Drug Delivery Technology®

May 2006 Vol 6 No 5

The Science & Fiction of Nanotechnology

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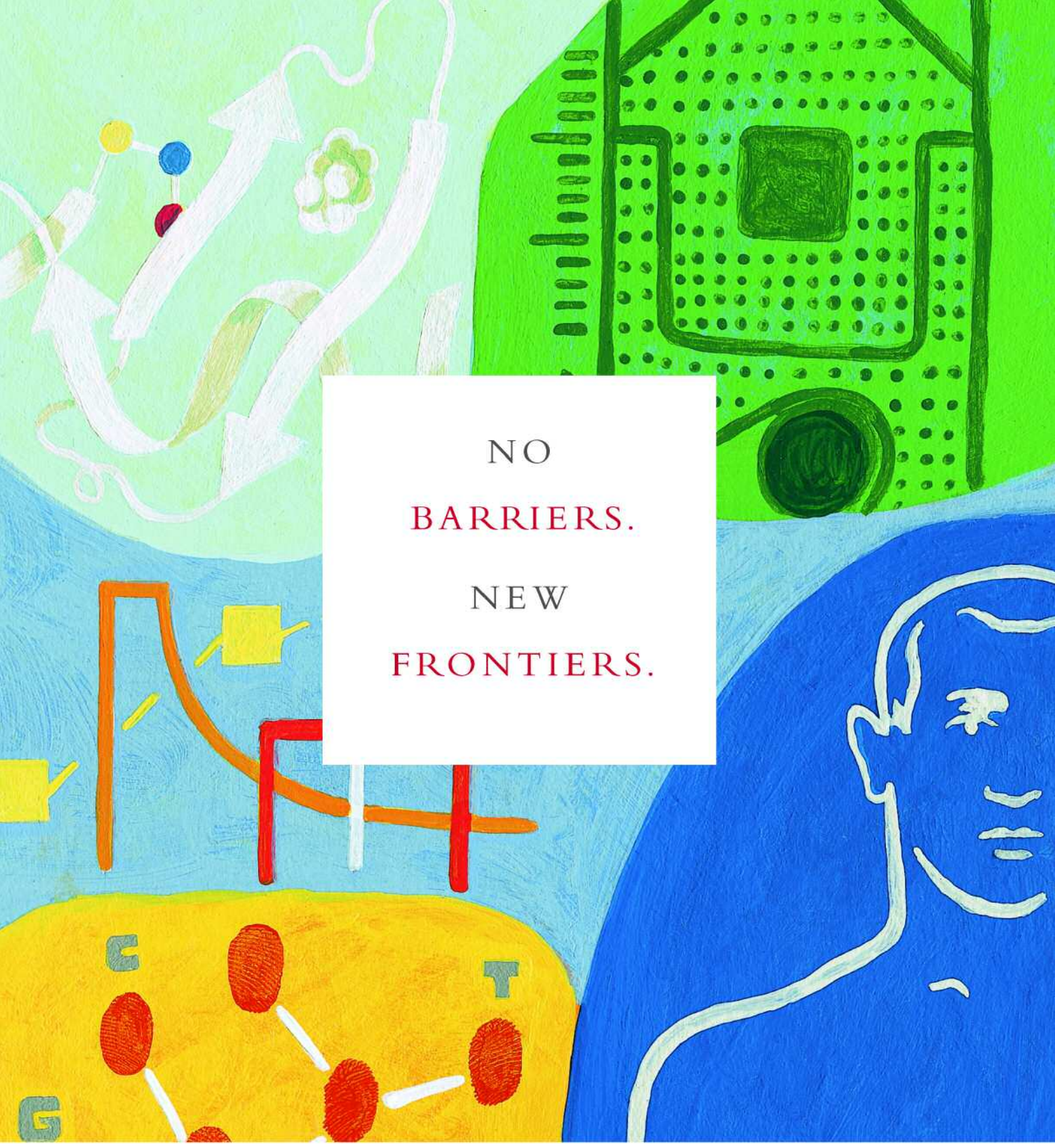

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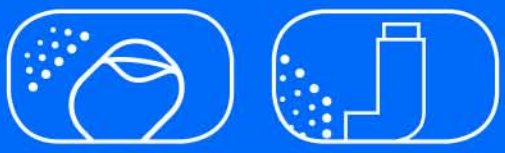

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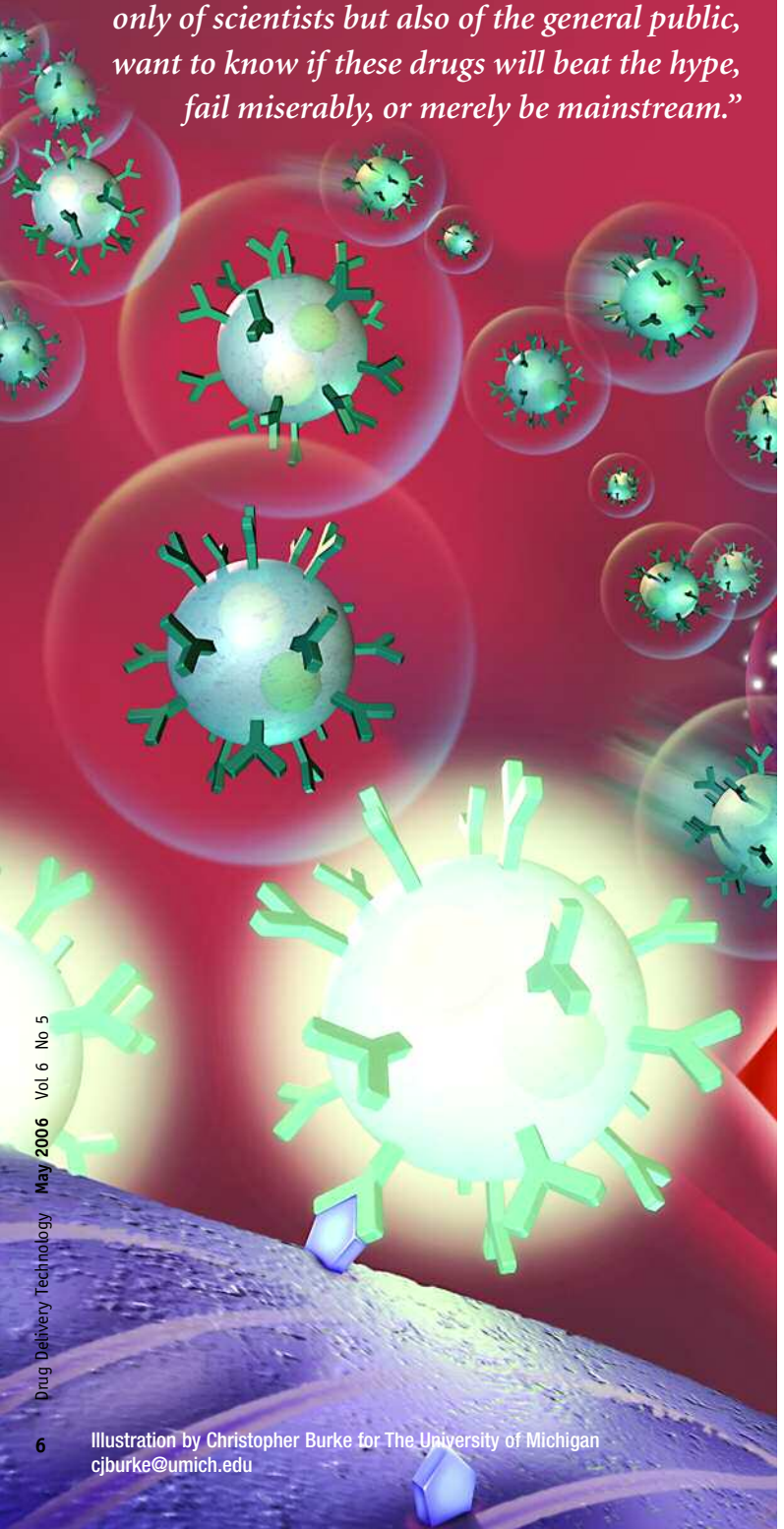

Illustration by Christopher Burke for The University of Michigan
cjburke@umich.edu

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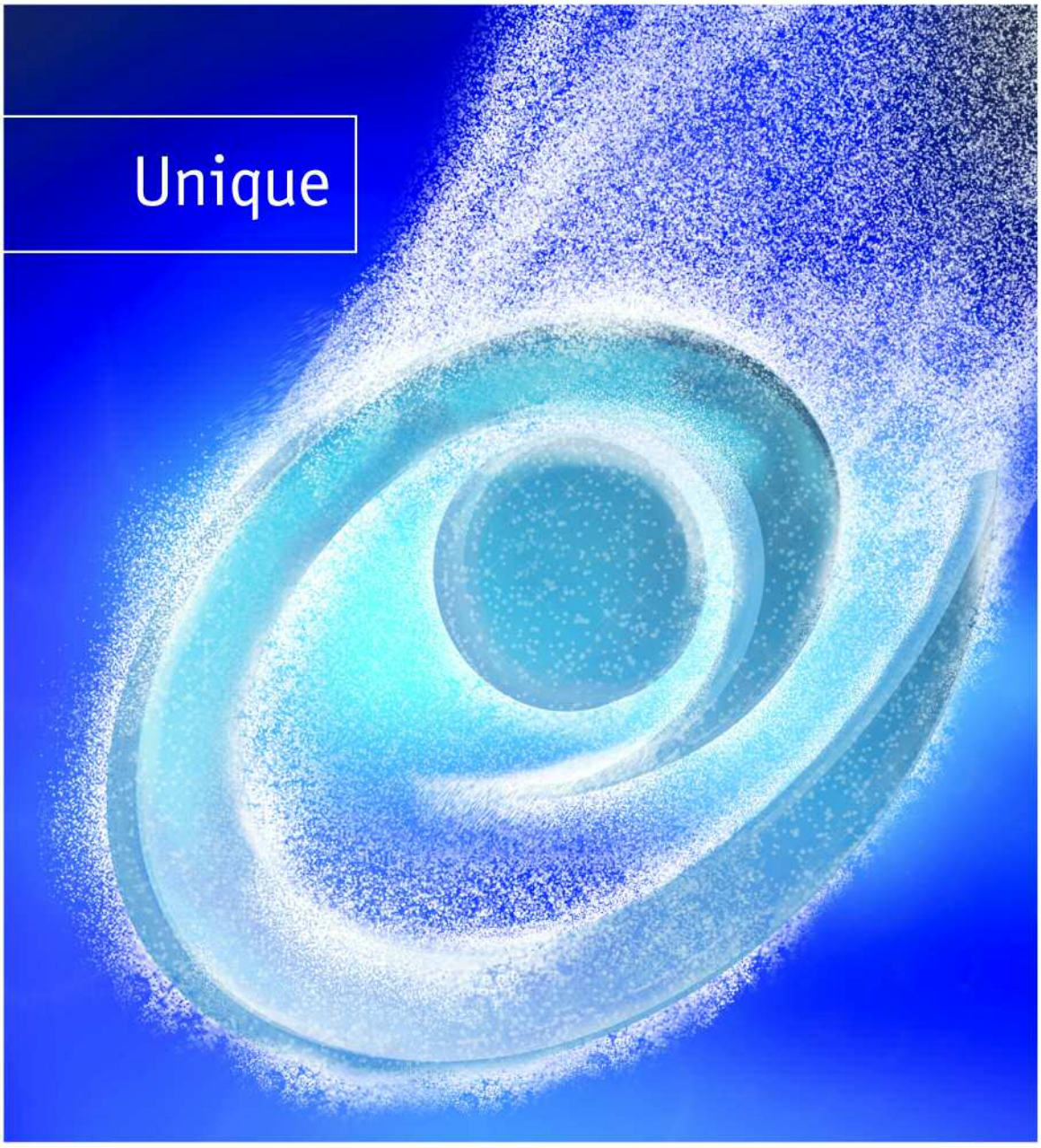

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"With the FDA taking ever more interest in use errors, ergonomic and human factors will increasingly come under the regulatory spotlight, but simply using design as a quick fix is missing the point. The more farsighted device manufacturers are now coming to the realization that marginalizing the industrial design component of the development cycle is an increasingly risky strategy."

