its first product (prenatal vitamin) to be commercialized in the second half of 2008. In addition, the company expects to engage in additional development and commercial alliances thereby expanding their product pipeline with new and existing partnerships in 2008.

IntelGenx Corp. is a drug delivery company focused on the development of oral controlled-release products as well as novel rapidly disintegrating delivery systems. The company uses its unique multiple-layer delivery system to provide zero-order release of active drugs in the gastrointestinal tract. IntelGenx has also developed novel delivery technologies for the rapid delivery of pharmaceutically active substances in the oral cavity based on its experience with rapidly disintegrating films. The company's research and development pipeline includes products for the treatment of osteoarthritis, pain management, hypertension, and smoking cessation.

DAVA Pharmaceuticals, a specialty pharmaceuticals company, is focused on developing and marketing a broad portfolio of pharmaceutical products. DAVA is aggressively building its product portfolio through a combination of acquisitions, strategic alliances, in-licensing transactions, partnerships, and development.

Vaginal Progesterone Seen as Equally Effective in Achieving Pregnancy Outcomes as Injectable Progesterone

A retrospective analysis of anonymous oocyte (egg) donation cycles, comparing the pregnancy outcomes between vaginally administered progesterone versus intramuscular (IM) progesterone injections, demonstrates that vaginally administered progesterone and IM progesterone achieve equal pregnancy outcomes, according to data presented by Brian Berger, MD, Boston IVF, at the Pacific Coast Reproductive Society annual meeting in Rancho Mirage, CA. The retrospective study was supported by a grant from Columbia Laboratories, Inc.

"We found no significant differences in pregnancy outcomes between patients treated with vaginal progesterone versus progesterone administered intramuscularly," said Dr. Berger. "Further, vaginal progesterone has the added advantage of avoiding painful intramuscular injections."

In 225 egg donor cycles, 105 patients received vaginally administered progesterone (CRINONE 8%, a bioadhesive progesterone gel) and 120 received IM progesterone. The implantation rate was 43.8% for vaginal progesterone versus 37.1% for IM progesterone ($p = 0.175$). Recipients treated with vaginal progesterone achieved a 58.1% pregnancy rate and a 51.4% delivery rate, versus a 53.3% pregnancy rate ($p = 0.503$) and a 48.3% delivery rate ($p = 0.689$) for patients receiving IM progesterone. The pregnancy loss rate was 10.5% for patients using vaginal progesterone and 10.8% for IM progesterone users ($p = 1.00$).

"This study clearly demonstrates that vaginal progesterone gel achieves the same pregnancy outcomes as progesterone administered via an intramuscular injection. This is important confirmation that CRINONE 8% offers patients an efficacious and more convenient option for providing progesterone support in infertility treatment," added Dr. Berger.

Boston IVF is one of America's most successful fertility centers, providing patients with unparalleled medical care and the best experience with the expertise of premier doctors and professional staff, who are affiliated with Harvard Medical School. It is world renowned for its highly successful and innovative infertility treatments, highest quality service, state-of-the-art methods, ongoing scientific research, and on-site complementary healthcare at its Domar Center.

CRINONE 8% was the first FDA-approved natural progesterone for progesterone supplementation or replacement as part of ART treatment for infertile women with progesterone deficiency, and is the only once-a-day treatment. CRINONE 8% is safe for use during pregnancy and has been safely used for a decade by tens of thousands of women globally to help sustain pregnancy in the first trimester. Its unique bioadhesive delivery system provides controlled and sustained release of progesterone directly where it is needed.

New Guidelines for Reconstituted Drug Devices

By: Patrick Ryan and Christopher Kadamus

The availability of an increasing number of lyophilized drug products, in combination with an industry-wide desire for simple, easy-to-use drug delivery devices, has created a need to reduce the complexity of traditional reconstitution devices and to moderate treatment risk. Successful device development is dependent on a clear understanding of user, regulatory, commercial, clinical, manufacturing, and formulation requirements. Unfortunately, a consensus on this broad set of requirements is not always easy to achieve. In response to the market demand and development challenges, Cambridge Consultants has made publicly available a *Reconstitution Injection Device Generic Requirements Specification**.

INTRODUCTION

The growth of the biopharmaceuticals industry has led to the development of many new drugs that utilize injection as the primary method of delivery. While many of these drugs have strong therapeutic benefits, some formulations have proved to be unstable in liquid form. To contend with their inherent instability, a number of these drugs are being produced in a lyophilized (freeze-dried) form. The drug is reconstituted immediately prior to patient application. With the revenue generated by the sale of these pharmaceuticals exceeding $20 billion, the market is eager for new devices that can reconstitute and deliver drugs efficiently and cost effectively.

While lyophilization provides a solution to combat drug instability and can assist in minimizing time-to-market, a multitude of challenges are implicit to the design of devices for reconstitution and delivery of freeze-dried drugs. Engineering devices to deliver these drugs requires intimate knowledge of the drug characteristics, including fragility and solubility, as well as knowledge of fluid dynamics, mixing techniques, and user requirements. The combination of the numerous and often conflicting requirements inherent to lyophilized drug delivery necessitates a robust device development methodology.

Reconstitution, as it applies to lyophilized drugs, involves the rehydration of a dry drug formulation with a diluent, typically Sterile Water for Injection (SWFI) or Bacteriostatic Water for Injection (BWFI). Historically, reconstitution was primarily accomplished by transferring the diluent from one vial to a second vial containing the dry drug. This procedure was performed manually, using the syringe that would ultimately be employed to administer the injection. Devices, such as vial adaptors, were created to aid in this process. However, even with assistance of adaptors, the process of manual drug reconstitution and administration using a standard syringe can be complex and necessitates multiple user steps. In recent years, an increased demand for drug delivery devices intended for non-clinical use, such as injection pens, has resulted in the development of a new class of self-administered injection products for drugs that require reconstitution.

Although the market is eager to see this type of new injection product, designing an injection device capable of reconstituting a lyophilized drug is not a trivial task. In addition to the safety, reliability, and regulatory requirements common to all injection devices, the process of reconstitution adds the technical challenge of combining a diluent with what is often a delicate compound. These compounds, many of which are biologics, can be denatured by heat, shear, and foaming. If improperly mixed, the formulation may not reconstitute completely or the molecules may aggregate to form particulates. In many cases, improper or incomplete reconstitution can lead to significant decreases in drug potency, drug loss, or patient injury. These concerns must be addressed early in the development process in order to ensure the greatest chance of regulatory approval and successful device commercialization.

THE REQUIREMENTS SPECIFICATION

A requirements specification is perhaps the most critical design input document created during device development. Attempting to develop a medical device with ambiguous, incomplete, non-specific, or conflicting requirements greatly increases the chance of failure while often adding unnecessary cost and time to the development plan. Furthermore, a requirements specification serves as the foundation for the Design History File, allowing requirements to be traced through the development process and specifying how the design will be validated.

The document recently released by Cambridge Consultants is a generic requirements specification intended for use in the development of injection devices capable of reconstituting lyophilized drugs. The document is generic in the sense that it covers the requirements that are common to developing any device of this type. Many of the requirements are fully developed and could apply to any such device, while others provide a framework, but require the inclusion of a quantity appropriate to the

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specific device being designed.

The requirements are drawn from a myriad of sources and compiled into a single document that is easy to use and capable of adaptation. Many requirements are based on FDA regulations and recognized international standards, including ISO, US Pharmacopeia, and ASTM. In addition to these "core" requirements, much of the value of this document is derived from the requirements based on the company's experience, which includes the design and evaluation of injection products and reconstitution devices, as well as a broader range of medical and consumer products. This experience is presented in sections covering safety, manufacturing, and non-clinical performance, including industrial design and human factors considerations. The final major contribution is a concise set of requirements that addresses the issues directly related to the act of reconstitution. These requirements are compiled from research pertaining to the science of reconstitution and focus on the most critical issues specific to the process.

BRIDGING THE PHARMACEUTICAL – MEDICAL DEVICE DIVIDE

Pharmaceutical companies often know a great deal about their formulation and therapeutic area, but may not fully understand the device requirements that lie outside of these topics. As such, they must often be guided by the device developers or component vendors in order to produce a device that can be successfully commercialized. A generic requirement specification, like the one at hand, arms pharmaceutical companies with the information necessary to protect themselves against many of the pitfalls that can arise early in the development stage, as well as allows them to participate in key design decisions that greatly influence development costs and timescales.

For device developers, the generic requirement specification serves as a roadmap to rapid, low-cost development. In a simple, "fill-in-the-blank" format, it can provide a sturdy framework that can be easily customized to meet the needs of a particular device. Use of this requirements framework reduces the chance of important features or benefits being overlooked. Through its generic nature, the document provides maximum benefit while still allowing for application to a range of possible embodiments. This requirements specification should be particularly valuable for development teams that do not have a great deal of experience in the areas of reconstitution and injection devices, enabling them to utilize consolidated research and the collective experience gained through the development, analysis, or assessment of hundreds of medical devices.

For both the pharmaceutical companies and the device developers, having a comprehensive template for requirements definition means development can begin sooner, progress more quickly, and carry less risk. More importantly, it can facilitate proper design of a device the first time, a concept critical to achieving rapid regulatory approval and curtailing time to market.

Developing intelligent methodologies for navigating an increasingly strict regulatory environment is essential for successful commercialization of the ever-growing number of drugs and the devices employed in the delivery of these drugs. Accomplishing these goals requires bridging the gap between pharmaceutical companies, device developers, and patients. To span this gap and provide a solid foundation for successful device development, Cambridge Consultants has produced a generic requirements specification document for reconstitution and injection devices.

SUMMARY

A generic requirements specification can be a powerful tool for accelerating a medical device development while simultaneously reducing risk. The generic requirements specification discussed in this column covers the requirements for single-use, fixed-dose disposable devices. Its modular nature, however, allows it to be adapted to encompass additional requirements essential to the development of delivery products with alternate life cycles. Included in these products are devices that are reusable, that can provide multiple or variable doses, or that are capable of different types of reconstitution, such as the creation of microsphere suspensions.

By equipping device developers and pharmaceutical companies with information that often lies outside their area of expertise, such a document enables development partners to communicate using a common language. Instituting this shared point of reference at the beginning of development can reduce program risks and lead to more rapid, efficient product realization.

**To obtain a free copy of the Reconstitution Injection Device Generic Requirements Specification or to inquire about adapting the specification for the development of a specific device, please visit the Cambridge Consultants website at www.CambridgeConsultants.com.*

BIOGRAPHIES

Patrick Ryan is a Mechanical Engineer in Cambridge Consultants' Drug Delivery Group. His expertise is in the areas of injection devices and reconstitution, and was the leading author of the recently published Reconstitution Injection Device Generic Requirements Specification. He earned his BS in Mechanical Engineering from the University of Massachusetts – Amherst.

Christopher Kadamus is a Principal Design Engineer at Cambridge Consultants in Cambridge, MA. During his 10-year career in the medical device industry, he has designed products for a variety of industry sectors, including drug delivery, endoscopy, general surgery, cardiac critical care, and in vitro diagnostics. Mr. Kadamus has worked extensively with drug delivery devices intended for non-clinical use, including injection pens, reconstitution devices, and inhalers. He holds a BS in Optical Engineering from the University of Rochester.

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MBO Discussion Series

Personal Guarantees: The Bad & The Evil

Part IV of The Born-Again Entrepreneur (February 2008)

By: Derek G. Hennecke, MBA

I suppose I could call them the good, the bad, and the evil, but personal guarantees are really only good from the lender's point of view. In fact, there are two words above all others that should strike fear into the heart of the would-be entrepreneur: *personal guarantee*.

Whatever you do, don't accept it as a necessary evil. Minimize it, eliminate it if you can, but don't just take it as a fact of doing business. Remember that those two little words combined house your worst nightmare.

Let's start with a definition. A personal guarantee is an unsecured promise that you will make payments if your small business is unable. Unsecured means that you're not using your assets (such as your house) to back it up: that would be collateral. But ultimately, when you sign a personal guarantee, you are not just putting your house on the line; you are risking your car, your 401k, your future salary, your kids' college funds, and their piggy banks.

Scared yet? Oh, it gets worse. It's not just your assets that are on the line. If you're married, your spouse may have to co-sign the promissory note. That means your jointly owned possessions are at risk as well as your spouse's assets and income. If your spouse is not a co-signatory, structure as many of your assets as possible as joint assets and/or put things in your spouse's name. These assets will not be on the table.

The stakes are high, and you're in it alone. In most cases, even though there are other managers in the buy-out, only one has to sign the personal guarantee: You.

Why do lenders want personal guarantees?

Quite simply, the personal guarantee is added insurance that you are serious about making your business work – and hence, repaying your loan. Look at it from the bank's point of view: If you aren't willing to put yourself on the line, why should they?

To the bank, the guarantee is a no-brainer. When

signed, the bank has recourse through the legal system if you fail to make your payments. Without it, there may not be much they can do.

How can I get out of it?

Now for the question on every would-be entrepreneurs mind: Oh dear God, how can I get out of this? Some of the literature will tell you that if a personal guarantee is required, you simply shouldn't sign. Basically, their argument is that if your business isn't solid enough to stand on its own, you shouldn't be buying it.

While that's great in theory, in my experience, that situation doesn't occur very often. The vast (and by vast, I'm speaking in cosmic terms) majority of lenders require personal guarantees from business owners for small business loans. You are probably going to have to sign one.

Still, let's talk about those few "outs" that are available. There is one silver bullet option — financing with business credit card loans is one way to avoid a personal guarantee. If you fit into this category, lucky you! Stop reading here.

If your business loan is too large for this, then your chances of avoiding the guarantee improve in direct proportion to your company's financial condition. The stronger your financial situation, the less likely you will need to provide the guarantee. If your company is strong enough to stand on its own, you are in a strong position and should choose the lender that doesn't require the guarantee. If your company's financial position is strong, but not THAT strong, you may be able to negotiate it away, for example, by paying a slightly higher interest rate.

In my case, we were a new company coming out of a much larger one, so there was little chance of making this particular nightmare go away, despite my spectacular projections. But I was able to negotiate a 1-year limit to the liability. When my employees and managers and I raised a toast to our first anniversary, I was also celebrating the demise of my personal liability contract.

Because I chose an LLC structure for the company, I'm pretty secure now, but it can come back if I ask for a larger commitment. If your business is structured as a sole proprietorship or a general partnership, be aware that even the lack of a personal guarantee is no guarantee. In some cases, the lender may still have the right to sue you personally, and if successful, to confiscate your personal assets to satisfy the loan.

Again, the personal guarantee is an evil that is pretty much limited to *small* business loans. As your company grows in size and revenue, lenders use this tool less often. Xcelience is now two and a half years old and I am in the process of arranging our first major expansion. The evil personal guarantee is no longer on the table.◆

BIOGRAPHY

Derek G. Hennecke, MBA
President & CEO
Xcelience

Mr. Derek G. Hennecke is a founding member of Xcelience. From 2004 to 2006, he served as Vice President and General Manager, Pharmaceutics and Biopharmaceuticals of MDS Pharma Sciences, Inc. In this capacity, he was responsible for the business and operations of MDS' CRO formulation development, including capsule development, tablet formulation, modified-release tablets, suspensions, solutions, suppositories, creams, ointments, and gels. Prior to joining MDS, Mr. Hennecke held various drug development management positions for DSM in Canada, Egypt, The Netherlands, and Mexico. In these roles, he built the operations or businesses to introduce various drug products for Europe and the US. Mr. Hennecke has also worked for Roche's research activities in Germany and Canada. He earned his BSc from the University of Alberta (Canada) and his MBA at the Erasmus University in Rotterdam, (The Netherlands).

INTRAEPIDERMAL DELIVERY

P.L.E.A.S.E.® (Painless Laser Epidermal System): A New Laser Microporation Technology

By: Yogeshvar N. Kalia, PhD; Yogeshwar G. Bachhav, PhD; Thomas Bragagna; and Christof Böhler, PhD

ABSTRACT

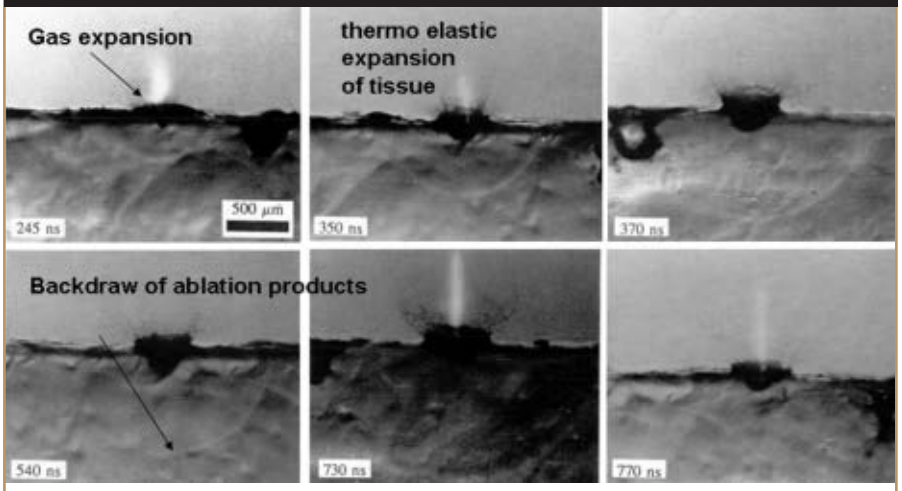
New technologies are required to widen the range of therapeutics that can be delivered across the skin and so allow the full potential of transdermal delivery to be realised. In this article, we describe the development of the P.L.E.A.S.E.® (Painless Laser Epidermal System), a novel technique for the controlled poration of the epidermis, and we report initial results demonstrating its ability to increase the transport of difficult-to-deliver small molecule and peptide therapeutics across the skin. We also present the findings of a tolerability study in human volunteers that confirmed its ready acceptance and mild effects on the skin. Due to the revolutionary technical features of the P.L.E.A.S.E. laser system and its ease-of-use, it is clear the technology has many potential therapeutic applications and that commercial opportunities are abundant.

INTRODUCTION

Transdermal delivery is a convenient alternative to oral administration for therapeutic agents with short half-lives and poor systemic bioavailability. However, in order to be delivered across the skin, these molecules must possess the appropriate physicochemical and pharmacological properties. Systemically acting drugs delivered from conventional patch systems must combine high potency with the appropriate lipophilicity and diffusivity to transit both the lipid-rich stratum corneum and the more aqueous epidermis at therapeutic rates, before entering the capillary network in the dermis. In recent years, several technologies have been investigated to develop systems capable of reversibly impairing skin barrier function and so expand the range of drugs that can be delivered by this route. These include physical methods to "porate" the stratum corneum (the principal barrier to entry into the body) in a "minimally invasive" manner.[1] All of these techniques rely on enhanced passive diffusion through the newly created micropores to facilitate drug delivery; and thus, the rate of transport depends on drug diffusivity and the concentration gradient. In addition to enabling the entry of low molecular weight drugs, removal of the stratum corneum raises the possibility of delivering therapeutic peptides and even small proteins across the skin, providing an alternative to parenteral administration.

Poration can be achieved mechanically by using microneedles or via the application of energy to thermally ablate the stratum corneum. The latter technique usually involves local heating through the application of arrays of resistive filaments/electrodes, which remove epidermal tissue through Joule heating effects. Recently, laser-based technologies have also been developed that aim to specifically excite water molecules present in the skin and use their explosive evaporation to create microchannels; this targeted excitation results in less thermal damage to neighboring tissue. In this overview, we describe a novel laser-based system and briefly outline its initial therapeutic applications.

FIGURE 1



Laser excitation at 2940 nm and its effect on biological soft tissue. Reproduced with kind permission from Prof. Dr. H. Lubatschowski at the Laser Centre Hanover (Hanover, Germany).

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INTRAEPIDERMAL DELIVERY

HISTORY OF LASER-ASSISTED DRUG DELIVERY DEVICE DEVELOPMENT

The use of laser technology as a means to facilitate transdermal drug delivery has several advantages. First, in terms of acceptability, the use of medical lasers has become far more common in recent years for both cosmetic and reconstructive surgery. Second, from a practical standpoint, the wavelength of the incident laser light can be varied and optimized to target a specific chromophore and so prevent thermal damage of the surrounding tissue. The ideal ablative laser for drug delivery would use a minimum of energy to create a maximum porated skin surface area through which drug could diffuse at enhanced rates (increasing permeation and as a consequence, bioavailability). In addition, it is essential to avoid thermal damage to the surrounding skin tissue, not only for patient compliance but also to allow optimal drug delivery through "open" pores (ie, pores that do not contain coagulated protein).

