Drug Delivery® Technology

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The Future of Oral Thin Films

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

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FEATURING

SPECIALTY PHARMA
Strategies For Business Development

Insight®

Adhesives Research

Insight Into Controlled Delivery

Corporate Description

Adhesives Research (AR) is one of the world's leading independent developers and manufacturers of pressure-sensitive adhesive (PSA) systems, custom-coated products, and specialty films. Three of the company's divisions develop platforms for drug delivery and brand protection.

AR's custom development capabilities include polymer synthesis, adhesive mixing, compounding, coating, and release liner design, which are supported by analytical capabilities. The company integrates all of these capabilities to formulate and manufacture unique products to meet customers' specifications.

Our extensive analytical capabilities allow for the characterization and quantification of key product attributes during development and production of commercial materials. We maintain separate cGMP production facilities and follow applicable regulatory guidelines for the manufacture of oral and transdermal pharmaceutical delivery systems. Active drug master files are maintained and complete production records are accessible to support all clinical and commercial manufacturing requirements.

Facilities

- Six segregated cGMP manufacturing lines for adhesive mixing and formulation, coating, laminating, and slitting (Glen Rock, PA, and Limerick, Ireland)
- A new 25,000-square-foot stand-alone facility for thin film, transdermal, biopharmaceutical, and oral/mucosal manufacturing
- State-of-the-art manufacturing equipment to produce feasibility, stability, clinical, and commercial quantities
- Dedicated R & D facilities with analytical support
- Established quality systems and support to ensure compliance with 21CFR 211 and 21CFR 820 guidelines

Major Products/Markets Served

AR Pharmaceutical provides skin-friendly adhesives and laminates for transdermal patches. Among the company's portfolio of adhesive technologies are:

- ***Enhancer Tolerant Adhesives (ETA)*** — enable the use of skin permeation enhancers in transdermals
- ***Ethanol Resistant Adhesives (ERA)*** — retain their physical properties in the presence of ethanol (or other polar liquids) for balance of adhesion and cohesion
- ***Polyisobutylene Adhesives (PIB)*** — feature chemically inert, synthetic rubber chemistry for reservoir, matrix, and other transdermal drug delivery systems
- ***Skin Contact Acrylic PSAs*** — are customizable to include attributes such as wear time and peel strength
- ***Stabilized Silicone PSAs*** — provide chemistry that is synergistic with drug substances and conductive adhesives for drug delivery devices
- ***Dissolvable and Erodable Chemistries*** — can be tailored for oral or topical sustained release

ARx™ offers custom-developed dissolvable film and adhesive platforms for:

- ***Oral Drug Delivery*** — dissolvable and buccal technologies for both immediate- and controlled-release applications
- ***Transdermal Drug Delivery*** — dissolvable and adhesive systems for topical and systemic delivery
- ***Biopharmaceutical*** — novel cast platforms for large molecule transdermal delivery

ARmark™ Authentication Technologies develops anti-counterfeiting technology in the form of covert markers that can be combined with custom-developed delivery systems for application to a variety of goods including pharmaceuticals and packaging. The covert ARmark™ markers are identified via digital micro-imaging hardware and customized software programs. The use of covert authentication markers to enhance product surety can:

- Positively impact the validation and verification of genuine goods
- Help manage brand theft, trademark infringement, piracy, counterfeiting, and forgery

A Multidisciplinary Approach

Adhesives Research employs a multidisciplinary team approach to support the product development and technological needs of pharmaceutical, diagnostic, biotechnology, and medical device customers. In addition, the company offers extensive expertise in raw materials selection, formulation, cGMP manufacturing, and quality compliance – allowing customers to incorporate their functional ingredients into unique delivery systems.

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THE ADVANTAGES

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Multiple Release Profiles
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Higher Perceived Value
Consumers view multi-phase, multi-compartment capsules as having a higher perceived value than ordinary tablets, capsules and soft gels.

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

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

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

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

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

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

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

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

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

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

Compounds
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A Dissolvable Future

"The recent launches of multi-drug combination products are just the beginning in advancing the application of OTF technology. The future of dissolvable films lies in multiple pharmaceutical, biopharmaceutical, and medical arenas."

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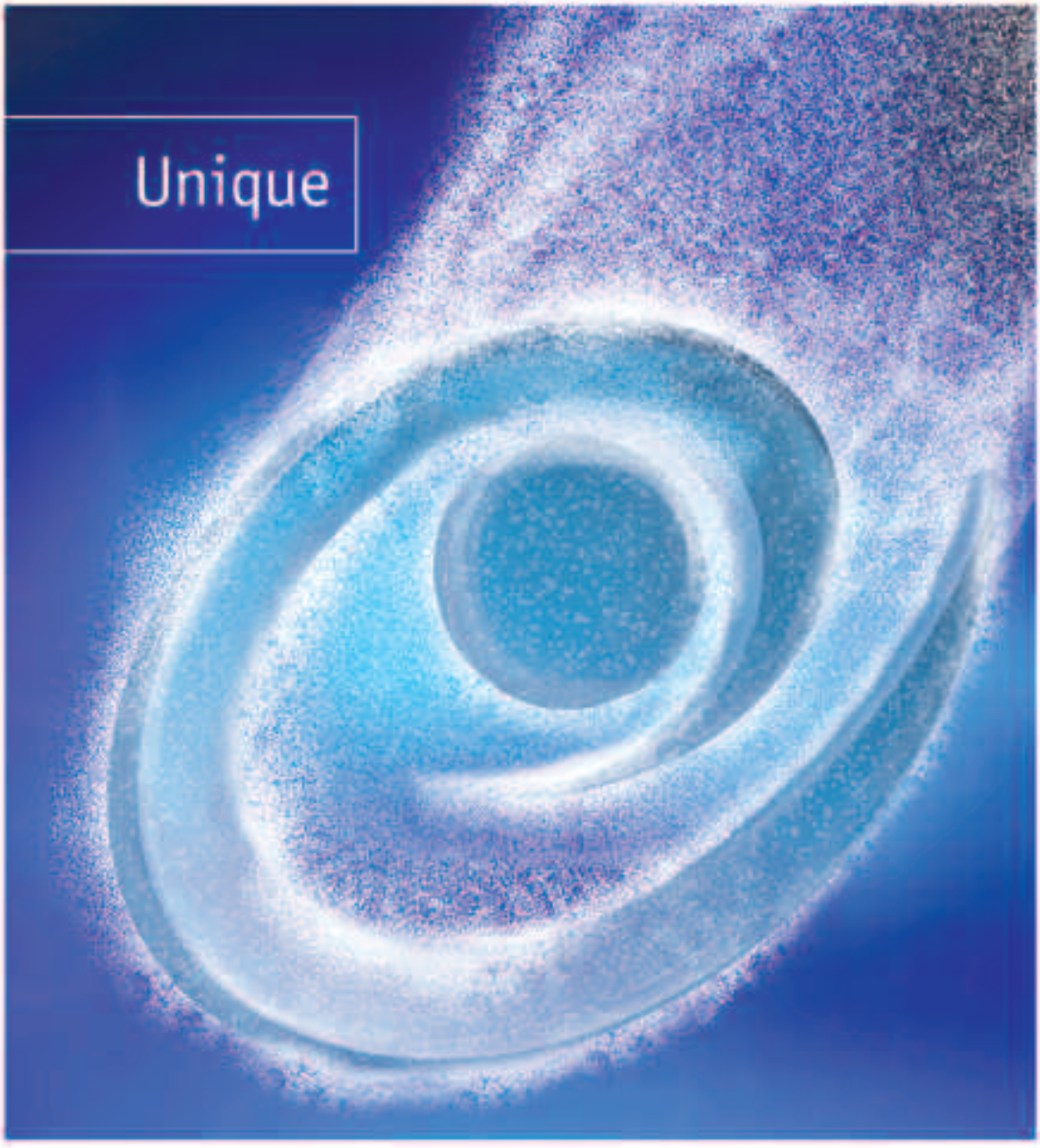

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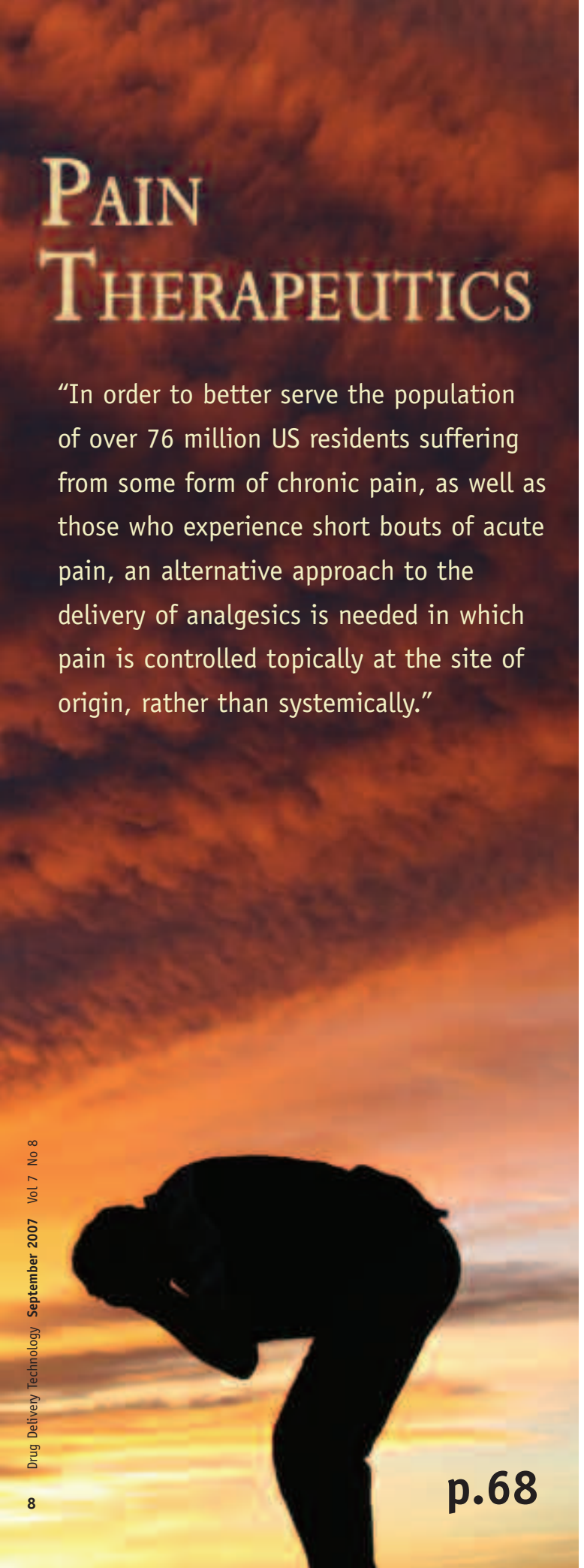

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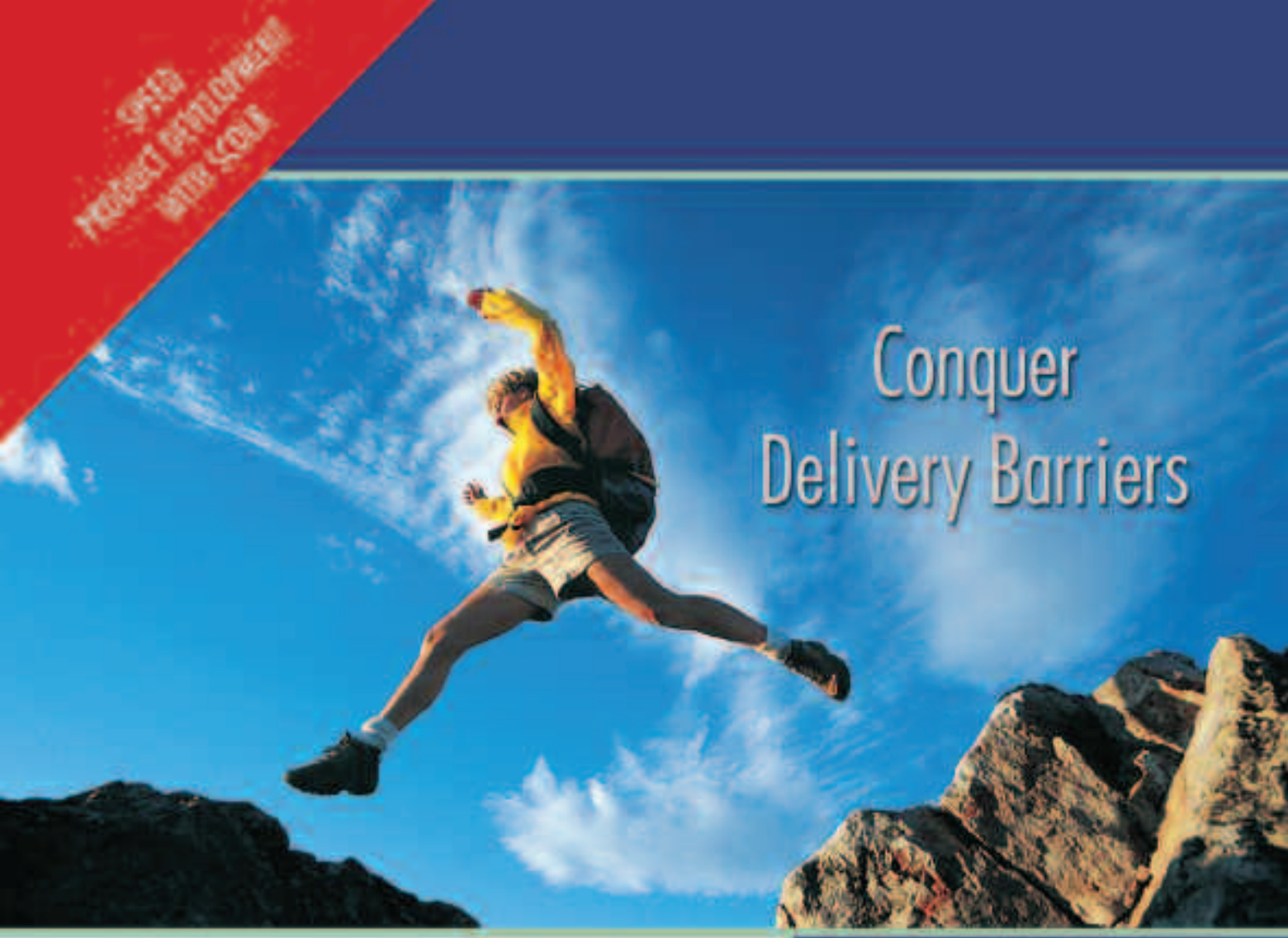

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Market News and Trends

Southern Research Institute Spin-out, Brookwood Pharmaceuticals, Acquired by SurModics for $62 Million

Southern Research Institute officials recently announced that the wholly owned drug delivery company it created in 2005, Brookwood Pharmaceuticals, has been sold to SurModics, Inc. for a package worth up to $62 million — $40 million in cash at closing and up to an additional $22 million in cash upon the successful achievement of specified milestones.

Brookwood provides proprietary polymer-based technologies to companies developing improved pharmaceutical products. The company's operations and its approximate 70 employees will remain in Birmingham, AL.

"We have been very impressed by the success Art Tipton and the entire Brookwood team has achieved in its short history as an independent company," said John A. Secrist, III, PhD, President and CEO of Southern Research Institute. "While we will miss having Brookwood as part of our extended organization, we are convinced that these two combined companies will be much more successful than they would apart. The Birmingham community has benefited from Brookwood's growth and presence, and we are very pleased that SurModics plans to retain Brookwood in Birmingham."

Secrist added that even in the very early discussions with SurModics, Southern Research officials asked that the acquisition be favorable to Brookwood employees, provide a real opportunity for Brookwood to grow, and that there was an opportunity for Brookwood to remain in Birmingham.

"This is a wonderful development for Southern Research, Brookwood, and Birmingham," said Carol Z. Garrison, PhD, Chairman of the Southern Research Board and President of the University of Alabama at Birmingham (UAB). "It speaks to the quality of the research pioneered at Southern Research Institute, as well as the Institute's fiscal health and strategic acumen."

"The support that Brookwood received from Southern Research, UAB, and the business community was consistent and enthusiastic," said Arthur J. Tipton, PhD, Brookwood's President and CEO. "Our roots are here in Birmingham, and I am excited about this transaction because it allows us to deepen those roots for Brookwood and its employees. I am equally excited that the moneys to Southern Research generated from this transaction — the most significant one-time payment in its 65 year history — will allow Southern Research to fund other bold initiatives to further its phenomenal history of innovation."

Bruce Barclay, President and CEO of SurModics, added, "We are very excited to welcome the employees of Brookwood Pharmaceuticals to SurModics . . . The combination of broader technology platforms and a broader customer base in several large markets helps fulfill several of our strategic objectives, including achieving greater diversification in our business."

Late in 2005, Southern Research spun out the organization's 30-year-old in-house Pharmaceutical Formulations group that focused on the development of time-release formulations for pharmaceutical delivery. At the same time, Brookwood acquired the Ohio-based external polymer manufacturing business of Alkermes, Inc., and began operating that business as a Brookwood subsidiary called Lakeshore Biomaterials, Inc. In the second quarter of 2007, Brookwood helped to create a new company, Aeon Biosciences, also based in Birmingham and included in this deal, which is working to develop a new cardiac stent.

"Our primary focus, since forming Brookwood, has been to use strong technologies and the skills of a talented staff to develop improved drug delivery products," said Dr. Tipton. "Our enthusiasm for this transaction is that it furthers what we in the combined entity can offer clients and expands opportunities to develop novel products."

Brookwood Pharmaceuticals will operate as a separate business unit of SurModics. Dr. Tipton will lead the team as Vice President of SurModics and President of Brookwood Pharmaceuticals, Inc. The company will remain in Birmingham. An important piece of Brookwood's business has been to supply biodegradable polymers through its subsidiary, Lakeshore Biomaterials, which will remain an important business focus in Birmingham.

Brookwood generates revenue from research and development fees, polymer sales, and royalty-generating licenses. The company generated $12.7 million of revenue in calendar year 2006, more than tripling the 2004 revenue earned while it operated as an in-house department within Southern Research. Since its spin-out, Brookwood has achieved strong year-over-year growth and, furthermore, Brookwood is profitable and cash flow positive. Brookwood's strength is in proprietary injectable microparticles and implant technology, both based on biodegradable polymer technology, to provide sustained drug delivery. The company currently has nearly 30 customer-paid development projects in progress from top pharmaceutical and medical device clients as well as smaller public and private companies. Customer projects target a number of key clinical indications in the diabetes, oncology, ophthalmology, cardiovascular, orthopedics, central nervous system, and alcoholism markets, in addition to other fields.

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Market News and Trends

Paladin & Glide Pharma Sign Exclusive Agreement for Novel Needle-Free Drug Delivery System

Paladin Labs Inc., a leading Canadian specialty pharmaceutical company, recently announced that it has entered into an exclusive license and distribution agreement with Glide Pharmaceutical Technologies Limited to develop and market Glide Pharma's innovative Glide SDI (Solid Dose Injector) needle-free drug delivery products in Canada. Under the terms of this agreement, Paladin will assume responsibility for local clinical trials, registration, marketing, sales, and distribution of at least three of Glide Pharma's pipeline products that include needle-free versions of sumatriptan, a leading migraine drug; octreotide, a peptide used in the treatment of acromegaly and neuroendocrine tumours; and fentanyl, a widely used pain medication used for breakthrough pain. According to IMS Canada, the combined markets for these three products exceeded $50 million in 2006.

"The Glide SDI provides tangible, important benefits to Canadian patients currently requiring daily injections. The ability to have needle-free versions of these gold standard treatments for migraine, acromegaly, and breakthrough pain will allow for better compliance and disease control. In addition, the Glide SDI mitigates needle-related complications, such as needlestick injuries and risk of cross-contamination," said Jonathan Ross Goodman, President and Chief Executive Officer of Paladin. "Glide Pharma's current pipeline of products nicely complements our existing pain and endocrinology portfolios."

"We are excited to be partnering with Paladin, a dynamic and creative company with a track record of successfully launching innovative pharmaceutical products in Canada," added Dr. Charles Potter, Chief Executive Officer of Glide Pharma. "The Glide SDI is ideally suited to the delivery of many drugs not only because of the simplicity of the device but also because of the enhanced stability and potential for controlled release of the drug when injected in a solid dosage form."

The two companies expect the first product under this agreement to be filed for Canadian regulatory approval in 2009. Financial terms of the agreement were not disclosed.

The Glide SDI is an innovative needle-free injection system that allows the delivery of drugs, vaccines, and other active pharmaceutical ingredients in a solid dosage form. The Glide actuator uses a spring mechanism to push solid drugs through the skin into the underlying tissue where they dissolve and are released into the patient's bloodstream. The device is simple to use, making it ideal for the self administration of drugs in the home environment. The system comprises a reusable, spring-powered actuator and a prefilled, disposable drug cassette. The used drug cassette can be disposed of with normal household waste and replaced with a fresh cassette holding the next dose. In the clinic, volunteers overwhelmingly stated that they preferred an injection with the Glide SDI to an injection with a standard needle and syringe.

Storing drugs in a solid dosage form typically makes them more stable and therefore refrigeration may not be essential, as is often the case with liquid formulations. The solid dosage form also enables immediate or controlled release of the drug into the blood stream, reducing the need for multiple injections. The Glide technology has the potential to generate substantial cost savings by eliminating the need to make arrangements for refrigerated storage of liquid drugs and for needle disposal, a major issue as 15 billion needles are used worldwide every year. It could also benefit patients with needle phobia and healthcare staff who suffer needlestick injuries, estimated at 600,000 to 800,000 annually, with the risk of HIV or hepatitis infection.

Acrux Announces Positive Clinical Trial Results With Combination Contraceptive Sprays

Acrux, the Australian drug delivery company, recently announced positive results from its Phase I clinical studies using two unique contraceptive skin sprays, each containing a progestin and an estrogen. The first study was a Phase I, pharmacokinetic study, investigating the delivery of a formulation combining Nestorone and the synthetic estrogen, Ethinyl Estradiol. A single dose of the combination formulation was applied to the forearm of healthy volunteers. The results showed that the dosing of the contraceptive spray provided effective delivery of both contraceptive agents, with blood concentrations of Nestorone and Ethinyl Estradiol in the target range expected to provide effective contraception. The spray was well tolerated, with no serious adverse events recorded.

"This is the first time that the Acrux MDTS spray technology has effectively delivered a formulation containing a combination of two drugs", commented Acrux CEO Richard Treagus. "We are particularly pleased that our transdermal spray has been successful with Ethinyl Estradiol, as this is the active pharmaceutical compound in approximately 3 out of every 4 oral contraceptive tablets."

Acrux plans to proceed with a multi-dose Phase I study in the second half of 2007. The study will be designed to demonstrate that therapeutic blood levels of the combination contraceptive are effectively maintained with once-daily dosing.

The second study was a Phase I pharmacokinetic study investigating the delivery of a formulation combining Nestorone and the natural estrogen Estradiol. A single dose of the combination formulation was applied to the forearm of healthy volunteers. The results showed that the dosing of the contraceptive spray provided effective delivery of Nestorone, with blood concentrations in the target range that is expected to provide effective contraception. The spray was well tolerated, with no serious adverse events recorded.

Analysis of blood concentrations of Estradiol was inconclusive, due to interaction with background levels of Estradiol in the study population. Acrux has established experience with Estradiol in hormone therapy, with its lead product containing estradiol currently in pre-registration in the US. This, along with in vitro results from a number of formulations containing Estradiol, gives the company confidence that it can deliver this novel combination contraceptive through the skin effectively. Acrux is planning a further Phase I study in the second half of 2007 in order to confirm these predictions.

"Our strategy over the past 12 months has been to rapidly demonstrate the broad applicability of the Acrux spray technology across a range of contraceptive products, including combination formulations. We have made material progress in this area, which has further strengthened our commercial prospects in the global contraceptive market," said Mr. Treagus.

Worldwide annual sales of hormonal contraceptives are approximately $6.7 billion, with combinations containing a progestin and an estrogen comprising more than 80%. Nestorone, which cannot be taken orally, is a fourth-generation progestin contraceptive that has no androgenic hormonal effects, and a good safety profile. MDTS is a small, hand-held, easy-to-use spray that is designed to provide an easy and convenient means to deliver a preset dose of a therapeutic drug via the skin. The spray applicator is placed gently against the forearm and an actuator button is pushed. A light spray containing a proprietary formulation of Nestorone is quickly absorbed into the skin. Nestorone is released into the blood stream on a sustained basis over 24 hours, providing a practical and convenient once-a-day dosing regimen. The spray is fast-drying, non-irritating, and invisible after application.

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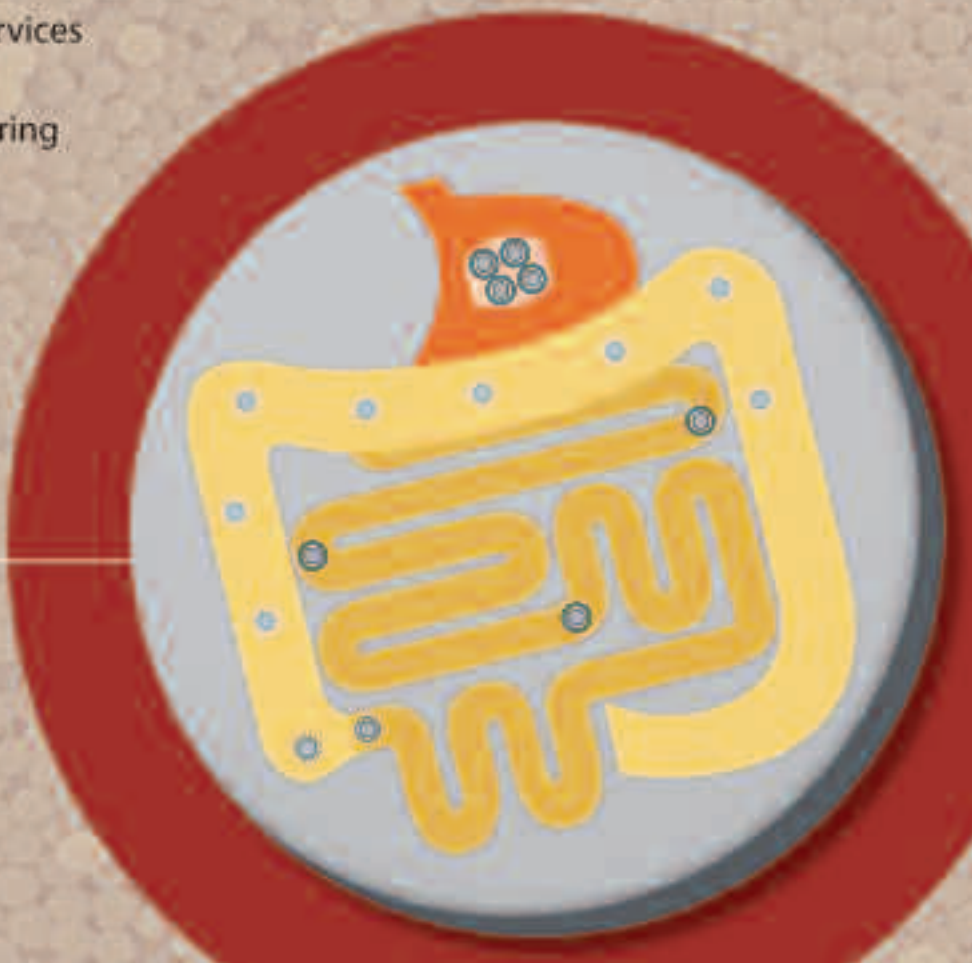

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CombinatoRx & Angiotech Pharmaceuticals Extend R&D Collaboration to Create Next-Generation Drug Device & Local Delivery Medicines

CombinatoRx, Incorporated and Angiotech Pharmaceuticals, Inc. recently announced an early extension of their collaboration based upon the successful advancement of a number of product candidates in relevant preclinical models. The joint research being conducted under the agreement to create next-generation drug device and local medicines has been extended beyond the initial 2.5-year term to a total of 5 years, resulting in a $7-million payment to CombinatoRx due before October 3, 2007.