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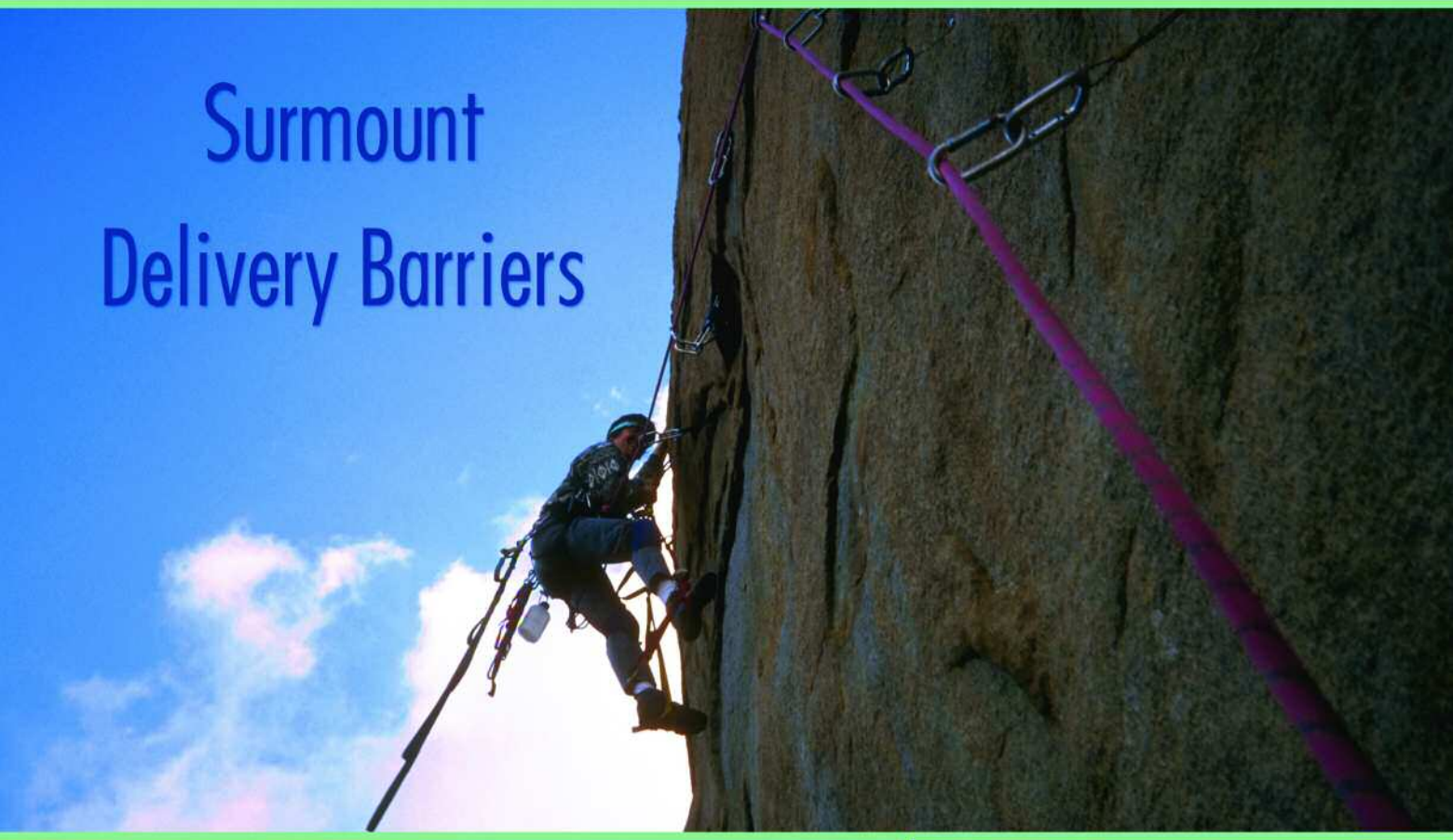
Surmount Delivery Barriers



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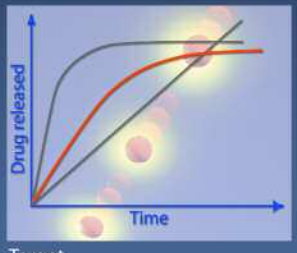
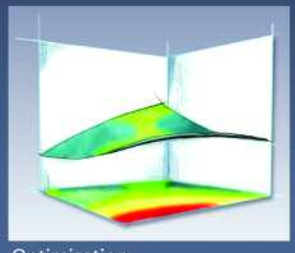


Target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Market News and Trends

Kurve Technology Announces Agreement With DARA BioSciences; Receives Frost & Sullivan Award

Kurve Technology, Inc., a leader in nasal drug delivery devices, recently announced the signing of an agreement with development-stage pharmaceutical company DARA BioSciences, Inc. (DBI). DBI focuses on the treatment of metabolic diseases, central nervous system disorders, and medical devices.

"We are impressed with the quality and flexibility of Kurve's technology platform and excited about combining Kurve's drug delivery technology platform with DARA's pharmaceutical formulations," said John Didsbury, Executive Vice President of DBI.

"DBI's research and development is the type of leading-edge pharmaceutical science for which our devices were developed," said Marc Giroux, Chairman and CEO of Kurve Technology, Inc. "We are thrilled to be working with the innovative team at DBI."

Incorporating patented Controlled Particle Dispersion and intelligent nasal drug delivery technologies, Kurve's ViaNase electronic atomizer intranasally delivers topical, systemic, and nose-to-brain medical therapies with greater efficacy and efficiency than traditional nasal delivery devices, such as spray pumps. ViaNase is the first nasal drug delivery device that saturates the entire nasal cavity, allowing delivery to the paranasal sinuses. In addition, ViaNase limits peripheral deposition of pharmaceutical formulations into the lungs or stomach. Kurve's most recent device offering (ViaNase ID) incorporates drug pedigree confirmation, lock-out technology, and an electronic display to curb counterfeit drug use and abuse while improving patient compliance.

DARA BioSciences, Inc., incorporated in Delaware in July 2002, is a development-stage company that acquires and develops therapeutic candidates and medical technologies directly or through subsidiaries and is focused on the treatment of metabolic diseases, central nervous system disorders, and cardiovascular indications. DBI is the parent company to Signum Pharmaceuticals, OnsetThera, Inc., NYVARA Pharmaceuticals, Inc., MIKKO Pharmaceuticals, and DARA Therapeutics, Inc. Additionally, DBI holds positions in Medeikon Corp., Surgi-Vision, Inc., SpineMedica, Inc. and Medivation, Inc.

Kurve also announced that Frost & Sullivan selected it as the recipient of the 2006 Business Development Strategy Leadership of the Year Award in the intranasal drug delivery market for successfully partnering their cutting-edge device technology with pharmaceutical companies.

"The limitations of manual spray pumps have long been known, but few companies have dedicated time and resources to improve delivery technology, instead focusing more on formulation design," says Frost & Sullivan Research Analyst Jason McKinnie. "Kurve has overcome obstacles, such as lack of accuracy, control of droplet size, and regulated velocity, and created a device that maximizes nasal mucosa exposure for both topical, systemic, and nose-to- brain drugs."

"Controlled Particle Dispersion is capable of delivering three preservative-free formulations: dry powder, suspension, and solution, and the individual dose ampoules are capable of storing small molecules, large molecules and proteins," added Mr. McKinnie. "Tests have shown very little degradation to proteins through this delivery, providing the capability to treat diseases or vaccinate with peptides thus boosting its value."

Kurve Technology is ensuring patients will soon get access to a more reliable and effective nasal delivery system and are therefore the worthy recipient of the 2006 Frost & Sullivan Business Development Strategy Leadership of the Year Award for the intranasal drug delivery market. Each year Frost & Sullivan presents this Award to a company that has exhibited excellence in business development within the industry. The Award recognizes the company's ability to best perceive consumer needs, develop products and/or services that meet consumer needs, successfully introduce products or services to the industry, and identify new market segments to expand the existing customer base. Through a combination of vision, technology, and successful marketing, the Award recipient has demonstrated superior market growth skills.

AerovectRx Receives FDA 510(k) Clearance for the First Nebulizer Drug Delivery System With Disposable Medication Cartridge

AerovectRx Corporation, developers of a new pain-free, inhaled drug delivery technology, recently announced that it received 510(k) clearance from the USFDA to market the first vibrating mesh nebulizer with a disposable medication cartridge. The new technology is planned for use to deliver a wide variety of specialty point-of-care therapies painlessly by inhalation rather than injections.

"Our unique, painless technology platform provides fast and easy delivery of a wide range of therapies and vaccines providing access to multibillion-dollar market opportunities, including influenza, idiopathic pulmonary fibrosis, and diabetes," said Matthew Kim, Founder and CEO of AerovectRx. "We believe that our technology is attractive to pharmaceutical companies seeking to maximize delivery of their drugs and also to physicians and patients alike seeking to remove the pain barrier of injections."

AerovectRx's technology centers on the proprietary AeroCell disposable drug cartridge that provides for highly efficient and effective inhaled delivery of therapeutics and a continuing revenue stream.

"Now that we have received our initial 510(k) clearance, we are focusing our efforts on commercializing this technology and further advancing business development discussions with potential partners. Our unique design provides for a platform that can be leveraged across multiple markets along with a disposable cartridge revenue stream in addition to the drug being administered. We plan to partner with pharmaceutical and biotechnology companies with established market presence and a sales and distribution infrastructure already in place," added Mr. Kim.

AerovectRx Corporation is an early stage company developing novel pulmonary drug delivery technology licensed from the US Centers for Disease Control and Prevention (CDC). Products under development by AerovectRx are designed to deliver a wide variety of therapies through multiple-use mass immunization and as well as personalized nebulizers. Initially targeted therapeutic candidates for the AerovectRx technology include treatments for asthma, cystic fibrosis, idiopathic pulmonary fibrosis, avian flu, and diabetes.

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Market News and Trends

AlphaRx & Proprius Pharmaceuticals Announce License Agreement for a Phase II Topical NSAID for Osteoarthritis

AlphaRx, Inc., and Proprius Pharmaceuticals, Inc., recently announced they have entered into a license agreement giving Proprius exclusive global rights (with the exception of Asia and Mexico) to AlphaRx's topical NSAID, Indaflex 2.5% Indomethacin Cream. Indaflex, which makes use of AlphaRx's proprietary formulation technology to deliver indomethacin through the skin and directly to the soft tissue surrounding the joint, is currently in Phase II clinical development in Canada for the treatment of osteoarthritis. In addition to Indaflex, the agreement gives Proprius rights to successor products and to all other topical NSAID products developed by AlphaRx.

Under the terms of the agreement, AlphaRx will receive an up-front payment of $1 million and will be eligible to receive additional milestone payments of up to $116 million for the successful development and commercialization of Indaflex, as well as double-digit royalties on worldwide sales. In addition, Proprius will assume the clinical development costs going forward.

"Given the adverse event profiles of oral NSAIDs and COX-2 inhibitors, and the withdrawals of rofecoxib and valdecoxib from the market, we believe Indaflex has the potential to fill a significant unmet clinical need," said Michael J. Walsh, President and CEO of Proprius. "With the right formulation, a topical NSAID offers the potential of matching or surpassing the efficacy of oral treatments while avoiding the side effects associated with circulating levels of these drugs. The preclinical and early clinical data with Indaflex are quite encouraging, and we believe Indaflex could be a market leader in this important area."

"This is a promising treatment," added Dr. Lee Simon, a Rheumatologist and former Director of the FDA's Anti-Inflammatory, Analgesic and Ophthalmic Drug Products Division and a clinical and regulatory consultant to AlphaRx. "Indomethacin is considered one of the most potent NSAIDs available, and Indaflex was shown to be superior to both oral indomethacin and rofecoxib in a non-clinical study. In addition, Phase I data show negligible concentrations of circulating indomethacin in human volunteers once topically applied, suggesting a very low probability of systemic adverse events, such as gastrointestinal or cardiovascular safety concerns."

"We believe Proprius is an ideal partner to maximize the potential of our topical NSAID drugs," said Michael Lee, CEO of AlphaRx. "The Proprius management team has a proven track record of successful development and commercialization of pharmaceutical products, and has previously been instrumental in raising hundreds of millions of dollars in private and public capital. We are confident Indaflex will be a major focus of the company and that they are committed to moving it forward aggressively."

Medtronic Receives FDA Approval for World's First Insulin Pump With Real-Time Continuous Glucose Monitoring

Medtronic, Inc., recently announced FDA approval of the MiniMed Paradigm REAL-Time Insulin Pump and Continuous Glucose Monitoring System, a progressive new therapy available for patients who use insulin to treat diabetes. For the first time in the history of diabetes management, an insulin pump integrates with REAL-Time continuous glucose monitoring (CGM). This new technology will help patients take immediate corrective or preventive action to maintain healthy glucose levels and delay or prevent diabetes-related complications, including coma, blindness, kidney failure, amputation, impotence, and heart disease.