Pulsed laser energy causes controlled vaporization of the skin according to the principles of selective photothermolysis.[2] The target tissue contains a chromophore that selectively absorbs energy at the wavelength of the incident laser pulse; in contrast, there is much less energy absorption by the surrounding tissue. The interaction between the energy from a far-infrared laser results in a thermomechanical reaction that destroys dermal vessels and denatures dermal proteins. However, for a mid-infrared laser (eg, in the 3000-nm range), the interaction involves a photomechanical reaction. At this wavelength, the chromophore is water, which is superheated within a few microseconds (sometimes a fraction of a microsecond is sufficient) causing its explosive evaporation. This is accompanied by immediate ejection of the desiccated tissue at supersonic speed, creating a characteristic "popping" sound (Figure 1).

This translation of laser energy into mechanical energy protects the surrounding tissue, since only a minimal amount of energy is left to dissipate as heat. Immediately after the target tissue reaches its peak temperature, it starts to cool down. The thermal relaxation time (τ) is defined as the time required for the tissue to cool to half its peak temperature. When laser pulse duration is greater than the thermal relaxation time, a stacking of the laser energy and rapid heat accumulation occurs, with concomitant tissue damage. This stacking effect is much less important with pulsed lasers in the 3000-nm range because they penetrate only 2 to 3 µm into superficial skin layers, and their pulse duration is smaller than τ.[3]

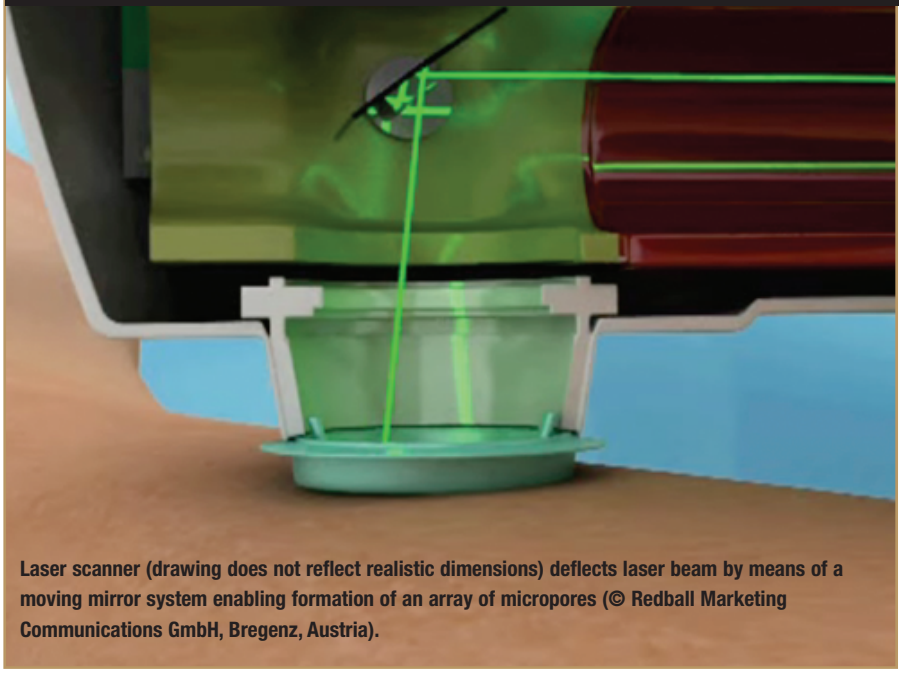
Historic Milestones: From Early Experiments to a Proven & Approved Method

UV-laser-assisted drug delivery was first described in 1987 by Steven L. Jacques at Harvard Medical School/Massachusetts General Hospital.[4] At about the same time, it

FIGURE 2

P.L.E.A.S.E. hand-held device used by self application (© Meyer-Hayoz Design Engineering AG, Winterthur, Switzerland).

FIGURE 3



Laser scanner (drawing does not reflect realistic dimensions) deflects laser beam by means of a moving mirror system enabling formation of an array of micropores (© Redball Marketing Communications GmbH, Bregenz, Austria).

was demonstrated that the use of mid-infrared lasers and pulse durations close to the thermal relaxation time of water reduced thermal damage of surrounding tissue to a minimum.[5,6] Subsequent reports described (1) increased permeation of hydrocortisone and γ-interferon after skin irradiation with a 2790-nm laser, and (2) 2940-nm lasers outperformed other laser systems for the transdermal application of 5-fluorouracil after skin ablation.[7,8] Other reports showed that the time required to induce full local anaesthesia with lidocaine could be significantly shortened from 60 to 5 mins following laser treatment, and in 2003-2004, an Australian company received a FDA 510(k) approval for its laser-assisted drug delivery devices in combination with lidocaine.[9] Furthermore, in 2004, Fang et al reported a study into the use of Er:YAG lasers to porate skin and facilitate delivery of a series of FITC-labelled dextrans with molecular weights ranging from 4.4 to 77 kDa.[10]

The development of the hand-held P.L.E.A.S.E. device by Pantec Biosolutions AG (Ruggell, Liechtenstein) represents a significant advance in both device design and capabilities with many advantages over older laser ablation technologies through the use of several unique features (Figure 2). Whereas currently marketed 3000-nm range lasers operate in wide area ablation mode, the P.L.E.A.S.E. device uses a laser scanner (Figure 3) to create an array of micropores in a predefined area, approximately the size of a US quarter or a one Euro coin. The system is programmed by a simple graphical user interface to generate from 1 to 5000 pores, thus controlling the dose delivered from the subsequently applied drug patch. The unit functions with a predetermined set of operating parameters [pulse width, fluence (energy density), and repetition rate] to guarantee fast, convenient microporation without carbonization and thermal damage of the surrounding tissue.

A skin layer detection system built into the device determines when the stratum corneum has been porated. This limits the amount of energy that is applied and ensures that the pores do not penetrate into the dermis and reach the sensory network. Furthermore, the device comprises a beam-shaping optical unit that modulates the "spearhead-shaped" laser beam into a so-called "top hat" profile (Figure 4 inset). This, in combination with the pulsed laser action, allows for accurate stepwise ablation.

In summary, P.L.E.A.S.E. provides the user with a safe, painless drug delivery method that controls drug dosage by varying the pore number and pore properties. It is envisaged that the system will serve as a "medical manager" as the intelligent combination of hardware and software will enable clinicians to provide an effective individualized treatment, while at the same time, prevent drug abuse and inadvertent misuse of the device.

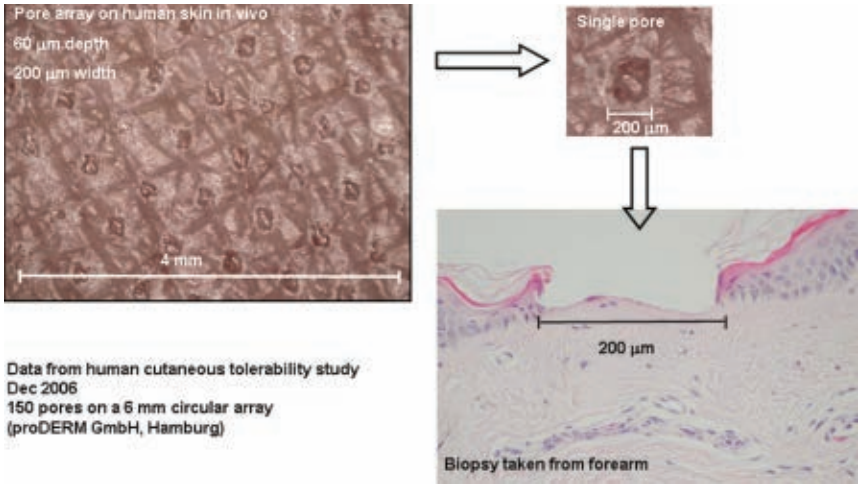
P.L.E.A.S.E. TREATMENT IS WELL TOLERATED IN VIVO

An in vivo cutaneous tolerability study was conducted to evaluate the effect of P.L.E.A.S.E. treatment on the skin (12 healthy volunteers, proDerm, Hamburg). The study included self-evaluation by the patients of the degree of discomfort; an objective assessment

FIGURE 4

The microchannels created in the skin consist of a series of cylindrical pathways through the outer epidermis (© Redball Marketing Communications GmbH, Bregenz, Austria).

FIGURE 5



Micropores created in the skin of human volunteers using the P.L.E.A.S.E. system (© proDerm Institute for Applied Dermatological Research GmbH, Hamburg, Germany, and Pantec Biosolutions AG, Ruggell, Liechtenstein).

by the investigator of application site erythema and oedema using biophysical measures of stratum corneum function and hydration, namely, transepidermal water loss (TEWL) and skin capacitance; and finally, visual examination of the pores using video- and stereomicroscopy following skin biopsy.[11]

The results showed that the patients' self-evaluations rated discomfort between none and slight. Only slight or moderate erythema was observed up to day 3 at the P.L.E.A.S.E. treatment site before falling to zero by day 5. Interestingly, lower erythema was observed in the study where the application site was occluded; under these conditions, irritation was already considered, on average, between zero and slight by day 2 and was effectively negligible by day 3. Similarly, oedema was also rated as zero or slight by day 2. Transepidermal water loss showed four- to six-fold increases 30 mins after P.L.E.A.S.E. treatment and maintained these elevated levels after 4 hrs; however, TEWL returned to ~two-fold higher than control within 24 hrs (day 2) and was at baseline by day 3. Skin hydration did not appear to be affected by P.L.E.A.S.E. treatment. The overall outcomes of the study were very encouraging, and there were no signs of thermal damage to the tissue surrounding the pores (Figure 5). In addition, the volunteers reported minimal or no discomfort during or after the poration procedure.[11] In summary, P.L.E.A.S.E. treatment was well tolerated by all of the subjects, there were no adverse effects, and any changes in the skin barrier were reversible.

THERAPEUTIC APPLICATIONS

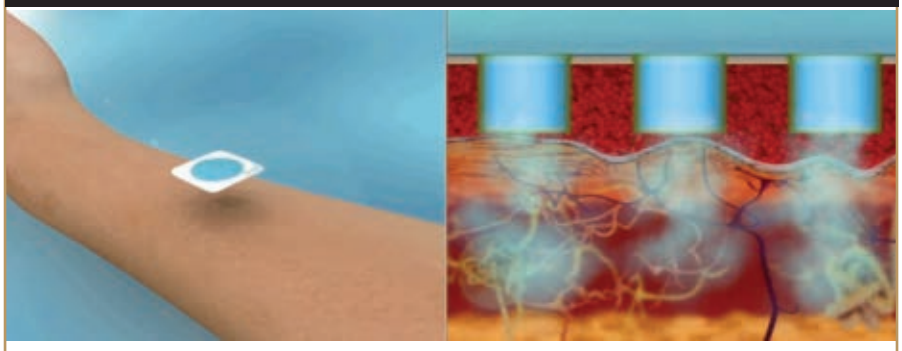
Pantec Biosolutions has identified a series of potential therapeutic applications for this pioneering technology, which involve both local and systemic drug delivery. The lead indication is the development of an integrated non-invasive solution for In Vitro Fertilisation (IVF) treatment to replace existing injection-based therapies.

During a typical IVF-stimulation cycle, women have to administer three hormones by self-injection.[12] Triptorelin, a GnRH superagonist, down-regulates specific hormonal activities and is injected subcutaneously (0.1 mg) starting 10 days before menstruation and then daily until its onset (total of ~30 injections). After menstruation, a daily FSH (follicle stimulating hormone; 150 IU, ~25 mcg) injection is required to induce follicle growth. On day 13, the follicles should be ready for "harvesting," and after ultrasound examination, ovulation is induced by a one-time injection of HCG. The oocyte is extracted 1 to 2 days after ovulation induction and further processed for in vitro fertilization. While IVF takes place outside the body, the patient starts daily intramuscular progesterone injections (50- to 100-mg oil formulation) for several weeks in order to prepare the endometrium for implantation of the fertilized oocyte, and also to conserve pregnancy. After 3 to 5 days of cultivation of the fertilized oocyte, the blastocyst is transplanted back into the uterus. Progesterone is administered intramuscularly until heart activity of the embryo is detected (about 6 weeks after fertilization). In the case of multiple pregnancies, progesterone is administered for at least 8 to 12 weeks and in some cases, until labor. It is also common to prescribe intramuscular progesterone injections until heart activity has started, and then switch to vaginal application of progesterone (although there is more variation in bioavailability, this reduces the pain of the therapy). It is clear that existing protocols require the patient to either self-administer, or with the aid of her partner, dozens of frequently painful injections.

Thus, there is a need to provide an efficacious, non-invasive alternative to the existing treatment. This also represents a considerable commercial opportunity as the estimated market sizes for progesterone, triptorelin, and FSH treatments are projected to be $300 million, $600 million, and $1 billion, respectively. Our initial objectives have been to demonstrate the delivery of therapeutic amounts of each hormone across P.L.E.A.S.E. treated skin, and currently, we are proceeding with a preclinical optimization of the respective formulations.

To date, we have determined in vitro transdermal delivery rates of progesterone from both commercial and in-house formulations, and a Phase I clinical trial is currently underway to determine in vivo pharmacokinetics. Preclinical studies with triptorelin have also been completed. The objective of these studies was to determine drug diffusion kinetics across porated skin as a function of pore number and pore depth. The latter was varied by modification of the number of pulses that were applied at each poration site. Although the stratum corneum, the principal barrier to transport, is only 10 to 20 microns thick, a deeper pore reduces the diffusional path length in the epidermal matrix; however, increasing the number of pulses and hence pore depth increases the risk of penetrating into the dermis and reaching the capillary and sensory networks. Thus, it is essential to determine the appropriate pore depth required to obtain the desired delivery

FIGURE 6



Application of the transdermal patch following laser microporation with the P.L.E.A.S.E. device enables rapid entry of the drug formulation into the epidermis and facilitates drug uptake by the dermal capillary network.

rates for each therapeutic agent.

Despite its low molecular weight (314 Da), passive transdermal delivery of progesterone is poor and sub-therapeutic. In our initial in vitro study, we compared the effect of P.L.E.A.S.E. treatment on the permeation of progesterone from three different formulations (including an already-marketed commercial product). Passive delivery across the skin was negligible for all three formulations; however, laser poration resulted in significant increases in drug transport (reaching ~1 mg/cm^2 for one of the formulations tested). This is ~20-fold higher than levels typically reported in the literature; obviously, optimization of the formulation will further improve delivery kinetics.

Triptorelin is a decapeptide GnRH agonist (MW 1311 Da) and, on account of its physicochemical properties, cannot diffuse passively across the skin. As described previously, current therapy involves daily subcutaneous injection of 0.1 mg. In preliminary transport studies using porcine skin in vitro, we have demonstrated the feasibility of delivering therapeutic amounts of triptorelin across P.L.E.A.S.E. treated skin. After 24 hrs, cumulative permeation of the peptide across full thickness skin (1 to 1.5 mm in thickness) exceeded 0.3 mg, which is three-fold higher than the current amounts administered by daily subcutaneous injection. The formulation requires optimization, and we need to investigate the transport kinetics further, but these are very promising initial data. In the coming months, we will begin studies into the transdermal permeation kinetics of FSH (glycosylated protein, MW 28-30 kDa).

We have also initiated programs to investigate the transdermal delivery of non-steroidal anti-inflammatory drugs (NSAIDS) into and across P.L.E.A.S.E. treated skin. Preliminary results show order of magnitude increases in permeation and skin deposition. If these findings are confirmed in vivo, then this may allow the range of indications for topically applied NSAIDS to be expanded.

These encouraging findings demonstrate the potential of the P.L.E.A.S.E. technology for both local and systemic applications, and we continue to explore new therapeutic opportunities. An internally funded clinical development program for IVF is underway to design commercial transdermal systems for use in conjunction with the P.L.E.A.S.E. device. The business model is to license our IVF product solution to pharmaceutical distribution partners. We can offer the "one-stop-shop" concept to the pharmaceutical and biotechnology industries for use with other therapeutics in which we take the API, develop a new product combining an innovative transdermal formulation and the P.L.E.A.S.E. device (Figure 6), and take it all the way through the market-approval process.

ACKNOWLEDGEMENTS

The authors would like to thank the entire Pantec Biosolutions team, including the Board of Directors, the scientific and medical advisory panels, and our partners in various companies around the globe for their tremendous efforts throughout the past 3 years. We also thank KTI/CTI (Innovation Promotion Agency, Bern, Switzerland) for financial support as well as Prof. Dr. Holger Lubatschowski of the Laser Centre Hanover (Hanover, Germany), Redball Marketing Communications GmbH (Bregenz, Austria), and Meyer-Hayoz Design Engineering AG (Winterthur, Switzerland) for providing the graphics used in this article.

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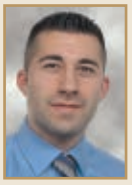
BIOGRAPHIES

Dr. Yogeshvar N. Kalia is a Senior Lecturer, School of Pharmaceutical Sciences at the University of Geneva (Switzerland). After completing his PhD in Chemistry at the Imperial College of Science, Technology and Medicine, he held postdoctoral positions in the Department of Biochemistry at the University of Cambridge and the School of Pharmacy at the University of California-San Francisco, before joining the University of Geneva in 1996. His research interests include (i) developing new formulations for topical and transdermal drug delivery (ii) the iontophoretic transport of therapeutic peptides across the skin (iii) the use of iontophoresis for dermatological applications (iv) the modification of drug molecular properties to increase transdermal transport (v) the development of minimally-invasive technologies for the transdermal delivery of macromolecules. His research is funded by public grants and through industrial collaborations. He has published ~80 scientific papers, presented ~80 abstracts at international conferences and is a co-inventor on 4 patents. He serves on the Editorial Boards of the *European Journal of Pharmaceutics and Biopharmaceutics* and *Expert Opinion on Drug Delivery*.

Dr. Yogeshwar Bachhav completed his Masters in Pharmaceutical Sciences, specializing in Pharmaceutical Chemistry, and his PhD in Pharmaceutical Technology, at the Mumbai University Institute of Chemical Technology, one of the leading institutions in the pharmaceutical sciences field in India. During his studies, he gained extensive experience in formulation development and drug delivery. He began a post-doctoral position in the School of Pharmaceutical Sciences at the University of Geneva in 2007.



Thomas Bragagna is the CTO of Pantec Biosolutions. There, he led his team to complete the development of the world's smallest and most efficient mid-IR lasers and laser diode drivers in only 3 years. His current main task is to shift device development to serial production. Mr. Bragagna brings into the company excellent general engineering and management skills as well as major experience in the generation and management of intellectual property. Previously at a Swiss-based company, he advanced his knowledge in high-power electronics, and in parallel, built up a logistics department with finally 13 employees. From that company, he moved to Pantec Engineering AG, a high-tech company in Liechtenstein working initially as a Test Field Engineer, later as an Application Engineer, and then as Head of the Department Electronic Systems. He is in constant training at various Universities to keep up with fast-track developments.

Dr. Christof Böhler is the CEO of Pantec Biosolutions (overlooking the formation of a start-up company into a viable commercial enterprise), responsible for general management, finance, and the management of clinical drug patch development projects. Dr. Böhler has over 10 years of experience bringing innovations successfully to the market in the pharmaceutical and biotech supply industries. Dr. Böhler earned his BS (Chemistry) and his PhD (Supramolecular Biopolymer Chemistry) from ETH Zurich, dealing with Biopolymeric Drug-Release Systems. He then moved to the US for post-doctoral studies at the Salk and Scripps Research Institutes in La Jolla, CA; became the Head of Development for a start-up biotech company in Zurich; and then moved into Product Management of Research Chemicals and Biologicals at Sigma Aldrich (Fluka AG, Buchs, Switzerland). During this time, he completed a post-graduate executive degree in International Management at the University of Applied Science Liechtenstein and UBC Vancouver in Canada. His career also included Business Development Manager Europe and Business Manager for Maybridge, a drug discovery service company, and finally Marketing Director, Drug Discovery Chemicals Acros/Maybridge (Fisher Scientific).

Special Feature

Can the Systemic Pulmonary Delivery Market Breathe Easy?

By: Cindy H. Dubin, Contributor

Pulmonary delivery devices boast several advanced features that enable efficient and safe drug delivery. The therapeutic areas of interest in systemic pulmonary delivery range from diabetes to pain management, including osteoporosis, migraine, sexual dysfunction, immunosuppression, smoking cessation, premature ejaculation, growth hormone deficiency, neurological problems, and even certain cancers.