"The extension of the research under our agreement with CombinatoRx allows the continuation of a very productive partnership in which we have made notable progress in just less than 2 years," commented Dr. William Hunter, President and CEO of Angiotech.

"This collaboration capitalizes on CombinatoRx's capability in the discovery of synergistic combination drug candidates and Angiotech's significant expertise in the development and commercialization of drug-device combinations and local interventional medicines," added Alexis Borisy, President and CEO of CombinatoRx.

In October 2005, CombinatoRx and Angiotech entered into a research and license agreement that granted Angiotech an option to evaluate and exclusively license compounds selected by Angiotech from the CombinatoRx clinical and preclinical pipeline and its proprietary bioinformatics database of synergistic combination pharmaceuticals for development and potential commercialization in certain medical device and local interventional applications. CombinatoRx also agreed to deploy its proprietary combination high throughput screening technology in a joint multi-year research initiative to identify novel drug combinations for multiple areas of strategic importance to Angiotech. Intellectual property from this research project will be jointly owned, and exclusively cross-licensed to CombinatoRx for traditional pharmaceutical uses outside the Angiotech fields of use.

Under the terms of the agreement, Angiotech has made an up-front license execution payment of $27 million to CombinatoRx plus a $15-million equity investment in CombinatoRx entitling Angiotech to license up to 10 CombinatoRx compounds for the Angiotech field, and up to five more compounds for an additional payment of $2 million per compound. Intellectual property from the research project component of the agreement is exclusively licensed to Angiotech in the Angiotech fields of use. CombinatoRx is eligible to receive development and regulatory milestone payments of up to $30 million for each product selected by Angiotech for development, in addition to royalties on cumulative commercial sales of such products.

CombinatoRx, Incorporated is pioneering the new field of synergistic combination pharmaceuticals and has a broad product portfolio in Phase II clinical development. Going beyond traditional combinations, CombinatoRx creates product candidates with novel mechanisms of action striking at the biological complexities of human disease. The lead programs in the CombinatoRx portfolio are advancing into later stage clinical trials based on the strength of multiple positive Phase IIa results. This portfolio is internally generated from the CombinatoRx proprietary drug discovery technology that provides a renewable and previously untapped source of novel drug candidates.

Angiotech Pharmaceuticals, Inc. is a global specialty pharmaceutical and medical device company with over 1,500 dedicated employees. Angiotech discovers, develops, and markets innovative treatment solutions for diseases or complications associated with medical device implants, surgical interventions, and acute injury.

Novartis' First & Only Skin Patch for the Treatment of Alzheimer's Disease Receives First Worldwide Approval in US

Novartis recently reported that its Exelon Patch (rivastigmine transdermal system) has received its first worldwide approval in the US as an innovative way to deliver an effective medicine for mild to moderate Alzheimer's disease patients through a skin patch instead of an oral capsule. This new therapy is the first and only transdermal treatment for this degenerative condition affecting millions of people in the US. Exelon Patch offers effective treatment based on placebo-controlled clinical trial results, showing significant benefits to patients in terms of their memory and overall functioning.

Exelon Patch maintains steady drug levels in the bloodstream, improving tolerability and allowing a higher proportion of patients to receive therapeutic doses compared to the capsule form of the medication. It is applied to the back, chest, or upper arm, and provides smooth and continuous delivery of medication through the skin over 24 hours. Gastrointestinal side effects are commonly seen with this class of drugs called cholinesterase inhibitors. The recommended dose of Exelon Patch greatly reduces these side effects, with three times fewer reports of nausea and vomiting than with the capsule form of the drug.

"Exelon Patch represents a significant advance in the treatment of this debilitating disease," said George Grossberg, MD, Director of Geriatric Psychiatry, St. Louis University School of Medicine, St. Louis, Missouri. "The unique delivery system helps both the patient and the caregiver by providing an easy way to manage their therapy. The patch provides a visual reassurance for the caregiver that the patient is receiving their medication and helps the patient stay engaged in their daily lives."

Exelon Patch is expected to be available in US pharmacies soon. The medication was submitted for review in the European Union in late 2006. The patch was designed with compliance in mind and was preferred to capsules by 70% of caregivers as a method of drug delivery, according to clinical study data, because it helped them follow the treatment schedule, interfered less with their daily life, and was easier to use overall than the oral medication.

The approval of Exelon Patch is based on results from the international IDEAL (Investigation of transDermal Exelon in ALzheimer's disease) clinical trial, involving nearly 1,200 patients with mild to moderate Alzheimer's disease. Exelon Patch showed similar efficacy to the highest doses of Exelon capsules and the recommended dose (9.5 mg/24 hours) was generally well tolerated by patients.

"Innovation isn't just about developing new compounds, but also about meeting therapeutic needs by taking existing knowledge and applying it in new ways," said James Shannon, MD, Global Head of Development at Novartis Pharma AG. "Exelon Patch addresses an important medical need by delivering a proven drug in an entirely new form that meets the needs of patients and their caregivers."

The US FDA also approved the use of Exelon Patch in treating patients with mild to moderate Parkinson's disease dementia.

Market News and Trends

Report Indicates Nanotechnologies Set to Shake Up & Shake Out Drug Delivery; New Study Estimates US Drug Delivery Market Value Might Reach Nearly $85 Billion

A new report from Cientifica Ltd., The Nanoparticle Drug Delivery Market, identifies who is positioned to be the winners and losers in the drug delivery market as new nanoparticles and nanostructured delivery techniques begin replacing existing polymer therapeutics that currently dominate the market.

The report, available at www.cientifica.com, projects that the total market for nanotechnology-enabled drug delivery will rise to $26 billion by 2012 from its current size of $3.39 billion, representing a compound annual growth rate of 37%. But this is just the beginning; the market could steeply rise after 2012, reaching potentially $220 billion by 2015 for these nano-enabled compounds.

With such enormous growth anticipated, the 300-page report examines over 60 different companies, including 38 drug formulation companies and 23 drug delivery companies, analyzing where they are in their product pipeline, the available market, and the value that their products add to drug delivery.

With 58 case studies of nanoparticle drug delivery platforms and technologies, it becomes possible both for investors and companies in the pharmaceutical industry to understand how nanotechnologies will impact the drug delivery market and the companies in the best position to exploit this growth.

Nanotechnologies have already begun to change the scale and methods of drug delivery and hold huge potential for future developments in this area. New formulations and routes for drug delivery have the potential to broaden the therapeutic potential of administered treatments by allowing the delivery of new types of medicine to previously inaccessible sites in the body. In contrast to developing completely new drug compounds, introducing upgraded formulations greatly reduces the risk, time, and capital invested in new drug development.

Nanoparticle drug delivery technology can enable reformulation of existing drugs to increase product life cycle, increase profitability, expand intellectual property estate, and discourage competition during a drug's most valuable years.

Research Director Hailing Yu commented, "A new value paradigm is taking shape in this market. By understanding how these nanostructured delivery techniques will shape the future of this market, investors and companies involved in the space will have a map for this new landscape."

In addition, Research and Markets has announced the addition of Drug Delivery Systems: US Market Outlook, Advances for Pharma, Biotech & Medical Devices to its offering. This research study is about drug delivery systems and provides readers with relevant information, insights, and analysis. This important medical opportunity is assessed in terms of technical and business areas. The participating companies are mapped to show where they fit in the industry landscape. This study reviews the kinds of drug delivery systems that are being used by pharma, biotech, or medical device companies.

The report discusses the broad range of drug delivery systems, the technical advances and the applications that drug makers might use. Key advances include orally dissolving tablets and filmstrips, needle- and needle-free injection systems, transdermal patches, transmucosal delivery, RNAi, drug-coated stents, PEG, nanotechnology, liposomes, monoclonal antibodies, gene delivery, and implants, which all contribute to the many ways that drugs or therapies can be delivered. Drug delivery systems are reviewed in terms of approaches used for delivering drugs targeting major diseases including cardiovascular, cancer, asthma, diabetes, and the central nervous system among others.

This market study shows that drug delivery technologies can help drug makers overcome some of their biggest challenges. The drug industry continues to see the commercial demise of major branded drugs that reach their patent expiration date. Billions of dollars in revenues are lost to generic drug makers each year. The technology can be used as part of a line extension strategy to extend the commercial life of their profitable products. Drug delivery can help rescue drug projects with technical challenges by using a customized delivery system.

The report also discusses the aforementioned topics with interesting and useful findings, estimating that the US drug delivery market value might reach nearly $85 billion by 2010. The research includes over 235 key alliances and M&As through 2006. It features 29 figures and tables to illustrate the findings or trends and profiles about companies important to the expanding drug delivery market, including detailed information about their business and technical activities.

Gilead Sciences & Parion Sciences to Co-Develop Pulmonary Drugs

Parion Sciences, Inc. and Gilead Sciences, Inc. recently announced they have entered into an exclusive licensing and co-development agreement focused on P-680, an epithelial sodium channel (ENaC) inhibitor discovered by Parion, a privately held, development-stage pharmaceutical company dedicated to treating serious diseases resulting from the failure of the body's mucosal defenses. The agreement grants Gilead worldwide commercialization rights to P-680 for the treatment of pulmonary diseases, including cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), and non-CF bronchiectasis. In addition, the companies will collaborate on a research program to identify other promising ENaC blocker-based drug candidates utilizing Parion's proprietary ENaC-based chemistry platform.

According to the terms of the agreement, Gilead will provide an up-front payment of $5 million for the license and make an additional $5-million investment in Parion. In addition, under the license, Gilead will supply research funding and may make payments upon achievements of certain milestones, resulting in a potential deal value of approximately $146 million. Parion will perform the IND-enabling studies for P-680 and will transition development responsibilities to Gilead during the Phase I clinical trial period. Parion will also be eligible to receive up to double-digit royalties based on potential future product sales.

ENaC inhibitors are unique therapeutic agents that stimulate and maintain hydration on the body's mucosal surfaces, including those on the lung, mouth, nose, eye, and gastrointestinal tract. Restoring the hydration of mucosal airway surfaces addresses the fundamental problem that produces infections in both acquired and genetic forms of chronic lung disease, including COPD and CF.

"This agreement validates the importance of ENaC inhibitors in the treatment of diseases involving defects in the innate defenses of the body's mucosal surfaces," said Paul Boucher, Director of Operations of Parion. "This partnership enables us to accelerate our development of P-680 and broaden our research programs. We are pleased to have the support of a company with an outstanding track record in the field of infectious diseases and pulmonary medicine."

"Gilead is committed to building a pipeline of novel respiratory therapeutics to advance the care of patients suffering from life-threatening diseases, and this partnership complements our program for development of aztreonam lysine for inhalation for treatment of CF-related lung infections," said A. Bruce Montgomery, MD, Senior Vice President, Head of Respiratory Therapeutics, Gilead Sciences. "We will work closely with Parion to complete preclinical development of P-680 in the hopes of advancing it into clinical studies."

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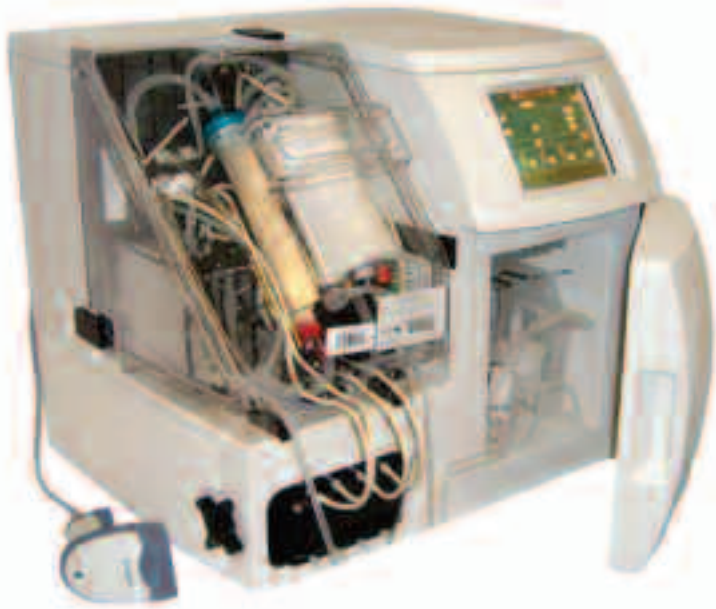

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Akela Pharma, Inc. Completes Patient Enrollment in its Fentanyl Taifun® Phase IIb Trial

Akela Pharma Inc., a drug development company focused on developing therapies for the inhalation, pain, and CNS markets, recently announced that it has completed enrolling patients in its Fentanyl Taifun Phase IIb trial. Fentanyl Taifun is a fast-acting Fentanyl formulation delivered using the company's Taifun dry powder inhaler platform.

Phase IIb for Fentanyl Taifun is a multi-centered, multinational clinical trial in cancer patients with severe persistent pain on maintenance opioid therapy. The first part of the trial is a single arm, open-label dose titration to evaluate the effective individual dose for significant pain relief with Fentanyl Taifun in the treatment of breakthrough cancer pain. The second part includes 28 responders from the open-label arm randomized to receive the titrated doses or placebo. The safety and efficacy data from this double-blind, placebo-controlled extension arm is expected to be available by early September 2007.

"The completion of patient enrollment in our Fentanyl Taifun Phase IIb marks yet another important milestone achievement in the development of our lead compound. We confidently anticipate being able to demonstrate once again the same superior formulation, technological platform, and unique therapeutic profile." said Dr. Halvor Jaeger, Chief Executive Officer of Akela Pharma Inc.

Chronic pain associated with advanced cancer is commonly treated with strong opioid analgesics, such as fentanyl. Breakthrough pain episodes are sudden and intense flares of pain that "break through" a long-acting continuous treatment, such as a transdermal patch or a slow-release tablet. Breakthrough pain episodes are common in cancer patients, often occurring several times a day.

Akela Pharma is an integrated drug development company focused on developing therapies for the growing multi-billion dollar inhalation, pain, and CNS markets. Its lead product, for the treatment of breakthrough cancer pain, is a fast-acting Fentanyl formulation delivered using the company's Taifun dry powder inhaler platform. Its pipeline also includes therapeutics for asthma, COPD, growth hormone deficiencies, and controlled substance abuse deterrent formulations.

Carrington Laboratories & Brookwood Extend GelSite Drug Delivery Technology Development

Carrington Laboratories, Inc. recently announced that its subsidiary, DelSite Biotechnologies, Inc., extended a joint development agreement with Brookwood Pharmaceuticals, Inc. The goal of this effort is to continue an expanded evaluation of GelSite, a DelSite patented drug delivery technology, as a matrix for injectable applications and for selected classes of drugs. This extension is built on the promising results and evaluations conducted by the joint technical team in the past year.

GelSite polymer is a high-molecular-weight anionic polysaccharide that exhibits distinct chemical and functional properties proprietary to the company. It is a naturally derived, biocompatible, resorbable biopolymer and is produced under cGMP with high purity at a kilogram scale. This technology has the potential to protect and deliver peptides and proteins effectively while reducing the frequency of drug administration.

Fewer injections will improve patient compliance, safety, and efficacy. Injectable, controlled- release applications for peptides and proteins are in the multibillion-dollar drug delivery market.

Under this new extended joint development program, the evaluation of GelSite technology will continue to be managed by a team of experts from Brookwood Pharmaceuticals and DelSite. "Brookwood Pharmaceuticals is internationally recognized in the field of drug delivery. The joint scientific team has made progresses in expanding the applications of the GelSite polymer for parenteral delivery of proteins and peptides. We are looking forward to the continued success of this program," said Dr. Carlton E. Turner, President and CEO of Carrington.

Strategies for Developing & Commercializing Next-Generation Medical Devices

By: Robert R. Andrews, MBA, MS

The emergence of combination products is changing the medical device landscape. Defined as two or more regulated components (drugs, medical devices, or biologics) combined through physical or chemical means, combination products inherently require two separate skill sets for development. Whereas medical device companies used to possess 100% of the expertise needed to develop a product, they must now share product development ownership with a biotech/pharmaceutical partner. The shared development model intensifies every aspect of product development from IP and regulatory issues to packaging and marketing strategy. For these and many other reasons described in this article, it is critical that products are well-targeted.

With countless combinations of device, pharmaceutical drug and/or biologic, the opportunities in this market are exponential. However, in order to be successful, a product must not only satisfy a real market need, but it must also be uniquely different from anything the competition has to offer.

ASSESSING MARKET DEMAND

Accurately assessing market demand is the first step toward developing a successful product. As with the entire product development process, medical device companies can benefit from using an external design engineering firm to conduct market research. Objectivity is a central ingredient in research and with no financial stake in the technology or device, an external engineering firm fits this profile.

There are several effective ways to establish needs in the market using customer and market research. These include one-on-one interviews, focus groups, telephone surveys, and conjoint and factor analyses. With conjoint analysis, medical device companies can gain insight into how trade-offs are made between competing characteristics of a product by evaluating how customers value product attributes individually and in a group. For example, if one characteristic diminishes the value of another, then a conjoint analysis will help identify which attribute is more important. By contrast, factor analysis focuses on grouping product characteristics together to determine which set of attributes has the greatest appeal. Finally, focus groups are very helpful in idea concept testing and understanding the healthcare environment.

It is critical to prioritize end-user needs according to relative importance to avoid developing a product that has unwanted features or is too costly. Identifying customer dissatisfaction with current products can also help companies avoid making the same mistakes as their competitors.

BRINGING NEW PRODUCTS TO MARKET

More than just identifying markets needs, combination product makers must consider the accessibility of the product to its target audience. For example, if a product is targeted for type 2 diabetes, then product developers should consider the elderly population a primary market, and make obtaining national coverage and reimbursement from the Centers for Medicare and Medicaid Services (CMS) a top priority.

Because CMS will require evidence that the combination product will provide a clinically more effective therapy than is

FIGURE 1

G.D. Searle's trandsdermal nitroglycerine patch used to treat patients with angina is an example of a combination product in which the device and drug are one entity.

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FIGURE 2

It is critical to consider manufacturing needs early in the development of combination products.

currently offered, combination product makers should identify clear differentiators at product concept. Similarly, CMS wants companies to demonstrate that the combination product will provide a significant health benefit. Product developers should therefore have some way of measuring the health benefits of their products. Although CMS is not supposed to consider cost when making a national coverage decision, there are recommendations for it to begin doing so. Combination product developers would be wise to design with cost in mind not only to preempt any decisions CMS may make in the future, but also to minimize threats from competing products.

Because CMS coverage will greatly influence physician adoption of the combination product, companies are advised to begin the reimbursement process as early as possible. This will help to decrease the lag time between FDA approval and CMS coverage, allowing the combination product to reach its target populations sooner.[1]

Although CMS has not defined a coverage decision process for combination products yet, following these guidelines will help steer the current generation of products in development toward CMS coverage.

With so many combination products currently in development, the challenges of introducing an original product in this market are multiplied. While development of combination products will require the formation of partnerships with biotechnology and/or pharmaceutical companies, medical device companies can also benefit greatly from involving an external engineering firm throughout the entire development process. Unlike medical device companies or their pharmaceutical partners, an outside engineering firm with multidisciplinary expertise possesses specialized knowledge of manufacturing, design, and regulatory issues for both industries. This dual-industry understanding gives outside experts the unique ability to engineer breakthrough concepts and anticipate potential problems that would not otherwise be obvious to either company.

While IP sharing is an inherent part of combination product development, working with a neutral engineering partner can minimize IP issues between medical device and pharmaceutical companies, while ensuring confidentiality and protection of the intellectual property of the products it develops. Engineering partners should advise and encourage pharmaceutical and medical device customers to apply for patents both separately and together for the drug, the device, and the combination of the two to ensure that each company's proprietary technologies are protected.

DESIGNING FOR MANUFACTURABILITY

As two separate regulated components, combination products present unique manufacturing challenges. Beyond the physical design challenges of combining the two entities, sterilization, validation, and drug/device interaction issues further complicate the development process. In addition, if chemicals, known as extractables and leachables, migrate from plastic medical device components, drug products can become contaminated. Because traditional device sterilization procedures, such as ethylene oxide gas (EtO), can render drugs ineffective, new strategies may need to be developed to ensure product sterility, especially for biological drugs.

Primary Mode of Action (PMOA) is defined as the single mode of action of a combination product that provides the most important therapeutic result. While each combination product has a PMOA that determines its assignment to one of three FDA regulatory centers for review, the process of defining the PMOA can be complicated in and of itself. To minimize regulatory confusion, it is best to establish an intended PMOA at the outset of the project. Of the three agencies to which a product can be submitted, the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), or the Center for Devices and Radiological Health (CDRH), the CDRH is often considered the shortest and clearest route to

regulatory approval.[2] Given the differences in scale, timeliness, and other matters, device and pharmaceutical companies may not always agree on PMOA. It is therefore beneficial to consult with experts, including regulatory counsel.

Regardless of whether the product is a combination device, traditional medical product, or an innovation in an altogether different market, planning for manufacturing should begin as soon as a product concept is developed. This will avoid developing a product that is extremely difficult to manufacture. It will also enable the company to determine whether standard equipment, a modified version of it, or a unique proprietary system will be required for manufacturing. For example, discovering that a product cannot be manufactured on standard equipment once the prototype has been finalized comes at a stage in the process when changes to either the product or the production machinery will be costly and time-consuming.

Just as an external engineering partner can recommend standard manufacturing equipment and customize proprietary solutions, it can also help medical device companies select a manufacturing partner to produce the product. Selection of manufacturing partners will depend largely on the technology planned for use in the device and the materials from which it will be constructed. In the case of combination products, more than one manufacturing partner is often required due to the complexity of the product.

NEW PARADIGMS IN PACKAGING

Packaging combination products is equally as challenging as designing, developing, and manufacturing them. Most combination products will require special barrier properties to protect pharmaceutical or biologic components from moisture and oxygen. For example, some drugs may require refrigerated storage to preserve their shelf life.

Because combination products can be used anywhere in a hospital or healthcare environment, packaging requirements will vary greatly depending on their intended use. For example, a double sterile barrier is required for devices that are used in operating rooms, whereas a single package is suitable for devices that are used in patient rooms.

As mentioned earlier, the integration of two different regulated entities complicates sterilization processes. Most drugs cannot withstand the high heat and humidity of ethylene oxide gas (EtO) typically used to sterilize medical devices in their packages. Combination product manufacturers will need to identify other suitable methods of sterilization, such as gamma irradiation, electron beam, or UV sterilization.

SUMMARY

Medical device and pharmaceutical companies have a unique opportunity to establish themselves as leaders in the burgeoning combination products market. With the exception of medical and pharmaceutical giants like Johnson & Johnson, in many cases, the most successful companies are not necessarily the most innovative, but rather the ones that are best at partnering and collaborating. This is because in the world of combination products, a medical device is only as innovative as its other half – the pharmaceutical component.

Outsourcing can help bridge the gap between the pharmaceutical and medical device industries by fostering collaboration and innovation among companies that often don't see eye-to-eye. External engineering firms possess the multidisciplinary expertise needed to understand both sides of the combination product equation, and can fill the knowledge gaps while ensuring IP protection. ◆

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BIOGRAPHY

Mr. Robert R. Andrews is the Medical Division Manager for the commercial group at Foster-Miller Inc., a QinetiQ company. He has more than 25 years of medical device experience managing product development and operations. He has 11 issued U.S. medical device patents. He earned his MBA from Bryant College and his Bachelors and Masters in Plastics Engineering from The University of Lowell. He can be contacted at (781) 684-4639 or randrews@foster-miller.com.

The Impact of Drug Delivery Devices: Finding the Right Device for Your Business

By: Ben Shand, MPhil, and Iain Simpson, PhD

In the Spring of 2007, Ben Shand, a post-graduate student taking a Masters degree in Bioscience Enterprise (MBE) at the University of Cambridge, prepared a dissertation on *The Impact of Drug Delivery Devices on the Pharmaceutical and Biotech Industries.* He was sponsored by Team Consulting Ltd, who specializes in medical product design and development. In this paper, Mr. Shand and Dr. Iain Simpson of Team summarize the research undertaken for the dissertation and discuss some of the key implications for companies looking to deliver their drug via injection or the respiratory route.

THE RESEARCH

Advancements in drug delivery technology promise to revolutionize how patients receive both new and old therapies. Many new therapies cannot be delivered orally. Moreover, the efficacy of many old therapies can be significantly enhanced using delivery methods that increase patient compliance, improve bioavailability, alter the drug's speed-of-action, or provide for targeted delivery. Research carried out for the dissertation covered the need for alternative delivery methods, the drivers for the industry, the current technologies being developed, and the strategies used by companies to incorporate drug delivery technology. It was focused on the key alternative delivery routes: advanced injector, intranasal, and inhalation. While advanced injector technology is the easiest conversion from a needle and syringe-delivered therapy, inhalation- and intranasal-delivered treatments will have a place in growing markets as companies pursue non-invasive techniques for drug delivery.