The MiniMed Paradigm REAL-Time System is made up of two components, a REAL-Time Continuous Glucose Monitoring System, and a MiniMed Paradigm insulin pump. The REAL-Time CGM System relays glucose readings every 5 minutes from a glucose sensor to the insulin pump, which displays to 288 readings a day (nearly 100 times more information than three daily fingersticks). REAL-time glucose information displayed on the insulin pump allows patients to take immediate action to improve their glucose control after taking a confirmatory fingerstick. The REAL-Time CGM System component is indicated for any patient 18 years of age or older, and insulin pump therapy for all patients requiring insulin.

"The approval of the MiniMed Paradigm REAL-Time System opens the door to the next generation of diabetes management," said Robert Guezuraga, President, Medtronic Diabetes. "As this is the first integrated insulin pump and continuous glucose monitoring system ever approved, we believe this new therapy will revolutionize the way patients manage their diabetes and will improve their lives."

Integrating an insulin pump with REAL-Time CGM is a major step toward the development of a "closed-loop" insulin delivery system that may one day mimic some functions of the human pancreas. Medtronic is testing future systems that would employ advanced scientific algorithms to proactively recommend insulin dosages to patients. Through this process, Medtronic anticipates developing an external, closed-loop system designed to simplify and improve patient diabetes management.

The MiniMed Paradigm REAL-Time System's continuous glucose sensor is a tiny electrode that is inserted under the skin using the Sen-Serter, a small device that patients or their caregivers can use at home to make sensor insertion easier. The sensor measures glucose in the interstitial fluid found between the body's cells, and is typically discarded and replaced after 3 days of use. Glucose measurements obtained by the sensor are relayed every 5 minutes from a transmitter to the insulin pump, which displays the glucose value, 3-hour and 24-hour trend graphs, as well as arrows to indicate how quickly glucose is moving up or down. In addition, an alarm alerts patients when glucose levels become too high or too low.

The MiniMed Paradigm REAL-Time System includes a "smart" MiniMed Paradigm insulin pump, which has a powerful built-in Bolus Wizard calculator to manage the complex diabetes math for patients. Smart insulin pumps recommend insulin dosages after considering the amount of insulin still "active" in the body, helping patients avoid dangerous hypoglycemic episodes caused when too much insulin is delivered.

Market News and Trends

Cambridge Consultants' & Chiesi Farmaceutici's Innovative Dry Powder Inhaler Nears Release

A new generation dry powder inhaler, NEXT, whose aim is to help improve the treatment of asthma and COPD (chronic obstructive pulmonary disease) through greater user appeal and more efficient and consistent drug delivery, was presented for the first time at the Respiratory Drug Delivery (RDD) conference in Florida this past April.

The NEXT DPI, designed by Cambridge Consultants and Chiesi Farmaceutici, consistently achieves 60% fine particle fraction and has successfully completed pharmacokinetic clinical studies. The device, currently being ramped up for manufacture, has also finished extensive user-group research in which both doctors and patients reacted positively to the DPI's features, which include a reliable dose counter, a simple user-interface, and a discreet and robust, yet modern, style. The device looks well positioned to capture significant market share as it delivers the critical benefits required by healthcare professionals and patients.

NEXT is a medium-resistance, breath-activated device that holds up to 120 doses and is the first of a new generation of bulk reservoir DPIs. The device is intuitive to use (simply open, inhale, and close) and has excellent dose uniformity. The concept was selected according to criteria that were identified as desirable for an ideal device in market research: portable, robust, intuitive, and provides feedback to let the patients understand that the dose has been correctly taken, guaranteeing an accurate and consistent dose delivery. In the same market research, in focus groups, the NEXT DPI obtained the consensus of those interviewed that it represents the device of the future. The combination of ease-of-use, high-performance, consistency, and reliability clearly benefits both patients and doctors.

Asthma is one of the world's most prevalent diseases, affecting between 100 million and 150 million people, according to the World Health Organisation (WHO). In the US alone, the American Lung Association claims that the disease affects over 20 million people, costs the country over $11.5 billion annually, and results in the death of over 5,000 people every year. The WHO ranks COPD as the fourth leading cause of death worldwide, a position it shares with HIV/AIDS.

"The results that we have received so far from clinical trials and user groups have been truly impressive," said Gaetano Brambilla, R&D Project Leader at Chiesi. "The combination of our innovative drug formulations and Cambridge Consultants' design expertise has resulted in a device that we expect to be very competitive toward the established market leaders."

"We started from scratch, creating new concepts for the NEXT device and through close collaboration with Chiesi, we developed a substantially improved device, both in terms of performance and user appeal," said Dr. David Ellis of Cambridge Consultants. "The entire development team is delighted with the results, and this device should have a positive impact on the lives of millions of asthma and COPD sufferers."

Chiesi Farmaceutici is a European pharmaceutical company, headquartered in Parma, Italy, dedicated to the research, development, and commercialization of ethical therapeutic products.

Cambridge Consultants has, for over 40 years, enabled its clients to turn business opportunities into commercial successes, whether launching first-to-market products, entering new markets, or expanding existing markets through the introduction of new technologies. It develops breakthrough products, creates and licenses intellectual property, and provides business consultancy in technology critical issues for clients worldwide.

Market News and Trends

Acuity Pharmaceuticals Continues Pipeline Expansion by Licensing a Novel Broad Spectrum Anti-Infective for Ophthalmic Use

Acuity Pharmaceuticals, Inc., a clinical stage, product-focused ophthalmic pharmaceutical company, recently announced that it has in-licensed exclusive worldwide development and commercialization rights to N-chlorotaurine (NCT), a novel, clinical stage, small molecule agent for the treatment of ophthalmic infections and other conditions. Acuity's lead compound, Cand5, is in clinical trials for wet age-related macular degeneration and diabetic macular edema, and represents the first clinical use of the gene-silencing technology called RNA interference.

NCT, which is a derivative of a naturally occurring substance in the body, has already completed pilot Phase II studies in Europe, where it has been shown to have promising antimicrobial activity and to be safe and well-tolerated in such applications as sinus and ear infections, as well as in viral conjunctivitis. NCT combines broad-spectrum anti-infective activity with very good tolerability, and its natural sterility and absence of preservatives make it a good candidate for ocular applications.

The first indication Acuity will pursue for NCT is for conjunctivitis, or pink eye, a common eye inflammation that is a major source of acute medical visits for eye care. NCT is expected to have utility in both bacterial and viral conjunctivitis, providing a major advantage because there currently is no approved treatment for the commonly occurring, viral form of the disease.

"NCT is a good fit with our expanding pipeline and supports Acuity's strategic focus of leadership in the development and marketing of novel therapies for ophthalmic diseases, particularly conditions that are currently poorly treated," said Dale Pfost, President and CEO of Acuity. "As a novel mechanism, broad spectrum anti-infective with properties that make it particularly suited for ophthalmic uses, NCT is an excellent addition to our portfolio. We believe that the clinical pathway to approval of NCT should be relatively straightforward, and its clinical and commercial potential across multiple ocular indications is significant."

In preclinical and clinical studies, NCT has demonstrated potential as a potent antimicrobial agent in the treatment of a broad range of bacterial, viral, and fungal infections, and its nonspecific oxidation mechanism is less susceptible to the development of drug resistance than conventional anti-infectives. The license includes proprietary modifications and formulations that are designed to optimize NCT for ophthalmic use.

Following a planned Phase I clinical trial for ophthalmic applications, Acuity will have sole responsibility for clinical development and commercialization of NCT in ophthalmic indications. The company will pay licensor Pathogenics, Inc., up-front and license fees, as well as development milestones and royalties. Further details of the agreement were not disclosed.

Founded in 2002, Acuity Pharmaceuticals is a product-focused ophthalmic pharmaceutical company applying proprietary technologies to the treatment and prevention of ophthalmic diseases. Acuity's lead clinical compound, Cand5, a small-interfering RNA (siRNA) therapeutic targeting VEGF, is in clinical trials for two of the leading causes of adult vision loss. Acuity recently completed a Phase II trial of Cand5 in age-related macular degeneration and is currently conducting a Phase II trial for diabetic macular edema. Acuity is applying its drug development expertise to a growing pipeline of novel agents for ophthalmic conditions. In support of these programs, Acuity is also developing proprietary technologies for ocular drug delivery.

Dowpharma Signs Fourth Collaboration Agreement in First Quarter of 2006 for Pfenex Expression Technology

Dowpharma contract manufacturing services, a business unit of The |Dow Chemical Company, recently announced it has signed its fourth collaboration agreement in the first quarter of 2006 for its Pfenex Expression Technology, a Pseudomonas-based technology. Pfenex Expression Technology accelerates speed to market for vaccines and biotherapeutics by improving quality, boosting yields of protein expression, and reducing the cost of existing microbial systems.

Dowpharma's fourth and most recent agreement was signed with Insmed Incorporated to advance the development of Insmed's IPLEX. Under the terms of the agreement, Dowpharma will express two proprietary Insmed proteins that are administered as a single complex, known as IPLEX, using Pfenex Expression Technology.

"With our recent collaborations with VGX Pharmaceuticals, Viventia Biotech, and now Insmed, we are experiencing tremendous growth and adoption of our Pfenex Expression Technology," said Nick Hyde, Global Business Director, Dowpharma. "It is currently successfully being used to manufacture cGMP material that will be used in clinical trials, and now we will express currently FDA approved proteins. Pfenex Expression Technology consistently outperforms other microbial expression systems and we look forward to working with Insmed in their drug development program."

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

Insmed Incorporated is a biopharmaceutical company focused on the discovery, Development, and commercialization of drug products for the treatment of metabolic diseases and endocrine disorders with unmet medical needs.

SCOLR Pharma to Raise $11.8 Million in Offering of Common Stock

SCOLR Pharma, Inc., recently announced it has obtained commitments to purchase shares of its common stock in a registered direct offering for gross proceeds of approximately $11.8 million. Under the terms of the transaction, SCOLR Pharma, Inc. expects to sell approximately 2.37 million shares of its common stock at $5.00 per share to a group of institutional investors. The closing of the offering is expected to take place on April 20, 2006 (at press time), subject to the satisfaction of customary closing conditions.

The company believes that the net proceeds from this offering, together with its cash and cash equivalents of $10.9 million and $2.4 million in short-term investments as of December 31, 2005, is sufficient capital to fund its planned operations through the end of 2007. Taglich Brothers, Inc., and Roth Capital Partners, LLC acted as placement agents for the transaction. The shares of common stock may only be offered by means of a prospectus.

Based in Bellevue, Washington, SCOLR Pharma, Inc. is a specialty pharmaceutical company leveraging formulation expertise and its patented CDT platform to introduce distinctive and novel OTC products, prescription drugs, and dietary supplements. SCOLR Pharma's CDT drug delivery platform provides distinctive products with tangible benefits for the consumer and competitive commercial advantages for licensees.

Market News and Trends

Noven & Shire Pharmaceuticals Announce FDA Approval of Daytrana Methylphenidate Transdermal System; First Attention Deficit Patch

Noven Pharmaceuticals, Inc., recently announced the USFDA has approved Daytrana (methylphenidate transdermal system) as a new therapeutic option for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children aged 6 to 12 years. Shire plc, the global licensee of Daytrana and market-share leader in the ADHD category, is expected to launch the product in the first half of 2006.

"The approval of Daytrana, the first non-oral medication for ADHD, is outstanding news for Noven, Shire, and patients," said Robert C. Strauss, Noven's President, CEO & Chairman. "For Noven, the approval advances our goal of commercializing our patented transdermal technology in diverse therapeutic markets with strong partners. For Shire, it adds an important new methylphenidate product to their portfolio of ADHD products, and reaffirms their position as the ADHD support company. And for patients, parents, and physicians, Daytrana represents a new once-daily therapy for children diagnosed with ADHD."

Upon receipt of FDA approval, Noven became due to receive a $50 million milestone payment from Shire. Noven also has the opportunity to earn additional milestone payments of up to $75 million, depending on the level of Shire's commercial sales of the product, and expects to earn a profit on the manufacture and supply of finished product to Shire.

Daytrana combines the active ingredient methylphenidate with Noven's patented DOT Matrix transdermal drug delivery technology. Daytrana and DOT Matrix are trademarks of Shire and Noven, respectively.

Noven Pharmaceuticals, Inc., headquartered in Miami, Florida, is a leading developer of advanced transdermal drug delivery technologies and prescription transdermal products. Noven's prescription patches are approved in over 30 countries, and a range of new patches are being developed in collaboration with Novartis Pharma AG, Shire plc, P&G Pharmaceuticals, Endo Pharmaceuticals, Inc., and others. Together with Novartis Pharmaceuticals Corporation, Noven owns Novogyne Pharmaceuticals, a women's health products company with over $120 million in annual sales. Among other products, Novogyne markets and sells Noven's Vivelle-Dot product, the smallest estrogen patch in the world, and the most prescribed transdermal estrogen therapy in the US.