The number of applicable therapeutic areas for this alternative method of delivery is high, and the market potential is estimated to be astounding. One statistics report indicates the pulmonary market reached $25.5 billion in 2006 and is continuing to grow at a steady pace.[1] Sales estimates for asthma and chronic obstructive pulmonary disease (COPD) products, for instance, in 2006 were over $18 billion. An aging population, poor air quality, and of course, smoking are the most likely explanations for this market growth.

"Clearly, there are numerous opportunities for improving upon existing therapies through improved efficacy, efficient delivery, and enhanced patient experiences," says David Broecker, President and CEO of Alkermes.

EXUBERANCE FOR EXUBERA FALTERS

Industry insiders agree that these doors of opportunity were opened by the FDA's approval of Exubera in 2006. Sylvia M. Findlay, Research Analyst, Pharmaceutical and Biotechnology, Frost & Sullivan, says that the excitement around Exubera "ignited the interest among the healthcare community and led to the development of various pulmonary delivery products in the pipeline."

"The development and launch of Exubera really helped to raise the awareness in the physician and pharmaceutical community about the potential of delivering proteins systemically to patients via the lung," agrees Mr. Broecker. "Exubera was able to clearly show that this approach was feasible, economically viable, and most importantly safe. It is very unfortunate for the scientific community and patients using the product that Exubera was withdrawn from the marketplace due to limited adoption by the prescribing community."

"Such first-generation products for systemic large-molecule delivery are important for gaining experiences for development of second-generation products," says Dr. Troels Keldmann, Managing Director at Direct-Haler A/S, a pulmonary and nasal drug delivery company in Denmark. "The discontinuation of this pioneer product calls for reflection. What is the perceived advantage — among stakeholders and patients — of the first-generation inhaled systems, compared to the most convenient and easy-to-use injection systems? Avoiding a needle may not necessarily lead to an overall attractive alternative. This underlines the importance of broad scope when evaluating drug delivery system alternatives."

"Exubera is still the only inhaled insulin product that has been approved and marketed. In many ways, it was a vehicle for many expectations and dreams in the pulmonary delivery community," adds Dr. Keldmann.

It is these dreams that are helping to move the pulmonary drug delivery industry forward. Companies such as Alkermes, Aradigm, DirectHaler, MicroDose, and 3M are among several companies that continue to invest in this development space.

(Ed Note: On April 9, 2008, Nektar announced the termination of all negotiations with potential partners for inhaled insulin due to increased number of lung cancer cases observed in ongoing clinical studies of inhaled insulin patients.)

ALKERMES IS AGGRESSIVE ABOUT AIR®

Alkermes continues to aggressively develop the AIR® technology. "Our most advanced program is ALKS-27, which we are developing in partnership with Indevus, and is currently in Phase II," says Mr. Broecker. This product utilizes the AIR technology for the treatment of COPD. ALKS 27 completed a Phase II clinical single-dose study with positive results reported in September 2007. "We believe ALKS 27 for COPD represents an exciting development opportunity to provide patients with a once-daily anti-muscarinic, both alone and in combination with other agents."

Additionally, Alkermes is working on developing a number of other non-disclosed AIR-based programs at various stages of development. One benefit of AIR is its ability to combine multiple active ingredients into a single particle, says Mr. Broecker. This is particularly important in the area of respiratory disease in which there has been a continued emphasis on combination therapies. "The use of combination products provides a very exciting opportunity for Alkermes," he says. "From the physician's perspective, this has the potential to provide highly effective therapies using a simple, patient-friendly delivery system."

AIR technology also provides Alkermes a strong competitive advantage in a complex regulatory environment, says Mr. Broecker. "The current regulatory environment is making the development of all pharmaceuticals more difficult each year, regardless of delivery route. However, one of the unique challenges facing the development of pulmonary products is the rigorous analytical characterization that must be completed to ensure the product performs as intended. It is in this context that AIR helps simplify the development process, reduce development expense, and ultimately enhance the patient experience. Thus, we believe that the AIR technology represents that gold standard for the delivery of compounds either locally to the lung or systemically via lung."

Alkermes had been working with Eli Lilly on two programs — AIR Insulin and AIR PTH — both of which were terminated recently due to Lilly business drivers, says Mr. Broecker.

ARADIGM TARGETS SEVERE RESPIRATORY DISEASES

According to company CEO and President Igor Gonda, Aradigm's greatest success in the past year has been the development of a sustained-release inhalation formulation for the treatment of infections associated with severe respiratory disease, such as cystic fibrosis (CF) and bronchiectasis. This formulation is being developed to reduce significantly the burden of chronic therapy in these debilitating diseases. "We believe this can be achieved by administering the antibiotic treatment just once a day," he says. "We expect to preserve the excellent antibacterial properties of ciprofloxacin for the local treatment in the lung, but with very low systemic blood levels of ciprofloxacin to avoid development of resistance and to reduce or eliminate altogether the systemic side-effects."

Aradigm successfully completed a Phase I study last year and initiated the Phase IIa efficacy study in cystic fibrosis patients, expected to be completed in the first half of this year.

Aradigm's focus is the treatment, and where possible, prevention of severe respiratory diseases. "We typically take either already approved drugs, or at least drugs with some data demonstrating

safety and efficacy in humans. We put the drugs into better formulations and delivery systems with the view to improve the quality of life of respiratory disease patients," says Mr. Gonda.

In addition to the ongoing clinical program in CF, Aradigm will begin Phase II testing of the inhaled liposomal formulation of ciprofloxacin in patients with non-CF bronchiectasis. These patients do not have an approved treatment for their respiratory infections, so there is a strong motivation to develop a safe and effective treatment for them, he says.

"We have also a very exciting collaboration with Lung Rx, a wholly owned subsidiary of United Therapeutics, on the pulmonary delivery of treprostinil, using our palm-size AERx Essence™ inhaler, for the treatment of another severe respiratory disease, pulmonary arterial hypertension," says Mr. Gonda. "Our collaboration with Lung Rx is with a second-generation prostacyclin, treprostinil, to be delivered with the AERx Essence device that affords convenience, portability, and minimum maintenance requirement similar to inhaled DPI and pMDI therapies for asthma, with the prospects of 2 to 4 doses administered throughout the day in the form of 1 to 3 puffs per dose."

On the prevention side, there is no doubt that the greatest contribution could be made with tobacco smoking-cessation treatments, he says. "We reported last year very encouraging data on the effect of inhaled pure nicotine, using the AERx Essence inhaler, on reduction of craving for cigarettes." He adds that this is an area where Aradigm needs a committed partner with the expertise and resources to fully address this major underserved medical need.

Mr. Gonda sees non-invasive rapid relief of severe breakthrough pain as a challenging problem in medicine. Aradigm has promising Phase IIb data with inhaled morphine in both cancer and post-operative pain. "We have impressive results in a small cancer pain trial with inhaled fentanyl," he says. "In general, the inhalation route using appropriate technologies for deep lung delivery affords very rapid systemic delivery of small molecules."

Almost without an exception, biologics have to be given by injection. Aradigm has shown, in multiple human clinical trials with a variety of biologics, the feasibility of its systemic delivery via inhalation. Mr. Gonda says, "The intra- and inter-subject variability is remarkably good with the AERx technology; it appears to be at least as good as with subcutaneous injections. Another lesson we have learned is that the biological response in humans using the inhalation route may be much better than the observed bioavailability using the blood concentrations (for example, for alpha interferon)."

Going forward, in the realm of treating severe respiratory diseases, Aradigm is looking for partners that would like to develop and commercialize systemic delivery of drugs and biologics using the company's inhalation delivery platform and the data it has collected in human trials. "We have human data using the AERx inhalation system with several biologics, including alpha and gamma interferon, growth hormone, insulin and insulin lispro, rhDNase, IL4 soluble receptor, and erythropoietin, and we are looking for partners who would like to commercialize these products," says Mr. Gonda. "We are utilizing the unique features of our inhalation delivery systems and formulations to improve the therapy of respiratory diseases. The benefits of treatment of respiratory diseases by inhalation are very well established — inhalation products represent the majority of the respiratory markets."

DIRECT-HALER A/S — SIMPLE & COMPACT

DirectHaler™ Pulmonary is a new device for dry powder intra-pulmonary delivery. The most advanced clinical programs have completed Phase II/III. Each pre-metered, pre-filled pulmonary dose has its own DirectHaler Pulmonary device. The device is hygienically disposable and is made of only 0.6 grams of Polypropylene. The device offers effective, accurate, and repeatable dosing in an intuitively easy-to-use device format. "We are encouraged about the relevance and prospects for these new devices," says Dr. Keldmann.

Dr. Keldmann says there is an industry need to create compact and simple-to-use inhaled delivery systems, something that Exubera was lacking. "Exubera was not received as expected by the market. Device size and handling were blamed. These events direct attention to simple and convenient, yet safe and performance-driven inhaled delivery systems," he says. "We believe that advanced formulation technology should be combined with simple, compact, but optimized, inhaled delivery device systems. The DirectHaler is a logical part of such a constellation."

In addition to compact size, Dr. Keldmann says that DirectHaler technologies possess characteristics that make them attractive for various applications and patient groups. These include the following:

- A single-use disposable concept, which is a new hygienic alternative compared to any multi-dose system;
- Each dose has its own device, which eliminates any risk of double dosing;
- Ease-of-use, which translates into ease-of-instruction and ease-of-checking a patient's technique;
- Transparent design for visual check and perception of dose intake;
- Minimized material consumption per device in manufacture (< 1 gram PolyPropylene); and
- Suitable for multiple-route combinations.

"With all of these features, DirectHaler is often considered for both chronic and acute applications," says Dr. Keldmann.

3M FOCUSES ON MDI & DPI APPLICATIONS

The opportunities for new asthma/COPD treatments that dose less frequently, as well as non-invasive protein and macromolecule inhaled drug delivery, continue to grow. For asthma and COPD, the portable inhalers market was estimated to be worth $23.5 billion in 2006, and is anticipated to grow to $44 billion by 2016. When assessing the total inhalation drug delivery market (including asthma, COPD, and inhaled proteins and peptides), it is anticipated to be worth $65 billion by 2016. 3M Drug Delivery Systems is working with partner companies to team their molecules with its inhalation drug delivery technology.

The year 2007 was extremely busy for 3M Drug Delivery Systems regarding inhalation technologies, including the launch of the 3M Integrated Dose by Dose Counter and the all-metal 3M Retention Valve.

"As the pharmaceutical industry becomes more competitive and companies strive to protect and differentiate their existing brands, patients proactively requesting branded medication becomes a focal point for product success," says Richard Moody, Laboratory Manager, 3M Global Inhalation Drug Delivery, Loughborough, UK. "In a consumer-savvy world, gone are the days of simply prescribing asthma treatments. It is essential that the needs and requirements for the patient-preferred medication are incorporated into all product developments. For this reason, 3M undertook significant global patient research during development of, and prior to, the launch of the integrated dose counter. The findings have proven invaluable, giving our partners the confidence that a familiar, easy-to-use inhaler with an integrated counter is the route for them."

Listening to partner and patient needs is a mantra at 3M. Mr. Moody says. "Inhalation valve development is an extremely complex process, with partners stating that some developments struggle to overcome moisture-ingression, formulation interaction, and loss of prime/loss of dose." With this in mind, 3M has developed and launched the 3M Retention Valve to overcome these problems. The valve combines an all-metal system with a clean Ethylene-Propylene Diene Terpolymer (EPDM) elastomer to address partners' formulation needs and improve performance. "By using an all-metal construction, we are able to offer a valve with low leakage, low moisture ingression, and low leachable and extractable compounds. The metal construction makes it possible to quickly scale-up from test to full commercial production even if minor modifications are required. Plus, it is a robust, patient-friendly design offering more than 7 days prime retention, good dose delivery, and smooth operation."

Currently, more than 50% of global metered dose inhalers (MDI) contain 3M technologies, says Mr. Moody. This could expand, he says, as 3M is currently working with several partners regarding dose counter opportunities.

3M is also looking at dry powder inhaler (DPI) opportunities. Mr. Moody indicates the goal here is to provide a simple formulation process across a platform that is applicable with a range of APIs, using particle-engineering technology that leverages 3M corporate technologies and the company's expertise in inhalation.

"Our aim is to reduce development time, increase drug delivery efficiency, reduce complexity, and improve performance under real-life conditions for DPI and MDI. The technology was evaluated first with MDIs, and then extended to include DPI platforms."

Surface-Modified Excipient Nanoparticles (SMNs) have been utilized in DPI formulations to improve flow properties and dispersion. The utility of SMNs in DPI applications was examined by standardized powder flow tests and cascade impaction to assess the impact of SMNs on the drug delivery efficiency. The flow properties of powder were shown to be greatly improved when a small amount of SMNs were included in the formulation. The enhanced powder flow was shown to provide efficient drug delivery, even when a very simple DPI device was used.

This technology is applicable to nearly all DPI formulation efforts because it simplifies the formulation process, says Mr. Moody. It will be particularly helpful for any drug or drug/excipient blend that is difficult to deliver efficiently or consistently. Because it enables the delivery of drug without carriers or bulking agents (eg, lactose), this technology will also be especially applicable to efficient delivery of high-dose formulations.

Initial inhalation toxicology testing has been successfully completed. Patent applications have been filed protecting the technology. Additional studies are ongoing, and the company anticipates further information will be available later this year.

MICRODOSE SETS SIGHTS ON ACUTE THERAPIES & SEVERE RESPIRATORY DISEASES

The MicroDose Dry Powder Inhaler (DPI) represents the next generation in inhaler technology. The device uses a piezoelectric vibrator to deaggregate the drug powder packaged in moisture-resistant aluminum blisters. The blisters are pierced with small needles prior to dosing to create openings into the flow channel of the device. The device is breath-activated, ie, the piezo is activated when an inhalation sensor detects a threshold level of the patient's inspiratory airflow. Given that the piezo is doing all the "work" of deaggregation and aerosolization, aerosol performance is independent of patient inhalation, patient posture, and patient coordination. The inhaler is reusable for 6 to 12 months.

According to Scott Fleming, Senior Vice President and Co-Founder of MicroDose, the company has a two-fold business strategy. One is to create improved partnered products by combining proprietary drug delivery technologies with pharmaceutical and

biotechnology company compounds. The other is to develop pharmaceutical products in-house using proprietary delivery technologies with generic drug substances, for late-stage partnering, co-marketing, or sale. These include respiratory compounds, respiratory supportive care, products for pain, and proteins and peptides.

MicroDose's partnered programs include multi-product development and licensing agreements with both Merck and Novartis for their compounds, the development of an inhaled insulin product through its QDose joint venture, and also an inhaler for the systemic delivery of a nerve agent antidote for the US Department of Defense in co-development with the University of Pittsburgh.

The inhaler has successfully completed two Phase I studies with insulin, and will enter clinical trials for two new products during 2008.

Mr. Fleming says that MicroDose will increase its focus on systemic delivery for acute and intermittent therapies, eg, breakthrough and acute pain, anti-infectives, as well as for locally acting acute or intermittent severe respiratory conditions. "The rapid onset of action, non-invasive delivery attributes, and site-specific delivery of pulmonary delivery being the drivers here, and even more importantly, the preclinical and clinical testing requirements are lower in many cases," he says. Thus, MicroDose is investigating product ideas that meet these criteria, and is actively seeking development collaborations needing an inhaler for delivery of their agents."

MicroDose is also doing what it can to meet FDA guidelines. "The biggest challenge all pulmonary delivery companies face is regulatory. The FDA's Draft Guidance is still not fixed, and the movement is toward even tighter and more onerous testing requirements. Not knowing what the requirements will be for approval in the future makes it hard for pulmonary companies to plan. MicroDose is fortunate in this regard, as we have developed an inhaler that overcomes many of the shortcomings of previous devices, namely, flow rate, coordination, and orientation dependence, all of which lead to poor dose-to-dose reproducibility, the most important criteria to the FDA."

SUMMARY

Pulmonary drug delivery is likely to spread to various therapeutic areas and thereby expand the market potential. Technological and product advancements are expected to redefine pulmonary drug delivery. Deep lung delivery, safety, flexible dosing, dose correction, and easy monitoring are essential for efficient pulmonary drug delivery, agree the experts.

Additionally, the biopharmaceutical market brings both opportunities and challenges for pulmonary system developers. The diversity of these diseases forces drug delivery companies to consider the nature of each indication individually. "Given this diversity, it will be difficult to apply takeaways from one particular area, such as diabetes to other segments such as cancer or rheumatoid arthritis," says Mr. Moody. "However, it is clear that with continuous investment in inhalation design, formulation, and technologies, the opportunities for non-invasive protein and macromolecule inhaled drug delivery continue to grow."

However, some are quick to point out that there are going to be roadblocks along the way to that growth. Mr. Fleming, for example, says that the pulmonary delivery of proteins for systemic absorption took two giant steps forward with the FDA approval of Exubera, and now has taken three steps back with the latest release of clinical trial results from Pfizer that showed a possible link to lung cancer. "This latest news will definitely set back the pulmonary delivery of systemic agents for chronic use by raising the safety bar for approval, likely requiring longer term carcinogenicity studies in future. This news, and the prior cancellation by NovoNordisk and Lilly of their inhaled insulin programs, reportedly due to lowered expectations for market uptake of inhaled insulins, has really left a pall over the whole segment."

"The pulmonary delivery industry is in the midst of a rapid change, as companies are refocusing their portfolios on product opportunities with more proximal approval timelines and enhanced probabilities of success," says Mr. Broecker. "During this transition period, we will likely see certain technology approaches taking the forefront, while others will be unlikely to survive. It will definitely be an exciting time to be in the pulmonary delivery space."◆

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BIOGRAPHY

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

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PROTEIN POWDERS

A Comparative Study of the Effect of Using Different Drying Techniques for Preparation of Inhalable Protein Powders on Their Aerosolization Performance

By: Magda Samaha, PhD; Ferial El-Khawas, PhD; Hoda El-Maradny, PhD; and Doaa Mohamed Ragab, PhD

ABSTRACT

The objective of this study was to compare three different methods for preparation of inhalable dry powders with respect to their aerosolization performance. Spray-drying, freeze-drying, and spray-freeze drying techniques were used to produce dry powders of different formulations of bovine serum albumin containing different concentrations of Pluronics F-127 and F-68. In general, increasing the concentration of Pluronics decreased the tap density (ρ, g/cm^3) and the aerodynamic diameter (Daer, μm).The in vitro deposition of the different dried powder formulations exited from a Handihaler® inhaler device to a twin-stage liquid impinger at 60 L/min resulted in different percentages of emitted dose and different respirable fractions. Accordingly, the blended ratios were optimized by considering these two inhalation indices. The highest values were obtained with 0.3% w/v Pluronic F-127 and 0.5% w/v Pluronic F-68.

The percentage respirable fractions of inhaled powder formulations in descending order were: spray-freeze dried > spray-dried > freeze-dried. The respirable fraction values of powders prepared with 0.3% w/v Pluronic F-127, measured using a Handihaler at flow rate 60 L/min, were 56.79%, 34.35%, and 31.1% for spray-freeze dried, spray-dried, and freeze-dried powders, respectively. According to the results obtained in this work, spray-freeze drying is highly recommended to produce dry powders for aerosolization, especially in the case of bovine serum albumin being that protein denaturation and aggregation are reduced during spray-freeze drying operation.

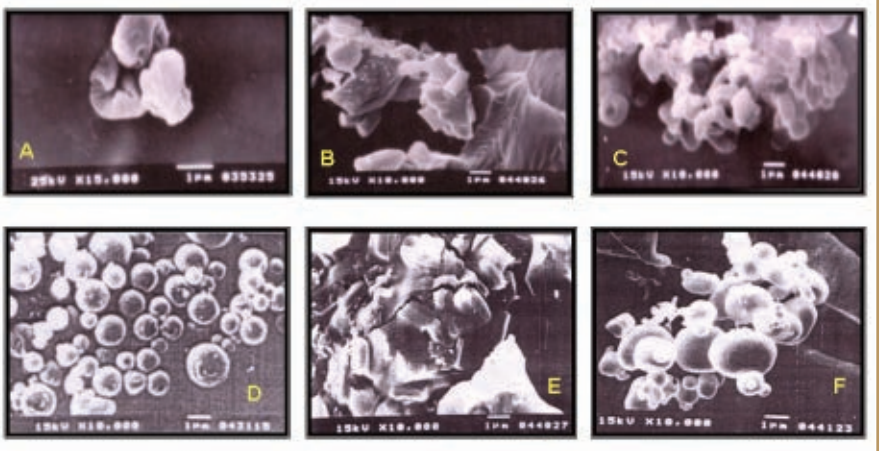
In conclusion, a proper combination of powder composition and drying technique produced inhalation powders with elevated respirable fractions and a physical environment favorable to protein stability.