The research for the dissertation was carried out over a 6-week internship, which was primarily research based, including secondary "desk" research and primary research conducted through in-person and telephone interviews as well as responses to an electronic questionnaire. The survey included industry experts from large pharma (13 respondents), employees of small-to-medium drug companies with an emphasis on those with pipeline candidates that indicated a potential interest in advanced drug delivery (50 respondents), and employees of drug delivery specialist companies (16 respondents) having different growth phases and strategies. Although we cannot do justice to a 10,000-word dissertation in this article, the key findings are summarized further.

IMPORTANCE OF DRUG DELIVERY TECHNOLOGY

There is a growing use and interest throughout the industry. About 68% of the respondent biotech and small pharmaceutical companies indicated they were actively developing products for advanced delivery. Although this level of interest may not be fully representative across the whole industry due to a likely skew in the companies responding in the research, it clearly shows that many drug companies are considering advanced drug delivery technologies during drug development. Moreover, all six major pharmaceutical respondents indicated they are working on drugs for advanced drug delivery. Of 16 drug delivery specialists who responded, 14 are reformulating existing drugs and pipeline candidates, 10 are working with pharma partners. Drug delivery technologies can provide a lifecycle management opportunity for all types of companies, particularly for big pharma whose pipelines are currently plagued with patent expiration and generic competition. Advanced drug delivery can also facilitate product differentiation, creating larger market share.

MARKET DRIVERS

Several factors are driving interest in drug delivery technologies. The primary research reveals that for many companies, user compliance is a key reason to improve drug delivery.

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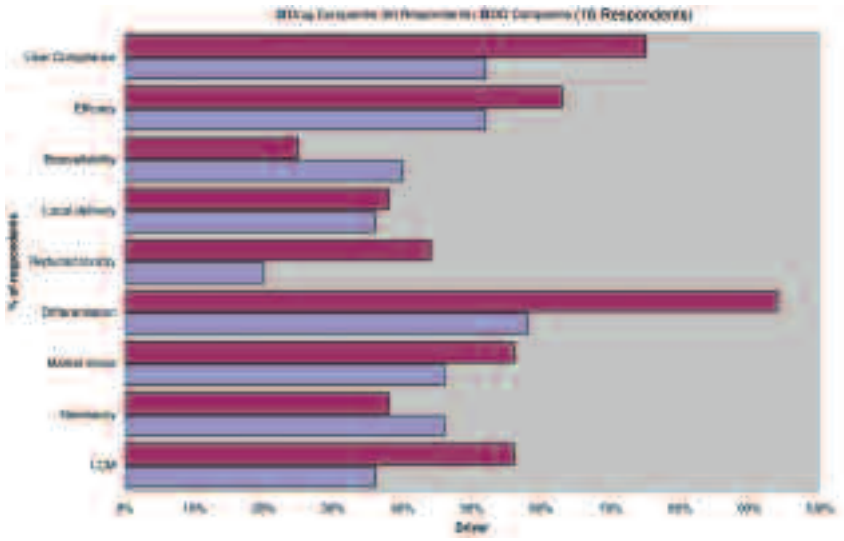
Exactly 52% of the biotech and small pharmaceutical companies and 75% of drug delivery specialists (Figure 1) indicated that improving user compliance was one of the most important technical reasons for improving delivery. It was also rated highly by 83% of the major pharma respondents and 69% of industry experts. Better user compliance leads to other key factors, including improving treatment effectiveness, as well as strategic advantages, such as product differentiation and hence increased market share. The development of macromolecule therapies, which are currently delivered via injection, will drive drug delivery technology interest. As more biologics come to market, companies may seek to enhance their products by using advanced drug delivery technologies for improving user compliance and effectiveness.

Drug delivery technology will affect all parts of the industry. The lifecycle management opportunity for major pharmaceutical companies has already been mentioned. Similarly, biotech and small pharmaceutical companies can take advantage of advanced drug delivery technology in order to differentiate their products and increase market share. More importantly, the outsourcing strategy for dealing with drug delivery (highlighted in Figure 2) creates growing opportunities for technology consulting groups, contract research organizations, law firms, and many other types of service companies who can facilitate the partnering and licensing relationships between drug companies and drug

FIGURE 1

Drivers for Drug Delivery Technologies



delivery specialists. Also important are the changing business development strategies for growing drug delivery specialists. Many drug delivery specialists (14/16 respondents) work on developing their own drugs in-house. In order for these companies to grow organically, they must establish technology licensing agreements to generate income and fund internal R&D.

DRUG DELIVERY TECHNOLOGY PROSPECTS

Although oral tablets will continue to be the choice of preference in the industry, inhalation, intranasal, and advanced injector technologies will all have their place. They can offer many advantages (eg, convenience, ease of use, and speed of action) such as in the delivery of opioids for the treatment of breakthrough pain. In particular, inhalation drug delivery is already a proven technology for the treatment of asthma and COPD with a market of around $20 billion.[1] With the approval of the first macromolecule delivered via inhalation in Exubera, Pfizer and Nektar have shown that this method for biologic delivery is suitable for systemic treatment and have satisfied the regulators that this approach is safe. As inhalation drug delivery technology advances, more macromolecule treatments may be delivered via this non-invasive route, particularly for chronic conditions. Intranasal delivery, while a relatively young technology in terms of advanced development, will also grow in treatment application. Like inhalation, intranasal treatments have proven to be successful for local conditions, such as allergies;

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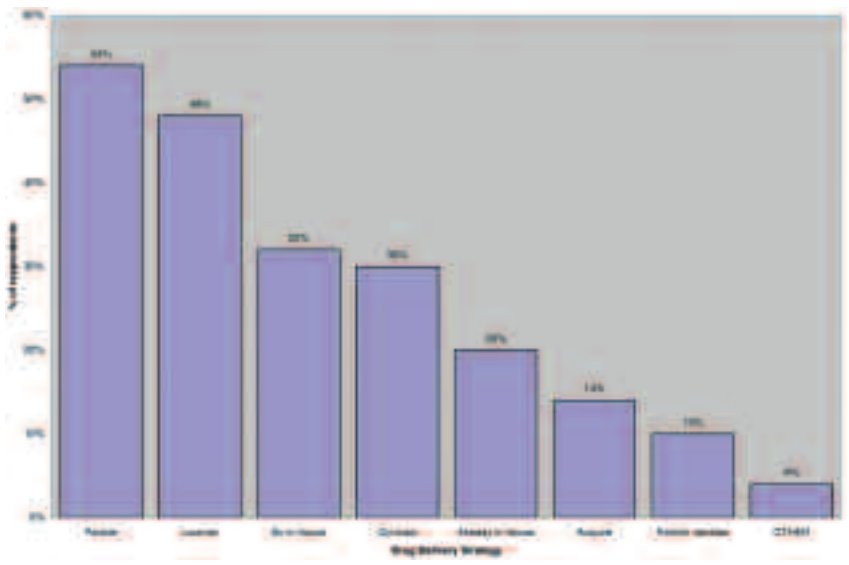
FIGURE 2

Drug Delivery Strategies



however, with a fast-uptake and potential to treat CNS diseases, intranasal delivery could overcome delivery obstacles, including transfer of medication across the blood-brain barrier. Injection delivery will always have a strong place in the industry. Dial-a-dose pen injectors are already in common usage for the delivery of insulin but are increasingly being used for other drugs that have similar delivery requirements. Another type of advanced injection technology is the autoinjector, which automatically introduces the needle into the patient and then delivers the drug. The use of the EpiPen® to deliver epinephrine for the treatment of anaphylaxis is the most common example of this type of device in the market, but autoinjectors are being increasingly used to address several issues, such as safety and ease of use, especially in situations in which self-administration is seen to be a key differentiator.[2]

Fundamentally, the conversion from the needle and syringe to an advanced injector is generally more straightforward than changing to any other delivery mechanism as it is easier to show equivalence. For this reason, the barriers to advanced injector delivery technologies reaching the market will tend to be lower. As biotech companies continue to develop novel biological products, injection technology will continue to grow in importance. The market for injected therapies is huge, at roughly $130 billion and growing. As a relatively mature market, new technologies, such as the aforementioned autoinjectors and pen injectors, must demonstrate improved patient compliance, convenience, and safety for differentiation.

ARISING ISSUES

One of the key issues to emerge from the research is the challenge facing companies who are developing drugs that will require non-oral delivery. Many of the companies cited are smaller biotechs who will not have a core competence in device development or assessment. How can they make sure that they find the right device for their business? Drawing on many years of experience in device development and decision support, Team Consulting suggests the following:

Getting the Right Device

The most important issue is to establish what you need from a potential delivery device, ensuring that you consider the requirements from all viewpoints. The first concerns tend to be about efficacy (quantity of drug, dosing regime, therapeutic window), and while these are key concerns, they should not be allowed to overshadow other vital elements. For example, if a drug is aimed at a specific age group, then the consequences need to be recognized in the device specification. Indeed it is of particular importance that the "voice" of the end-user be considered throughout the process. Nobody will be unaware of the need to meet regulatory requirements, but understanding what those requirements are for drug delivery technologies may be a challenge for many companies who do not have device expertise in-house and won't know about, for instance, FDA guidance on human factors engineering or safety issues around lock-outs, anti-double dosing, dose counting, etc.

TABLE 1

Examples of Delivery of Fentanyl for Breakthrough Cancer Pain Using Device Technology

Delivery Route	Product	Company	Status
Transdermal	PassPort Patch	Altea	Phase I
Sublingual	AD923	Sosei	Pre phase III
Inhaled	Fentanyl Taifun®	LABPharma	Pre phase III
Inhaled	AZ-003 (Staccato fentanyl)	Alexza Pharmaceuticals	Phase I
Inhaled (nebulisation)	AeroLEF™	YM Biosciences	Phase IIb (completed)
Nasal	Nasalfent	Archimedes Pharma Ltd	Phase III
Nasal	Instanyl Spray	Nycomed	Phase III
Buccal	RapidMist™ fentanyl	Generex	Phase I

You need a thorough set of device requirements for the specification, and you need them early in the process before you look at available technologies. Make the most of people who can offer decision-support services early in the process, whether they are IP advisors, regulatory advisors, or device experts. At Team Consulting, we've found it invaluable to build up a detailed non-confidential database of available inhaler technologies and their characteristics to assist us when working with our clients in decision-support and technical due diligence.

Your specifications will become a living document, which will change as your development progresses. It should include the following considerations of what the device needs to offer:

- **FOR THERAPY:** Usually the easiest list to produce, with the emphasis typically on issues such as efficacy, speed of action, size of therapeutic window, dose size, and delivery regime (unit dose or multidose?). The amount of drug to be delivered will determine the formulation (pure or blended) and the device.

- **FOR THE USER:** The list is potentially extremely long, but might include in what situation (or even orientation) will the device be used, and how does that impact upon device performance? Is it intended for home administration or by a nurse? How much training will be needed? What would be desirable or necessary in terms of portability and robustness? What are the implications of the dosing regime – would users ideally want to have several days' supply of drug with the device? What happens if people don't achieve the required dose? What feedback should the user receive?

- **TO MEET REGULATORY NEEDS:** Managing risk is of paramount importance. Areas for assessment will include user issues, manufacturability, reliability, the possibility of minors or abusers accessing the drug, the need for safe drug storage, lock-outs, prevention of overdose, and the suitability for the target demographic. Companies may realize their drug may be open to abuse, but might not know how the device can be regulated to help or the type of strategies that companies are using to get their devices approved in this area.

- **COMMERCIALLY:** There is almost always a need for differentiation, and although companies can usually achieve this through the drug properties, they may not have the expertise to specify and select a device that will appeal to the given market segment. Launch needs to be timely (speed to market is always an issue) and at a cost the

SIDEBAR

Compliance: *Increasing compliance and thereby increasing the effectiveness of therapy was seen by the majority of respondents in the survey as a major driver in the development of drug delivery technologies. Under-medication is the "non-compliant behavior" that is of most industry concern, as drugs are often not taken as prescribed. It is important not to over-simplify the issues underlying this behavior (whether intentional or unintentional), which are often complex, psychological, and difficult to define, let alone address. However, there are elements of device design that can remove significant barriers to correct use. If, for instance, a drug delivery device design makes it easy for a patient to deliver the correct dose, know that the dose has been delivered through clear feedback and, at the same time, makes it difficult for the patient to receive an incorrect dose. Other features, such as reminder alarms, recorded history of use, timed lock-outs for prevention of overdose, and child safety, can all contribute to successful and safe device use and offer the potential for market differentiation. Ensuring user safety through the incorporation of good human factors engineering within a device development program is recognized as important by the FDA, and all companies looking for FDA approval will need to show evidence that this has been tested using both analytical and experimental techniques.*[3] *At Team Consulting, we approach this through a combination of lab-based analyses and observational user trials that we undertake wherever possible early in the development, using device models. This enables feedback into the design process and further trials to be carried out as appropriate. These trials focus on watching interaction with a device rather than asking for opinions – they help us to assess how easy a device is to use correctly, what could go wrong, and what would happen if it did. We assess opportunities for error and assist our clients in mitigating risk by designing them out, focusing on any that pose a serious risk. These assessments, which are a valuable part of any device development process, can also assist the device selection process, giving an idea of the potential usability of a fully designed device or technology.*

purchasers will buy. Your device must also be viable in the IP landscape, and there is a danger of exclusion through competition, for example, the organization that owns your preferred device may already be involved in a competing program. An interesting case study is likely to develop from the introduction of a number of competing inhaled insulin products throughout the coming years. Not only do these need to establish benefits over existing injectable products (in order to justify a higher price), but the inhaled products will also need to differentiate amongst themselves. Following the launch of Exubera, new entrants may offer benefits, such as high bioavailability and perceived safety (by the removal of excipients from their formulations), but the real differentiation might well be realized by superior usability of the devices themselves and their ability to provide good patient feedback

The aforementioned are obviously artificial, and issues will bleed across categories, but it is important for there to be someone on the team who can represent the interests of each as early as possible in the process.

As an example of the considerations that are required when assessing device options, we can consider opioid delivery for breakthrough cancer pain. It's a therapy that requires a delivery mechanism to provide acceptable bioavailability and fast onset of

therapeutic benefit. It needs to be suitable for self-administration by patients who may not be directly supervised, but accidental access to the drug by, say, children, must be avoided. There is also the hazard of overdosing, which may be addressed in a number of ways, such as the use of a lock-out mechanism. Because the drug is addictive, it will be open to abuse, so disposal of unused drug needs to be considered. A number of players are addressing this unmet meet (Table 1). In most of these cases, clinical studies have already established the feasibility of the drug-device combination, but device features and patient usability are likely to be an important determinant in their relative market success and the ability to displace the existing Actiq lozenge product throughout the coming years.

When your specification is well understood, you can screen to find the best fit. Assessing the potential of an as-yet-undeveloped technology alongside a finished or near-finished device is challenging, but valuable, as there may be opportunities to enhance it during further development. (see Licensing-in, best practice in technology selection. *Drug Delivery Technology*. 2004;4(6):72-74).

SUMMARY

The survey reported in this paper has highlighted the likely increase in demand for advanced drug delivery technology. In many cases, the uptake of device technology has been driven by an increasing emphasis on large molecule drugs, which cannot be delivered via the oral route, in the pipelines of pharmaceutical and biotechnology companies. However, with limited healthcare budgets and the apparent difficulties in developing new drugs that show sufficient advantages over existing generic formulations to justify higher prices, the ability to achieve differentiation for both new and existing products in other ways is of increasing interest. Advanced delivery technology, especially in the areas of injection, inhalation, and nasal delivery, can provide a competitive advantage in a number of ways, which include safety, speed of action, ease of use, and compliance. When assessing potential partnering opportunities, it is important to explore issues, such as development time and risk and device usability, in addition to the usual IP and commercial considerations. With an increasing range of technologies available for license, it may be a buyers' market, but it is easy to make a less than optimum choice of technology and partner, so let the buyer beware! ◆

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BIOGRAPHIES

Mr. Ben Shand is a graduate of the Masters in Bioscience Enterprise (MBE) course at the University of Cambridge. As a former student of Biology and Business at the University of South Carolina, Mr. Shand came to Cambridge in order to study the biotech and pharmaceutical industries in this multidisciplinary course, covering science, business, and law. Throughout the course, he undertook an internship with Team Consulting to work in the company and conduct research for his dissertation on the impact of advanced drug delivery – focusing on those that involve a hard device. He will be returning to the US at the end of his time in Cambridge to pursue work in business development with companies in the life science sector.

Dr. Iain Simpson is a Senior Consultant at Team Consulting and a Physicist by training. He has more than 10 years of experience in healthcare product development, including technical due diligence on drug delivery and medical devices and management of multidisciplinary multi-partner projects. Prior to joining Team in 1999, he was a Technical Manager of an instrumentation company and previously worked for a major UK technology company on sensor and microsystems developments. He has a broad interest in product development and is especially interested in IP and emerging technologies. He is currently Chairman of the R&D Society.

DISSOLVABLE FILMS

The Future of Dissolvable Films

By: Scott D. Barnhart, MS, and Martha S. Sloboda, MBA

INTRODUCTION

Dissolvable oral thin films (OTFs) are a proven technology for the systemic delivery of active pharmaceutical ingredients (APIs). Pharmaceutical companies and consumers, particularly pediatric and geriatric patient populations, have adopted OTFs as a practical alternative to traditional OTC medicines, such as liquids, tablets, and capsules, because of the various benefits of the films (fast, accurate dosing; safe, efficacious format; convenience; portability). The next generation of dissolvable films is being designed to move beyond immediate-release oral delivery into applications such as implantable, topical, sublingual, and gastro-retentive platforms for the delivery of both small and large molecules. This work is the direct result of the flexibility in dissolvable film design and manufacture. This article attempts to outline the next generation of films, the benefits of the platform across delivery routes, and the primary considerations in formulating for novel applications.

HISTORY OF THE DISSOLVABLE FILM FORMAT

By now, most consumers are familiar with the dissolvable thin film platform marketed by pharmaceutical and consumer companies for such products as confectionaries (breath mints), personal care (soap, vitamins) and over-the-counter (OTC) medicines (cough and cold, anti-gas, sore throat pain). OTFs have become an accepted alternative dosage form for pharmaceutical manufacturers to deliver medicines that are usually available as liquids, tablets, or capsules. They are now a proven commercial platform with the recognized benefits of fast, precise systemic dosing in a safe, effective format that offers convenience and portability. These benefits serve to increase patient compliance and have been proven to be well-tolerated, especially with geriatric and pediatric patient populations who may have difficulty swallowing pills.[1]

FUTURE PHARMACEUTICAL APPLICATIONS FOR DISSOLVABLE FILMS

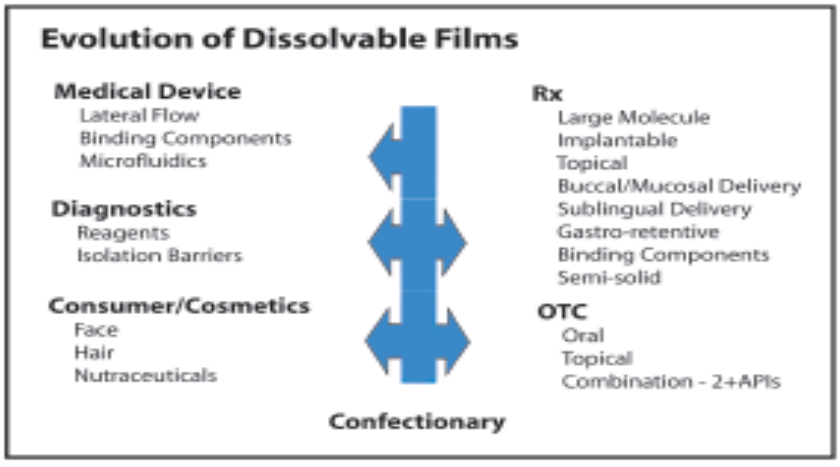
The recent launches of multi-drug combination products are just the beginning in advancing the application of OTF technology. The future of dissolvable films lies in multiple pharmaceutical, biopharmaceutical, and medical arenas (Figure 1). Ongoing work suggests that OTFs are ideal for delivery options such as gastro-retentive delivery and have distinct physical and chemical benefits as a binding and/or coating component within a product, among others (Table 1).

Dissolvable films are being considered in certain gastro-retentive dosage forms in which water-soluble and poorly soluble molecules of different molecular weights and sizes are contained in film form.[2] The dissolution of a sustained-release film may be controlled by the hydrochloric acid and enzyme secretions of the gastrointestinal lining and thereby could be used to deliver drugs for the treatment of gastrointestinal diseases and disorders.[3]

Current binding agents used in

FIGURE 1

Evolution of Dissolvable Films



Holding for Bilcare ad

TABLE 1

Potential Rx Applications for Dissolvable Films

- Gastro-retentive
- Binding component
- Large molecule
- Topical
- Implantable
- Buccal/mucosal delivery
- Sublingual delivery
- Semi-solid

TABLE 2

Identification	Film Composition Information				Disintegration Time (sec)
	Low Mw Cellulose	Low Mw Polymer	High Mw Cellulose A	High Mw Cellulose B	
Example A	1	-	-	-	18
Example B	1	0.9	-	-	8
Example C	1	1	-	-	5
Example D	-	-	1	1	24

*Note: Test average of n=4; Polymer content provided as ratio

pharmaceutical manufacturing could be replaced by dissolvable films. For example, a dissolvable film could be used to encapsulate a compressed tablet or hold a multi-layered system together to allow for controlled release of the dose. The layers remain segregated until the film is activated by water. Dissolvable films could provide the additional benefit of containing a separate drug within the film that would remain segregated from the primary dose until released by water.[4] In addition, when used as a coating agent, dissolvable films avoid BSE/TSE concerns while also drawing on non-genetically modified ingredients

FLEXIBILITY OF DISSOLVABLE FILM TECHNOLOGY

In addition to the potential to deliver many different types of APIs, the primary benefit of dissolvable film technology to pharmaceutical manufacturers is the flexibility of the format. Dissolution rate, materials selection, and the rate of absorption can be controlled. Precision manufacturing capabilities provide manufacturers an advantage in bringing a new product or extension of an existing product to market.

Dissolution Rate

Oral thin films are capable of more than just the immediate release of APIs, as demonstrated by the existing products currently on the market. The technology can be customized for controlled oral dissolution that ranges from seconds to hours. Particular attention to the selection of excipients is the key to developing a thin film oral dosage form that may disintegrate very rapidly for immediate-release applications or that may disintegrate slowly for controlled-release applications (Table 2).

Materials Selection

The OTF format offers pharmaceutical companies an unlimited set of raw materials to select from when developing and delivering APIs. These materials include traditional aqueous-soluble as well as non-traditional, non-aqueous-soluble ingredients, such as solvent-soluble materials.

Emulsions may be prepared as oil-in-water phases. Emulsions are typically used for the manufacture of aqueous-based formulations with an oil-soluble ingredient, such as a flavoring that has been added. These materials can be processed on manufacturing equipment using flammable and non-flammable ingredients.[1]

Dispersion of a non-soluble API may be prepared in film form. The dispersed phase within the bulk fluid must remain uniform throughout the film manufacturing process to prevent segregation of the API. Fluid rheology is an important consideration for assurance that the dispersed phase remains suspended.

Established and effective taste-masking approaches used to formulate APIs in syrups and soft-chew dosage forms can be applied to APIs in the thin film oral dosage format. Successful taste-masking methods that have been used include traditional flavor and sweetener combinations, encapsulation, or particle coating, and complexation with ion exchange resins.[5] It is important to consider and recognize any taste-masking techniques that result in discrete particles. Particle size is a critical factor in the manufacturing process and depends on the coating method selected. Generally, particles larger than 250 microns could present problems for some coating techniques if they accumulate in the fluid flow path, which could cause scratches on the surface of thin coating layers.

Manufacturing

The manufacture of OTFs is a multi-step, precise process that controls the functional properties of the films: thickness, width, drug concentration, residual volatiles, tensile strength, and disintegration rate.[1] Within the various steps of the manufacturing process, the coating process is the key to the successful development of OTFs (Figure 2). Multiple techniques, such as liquid casting or 100% solids extrusion,

are used to create thin films. The manufacturing process for OTFs is based on existing manufacturing techniques that have been proven in other applications that use and commercially manufacture high-precision polymers and coatings, such as transdermal drug delivery systems.[1] This is important because of the need to hold tight tolerances of the film when manufacturing products with highly potent compounds and APIs with a narrow therapeutic index in order to produce a uniform pharmaceutical product with low variability within a thin film lot.

Absorption Profile/Rate

Oral thin films are inherently water-soluble and disintegrate in the oral cavity. They can have muco-adhesion properties that cause the dose to adhere to any mucosal surface within the oral cavity until disintegration is complete. Upon complete disintegration, absorption of the API may occur through the buccal mucosa. Esophageal absorption may also occur during the process of swallowing saliva that contains the dissolved API. The majority of the dose ultimately ends up in the stomach and is absorbed in the GI tract in a similar manner as a traditional tablet.

A traditional oral dosage form requires a fixed amount of time for stomach fluids to dissolve the entire tablet or capsule. Unlike traditional oral dosage forms, an OTF is completely dissolved in the oral cavity and therefore, the entire API payload is immediately available for absorption to the systemic circulation. In terms of bioavailability, the AUC for an OTF versus an oral tablet or capsule may remain unchanged; however, Tmax may be shorter. There are certain medical disorders in which an earlier therapeutic effect may be warranted and advantageous.

Oral thin film technology is comparable to other oral dosage forms for the delivery and absorption of APIs in the GI tract. OTFs are compatible with microspheres and other specialized release technologies. Dissolvable films may also offer expanded bioavailability potential versus other delivery methods. The chemistry of OTFs may enhance specific API uptake, depending upon the API. The format allows for the ability to load as much as 50 mg or more of a single API or combination of APIs.

SUMMARY

Dissolvable film technology has evolved from a confectionary novelty item to a proven platform for delivering APIs in an alternative format that is beneficial to both consumers and pharmaceutical brand owners. The flexibility of the dissolvable film technology platform – from dissolution rate to materials selection to manufacturing – offers the future potential for expanded applications across different delivery routes in multiple pharmaceutical, biopharmaceutical, and medical markets, including, but not limited to, gastro-retentive delivery and use as a binding and/or coating component.