Halozyme Receives Approximately $1.9 Million From Exercise of Warrants

Halozyme Therapeutics, Inc., a biopharmaceutical company developing and commercializing recombinant human enzymes, recently announced that since January 1, 2006, holders of the company's various outstanding warrants have exercised rights to purchase a total of 1,476,601 shares of common stock, resulting in net proceeds to the company of approximately $1.9 million. Halozyme intends to use the proceeds to continue the advancement of its lead oncology product candidate, Chemophase, and to commercialize Hylenex for use as an adjuvant to increase the absorption and dispersion of other injected drugs.

Halozyme is a biopharmaceutical company developing and commercializing recombinant human enzymes for the drug delivery, palliative care, oncology, and infertility markets. The company's portfolio of products is based on intellectual property covering the family of human enzymes known as hyaluronidases. Halozyme's recombinant human enzymes may replace current animal slaughterhouse-derived extracts that carry potential risks of animal pathogen transmission and immunogenicity.

The company has received FDA approval for two products: Cumulase, the first and only recombinant human hyaluronidase for cumulus removal in the IVF process; and Hylenex for use as an adjuvant to increase the absorption and dispersion of other injected drugs. The versatility of the first enzyme, rHuPH20, enables Halozyme to develop the product as a medical device, drug enhancement agent, and therapeutic drug.

BUSINESS DEVELOPMENT

Sourcing a Pipeline for a Specialty Pharmaceutical Business Model, Part II

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

In last month's column on the topic of pipeline sourcing, we discussed the importance of kicking off the sourcing process by taking a strategic, portfolio view. This step provides critical focus for your business development and scientific resources, allowing them to work toward a clear strategy while minimizing distractions. In this second installment, we will address the tactical process of sourcing and ultimately vetting the world of product opportunities. We will narrow the scope to internally generated product opportunities that use innovative drug delivery technology. We can begin by first defining the key challenges to pipeline sourcing, and then discuss the approaches that successful companies use to overcome these challenges.

GENERATING PRODUCT CONCEPTS

"God gives every bird a worm, but he does not throw it into the nest." - Swedish proverb

As the quote above suggests, finding new product opportunities is not an easy endeavor. This is especially true if the goal is to find products with the potential to achieve blockbuster status. To help define the challenges that drug delivery companies face, we spoke to six companies that have successfully developed solid pipelines using their drug delivery technologies (Table 1).

What is interesting about the Table is the wide breadth of issues that were cited. However, there are some common themes. The biggest concern generally relates to resourcing/prioritization, and is reflective of the fact that financial and human resources are invariably limited. The second issue is related to the regulatory and reimbursement environment, where cost pressure, safety, and quality concerns make it increasingly difficult to develop viable specialty pharmaceutical products (eg, marginal products may not pass the pharmaco-economic test). The last main issue is relating to the process of getting the right individuals involved, providing them with the right information, and nurturing creativity such that new product opportunities are identified and championed.

The good news is that companies with novel drug delivery technologies are in an excellent position to source and develop solid pipeline products. This is because the company's internal technology adds inherent value and protection to a well-conceived product concept, helping to overcome some of the clinical, regulatory, or pharmaco-economic hurdles. Moreover, these companies by their very nature are often led by entrepreneurs, risk-takers, or uniquely gifted scientists who foster creativity. This provides a winning foundation on which to nurture innovative opportunities. The real question then is how to channel this creative energy and technology to select the best of the best in the true business and clinical sense.

THE PRODUCT EDGE: A 5-STEP APPROACH

"Opportunity is missed by most people because it is dressed in overalls and looks like work." -Thomas Edison

Despite the tremendous focus on products and the drying of pharmaceutical pipelines, it is somewhat surprising to learn that most companies have yet to invest in systematic methodologies to identify, screen, and champion creative product opportunities. The result is that all too often great product ideas fall through the organizational cracks, lack a product champion, or are missing the right supporting information that is required to turn a "conceptual idea" into a "viable product opportunity." Ask yourself: Do you know who to contact at your organization if you have a great product idea? What supporting information will you need to bring to get their attention? Who will champion it from there?

Much of this can be improved by developing a clear, repeatable process for identifying and vetting product opportunities. At Valeo Partners, we believe that the key ingredients can be distilled to a 5-step recipe for product success.

1. Define the strategy
2. Get the right team involved
3. Periodic brainstorming
4. Gather critical information
5. Develop a business case


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There are many bells and whistles that can be added to improve the aforementioned list (eg, performance incentives, metrics, tools, etc), but we believe that if you can get these 5 fundamental steps right, good things are sure to follow.

TABLE 1

Company A	Assembling the right team	Getting the right information	Nurturing creativity
Company B	Applying human and financial capital	Achieving blockbuster status	Gaining regulatory approval
Company C	Applying human and financial capital	Identifying product champions	Fostering entrepreneurial spirit
Company D	Challenging regulatory environment	Justifying premium pricing	Expanding IP and exclusivity
Company E	Applying human and financial capital	Timing	Capital
Company F	Balancing data needs vs time spent	Balancing budget vs. market research	Consensus on prioritization

What are the three biggest challenges in generating product concepts?

Defining the Strategy

As discussed in last month's article, the first step is to define a clear strategy for identifying new product opportunities. This is typically developed by an executive or portfolio-level group in your organization, as these decision-markers are ultimately responsible for balancing resources and prioritizing the direction of the R&D pipeline. Given this foundation, the creative engine within the organization can align its efforts with the strategy, providing much-needed focus.

Getting the Right Team Involved

The next critical step is to get the right cross-functional team involved, with the goal being to maximize the creative outcome while minimizing the time commitment by those functions on the periphery. Product concept teams vary from company to company. In our experience, larger companies tend to have more formal cross-functional membership, while smaller companies may assign a single leader to manage the effort. Cross-functional teams most often include representatives from Business Development, Formulation (or equivalent function for devices), Marketing, and Clinical Development. If not on the core team, Regulatory, Legal, Quality, and Manufacturing/Operations functions are generally consulted ad hoc as needs arise. For smaller companies with teams, executive managers may fill some of these roles, perhaps wearing dual hats.

The team approach has several advantages, including broader organizational input, better consensus on recommendations (eg, more potential champions), clear ongoing organizational responsibilities, more assigned hands on task, and critical continuity of the overall process (eg, if a solo leader were to leave the company, you might find yourself starting from scratch). Regardless of the mix, however, the bottom line is that having the right people involved on an ongoing basis is a critical factor for success.

Periodic Brainstorming

Creativity matters. Once the right people are involved, it is critical to set up a mechanism to get the creative juices flowing. Of all the potential techniques, most companies site periodic brainstorming sessions as the best tactical approach to accomplish this goal. Many companies conduct internal brainstorming on a periodic basis (eg, twice per year) and then augment it with outside expertise to provide a fresh perspective. For example, we are often asked to help concept teams screen the vast pool of potential candidates for a given technology/therapeutic area and bring back a tiered list of potential opportunities. The results of this exercise are then used as a basis for group brainstorming with both consultant and client, thus providing an easy way to bring external perspectives to an ongoing internal effort. Remember that there are no bad ideas at this stage, so it is best to record all candidates such that opportunities are not lost (eg, use a "watch list" even if they don't move forward). I like to relate the quote of Charles Brower who said, "A new idea is delicate. It can be killed by a sneer or a yawn; it can be stabbed to death by a joke or worried to death by a frown on the right person's brow."

Gather Critical Information

Brainstorming inevitably leads to a list of potential opportunities that need to be vetted against market, patent, and competitive realities. In this step, the critical information is gathered to identify showstoppers, risks, or support the business case for moving forward. This step is a frequent source of delay at many companies that have not developed consensus on what information is required to move forward with a go/no-go decision or prioritization. Thus, many teams reinvent the wheel for each opportunity or have constant iterations before decisions are made. A simple outline of

"here's what we need, and to what degree of detail" will do wonders to grease the skids and get this step back on track. Also, it provides an easy basis for outsourcing to external contractors that are often asked to assist in gathering critical data to support the market research.

Developing a Business Case

The end result of the vetting process is an individual business case, typically tied with a recommendation to support (or otherwise delay/kill) an individual opportunity. At a high level, business cases typically provide an overview of the opportunity from a commercial, clinical, patent, and regulatory perspective, along with accompanying risks related to each of these categories. Primary drivers for recommendations are typically financial indicators (eg, projected return on investment or net present value) as weighed against known risks. In its entirety, the purpose of the business case is to define the benefits versus risk of an opportunity in a manner that can support a fact-based business decision. The degree of detail that is required is ultimately dependent on the degree of risk management is willing to take when compared to the time and resource investment that is required to obtain the data. This may seem like a lot of work; but rest-assured that your investors, management, and key personnel will rally around a company that has become an expert in developing great products.

BRINGING IT ALL TOGETHER

In summary, we have outlined both a critical set of challenges relating to product sourcing, as well as a basic framework that drug delivery companies in transition can use to build a process to overcome these challenges. This basic concept generation and assessment framework is designed to fully integrate with a strategic portfolio and prioritization process we defined in last month's article. Working in concert, these two elements ensure that the pipeline is full of creative opportunities, strategy is aligned with priorities, resources are applied to the best projects, roles and responsibilities are clear, and investment decisions are made based on a clear business case. The morale of the story for drug delivery companies in transition is that there is no better place for investment than in ways to ensure that the right decisions are made on the right products. ♦

BIOGRAPHIES

Dr. Christopher Robinson is a Founding Partner of Valeo Partners, where his primary focus is in helping clients develop winning business strategies, generate innovative product concepts, evaluate market opportunities, and optimize portfolio strategies. Dr. Robinson brings a results-oriented philosophy to traditional strategic consulting and has extensive experience working with executive management and cross-divisional project teams to turn strategy into proven results. Prior to joining Valeo, he was a management consultant at a global strategy consultancy focused on product development strategy, business process optimization, and implementation. He earned his MBA from Cornell University with specialization in venture capital and entrepreneurship and his PhD in Immunology from the University of Florida, where he focused on autoimmune diseases and genomics. He also earned a BS in Molecular Biology from Lehigh University.

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

ATTORNEY REVIEW

The FTC on Pharmaceutical Patent Litigation Settlements: Not Walking Softly, but Still Carrying a Big Stick?

By: Clifford M. Davidson, Esq.

There is a palpable tension between certain federal courts and the Federal Trade Commission concerning pharmaceutical brand-generic patent litigation settlements. The United States Patent and Trademark Office (PTO) awards lawful monopolies to patent owners. Those patents are then challenged through the courts by generic manufacturers as part of the Hatch-Waxman framework. On one side, federal courts favor settlements of patent infringement litigations; and on the other side, the Federal Trade Commission (FTC) conservatively views any payment from a brand manufacturer to a generic manufacturer in return for the generic manufacturer's delay of market entry to be illegal. The FTC aims to protect the public against unlawful anticompetitive practices. Recently, three federal circuit courts have considered the legality of brand-generic patent litigation settlements.

To review, pursuant to the Medicare Modernization Act (MMA), brand-generic patent settlement agreements must be submitted to the FTC for approval. While patents award limited term monopolies to inventors that disclose their discoveries, the FTC ensures that the public is not injured through illegal anticompetitive activity. The FTC has recently focused on brand-generic patent litigation settlements resulting from numerous practices by brand and generic manufacturers that have been found to be anticompetitive and illegal.

A decision from the Second Circuit Court of Appeals involved the drug tamoxifen citrate used for the treatment of breast cancer. The suit was brought by consumers against Astra Zeneca (who manufactured a branded version of tamoxifen citrate), challenging their patent litigation settlement with generic competitor Barr Laboratories. The settlement involved quarterly payments of $10 million and a license for Barr to sell an authorized generic manufactured by Astra Zeneca. Following the lower court's finding that the settlement was not illegal, the consumers appealed to the Second Circuit Appellate Court. Though the consumers challenged the large amounts of the payments, the Second Circuit held that these payments are not *per se* illegal. *Joblove v. Barr Labs., Inc. (In re Tamoxifen Citrate Antitrust Litig.)*, 429 F.3d 370 (2d Cir. 2005). The Second Circuit Appellate Court held that "[i]f however, there is nothing suspicious about the circumstances of a patent settlement, then to prevent a cloud from being cast over the settlement process, a third party should not be permitted to haul the parties to the settlement over the hot coals of an antitrust litigation." [citing *Asahi Glass Co. v. Pentech Pharms., Inc., 289 F. Supp. 2d 986, 991-92 (N.D. Ill. 2003)]. The Second Circuit also provided guidance as to* "suspicious circumstances." When a settlement is used as a device for circumventing antitrust law, it is vulnerable to an antitrust suit. One example would be where a brand manufacturer obtains a patent that it knows is almost certainly invalid (that is, almost certain not to survive a judicial challenge), sues its competitors, and settles the suit by licensing them to use its patent in exchange for their agreeing not to sell the patented product for less than the price specified in the license. In such a case, the patent, the suit, and the settlement would be devices for fixing prices, in violation of antitrust law. See: *Joblove v. Barr Labs., Inc. (In re Tamoxifen Citrate Antitrust Litig.)*, 429 F.3d at 392. The Second Circuit did not take the opportunity to consider a scenario where the patent is clearly not infringed by the accused generic product.