INTRODUCTION

Aerosolization is an effective technique to deliver therapeutic substances to the respiratory tract. Among aerosol generation systems, dry powder inhalers present several advantages.[1] Biopharmaceutical protein powders find increasing applications in dry powder inhalation. In general, methods available for preparing protein powders are limited due to certain protein's sensitive nature to processing environments. This is particularly true for preparing dry powder aerosols in which aerodynamic particle size (< 5 μm) and size distribution are pivotal.[2]

Drying as such is an important unit operation within the pharmaceutical industry.[3] Spray-drying (after freeze-drying) is the method most widely used for drying biomolecules. In fact, spray-drying has been applied to a variety of substances, such as peptides, antibiotics, vaccines, and carrier particles.[4-7] Spray-drying offers some advantages to other drying methods. One of the principal advantages of spray-drying is the narrow size

FIGURE 1



Scanning electron micrographs of pure bovine serum albumin dry powders prepared by spray-drying (A), freeze-drying (B), and spray-freeze drying (C). Spray-dried, freeze-dried, and spray-freeze dried powders of bovine serum albumin blends with Pluronic F-127 are presented in micrographs (D), (E), and (F), respectively.

distribution of powders.[7] This ensures, assuming an appropriate mass median aerodynamic diameter (MMAD), a maximum deposition of the embedded drugs in the tracheo-bronchial and deep alveoli regions for normal inhalation rates.[8] Moreover, the morphology and density of particles also can be controlled.[3] Surface denaturation at the air/liquid interface of sprayed droplets may play a significant role in protein degradation. Spray-drying of mannitol-formulated human growth hormone at room temperature resulted in increased protein degradation by increasing the atomizing air rate, which suggested degradation at the air/liquid interface during spray-drying.[9] Adding polysorbate 20 into the liquid feed significantly reduced the formation of insoluble human growth hormone aggregates.[10]

Although a relatively expensive process, freeze-drying can offer advantages for relatively unstable compounds.[11] During the process of freeze-drying, the solvent is frozen and then removed by sublimation in a vacuum environment. The low temperature maintained during the entire process minimizes thermal degradation of the drug compound.[12] A formulation for freeze-drying may consist of one or more excipients that perform one or more functions. Poly-ethylene glycol (PEG), Brij (non-ionic surfactant), and sugars are examples of excipients that are good candidates during freeze-drying.[13,14]

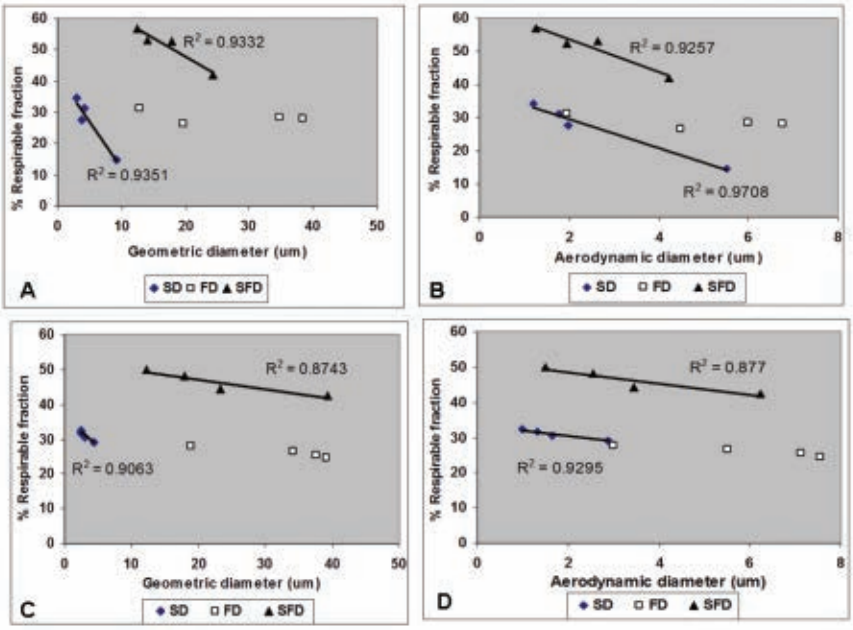
On the other hand, spray-freeze drying and supercritical fluid antisolvent have recently emerged as promising techniques for producing inhalable powders.[15,16] The spray-freeze drying method has been introduced with an aim to overcome some of the limitations of both spray-drying and freeze-drying techniques, ie, heat and stress.[2] Spray-freeze drying can reduce shear stress by preparing particles with a small aerodynamic diameter from droplets with a larger diameter. It can also reduce heat stress by processing formulations in a cold environment and by providing a surface-to-volume ratio favorable for quick drying.[17] Nguyen et al illustrated a method for preparation of different formulations of proteins using a spray-freeze drying technique.[2] The particles formed by this method can be suitable for delivery of the therapeutic proteins by pulmonary administration.[2] Kuo and Hwang investigated the feasibility of using spray-freeze drying to produce DNA dry powders for non-viral gene delivery.[18] Spray-freezing into liquid has been used to prepare porous microparticles of insulin, albuterol sulphate/PEG particles and to enhance the dissolution rates of poorly soluble drugs, such as danazol and carbamazepine.[19]

In addition, the application of supercritical fluids for preparation of dry powder proteins as well as particle design has recently emerged as a promising technique for producing powders for inhalation. Carbon dioxide is the most widely used solvent because of its easily accessible critical parameters.[16]

Pluronic surfactants, used for inhalation dosage forms, are a series of block copolymers of poly (ethylene-oxide)-block-poly (propylene-oxide)-block poly (ethylene-oxide) with various hydrophobicities. Application of Pluronics in microparticulate delivery systems led to stabilizing the protein.[20]

The aim of this work was to further characterize and evaluate powder formulations dried using different drying techniques in terms of aerosolization parameters in order to determine which formulation and method of drying could be the most suitable for pulmonary protein delivery.

FIGURE 2



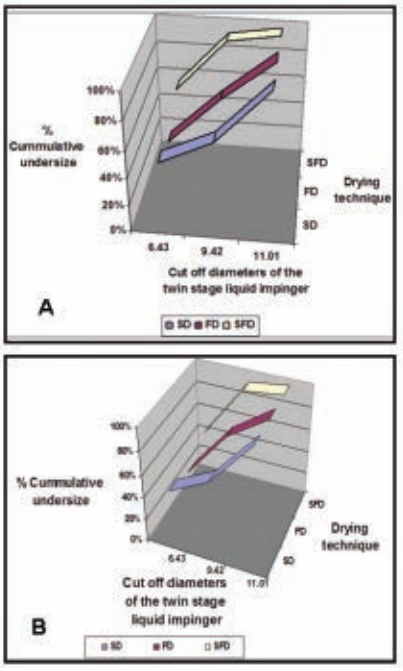
Plot of the geometric diameter and aerodynamic diameter versus the % respirable fraction of bovine serum albumin dry powders prepared using Pluronics F-127 (A & B) and F-68 (C & D).

MATERIALS & EQUIPMENT

Bovine serum albumin, 95% albumin, and Pluronics F-127 and F-68 were obtained from Sigma-Aldrich, pf, Switzerland. The hard gelatin capsules were obtained from Novartis Pharmaceuticals, UK Ltd, England.

The following equipment was used: freeze-dryer (Labconco, FreeZone® 6 Liter Benchtop, US), spray-dryer (Lab Plant Ltd, England), laboratory-scale spray-freeze dryer with an atomization nozzle (Farmasol, Italy), particle size

FIGURE 3



Plot of the % cumulative undersize versus the cut-off diameters of the twin-stage liquid impinger of bovine serum albumin dry powders prepared using Pluronics F-127 (A) and F-68 (B).

analyzer (Cilas L-100, Quantachrom, France), twin-stage liquid impinger (locally made), MLW Vibrator for tapped density determination (VEB MLW Labortechnik, Germany), UV spectrophotometer (Perkin Elmer, Lambda, 3B, US), and Handihaler (Boehringer Ingelheim Pharma GmbH & co. KG, Germany).

FORMULATIONS OF THE DRY POWDERS

Different concentrations of Pluronics F-127 and F-68 were prepared. Pluronic F-127 or Pluronic F-68 was dissolved separately in 50 mL of distilled water. Each solution of Pluronic F-127 or Pluronic F-68 of different concentrations was mixed separately with 0.1% w/v BSA solution. The Pluronics concentrations F-127 or F-68 in the mixture were varied (0.5, 1, 2, 3, and 5 mg/mL). All prepared solutions with different concentrations of Pluronic F-127 and Pluronic F-68 were spray-dried, freeze-dried, and spray-freeze dried.

Spray-Drying

Dry powder of bovine serum albumin BSA containing different concentrations of Pluronics (F-127 and F-68) were made by spray-drying.[21] Solutions were pumped into the drying chamber of the spray-dryer. The spray-dryer operates on the principle of a nozzle spraying in a parallel flow. In the present experiment, the inlet air temperature was established at 150°C, the pump flow rate was 10 mL/min, the aspirator was set to 40 m^3/hr, and the atomizing air was 700 L/hr. The outlet temperature depended on the inlet temperature, the pump, and aspirator flow rates, and was 75°C. The solution was pumped into the feeding system of the spray-dryer. The resultant powder was blown through the cyclone separator and collected in a container.

Freeze-Drying

A lyophilization vial was filled with the prepared solutions of BSA. The freeze-dryer was operated at a previously adjusted shell temperature (-40°C) and a pressure smaller than $133 \cdot 10^{-3}$ m bar. Samples were shell frozen by submersion in cooling mixture for at least 30 min. Vials were then placed in a lyophilizer for 48 hrs. The vials were finally stoppered under vacuum prior to unloading from the freeze-dryer.[11]

Spray-Freeze Drying

Spray-freeze dried powders of BSA containing different concentrations of Pluronics (F-127 and F-68) were prepared using a laboratory-scale spray-freeze dryer. An atomization nozzle was suspended at a specified height above a 100-mL glass vial. The atomization nozzle was operated at a power of 2.9 W. The solution was sprayed into the vial using a peristaltic pump with a feed rate of 3 mL/min. During the atomization process, the whole vial was submerged into the cooling mixture (-40°C) to ensure low temperature. The filled vials were then placed in a lyophilizer.[2] The powders prepared by the three different drying techniques were then collected separately and analyzed.

PARTICLE SIZE, DENSITY & SURFACE MORPHOLOGY

Visualization of particle size and morphology was achieved using a conventional scanning electron microscope (SEM).[22] The particle size distribution of the primary powders was measured in suspensions using a Cilas laser diffractometer. Isopropyl alcohol was used as a dispersion medium, and the dispersion was vortexed for 1 min before sizing. The polydispersity of the powders was expressed by the Span Index in the following equation:

$$Span\ Index = [D_{(v,90)} - D_{(v,10)}/D_{(v,50)}]$$

Where, $D_{(v,90)}$, $D_{(v,10)}$, and $D_{(v,50)}$ are the equivalent volume diameters at 90%, 10%, and 50% cumulative volume, respectively. The particle size of the primary powders was described by the volume median diameter (VMD).[23] The powder density (ρ) was evaluated by tap density measurements.[24] Cylinders containing the powder samples were fixed to a vibrator and tapped for 5 min until no change in the powder volume occurred. Experiments were performed in duplicate and were highly reproducible.

The theoretical aerodynamic diameter of individual particles, Daer, was calculated based on the following equation:

$$Daer = (\rho/\rho_1)^{0.5} \cdot D$$

Where (ρ) is the powder density, (ρ_1) is the density of water (equal to 1 g/cm^3), and (D) is the volume median diameter of particles.[22]

IN VITRO AEROSOL DEPOSITION

The dispersion behavior of each powder was assessed using a twin-stage liquid impinger (TSLI) with a glass throat (USP apparatus 2). The powder was aerolized using Aerolizer® and Handihaler dry powder inhaler devices (DPIDs), and was dispersed at two different flow rates (30 and 60 L/min). The deposition pattern in TSLI was fractioned into the amount of drug deposited on the capsule and device, throat, first stage, and second stage of the impinger. The amount of drug at each compartment was then determined by spectrophotometric analysis. For all of the deagglomeration experiments, the test powder was used in its original state collected from the spray-dryer. No post-treatment was applied to the powder. The sample powder was weighed using an analytical balance. Two powder doses (20 mg each) were filled into hard gelatin capsules and loaded individually into the inlet of the DPID.[21] After dispersion of the powder into the impinger was completed, the amount of drug at each compartment of the impinger was measured by spectrophotometric analysis at γ_{max} 280 nm. The fine particle fraction (FPF) or equivalently the respirable fraction (RF) is the percentage of the total dose at stage 2, corresponding to particles less than 6.4 µm. The emitted dose (ED), which is the percentage of the total powder mass exiting the capsule, was also determined and calculated as the following equation:

ED = Total Powder Mass – Amount of Drug Collected at the Capsule & Device (C,D)

The cumulative mass of powder less than the stated size of each stage of the liquid impinger was calculated and plotted, on a log paper, as percent of total mass recovered in the impinger against the effective cut-off diameter. The experimental mass median aerodynamic diameter (MMAD) of the particles is defined from this graph as the particle size at which the line crosses the 50% mark, and the geometric standard deviation (GSD) was calculated according to the following equation:

$$GSD = (X/Y)^{0.5}$$

Where X and Y are the particle sizes at which the line crosses the 84% mark and the 16% mark, respectively.[22]

RESULTS & DISCUSSION

The site of deposition and the deposition patterns of the inhaled aerosol from dry powder inhaler devices were influenced by the physical properties of the aerosol cloud, which can be attributed to those related to the dry powder formulation and to the drying technique. Figure 1 illustrates the SEM micrographs of albumin powders prepared by spray-drying (SD), freeze-drying (FD), and spray-freeze drying (SFD) in absence and presence of Pluronics, respectively. Figure 1A confirms that SD particles showed spherical dimpled shapes, while FD product consists of porous, spongy fragile particles incorporating large

TABLE 1

Drying Technique							
Type of Pluronic	Pluronic Concentration (% w/v)	Spray-drying		Freeze-drying		Spray-freeze drying	
		Geometric Diameter D_{50}(µm)	Span Index	Geometric Diameter D_{50}(µm)	Span Index	Geometric diameter D_{50}(µm)	Span Index
Pluronic F-127	0.1	3.74	3.19	38.37	2.01	24.28	1.61
	0.2	4.14	2.20	34.65	1.92	17.80	1.87
	0.3	2.92	2.15	12.81	1.45	12.48	1.76
	0.5	9.31	1.35	19.73	1.54	14.04	1.31
Pluronic F-68	0.1	4.42	1.89	39.19	2.06	39.38	1.73
	0.2	3.11	2.68	37.59	1.98	23.22	1.75
	0.3	2.57	2.21	34.15	2.08	18.02	1.34
	0.5	2.45	3.14	18.96	1.61	12.25	1.42

Effect of Pluronic type, concentration, and drying technique on the geometric diameter and Span Index of bovine serum albumin dry powders.

TABLE 2

Drying Technique							
Type of Pluronic	Pluronic Concentration (% w/v)	Spray-drying		Freeze-drying		Spray-freeze drying	
		Tap Density (g/cm^3)	Aerodynamic Diameter (µm)	Tap Density (g/cm^3)	Aerodynamic Diameter (µm)	Tap Density (g/cm^3)	Aerodynamic Diameter (µm)
Pluronic F-127	0.1	0.280	1.990	0.031	6.760	0.030	4.210
	0.2	0.180	1.770	0.030	6.000	0.012	1.950
	0.3	0.170	1.200	0.023	1.940	0.100	1.250
	0.5	0.350	5.510	0.052	4.490	0.035	2.630
Pluronic F-68	0.1	0.430	2.890	0.037	7.540	0.025	6.230
	0.2	0.280	1.650	0.036	7.130	0.022	3.440
	0.3	0.260	1.310	0.026	5.500	0.020	2.550
	0.5	0.160	0.980	0.025	2.990	0.015	1.500

Effect of Pluronic type, concentration, and drying technique on the tap density and aerodynamic diameter of bovine serum albumin dry powders.

TABLE 3

Drying Technique	Pluronic Concentration	Pluronic F-127			Pluronic F-68		
		% Impaction Loss	% Emitted Dose	% Respirable Fraction	% Impaction Loss	% Emitted Dose	% Respirable Fraction
Spray-freeze drying	0.1	42.33	84.30	41.97	49.50	91.87	42.37
	0.2	42.16	94.60	52.44	48.58	92.95	44.37
	0.3	42.11	98.90	56.79	49.04	97.12	48.08
	0.5	42.10	95.10	53.00	48.33	98.30	49.97
Freeze-drying	0.1	44.98	72.98	28.00	51.39	75.85	24.46
	0.2	31.36	59.85	28.49	50.15	75.53	25.38
	0.3	50.69	81.79	31.10	50.38	76.99	26.61
	0.5	40.85	67.31	26.46	66.78	94.60	27.82
Spray-drying	0.1	28.75	56.28	27.53	32.80	62.05	29.25
	0.2	38.07	69.35	31.28	36.02	66.54	30.52
	0.3	40.45	74.80	34.35	38.52	70.02	31.50
	0.5	38.31	52.91	14.60	41.02	73.41	32.39

Effect of Pluronic type, concentration, and drying technique on the aerosolization performance of bovine serum albumin dry powders.

interparticulate voids (Figure 1B).

However, SFD creates spherical, highly porous particles (Figure 1C). Although the atomized droplets were spherical in shape, the shape of the dried particles might change depending on the drying techniques and protein formulations. Addition of block copolymer showed prominent effect in the case of SD rather than other techniques (Figure 1D through 1F), and more basically spherical particles were observed. On the other hand, surface morphology of powders, including different concentrations of Pluronics, was similar.

Table 1 demonstrates the effect of different Pluronic concentration on the aerosolization performance of dry powders prepared by the three drying techniques. The least D_{50} values were observed for SD formulations, ie, 2.92 µm for Pluronic F-127 (0.3% w/v) and 2.45 µm for Pluronic F-68 (0.5% w/v). SD, FD, and SFD produced powders of different physical and aerosol dispersion properties. The FD and SFD powders had a larger median particle size than SD. This can be attributed to the spray-drying conditions used in this study. The droplet generated during spraying with the spray-dryer is larger than the size of the dried particles, as evaporative loss of water leads to particle shrinkage during spray-drying.[25] However, in the absence of hot-air drying, atomized droplets during SFD maintained their spherical shape and size upon immediate freezing, and the subsequent drying process did not affect the shape or the size.[2] For all powder formulations, increasing the concentration of Pluronics exhibited a decrease in volume median diameter (D_{50}, µm), except for the powder containing 0.5% w/v Pluronic F-127.

Polydispersity is expressed by the Span Index. SD powders showed the highest Span Index values, ie, 2.15 at 0.3% w/v Pluronic F-127 and 3.14 at 0.5% w/v Pluronic F-68. The high Span Index values indicate a wide size distribution for the SD powders. The Polydispersity Index affected the impaction loss of inhalation dry powders. The higher Span Index values, the greater the deposition at the oropharynx.[23] It thus appears that the aerosolization performance reached its peak level at a given optimum concentration of Pluronics, irrespective of the technique used.

Table 2 shows the effect of different concentrations of Pluronics and drying techniques on the powder tap density and aerodynamic diameter. Increasing the concentration of Pluronics in the solution to be dried greatly decreased the powder tap density, and subsequently the Daer was reduced. It is generally accepted by most researchers that particles with an aerodynamic diameter from 1 to 6 µm are suitable for systemic drug delivery.[21] Our results showed that all prepared powders lied in the acceptable aerodynamic diameter range. The smallest aerodynamic value was observed for SD powder prepared with 0.3% w/v Pluronic F-127 (1.2 µm) and 0.5% w/v Pluronic F-68 (0.98 µm). For further confirmation of aerodynamic particle size, the % RF, % ED, and impaction loss was determined using twin-stage liquid impinger at 60 L/min and is demonstrated in Table 3. The impaction loss was found to be affected by the geometric diameter. In comparison with the smaller geometric diameter particles, the impaction loss for larger particles was much higher, as impaction loss is proportional to the square of the particle or agglomerate size.[23] A greater proportion of larger particles were observed for SFD and FD rather than SD formulations, and these particles would have the potential to impact with the throat. Larger particles could also act as carriers with binding sites onto which the smaller particles adhere, forming agglomerate for impaction.