FIGURE 2

The Coating Process is Key to the Successful Manufacture of OTFs

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BIOGRAPHIES

Mr. Scott D. Barnhart is the Technical Director for ARx™, LLC, a subsidiary of Adhesives Research, Inc. He has extensive experience in adhesive formulation and process capabilities for transdermal drug delivery systems and the development of the company's dissolvable film platform. Mr. Barnhart earned his BS in Chemistry and Biology from The Pennsylvania State University and his MS in Organic Chemistry from Shippensburg University. He is a member of the American Chemical Society and the American Association of Pharmaceutical Scientists.

Ms. Martha S. Sloboda is the Business Manager for ARx™, LLC, a subsidiary of Adhesives Research, Inc. Since joining Adhesives Research in 2000, she has helped grow the company's pharmaceutical components business and has been instrumental in the development and growth of ARx as a manufacturer and supplier of complete drug delivery systems, including dissolvable films and transdermal tapes. She earned her BA in Japanese with a concentration in Economics from Connecticut College and her Executive MBA from Loyola College in Maryland.

NANOTECHNOLOGY

Nanotechnology – Government Funding Driving Infrastructure

By: Joan Brodovsky, Frost & Sullivan Consultant

INTRODUCTION

With a view to building an infrastructure that will advance nanotechnology research, the Federal Government in the 1990s created the National Nanotechnology Initiative (NNI). The investment, totaling an estimated $7 billion throughout the past decade, was expected to drive economic growth and lead to scientific advancement. While the impact of this young discipline is not fully known, tremendous advancements in biotechnology and healthcare are beginning to emerge.

MISSION OF THE NNI

The NNI was charged with four goals: (1) maintain a world-class R&D program; (2) facilitate technology transfer to develop products that will promote economic growth; (3) support responsible development of nanotechnology; and (4) develop educational resources, a skilled workforce, and the support infrastructure and tools to advance nanotechnology. Through these goals and increasing funding, numerous papers and patents have been published helping advance the basic understanding of nanotechnology as well as applications of the technology.

One of the seven strategic initiatives the NNI developed was the creation and support of research facilities. Since 2001, the group has contributed to more than 60 university laboratories and centers across the country. The centers train and support researchers, provide an interdisciplinary approach, and spawn a developmental ground to translate academic research into industrial endeavors. Most centers focus on one of the wide-ranging applications of nanotechnology, including genetic engineering, biopolymers, biomedical devices, protein folding, biometric conductors, and nanomedicine.

DRUG DELIVERY LEADS NANOBIOTECHNOLOGY DEVELOPMENT

Drug delivery is the most advanced of all nanobiotechnology as patients are already benefiting from some of the discoveries made in the laboratory. Transferring academic research into economically viable applications is difficult, but the three following companies have entered or are attempting to enter the commercial market with nanotechnology-based applications.

Elan

Elan's NanoCrystal® Technology is one of the first nanoparticulate technologies to successfully commercialize nano-scale products. It was developed through one of the basic premises of the science: make particles in the nano-scale. The NanoCrystal technology yields particles of about 100 nm and is useful for making some drug compounds more soluble, allowing for enhanced drug delivery mechanisms. NanoCrystal particles are produced by milling the drug substance using a proprietary, wet-milling technique, which are then stabilized to prevent agglomeration. The result is an aqueous dispersion of the drug substance that behaves like a solution. The drug in nano-form can be incorporated into common dosage forms, including oral, inhalation, and injectable forms, with the potential for substantial improvements to clinical performance. To date, four products have been commercialized using Elan's NanoCrystal Technology - Wyeth's immunosuppressant Rapamune®, Merck's anti-emetic Emend®, Abbott's cholesterol blockbuster TriCor®, and Par's Megace® ES. Collectively, these products achieved in-market sales of over $1.5 billion in 2006. Additionally, 18 compounds are in Phase I or later in development for clients or as Elan-funded projects.

Nucryst

Nucryst Pharmaceuticals is employing one of the oldest antibacterials, silver. Until now, its instability and low solubility have limited its usefulness. Nucryst's nanocrystalline silver can be used to destroy vancomycin- and methicillin-resistant pathogens common to hospital environments. So far, bacteria have not developed resistance to silver in the way they have to the antibiotic molecules developed since penicillin came on the market.

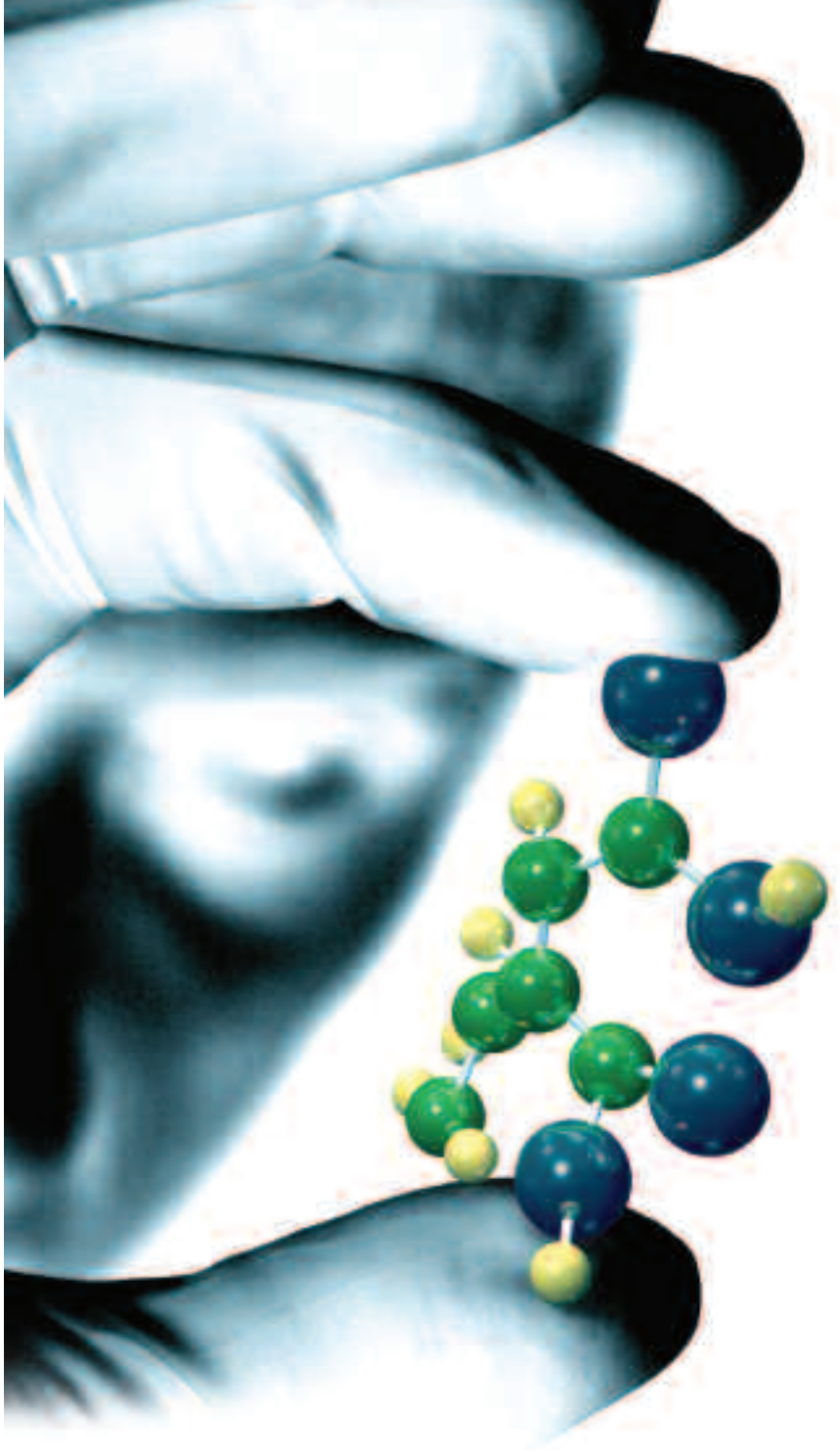
The nanocrystalline form of the silver enables antimicrobial action to take place in as little as 30 minutes, a considerable advantage over the use of bulkier silver particles. The company's first product, Acticoat, is a burn dressing, impregnated with nanocrystalline silver. When applied, it is active for at least a week, permitting a significant change for patients with large area second- and third-degree burns who previously had to suffer daily dressing changes. In addition to being antimicrobial, nanocrystalline silver is an anti-inflammatory agent and thus has the potential to treat atopic dermatitis and certain respiratory conditions.

Flamel

Flamel's Medusa, which uses nanoparticle technology to stabilize the in vivo release of human insulin, has concluded Phase IIa clinical trials. The technology takes advantage of polymeric leucine and glutamate to capture and stabilize the insulin protein, allowing for its slow and controlled release for 24 hours.

APPLICATIONS OF RESEARCH BEGINNING TO EMERGE

Many nanobiotechnology applications remain unimaginable. Several now emerging from research show promise as diagnostic agents, neurological tests, or enhanced drug delivery.



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NANOTECHNOLOGY

Diagnostic Agents

Because many of our diseases occur on a nanometer scale, as a molecular mistake in our DNA, nanometric pharmacology is an attractive research area. Cancer begins from one cell and can take up to 10 years to cause symptoms or become diagnosable. A technique to enhance detection, identifying cancer cells at the 10- or 100-cell stage, would be a tremendous asset to early treatment and prevention of metastatic cancer.

Researchers at Georgia Tech, under the Cancer Nanotechnology Excellence program of the NNI, built molecular beacons of 10 nm in diameter in the form of a multilayered sphere. A tag on the outermost layer binds to a molecular array characteristic of a particular cancerous cell, but not of a healthy cell. The inner layer contains a light-producing semiconductor 5 nm in diameter - a quantum dot - that emits light of a characteristic wave length. When illuminated by a laser, the light from a concentration of tagged cells is distinguished against the background glow that emanates from normal tissue. Shown to detect human prostate cancer cells implanted in mice, the technology shows promise as a screener for incipient cancer.

At Rice University, where the Center for Nanoscence in Biological and Environmental Engineering is part of the NNI, single-walled carbon nanotubes (SWNTs) coated with a surfactant, were used in rabbits as a contrast agent. The serum concentration, followed by their fluorescence in the near-infrared, fell exponentially, with a half-life of 1 hour. The absence of acute toxicity was considered promising, and the group looks forward to their application in pharmaceutical systems.

The Bioengineering Department at Rice is working on the medical applications of metal nanoshells with tunable optical properties. They can absorb or scatter light in the near infrared, at wavelengths where tissue and blood are relatively transparent. In one proven application, the shells absorb light, converting it to heat that destroys nearby tissue. Specific antibodies conjugated to the nanoshell surfaces will bind selectively to the corresponding cancerous cells. Exposing the tumor to the correct wavelength of light dispatches the cells to which they are bound.

Neurology

One of the most interesting uses of nanodevices has been demonstrated by a group of chemists at Harvard, also a recipient of NNI funding, who interfaced arrays of silicon nanowired transistors with axons and dendrites of cultured rat neurons. The artificial synapses could detect, stimulate, and inhibit the electrophysiological signals propagated along the axons and dendrites. The technique has potential both as a research tool and an agent for real-time cellular assays for drug discovery.

Drug Delivery

Researchers at UCLA have used mesoporous silica particles to construct supramolecular nanovalves by attaching naphthalene-containing dialkylammonium tethers to them. The pores of the silica were filled with coumarin, an anticoagulant drug, and macrocyclic polyethers then used to cap the pores, by hydrogen-bonding to the dialkyammonium ions of the tethers. An increase in the pH deprotonates the ions, breaking the hydrogen bonds, unthreading the polyether cap. The coumarin stored in the pores flows out, under control of the pH. The system has an application waiting in the targeted delivery of drugs.

At the University of London's School of Pharmacy, a group has shown that nanotubes, acting as nanoneedles, can pierce the plasma membrane of living cells and move directly into the cytoplasm without causing cell damage or death. The nanotubes pass the membrane regardless of the chemical moiety grafted onto the tubes. Targeting cancerous cells with nanotubes tagged with specific molecules that can reach the intra-cellular structures is an expected step of this research.

BIRTH OF A SCIENCE LEADS TO FUTURE HOPE

Richard Smalley, who leveraged the prestige from his 1996 Nobel Prize in Chemistry for the discovery of the "Buckyball" to proselytize, in the halls of Congress, his faith in nanotechnology as a breakthrough, was the one person most responsible for the United States' program to develop the science. He began that year, 1996, to talk to people in the government, and they listened. His skill in presenting made powerful people release the funding that the initiative needed. He did it by telling stories that could relate to the legislators and administrators, such as explaining his own alopecia from chemotherapy as a result of a crude chemotherapy that could be refined if nanoscale drugs were developed. It was Mr. Smalley who gave the NNI gravitas with his prestige and passion.

While the Buckyball has itself been a difficult molecule to use, its synthesis changed the viewpoint for carbon chemistry, until then seen by organic chemists as two-dimensional.

Nanotechnology is the United States' new research frontier. Its massive government funding and its early harvest of commercially viable products make it worthy of the investment and the scientific community's continued interest.

BIOGRAPHY

Ms. Joan Brodovsky, before joining Frost and Sullivan, was an independent consultant in Mexico City for the chemical and pharmaceutical industries. Her curriculum includes work in the quality control laboratory of a pharmaceutical laboratory; an appointment as Associate Professor at the Universidad Iberoamericana,where she taught Chemistry; and posts in both an industrial and a medical dot com as writer and editor. She also founded and directed Boxit, a record storage business. Ms. Brodovsky served at Infotec, an arm of the Mexican National Science and Technology Council dedicated to providing information services to the industry, where she held the position of Director for Services to the Pharmaceutical Industry. Her own business, Joan Brodovsky Consultores, was dedicated to providing market research to pharmaceutical and chemical industry clients. In this context, she prepared market studies on such products as radiodiagnostic agents, oncological drugs, anti-rheumatic drugs, AIDS inhibitors, and analytical instruments. She has written on the Mexican pharmaceutical industry, industrial policies in Korea, and the implications of changes in Mexican patent law. Her undergraduate degree in Chemistry is from the University of California at Berkeley and her MS is in Physiology from Stanford University. She did biochemical research at Stanford and at the Albert Einstein Medical Center in Philadelphia.


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INHALATION FOMULATION

Nebulizable Nanoparticle Dispersions: A Novel Inhalable Dosage Form

By: Andrew Loxley, PhD, and Ismar Dizdarevic

INTRODUCTION

The inhalation route, employed primarily for drugs acting in the respiratory tract, is now being expanded for use in systemic drug delivery. A properly designed drug delivery system utilizing the inhalation route can help overcome many of the hurdles associated with conventional therapies: difficult formulation, poor bioavailability, poor patient compliance, and of course, first pass issues. For example, most protein drugs are difficult to deliver through conventional delivery systems because they degrade, either partially or completely, before they reach their therapeutic target. Avoiding the digestive tract not only increases the deliverable therapeutic dose, but also lowers the risk of unintended adverse events such as irritation of the GI tract. Furthermore, by delivering drugs via nanoparticles, one is able to increase the surface-area-to-volume ratio, effectively augmenting the drug's bioavailability through faster dissolution and release rates.

AQUEOUS AEROSOL DELIVERY

In the past, systemic delivery of drugs via the lungs has been achieved by aerosolizing a solution or suspension of the active. Examples of such devices include nebulizers, metered dose inhalers, and nasal spray devices. The aerosol formed by a nebulizer consists of droplets with diameters between approximately 1 to 10 microns, an ideal size range for delivery to the lungs via inhalation. Smaller particles tend to be exhaled immediately, while larger particles tend to adhere to the back of the throat when inhaled, and do not reach the lungs.

Such targeted delivery to the lungs is not a new development by any means; a number of drugs in today's markets employ this mechanism. In hospitals, for example, Ribavirin (virazole) is delivered via nebulizer for treatment of respiratory syncytial virus and other viral diseases. However, this drug crystallizes wherever the nebulized mist lands, including equipment, bedding, and the patient, thus creating a hazard to health workers. Of course, delivery of dry powders of actives and non-aqueous dispersions of microcrystalline drugs have been in use since the 1950s in metered-dose and dry powder inhalers, though doses are typically low and the metered dose inhalers require organic propellants.

More recently, a joint venture between Pfizer and Aventis has led to the development of Exubera, an inhalable dosage form of insulin. The common thread between Ribavirin and Exubera is that both drugs are

FIGURE 1

Encapsulation of Model API 0.1% w/w Loading

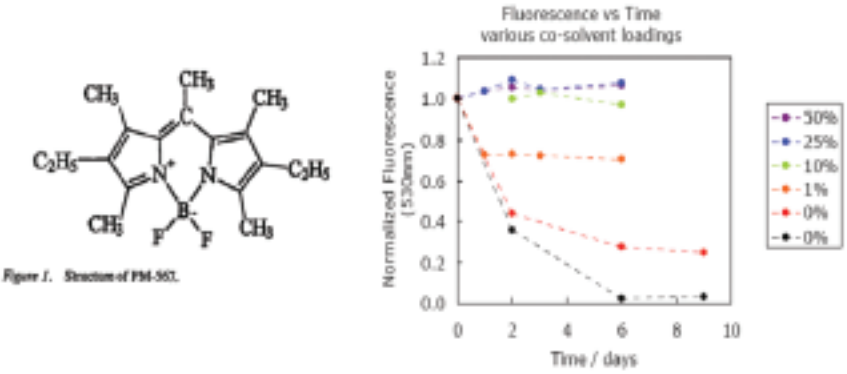


Figure 1. Structure of PM-567.

relatively water-soluble. Delivery of drugs in higher doses from aqueous vehicles is an attractive approach; Ribavirin's solubility of 142 mg/ml enables nebulized delivery in an aqueous system, while the insulin protein can be delivered as a dry powder that is bioavailable owing to the protein's inherent hydrophilic properties.

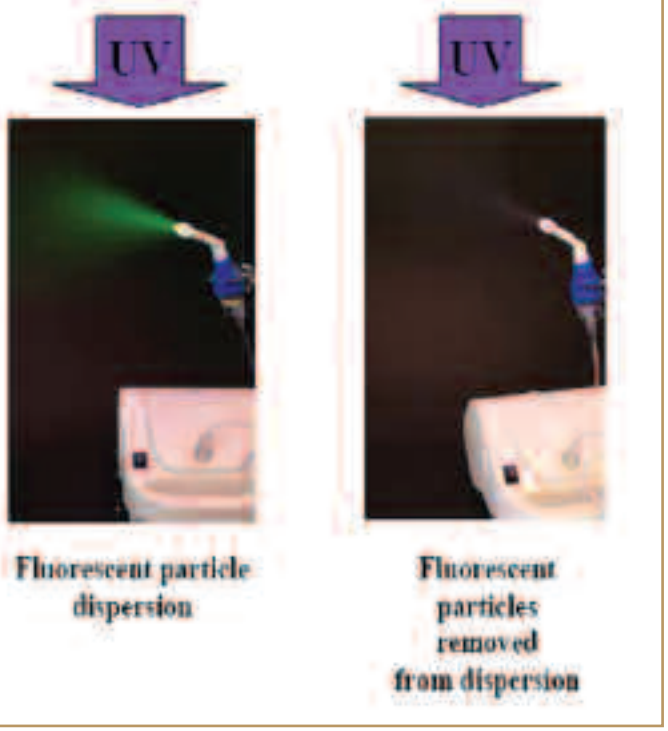
CHALLENGES & POTENTIAL SOLUTIONS FOR HYDROPHOBIC DRUGS

On the other hand, delivery of poorly water-soluble drugs presents a bigger problem for aqueous aerosol delivery to the lungs, for example larger drug particles in a dispersion of the active can, and do, block the nebulizer orifice, and can settle in the dispersion over time, causing dosage consistency issues. Thus there is a need for aqueous inhalation formulations of hydrophobic drugs that have the following characteristics: controlled particle size, improved deposition efficiency, targeting, trafficking through the mucus membrane, bioavailability, sustained release and stability (particularly for higher solids formulations).

Recently, researchers at Particle Sciences developed a technology by which hydrophobic APIs can be encapsulated in wax nanoparticles in aqueous dispersion that can be effectively nebulized via an over-the-counter nebulizer. For nebulization studies, nanoparticle dispersions were prepared in which the nanoparticles contain either a hydrophobic fluorescent dye for particle tracking studies, or a hydrophobic non-nucleoside reverse-transcriptase inhibitor HIV microbicide as proof of concept for hydrophobic drug encapsulation. A proprietary melt-chill process was used to prepare the active-loaded nanoparticles, using only biodegradable, non-toxic, Generally Regarded As Safe (GRAS) excipients, such as natural carnauba wax. Figure 1 shows the molecular structure of the pyrromethene 567A fluorescent dye, and the fluorescence stability of the nanoparticle dispersion in which it was encapsulated. A 10% co-solvent is required in the nanoparticles to maintain fluorescence for longer than 1 week. Below this concentration, aggregation of dye molecules within the particle appears to lead to fluorescence auto-quenching. This suggests that a small amount of co-solvent should always be used when encapsulating the API to maintain stability.

FIGURE 2

UV Analysis of Nebulized Plume



The nanoparticle dispersions containing dye were readily prepared with a Z-average particle diameter of 480 nm and when nebulized, the plume glowed to a brilliant green under black light illumination, indicating the presence of fluorescent particles in the aerosol droplets (Figure 2). To confirm the fluorophore was encapsulated within the wax nanoparticles and not simply dispersed in the water phase, the nebulized dispersion was collected,

FIGURE 3

Droplet Size Distribution of Nebulized Aerosol

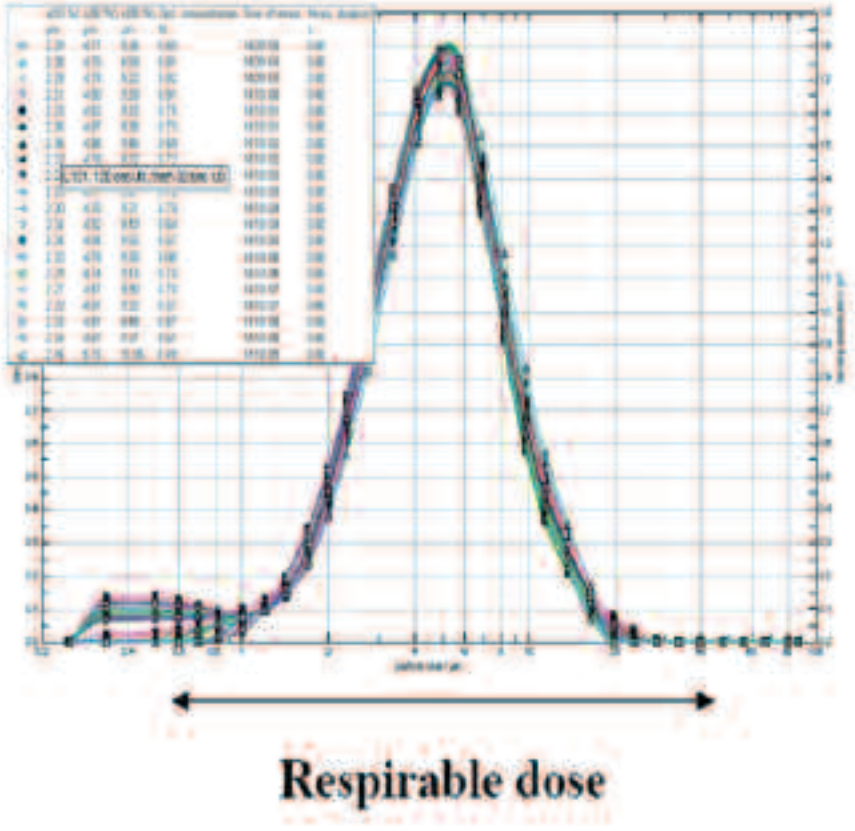


FIGURE 4

NGI Used at MSP

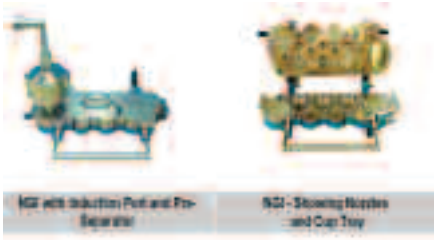
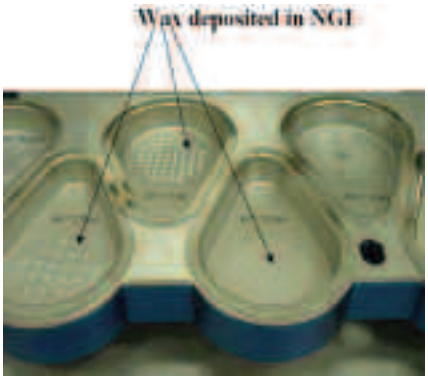


FIGURE 5

Wax Deposited Efficiently in NGI



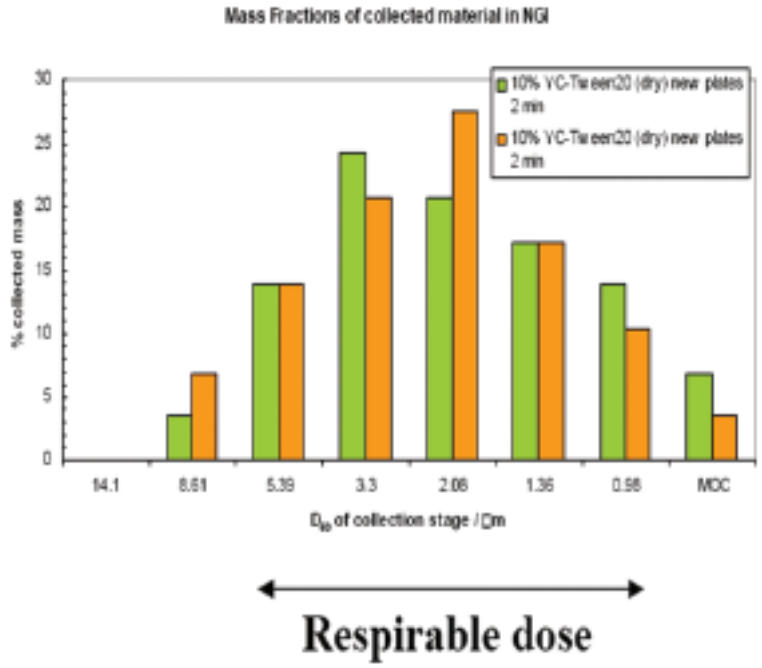
centrifuged to remove particles, and the supernatant examined for traces of dye. As expected, the supernatant showed zero fluorescence. Conversely, the plume formed by nebulizing the fluid after removing the particles by filtration does not fluoresce. The nanoparticles were the same size after nebulizing the dispersion as before, indicating good dispersion stability upon nebulization.