In the Sixth Circuit, a suit was brought by consumers against Hoechst Marion Roussel, Inc. (HMR) who manufactured a branded version of diltiazem hydrochloride (for treatment of cardiovascular conditions), and generic challenger, Andrx Pharmaceuticals, Inc. The parties entered into a patent infringement settlement agreement where Andrx received quarterly payments of $10 million to not enter the market even after the generic received FDA marketing approval. Because the ANDA that Andrx filed was prior to the MMA (closing loopholes leading to gaming of 180-day generic exclusivity), the failure of Andrx to enter the market effectively blocked all generic competition to HMR's product. Because the anticompetitive effect of this agreement, the lower court's holding of the settlement per se illegal was affirmed by the Sixth Circuit Appellate Court. *See: In re Ciprofloxacin Hydrochloride Antitrust Litig.*, 363 F. Supp. 2d 514 (D.N.Y. 2005).

In the Eleventh Circuit, a suit was brought by the FTC challenging the settlement agreement between brand manufacturer Schering and generic challengers Upsher Smith and ESI involving K-Dur® (extended-release potassium chloride). The Upsher agreement involved a delayed entry of Upsher's generic product (not extending beyond the patent term), and a three-part license agreement where Schering paid Upsher for rights to market five of Upsher's products. Under the agreement, Schering was to pay $60 million in initial royalties to Upsher; $10 million in milestone royalty payments; and 10% to 15% royalties on sales. Under the Schering-ESI settlement, ESI would launch its generic 3 years prior to the expiration of the patent term in exchange for a $10 million payment to ESI. A simultaneous license agreement paid ESI $15 million for licenses to its enalapril and buspirone products for overseas sale.

The FTC's case against Schering was initially heard by an administrative law judge (ALJ) who determined that the settlements were not per se illegal and that Schering did not maintain an illegal monopoly in the potassium chloride supplement market. Upon appeal to the full Commission, the ALJ's decision was reversed. The Commission found that the settlements, though not *per se* illegal, were exit payments leading to a delay of generic competition and injury to competition and the public. The Commission added that the payments to Upsher and ESI were not legitimate payments for the licenses Schering obtained. Consequently, the Commission prohibited settlements under which the generic received anything of value and agrees to defer its own research, development, production, or sales activities. An exception to this prohibition was settlement payments for litigation costs. Where payments did not exceed $2 million, the par-

ties would not need to worry about an antitrust attack.

Schering subsequently appealed to the Eleventh Circuit Appellate Court, which reversed the full Commission, holding that the settlements were not illegal as being anticompetitive. The Court relied on the Valley Drug decision, holding that "in the context of patent litigation, however, the anticompetitive effect may be no more broad than the patent's own exclusionary power. *Valley Drug*, 344 F.3d at 1309. Where the *Valley Drug* case involved a delay of generic competition beyond the patent by foreclosing other generics because of gaming with the Hatch-Waxman framework, the present case does not foreclose other patent challenges from entering the market.[1] To expose those agreements to antitrust liability would obviously chill such settlements." *Schering-Plough Corp. v. FTC*, 402 F.3d 1056, 1064 (11th Cir. 2005). The Court further noted that there was no evidence suggesting that the asserted patents were invalid, or that the resulting infringement suits against Upsher and ESI were shams. *Schering-Plough Corp. v. FTC*, 402 F.3d at 1068. Because other generics were not blocked from challenging the Schering patents, and because the agreements to delay entry were for a period shorter than the patent term, the agreements were deemed to not result in an unreasonable restraint on trade. Id. Lastly, the Court encouraged settlements and noted that settlements were endorsed by the Supreme Court in *Standard Oil Co. v. United States,* 283 U.S. 163, 170-71 n.5, 75 L. Ed. 926, 51 S. Ct. 421 (1931). The Court also reasoned that the full Commission's opinion would leave brand-generic settlements, including those endorsed by a federal court, with little confidence. *Id*., at 1072. The general policy of the law is to favor the settlement of litigation, and the policy extends to the settlement of patent infringement suits." *Id*.

The FTC has shown no indication that it will reconsider its position, although the Eleventh Circuit contradicted its view on patent litigation settlements. Following the Eleventh Circuit's denial of FTC petition for a rehearing, the FTC petitioned the United States Supreme Court to reconsider the Eleventh Circuit decision. In its brief to the Supreme Court, the FTC raises the evidentiary issue regarding whether the Eleventh Circuit should have deferred to the ALJ or the full Commission for findings of fact. Substantively, the FTC asks the Supreme Court to decide whether an agreement between a brand patent holder and a generic challenger, where the patent holder makes a substantial payment to the challenger for the purpose of delaying the challenger's entry into the market, is an unreasonable restraint of trade. The FTC argues that agreements between competitors should not escape anti-trust scrutiny simply because the agreement is within the potential scope of the patent. The FTC maintains its hard line rule that settlements involving payments from the patentee to the generic competitors to induce them to abandon their patent challenges and to delay generic entry raise serious antitrust concerns. The FTC has taken the position that every day that the [Hatch-Waxman] statutes are thwarted because a generic is paid to stay off the market is a day that prescription drug prices remain higher than a competitive market would have provided.

The FTC makes several arguments challenging the Eleventh Circuit decision citing "fundamental errors." First, the FTC asserted that the Eleventh Circuit erred in assuming that the Upsher and ESI products infringed the asserted patent (it is black-letter patent law that the patentee bears the burden of proof on this issue). The FTC asserts that patent infringement was vigorously contested, and that if any assumption is appropriate, it is that the competing products did not infringe the patent. Is the FTC taking the position that the patentee must prove infringement and/or validity in order for a settlement agreement to be upheld?

WHAT IS NEXT?

At this point, it is not clear whether the Supreme Court will hear this controversy. If it decides to grant certiorari, and upholds the Eleventh Circuit, the FTC will likely change its recent perspectives on patent litigation settlements. On the other hand, a reversal of the Eleventh Circuit decision would lead to a change in several present settlement agreements currently before the FTC for approval. Many of these agreements involve simultaneous license agreements and other payments that the FTC may challenge. It will be interesting to see how big or small the FTC's stick could become! ♦

REFERENCES

1. For purposes of antitrust analysis, the relevant market must be determined. The patents for Schering's product only protected against a specific type of delayed-release potassium chloride. Schering's patent protection did not block other manufacturers from selling the drug in immediate-release form or in a controlled-release form that was not bioequivalent to K-Dur.

BIOGRAPHY

Clifford M. Davidson, Esq. is a founding partner at Davidson, Davidson & Kappel, LLC, an Intellectual Property law firm with offices in New York City and Frankfurt, Germany. He counsels pharmaceutical clients in pharmaceutical patent-related matters, including patent prosecution, freedom to operate and infringement opinions, due diligence and tech-transfer, and litigation (including ex parte and inter partes proceedings worldwide). He has assisted specialty pharma and drug development companies to create significant patent portfolios, and the patents he has written and the patent portfolios he has created have been recognized as creating significant value for his clients. He has written patents covering virtually all areas of drug development, and has pioneered strategic patent focus on the pharmacokinetic profiles and the pharmacologic activity of drug/drug formulations. Mr. Davidson earned his BS in Pharmacy and his JD from Rutgers University and is a member of the New York and New Jersey Intellectual Property Law Associations, the American Pharmaceutical Association, and The Controlled Release Society.

His area of expertise includes new chemical entities; new pharmaceutical formulations (including controlled-release oral dosage forms, injectables, transdermals, ophthalmics, inhalation, intranasal, sublingual, suppository, and implantation administration); new combinations of previously known drugs; new modes of administration of previously known drugs; method of treatment; pharmaceutical excipients; and methods of preparation.

ADVANCED DELIVERY DEVICES

Highly Efficient Electrostatic Aerosolization of Liquid Formulations in a Battery-Operated, Hand-Held Device

By: David P. Cline, PhD; John W. Denny, MBA; and Bruce D. McVeety, PhD

INTRODUCTION

The Ventaira inhaler uses the Mystic™ inhalation technology to efficiently and reproducibly generate aerosol droplets in the 1 to 5 m range for pulmonary delivery. This is accomplished using an electohydrodynamic process that applies an electrical field over a flowing liquid. This electrical stress overcomes the surface tension of the liquid causing it to disperse into uniformly sized droplets. Ventaria has designed and built a hand-held device from injection-molded plastic parts that uses conventional batteries (9 volt or AAA) and a custom electronics board. Performance of the highly efficient device is reproducible, robust over a range of temperatures, relative humidities, inhalation flow rates, and is independent of device orientation.

THE MYSTIC™ TECHNOLOGY

The Mystic technology generates non-pressurized, nearly monodispersed respirable aerosols by an electrostatic spray process called electrohydrodynamics (EHD). EHD is a patented process by which an electric field is applied to a conductive liquid. This is accomplished by transferring high-voltage direct current (DC) through an array of electrodes, creating a field of discharge ions in front of a multi-spraysite nozzle. These positively charged ions induce an accumulation of charge at the liquid's surface, causing a Taylor cone to form at each spray site. As the surface charge overcomes the surface tension of the liquid, a fine mist of nearly monodispersed droplets is formed. As the droplets pass through the field of ions, their charge is subsequently neutralized (Figure 1).

The inhalation technology produces low-velocity clouds of uniformly sized particles with extremely high efficiencies, enabling consistent delivery of drug throughout the lungs. The non-pressurized aerosol mist is easily inhaled using the patient's normal inspiratory breath. A unique feature of this technology is that the median aerosol particle size can be adjusted to target different regions of the lung by adjusting the electrical field strength and liquid flow rates as well as by adjusting the physicochemical properties of the formulation.