The % ED can also be affected by polydispersity of the primary powders (Span Index). The effect tends to be more prominent in the case of SD formulations. Compared with the larger Span Index of spray-dried powders, the % ED for smaller ones was much higher as in the case of freeze-dried and spray-freeze dried powders. Drying technique as well as Pluronic concentration significantly affected the % RF of emitted dose. Increasing the concentration of Pluronics significantly increase the % RF except for the powder prepared using 0.5% w/v Pluronic F-127. SFD exhibited higher RF values. For example, the % RF values of powders prepared with 0.3% w/v Pluronic F-127 were 56.79%, 34.35%, and 31.10% for SFD, SD, and FD powders, respectively. Generally, the percentage drug deposition at stage 2 of the twin-stage liquid impinger for SFD samples was significantly larger than that of SD

and FD formulations. SFD showed larger fused particles that resulted in the reduction of % RF significantly. SFD particles were highly deformed from their spherical shape but maintained excellent aerosol performance (highest % RF and % ED).

Figure 2 illustrates the plot of % RF versus geometric diameter and aerodynamic diameter for Pluronics F-127 and F-68. Good coefficient of correlation was observed for SFD and SD formulations ($R \approx 0.9$), while absence of correlation in the case of FD powders. To assess our results, a plot of mass aerodynamic diameter versus cumulative percentage undersize can be used to study the effect of particle size as well as drying technique on powder dispersibility (Figure 3). SD and FD powders showed a similar dispersibility with a slope of about 0.07. However, the SFD powders showed a slightly higher slope (0.09), suggesting lower degree of dispersibility. On the other hand, the calculated MMADs were 7.43 µm, 7.47 µm, and 5.63 µm for SD, FD, and SFD powders prepared with Pluronic F-127, respectively. These results suggest that the superior aerosol performance by the SFD powder might be simply due to its smaller mass aerodynamic particles size despite its larger physical size D_{50}(µm). Based on this discussion, one can recommend the use of spray-freeze drying technique to produce large porous particles which are aerodynamically favorable for aerosol delivery.

CONCLUSION

In conclusion, this study has shown that the drying technique would affect the amount of fine particles (% RF) generated in aerosol clouds. SFD powders with a lower polydispersity have produced higher % RF and higher % ED. It has been demonstrated that SFD is a feasible technique for preparing protein aerosol powders, which showed much better aerosol performance than SD and FD powders. This was attributed to better aerodynamic properties as a result of the powders' large porous characteristics. Overall, SFD is a more efficient process in terms of product recovery and product quality.

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Prof. Dr. Magda Samaha earned her PhD from the University of Wisconsin, Madison, in Pharmaceutics with Professor Dr. Gordon Amidon as her advisor. Dr. Samaha has had a major role in developing correlations of solubility parameters of pharmaceutical solids with other physical quantities, for instance, the advancing and receding contact angles of polymers, the surface free energy for a number of drugs, and the CMC of polyoxyethylated ionic surfactants. She is currently the Head of the Industrial Pharmacy Department at the College of Pharmacy, University of Alexandria in Egypt. She has participated in several joint research articles relating to the optimization of drug delivery from dry powder inhalers using different drying techniques.

Prof. Dr. Ferial El-Khawas earned her PhD in 1965 from the Faculty of Pharmacy, University of Alexandria, Egypt, under the supervision of Prof. Tawashi. Since then, she has actively participated in both teaching and research in the field of Industrial Pharmacy both in Egypt and abroad. She has supervised a number of Masters and Doctorate programs and has published a number of research papers in various local and international journals. Her research field includes topics on powder technology, drug stability, product formulation and optimization, and recent non-conventional dosage forms. Prof. El-Khawas has also occupied various administrative positions during her academic career, such as Head of the Department of Industrial Pharmacy and Vice Dean of the Faculty of Pharmacy, University of Alexandria.

Dr. Hoda El-Maradny earned her PhD from the Faculty of Pharmacy, University of Alexandria, Egypt, under the supervision of Prof. El-Khawas and Prof. Samaha. Her PhD thesis is titled Evaluation of Fluidization Technique in the Processing of Pharmaceutical Solid Dosage Forms. Her research topics are related to sustained-release dosage forms, pulsatile-release tablets, and powder technology for inhalable dry powder formulation.

Dr. Doaa Mohamed Ragab is an Assistant Lecturer of Industrial Pharmacy, Faculty of Pharmacy, Alexandria University, Egypt. She recently earned her Masters under the supervision of Prof. El-Khawas, Prof. Samaha, and Dr. El-Maradny. Her thesis is related to the development and characterization of inhaled formulations for systemic drug delivery. Her research interests include topics related to drying technology, such as spray-drying, freeze-drying, spray-freeze drying, and supercritical fluid technology for preparation of hollow porous particles.

GAMMA SCINTIGRAPHY

In Vivo Performance Assessment of Inhalation Devices

By: Peter D. Scholes, PhD, and Karen Jones, PhD

INTRODUCTION

The inhalation market is estimated to be growing at 8% annually and is predicted to reach a value of $20 billion by 2010.[1] Driving this growth is continued innovation in compound, formulation, and delivery system design. In this article, we look at the increasing role gamma scintigraphy can play in optimizing inhaled devices and understanding how device/molecule/formulation variables impact delivery efficiency. Giving a uniquely visual representation of drug deposition, gamma scintigraphy is already adding significant value to early drug development, and looks set to find even wider application.

Key to any successful therapeutic regimen is the ability to deliver the drug to the right target site at the right time. Pulmonary or nasal delivery of drugs has become an increasingly popular route of administration, not only for localized therapies, but also for the treatment of certain systemic disease. It offers the benefits of a highly vascularized, large surface area for absorption that can promote high bioavailability and rapid onset of action. For biomolecules, pulmonary delivery can provide a viable alternative to intravenous administration.

REGULATORS GET ON BOARD

Given the lack of in vitro models truly representative of in vivo delivery of inhaled medicaments, the use of gamma scintigraphy to visualize deposition within the nasal and pulmonary regions has gained widespread acceptance. Late in 2007, the Committee on Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) published updated draft guidelines on the requirements for clinical documentation for orally inhaled products. The new guidance places imaging at the center of pulmonary deposition investigations.[2]

A PIVOTAL ROLE FOR GAMMA SCINTIGRAPHY

Looking back, gamma scintigraphy has been used in inhaled product development for more than 20 years. Early applications centered on determining optimal regional delivery sites in order to maximize safety or efficacy profiles for existing inhaled drugs.[3] Utilization increased significantly throughout the 1990s given the increased innovation in delivery systems, which was fuelled by the chlorofluorocarbon (CFC) to hydrofluoroalkane (HFA) transition for pressurized metered dose inhalers (pMDIs), and the expansion in dry powder inhaler (DPI) device technology. Objectives and endpoints of these studies were primarily focused on maximizing or improving in vivo lung deposition of the inhaled medicament compared to existing technologies.[4]

Recent interest in pulmonary and nasal administration now provides extended opportunities for gamma scintigraphy (Figure 1), including the following:

FIGURE 1

Application Area	*Value added by gamma scintigraphy*
Systemic delivery	Combined scintagraphic/PK studies to investigate bioavailability
Proof of concept	Model validation in patient rather than volunteer groups
Active transport	Study receptor mediated transport
Patient compliance	Validate design improvements to devices
Device optimization	Select optimal device characteristics
Nasal targeting	Visualize and quantify delivery
Device bridging	Data accepted as surrogate for therapeutic equivalence
Competitive positioning	Demonstrate superior performance

The role of gamma scintigraphy in inhaled product development.

FIGURE 2

Formulation	A freeze-dried cake containing a peptide molecule and other excipients
Flow rate selection	An in-house inhalation profile reorder was used to asses the resistance of the ODPI system; investigations concluded that healthy volunteers could consistently generate peak inhaled flow rates (PIFs) of 30-40 L/min. PIFs of 20 and 40 L/min were selected for the *in-vivo* study
In vitro testing	Particle size distribution and emitted dose (ED) of the formulation were evaluated at 20, 30 and 40 L/min. Fine particle fraction (FPF, <5 µm) and ED data were calculated as a percentage of metered dose
In vivo testing	Radiolabeling studies were performed in accordance with appropriate standards. A clinical study of 7 healthy volunteers was conducted to determine the whole lung deposition of the formulation by gamma scintigraphy following inhalation at the targeted PIFs of 20 and 40 L/min. The actual flow profiles and PIF values for each inhalation were recorded

Experimental Details

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GAMMA SCINTIGRAPHY & PHARMACOKINETICS IN COMBINATION

Integrated scintigraphic/pharmacokinetic (PK) studies enable researchers to study systemic bioavailability of inhaled small and macromolecule drugs. For example, workers reported that the widespread lung deposition of insulin gave plasma PK parameters comparable to intravenous infusion, with a t_{max} of less than 15 minutes.[5] Earlier work found that a novel DPI delivery system for tobramycin gave a doubling in C_{max} and total exposure compared to nebulizer delivery over a 15-minute administration at a four-fold reduced dose.[6]

In addition, pharmacoscintigraphic studies can be applied as part of lead candidate selection to ensure optimal physicochemical properties for systemic or local delivery. Furthermore, combined scintigraphic and ^{14}C microdose studies could investigate full pulmonary and systemic PK parameters with a crossover intravenous dose.

DEVICE OPTIMIZATION & COMPETITIVE POSITIONING

Selection of optimal device design characteristics can lead to improved delivery performance. Scintigraphic deposition studies have been used to demonstrate how the novel Tempo™ Inhaler improved delivery performance in comparison to marketed pMDI technologies for fluticasone propionate by doubling the fine particle fraction (FPF) and reducing oropharngeal deposition.[7] Given increased research in novel valves and actuators for pMDIs, and active and electronic devices for DPIs, all aimed at improving device robustness in the hands of patients, the use of such studies will become more routine.

Scintigraphic techniques have also demonstrated the superior performance of the Respimat® device. It gave a more efficient and peripheral lung deposition (52% of delivered dose) than either a corresponding DPI (18% to 29%) or pMDI (9%) device.[8] This increased peripheral deposition identified an opportunity

FIGURE 3

Direct Visualization of Drug Delivery
Image analysis technologies provide insight into the efficiency of different inhalation devices and the suitability of different inhaled formulations. Studies provide guidance on appropriate dosing levels, identify safety concerns, and highlight potential patient compliance issues.

prior to conducting pivotal efficacy trials for a reduction in dose to achieve the same therapeutic effect.

UNDERSTANDING DEVICE/FORMULATION VARIABLES ON DELIVERY EFFICIENCY FOR SYSTEMIC THERAPIES

Systemic delivery of peptides and proteins to the lung using the breath-actuated Otsuka Dry Powder Inhalation (ODPI) system has been investigated.[9] Breath actuation relies on a patient's inspiratory effort, something that can vary significantly, potentially leading to variability in dose delivery. A recent study by Pharmaceutical Profiles looked at the delivery characteristics of the ODPI system when different inspiratory efforts were used (Figure 2).

By comparing in vitro and in vivo data, the study was able to confirm that, despite the fine particle fraction being dependent on flow rate in vitro, the ODPI system consistently delivered drug to the lungs with high efficiency, and that deposition was independent of inspiratory effort over a clinically relevant range of peak inhaled flow rates. The gamma scintigraphy images suggested that the device is suitable for reproducible deep lung delivery of therapeutics intended for the treatment of systemic indications.

SUMMARY

Gamma scintigraphy has made significant contributions to the historical development of inhaled products and devices. Applications for pulmonary and nasal drug delivery continue to expand the role scintigraphy can play within product development programs. The technique provides valuable insight, ensuring that data-driven decisions can be taken to optimize delivery systems and dosage regimens. Furthermore, the growing acceptance of scintigraphic techniques by regulatory authorities suggests they will have increased importance in the future development of inhaled products.

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Dr. Peter D. Scholes spent 15 years working for 3M Pharmaceuticals, where he gained project management and leadership skills as well as hands-on experience in drug development processing. In 2007, he became Vice President of Pharmaceutical Sciences at Pharmaceutical Profiles. A member of the Royal Pharmaceutical Society of Great Britain and the Academy of Pharmaceutical Sciences, Dr. Scholes retains his connections to academia. In 2002, he stood as industrial supervisor of a PhD studentship at the University of Strathclyde and was a visiting lecturer at University of Aston for four years. Dr. Scholes earned his PhD in Pharmaceutical Drug Delivery, Department of Pharmaceutical Sciences, University of Nottingham.

Dr. Karen Jones completed her Post-doctoral studies in Human Cardiovascular Disease at Harvard Medical School/Howard Hughes Medical Inst, Boston. She spent 4 years at Incyte Genomics, where she gained experience in drug discovery research using bioinformatics and high throughput genetic analyses, culminating in more than 20 peer-reviewed scientific publications and issued patents. Dr. Jones has 8 years experience in product development and marketing of services for pharmaceutical research, preclinical, and clinical development following business development and marketing positions at Incyte, Oxagen, and Cyprotex plc. Dr. Jones earned her PhD from UCL/Imperial Cancer Research Fund and is currently Vice President of Marketing for Pharmaceutical Profiles.

SUSTAINED RELEASE SOLID DISPERSIONS

Development of Sustained Release Solid Dispersions Using Factorial Design

By: Monika, MPharm; Harish Dureja, MPharm (PhD Student); and A.K. Madan, PhD

ABSTRACT

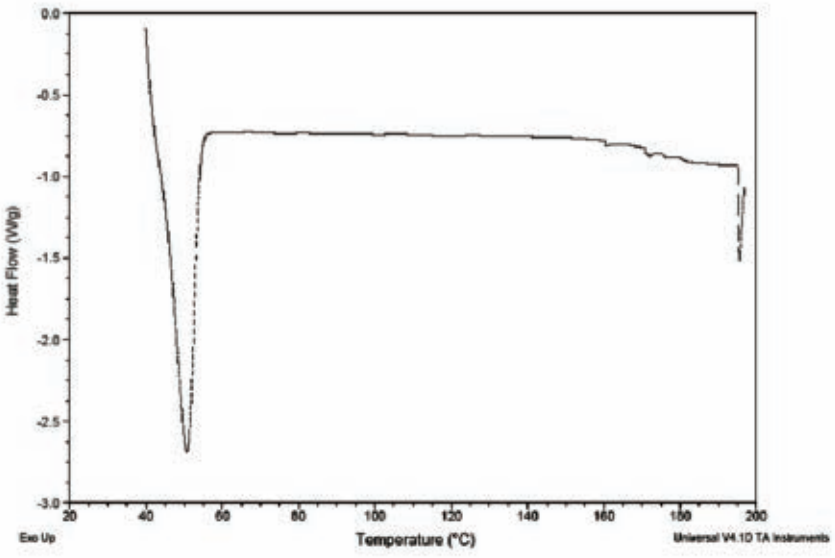
Sustained release solid dispersions (SRSDs) were prepared by incorporating Glibenclamide:Poloxamer-407 solid dispersion (SD) in a rate-controlling carrier (Eudragit RS100). Glibenclamide was employed as the model drug. Poloxamer-407 was used as a hydrophilic carrier to enhance the dissolution rate of the sparingly soluble drug Glibenclamide. Factorial design was applied to study the effects of relative proportions of Glibenclamide, Poloxamer-407, and Eudragit RS100 on drug dissolution. Solid dispersions were characterized by DSC and FTIR spectroscopy. The SDs were also subjected to scanning electron microscopy and particle size analysis. ANOVA was also applied on the cumulative percent of Glibenclamide release. The in vitro dissolution rate of SRSD was found to be slower than the SD of Glibenclamide. The mathematical model developed in the present study can be used to predict the cumulative percent of Glibenclamide released from SRSDs.

INTRODUCTION

The term solid dispersion was initially used by Sekiguchi and Obi in 1961 and has grown to become one of the most active ideas in the pharmaceutical field because of promises by dissolution retardation.[1,2] Chiou and Reigelman defined the term solid dispersion as "a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by fusion, solvent, and melting solvent method."[3] Dispersions obtained through the fusion process are called "melts," and those obtained by the solvent method are referred to as "co-precipitates and co-evaporates."[4] The technique of SD has been widely used to prepare both fast-release and sustained-release drug preparation via the melting, solvent, or melt-solvent method.[3] Various polymers used for dissolution enhancement or sustained-release SDs have been used, such as Polyvinylpyrrolidone, Polyethylene Glycol, Gelucire 44/14, Poloxamer 188, Eudragit RS100 or RL100, Ethylcellulose, and Chitosan.[5-12]

In this present study, the SDs were prepared using both the fusion and melting solvent method. The SRSD was prepared using the sparingly soluble

FIGURE 1



DSC of SRSD (batch 8F).

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drug Glibenclamide, using Poloxamer-407 as a hydrophilic carrier and Eudragit RS100 as a hydrophobic carrier. The aim of the work was to quantify the role of critical variables of SRSDs using statistical experimental design.

MATERIALS

The active ingredient, Glibenclamide (Cadila Pharmaceuticals) is a thermostable compound with a melting point 174°C to 176°C. Eudragit RS100 (Evonik) and Poloxamer-407 (Dr. Reddy's Pharmaceuticals) were used as received.

DEVELOPMENT OF SUSTAINED RELEASE SOLID DISPERSIONS (SRSDs)

Preparation of Solid Dispersions (SDs)Using Poloxamer-407

The SDs (batches 1F to 4F) were prepared via the melt method reported by Sekiguchi and Obi.[1] Required quantities (15 to 50 mg) of Poloxamer-407 were weighed and heated to 60°C. The requisite amount of Glibenclamide (2.5 to 5.0 mg) was added to molten vehicle with continuous stirring. The molten system was allowed to cool to produce an SD and subsequently passed through sieve No. 40.

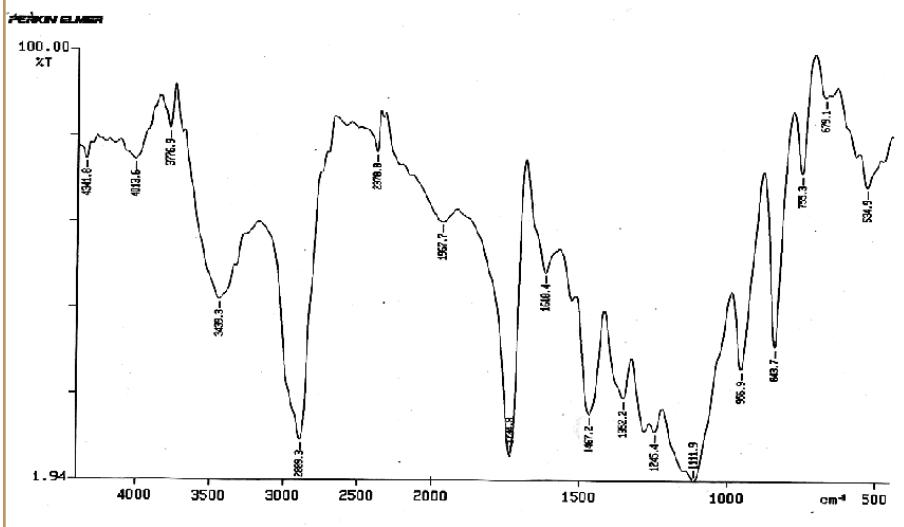
Preparation of Sustained Release Solid Dispersions (SRSDs)

The SRSDs (batches 5F-8F) were prepared according to the melt-solvent method as reported by Chiou and Reiglman.[3] The immediate-release SD of Glibenclamide was dissolved in a 50-ml ethanolic solution of Eudragit RS100 with continuous stirring. The solvent was evaporated under vacuum to obtain SRSDs and subsequently passed through sieve No. 22.