To guarantee that the formulated wax particles formed aerosol droplets of a respirable dose, real-time particle sizing of the nebulized mist was required. Collaborators at Sympatec Corp. in Lawrenceville, New Jersey, determined the size of the aerosol droplets containing the 480-nm wax particles using a HELOS Laser Diffraction Particle Size Analyzer. Figure 3 illustrates that the majority of nebulized droplets have diameters that fall well within the ideal range for maximizing respirable dose, with a D50 diameter of 4.8 microns, and D90 diameter of 9.5 microns.

With a reliable method to encapsulate drugs in wax nanoparticles stable enough for nebulization, forming aerosol droplets of the appropriate size for pulmonary delivery, all that remained was to determine if the droplets had the ability to target even the deepest lung cavities. For the final phase of the project, Particle Sciences' researchers collaborated with MSP Corp. in Minneapolis/St. Paul, the manufacturer of the Next Generation Cascade Impactor or NGI (Figure 4). This device is used to simulate deposition of particles into the lung. The deposition distribution of the nanoparticles in the NGI was

FIGURE 6

Fractional Deposition Distribution - The Wax Nanoparticles are Deposited Ideally for Pulmonary Delivery



determined. The photograph in Figure 5 shows that the majority of nanoparticles (27%) were recovered from the stage of the NGI in which 2-micron aerosol droplets containing them were collected. All of the nanoparticles were deposited in stages corresponding to 0.96- to 8.6-micron aerosol droplets, as shown by the fractional deposition histogram in Figure 6. This demonstrates that the nanoparticles should be readily delivered to the lungs when delivered via nebulizer.

PARTNERSHIP OPPORTUNITIES

Having successfully produced stable nanoparticulate dispersions of encapsulated poorly water-soluble dyes and drugs, and demonstrating that these nebulized dispersions are ideal for pulmonary delivery, Particle Sciences filed for patent coverage of the technology and is now in talks with potential partners interested in applying the technology to their pulmonary delivery projects in areas such as cystic fibrosis and asthma treatment.

BIOGRAPHY

Dr. Andrew Loxley, is Manager of Special Projects at Particles Sciences Inc., a contract research organization in Bethlehem, PA, specializing in pharmaceutical formulation development. He leads a variety of projects, many based on novel and proprietary nanotechnologies, in fields from HIV vaccine and microbicide development to gene-silencing SiRNA delivery. Prior to joining Particles Sciences, he worked as a researcher in the nanotechnology space. British-born, he earned his BSc in Chemistry from the University of Sussex and his PhD in Physical Chemistry focusing on Microencapsulation from the University of Bristol.

Mr. Ismar Dizdarevic, born in Bosnia and Herzegovina, raised in New Jersey, earned his BS from Lehigh University. He is currently pursuing a degree in Medicine at Jefferson Medical College.

Special Feature

Hand-Held Injection Systems Boast Safety & Efficiency

By: Cindy H. Dubin

Contrary to the belief 10 years ago that novel delivery systems would take the place of injection systems, the hand-held injection market has proven that it has the ability to get product into the body faster and easier than ever before. Finer needles and autoinjectors have helped improve the method of injection by making the delivery systems more user friendly, eliminating the fear of pain by many patients. Thus, the line between needle-based and needle-free devices is not as sharp as it once was.

The hand-held market today is being driven by multiple factors, says J.D. Haldeman, VP, Commercial Strategy & Corporate Communications at Zogenix, Inc.

First, the shift in treatment setting continues, from the office and clinic, to homecare and medication self-administration. This shift is primarily driven by payers who are seeking to drive treatment to lower cost sites of care. Patients undertaking self-administration need the assistance of hand-held delivery systems. Further, consumers are becoming more interested in understanding and participating in their own care, increasing the use of medications in the home. Finally, the products themselves are driving the market. As hand-held devices become easier to use, and as more products are available, patient uptake will continue to grow.

Biopharmaceutical research and development is sure to significantly increase the number of injectable drugs coming to market throughout the next few years. Biotech also plays a big part in the market growth. In 2005, global biotech revenues reached more than $60 billion. This represented a 16.5% increase over 2004, and this rate of growth is expected to continue through the decade. Some estimates have the market doubling by 2011. Traditionally, biotech drugs have targeted serious indications and orphan diseases. In 2004, three of 10 orphan drug approvals by the FDA were biopharmaceuticals. Due to the seriousness of these diseases, the focus has rightly been on rapid efficacy. In the process, the concepts of minimally invasive therapies or patient-friendly delivery systems have taken a back seat.

However, the future of biotech lies in more prevalent diseases and products aimed at much broader patient populations, and the focus will also increasingly be

FIGURE 1

Antares Pharma's Hand-Held Injection Devices A) Medi-Jector Valeo™ B) Medi-Jector Vision® C) Vibex™

on chronic diseases. In this new world, delivery methods that lead to higher patient acceptance will be key, including novel delivery forms for self-administration, such as hand-held devices. These must be simple, to eliminate as many variables as possible, and ensure accurate delivery.

While advanced drug delivery techniques continue to hold promise for unique methods of administration, the traditional injection is still the dominant paradigm. However, the costs and intransigent safety problems associated with sharps, along with consumer demand and the move to alternate-site care, are pushing for alternatives to traditional needles and syringes faster than advanced delivery technologies can come online. The alternative in the short-term appears to be the growing industry of needle-free injection and safety-engineered syringes. These devices, ranging from simple sheathed safety needles to complex gas jet injection systems, are competing in a vigorous marketplace, some sectors of which are growing at an annual rate in excess of 20%.

"We have been using needle technology from the 1800s to deliver 21st century, cutting-edge biotechnology drugs," says Ms. Haldeman. "It is time for the future of hand-helds, the future is now, and the future is needle-free."

She says that needle-free has all the obvious advantages of eliminating sharps hazards and disposal, a key focus for both healthcare providers and patient users. Further, needle-free opens the market to the many patients who have resisted more effective therapies simply due to their fear of needles and self-injection. Finally, needle-free is simply easier to teach, easier to use, and easier to dispose of. Ease-of-use and human factors are also at the forefront for all patient-used technology. Patients are no longer accepting complicated devices — doctors/staff don't have time to train patients, and patients are demanding better. A product that requires more than three to five steps is going to become a thing of the past. And, the FDA is becoming more demanding in terms of usability testing and clarity of patient instructions, adding further pressure to increase ease-of-use.

NEEDLE-BASED DEVICES

According to Mark A. Hassett, Executive Vice President, Sales, Marketing, Business Development of SafetySyringes, Inc., the US safety (syringe) device market is growing rapidly due to competitive pressures.

"In the therapeutic fields of LMWH, EPO, vaccines, and self-injection, the move to better/safer delivery devices is now being influenced by pharmas adopting such devices, giving them potential market share advantages. Therefore, other competitive indications are reacting to stay competitive and hold market share."

In the EU, the these same therapeutic fields are being driven by more forceful legislation, ie, TRBA 250 in Germany, which made the use of safety devices mandatory as of August 1, 2007.

Add to this the fact that as homecare administration of drugs becomes more prominent in the industry, it is important that hand-held technology be accessible to a broader range of end-users. For this reason, future device designs will be more complex as they focus more than ever on safety, ease of use, and accuracy of dose delivery, says Daniel MacDonald, Vice President, Engineering Services, Duoject.

There is also more talk about drug reconstitution, and many delivery companies, like Duoject and West Pharmaceuticals, are developing transfer systems that take a powder drug and liquefy it for injection.

"Although the goal of many pharma companies is to provide drugs in liquid form for efficient administration, many drugs are not sufficiently stable in solution and are required to be in dry form," explains Mr. MacDonald. "It is therefore important that the hand-held technology industry develop intuitive devices that cater to the dry-form drug market as well as the liquid form."

NEEDLE-FREE INJECTION

Long considered a niche technology with limited practical value, needle-free injection (NFI) is about to shed its image as an out-of-the-mainstream drug delivery technique, according to a new report from Greystone Associates. The convergence of improved device designs, patient sentiment, and new therapeutic applications is re-making NFI into an attractive technology being pursued by a number of major pharmaceutical companies. As interest in NFI increases, collaborations and acquisitions between NFI companies and drug developers are reshaping the competitive landscape.

In the past year, the level of alliance activity between injection device designers and drug developers has heated up, reflecting the convergence of a number of market forces. Collaborations and licensing deals executed in 2006 include Teva's deal with Antares for the development and supply of a new disposable injection device; Aradigm's asset sale of its Intraject technology to Zogenix, which plans to complete development and commercialize the Intraject Sumatriptan product for migraine; and Biovalve's sale of a majority interest in its Valeritas drug delivery subsidiary to Paramount Acquisition Corporation. Greystone expects this trend to continue throughout 2007.

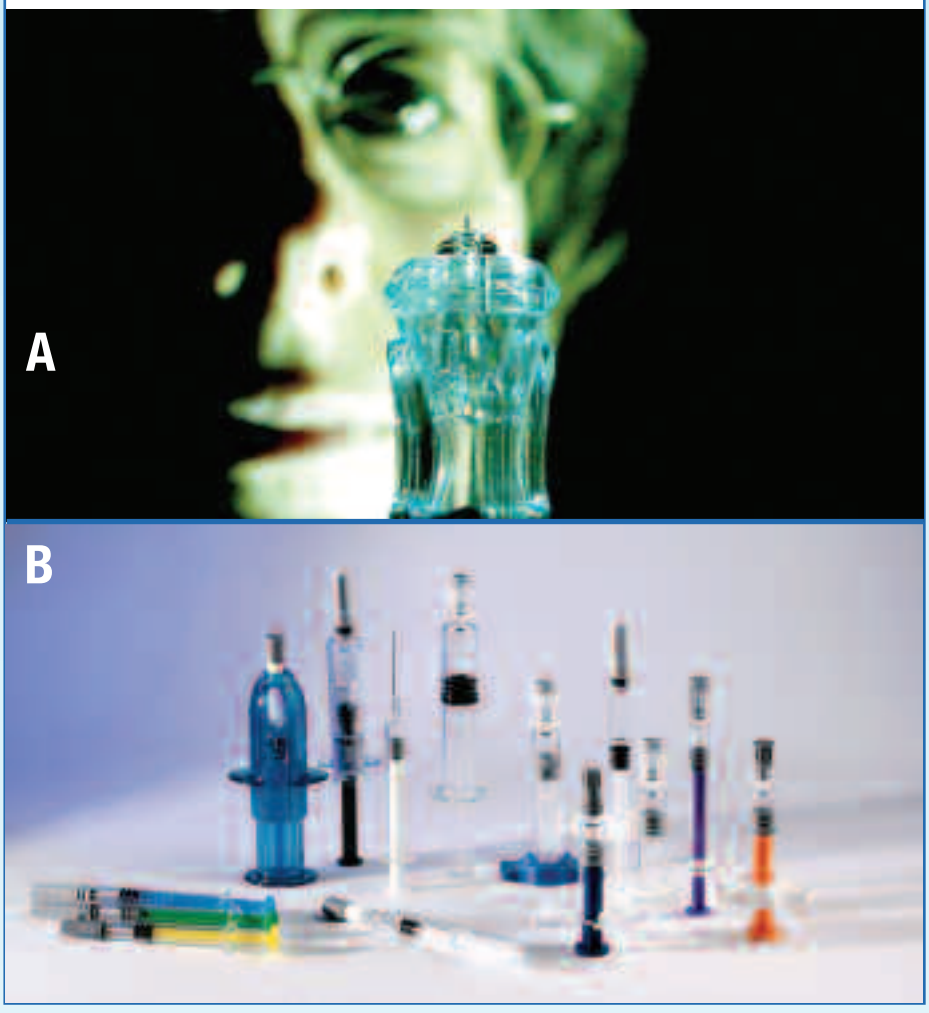
Mike Kasprick, Vice President, Business Development, Devices Group, Antares Pharma, agrees with Greystone's insights. "There is a recognition of the potential value added by needle-free devices, and the resulting evolution of some device developers to become Specialty Pharma companies based on this opportunity. Looking back throughout the past year, you can see the changes in our industry. In addition, we have seen the drug developers recognize the potential value of needle-free injection and the relatively low development costs and risks in comparison to other delivery technologies, such as pulmonary."

According to Mr. Kasprick, the following are some of the key market drivers for needle-free devices:

- The number of injectable products being developed/launched is increasing, driven by robust biotech pipelines that contain many large-molecule compounds that must be injected.
- The trend toward self-administration is continuing to grow, driven by the need for frequent administration of many new injectable products along with the desire to control healthcare costs associated with

FIGURE 2

BD Medical – Pharmaceutical Systems' Microneedle (A) & Various Hand-Held Devices (B)



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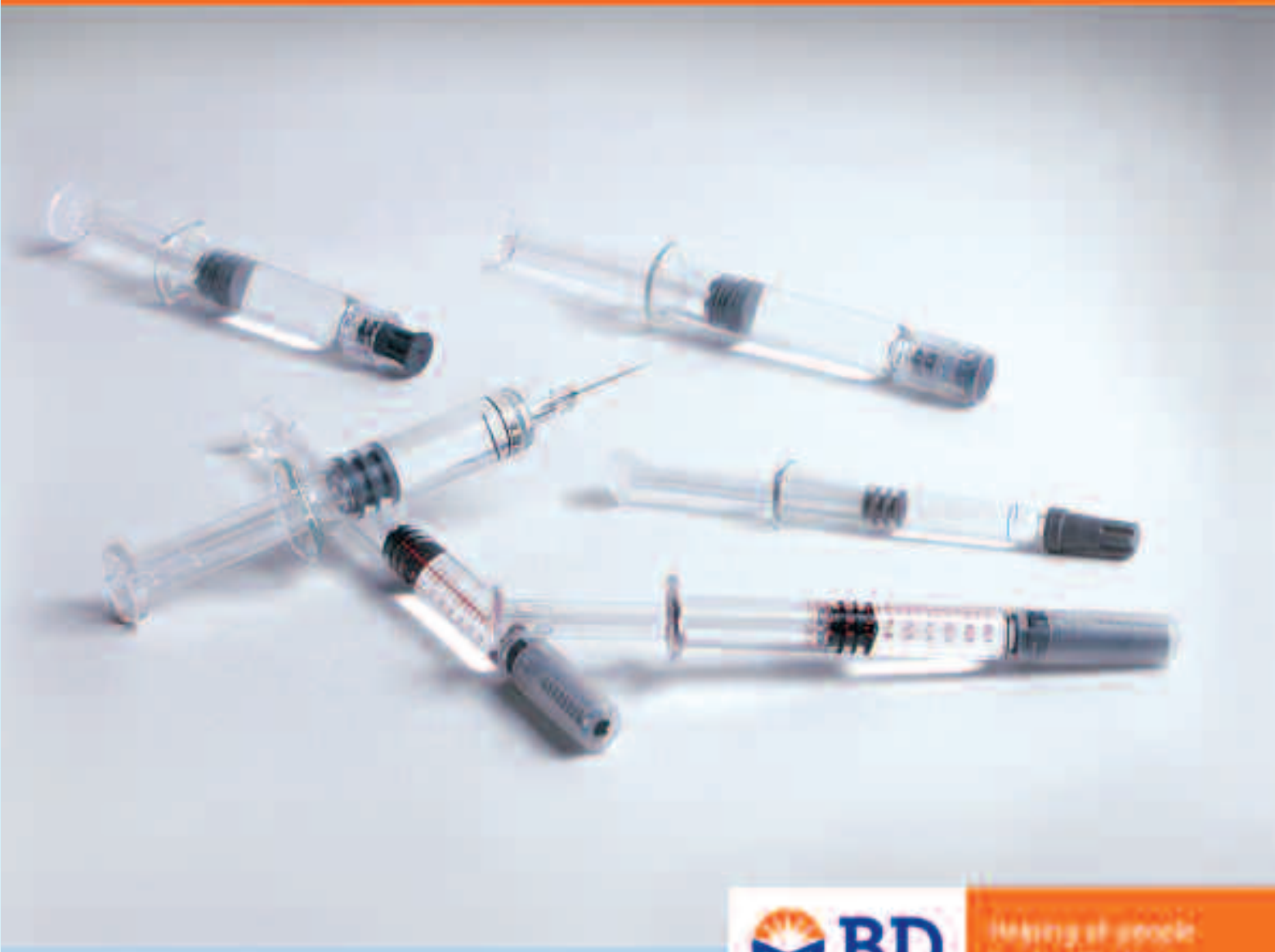

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- There is increasing demand for product differentiation, which is frequently offered by delivery system as seen in the growth hormone market.

Additionally, the biotech revolution is bringing in a range of protein-based therapeutics into the marketplace at a rapid pace (more than 300 products in active development). These protein-based therapeutics, especially monoclonal antibodies (MAbs), which are otherwise challenging to deliver non-invasively, will continue to be formulated as injectables. There appears to be tremendous opportunity for needle-free technology to have a major impact in the industry.

ANTARES PHARMA FOCUSES ON REUSABLE DEVICES

Antares is responding to the aforementioned by providing needle-free injection technology for drugs in key market segments. The ValeoTM injection device is Antares Pharma's next-generation reusable needle-free injector. It is a pen-style injector that incorporates a glass cartridge as the drug container, whereas the current product, the Medi-Jector Vision®, draws the drug from a conventional vial prior to injection. Mr. Kasprick says Antares' goal in developing this device was to make it smaller and more portable for patients.

"The VibexTM mini-needle injector competes in the autoinjector space," he adds. "It incorporates a glass, prefilled syringe, but adds some benefits: 1) the short needle insertion depth ensures that the drug is delivered to the target subcutaneous tissue and not as deep as the muscle tissue; 2) it is a very simple and intuitive 3-step device (remove safety, remove device cap, press against injection site); 3) patients like the device because it provides a quick (less than 2 seconds) and comfortable injection; and 4) it can deliver viscous materials effectively due to its higher injection force."

"We offer commercialized injectors in the fields of growth hormone and insulin administration. We also have a collaboration with Lilly for the fields of diabetes and obesity — two fields of significant importance and opportunity. Antares is focused on reusable needle-free devices for treatment of chronic conditions. We have chosen to focus on this segment of the market because of the significant market opportunity from these fields and because of certain technical challenges associated with prefilled needle-free injectors that might be used for short-term or intermittent injection regimens," says Mr. Kasprick.

FIGURE 3

Duoject's Airless DC, a Reconstitution Device Specific for Microsphere Resuspension

BD INVESTIGATES MICRONEEDLES & PREFILLED SYRINGES

BD Medical – Pharmaceutical Systems offers a variety of prefillable syringes and self-injection devices. BD provides a wide range of parenteral drug delivery systems, which are designed to meet healthcare professionals' demands for safety and convenience while fulfilling patients' needs for comfort.

According to Philip Green, Director, Alternative Drug Delivery Systems, BD is investigating the use of microneedles to deliver a variety of drugs and vaccines. "These hand-held microdelivery technologies have the ability to target the delivery of vaccines, anti-cancer agents, and other drugs to specific parts of the body," he says. "Throughout the past few years, BD has generated exciting preclinical and clinical data, and we currently have several important collaborations in this area. This includes our relationship with sanofi-pasteur as well as multiple research partnerships in the area of therapeutic cancer vaccines."

BD Medical – Pharmaceutical Systems' primary business is focused in the area of needle-based delivery systems. However, BD has already developed a nasal delivery system (BD Accuspray™), which provides non-invasive delivery of drugs and vaccines to the nasal passage in a convenient Hypak™-based prefilled delivery system. BD Accuspray is currently on the market to deliver the flu vaccine known as FluMist® (sold by MedImmune).

In addition, BD has recently created a new group within the BD Medical - Pharmaceutical Systems unit known as Alternative Delivery Systems (ADS) to

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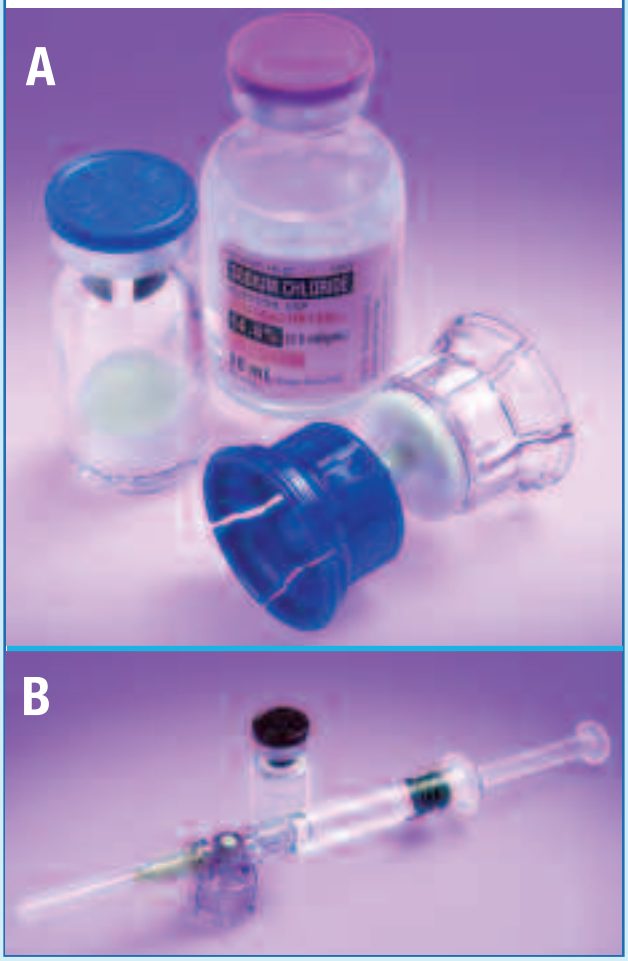
FIGURE 4

West Pharmaceutical Services' Mix2Vial (A) needleless reconstitution systems enable simple vial-to-vial transfer and mixing between diluent vial and lyophilized drug vial. The MixJect (B) transfer system is a single unit for reconstituting a powder drug with a diluent prefilled syringe. Upon reconstitution, the drug is available for immediate injection with a dry integral needle.



investigate opportunities for new emerging delivery technologies. The group will focus on both needle-free and needle-based technologies to solve unmet needs within the pharmaceutical industry.

In the area of needle-based delivery, Mr. Green sees many hot areas that are being worked on by industry. Two examples he believes to be promising for the future include use of microinfusion pumps for convenient non-IV delivery of high volume (> 2 ml) of liquids; and enhanced immunization of prophylactic and therapeutic vaccines using minimally invasive systems, such as microneedle delivery technologies.

Brian Lynch, Senior Product Manager, BD Hypak, says, "Overall, we have seen that the market is more focused on safer delivery systems and administration practices to reduce errors. We have also seen a shift toward unit-dose packaging to better enable drug traceability in the marketplace. The use of prefillable syringes can help address each of these issues."

"On the vaccine side, we have seen the continued trend for preservative-free container closure systems," says Janice Fajarito, Product Manager, BD Hypak. "This has fueled the trend away from multi-dose vials for vaccines and toward unit-dose packaging, primarily prefillable syringes. This has also helped extend vaccine availability because of the significant reduction in overfill required with prefills (versus vials). Additionally, we have seen an increasing number of pharmaceutical companies use delivery devices as a means to differentiate their drugs in the marketplace."

According to Mr. Green, there has been a major increase in the market size of biotechnology drugs throughout the past few years to which BD is well poised to respond. In parallel with the market expansion, Mr. Green also notes an increase in pharma pipeline and acquisition activity for novel biologicals, specifically monoclonal antibodies, antibody fragments, and vaccines. These agents cannot be delivered via the oral route and need to be injected via IV, subcutaneous, or intramuscular means. Many of the diseases that are being targeted for these new agents are chronic in nature and require frequent administration over long periods. Much activity is in the area of autoimmune diseases (eg, arthritis and psoriasis), MS, diabetes and obesity, macular degeneration, Alzheimer's disease, immunotherapy of cancer, and respiratory disease. Chronic administration of these agents in non-hospital settings is clearly highly desirable.

He says BD is responding to these market drivers by offering a series of new and emerging drug delivery products, including liquid and reconstitution self-injection pens and autoinjection technologies as well as microinfusion systems for subcutaneous delivery of agents that cannot be readily delivered using hand-held self-injection systems.

"Microneedles are also being developed to meet the needs of emerging vaccines. As mentioned earlier, we have also created the ADS group to investigate opportunities for BD in new emerging delivery technologies, says Mr. Green."

"With the continued growth in the vaccine and biotechnology sectors, there has been a need for the scientific understanding of the compatibility of complex molecules and container closure systems," adds Mr. Lynch. "Through collaboration with customers, BD is focused on developing solutions to ensure long-term drug suitability for prefillable drug delivery systems."

In the area of glass prefillable syringes, BD has developed two novel container closure systems that address healthcare market needs for security and

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BD Medical – Pharmaceutical Systems has three new self-injection technologies: a disposable autoinjector; a next-generation reconstitution system; and a solution for delivering high-volume, high-viscous drugs into the subcutaneous tissue. The main features of these products are that they are intuitive, easy-to-use, and require a minimal number of steps, says Michael Ratigan, Worldwide Self-Injection Platform Director.

The microinfusion and microdelivery systems are currently in clinical testing with BD partners, and the company expects its first products to be launched around 2010.

DUOJECT TACKLES LYOPHILIZATION

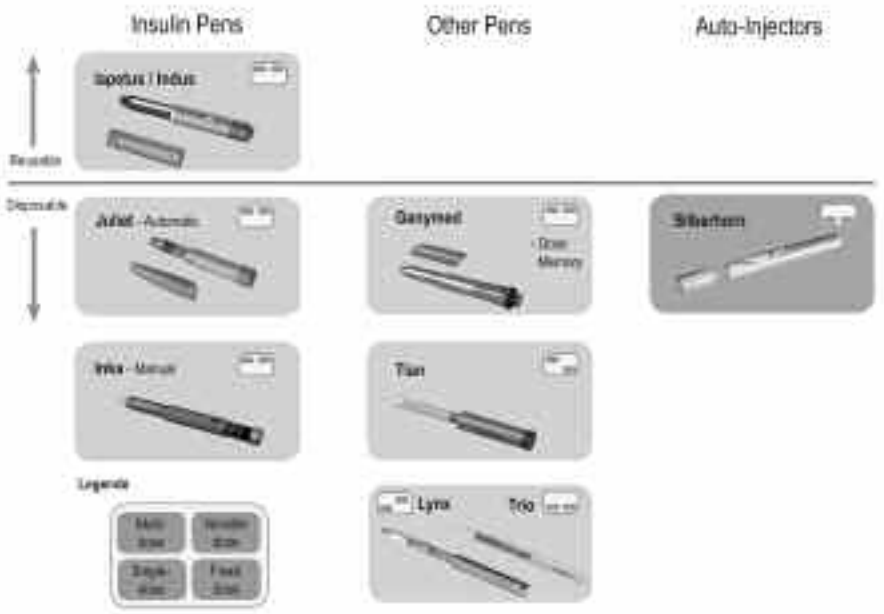
Duoject specializes in Injectable Drug Transfer and Delivery devices for the biotechnology and pharmaceutical industry. It is focused on lyophilized drug reconstitution devices for packaging a range of medications for hospital settings as well as homecare use. Recently, Duoject developed the Airless DC, a reconstitution device specific for microsphere resuspension.