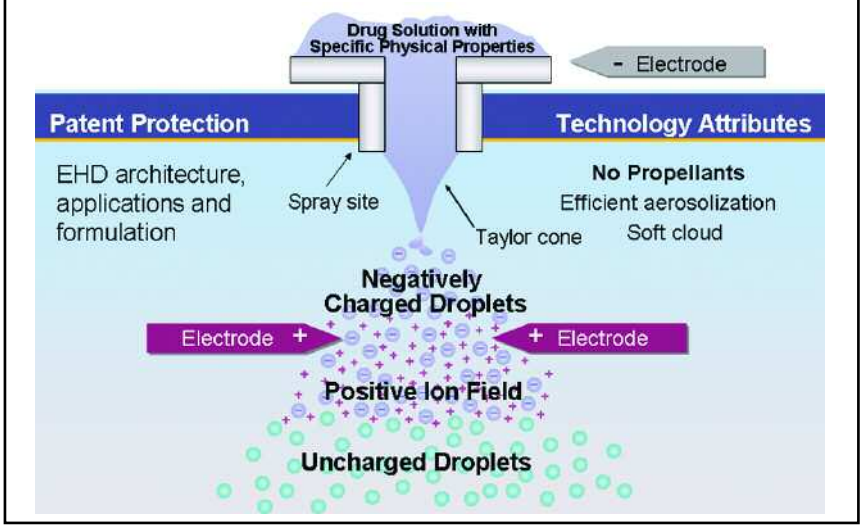
FORMULATION

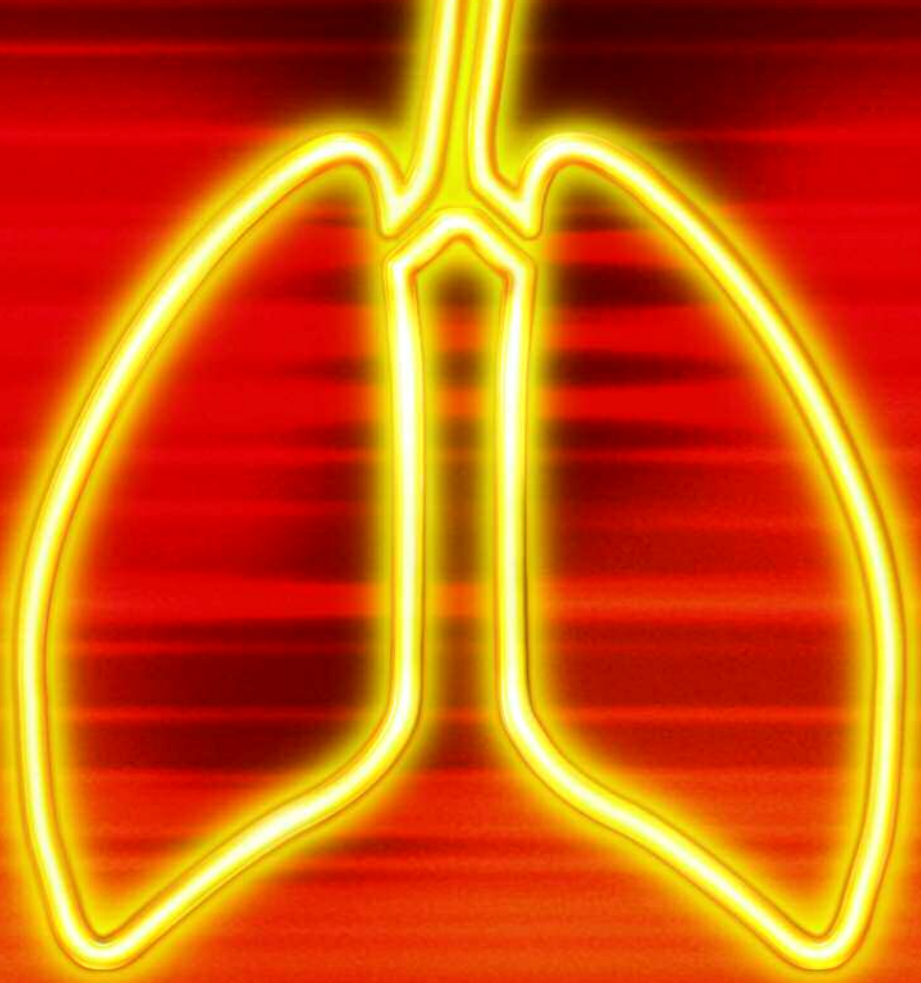
Ventaira's liquid-based formulation technology has several advantages over other existing aerosol formulation methodologies. One advantage of the company's solution-based formulations is that they allow for rapid formulation development with new APIs and only require small amounts of material to determine feasibility. Additionally, this advantage facilitates rapid initiation of early phase clinical studies.

Currently, Ventaira utilizes a highly ethanolic formulation vehicle that has allowed a series of compounds with a

FIGURE 1

Electrohydrodynamic Aerosolization Process





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Baxter

FIGURE 2

Photographs of Ventaira's Phase II Clinical Inhaler (left) & Commercial Inhaler (right)

wide array of physical properties and therapeutic applications to be quickly formulated and tested. The company has demonstrated the ability to formulate stable solutions of a range of compounds that exist as free acids, free bases, oils, and volatile liquids. An advantage of this vehicle is that there is no need to identify a stable salt form. Another advantage of the ethanolic formulations are that they are self-preserving by nature, and do not require additional preservatives to maintain the microbial-free integrity of the formulation.

Through the manipulation of formulation physicochemical properties, Ventaira has demonstrated the ability to change the aerosol's median particle size, allowing the targeting of specific lung regions for drug deposition.

The company is currently working to expand the current formulation space to include stable nanoparticle suspensions and more highly aqueous formulations. It has recently demonstrated the ability of the Mystic technology to spray stable suspensions containing 500-nm model particles loaded at concentrations of 1% w/v. A marker compound used in the formulation demonstrated an efficient aerosol was produced with greater than 80% of the aerosol less than 5.8 µm, as determined by cascade impaction.

DEVICE DESIGN

The device is a small, hand-held, battery-powered, breath-activated inhaler that delivers therapeutic drugs to the pulmonary system. It utilizes electronics, software, and mechanical subsystems to aerosolize metered volumes of formulation. Throughout the development process, Ventaira has maintained a keen focus on designing for manufacturability and has consistently worked to move from early machined prototypes into fully molded components as quickly as possible. This has enabled the company to greatly compress design and development iterations and improve the manufacturability and performance characteristics of the final product. As a result, Ventaira has completed development of the Phase II clinical inhaler and has signed an agreement with Nypro (Clinton, MA) to manufacture the inhalers under GMP conditions. In addition, the company has recently completed a miniaturization of the Phase II inhaler that will become the first commercial Mystic inhaler (Figure 2).

The devices consist of four major systems. These include the mouthpiece/nozzle assembly, the drug container, the metering system, and the power supply/electronics board. Aerosolization of the formulation occurs within the mouthpiece/nozzle assembly, which contains the spray sites and discharge electrodes.

The drug container assembly is made from high-precision injection-molded components that are FDA approved for contact with drug substances. The drug container is similar in design to a syringe. By using such a design, Ventaira has been able to adapt both the filling equipment and processes that have been developed by the pharmaceutical industry for prefilling syringes. One of the drug container design features is that it can easily be made into a removeable/replacable cartridge if a particular device application required such flexibility.

The metering system is comprised of a small DC motor driving a custom gear train that is designed to accurately meter volumes with a resolution of 1 L. Through the use of electronics and high-precision metering, the devices do not require priming even after long periods of inactivity.

The electronics board contains embedded custom software that provides controls for the operation of the metering system, high voltage, power on/off cycle, the dose counter, and the breath sensor.

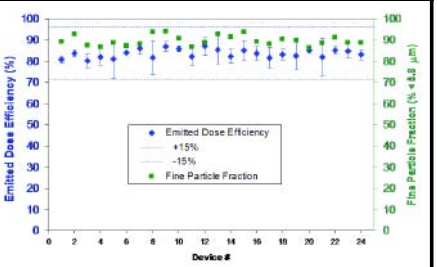
Breath sensing is accomplished using a transducer that is mounted to the electronics board and is interfaced to the mouthpiece/nozzle assembly. When a patient inspires through the device, air flow is detected, and the dose is aerosolized. This breath-activation feature coupled with the non-pressurized aerosol generated by the Mystic technology simplifies coordination of the inhalation maneuver with the actuation of the device.

In the future, the device electronics could be easily modified to provide the ability to offer programmable dose controls, patient compliance monitoring, and electronic lock-outs for pain management therapies.

INHALER PERFORMANCE

Ventaira recently conducted a trial build of Phase II inhalers. A key feature of this build is that all of the plastic components used in the inhaler were produced from an

FIGURE 3



Emitted Dose Efficiency & Fine Particle Fraction (% < 5.8 Ìm as determined by cascade impaction) of 24 Inhalers Made With Injection-Molded Plastic Components

BD Accuspray™
Nasal Spray System

Continuous Innovation

BD has developed the BD Accuspray nasal spray system based on the proven BD Hypak SCF™ technology to respond to innovations and advances in nasal delivery techniques.
The BD Accuspray system can be filled on many high-speed lines that process BD Hypak SCF syringes. BD Medical - Pharmaceutical Systems (BDM, PS) provides customizable mono- and bidose holders. BDM, PS supports you from the development phases through manufacturing with technical and regulatory support.

- Proven technology in BD Hypak SCF syringes
- Reproducible and consistent spray pattern
- Easy to fill
- Tamper evident bidose holder
- Customizable
- Potential to eliminate preservatives
- Starter kit available
- Proven market expertise

BD

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Pharmaceutical Systems
1 Becton Drive
Franklin Lakes, NJ 07417

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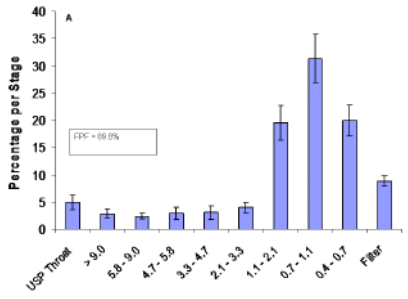
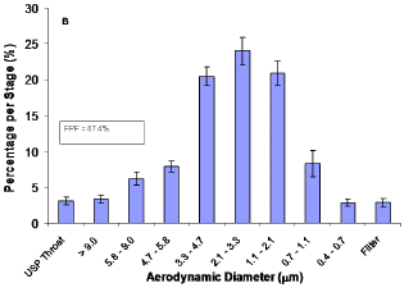
FIGURE 4a



Average Particle Size Distribution of 24 Inhalers Determined by Cascade Impaction

FIGURE 4b



Average Particle Size Distribution of 5 Inhalers With a Formulation Modified to Target a Larger Median Particle Size

injection-molded process, including all components in direct contact with the formulation. Following the build, all of the devices were evaluated for emitted dose efficiency and fine particle fraction (% < 5.8 µm as determined by cascade impaction) to exmine the reproducibility of the design. The formulation used in these devices contained fluticasone propionate with which the company plans to conduct a Phase II trial later this year. The highly efficient inhalers exhibited excellent reproducibility, both in terms of the amount of drug delivered and in the generation of particles less than 5.8 µm, which are of a size range expected to reach the lung (Figure 3).

The aerosol generated from the inhalers had a mass median aerodynamic diameter (MMAD) of 1.0 µm. Particle size distribution data generated using the 24 inhalers is shown in Figure 4. Also shown is particle size distribution data using a formulation modified to generate an aerosol with a larger median particle size (MMAD = 2.4 µm). These data demonstrate the ability of the technology to tailor the particle size of the aerosol to target different regions of the lung. Ventaira is currently conducting a scintigraphy/PK study to evaluate in vivo deposition and pharmacokinetics of these formulations.

Robustness

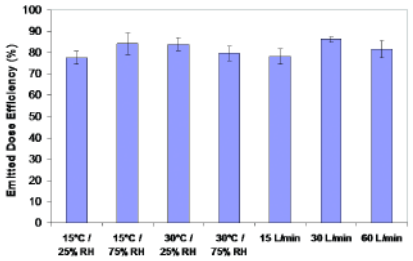
As with all inhalation devices, it is important that they maintain their performance over a range of environmental and patient-use conditions. Recognizing this, Ventaira initiated experiments early in the development process to examine the influence of temperature, relative humidity, orientation, and inhalation flow rate on aerosol performance.

The reproducibility of the aerosol generated from the Phase II clinical inhaler over a range of temperatures (15°C to 30°C), relative humidities (25 to 75% RH) and inhalation flow rates (15 to 60 L/min) is shown in Figure 5, and the insensitivity to device orientation is shown in Figure 6.

Patient Use

The most important attribute of an inhalation device is that it performs reliably and reproducibly over the course of the product's use and is not sensitive to normal types of mishandling. Figure 7 shows a consistent amount of drug is delivered even after successive drops, demonstrating the mechanical ruggedness that has been designed into the device. Additionally, Figure 8 shows the device performs consistently over a 1-month period, and the amount of drug delivered remains consistent even when the device is not used for several days.

FIGURE 5



Emitted Dose Efficiency of a Representative Inhaler Tested Over a 15°C to 30°C Temperature Range, a 25% to 75% Relative Humidity Range & a Range of Inhalation Flow Rates (15 to 60 L/min)

FIGURE 6a

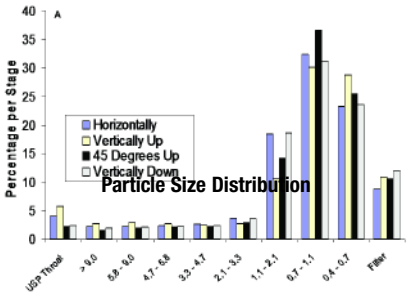
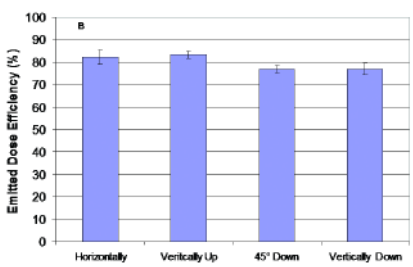


FIGURE 6b

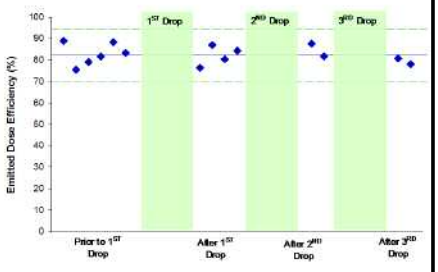


Emitted Dose Efficiency of the Inhaler When Operated in Various Orientations

SUMMARY

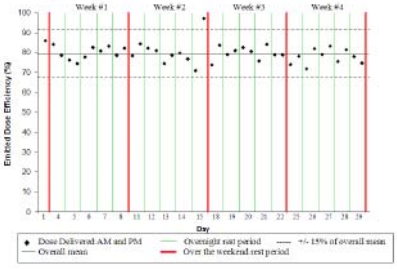
The Ventaira Mystic technology and device represent a step change in technology over existing products used for pulmonary drug delivery. Robust, superior performance has been successfully combined with a soft mist, breath-activated, hand-held device. In addition, the subsystem design approach has allowed the company to design an inhalation platform that can be reconfigured into a variety of external shapes and sizes, allowing it to physically adapt to market demands and fulfill consumer requirements. ♦

FIGURE 7



Robustness of Inhaler Efficiency Following Successive Drops From a Height of 6' Onto a Tiled Concrete Floor, Data are From Individual Actuations

FIGURE 8



Emitted Dose Samples Collected AM & PM (2 actuations per determination) Demonstrating Consistent Performance Over 1-Month Period

BIOGRAPHIES

Mr. John Denny, Vice President of Product Development, has 28 years experience leading multinational teams to design and manufacture products for the global marketplace. Prior to this, he was Vice President, Product Development for Oriel Therapeutics, where he was responsible for device research, design and development, supply chain management, and quality systems. He was also a Director at GSK, responsible for all new device projects for the respiratory business. While at GSK, Mr. Denny developed and implemented a program to improve cross-functional input for new product development, ensuring devices meet design for manufacturing requirements. He was also Founder and President of Develotech, Inc., a design company created to improve new product development lead times for the manufacturing and service industries. In addition, he has held key engineering positions at Hubbell, Inc., and Crouse Hinds Company. He earned his BS Mechanical Engineering from the United States Military Academy, West Point, NY and his MBA from Columbia University.