Experimental Design

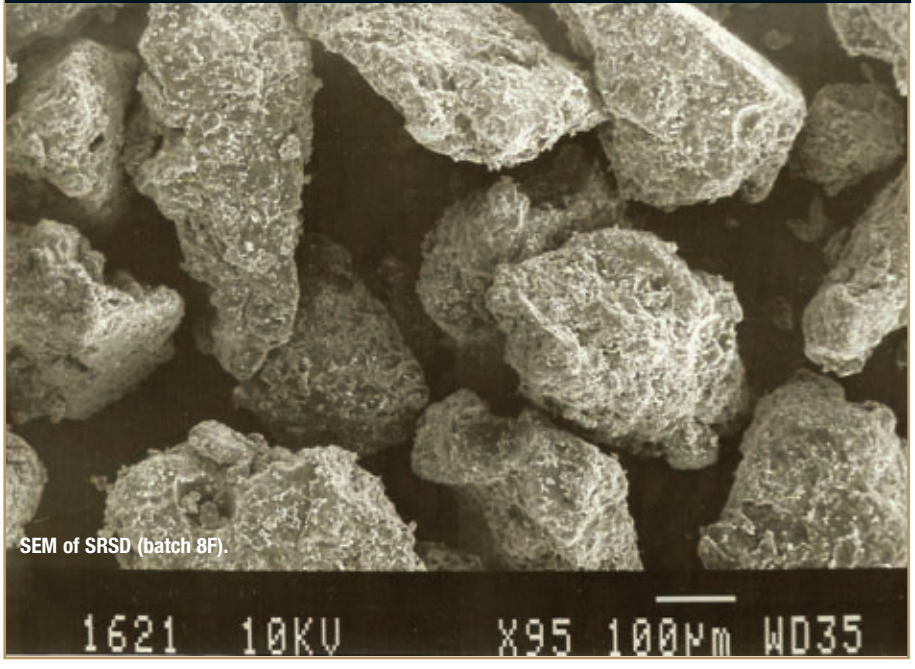
Selected formulations of SRSDs were prepared according to statistical experimental design. The use of factorial design facilitated evaluation of effect of independent variables on the dissolution profile of Glibenclamide. To evaluate two factors (n) at two levels (k), the factorial design (k^n) consisted of four batches of each SD (Table 1).

FIGURE 2



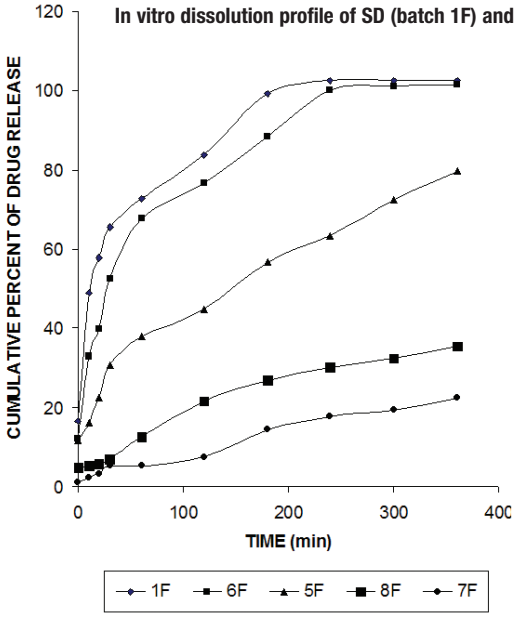
FTIR spectra of SRSD (batch 8F).

FIGURE 3



SEM of SRSD (batch 8F).

FIGURE 4



Differential Scanning Calorimetery (DSC) Study

The melting behavior of pure Glibenclamide, hydrophilic Poloxamer-40, hydrophobic Eudragit RS100, and solid dispersions (SD and SRSD) were evaluated by DSC (Waters, Q10 V9.0 Build 275). Samples were sealed in aluminum pans and scanned from 40°C to 250°C at a heating rate 10°C/min in an atmosphere of nitrogen gas.

Fourier Transforms Infrared Spectroscopy (FTIR) Study

Infrared absorption spectra (Perkin Elmer Paragon 1000 IR Spectrophotometer) of pure Glibenclamide, hydrophilic Poloxamer-407, hydrophobic Eudragit RS100, and solid dispersions (SD and SRSD) were obtained using a potassium bromide disc under static air.

Scanning Electron Microscopic Study

The surface characteristics of SDs and SRSDs were examined using a scanning electron microscope (Leo-435VP). Each SD and SRSD were sprinkled on a sample holder using double-sided adhesive tape, and a layer of gold palladium was vacuum evaporated onto its surface using agar sputter coater. Each sample was examined with a scanning electron microscope.

Particle Size Analysis

The particle size of pure Glibenclamide solid dispersions (SD and SRSD) was measured using a Mastersizer 2000 (Malvern Instrument Limited).

In Vitro Dissolution Study

The in vitro dissolution study was performed in a USP apparatus II by using a sample equivalent to 10 mg of Glibenclamide in 900 ml of phosphate buffer (pH 7.4). The phosphate buffer was stirred at 75 rpm at 37°C ± 0.5°C. Samples (5 ml) withdrawn at fixed intervals were immediately analyzed for Glibenclamide concentration spectrophotometrically (300 nm), directly or after appropriate dilution with phosphate buffer (pH 7.4). The sample withdrawn was replenished with equal amount of phosphate buffer (pH 7.4). The dissolved amount of Glibenclamide at each specific time interval was calculated as a percentage of the total amount of Glibenclamide.

Content Uniformity Study

Ten samples of SRSD containing an equivalent amount of 10 mg of Glibenclamide was added to a volumetric flask (50 ml) containing methanolic HCl (40 ml). The flask was shaken for 15 minutes, and final volume was made up using methanolic HCl. The sample was filtered and assayed for Glibenclamide spectrophotometrically at 300 nm.

RESULTS & DISCUSSION

Factorial design was used to perform statistically valid experiments. The real value of factors was transformed to facilitate orthogonality of results and easy calculations. The SRSDs were prepared using the sparingly soluble drug Glibenclamide, using Poloxamer-407 as a hydrophilic carrier and Eudragit RS100 as a hydrophobic carrier.

The thermograms of SDs (batches 1F to 4 F) were evaluated to identify the ratios of Glibenclamide and carrier. The ratio 1:6 (1F) was selected for SRSD development for two reasons: 1) existence of drug at molecular level as evidenced by the absence of melting endotherm of Glibenclamide in the thermograms and 2) presence of minimum amount of carrier.

The thermal profiles of the pure

components exhibited a single endotherm corresponding to its melting point. A single endothermic peak in the case of Glibenclamide and Poloxamer-407 at 176.74°C and at 56.98°C, respectively, corresponds to their melting points. Exothermic effect in the case of Eudragit RS 100 at 150°C to 158°C corresponds to its glass transition temperature. The DSC scan of SRSD (batch 8F) lacks endotherm at 176.74°C corresponding to the melting point of Glibenclamide, indicating its presence in an amorphous form (Figure 1).

The infrared spectrum of SRSD (batch 8F) exhibited significant differences in the intensities of the absorption peaks. Broadening of various absorption peaks with a slight shift in the position to a lower wavelength was observed, which may be attributed to the absence of the intermolecular hydrogen bonding in the Glibenclamide present in the SDs (Figure 2).

The surface morphology of SRSD (batch 8F) is shown in Figure 3. The surface of SRSD was seemed to be columnar shaped.

The analysis of particle size distribution indicated that the maximum volume of particles of pure Glibenclamide are in the size range of 22 to 30 micrometers, SDs containing Glibenclamide and Poloxamer-407 are in the size range of 416 to 978 micrometers, and SRSDs are in the size range 548 to 630 micrometers.

The role of critical variables of SRSDs, such as amount of Glibenclamide and amount of carrier(s), ie, Poloxamer-407 and Eudragit RS100, was studied on cumulative percent release of the drug.

In vitro dissolution study revealed that SRSDs have a slower rate of dissolution in comparison to SDs (Figure 4). In SRSDs, the cumulative percent of Glibenclamide release increases with a high level of Glibenclamide and low value of carrier, whereas the high concentration of carrier decreases the cumulative percent of Glibenclamide release. To determine the magnitude of contribution of factors toward cumulative percent of Glibenclamide release, multiple linear regression analysis was performed. The model developed from multiple linear regression for estimating cumulative percent of Glibenclamide release (Y) can be represented mathematically as per the following equation: $Y = 37.57 + 1.53\ X_3 - 0.37\ X_4$. Where X_3= amount of Glibenclamide present in SDs containing hydrophilic Poloxamer-407 and X_4 = amount of hydrophobic Eudragit RS100.

Analysis of Variance (ANOVA) (Table 2) was applied to study the fitting and significance of the mathematical model to estimate cumulative percent of Glibenclamide release. F = 17.047 shows regression to be significant. The proposed model, therefore, may be used as a mathematical tool for determining cumulative percent release of Glibenclamide from SRSDs containing hydrophilic Poloxamer-407 and hydrophobic Eudragit RS100. All 10 samples for SDs and SRSDs comply with

TABLE 1

Preparation of Solid Dispersions

Batch	X_1 (mg)	X_2 (mg)
1F	-1 (2.5)	-1 (15)
2F	+1 (5.0)	-1 (15)
3F	-1 (2.5)	+1 (50)
4F	+1 (5.0)	+1 (50)

Preparation of Sustained Release Solid Dispersions

Batch	X_3 (mg)	X_4 (mg)
5F	-1 (5)	-1 (25)
6F	+1 (10)	-1 (25)
7F	-1 (5)	+1 (100)
8F	+1 (10)	+1 (100)

X_1 – amount of Glibenclamide
X_2 – amount of Poloxamer-407
X_3 – amount of Glibenclamide present in SD
X_4 – amount of Eudragit RS100

Development of solid dispersions (SDs) and sustained release solid dispersion (SRSDs).

TABLE 2

	Degree of Freedom	Sum of Squares	Mean Square	F	F-Significance
Total	3	2748.68	--	--	--
Regression	2	2670.365	1335.18	17.047	0.168
Residual	1	78.322	78.377	--	--

ANOVA of regression (cumulative percent of Glibenclamide release).

the specified requirements for the uniformity of Glibenclamide content (9.70 ± 0.557 mg).

CONCLUSION

The technique of SD has been widely used for the enhancement of dissolution or sustained release of drugs. For the sparingly soluble drug Glibenclamide, the technique of SD using hydrophilic Poloxamer-407 and hydrophobic Eudragit RS100 carrier was successfully utilized for the development of SRSDs. The SRSDs have shown a slower rate of dissolution in comparison to SDs. The developed SRSDs of Glibenclamide could be processed into tablets or capsules. Application of factorial design revealed that a high level of hydrophobic Eudragit RS100 decreases the cumulative percent of Glibenclamide release. The proposed mathematical model can be used for predicting cumulative percent release of Glibenclamide from SRSDs, and also possesses immense potential for designing SRSDs with desired Glibenclamide-release characteristics.

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BIOGRAPHIES

Prof. A.K. Madan earned his two Bachelors degrees in Pharmacy and Chemical Engineering, his Masters in Pharmaceutics, and his PhD in Chemical Engineering from the Indian Institute of Technology, New Delhi. He has 12 patents and more than 80 research publications in leading journals to his credit. His research areas include pharmaceutical process development, chemical computation, structure-activity/property relationship, pharmaceutical quality control, pharmaceutical technology, and biotechnology. His expertise is simply recognized by the fact that he is acting as a referee for review of manuscripts for a large number of international journals of repute and some of the mathematical tools developed by him for drug design have been incorporated in leading software marketed by multinational companies. Presently, he is working as Dean, Faculty of Pharmaceutical Sciences, M.D. University, Rohtak.

Harish Dureja studied Pharmacy at C.C.S. University (India) and earned his Masters in Pharmaceutics from Punjabi University (India). His research areas include transdermal drug delivery systems, pharmaceutical process development, and chemical computation. He has more than 30 publications to his credit and is currently working as a Lecturer in the Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak. He is also pursuing his PhD at M.D. University, Rohtak.

Ms. Monika earned her Masters in Pharmaceutics from M.D. University, Rohtak. Her research focuses on development of sustained release solid dispersions. Currently, she is working as a Lecturer at Doon Valley Institute of Pharmacy and Medicine, Karnal, India.

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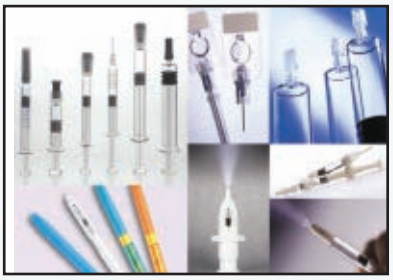
Prefillable Delivery Systems



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

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

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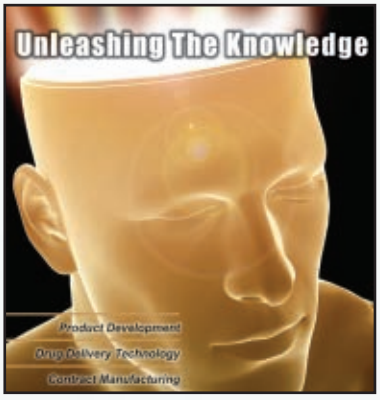

It is critical for a service provider to meet the technical, financial, and timing demands of projects and offer clients first-class expertise and capabilities throughout the world. The Glatt Group has been supplying solid dosage technology, equipment, integrated systems, and processing expertise to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

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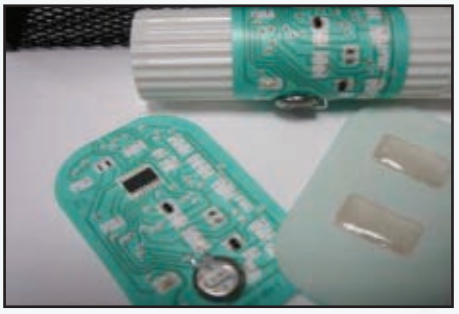
Iontophoretic Patch



Isis Biopolymer, Inc. is expanding the capabilities of active transdermal drug delivery with its breakthrough product, the Isis Patch. The first compact, wireless, active iontophoretic patch to be fully programmable by healthcare professionals, the Isis Patch enables physicians to control activation, monitor use, and adjust drug delivery to each patient. Proprietary hydrogels allow dosing of multiple drugs, as well as a wide variety of drugs. A smaller, softer, and more flexible design resembles a band-aid, while hypoallergenic, skin-friendly polymers eliminate irritation and enable the patch to be worn for up to 7 days with superior adherence to the skin. Isis Biopolymer's lower cost, environmentally friendly manufacturing process reduces the cost of conventional iontophoresis by much as 50%. For more information, contact Isis Biopolymer at (401) 921-6873 or visit **www.isisbiopolymer.com**.

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Niche Generics & DPI

PH&T is an Italian pharmaceutical company engaged in research, development, and production of generic drugs for specialist therapies and innovative medical devices, to be sold through licensees and distributors. PH&T selects products, mainly in niche areas, that are both scientifically sound and technically complex. The Company has a wide range of experience in the development of oral slow-release formulations, nasal sprays, and injectable products and in product registration in Europe throughout multistate and decentralized procedures. Quality of the product, careful selection of client companies, reliable assistance in regulatory affairs, and active marketing support in the commercial phase are PH&T keys to success. PH&T has also developed and patented Turbospin ®, a simple and effective single-dose, multi-use DPI. For more information, visit PH&T at **www.phtpharma.com**.

Pharmaceutical Product Development

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Pulmonary Delivery Solutions

Rexam Pharma is one of the largest manufacturers of pharmaceutical plastic primary packaging, drug delivery systems, and medical devices. Its expertise in plastic injection and high-speed automated assembly enables them to offer innovative products. Key players in the pharmaceutical industry have trusted Rexam Pharma to develop and industrialize pulmonary drug delivery devices for strategic products. Be it for Customized Devices, Dry Powder Inhalers, Pressurized Metered Dose Inhalers, Dose Counters, or Metering Valves and Applicators, Rexam Pharma is a partner of choice for all pulmonary drug delivery solutions. Meet us at the RDD (Respiratory Drug Delivery) conference May 11-15 in Scottsdale, AZ. For more information, contact Rexam Pharma at (847) 541-9700 or visit **www.rexam.com/pharma**.

Formulation Technology

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For drug developers concerned about formulating poorly soluble compounds, SOLIQS Meltrex is the drug delivery solution. SOLIQS has adapted melt extrusion processes to the manufacture of pharmaceutical formulations, and offers its collaborating partners formulation know-how, competence in polymer and analytical research, and dedicated resources from early feasibility studies through production. Meltrex technology applies heat and pressure to a mixture of active ingredient and thermoplastic polymer. No water or other solvents are necessary. The melt is then extruded and shaped as tablets, granules, pellets, sheets, sticks, or powder. The result is improved bioavailability, specifically designed release profiles, competitive costs, and opportunities for patent protection and life cycle management, adding value to both new molecular entities and established products. SOLIQS and Meltrex are a safe solution for insoluble drug substances. For more information, contact SOLIQS at (877) 765-4771 or visit **www.soliqs.com**.

DRUG DELIVERY Executive

EMISPHERE

The "New" Emisphere: Impacting the Future of Drug Delivery

Michael V. Novinski
President & CEO
Emisphere Technologies, Inc.

"One of the first things I did when taking the helm at Emisphere was to reassess our technology. That reassessment convinced us that, when it is applied properly, the technology can be life-changing for many patients and bring enormous benefits to healthcare treatment."

Emisphere Technologies, Inc., (NASDAQ: EMIS), with corporate headquarters in Cedar Knolls, NJ, and its Scientific Center in Tarrytown, NY, is a biopharmaceutical company that has developed a broad-based proprietary drug delivery platform known as the eligen® technology. This technology makes it possible to deliver a therapeutic molecule orally without altering its chemical form or biological integrity. The key benefit of the eligen technology is that it improves the ability of the body to absorb diverse molecules by means other than injection. Drug Delivery Technology recently interviewed Michael V. Novinski, President and Chief Executive Officer of Emisphere, to discuss the company's technology, product pipeline, and its future strategic direction.

Q: The last time we spoke with Emisphere was in 2002. How have things changed throughout the past 6 years?

A: I took over the reigns of Emisphere in May 2007. Since then, I am pleased to say, a "new" company has emerged. We determined that we needed to take steps to enhance the effectiveness of the organization, including an evaluation of our technology and an assessment of the company overall. So we put together a plan, which we are executing, beginning with a restructuring of Emisphere across the board to facilitate communication and better management. I re-staffed the organization at the senior level. These critical additions included Michael R. Garone, Chief Financial Officer; Paul Lubetkin, Vice President, General Counsel and Corporate Secretary; and Gary I. Riley, DVM, PhD, Vice President, Nonclinical Development and Applied Biology. In conjunction with adding staff in key management roles, we have established necessary business processes for adequate control. We cut costs through productivity gains and headcount reduction, and eliminated excess overhead, such as by moving our corporate headquarters to Cedar Knolls and subleasing part of our more expensive scientific space in Tarrytown. We have also put in place the necessary scientific processes to improve rigidity and reliability of data, and have re-evaluated our eligen technology.

Q: What can you tell our readers about your eligen delivery platform?

A: Emisphere's eligen technology improves the body's ability to absorb select molecules, leading to significant, not merely incremental, improved oral bioavailability. Emisphere's synthetic chemical carriers provide a demonstrated safe method of chaperoning molecules across biological membranes, such as those of the gastrointestinal tract, without impacting their benefit. The main properties that we are interested in seeing in the drugs that we use with eligen are water-soluble drugs that have poor permeability characteristics that are the small- or medium-size molecules with a weight of less than 10,000 or 10 kd. The eligen technology can be applied to the oral route of administration as well other delivery pathways, such as buccal, rectal, inhalation, intra-vaginal, or transdermal. One of the first things I did when taking the helm at Emisphere was to reassess our technology. That reassessment convinced us that, when it is applied properly, the technology can be life-changing for many patients and bring enormous benefits to healthcare treatment. The eligen delivery system can enhance overall healthcare, including patient accessibility and compliance, while benefiting the commercial pharmaceutical marketplace – and driving our company's valuation.

Q: Can you give us an example of an application of your eligen technology?

A: In early February, Emisphere announced the results of animal studies that demonstrated proof-of-concept that absorption of oral vitamin B12 using Emisphere's eligen technology was 15 to 30 times greater than with the same dose of oral vitamin B12 administered alone. In March, we released the results of a second phase of animal studies demonstrating that our eligen technology enhanced the absorption of oral B12 at considerably lower doses than the previous study and, most importantly, at levels that are more physiologically relevant. Confirming the original study, overall absorption of B12 using eligen technology was 18 times greater than with the same dose administered alone. Simply put, oral delivery of Vitamin B12 using eligen technology is more efficient, more convenient, and less costly than B12 injections. Vitamin B12 deficiency is a significant health issue. Nearly 40% of the US population is B12 deficient, according to research done by Tufts University in Boston. This includes a sizable number of patients who are severely deficient and are currently being treated. Further, a vast number of people are completely unaware that they are B12 deficient and will eventually need treatment. Currently, some 5 million people in the US are taking more than 40 million injections of B12 per year to treat a variety of debilitating medical conditions, which can include pernicious anemia, neurological changes, fatigue, weakness, and other symptoms. Another 5 million are consuming more than 600 million tablets of B12 orally. And the worldwide market is, at least, double these numbers.

Q: What other products are currently in your pipeline?