A special feature of the Airless DC, when connected to a double-chamber reconstitution syringe, is its ability to eliminate air in the system before resuspension. It provides a separate sterile container into which the admixture "slurry" is quickly transferred. During this transfer, the proprietary piston in the Airless DC permits all of the head-space in the device to escape through a special hydrophobic membrane. Transferring the admixture back and forth from one container to the other provides efficient high shear and airless mixing of the microperes, greatly improving resuspension consistency.

According to Mr. MacDonald, Duoject takes pride in the fact that all of its reconstitution technologies provide safe, simple, and accurate operations for the end-user, such as the absence of exposed needles, minimal number of user steps, and low drug hold-up. Duoject also customizes each of its devices to fit the specific requirements of the drug application, which ensures an optimal, and in some cases, proprietary delivery device for its pharma clients.

"Although today's hand-held devices, such as pen injectors, are mostly used for multidose delivery of liquid drugs, many dry form medications can now be reconstituted before injection using devices such as Duoject's Pen-Prep XR system, which rehydrates and prepares the drug for injection by traditional pen injector systems," says Mr. MacDonald.

FIGURE 5



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WEST PHARMACEUTICALS OFFERS TRANSFER SYSTEMS

According to Graham Reynolds, Vice President, Reconstitution and Transfer Systems of West Pharmaceutical Services, biotech drugs are driving the need for users to mix or reconstitute the product before injection. "Our focus is on making that process safe, effective, and convenient, while retaining the efficacy of the injection," he says.

West has several products on the market to enable patients, caregivers, or healthcare professionals to reconstitute products in a variety of environments. MixJect™, used by Bayer Schering Pharma for Betaseron™, a treatment for MS, is a convenient system that enables

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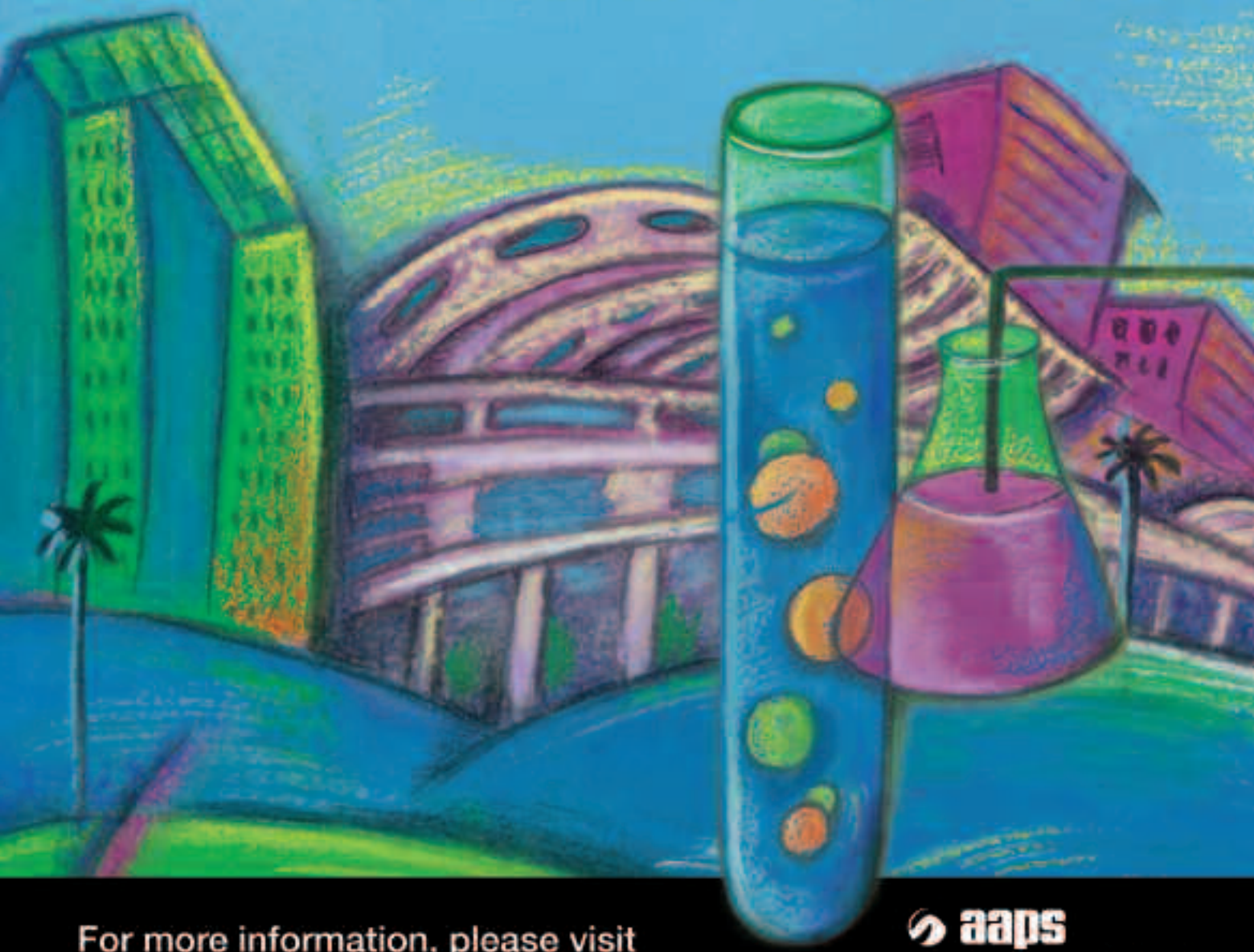

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simple preparation of powder drugs to be reconstituted by a diluent from a prefilled syringe. The reconstituted drug in the syringe can then be administered using an autoinjector or by direct injection.

Mix2Vial™ is a dual-sided device that allows rapid transfer of the diluent from a vial into a drug with a vacuum. The mixed drug is easily transferred into a syringe. Mr. Reynolds says this needleless system is ideal for hemophiliacs and is marketed with drugs, such as CSL Behring's Helixate™.

Vial2Bag™ is a needleless system that enables safe and convenient reconstitution and transfer of a drug between a vial or syringe and any solution-filled IV bag. The system connects to standard IV bags through the IV set port so it can be used with all manufacturers' bags.

Finally, West prides itself on its needle-free transfer device (NTD™), which facilitates the rapid transfer of a diluent into vials.

YPSOMED'S PLATFORM APPROACH

Ypsomed has taken a platform approach to meet the growing market needs for innovative customized injection devices. The platform technologies are developed with direct handling input from customers and patient groups to reach of proof-of-concept as quickly as possible. To do this, Ypsomed has broadened its pre-project development, handling study evaluation, and industrial design capabilities. This allows Ypsomed to provide the most innovative injection systems while keeping project times for our partners as short as possible, explains Ian Thompson, Head of Business Development, Ypsomed AG.

"We have six key disposable device platforms covering insulin pens, fixed-dose and dose memory pens, dual-chamber cartridge pens, and disposable autoinjectors. Of these platforms, the disposable dual-chamber pens and the disposable autoinjector are meeting the most interest in the growing market for new biologic therapies. The main reusable device we are focusing on is a reusable insulin pen with an automatic injection feature to help patients perform injections using fine pen needles."

Continues Mr. Thompson, "Ypsomed disposable pen and autoinjector devices are highly developed yet easy to use technologies with the full set of convenient features, such as easy-to-read displays and audible/tactile feedback. Needle safety is a standard feature of the disposable autoinjectors, and our new safety pen needle provides the same level of safety for the cartridge-based pen devices."

He indicates that the demand for Ypsomed devices is growing based on a broad range of new injectable therapies. "We are also gearing up to handle pharmaceuticals so that we will be able to provide final assembly of the prefilled cartridge or syringe with the device."

ZOGENIX EXPLORES PROTEIN ADMINISTRATION

Zogenix is responding to market trends in multiple ways. "First and foremost, our goal is to make the administration of subcutaneously injected medications as simple as possible," says Ms. Haldeman. "Our Intraject technology takes literally just three steps to deliver, encouraging broader patient use and patient confidence that they really can deliver their medication properly themselves."

FIGURE 6

Zogenix's Intraject technology takes literally just three steps to deliver, encouraging broader patient use and patient confidence that they really can deliver their medication properly themselves

Zogenix is also a Specialty Pharmaceutical company with a unique perspective —it combines the sensibility of a drug company with the technology of a drug delivery system. Zogenix has begun to explore the administration of proteins and monoclonal antibodies using the Intraject technology, and the results are promising, she says. "Given its profile, Intraject may prove to be the perfect delivery method for biopharmaceutical administration," says Ms. Haldeman. Intraject is also particularly suited to delivering highly viscous medications, such as biotech drugs and depot-type products, which are also experiencing market growth.

"When Intraject enters the market, it will be the culmination of more than a decade of development to bring this technology to market," she adds.

Zogenix's key focus is preparing for, and successfully launching, its first product, sumatriptan in its needle-free delivery system. "As the first and only injectable triptan in a simple, needle-free delivery system, we provide the quickest possible relief for migraine sufferers, in the easiest-to-use delivery system. Our product is prefilled, single-use, disposable, and requires just three steps to deploy," adds Ms. Haldeman.

"We believe our sumatriptan product has the opportunity to grow the market in a unique way. Physician research reveals that 50% of migraine sufferers will not entertain the idea of a needle injection. However, with a simple, needle-free delivery system like Intraject, nearly 100% of doctors say they will be more willing to offer this to their patients — and they expect many of them to try it. This will grow the current injectable sumatriptan market beyond its current $200 million mark into the multi-billion dollar oral and nasal triptan market. We are also looking for other product candidates to put in our needle-free delivery system. And, we have had broad interest from a number of companies who would like to explore using our technology to deliver their products, particularly biotech products."

The target audience for sumitriptan is migraine and cluster headache sufferers and those who treat them. Zogenix is currently preparing its NDA for this product and will launch it upon the sumatriptan patent expiration in February 2009.

On a braoder note, R&D activities are varied. The company is investigating multiple different medications that are candidates for use in its delivery system. Zogenix is also investigating future generations of its current delivery system.

SUMMARY

Whether needle-free or needle-based, industry experts predict that the quest continues for smaller, painless, safer, and more efficient hand-held injection systems. Companies will find novel ways to differentiate their technologies to meet the demands of pharma and biotech firms as well homecare providers and most importantly, patients.

Ms. Haldeman predicts that the hand-held injection market will explode, "and needle-free will lead the way." She adds, Due to the growth of biotech products for more common diseases, and the pressure of payers, more product will move from delivery by healthcare providers to delivery by patients and consumers. In this environment, hand-held injectors will have to become more intuitive and easier to use. Once needle-free is established in the market, consumers and healthcare providers will come to expect the safety and ease of use it affords. No longer will 21st century drugs be delivered in technology from the 1800s. Needle-free will be the technology that finally drives this change."

"I expect we will see more customization of delivery technologies rather than "off-the-shelf" offerings as pharma and biotech companies look for devices to differentiate their product offerings or for devices that solve specific delivery challenges (large/small doses, high-viscosity materials, etc)," says Mr. Kasprick of Antares. "I also believe that we will see a philosophical shift from viewing injection devices as convenience items to viewing them as a critical element of a successful drug product as they reduce the barriers to self-injection, thereby increasing patient compliance, and as they help ensure proper administration of the drug."

Mr. MacDonald of Duoject agrees that improving patient compliance is essential to the success of the injectable market. "The recent increase in controlled-release drug technologies, such as microspheres, provides a major benefit in the injectable market by reducing the number of injections a patient will receive over the course of his treatment."

The same is echoed by West Pharma's Mr. Reynolds. "People want simple and effective ways to get drug into the body. If that is not orally, the traditional way is injection. There will always be a place for injectables."

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.

ADSORPTION

Adsorption in Pharmacy: A Review

By: H. Dureja, MPharm, and A.K. Madan, PhD

INTRODUCTION

Adsorption is the phenomenon by which the molecules of gas, vapor, and liquid spontaneously concentrate at a contacting surface without undergoing chemical reaction, thereby forming a surface or interfacial layer.[1] The material in the adsorbed state is called the adsorbate, and that in the adjacent bulk gas or liquid phase is the adsorptive. The adsorbing solid material is termed the adsorbent.[2] Adsorption has been extensively reviewed in the past, and applications of adsorption in the diverse areas of pharmacy have been reviewed in the present article.

Although certain phenomena associated with adsorption were known in ancient times, Scheele in 1773 and Fonata in 1777, who reported some experiments of uptake of gases by charcoal and clays, carried out the first quantitative observations. Systematic studies of adsorption that date from the work by de Saussure started in 1814; he discovered the exothermic character of adsorption processes and was the first to pay attention to the commonness to adsorption. Chappuis measured adsorption of ammonia on charcoal and asbestos at a constant temperature. He made the first calorimetric measurement of heat evolved during wetting of adsorbents by liquids. The term adsorption was proposed by du Bois-Reymond but introduced into literature by Kayser in 1881, and he introduced the terms adsorption and isotherm or isotherm curveas well as developed some theoretical concepts that became basic to the monolayer adsorption theory.[3]

In general, adsorption appears to take place as a result of unsatisfied forces on a surface creating a force field in the immediate environment, which attracts and holds for the finite time the molecules of contacting species. In practical terms, the adsorption energy determines the strength with which the molecule is adsorbed relative to other molecules in the force field. Adsorption reduces the imbalances of attractive forces that exist at the surfaces of all solids and hence reduces the surface-free energy of the heterogeneous systems. Adsorption can result either from universal van der Waals interactions (physical adsorption, physisorption), or it can be a character of a chemical process (chemical adsorption or chemisorption).[4] Various characteristics of these two types of adsorption are provided in Table 1.[2,5] In adsorption, a solid is used to remove a constituent from a fluid by selective forces existing on the solid surface. The solid is usually in a form that provides a very large surface-per-unit weight, which implies that the adsorption is porous in nature. The forces that keep the solute on the surface of adsorbent are residual valency forces, and the unoccupied sites get filled up by the striking molecules, the rate of adsorption decreases until at equilibrium, when the number of molecules that strike the surface and get retained will equal the number of molecules that rebound from the surface-per-unit time.[6]

The fundamental concept in adsorption science is the adsorption isotherm. The correct interpretation of an experimental adsorption isotherm can be realized in terms of mathematical adsorption equations. There was no such theory that enabled interpretation of adsorption isotherms before 1914. The Freundlich equation was used but was not

TABLE 1

	Physical Adsorption	Chemisorption
Specificity of surface adsorption sites of reaction	Low	High
Adsorbate structure	Monolayer and/or multilayer	Only monolayer
Changes in electronic state (visible, UV, IR spectra)	Weak: Polarization	Strong: Electron transfer
Chemical nature of adsorptive in the adsorbed state	Unchanged	May be (irreversibly) changed
Energy of adsorption	Low, < 2 or 3 times latent heat of evaporation	Very small to very high; exothermic or endothermic
Activation energy	None	Small to high
Adsorption-desorption	Reversible	Irreversible
Rate of adsorption (excluding transport process)	High	Depends on activation process
Temperature dependence	Decreasing with increasing temperature	Depends on reaction; possible over a wide temperature range

Characteristics of Physical Adsorption & Chemisorption

justified theoretically. According to McBain, Van Bemmelen proposed the empirical equation in 1888. The so-called Freundlich adsorption isotherm was also proposed by Boedecker in 1895 as an empirical equation. This equation is known in literature as Freundlich's equation because Freundlich assigned great importance to it and popularized its use. In 1914-1918, there were two independent descriptions proposed for the adsorption phenomenona. These descriptions were associated with such names as Langmuir and Eucken as well as Polanyi. Langmuir, for the first time, introduced a clear concept of the monomolecular adsorption on energetically homogeneous surfaces.[3] Langmuir was awarded the Nobel Prize in chemistry for his discoveries and research in the realm of surface chemistry.[7] The Langmuir isotherm has been widely used to characterize the adsorption of solutes from aqueous solutions. Another milestone toward development of dsorption science was the multilayer isotherm equation proposed by Brunauer et al in 1938. The multilayer adsorption theory was preceded by two significant papers by Brunauer and Emmett, which appeared in 1935 and 1937. Brunauer, Emmett, and Teller extended the Langmuir model to multilayer adsorption, and their equation represents a wide range of adsorption isotherms. Their equation has also been of value in determining the total surface areas of porous and finely divided solids using an adsorption technique.[6] The BET theory, despite many restrictions, was the first attempt to create a universal theory of physical adsorption.[8]

Adsorption can be carried out in fixed, moving, or fluidized beds. Of these, the fixed bed is the most simple and operated on a batch-wise basis. In the fixed bed system, the solid adsorbent is held stationary over a suitable false bottom in a column that is usually cylindrical and held vertical, and the gas to be purified is passed through the bed at a convenient velocity, which should be lower than the attrition velocity.[6] A fixed bed adsorption apparatus was patented in which no cavity is formed in an inner tube packed with an adsorbent, and breaking and clogging of strainers and generation of static electricity due to flow of the adsorbent were prevented.[9] An application of the moving bed technique is in the Hypersorber described by Berg.[6] A patented artificial moving bed includes a fluid distribution apparatus consisting of an upper and lower fluid distributor and a plurality of processing chambers held and fixed between the upper and lower fluid distributor, ultimately allowing continuous operation.[10] Fluidized bed adsorption can substantially simplify the recovery of products from fermentation.[11]

Development and application of adsorption cannot be considered separately from the development of technology for the manufacture of adsorbents applied on the laboratory and industrial scales. A complete statistical description is especially complicated by the heterogeneity of the solid materials, which include porous adsorbents, ie, the majority of the industrial adsorbents.[3] Solid adsorbents are classed as polar or non-polar. On the polar surface, ion-dipole or dipole-dipole interactions with the adsorptive are more prominent than the interaction due to dispersion forces. On non-polar surfaces, the latter predominates. Polar adsorbents have a polar group exposed to their surfaces and are consequently high-energy, hydrophilic adsorbents. Low-energy, hydrophobic adsorbents are non-polar adsorbents, such as active carbon, which was the first widely used adsorbent. Some are positive (electron acceptors) or negative (electron donors), acidic, or basic adsorbents, respectively. The surface nature of some solids is intermediate between these two forms, ie, semipolar. A polar molecule has a dipole moment or a group or even a bond that is electrically dissymmetric; a non-polar molecule lacks this feature. The competition for adsorptive can be made to depend on polar versus non-polar interactions. A polar adsorptive will tend to prefer more polar phases; a non-polar adsorptive prefers more non-polar phases. Polar, non-polar, and semi-polar adsorbents have been exemplified in Table 2.[2,4,12]

TABLE 2

Polar	Non-Polar	Semi-Polar
Metals	Sulfur	Cellulose Ether
Metal Oxides	Talc	Polyamide
Activated Alumina	Carbon Black	Polymethacrylates
Magnesium Oxide	Charcoals	
Magnesium Hydroxide	Graphite	
Barium Sulfate	Paraffin	
Calcium Carbonate	Stibnite	
Magnesium Carbonate	Metallic Sulphide	
Zeolites	Organic Resin	
Bentonite & Veegum	Polyethylene	
Ion Exchange Resin	Polycarbonate	
Porous Glass	Polyvinylchloride	
Quartz	Polytetrafluorethylene	
Titanium Dioxide		
Colloidal Silica		
Porous Silica Gel		
Purified Kieselguhr		
Kaolin		
Attapulgite		
Polyvinylpyrollidone		
Polyvinylalcohol		
Dextrans		

List of Adsorbents

FACTORS AFFECTING ADSORPTION

The process of adsorption is affected by various factors, such as time, pH, specific surface area, cross-linking time, surface-free energy, and nature of adsorbent used. Said et al observed that the maximal adsorption capacity of aeruginosa toxin onto kaolin occurred at pH values below 4.1, while minimal values were observed at pH 4.1, 7.4, and 8.0, and average adsorption occurred at pH 5.0 and 6.0.[13] The effect of cross-linking time on the adsorption characteristics of microcapsules containing activated charcoal was investigated using creatinine as the model adsorbent. It was found that changing the cross-linking time of the coacervate could control the adsorption rate on microcapsules containing activated charcoal.[14] The factors of time, pH, and concentration of active ingredient were studied during the adsorption of omeprazole on latex particles, and it was concluded that time is not an influential

factor, acid pH values produce the greatest adsorption, and increase in concentration increases the adsorption.[15] The percentage adsorption of polyanions onto coral depends mainly on their charge density, with sulfate groups being more important than carboxyl groups. Adsorption of glycosaminoglycans was found to be driven by electrostatic interactions with calcium sites of coral that are dependent on pH and blocked in the presence of high amounts of salt. Large amounts of chondroitin sulfate are adsorbed onto coral, and sulfate groups are of paramount importance in the adsorption process.[16] A study has been made on the effects of the state of sorbed water, surface-free energy characteristics, and particle size on the adsorption of fine antibiotic powders (ampicillin and amoxycillin trihydrates, cephalexin monohydrate, and erythromycin ethylsuccinate) onto a special type of sorbitol (instant). The presence of sorbed water increased the adsorption of ampicillin and amoxicillin and (due to a contribution of capillary forces and their ability of hydrogen bonding at plasticized regions of sorbitol) with higher moisture content and molecular mobility, the adsorption of low interfacial energy cephalexin monohydrate did not increase (presumably due to lack of intermolecular hydrogen bonding ability) and erythromycin ethylsuccinate adsorption decreased (probably due to masking of the interparticle forces).[17] These studies revealed that the pH, particle size, concentration of active ingredient, and nature of adsorbent mainly influence the process of adsorption.

ADSORPTION'S ROLE IN PHARMACY

The process of adsorption has numerous applications of diverse nature in the pharmaceutical field from formulation of various dosage forms to taking up poisons found in living organisms.

Enhancement of Bioavailability

Improvement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. The poor dissolution characteristics of relatively insoluble drugs have long been a problem to the pharmaceutical industry. Surface adsorption is one of the methods used to reduce the drug particle size by increasing the surface area available to the dissolution medium. The technique of surface adsorption was first reported by Monkhouse and Lach. The use of adsorbents can facilitate the increase in dissolution of relatively insoluble powders, such as indomethacin, aspirin, sulfaethiadole, griseofulvin, reserpine, chloramphenicol, oxolinic acid, probucol, and hydrochlorthiazide, by increasing the surface available for contact with the dissolution media by achieving equilibrium in an organic solvent on an insoluble excipient with an extensive surface.[18] The effect of specific surface area, pH, as well as the type antibiotic on the adsorptive capacity of microcrystalline cellulose revealed that the smaller the particle size of microcrystalline cellulose, the more drug was adsorbed, a property that is more apparent in aqueous ampicillin solution, while amoxycillin was highly adsorbed in acid solution. Higher rates of antibiotic elution were obtained in acid solutions than in aqueous media. Amoxycillin showed a higher elution relative to ampicillin to the extent of complete desorption in gastric pH solution.[19] The adsorption of nalidixic acid onto ethylcellulose, aluminium magnesium silicate, and silicon dioxide at various temperatures and the extent of such adsorption were investigated, and the effects of certain hydrophilic polymers and surface-active agents commonly included in pharmaceutical preparations on the solubility of nalidixic acid were also determined.

With the exception of cetyl alcohol, all the agents achieved an increase in the solubility of drugs. With regard to hydrophilic polymers, methylcellulose, polyvinylpyrollidone, and polyethylene glycol, the increase in equilibrium solubility of drug was of comparable degree at all polymer concentrations and temperatures used.[20] The technique of surface adsorption has been employed to improve the dissolution characteristics of flufenamic acid using magnesium aluminum silicate and microcrystalline cellulose as an adsorbent.[21] The surface adsorption of indomethacin to kaolin or avicel can improve the dissolution rate of drug in water. However, the addition of polyvinylpyrollidone to indomethacin adsorbates resulted in further improvement in the dissolution rate of indomethacin-kaolin adsorbate.[22] Nedocromil sodium has been fully dehydrated in a vacuum, and their water vapor adsorption characteristics were quantitatively assessed at different water pressures over a temperature range 20°C to 40°C. The measured values of water vapor diffusivity into the structure have been used to predict water solubility of nedocromil sodium trihydrate, and the results show good agreement to reported solubilities.[23] To enhance the dissolution of a poorly water-soluble drug, BAY 12-9566, the combination of a solid dispersion and surface adsorption technique was used with magnesium aluminosilicates as a surface adsorbent.[24] To improve the solubility and oral bioavailability of another poorly water-soluble drug, 3-bis(4-methoxyphenyl) methylene-2-indolinone (TAS-301), it was found (based on its melt adsorption on porous calcium silicate) that the TAS-301 dissolution rate from the melt-adsorbed product was markedly enhanced compared with drug crystals.[25]

Conversion of Crystalline State Into Amorphous State

Seven drugs, including four carboxylic acid-containing drugs (Bay 12-9566, naproxen, ketoprofen, and indomethacin), a hydroxyl-containing drug (testosterone), an amide-containing drug (phenacetin), and a drug with no proton-donating group (progesterone), were studied by Gupta et al. The magnesium aluminium silicate was used as the surface adsorbent, and it was found that the conversion of crystalline drug to the amorphous hydrogen bonded to magnesium aluminium silicate seems to increase the dissolution.[26] Pasquale and Aldo patented a method of making nimesulide more bioavailable by adsorption on a polymeric carrier with use of the solubilizing technique in an organic solvent or by cogrinding in a high-energy mill.[27] They selected a group of substrates, carriers of the polymeric type in order to obtain an inclusion complex containing nimesulide in an amorphous form, which has a greater bioavailability than nimesulide in crystalline form.