Dr. Bruce D. McVeety, Vice President, Pharmaceutical Development, joined Ventaira in May of 2000. Over the past 5 years, Dr. McVeety's responsibilities have included helping to build Ventaira's research facilities, helping to develop internal processes for GMP compliance, leading the analytical chemistry, formulations, and aerosol research groups, and managing drug product development programs with pharmaceutical partners. Dr. McVeety brings over 18 years of experience in applied research and development with a specific focus in aerosol science. Prior to Joining Ventaira, Dr. McVeety was a Research Leader for Battelle at the Pacific Northwest National Laboratory, where he worked in the areas of atmospheric transport and deposition of aerosols, preclinical inhalation toxicology of pharmaceutical aerosols, aerosol drug delivery device development, and the development of analytical methodology for the study of tobacco smoke chemistry. Dr. McVeety earned his PhD in Analytical Chemistry from Indiana University and his BS in Chemistry from the University of Idaho.

Dr. David Cline is Director of Labs at Ventaira Pharmaceuticals, where he leads the medicinal aerosol group, which assists in the development of a pulmonary delivery device based on electrohydrodymanic aerosolization. Previously, he was an Analytical Chemist at Alpharma, developing and validating HPLC and GC methods for a variety of dosage forms, including oral solutions, suspensions, and metered dose inhaler and nebulizer formulations. He also worked as an Analytical and Development Associate at Guilford Pharmaceuticals, developing and validating analytical methods for biodegradeable polymer products as well as developing and optimizing processes for incorporating active pharmaceutical agents into biodegradable polymer matricies. He attended graduate school at the University of Maryland in the Department of Pharmaceutical Sciences and worked with Richard Dalby focusing on pulmonary drug delivery. His graduate work focused on the relationship between surface energy and specific surface area of dry powder inhaler formulations and aerosol performance.

INTRANASAL DELIVERY

Sniffing Out New Sources For Growth

By: Daniel Ruppar, Research Analyst, Pharmaceuticals & Biotechnology, Frost & Sullivan

INTRODUCTION

The pharmaceutical industry is constantly looking to improve its products, and at the same time, find new avenues for revenue generation. This is done through a multitude of drug development scenarios, including reworking an existing product and investigating new ways of dosing and delivery. Research and clinical development is ever ongoing in terms of improvements of human in vivo performance. Often, when drug products are discussed, the focus revolves entirely around oral and injectable methods of delivery. That type of myopic discussion misses the fact that there are other areas, such as intranasal delivery, which have the potential to perform as well, or often give superior treatment results. In addition to being a delivery path for new products, intranasal delivery can also serve as a way to transform and innovate products already in the market. The intranasal drug delivery market in the United States was estimated at $2.4 billion in 2005. Future growth and expansion of the intranasal sector is expected to continue, especially as companies continue to move focus from converting existing products to novel drugs that are designed as an intranasal product from the ground up.

WHY THE NOSE?

For most people, the nose is perceived as merely the portal for the sense of smell, and it serves in that capacity in terms of enabling people to sense things around them, malodorous and not. The nose, however, has other important tasks to perform that benefit the body. In addition to sensory applications, it plays a vital role as a particle filter and also warms and humidifies the air that passes through it. The nose therefore keeps the lungs protected and enables any undesirable matter to be disposed of.

The nose is also an ideal portal for drug delivery and presents a number of key selling points to the market. First, there is the aspect of needle elimination for products currently delivered through injection. Patient self-administration of an injectable product is often a burden, not only in terms of preparation and disposal, but in terms of added stress and discomfort due to the fact that it utilizes a physically invasive delivery mechanism. For those injection products for which a patient needs to return to a clinical setting in order to be dosed, an additional hurdle is created and adds to the difficult stack of potential reasons why a patient may have problems adhering to treatment. Intranasal delivery presents the potential opportunity for patients to take their medication in the comfort of their own home, office, or wherever they may be during the day, and at the same time can place the product in a much more attractive light and allow for increased probability of adherence to prescribed therapy. Nasal dosing also offers patients with the potential for the fastest method for drug delivery. This is really a prime area of differentiation, especially in the pain sector, as quick onset of action is a key point that can differentiate products in the market. Quick onset of pain relief has a number of potential uses, especially in cases of trauma, military field applications, the emergency room, and during cancer treatment. An additional aspect of nasal delivery that can be exploited for the purpose of product innovation is the direct route to the brain, bypassing the hurdle of getting a drug to cross the blood-brain barrier. This is especially important for products with CNS applications. There are also a variety of products currently in the market, both OTC and prescription based, that are slotted for localized disease treatment in the nose. This, however, is not the endpoint for what can be achieved from a nasal approach to drug delivery. Systemic product delivery via the nasal passage is really the bigger picture and provides a variety of potential advantages and positive points of approach that benefit both patients as well as the companies involved. Intranasal vaccination also has the potential to perform well due to the combination of local and systemic exposure to the vaccine, creating a larger shield for the patient.

FIGURE 1

Still relying on yesterday's technology?

Yesterday's spray bottles are no match for today's drug formulations. Deliver your drug therapies with the most advanced nasal drug delivery device available today – ViaNase ID.™

ViaNase ID stands alone as an electronic atomizer that saturates the entire nasal cavity to deliver topical, systemic and nose-to-brain formulations with greater efficacy and efficiency than traditional nasal delivery devices. The first nasal drug delivery device to incorporate drug pedigree confirmation, lock-out technology, and an electronic display, ViaNase ID helps curb counterfeit drug use and abuse.

Combining Controlled Particle Dispersion™ and intelligent nasal drug delivery technologies, ViaNase ID delivers on the promise of your advanced drug therapies.

Find out more about the ViaNase family of electronic atomizers. Contact Kurve Technology at (425) 640-9249 or info@kurvtech.com.

www.kurvetech.com

Kurve TECHNOLOGY

INTRANASAL DELIVERY

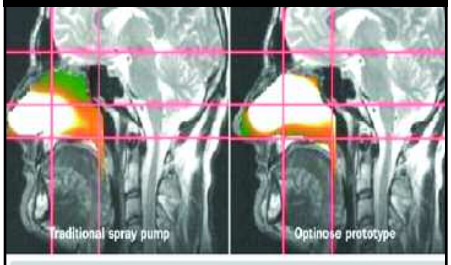
CURRENT TECHNOLOGY

There are a number of devices that can be used for intranasal delivery. The most common way that drugs are delivered via the nasal passage is through mechanical metered dose spray pumps. This technology is typically used for products to treat diseases, such as osteoporosis, migraine, and allergy products. Mechanical metered dose spray pumps are able to serve the purpose for many products, but the technology is not without numerous faults, which is why there are companies working on improved devices for intranasal delivery applications. Mechanical metered dose spray pumps currently have the greatest reproducibility success in terms of dosing. The pumps are modified by the respective product manufacturers to release a precise amount of liquid drug in a plume shape that expands out from the exit point on the device. The particle size for these products delivered in this manner is very important and is kept on the larger side (45 to 65 micrometers) in order to keep the amount deposited in the lungs to a minimum. Currently, the Food and Drug Administration has a limit that only 5% of the per dose dispersion is allowed to hit the lungs.

DEVICE IMPROVEMENTS

Technology improvements are being sought on the device side in order to create more effective methods to physically deliver an intranasal drug product. Current delivery methods, such as nasal spray bottles and metered dose inhalers, are constrained in their effectiveness by factors, such as suboptimal nasal cavity product penetration, as well as effectively balancing particle size with maintaining low levels of lung inhalation. This is not a trivial issue as many products only hit the anterior region, thereby missing the mark from where the technology should be to garner the best therapeutic result. Other aspects of current intranasal delivery devices that leave something to be desired include characteristics, such as post-dosing aftertaste, headache, and nasal irritation. Advancement in device technology is one area that is capable of making real headway in improving interest in this sector of the pharmaceutical market.

FIGURE 2



White areas in the nose: 20-100% of maximum intensity
Orange areas in the nose: 0-20% of maximum intensity
Green areas in the nose: no deposition

Gridlines are used to calculate regional distribution; Gamma-scintigraphy images from the same subject; Cumulative distribution during 32 minutes

Source: OnDrug Delivery 3rd issue August 2005. www.ondrugdelivery.com

Kurve Technology

Kurve Technology, Inc., with its Controlled Particle Dispersion (CPD) technology (Figure 1) has developed a delivery product that is able to saturate the entire nasal cavity, including the paranasal sinuses. Kurve's delivery product, Vianase can be utilized for both topical and systemic products to yield superior results over what is achievable with currently marketed nasal spray pumps. Vianase also has the potential to deliver products directly to the brain. This product uses "vortical flow" to achieve it's multiple advantage points over traditional technology. Kurve has also incorporated anticounterfitting and antitampering technology into its Vianase ID version in order to prevent potential unintended usage. This intelligent delivery system provides an important asset especially from the aspect of dose control, which is very important in application areas, such as pain management.

OptiNose

OptiNose AS, has approached delivery innovation from the concept of bi-directional delivery. This strategy looks at delivering both powder and liquid products while the patient is exhaling, thereby circumventing the issue of lung inhalation. Eliminating lung exposure during dosing with this device enables a smaller particle size to be used in the drug formulation. Exhalation into the device automatically triggers particle release at a moment where the positive dynamic pressure expands the narrow nasal passages, which in turn is able to aid the drug in achieving greater delivery penetration. Through this delivery technology, the airflow carrying drug particles to the target sites enters the nose through a sealing nose piece inserted in one nostril and exits through the other, allowing for both systemic and local topical delivery to the total nasal region, while significantly improving delivery to specific areas such as the olfactory region. Greater olfactory region exposure is important, as that is a point of direct access to the brain. The two-point fixation of the device enhances device stability and comfort during actuation.

WHAT'S IN THE PIPELINE?

Many companies are working on pipeline compounds that approach improving intranasal drug delivery by focusing on formulation technologies. For localized topical products, a minimal modification of formulation is required to create an intranasal product, and this typically focuses on particle size in order to try to prevent the product from coming back out of the nose or moving easily into the throat or the lungs. Systemic products require more of a specific fine-tuning of the formulation's particle size. This is to both prevent the same general issues that exist for a localized product, and at the same time, enable the proper dosing control that would be required to maintain safe and accurate delivery of the drug.

Nastech

Nastech Pharmaceuticals has approached intranasal applications through its focus on tight junction biology. Tight junctions exist throughout the body, and Nastech is looking to take advantage of that in several areas, one being nasal tissue. The company is looking for compounds that increase permeability of the tight junction, without harming junction cells or altering the structure of the molecule being delivered. In finding compounds that can open the barrier and allow for drugs to be passed through, the company is focusing on issues, such as how to deliver larger molecules, providing access of compounds to the

CNS directly, and improving the amount of a drug in the blood. Nastech currently has an obesity product, PYY3-36, in Phase II clinical trials. This peptide compound is an anti-obesity product focusing on appetite reduction. As the prevalence of obesity is an ever-growing problem, it requires a multifaceted approach to control and treatment. New ways to slot products into a patient's therapeutic regimen, especially those that are convenient to use and will therefore promote adherence to therapy, are very important to that type of chronic disease treatment. Nastech also has partnered with Proctor & Gamble for PTH1-34, which is a nasal version of Eli Lilly's Forteo (teriparatide) for osteoporosis. Forteo is currently delivered by subcutaneous injection. PTH1-34 is currently in Phase I clinical trials. This product is a good example of a drug that is not for a small niche area or presently generic being reformulated for intranasal delivery; it is that type of product that has the potential to contribute on the larger side to market revenues and at the same time provide an improved product to patients.