A: Prioritizing our pipeline for products most likely to succeed with highest return represents the core of the company's value proposition and creates significant opportunities for growth. This includes marquee products that demonstrate the most promise through unmet market needs. Emisphere's pipeline includes product candidates that are in, or have reached, clinical development and a variety of preclinical research and development programs, both independently and in collaboration with major pharmaceutical companies. In addition to an improved formulation of oral Vitamin B12, which I've discussed, promising marquee products in the pipeline include oral Salmon Calcitonin for osteoarthritis and osteoporosis, currently in development with Novartis Pharma AG and its development partner Nordic Bioscience. Novartis is conducting two Phase III clinical studies for osteoarthritis, with enrollment in the first trial to be completed by the third quarter of 2008 and enrollment for the second Phase III trial to be complete mid-2009. Osteoporosis Phase III trials are also ongoing, with enrollment completion expected in the first half of 2008. Among these Phase III studies, there will be more than 5,000 clinical study patients using the eligen technology in 2008. Approximately 10 million Americans are being treated for osteoporosis, with an additional 34 million at risk of developing the disease because of low bone mass. In addition, about 21 million Americans have osteoarthritis. Our Salmon Calcitonin product could be the first disease-modifying treatment ever available to treat osteoarthritis. In addition to oral Vitamin B12 and calcitonin, we are conducting early research using our eligen technology and GLP-1, a potential treatment for type 2 diabetes. A second, early stage human study of an oral formulation that combines PYY and GLP-1 has commenced. We expect publication of the first study in medical journals sometime mid-year, with the results from the second study available to the public around the same time. We are confident that our current pipeline presents us with numerous opportunities to explore and exploit our technology, which we intend to do to the fullest.

Q: How would you characterize your strategy for ensuring the company's financial health and viability for the future?

A: Among our primary strategies is to establish and pursue products for internal commercial development against reasonable investments. In terms of our product development criteria, we are looking at large markets (greater than $1 billion) in which we can address unmet medical needs through clearly differentiated product profile benefits. We also maintain a commitment to enhancing existing high-value partnerships with leading pharmaceutical companies as well as forming new ones. These collaborations will not only bolster our pipeline development, but will also improve the company's overall financial position. We believe that as we move forward and get closer to realizing the commercialization of our technology, our stock price will reflect a higher value, while we make a substantial impact on the future of drug delivery. ◆

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Genzyme Pharmaceuticals

Protein & Peptide Contracting

What You Need to Know About Hiring a Contractor

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

Contract Manufacturing Organizations (CMOs) and Contract Research Organizations (CROs) have gone through a nip-tuck of sorts to present a new face to Specialty Pharma — that of biotech expert. A 2008 Buttefire.com article reports that biotechnology has become a particular focus area for CMOs as the number and variety of new biotechnology-based drugs, moving rapidly out of development and through the final phases of clinical trials into full-scale production, continues to grow.

According to the market research report Global Protein Therapeutics Market Analysis, the Protein Therapeutic Market was valued in excess of $57 billion in 2006 and could grow at a CAGR 12.83% up to 2010. The market is presently dominated by monoclonal antibodies, and insulin, interferon beta, G-CSF, and coagulation factors are also exhibiting double-digit growth rates. One of the biggest opportunity areas will be in biogenerics, which is expected to create a multibillion dollar market.

Additionally, the peptide market is growing nearly twice as fast as that for all other types of pharmaceuticals due to the increased number of therapeutic targets and improved delivery methodologies. There are 67 therapeutic peptides on the market, 150 in clinical phases, and 400 in preclinical stages. The market size for 2007 is estimated to be $3 billion.

Specialty Pharma magazine recently asked some of today's leading contractors to describe this new landscape and how they are working with Specialty Pharma clients to deliver these new products to the market quickly and cost efficiently. Participants in this group are: Gary Hu, Vice President Sales and Marketing, American Peptide Company, Inc.; Rodney Lax, PhD, Director of Sales and Marketing, PolyPeptide Laboratories Group; and Torsten Woehr, PhD, Director, Commercial Development, Genzyme Pharmaceuticals.

Q: *How are you accelerating product development for your protein/peptide clients?*

Dr. Lax: The most important things a peptide CMO can do to support product development for its customers is be flexible, respond quickly, and not cut corners. We accelerate product development by providing our clients with peptide-based APIs in the quantities and quality that they require for pharmaceutical development. This actually involves a number of different services that have to be coordinated. The development of a robust, scalable, and economical manufacturing process might seem to be the most obvious contribution of the CMO, but the input from analytical development during pre-GMP and initial GMP campaigns as well as providing a fully compliant GMP environment ensures a smooth progress through clinical trials and approval.

We are seeing significantly more complex peptides entering clinical trials. Peptides with sequence lengths exceeding 40 amino acids or with multimeric structures are becoming quite common. Without an appreciation of the analytical and manufacturing issues associated with such structures, it is easy to overlook issues that need addressing whilst the project is in its development stage.

It is imperative that customers developing peptide therapeutics receive proper guidance on what the FDA (or other regulatory authorities) will require, and that the associated services are conducted at the proper time. The Regulatory Authorities will be looking critically at these GMP issues when a customer makes their submissions, and going back and redoing these exercises later can be extremely costly and time-consuming, and in some cases, can result in the failure of a project.

Mr. Hu: American Peptide Company has been a leading manufacturing partner for peptides and peptide conjugates for the past 20 years. Our Total Peptide Management™ services support clients in the drug development process from preclinical through commercial stage. Our value-added services include process development, analytical/process validation, method validation, stability studies, CMC, DMF, and regulatory support. In addition, we work closely with our customers to build a strong relationship to serve as an extension of their needs in the area of API manufacturing. This would include supplying peptides for their R&D, process development, preclinical, and clinical needs.

Dr. Woehr: Through Genzyme Pharmaceuticals' peptide custom manufacturing expertise and close collaborations with Mimotopes and Brookwood Pharmaceuticals, we are able to offer a full set of services designed to accelerate product development at every development stage from discovery research to commercial manufacture of finished product. This turnkey approach is integral to our strategy of supplying every link in the peptide chain and differentiates us from other custom peptide manufacturers. Mimotopes offers more than 20 years of industry experience in proprietary peptide library synthesis technologies for hit-to-lead optimization studies. On the other end of the pharmaceutical value chain, Brookwood Pharmaceuticals is a leading peptide drug delivery company with proprietary injectable microparticle and implant technologies. Our peptide customers appreciate the option of accessing the full range of this integrated service platform for the development of sophisticated peptide APIs with optimized stability, solubility, formulation compatibility, and dosing regimen.

Q: *What should clients understand about working with you throughout technology transfer?*

Mr. Hu: We foster open communication with our clients through regular teleconferences and meetings. The manufacturing process is controlled with in-process sampling in which critical process parameters are monitored. Manufacturing is performed under strict adherence to FDA regulations 21 CFR, parts 210 and 211. Our quality system, controls, and procedures are strictly followed and thoroughly documented during manufacturing by our trained staff of highly qualified/experienced specialists. Quality Control subjects the final bulk peptide drug substance to a battery of analytical tests to ensure the delivery of consistent, well-manufactured, pure pharmaceutical-grade peptides.

Dr. Woehr: At Genzyme Pharmaceuticals, we handle questions around process IP and tech transfer in a very flexible manner. In general, we provide our clients with informational copies of our batch records under a CDA and are open to negotiating process tech transfer rights.

Dr. Lax: Tech transfer of GMP manufacturing processes from client to CMO or vice-versa is not that common. Obviously, no CMO wants to duplicate efforts, so we are very open to learning from the customer what they have already been able to achieve in terms of synthesis or purification, but this type of transfer is usually in a pre-GMP environment and really does no more than build the basis for establishing an initial strategy for the GMP process. If the project is still at an early phase, we will do our best to optimize the synthetic procedure for large-scale GMP manufacturing with the intent to develop a robust, scalable, and economic synthetic process. We will share any improvements we make with our customers in an open manner.

On the other hand, tech transfer of GMP analytical procedures occurs more frequently because either the client already has a satisfactory method in place or the CMO needs to transfer the methods to the clients fill/finish facility or other contract partners. What one should be aware of is that the tech transfer of analytical methods requires close interaction of both the innovator and the recipient. The sooner the two parties cooperate, the smoother the transfer will be. Slight differences in equipment or in-house resources can lead to significant differences in analytical results.

Q: *What quality & regulatory issues come into play with proteins & peptides?*

Dr. Lax: We only manufacture peptides. The main issue right now is definitely that of the impurity profile. Current guidelines in the US exclude complex peptides. But what is a "complex" peptide? Certainly a tetrapeptide could be considered to be a small molecule, but a 40-mer with over 1012 potential impurities? What is needed is a set of guidelines that address the issues of complexity and the phase of clinical development.

With no guidelines in place, some clients are applying small molecule guidelines to more complex peptide sequences. The result will be that potentially interesting and safe drugs may not reach the market due the costs of trying to meet commercially unachievable and potentially unnecessary specifications.

Mr. Hu: Quality of the peptide at my company is controlled throughout the entire manufacturing process. High-quality raw materials are purchased from qualified vendors and carefully evaluated by testing each item by quality control and released by quality assurance prior to use in manufacturing. Setting the standard for purity from preclinical to GMP, American Peptide works with clients to match their needs at their stages of drug development. We assist our clients in addressing regulatory questions as related to the manufacturing process for purity, chemistry, manufacturing process, analytical testing, and controls. In addition, American Peptide provides services and helps in performing API and final product stability; process validations; and DMF filings and prepares and completes CMC sections for our client's FDA/regulatory filings. In the past 4.5 years, American Peptide has had 3 FDA routine inspections with no reported 483s.

Dr. Woehr: The regulatory requirements for synthetically produced peptides are very similar to those for classical small molecules. However, the FDA and EMEA recently published new guidelines proposing more narrow limits for related substances, which could mean additional challenges from an analytical point of view. Accordingly, peptide-related impurities above 0.2% should be minimally identified and characterized; those above 1.0% require full identification and characterization.

Q: *What is today's trend in protein/peptide manufacturing?*

Mr. Hu: From the research market, High Throughput Screening (HTS) using peptide arrays and peptide libraries have been in high demand for discovering leading compounds. For process development, route scouting in synthesis and purification optimization will enable higher yields for peptides moving into large-scale production. Scale-up solid-phase and solution-phase peptide synthesis and organic conjugations to proteins and PEG are the trend with customers moving from preclinical to Phase I, II, and III stages. Modifications to peptides such as PEGylation, Glycosylation, and Phosphorylation are also common in today's peptide manufacturing.

Dr. Woehr: The number of peptide therapeutics in development is growing again. The discovery of naturally occurring peptides with interesting properties, advances in peptide delivery technologies, and lower production costs made this revival possible. Standard amino acid derivatives, the raw materials for peptide manufacturing, nowadays can be purchased on the global market at much lower prices than a decade ago. On the other hand, we see a trend to longer peptides, often containing difficult sequences that may cause aggregation, insolubility, and ultimately poor product yields. We address this problem with in-house produced, peptide solubilizing pseudo-prolines and dimethoxy benzyl (Dmb) building blocks. The use of these new peptide backbone protection groups results in crude peptide material with higher yield and improved purity. We find that the cost for these high-value building blocks is easily compensated by simplified purification protocols for the final peptide API.

Dr. Lax: In terms of peptide-based drug substances, we have been seeing a continued increase in interest since 2003, and we expect this to continue. Peptides are generally considered to be very safe drug substances because they are rapidly degraded into naturally occurring building blocks and metabolites. Moreover, because most peptide drugs (unlike small molecules) are based on naturally occurring sequences, evolution has had ample time to ensure high selectivity, thereby reducing the risk of unanticipated side effects. However, most peptides cannot be taken orally, so drug delivery devices and LAR formulations are required to ensure effective and compliant usage. We expect to see an increasing number of advances made in this area.

Q: *Are you a proponent of design for delivery when it comes to protein/peptide delivery? Why or why not?*

Dr. Lax: Well, yes and no. We certainly recognize that some sequences and motifs in peptides cause problems in terms of manufacturing and stability of the final drug substance/product and wish that the client had maybe chosen another sequence. However, focusing too closely on "easy-to-make" sequences at the start of a project may mean missing the best lead candidate.

If you are going to design your own peptide, you might try avoiding using really exotic amino acids, which are not commercially available from more than one vendor in large quantities. When you move to large-scale GMP manufacture, sourcing these may throw your project back a year or so, and they are unlikely to ever become economic commodities. You should recognize that longer peptides (above 35 amino acids or more) are going to be a challenge in terms of controlling impurity profiles. Also remember that peptides coming from a non-GMP environment generally look purer than they are because there is limited analytical development and may be capable of being manufactured in higher yields because at small scale, the concentrations of starting materials and reagents are not representative of what would be economically possible at large scale.

Dr. Woehr: We are a strong proponent of designing peptides not only for potency and molecular target selectivity, but also for delivery. Considering the delivery aspect early in peptide drug development may improve the peptide's drugability and shorten its overall development time.

Genzyme Pharmaceuticals entered into collaboration with Brookwood Pharmaceuticals, a drug delivery company whose scientists have experience formulating peptides for long-acting parenteral formulations using biodegradable PLG polymers to achieve systemic and site-specific delivery for days, weeks, and months following a single administration. The result of the collaboration is a formulation service tailored to screening and optimizing peptide properties for drug delivery known as the Design for Peptide Delivery℠ program.

Chemical modification of peptide APIs may improve their compatibility with a given delivery system and thus its drugability. However, such chemical modifications may impact selectivity and/or potency of a peptide drug. Chemical modifications for rendering

peptides more suitable for formulation therefore need to be evaluated during lead optimization. Physical and physico-chemical modifications on the other hand are less disruptive and can be screened for formulation compatibility post candidate selection. A typical example is the screening of alternative salt forms.

Mr. Hu: We support customers in a consultative manner in regard to design for delivery of peptides. From early stage, our Total Peptide Management™ program assists researchers to design peptide sequences within their parameters in consideration of stability issues and down stream scale-up difficulties due to the nature of the peptide sequences.

Q: *What challenges is the industry currently facing?*

Dr. Woehr: Lengthy FDA approval processes and the complexity of treatment lead to costly development programs that force many companies to face financial consequences before their ideas come to fruition. Another industry challenge is the delivery of a complex, and sometimes unstable, molecule that is otherwise efficacious.

Mr. Hu: The demand for peptide APIs exceeds the supply. The industry recognizes this demand and is steadily increasing its capabilities and improving production efficiencies to help meet the clients' needs for process development, preclinical and clinical development, formulation, and timing for product delivery. The challenges that the industry recognizes can be divided into two areas. The manufacturing of peptide APIs can be a very complex process with many steps, in which understanding detail and quality are needed to prevent deviations resulting in loss of quantity and quality. Second, is that the procurement of specialty raw/starting materials may be difficult to obtain within a reasonable time frame.

Q: *What typical hurdles are clients seeking your help in overcoming?*

Dr. Lax: Our clients have lead candidates that they want to develop into drugs. We help them by manufacturing these in the quantities and quality required for pharmaceutical development and regulatory approval.

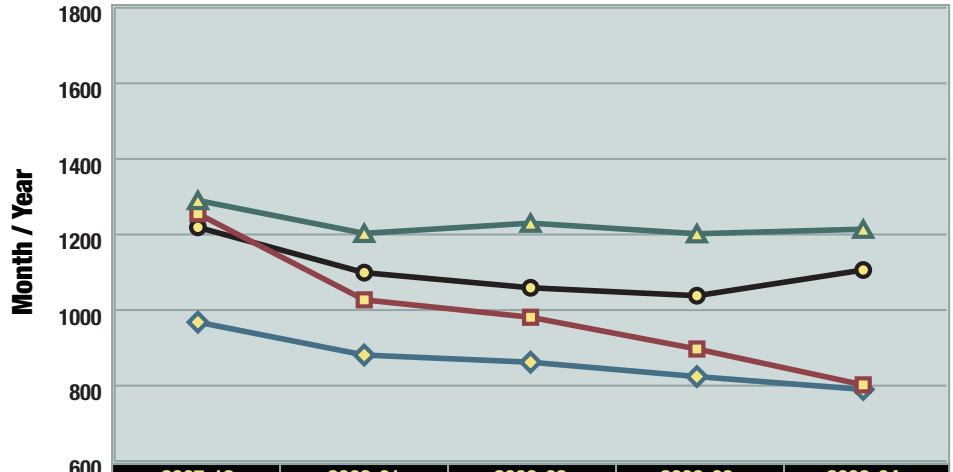
Dr. Woehr: We see an increased demand for fatty acid or lipid-conjugated peptide drugs. Such conjugates are known to have superior serum stability, extended circulation times, and in some cases, may facilitate passive transport through the membrane bilayer. Genzyme Pharmaceuticals draws upon extensive experience in lipid chemistry for the development of economical manufacturing processes for such peptide conjugates.

Mr. Hu: Clients choose American Peptide Company for help in process development, solubility, counter ion selection, and stability issues in large-scale production as well as for regulatory support. We also understand that timely delivery of the API can significantly cut costs and save the client money, which can also help with drug-to-market timing. Clients return to us for quality, consistency, and to continue our valued customer relationship. APC enjoys helping and being a partner with our clients to bring drugs to the market in an economical and efficient manner. ◆

Facts & Figures

For index methodology and more detailed analysis please visit www.bionumbers.com

Bionumbers Composite Index



*The indexes refer to Market Capitalization rather than Share Price

	2007-12	2008-01	2008-02	2008-03	2008-04
CSPI	1,290	1,203	1,230	1,202	1,214
ESPI	1,255	1,027	981	897	802
DDI	968	881	862	824	790
NASDAQ	219	1,099	1,059	1,038	1,106

Index Value

CSP Index Value: 1214 | Change YTD: -5.9% | Change M/M: +1.0% | Total Index Capitalization: $51.0 Billion

Top 5 Capitalizations YTD Change		
Shire	$10.9 Billion	-15%
Hospira	$6.6 Billion	-2%
Warner	$4.5 Billion	0%
Perrigo	$3.7 Billion	+12%
Endo	$3.3 Billion	-9%

Top 5 Gainers YTD Change	
Millbrook	+340%
Encysive	+181%
Collagenex	+75%
Avanir	+71%
Draxis	+47%

Top 5 Laggards YTD Change	
Ista	-59%
Barrier	-38%
Indevus	-33%
Angiotech	-33%
Alkermes	-29%

ESP Index Value: 802 | Change YTD: -36.1% | Change M/M: -11.0% | Total Index Capitalization: $2.2 Billion

Top 5 Capitalizations YTD Change		
Nektar	$424 Million	-32%
Durect	$348 Million	-27%
Pain Therapeutics	$310 Million	-34%
Cadence	$267 Million	-38%
Alexza	$219 Million	-13%

Top 5 Gainers YTD Change	
Acusphere	+7%
Catalyst	+6%

Top 5 Laggards YTD Change	
Keryx	-94%
Elite	-65%
Epicept	-58%
Spectrum	-39%
Cadence	-38%

DD Index Value: 790 | Change YTD: -18.4% | Change M/M: -4.1% | Total Index Capitalization: $8.9 Billion

Top 5 Capitalizations YTD Change		
Biovail	$1.7 Billion	-20%
Alkermes	$1.1 Billion	-29%
Surmodics	$821 Million	-18%
Eurand	$738 Million	+6%
Halozyme	$444 Million	-20%

Top 5 Gainers YTD Change	
Labopharm	+94%
Momenta	+60%
Acura	+50%
Psivida	+9%
Acusphere	+7%

Top 5 Laggards YTD Change	
Vyteris	-74%
CytRx	-69%
Elite	-65%
Emisphere	-43%
Nastech	-41%

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Executive Summary

Nancy Gray
Vice President of Corporate Development
Southern Research Institute

Southern Research Supports Drug Discovery & Development

By: Cindy H. Dubin, Contributor

Southern Research Institute is a not-for-profit center for scientific research, affiliated with The University of Alabama at Birmingham. Founded in 1941, Southern Research is known for being a leader in preclinical drug discovery and development. Public and private sector clients include the National Institutes of Health as well as major companies in the pharmaceutical and biotechnology industry. In 2005, Southern Research created Brookwood Pharmaceuticals, a wholly owned drug delivery company that provides proprietary technologies and formulation services to pharmaceutical and biotechnology clients seeking delivery methods that will enhance or extend the market opportunity of their therapeutic compounds. The company was sold to SurModics, Inc. in 2007. Today, Southern Research has technical research divisions focused on Drug Discovery and Drug Development. The company leads major international screening programs for emerging infectious diseases, such as SARS, hepatitis, West Nile, and influenza, including the H5N1 Avian flu virus as well as biological pathogens, such as anthrax, tularemia, and smallpox. The Drug Discovery Division at Southern Research received $11.6 million to establish one of nine non-government centers in the Molecular Libraries Screening Center Network, part of the NIH Roadmap Initiative to expedite the discovery of new drugs. The company has also developed the protocol for combination chemotherapy and developed chemical agent monitoring and detection systems that have served as the industry standard for years. Nancy Gray, Vice President of Corporate Development for Southern Research recently spoke with Specialty Pharma magazine about how the Drug Discovery and Development divisions have worked to discover, screen, and develop new drugs and vaccines for cancer, HIV, hepatitis, tuberculosis, influenza, central nervous system diseases, and neurological disorders.