Sustained Release of Drugs

The in vitro adsorption and desorption characteristics of six strongly acidic resins as a sustained-release drug delivery system were

studied by Burke et al using propanolol hydrochloride as a model drug.[28] In vitro dissolution showed that one cation exchange resin has potential as a sustained-release drug delivery system. To develop a sustained-release dosage form employing a drug-clay interaction, the adsorption of phenformin hydrochloride from aqueous solution on bentonite, montmorillonite, kieselguhr, china clay, fuller's earth, and kaolin was studied. The result showed that montmorillonite and bentonite possesses significant adsorptive capacities, and bentonite drug complex and montmorillonite drug complex showed prolonged action of phenformin hydrochloride.[29] The adsorption and desorption of drugs and inorganic ions to and from polycarbophil were investigated to determine the suitability of polycarbophil as a carrier for sustained-release dosage formulations. Both in vitro and in vivo experiments with polycarbophil-atropine sulfate complex demonstrated the gradual release properties of the system and concluded that polycarbophil is able to bind certain ions and drugs and then release them over a period of time in a predictable and reproducible manner.[30] Sustained release of Newcastle disease vaccine's antigen was achieved through an adsorption/desorption release test and found that porous microspheres have a higher adsorption efficiency and slower release rate of antigen when modified chemically with 3-chloro-2-hydroxypropyl trimethyl ammonium chloride.[31] Dry adsorbed emulsion is an intricate system initiated by water-in-oil emulsion, which is changed into a free-flowing powder by using two adsorbents with suitable polarities. Dry adsorbed emulsion could be considered a sustained-release form for sparingly soluble as well as hydrophilic drugs. The dissolution of dry-adsorbed emulsion containing theophylline suggested the dry-adsorbed emulsion behaved as an inert hydrophobic matrix in which the drug release occurred by diffusion throughout a porous network created by the medium into the dry adsorbed emulsion structure.[32]

Effect on Therapeutic Efficacy of Drugs

It has been shown that the adsorption of proteins on silicone-coated surfaces is caused by hydrophobic interactions, hence the adsorption of drugs on silicone-coated surfaces should also be due to hydrophobic bonding. It was also found that silicone-coated glassware or other apparatuses is also incompatible with precise administration of diazepam, even though the amount of diazepam adsorbed on the siliconized surface is low.[33] Parker and MacCara reported that diazepam injections were incompatible with plastic bags, in which the solution showed a greater than 24% loss of potency.[34] The adsorption of diazepam on magnesium trisilicate, magnesium oxide, aluminium hydroxide, calcium carbonate, magnesium carbonate, bismuth oxycarbonate, bismuth subsalicylate, talc, dibasic calcium phosphate, magnesium stearate, kaolin, and charcoal was studied at 37°C. With the exception of charcoal, magnesium trisilicate exhibited the highest absorptive capacity for the drug. Talc and dibasic calcium phosphate had the lowest adsorptive power, while the other materials tested had intermediate adsorption properties. The magnesium trisilicate decreased the dissolution of tranquilizer.[35] It was stated that ampicillin was 74% adsorbed onto montmorillonite, but the pharmacokinetic parameters and gastrointestinal availability of the drug were not altered.[36] On the other hand, irreversible uptake of ampicillin and amoxycillin by attapulgite, magnesium trisilicate, veegum ,and kaolin was confirmed.[37] Urinary excretion data showed decreased bioavailability of ampicillin and amoxycillin on prior administrations of kaolin.[38] Drug adsorption on silicone-coated surfaces and non-coated glass surfaces were studied using porous glass as a reference standard for glass containers. Silicone-coated surfaces of pharmaceutical glass containers decrease adsorption of drugs. However, in practice, silicone-coated surfaces adsorb more secretin, insulin, atropine, physostigmine, and diazepam than non-coated glass surfaces. The antibiotics adsorb weakly or not at all onto non-coated glass surfaces and passes through the non-coated porous glass medium.[39] The tendency of insulin to adsorb on the surface of solution containers and infusion devices aggravated the complications in the administration by undergoing self-association into oligomers and macromolecular aggregates. It was found that the addition of a certain range of urea to insulin solutions greatly reduces both self-association and surface adsorption.[40] The minimum inhibitory concentration of the tested antibiotics increased in the presence of microcrystalline cellulose with decreased particle size. It was concluded that concomitant presence of microcrystalline cellulose as a directly compressible vehicle, diluent, or disintegrant for tablets; as suspending agent in suspensions; or as fillers in capsules may interfere in the bioavailability or local antimicrobial activity of ampicillin or amoxicillin.[19] It was investigated whether an interaction takes place between propranolol hydrochloride and adsorbents when antacids are taken concomitantly with beta-blockers. The in vitro results showed that the concomitant use of propranolol hydrochloride and magnesium trisilicate, magnesium hydroxide, dihydroxy aluminum sodium carbonate, kaolin, and magnesium carbonate could affect the bioavailability of the beta-blockers adversely.[2] Most antacids consist of calcium carbonate and magnesium and aluminium salts in various compounds or combination. The antacids, except sodium bicarbonate, may decrease drug absorption by adsorption or chelation of other drugs.[41]

Reduction in Toxicity of Drugs

Various adsorbents may be used for the emergency treatment of drug poisoning. In vivo studies with atropine sulfate demonstrated that these compounds might be removed from gastric and intestinal content by adsorption on anion and cation exchange resin, thus reducing the acute toxicity.[42] An in vitro study revealed that dextoamphetamine, primaquine, chlorpheniramine, colchicines, diphenylhydantoin, aspirin, iodine, phenol, and propoxyphylline were very efficiently adsorbed in high concentrations by activated charcoal, whereas quinacrine, meprobamate, chlorpromazine, quinine, chlorquine, quinidine, glutethimide, and methyl salicylate were less efficiently adsorbed. Activated charcoal is a promising therapeutic agent in managing acute ingestion of toxic agents.[43] Activated charcoal is a remarkably effective agent for the treatment of intoxication. The activated charcoal is able to adsorb a wide range of substances, and it can diminish their systemic absorption from the gastrointestinal tract.[44] Administration of activated charcoal after pheniramine ingestion in dogs resulted in significantly lower blood levels, indicating

that charcoal is ideal in the first-aid treatment of pheniramine poisoning.[45] Neuvonen and Elonen demonstrated that activated charcoal, even if administered after absorption was complete, could decrease the terminal half-life of orally administered phenobarbitone, carbamazepine, and phenybutazone.[46] It is evident that concurrent administration of certain substances can interfere with charcoal's ability to adsorb toxins. A study indicates that no clinically significant interaction occurs between the magnesium citrate and activated charcoal in either fluid, and that these two agents can be given simultaneously without decreasing the binding capacity for aspirin.[47] Orally administered activated charcoal has been used for a numbers of years to bind drugs in the bowel and thereby prevent absorption after an overdose. Activated charcoal not only inhibited absorption from the gastrointestinal tract but also increased the clearance of drugs from the systemic circulation. The use of orally administered charcoal has been shown to increase the elimination of intravenously administered digoxin, phenobarbitone, and theophylline. Oral administration of repeated doses of activated charcoal significantly increased the systemic clearance of intravenously administered theophylline and decreased its elimination half-life.[48] Activated charcoal was effective in preventing absorption of verapamil when it was administered immediately after verapamil ingestion. In slow-release formulations, charcoal reduced verapamil absorption by over 30% even when given 4 hrs after verapamil.[49] Activated charcoal hemoperfusion is effective in blood purification for removal of various toxic materials and waste metabolites, directly. Chitosan-encapsulated activated charcoal beads have been extensively investigated for removal of various toxins, such as urea, creatinine, uric acid, bilirubin, etc.[50] In drug overdoses (such as those with fluoxetine, an antidepressant), administration of activated charcoal is recommended.[51] A study revealed that activated charcoal and talc adsorbed ciprofloxacin effectively. The activated charcoal exhibited a higher adsorptive capacity for ciprofloxacin than talc, and both can be used as effective antidotes in ciprofloxacin poisoning.[52]

Adsorbents as Therapeutic Agents

Adsorbents, such as kaolin, are used for the treatment of diarrhea, alone or in combination with antibiotics, antispasmodics, and analgesics. Adsorbents act by virtue of their ability to adsorb toxins and bacteria.[53] Bruker et al found that attapulgite significantly reduced the toxic effects of both cholera and E. coli enterotoxins.[13] Antacids are the preparations that are primarily designed to neutralize gastric acid. The capacity to neutralize gastric acid is therefore a prime factor in the efficacy of antacids. The compound most frequently used in classical formulations are weak bases and include sodium bicarbonate, calcium carbonate, magnesium carbonate, magnesium hydroxide, magnesium hydroxide, aluminium hydroxide, aluminium phosphate, and magnesium trisilicate.[54] An oral adsorbent AST-120 (kremezin) is effective in removing circulating uremic toxins from the gastrointestinal tract and retards the progress of chronic renal failure (CRF). AST-120 is widely used as an approved drug in Japan for the treatment of undialyzed uremic patients to delay the progression of CRF [55]. The adsorbents for an oral administration, according to present invention, comprises a porous spherical carbonaceous substance having a pore volume within a specific scope, and exhibits an excellent absorbability of harmful toxins in gastrointestinal tracts despite a low absorbability of useful components, such as digestive enzymes in the body, when orally administered. These adsorbents may produce a remarkable curative effect.[56]

Extraction & Purification

Extraction and purification of antibiotics: danubomycin by adsorption on activated charcoal, activated earth, or ion exchange resin; lankavamycin or lankavacidin or a mixture; and avilamycin by adsorption (eg, on fuller's earth) have been patented by CIBA Ltd.[57-59] Orange oil was partially fractionated by adsorption of the oxygenated compounds onto porous silica gel, with full utilization of its adsorption capacity, and then further purified by desorption onto supercritical carbon dioxide.[60] Adsorption has been used for the purification of anaesthetics and removal and purification of vitamins. Lately, adsorbents have been used for the purification of blood from noxious substances using chemisorption.[3]

Drug Loading

The loading of nanoparticles and liposomes with drugs can be achieved by adsorption. The characteristics of incorporation and adsorption of pilocarpine and daunorubicin onto poly (butyl-2-cyanoacrylate) nanoparticles has been studied, and the maximum drug capacity was found to be dependent on the method employed for loading of the compound, the nanoparticles' composition, the compound itself, and the pH of the solution. A linear correlation was found between the amount of compound incorporated into the nanoparticles and the time for 50% release.[61,62] Charged enzyme-containing lipid vesicles are often prepared by adding a certain amount of a negatively charged amphiphile or a positively charged lipid. The presence of charges in the vesicle membrane may lead to an adsorption of the enzyme onto the interior or exterior site of the vesicle bilayers. The enzyme molecules were expected to be released from the vesicles at the target site, and the vesicles in these cases serve as the carrier system.[63]

Taste Masking

Bitter drugs can be rendered tasteless by adsorption.[64] Uses of ion exchange resin in the pharmaceutical industry include taste-masking, drug stabilizers, tablet disintegrants, and drug delivery systems.[27]

Improvement of Content Uniformity

The uniform distribution of very low dose drugs can be elegantly achieved by adsorption onto a carrier material with a large specific surface. Poor solubility can simultaneously be improved.[65] Adsorption of active ingredients onto large surface areas of colloidal and porous silica can be used to regulate drug release or for the uniform distribution of the drug in solid-dosage units with a very low drug content.[66]

Reduction in Hygroscopicity

The amount of moisture adsorbed by drugs and excipients at a certain temperature and relative humidity will influence flow, compression characteristics, and the hardness of granules and tablets. In addition, moisture transmission through polymers and free films may be useful for characterization of possible effects on the dissolution and the transport of

drugs from the dosage forms. Better understanding of the effect of moisture adsorption phenomena will give useful information that may be employed to develop a successful formulation.[67] Hygroscopic extracts can be stabilized by adsorption onto tricalcium phosphate or silica.[68]

Investigating Drug Actions

Abe and co-workers have shown that adsorption onto the activated carbon surface is hydrophobic and have accumulated carbon absorbability data on chemicals of diverse structure. The adsorption of 18 local anesthetics onto an activated carbon surface showed excellent correlation between log carbon surface adsorption and the log minimum nerve-blocking values in both ionized and unionized drugs, which concludes that activated carbon absorbability provides an accurate measure for the interfacial hydrophobic-hydrophilic interactions that play an important role in various biological processes and may be used as a convenient tool in investigating drug actions.[69]

Clarification & Decoloration

Adsorbents are used as filter aids for removing colloidal mucuses from liquids, thereby preventing viscous blocking of filter media. Clarification and decoloration can also be achieved, depending on the adsorbent. Suitable adsorbents are kieselguhr, silica, magnesium carbonate, paper pulp, cellulose, ion exchange resin, and charcoal.[70] In any of these processes, however, a loss of active ingredient by coadsorption may occur.

Stability of Suspensions

Adsorbed substances can contribute to suspension stability by hindering uncontrolled coagulation and caking of the particles. The stabilization of pharmaceutical suspensions is often termed as controlled flocculation. By the adsorption or coadsorption of surfactants, polymers, or ions onto particles, their surface charges are reduced, and simultaneously, they aggregate loosely by bridging. Such suspensions redisperse readily upon shaking and do not cake.[71] In dispersions of hydrophilic colloids, such as silica, the adsorption of surfactants onto particles can yield thixotropic gels, which stabilize larger suspended drug particles against sedimentation.[2] Suspensions of crystalline solids having low to moderate solubility in the dispersion medium tend to show crystal growth upon storage. Adsorpted polymers, colors, or surfactants can inhibit the growth. The corresponding adsorbates hinder the crystallization of the dissolved drug molecules onto the particle surfaces.[72]

Processing of Oils & Extracts

Volatile essential oils released during milling of plants can be recovered via adsorption from the gas phase onto microcrystalline cellulose or charcoal. Essential oils and fluid extracts can be solidified by adsorption onto porous silica or magnesium carbonate or oxide or hydroxide. The resulting dry, free-flowing powder contains up to 40% liquid and can be easily processed into capsules, tablets, and suppositories. Their availability can be improved by incorporating surfactant into the adsorbate.[2]

CONCLUSION

This review simply reveals a glimpse of the exciting potential of adsorption for innumerable applications of diverse nature, particularly in the pharmaceutical sciences. Some examples include the improvement in dissolution profiles, detoxification, and pollution control in pharmaceutical units. There is strong need for exploitation of adsorption's vast potential, particularly in basic drug manufacturing units for the improvement of dissolution rate and content uniformity simultaneously with significant reduction in the overall cost of the final product.

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References available upon request; please contact Dan Marino at dmarino@drugdeliverytech.com.

BIOGRAPHIES

Mr. 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, and Rohtak. He is also currently pursuing his PhD at M.D. University, Rohtak.

Prof. A.K. Madan is one of the rare professionals possessing Bachelors degrees in both Pharmacy and Chemical Engineering, a Masters degree in Pharmaceutics, and a 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 many international journals of repute, and some of the mathematical tools developed by him for drug design have been incorporated in leading software being marketed by multinational companies. He is currently working as Dean, Faculty of Pharmaceutical Sciences, M.D. University, Rohtak.

DRUG DELIVERY
Penwest Executive

PENWEST: A SPECIALTY PHARMACEUTICAL COMPANY LEVERAGING ITS DRUG DELIVERY TECHNOLOGIES

Ms. Jennifer L. Good
President & CEO
Penwest

"This initiative will help fund the expansion of our pipeline, generate an earnings stream from the products we develop, and enhance our relationships with industry leaders. By increasing the number of molecules being developed with our technology, we also hope to expand our formulation knowledge base."

Headquartered in Danbury, Connecticut, Penwest is a drug development company dedicated to bringing to the marketplace innovative products that help improve the lives of patients. The company's goal is to identify, develop, and commercialize products that address unmet medical needs, primarily for disorders of the nervous system. Currently, Penwest is applying its expertise to a pipeline of potential products that are in various stages of development. Drug Delivery Technology recently interviewed Ms. Jennifer L. Good, President and Chief Executive Officer of Penwest, to discuss how her company intends to commercialize these products independently through its own specialty neurology sales force and through third-party alliances with pharmaceutical partners.

Q: Can you tell us a little about the history of Penwest?

A: Penwest, which became a public company in 1998, was established primarily as a drug delivery company. The company also had a successful excipients division that was sold in 2003 to a German company, Josef Rettenmaier Holding GMBH and Co. KG. At that time, Penwest's initial strategy was to out-license the TIMERx® technology to pharmaceutical partners to develop branded or generic drugs. The pharmaceutical partner was responsible for the drug development, marketing, manufacturing, and distribution of the product.

TIMERx, Penwest's core technology, is an extended-release matrix technology based on xanthan and locust bean gums. It is highly flexible, well patented, and has been approved by various regulatory authorities throughout the world. We have also developed two additional oral drug delivery systems based

on the TIMERx technology, Geminex® and SyncroDose™.

Geminex provides independent release of combined active ingredients through a bi-layer tablet. This technology expands drug product options to include: two unique sustained-release compounds; immediate-release and sustained-release compounds from the same or different drugs; or two unique-release profiles for two different isomers from the same drug. Some of the disease states that could benefit from Geminex include diabetes, cardiovascular disorders, and neurological disorders.

SyncroDose provides true chronotherapeutic drug delivery. It works with the body's biological clock to customize the delivery of a drug, reduce dose, and improve efficacy. Some of the disease states that could benefit from chronotherapeutic delivery include arthritis, asthma, cancer, cardiovascular disorders, and neurological disorders.

One of Penwest's early collaborations was with Mylan Pharmaceuticals. Using the TIMERx technology, we collaborated with Mylan to develop the first generic equivalent to Pfizer's Procardia® XL. At the time, this was significant as this formulation was the first generic equivalent to a product that had been developed using Alza's Oros system. The nifedipine product developed with Mylan was also commercialized in various countries in Europe and in South America.

Also during this time, Penwest entered into a collaboration with Endo Pharmaceuticals to co-develop oxymorphone ER utilizing the TIMERx technology. Oxymorphone ER was approved in June 2006 and commercialized under the brand name Opana® ER. The drug is indicated for the treatment of moderate-to-severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. Endo currently has a sales force of 690 representatives, and Opana ER is being detailed in first position for the majority of this sales force.

Q: Why did you decide to move your initial business model of becoming a drug delivery company to a specialty pharma company focused on products that treat disorders of the nervous system?

A: A couple of years ago, we decided to evolve Penwest's strategic focus from drug delivery to drug development. As part of this transition, we began to emphasize the development of our own proprietary pipeline of products focused on disorders of the nervous system. The primary reason for this evolution in the strategy was to capture more of the economic value of the drug as well as to control the overall development timeline. Although there is more risk in drug development, there is also more control. The company chose to focus on disorders of the nervous system for two primary reasons. The first is the excellent fit of neurology with the TIMERx technologies. Neurological

disorders usually require chronic/ongoing therapy, often self-administered in non-clinical settings. This points clearly to the use of long-acting oral dosage forms. Maintaining constant plasma levels of an active compound while decreasing dosing frequency is also beneficial in neurology therapies. Penwest's technologies can help with compliance and safety by delivering a steady stream of medicine.

The second reason we decided to shift into the neurology area relates to sales and marketing. Prescriptions for neurological products are typically written by neurologists – a relatively small group. Penwest has realized that the type and size of sales force needed to address this market fits with the specialty pharma model and can be achieved more quickly than that required to reach, for example, a large number of primary care practitioners. We believe we could successfully build and run the sales force needed to cover the neurology area.

Q: Since you have changed business strategies, why have you decided to continue to out-license the TIMERx technologies?

A: Following the approval of Opana ER, we received a number of inquiries from companies that are pursuing brand management strategies for their products and were attracted to our TIMERx technologies. The TIMERx technology has the advantage of being approved in both the US and Europe, is protected by patents, and has been scaled to commercial-size quantities. In order to take advantage of this interest without putting a strain on our organization, we established a separate business unit, working with a third- party formulator, to focus exclusively on engaging in drug delivery formulation. We entered into a collaboration agreement with Pharmaceutics International Inc. (PII) in March 2007 under which PII agreed to conduct formulation work for drugs using our proprietary oral drug delivery technologies. This business unit has access to the TIMERx technologies, and its objective is to leverage our investment in these technologies through standard licensing arrangements with partners.

Q: Can you describe how the process works with PII?

A: Under the terms of the collaboration, PII conducts formulation work for drugs being developed with third parties that license Penwest's drug delivery technologies. Penwest has one of its own scientists dedicated to overseeing the formulation work being done at PII to help with the knowledge transfer surrounding the TIMERx technology. In addition, PII may also independently identify new product development opportunities for the collaboration. PII has agreed to assume primary responsibility for formulation development with technical guidance and oversight from Penwest, and may also assume responsibility for clinical trial material manufacturing and commercial manufacturing.

Q: What are some of the benefits to Penwest of this drug delivery formulation initiative?

A: This initiative will help fund the expansion of our pipeline, generate an earnings stream from the products we develop, and enhance our relationships with industry leaders. By increasing the number of molecules being developed with our technology, we also hope to expand our formulation knowledge base. We believe this technology is broadly applicable to a wide range of drugs, and we want to ensure that we are leveraging its value.

Q: What is Penwest's strategy for growth going forward?

A: Building on our past successes, we launched a clear, well-defined strategy for growth: to develop a portfolio of products targeting disorders of the nervous system. Our current development pipeline includes products for the treatment of various neurological disorders, including pain, Parkinson's disease, spasticity, and orphan mitochondrial diseases. As we build our internal portfolio, we are both advancing the product candidates currently in our pipeline and generating new product concepts. We will continue to focus on products that can be developed using a 505(b)(2) regulatory strategy, enabling us to move more quickly by improving formulations of products that have previously been approved by the FDA. We also have efforts underway to in-license new technologies and product candidates to augment our portfolio. These products will have longer exclusivity periods than those developed utilizing the 505(b)(2) strategy because they will be NCEs, orphan drugs, or have other patent barriers due to novel technology. In July 2007, we announced a collaboration in orphan mitochondrial diseases with Edison Pharmaceuticals in which we in-licensed two compounds for development.

Q: What makes Penwest attractive as a formulation business partner?

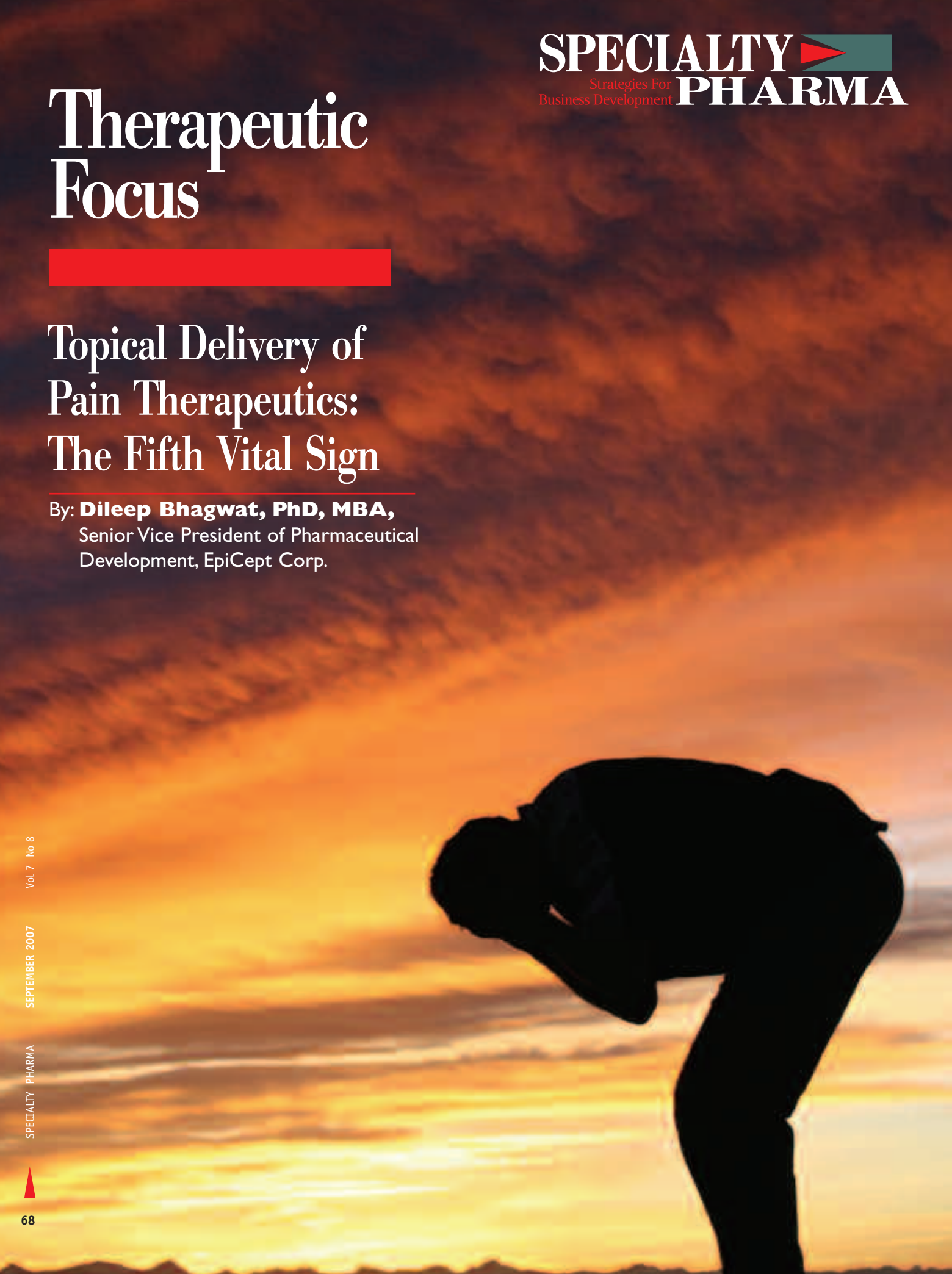
A: The TIMERx technology is a flexible, proven technology that has been approved by regulatory authorities in both the US and Europe. Penwest in combination with PII bring a depth of formulation experience to help formulate products to achieve the desired pharmacokinetic profile desired by our partners. This is a business that we have more than 10 years of experience in, with both branded and generic drugs. We believe we can be an excellent technology provider to meet our partner's needs with branded, generics, OTCs, and even nutritionals. ◆

SPECIALTY PHARMA
Strategies For Business Development

Therapeutic Focus

Topical Delivery of Pain Therapeutics: The Fifth Vital Sign

By: **Dileep Bhagwat, PhD, MBA,**
Senior Vice President of Pharmaceutical Development, EpiCept Corp.