Q: ***What accomplishments have your company achieved in the past year?***

A: With six FDA-approved drugs and another six compounds in late-stage preclinical and early clinical development, Southern Research continues to demonstrate value to its partners in the search for tomorrow's breakthrough discoveries. Since its founding in 1941, Southern Research has evaluated approximately 50% of all FDA-approved cancer drugs and tested 75% of the anti-viral drugs. Southern Research offers joint discovery programs with out-licensing of clinical candidates and a comprehensive array of drug development services, including medicinal and combinatorial chemistry, high-throughput screening, molecular and cellular biology, lead optimization, ADME/PK, toxicology, and clinical pharmacokinetics. Perhaps most notable in 2007 was the sale of our spin-out company, Brookwood Pharmaceuticals, to SurModics, Inc. Brookwood, as stated earlier, was created in 2005 from the Pharmaceutical Formulations/Drug Delivery group within Southern Research Institute.

Q: ***Could you tell us more about Southern Research's cancer research?***

A: The discovery of small molecule cancer chemotherapeutic agents has been a major focus of Southern Research's Drug Discovery Division for more than 45 years. Southern Research evaluates hundreds of compounds as anti-cancer agents for government, large pharmaceutical companies, biotechnology companies, universities, and foundations. And because of this, we have worked with every mechanistic class of anti-cancer agents. With six FDA-approved drugs and another six compounds in late stage development, Southern Research's track record in early drug discovery continues to grow. Currently, six new, important cancer compounds are in late stage preclinical and early clinical trials due to Southern Research. Southern Research offers a variety of services and capabilities, including:

- A proprietary library of 10,000 compounds, one of the largest collections of nucleosides in the world;
- Hollow fiber assay services, which allow scientists to evaluate anti-cancer agents against multiple tumor cell lines, in the same animal, with results in just 10 days. This model is referred to as a "test tube in a mouse;" and
- An Angiogenesis Program: screening services to explore pro- and anti-angiogenic activities in compounds to support the development of angiogenic regularly compounds. Angiogenesis is the process of forming new blood vessels. Southern Research's Angiogenesis Research Program provides insight into understanding mechanisms of tumor progression and metastasis. The studies have revealed important proteins as targets for angiogenesis and identified several compounds with potent anti-angiogenic activities.

The Cancer Therapeutics Department at Southern Research has been involved with numerous National Cancer Institute (NCI) grants and contracts throughout the years either as principal investigator or core laboratory.

Q: ***What are the strengths supporting the company's growth and business development?***

A: We have a very unique business model: part academic or basic research and part contract research organization. Combined, we cover the full spectrum in drug discovery and development research. And because of our experience, track record, and business model, we are a team that is very much focused on translating basic research and moving promising drug candidates to market. This is something we've done for decades.

Q: ***What should compel investors to include Southern Research as part of their investment strategy?***

A: Southern Research is an organization with a great deal of success in evaluating successful drug candidates and in evaluating successful business ventures, such as the creation, spin-out, and sale of Brookwood Pharmaceuticals. We anticipate that future new initiatives within Southern Research may generate opportunities for investors to fund specific projects or programs. We also believe we have a unique understanding of the life sciences marketplace, which could be of value to biotech and pharmaceutical investors. In addition, we continue to accept donations as part of our endowment fund to support basic drug discovery research.

Q: ***What are some of the challenges Southern Research faces going forward, and what are the future possibilities?***

A: We are vulnerable to the same types of challenges other not-for-profit research organizations and even commercial businesses face, which is that of increasing competition in an environment of decreasing funding opportunities. Still, we are inspired by the success of our Brookwood Pharmaceuticals spin-out, and we are actively looking for innovative ways of replicating that kind of success, while also looking to capture more value from our intellectual property development. We believe the future is full of possibilities. ■

Oncology Therapeutics: A New Solution for Anthracycline Extravasation

By: Lisa Schulmeister, RN, MN

Introduction

Anthracycline chemotherapy drugs are commonly used to treat breast cancer, lymphoma, and leukemia. This drug classification includes doxorubicin (Adriamycin), daunorubicin (Cerubidine®), epirubicin (Ellence®), and idarubicin. Anthracyclines are administered intravenously into the forearm or a central venous access device, such as an implanted port.

A unique complication associated with anthracycline chemotherapy drugs is severe tissue damage that occurs when they leak from the vein or are inadvertently administered into the tissue. Leakage into the tissue is called extravasation.

The incidence of anthracycline extravasation is unknown, although estimates range from 0.01% (one in 10,000 patients) to as many as 6% of patients.[1] When an anthracycline extravasation occurs, tissue damage begins to occur within days and progresses over time. Patients often require surgical intervention to remove the dead tissue, and many are permanently disabled and disfigured (Figure 1). Surgical intervention typically requires delay or discontinuation of the patient's chemotherapy treatment, which increases the risk of disease progression or recurrence.

Extravasation has been recognized as a potential complication of chemotherapy administration since the 1970s, when anthracyclines entered the marketplace. The severity of this complication prompted the search for effective anthracycline extravasation treatments. Various local treatments, including topical cooling, injection of anti-inflammatory agents, application of dimethyl sulfoxide (DMSO), and others have been studied for nearly 4 decades, but none has been effective in preventing tissue necrosis from occurring when anthracyclines inadvertently extravasate into the tissue.[2]

TopoTarget, a biopharmaceutical company headquartered in Denmark, was founded in 2000 by practicing clinical oncologists. TopoTarget's research focuses on key cancer enzyme regulators, such as topoisomerase II inhibitors, histone deacetylase (HDAC), and mammalian target of rapamycin (mTOR). TopoTarget researchers discovered that intravenous dexrazoxane, a topoisomerase II inhibitor and iron chelator, prevented anthracycline tissue damage in a mouse model. Subsequent preclinical studies determined that the effectiveness of dexrazoxane is dose- and schedule-dependent.[3]

Clinical Efficacy

Two multicenter clinical studies were conducted in Europe to determine if dexrazoxane treatment would reduce the need for surgical intervention following anthracycline extravasation. Unlike previous studies of extravasation treatments, patients in these studies had anthracycline extravasation confirmed by tissue biopsy. Eighty patients were enrolled in the studies, and 57 were evaluable (the majority of patients that were not evaluable had absent or negative tissue biopsies). Treatment was started as soon as possible and within 6 hours of the anthracycline extravasation, and patients received additional doses on days 2 and 3. Dosing is based on the patient's body surface

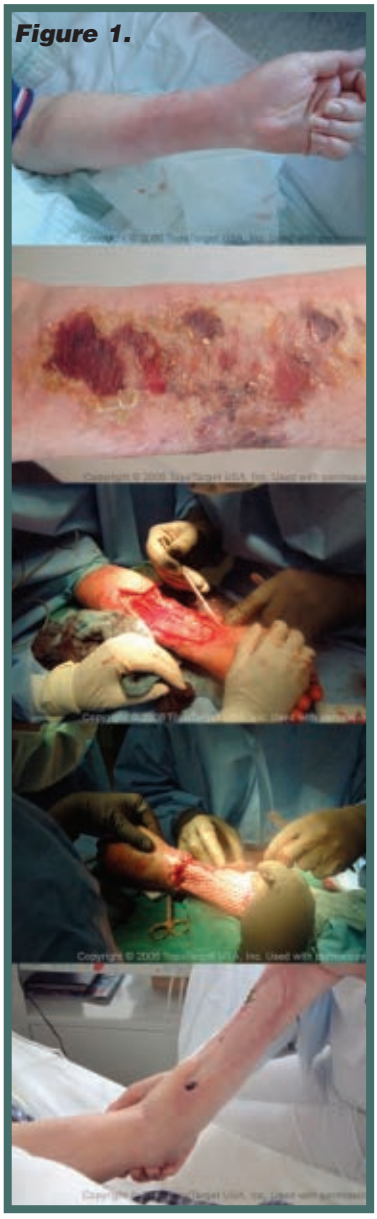

Figure 1.

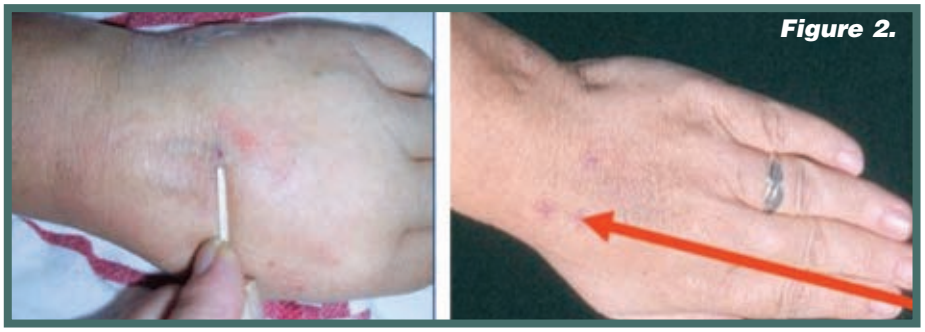

Figure 2.

Figure 3.

area, and the dose is reduced for patients with renal impairment. In the first study, none of the 19 evaluable patients required surgical intervention following biopsy-confirmed anthracycline extravasation, and none had late sequelae. In the second study, one of 38 evaluable patients and one non-evaluable patient required surgery for tissue necrosis (overall efficacy in the two studies is 98.2%). Thirteen patients had mild late sequelae that included infusion site pain, fibrosis, and local sensory disturbances. The majority of patients (72%) did not experience any delays in chemotherapy treatment.[4,5] Figure 2 shows an anthracycline extravasation prior to and following treatment. The patient's skin integrity remained intact, and surgical intervention was not required.

Marketing authorization of dexrazoxane (Savene™, TopoTarget A/S, Copenhagen, Denmark) as a treatment for anthracycline extravasation received European Commission approval in July 2006. The United States Food and Drug Administration approved Totect™ (dexrazoxane for injection, TopoTarget USA, Rockaway, NJ) in September 2007.

Totect is packaged as an emergency treatment kit for single patient use. The kit contains a complete 3-day anthracycline extravasation treatment (Figure 3).

Potential Market

Because the incidence of anthracycline extravasation is low, the population of patients expected to benefit from this treatment is considered small enough to be designated Orphan Drug qualified (population less than 200,000 patients per year). Both the European Commission and the FDA have designated Totect an Orphan Drug, which grants TopoTarget 7 years of marketing exclusivity.

Patients are at risk for extravasation every time they receive an anthracycline. The estimated number of anthracycline doses administered in 2006 was 500,000 (based on IMS USA usage data). Therefore, the total number of anthracycline extravasations in the US could range from 500 per year to 30,000 per year. It is expected that between 500 and 1000 Totect kits will be purchased per year.

Every patient who receives an anthracycline is at risk for extravasation. Although not all patients diagnosed with breast cancer, lymphoma, and leukemia receive anthracyclines, many do, and these patients are at risk for extravasation each time they receive an anthracycline. Breast cancer treatment protocols, for instance, typically include four to six anthracycline doses given over a 2- to 6-month period of time.

Before the introduction of Totect, patients frequently required surgical intervention and experienced significant sequelae following anthracycline extravasation. Healthcare providers and patients were understandably distressed whenever this complication occurred. Some patients alleged negligence, pursued legal action, and jury awards of half a million dollars were not uncommon. Further, many patients lost trust in their healthcare providers and sought care elsewhere.

TopoTarget has several drugs in development, including intravenous and oral belinostat, which is being studied in hematologic and solid tumors in Phase II clinical trials. Other drugs are valproic acid, administered topically for basal cell carcinoma and acne, and given orally for familial adenomatous polyposis. Totect is being studied in patients with brain metastasis and a total of nine drugs are in clinical development. In June 2007, TopoTarget acquired the Swiss biotech company, Apoxis SA (now TopoTarget SA). This acquisition further strengthened TopoTarget's pipeline and added protein chemistry expertise to the company's existing core competencies. ◆

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Ms. Lisa Schulmeister, RN, MN

Ms. Lisa Schulmeister has 30 years of oncology nursing experience and is an oncology-certified nurse. She earned her BS from Hartwick College in Oneonta, NY, and her Masters of Nursing from Louisiana State University in New Orleans. Ms. Schulmeister has written numerous peer-reviewed publications on chemotherapy extravasation and has lectured on this topic at regional and national meetings. She serves on the review boards of several biomedical journals and was inducted into the American Academy of Nursing in 2006.

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EXTERNAL DELIVERY

The Glamour of Flying

By: John A. Bermingham

Business air travel was glamorous and fun at one time. I think that it was before I was born. Throughout the past 2 weeks, I have been in Phoenix, Sedona, and Tampa. During those trips, I began to note all of the things that I hate about flying. So I developed a list of 10 things that drive me crazy when I am traveling on commercial airlines, all developed from personal experience.

THE TOTALLY UNPREPARED PERSON AT THE SECURITY CHECKPOINT: This is the person who waits until he is at the x-ray machine before he begins to untie his shoes, take off his jacket, unload the laptop into a bin, take out his baggie of 3-oz liquids, take off his watch and belt, and then initiates the search for his boarding pass.

BAG OVER THE SHOULDER: This is the person who carries his computer case or backpack over one shoulder while walking down the aisle to his seat. This person will manage to hit everyone the passes in the head or chest who occupies an aisle seat.

CARRY-ON TOO LARGE FOR THE OVERHEAD STORAGE BIN: This is the person who boards late and cannot find adequate room in the overhead for his suit case. He first mashes yours and others' suitcases around in order to pry open some space. Then, when he can't fit the bag into the bin sideways, he puts it in with the bag sticking out 6 inches from the edge of the bin, ensuring that the overhead door cannot be closed. He then takes his seat, leaving the problem of closing the overhead to the flight attendant.

ARMREST UP: This is the unfortunate person who is too large fit in a seat meant for small children. So he puts the armrest in the up position in order to share your seat with you. He becomes very indignant when you insist that the armrest be placed in the down position and that he squeeze himself into his own seat.

UNDER SEAT SPACE GRABBER: This is the person either seated in front of you or next to you who has placed his carry-on under the seat in front of you, leaving you no place to put your briefcase. This is generally done due to the person wanting to have open space in front of himself in order to stretch out his legs.

OBLIVIOUS PARENT WITH THE SPOILED BRAT CHILD: This is the child who warms up in the gate area by screaming at the top of his lungs running around uncontrolled by the parent(s). Once on the plane, the mega-brat's screaming gets louder punctuated by the word NO! The parent(s) of the mega-brat solve the problem by allowing the little darling to run around in the aisle causing unlimited pain and suffering to the passengers and flight attendants.

CELL PHONE SHOUTER/AISLE BLOCKER: This is the person who boards the plane while shouting into his cell phone. He attempts to put his bag into the overhead with one hand, shakes off his coat, appearing to be having a convulsion, works on removing his newspaper from his briefcase, and more — all because he will not release the cell phone from his other hand. He does this while standing in the aisle setting up a blocking position that stops the entire boarding process.

SEAT BACK GRABBER/FULL RECLINEER: This is the person who has zero leg strength. So when he stands up, he grabs the back of your seat, and sometimes your hair too, and pulls himself up with his arms bending your seatback way back. This normally happens when you have finally fallen asleep. This is the same person who, as soon as the plane takes off, puts his seat in full recline for the duration of the flight, causing claustrophobia for the person seated behind him.

SEAT TAPPER: This is the person sitting behind you who is nervous or listening to an iPod and continuously taps your seat with his foot. It will stop only when the flight attendant instructs everyone to shut their electronics down on the approach to landing.

CHATTY PERSON WITH GARLIC BREATH: This is the person who wants to talk the entire trip oblivious to the fact that you are trying to do work, read a book, or just sleep. I have found that normally this person also has eaten a garlic sandwich for breakfast.

I bet most or all of you have often experienced these same people when traveling. Ain't traveling grand! ◆

BIOGRAPHY

John A. Bermingham is currently the President & CEO of Lang Holdings, Inc., an innovative leader in the social sentiment and home décor industries. He was previously the President, Chairman, and CEO of Ampad, a leading manufacturer and distributor of office products. With more than 20 years of turnaround experience, Mr. Bermingham also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona Corporation, and Rolodex Corporation. He turned around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served 3 years in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes, earned his BA in Business Administration from Saint Leo University, and completed the Harvard University Graduate School of Business Advanced Management Program.

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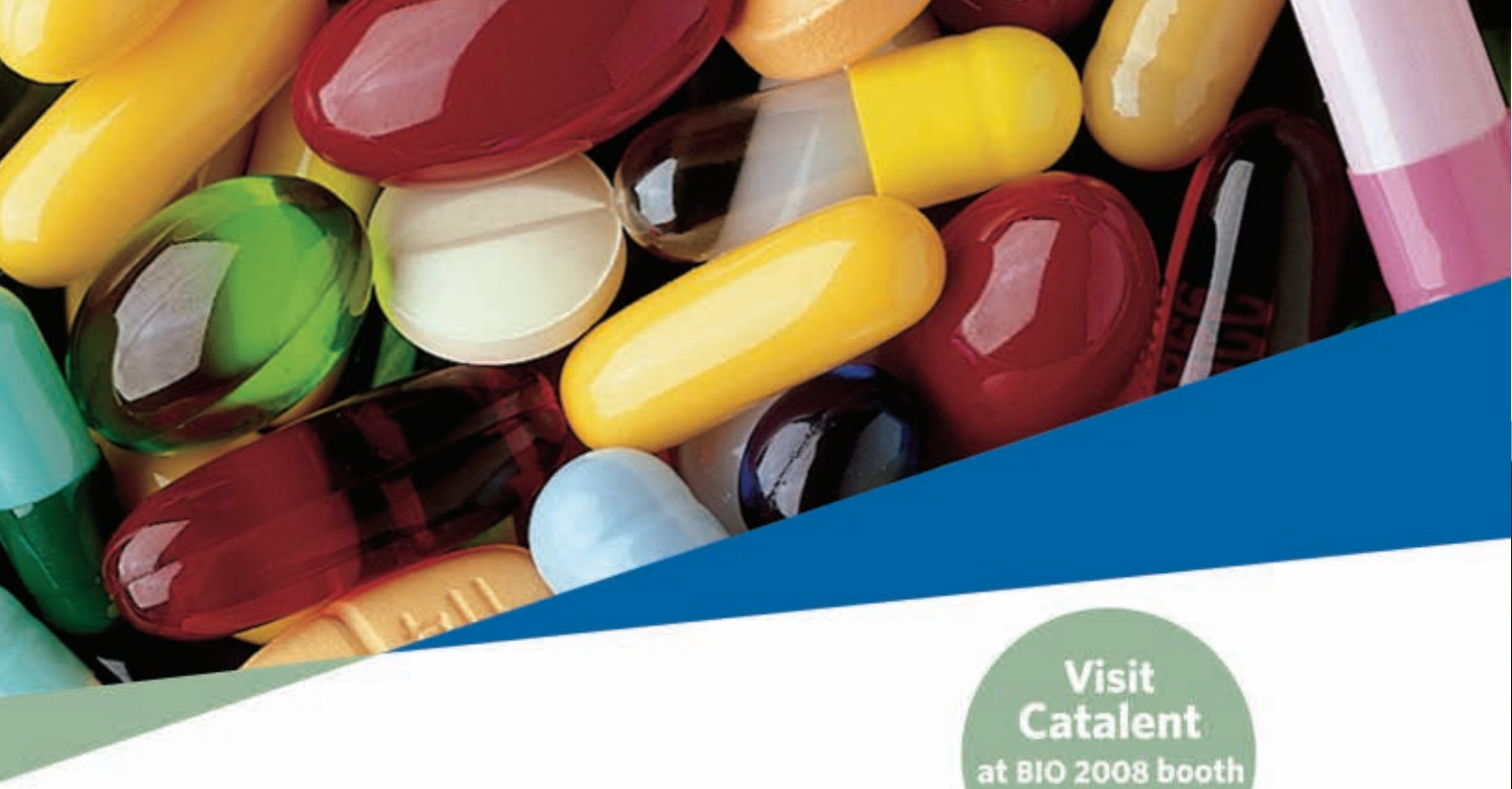

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