Introduction

Pain is a natural and essential function of the body. It serves as a warning of actual or imminent damage to tissues and organs, either through disease or injury. Like blood pressure, pulse, respiration, and temperature, pain has recently been recognized as the fifth "vital sign" that provides important clues to the health and well-being of a patient. While it serves as a tool for doctors to aid in the diagnosis of disease and monitor treatment and recovery, continued or excessive pain can erode the quality of life and even prevent further recovery from the illness or injury. Pain may be caused by trauma due to accidents, sports injuries, repetitive stress injuries, or surgery, etc. or by diseases, such as arthritis, multiple sclerosis, and cancer, or nerve damage brought on by diabetes or infections. Among the most commonly medicated symptoms are headaches and back pain.

There are a variety of analgesic treatments to treat pain, creating a total US market of $19.2 billion in 2005, which is expected to grow at a compound annual rate of 6.6%.[1] In that same year, analgesics were the fourth most prescribed class of medications in the US with more than 246 million prescriptions written. Despite the vigorous market in pain management, many products fall short of being fully effective while avoiding pitfalls, such as harmful side effects and addiction. Common over-the-counter medications, such as acetaminophen and aspirin (acetylsalicylic acid), may be very effective for pain and fever relief, but can be toxic with long-term use, leading to liver damage or gastrointestinal irritation and bleeding. Opioid drugs, quite effective for chronic pain, lead to physical dependence associated with withdrawal symptoms when drug use is discontinued and, in some patients, the development of addiction. The undesirable side effects of drugs, such as OxyContin® and Vioxx®, have mired them in controversy, litigation, strict regulatory control, and market withdrawal.

It is estimated that more than 76 million people in the US suffer some degree of disability due to pain, but because of susceptibility to adverse effects, or just the fear that they might arise, not everyone is receiving adequate treatment.[2] Although most cases of pain are localized to a certain area of the body, such as a joint in arthritis pain, or the healing wound of a surgical incision, treatment is usually given systemically, raising the dose of the drug throughout the body and the risk of adverse reactions. In a growing number of cases, it has been demonstrated that topical delivery of pain medication can be quite effective, while avoiding the side effects of systemic administration.[3]

Anatomy of Pain

Pain signals are transmitted to the brain through specialized sensory neurons called nociceptors. Nociceptors can be found on almost every surface and organ of the body. There are three main classes of nociceptors categorized by the type of stimulus that prompts them to transmit a signal. Thermoreceptive nociceptors are triggered by extreme temperatures that can potentially cause damage to tissues. Mechanoreceptive nociceptors send a pain signal in response to pressure stimuli. Polymodal nociceptors respond to temperature, pressure, as well as chemicals released by cells (such as those produced through the inflammatory response). When any of these neurons are triggered, a cascade of neurotransmitters is released, each having a different role in the pain response, including the inhibition or enhancement of the pain signal, or the enhancement of an immune response. The signal makes its way through the nociceptor to the spinal cord, where it is sent to the thalamus, and ultimately to the somatosensory cortex in the cerebrum. That is where pain enters into consciousness and the patient perceives the pain and forms a subjective impression of discomfort. Given the same magnitude of signal, different individuals will have a different level of sensitivity and tolerance to pain. Nociceptive pain can be:

- ***Cutaneous*** — caused by injury to the skin and other tissues near the body surface, often resulting in sharp pain.

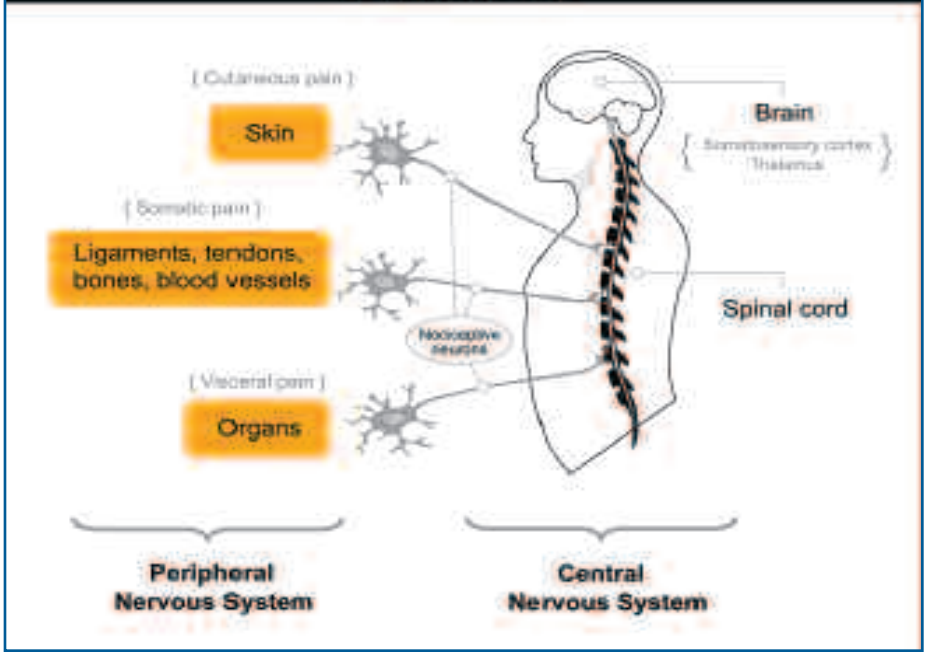
- ***Somatic*** — caused by injury to deeper tissues, such as ligaments, tendons, bones, and blood vessels. Because somatic nociceptors are relatively scarce, pain is usually more dull and poorly localized than cutaneous pain.

- ***Visceral*** — caused by injury to the organs. Visceral nociceptors are even more scarce than somatic nociceptors, resulting in pain that is deeper, more aching and dull, and more poorly localized than somatic or cutaneous pain.

In contrast to nociceptive pain, neuropathic pain originates from damage to the nerve tissue itself, disrupting the ability of the nerve to transmit accurate information to the brain, and leading to painful stimuli when there is no clear physiological cause. This can occur as a result of nerve damage caused by diabetes, infectious diseases such as herpes zoster or HIV, autoimmune conditions such as celiac disease, cancer (e.g., nerve compression by a tumor), chemotherapy, and surgical injury.

FIGURE 1

Pain Pathways



Systemic Versus Topical Delivery

There are three major classes of drugs used in the treatment of acute and chronic pain: non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and other drugs with analgesic effects (e.g., antidepressants, anticonvulsants, and local anaesthetics). Treatment of pain, particularly neuropathic pain, with NSAIDs and opioids is often inadequate. These drugs are typically delivered systemically and absorbed into the bloodstream, with the delivery mechanism occurring orally, via injection, or through a transdermal patch. With opioid drugs and other drugs with analgesic effects, it is often necessary to titrate the dosage until an adequate level of pain relief is achieved without introducing serious side effects. The actual therapeutic window is small, leading to only modest relief of pain. Despite their wide-spread use, the limitations of current systemically delivered analgesics are well documented, and the potential side effects associated with their use are significant. For systemically-delivered opioids, side effects and risks can include the following:

- Respiratory distress, nausea, vomiting, dizziness, sedation, constipation, urinary retention, and severe itching.
- The need for increased dosing and the potential for addiction.
- Potential harmful interactions with other drugs.
- Physicians may be prone to prescribing less-than-adequate doses due to concerns about addiction and abuse.

Risks and side effects for systemically delivered NSAIDs and other analgesic therapies potentially can include the following:

- Kidney failure, liver dysfunction, coagulation disorder, gastric ulcers, and nausea.
- Hospitalizations and death: A report in 1999 recorded an annual rate of 16,500 NSAID-related deaths and over 103,000 patients hospitalized from NSAID complications.[4]
- Potential harmful interactions with other drugs.
- The concern over adverse side effects may lead doctors to prescribe treatments less often and at lower doses than may be needed to alleviate pain.

Avoiding the risk of harmful side effects, patients often choose to forego treatment for pain or take lower doses that do not provide adequate relief. In order to better serve the population of over 76 million US residents suffering from some form of chronic pain, as well as those who experience short bouts of acute pain, an alternative approach to the delivery of analgesics is needed in which pain is controlled topically at the site of origin, rather than systemically. The use of creams, gels, aerosols, and lozenges can allow for a much higher local concentration of drug and greater control of the time interval of application. Topical delivery of analgesics can lead to lower systemic levels of the drug, which in turn lowers the incidence of adverse effects.[5] The chances of drug interactions are minimized, and dosages can be adjusted more freely to address the pain, rather than avoid the side effects. Topical analgesics are generally well tolerated, with adverse reactions often limited to local cutaneous irritation. Ease of use is also a major advantage toward assuring patient adherence to treatment.

Topical delivery of analgesics is appropriate for both acute and chronic pain conditions. Because chronic pain can involve peripheral and central neural activity, it is likely that topical applications will be more successful if

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the peripheral component is dominant. A number of topical pain therapies exist (capsaicin, lidocaine, diamorphine, NSAIDs), and studies have confirmed their effectiveness and relatively mild side-effect profile. This promising area of research and development has generated considerable interest in finding other appropriate drugs for topical analgesics as a safer, more effective alternative to systemic therapies.

EpiCept's Drug Delivery Approach

EpiCept is seeking to advance the treatment of acute and chronic pain by pursuing the use of topically delivered analgesics that do not contain the liabilities and side effects inherent to drugs that require therapeutic systemic levels to be effective. The company's product candidates target moderate-to-severe pain that is influenced, or mediated, by peripheral nerve receptors located just beneath the surface of the skin. Recent studies have indicated that these peripheral nerve receptors play an important role in both the sensory perception of pain as well as the transmission of pain impulses to the brain. Because EpiCept's drug products provide topical delivery of analgesics that are administered directly at the point where the pain signal originates, drug concentrations are localized, resulting in significantly lower (sub-therapeutic) systemic blood levels. The company's strategy is to use well-known (FDA-approved) analgesics in a topical formulation, which can provide patients with significant pain relief, while bringing about fewer adverse side effects, fewer drug-to-drug interactions, and lower potential for abuse.

EpiCept has three prescription pain product candidates in advanced clinical development. These product candidates are part of a portfolio that includes LidoPAIN® SP (for surgical pain), LidoPAIN® BP (for back pain), and EpiCept™ NP-1 Cream (for neuropathic pain).

LidoPAIN SP is a sterile lidocaine hydrogel patch applied once daily and designed to provide sustained topical delivery of lidocaine to a post-surgical incision or post-traumatic sutured wound in order to relieve post-operative pain and minimize the need for systemic administration of narcotics, NSAIDS, or Cox II inhibitors. More than 45 million in-patient surgical procedures are conducted annually in the US and many, if not most, may be more effectively treated with a topical rather than systemic delivery of analgesics.[6]

LidoPAIN BP is an analgesic non-sterile patch designed for topical delivery of lidocaine for the treatment of acute or recurrent muscular skeletal lower back pain. Back pain is one of the most common conditions of pain in the US, affecting more than 27% of people.6 Very few effective treatments are currently available.

EpiCept NP-1 Cream is a topical analgesic cream designed to provide effective, long-term relief from the pain of peripheral neuropathies. It is estimated that neuopathic pain affects 3% to 8% of the population and is associated with other conditions that induce injury in peripheral nerves, including herpes zoster, or shingles, diabetes, chemotherapy, HIV, and other diseases.[7] Neuropathic pain can also be caused by trauma or may result from surgical procedures. EpiCept NP-1 Cream is a patented formulation containing two FDA-approved drugs, a 4% concentration of amitriptyline (a widely used antidepressant) and a 2% concentration of ketamine (an NMDA antagonist that is used as a short-acting anesthetic). Because each of these ingredients has been shown to have significant analgesic effects and because NMDA antagonists, such as ketamine, have demonstrated the ability to enhance the analgesic effects of amitriptyline, we believe the combination is a promising candidate for the development of a new class of analgesics.

The combination topical cream has completed two Phase II clinical trials, including a placebo-controlled factorial trial (which suggested that the combination was well tolerated and more effective than either drug used alone), and a dose response clinical trial. EpiCept also conducted an open label pharmacokinetic study with NP-1 Cream in 36 healthy adults where a fixed dose of the cream was applied to the back thorax every 12 hours for 2 days. Pharmacokinetic samples were collected for amitriptyline, nortriptyline, ketamine, and norketamine up to 96 hours after the first application. NP-1 Cream was found to be safe and well tolerated at its therapeutic local dosage. Low (sub-therapeutic) systemic levels of amitriptyline and ketamine indicate a local mechanism of action rather than a systemic one.[8-10]

Ongoing Phase II and Phase III clinical trials are examining safety, efficacy, disability modification, and quality of life provided by the NP-1 Cream for patients with chronic lower extremity pain due to diabetic peripheral neuropathy and post-herpetic neuropathy (Phase II), and chemotherapeutic neuropathy (Phase III), which may affect as many as 80% of patients undergoing non-surgical treatment for advanced breast cancer.[11]

Using current standards of treatment, neuropathic pain can be very difficult to treat. Opioid analgesics typically offer only partial relief and are usually not provided as a first-line treatment. Neuropathic pain can also be treated with NSAIDs; tricyclic antidepressants such as amitriptyline; and


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anticonvulsants, such as gabapentin and pregabalin. The antidepressants reduce neuropathic pain at smaller doses than their therapeutic dose for depression, suggesting that they may work by different mechanisms on neuropathic pain.[12,13] Possible mechanisms of action include mu-opioid, alpha 5HT, and NMDA receptor interactions and Na^+ channel-blocking, modulation of descending norepinephrinergic, and serotonergic pathways in the spinal cord to block pain signals from traveling to the brain. But even with multiple therapeutic options, neuropathic pain responds poorly to available systemic treatment and often gets worse rather than better, leading in many cases to serious disability.

There is evidence that glutamate (NMDA) receptor antagonists can act on peripheral neurons to alleviate nociceptive and neuropathic pain.[14] The non-competitive NMDA receptor antagonist ketamine has demonstrated both analgesic and anaesthetic effects through multiple modes of action. Sometimes applied as a topical or locally injected anaesthetic, ketamine blocks NMDA and 5HT receptors, Na^+ and Ca^+ channels, while reducing edema associated with inflammation.

Combining drugs with complementary mechanisms can offer many advantages in the treatment of complex conditions and disorders. Both ketamine and the tricyclic antidepressant amitriptyline exhibit analgesic effects on peripheral neurons when applied locally and are market-approved drugs with known safety and efficacy profiles. Combined into a topical cream, as in NP-1, their beneficial effects can be superior to the effects of either drug alone. Because of the reduced risk of drug-to-drug interactions, such combinations can be designed into many topical analgesic formulations.

Summary

The cost to society associated with pain has been estimated at $100 billion annually in the US, including direct costs, such as medical expenses and the indirect costs of lost productivity.1 Addressing this tremendous burden to public health and society, pain management has become one of the most active areas of research and drug development. The societal burden and the need for solutions will only become greater with an aging population in which the prevalence of pain increases among the elderly. About 25% of people over 60 years experience pain, while 20% take analgesic medication for conditions such as arthritis, back pain, and nerve damage caused by diabetic neuropathy. Topical formulations of both existing and novel therapeutics will offer renewed hope that both acute and chronic pain can be treated more safely and effectively. ■

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Dr. Dileep Bhagwat has been EpiCept's Senior Vice President of Pharmaceutical Development since February 2004 and has more than 20 years of pharmaceutical experience developing and commercializing various dosage forms. Prior to joining EpiCept in 2004, Dr. Bhagwat worked at Bradley Pharmaceuticals as Vice President, Research and Development and Chief Scientific Officer. From November 1994 through September 1999, Dr. Bhagwat was employed at Penwest Pharmaceuticals in various capacities, including Vice President, Scientific Development and Regulatory Affairs and at Purdue Frederick Research Center as Assistant Director of Pharmaceutical Development. Dr. Bhagwat holds many US and foreign patents and has presented and published on dosage form development and drug delivery. Dr. Bhagwat earned his BS in Pharmacy from Bombay University, his MS and PhD in Industrial Pharmacy from St. John's University in New York, and his MBA in International Business from Pace University in New York.

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Executive Summary

Mr. Paul R. Edick
President, CEO & Board Director
MedPointe

MedPointe Seeks Niche Markets to Build Empire

By: Cindy H. Dubin, Contributor

MedPointe is a Specialty Pharmaceutical company that develops, markets, and sells branded prescription therapeutics in the areas of allergy/respiratory, CNS/neurology/epilepsy, and cough/cold. Headquartered in Somerset, NJ, MedPointe seeks to capitalize aggressively on opportunities through product acquisitions, co-promotion, joint ventures, licensing, and other partnership arrangements. This past July, MedPointe signed a definitive merger agreement with Meda AB, a European Specialty Pharmaceutical company. Upon closure of the transaction, it will become the US segment of Meda's global business. Paul R. Edick, President, CEO, and Board Director of MedPointe, recently spoke with *Specialty Pharma* magazine to explain how all of this is helping the company become a world-class Specialty Pharmaceutical company.

Q: ***What sets MedPointe apart from its competitors?***

A: We recognized early on that the "buy-and-revive" model was not sustainable. With the support of our investors, we had the ability to invest in the development of our own product pipeline. In the immediate term, we are using proven molecules to create innovative new products that are more effective or faster acting and offer added benefits to patients. This year, we're reinvesting almost 16% of our net revenue back into development projects. Only a few Specialty Pharmaceutical companies invest this heavily in their own pipeline, and even fewer have a pipeline. We're also leveraging our management team's wealth of industry knowledge and entrepreneurial spirit to develop new products that will provide incremental clinical and lifestyle benefit to patients.

Another point of distinction is our sales force. We've built one of the best teams in the business. Our organization is very experienced and composed of professionals who have a solid grounding in all of our therapeutic areas. Not only are they recognized as leaders in these areas, they have forged strong relationships with the professional community and have been able to compete with much larger companies successfully. In addition, we believe educating the consumer is an important aspect of providing access to the best solutions. Last year, we initiated incremental investment in our lead brand Astelin® Nasal Spray, an antihistamine approved for both seasonal allergic and vasomotor rhinitis, with our first-ever direct-to-consumer (DTC) campaign, which proved to be very

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successful in creating brand awareness. Astelin's double-digit sales growth versus the prior year outpaced the category growth as a result of this initiative.

Q: ***What makes MedPointe attractive as a potential partner or an investment prospect?***

A: MedPointe has a strong financial track-record. Since the company's inception in 2001, we have been profitable, and we quickly established a competitive position in the allergic rhinitis market.

We have very strong relationships with our investors, all of whom have been with us since we opened our doors. In fact, our growing brands, late-stage pipeline, and aggressive Specialty Pharmaceutical model recently attracted European drugmaker Meda AB, which announced its intention to enter the US pharmaceutical market with the acquisition of MedPointe.

Finally, our management team also has a rich history in the pharmaceutical industry, each member averaging over 20 years of experience in the sector. We are focused on a goal and have shown the capabilities to be nimble and efficient, which in turn allow us to pioneer our future.

Q: ***Please describe your business model and how is it unique?***

A: Our business model and operating principles have been developed to meet the exciting opportunities and challenges of the Specialty Pharmaceutical market. We have learned from both the successes and the failures of the companies that came before us, and this has enabled us to evolve quickly. Unlike many of the earlier ventures, which were unable to capitalize on internally developed assets to secure their future, MedPointe is building that element of its future aggressively. MedPointe is a fully integrated enterprise with R&D, manufacturing, and commercial capabilities that possess a targeted approach to the pharmaceutical industry. We have leveraged both acquisition and internal product development to build our company and will use that model to grow and expand. We are positioned to become a leader in the Specialty Pharmaceutical sector both here in the US and globally, and have demonstrated that we can compete successfully with some of the larger pharmaceutical companies through the marketing of our core therapeutic brands. We are profitable, have positive cash flow, have double-digit growth with our key marketed brands, and our 5-year outlook calls for incredible growth versus the industry.

Q: ***What drugs do you have in development, and what is their market potential?***

A: In the short-term, we're focused on developing innovative new products with our existing molecules. Our immediate goal is to broaden and improve our drugs' efficacy, tolerability, and applicability. Current Phase III clinical programs for two of our lead brands will yield a range of marketable products in 2007-2011. MedPointe will also increase its presence in the allergy market with the development of a new category of allergic rhinitis products and the next-generation of existing treatments. Part of MedPointe's vision is to develop products that are designed to solve patient's health concerns. For example, Astelin Nasal Spray is the only nasal antihistamine with excellent decongestant effect that is not a steroid and does not have a decongestant component; it is purely topical. This provides a solution for consumers who do not want to take steroids. Future products will take into account that a steroid component is key for many patients, providing highly effective alternatives for physician and patient.

Q: ***What are you looking for from other companies as far as in-licensing?***

A: We continue to seek acquisition of current marketed products, as well as late-stage development projects, in our focus therapeutic areas.

Q: ***What are your long-term goals/objectives for the company?***

A: Our goal is to be a $1- to $3-billion enterprise in the next 3 to 5 years, and certainly the recent announcement from Meda will enhance our chances of reaching this goal. We expect to have a solid business base in current areas of therapeutic focus upon which we can add products. Once we have launched our most near-term products, we will use incremental funds to add late-stage development products to our pipeline. We may also enter additional therapeutic areas.

Q: ***What has been your business strategy to enrich the pipeline?***

A: In the past 4 years, we have increased our investment by more than 400% in our own development pipeline. The initial development strategy is to focus on utilizing current assets to build new innovations, concentrating on late-stage clinical programs for our lead products, such as Astelin Nasal Spray. Each of these products will be brought through the clinical trial process to commercialization in a strategic and efficient manner. We will capitalize on our strong relationships with professional customers to spur market demand. We also have one new chemical entity in Phase I development for the treatment of epilepsy.

Q: ***Name one highlight and one low point for the company? To what do you attribute each?***

A: The most evident low point for us was in early 2005, when Astra-Zeneca cancelled a distribution deal we had on one of its neurology products. The product represented a sizable piece of our business and losing it so abruptly caused us to have to reduce our commercial organization by over 200 people. What we did was meet the challenge head on. We reorganized, found spots for as many people as we could, and took care of those who couldn't stay as best we could. We then immediately focused on our other products, our development projects, and winning in the marketplace. We had an excellent 2005, and in 2006, we set new records for growth. We have also hit every development milestone we set for our clinical programs to date. The highlight came in early 2006 when we resumed expansion and launched our DTC effort, a major milestone for us. We also had many people who had to leave us in 2005 call and ask to come back. That says a lot about the kind of company we're building. Great people want to be with other great people at great places. Of course, the Meda transaction is another highlight as it serves as further proof of the success of our business model in just 6 short years.

Q: ***What is the one mistake you want to avoid going forward?***

A: Our commitment is to come to work every day and keep the momentum going, always looking to take current projects and future ideas to the next level. We never want to lose our entrepreneurial spirit or market agility. While growing, we are looking to simultaneously develop systems and technologies to help our customers, sales force, and patients feel as though they are still dealing with a company large enough to handle the business and small enough to still be very hands-on and personable.

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

A: The unexpected. Every day there is a new challenge to our industry, a new effort to undermine innovation or otherwise make it cost prohibitive. You have to worry about what is beyond your control so you can plan to navigate through it as you build an enterprise, especially a small entrepreneurial one. That said, MedPointe's growth and innovation continues to amaze me, and I find myself reviewing programs over and over again to make sure we can deliver on the successes that we have promised ourselves, our employees, our investors, our new partner, and our customers. ■

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The Curse of the Sacred Cows

By: John A. Bermingham

One of the more formidable traps that any person can fall into in their company is to not recognize who the sacred cows are, the danger they represent, and how to treat them. What is a sacred cow you may ask? A sacred cow is a person or policy that is a barrier to success that everyone knows about but no one wants to talk about or confront. Either way, be they people or policies, sacred cows are killer to a company. They keep you stuck in the mud when you are trying to make progress. They jeopardize bright competent executives. They are a common cause of failure.

Let's take the people issue because sacred cow policies and procedures are much easier to deal with. Sacred cows are generally people who lost their effectiveness years ago but are untouchable. They are people who did not grow with the company and are ineffective in their responsibilities. They keep doing the same thing over and over, each time expecting improved results.

My experience throughout the years has shown that almost every company has sacred cows in diverse areas. They are people who have ingratiated themselves with members of the Board, investors, and senior management because they are incompetent people who politic on a consistent basis due to their shortcomings. They can also be people who have been with the company for many years and are, hence, a sacred cow.

When I go into a company to turn it around, I first look at the culture and condition of the company to determine who the sacred cows are and if they can be reprogrammed or moved to a different position in which they can add value. If not, you have to begin the "turn sacred cows into hamburger" process. There are all types of sacred cows, and the following are some examples:

- The people who have their own little fiefdom and no one dares tell them that the world passed them by years ago. They tend to surround themselves with inexperienced or ineffective sacred calves that shout out accolades of the talent of the sacred cow to the Board and follow obediently in the sacred cow's hoof prints.

- The people who continue to adhere to a strategy or methodology from long ago that no longer fits the company.

- The people who are the "yes persons" of the Board or senior management.

Now for the most dangerous sacred cow: the back-channel sacred cow. Back-channel sacred cows are people who continually smile at you and tell you that they are on your team. Then when you are not around, they make negative comments behind your back or look to find ways to cause you problems. What's worse is they take information, modify it to their advantage, and then present the misinformation to the Board, investors, or senior management in a way that is of course advantageous to them and very bad for you. They take the position with the Board or senior management of, "if you really want to know the actual information, then you need me to feed it to you Mr. or Ms. Board member. The CEO is not telling you the whole story." They are very slick and convincing with the Board or management in order to strengthen their sacred cow position at your expense.

I once ran into a back-channel sacred cow. I had to quickly turn this sacred cow into hamburger due to the danger this person presented to me and the company. This person was feeding misinformation to several Board members in an attempt to bond with the Board at my expense. I quickly began developing what I refer to as a "Phoenix File." This is a file in which I place every bit of factual information that pertains to a back-channel sacred cow. E-mails, memos, letters, verbal communications transcribed to written notes, etc. Then when the file is large enough, I meet with the Board to prove that I had presented factual information, and the sacred back-channel cow had presented skewed and misleading information to them. You have to be delicate here as you are also telling the Board that they were suckered by the sacred cow. So whenever you meet a sacred cow, work quickly to turn them into hamburger. Otherwise you may be the one who is put out to pasture! ◆

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 three 3 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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