Javelin

Javelin Pharmaceuticals, through the utilization of its ChiSys carbohydrate polymer, has developed a way to achieve predictable blood levels of morphine via nasal delivery. Javelin's ChiSys technology is able to provide enhanced mucosal drug absorption and is able to prevent the drug from quickly leaving the sinus cavity through promoting high levels of drug adhesion to the mucosal layer. The company's Rylomine (intranasal morphine) product is currently in Phase II clinical trials and is a novel formulation of morphine with Javelin's ChiSys polymer. This product could provide an important new option for morphine use, as it would combine the fast onset of action inherent of injectable morphine with the ease of patient self-dosing currently seen with oral morphine. Javelin's intranasal morphine would have both of those important characteristics, thereby providing it with a potential competitive advantage.

THE FUTURE

Intranasal delivery is an area of the pharmaceutical market that has a very large amount of untapped potential. As companies look to the future and are forced to rethink more classical blockbuster product models in order to continue to create new sources of product revenues, concepts, such as technology transfer and extension strategies for life cycle management, are expected to come more to the forefront of the collective industry brain. The advantages and upside that intranasal products and the associated delivery technologies can provide to the industry across the board is a source-point of billions of dollars that is there for the taking.

How fast that growth occurs and the total peak of the associated revenues is governed by several factors. The combination of technology improvements from both the formulation side and the device side are expected to allow for continued overall interest and growth for the intranasal delivery sector. The products that provide new realms of growth for the market can come from either reformulation of existing products, or by designing new products specifically for intranasal use. In order for the market to really come into its own, industry focus will have to be more on products for diseases with larger patient populations as well as the development of novel products that are able to exploit the benefits of a properly delivered intranasal product. The real test of the future potential of intranasal drug delivery will be in a novel product designed for intranasal delivery from the outset for a widely prevalent disease incorporating one of the more effective device technologies currently in the works. Once a product like that hits the street, the industry could really see the larger potential of an intranasal drug delivery product's true capabilities.

BIOGRAPHY

Mr. Daniel Ruppar is a Research Analyst in the Pharmaceuticals & Biotechnology group of Frost & Sullivan. His primary coverage focus is in the area of cardiovascular diseases, with recent work focusing on the Cholesterol Market as well as the Anticoagulant and Antiplatelet Drug Markets in the United States. In that, he provides insight into individual drug forecasts, analysis of development pipelines, as well as evaluating treatment trends and clinical trial results. Prior to joining Frost & Sullivan, Mr. Ruppar spent 9 years in research and development in the pharmaceutical industry as a medicinal chemist. He has co-authored four journal publications for his work in chemistry in various peer-reviewed scientific journals, such as the Journal of the American Chemical Society, Tetrahedron Letters, and Bioorganic and Medicinal Chemistry Letters. He is also a co-inventor on four patents for his work in drug discovery. Mr. Ruppar was a long-standing member of the American Chemical Society, Organic Division. He earned his BS in Biochemistry with a minor in Economics from Trinity University and performed his research training in chemistry in the laboratory of Dr. Michael P. Doyle.

NANOTECHNOLOGY

Nanodrugs: Fact, Fiction & Fantasy

By: William Vine, MD, PhD; Kui Gao, PhD; Julian L. Zegelman, JD; and Sandra K. Helsel, PhD

ABSTRACT

Nanodrugs are heterogeneous structures, which capitalize on their small size to target human disease. Classic structures like liposomes are approved therapy for cancer and infectious disease. Newer materials, such as nanocrystals, offer a general approach to improve formulations sufficiently to achieve multiple FDA approvals. Many others, such as dendrimers, polymeric micelles, quantum dots, and inorganic nanoshells are under active development for both incremental and revolutionary improvements in therapy. For example, a revolutionary concept is to actively target, image, and kill tumors – a smart bomb of cancer chemotherapy. Thus, our future may include a real version of the nanobot of science fiction.

INTRODUCTION

Nanodrugs existed well before the prefix "nano" was popularly applied to technology, government initiatives, or drugs. One of the authors conducted commercial, preclinical development of an oral formulation of targeted, liposomal insulin. This work was contemporaneous with the first known and little recognized use of the term "nanotechnology" in Japan in the 1970s. Later, popular science fiction created the term "nanobots" to describe nano-sized robots as therapeutic entities. Now, entities remarkably similar to these nanobots are under development and promoted by the popular press as near sale at your local pharmacy. This article accepts the challenge to describe and distinguish fact, fiction, and fantasy in the world of nanodrugs. However, it is not designed as an exhaustive review.

Only imagination seems to limit the size, shape, composition, structure, and functionality of nanodrugs. On second thought, size may be limited by your concept of nanotechnology. The official definition by the National Nanotechnology Initiative, "The understanding and control of matter at dimensions of roughly 1 to 100 nanometers, where unique phenomena enable novel applications," tends to be loosely applied to nanodrugs.[1] The appearance of unique or desirable properties permits greater latitude in size than the official sanction.

The default shape for nanodrugs is spherical, in part because many materials prefer it and in part because of ease in manufacture; but cylinders, disks, cubes, and random appear as needed. Not surprisingly, composition includes biologics, organics, inorganic semiconductors, and none of the above. Structures include classic forms, such as liposomes and micelles; prototypical nanostructures, such as fullerenes, quantum dots (QDs), nanoshells (NSs), and dendrimers; and additional forms, such as nanocrystals, cyclodextrins, a long list of miscellaneous nanoparticles, and unclassifiable nano-sized materials. The range of composition and structure highlights a powerful attribute of nanodrugs: their great diversity.

Nanodrugs utilize multiple approaches to create new therapeutic entities and to improve on the old ones. Doxorubicin, a classic drug for treatment of cancer, has proven advantages in the treatment of Kaposi's sarcoma, refractory ovarian cancer, and potential advantages for others when enclosed in a nano-sized liposome (Doxil®).[2-4] A futuristic concept of the multifunctional platform simultaneously targets, images, and destroys tumors with a nanoparticle tens of nanometers in diameter. While not yet implemented clinically, a variety are being developed and tested in laboratory experiments, for example, Gao et al and Loo et al.[5,6]

Nanodrugs provide hope where current drugs have failed, in part because of the following advantages in critical parameters: 1) solubility, 2) bioavailability, 3) distribution by both passive and active targeting, 4) half life, and 5) imaging.[2,7-11] However, the toxicology of nanodrugs as a group and individually is poorly defined, under active investigation, and beyond the scope of this review.[12-14] Clearly, not all nanodrugs will possess all these advantages, including decreased toxicity, but their rational design offers the potential.

NANODRUGS

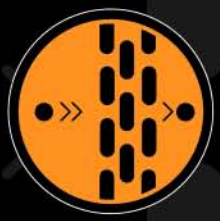
Liposomes

Liposomes may be the first nanodrug studied academically and sold commercially. They are formed classically from phospholipid bilayers. The bilayers encapsulate a drug within diameters as small as 25 nm, but typically somewhat larger.[3,10,15,16] Doxil® (Ortho Biotech), like many liposomal drugs, is modified on the surface with polyethylene glygol (PEG) to avoid the reticuloendothelial

Lipid Based Drug Delivery Technologies

LIPOBRIDGE™

Compounds that facilitate drug transport across the blood-brain-barrier into the CNS



LipoBridge™

LIPOMASK™

Compounds that increase the circulation time of lipid particles, improving drug efficacy and safety

LipoMask™

ACTISOLV™

Compounds that solubilize hydrophobic drugs normally insoluble in aqueous media

ActiSolv™

Contract Manufacturing of APIs, Intermediates and Critical Excipients

CUSTOM PEPTIDE MANUFACTURE

SYNTHETIC LIPID DEVELOPMENT AND MANUFACTURE

AMINO ACID DERIVATIVES

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Pharmaceuticals

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system to achieve longer half-lives and improved target concentrations.[3,4] Other approved liposomal drugs include Ambisome®, (liposomal amphotericine B, Gilead, Fujisawa), Myocet® (liposomal doxorubicin, Elan), and Depocyt® (liposomal cytosine arabinoside, SkyePharma) with more drugs currently in clinical trials.[17,18] Variations of liposomes under investigation include cationic liposomes used as gene delivery vehicles and liposomes targeted to tumors or brain.[16]

Micelles

Classic micelles are a smaller, monolayer analog of liposomes formed from surfactants with a hydrophobic interior. Micelles, so formed from PEG-phosphatidylethanolamine, containing taxol and modified by covalently attached antibodies, can improve delivery to and inhibit growth of transplanted tumors in mice.[19] Micelles made of designer-block copolymers, also known as polymeric nanoshells, can resemble the exterior/interior hydrophilic/hydrophobic composition of classic micelles or invert the design to create phase-inverted nanoencapsulation (PIN).[11,20-24] Polymeric micelles may improve drug and DNA delivery to tumors and the CNS by enhanced permeability and retention (EPR), also known as passive targeting, which is a function of size and surface chemistry.[9,11,21,24-27] The hope is that PIN can improve oral bioavailability of peptides, DNA and other molecules.[23,28] Micelles also may be the starting material for structures as diverse as titanium dioxide and organically modified silica particles to yield a drug or a drug carrier.[29,30]

The versatility of polymers leads to alternative nanostructures for drug delivery. They are the basis of not only block copolymeric micelles, but also of entrapping agents (polymeric nanospheres), nanogels, drug-polymer conjugates, and dendrimers.[11,10,31-35] For example, the approved drug, Abraxane, is prepared by high-pressure homogenization of paclitaxel in a humane serum albumen solution. The resulting product is a drug with improved pharmacokinetics, response rate, and toxicity.[36,37] Basulin, an insulin formulation in a diblock-polymer nanoparticle of leucine and glutamate, is in Phase II trials.[38,39] Nanogels are hydrophilic, cross-linked copolymers that can, for example, enclose fludarabine for improved delivery or entrap a drug, which is partially covalently attached as well.[29,40] Of course, there are drugs that are simply covalently bonded to copolymers and include various formulations of doxorubicin attached to copolymers like hydroxypropylmethacrylamide, which are also in clinical trials.[32,33]

Dendrimers

Dendrimers, a special case of synthetic polymeric nanodrugs, have a central core, internal branches, and terminal groups symmetrically distributed in three dimensions.[35,41] Mono-disperse dendrimers provide a controllable, well-defined nanoscale sphere carrying multiple attachment sites and a hydrophobic interior for binding and release of hydrophobic chemicals. Although it was Tomalia et al and Newkome et al in the early 1980s who pioneered dendrimers, their commercial use in drug delivery is still in its infancy.[42,43] Australia-based Starpharma Holdings Ltd. has developed a water-based gel polylysine dendrimer called VivaGel® (SPL7013) with a surface modified to bind HIV gp120 proteins and has progressed to Phase II studies.[44] Starpharma is in collaboration with Dendritic Nanotechnologies and Dow Chemical to develop dendrimer-based cancer therapeutics.

NanoBio Corp. has licensed dendrimer platforms from the Center for Biologic Nanotechnology at the University of Michigan. They are developing NB-001, an anti-herpes drug, expected to begin Phase III trials this year; NB-002 targets nail fungus in a trial to begin this year; and others such as NB-003 for vaginal infection, NB-004 for genital herpes, NB-005 for shingles, and NB-006 for influenza are under preclinical development.[45]

Thus, the potential for dendrimers to provide a uniform, controllable drug delivery platform targeting cancer and other diseases is under active commercial development even as toxicity issues, if any, are being defined.[35]

Quantum Dots & Nanoshells

Materials manufactured from semiconductors/conductors, such as quantum dots or nanoshells might well be the essence of quintessential modernity. Quantum dots possess a semiconductor core modified for enhanced fluorescence.[5,46,47] Inorganic NSs have a dielectric core surrounded by a thin metal shell.[48] Both QDs and NSs have tunable optical properties and surfaces compatible with the attachment of biocompatible and biofunctional molecules. These modifications can produce multifunctional nanoparticles that target, image, and treat various diseases like cancer and are being evaluated in preclinical testing.[47,49]

The targeting of QDs or NSs can be passive or active. Passive targeting is based on size, external coating, and tumor vascular permeability.[5] On the other hand, active targeting uses tumor-specific ligands or antibodies.[5,49,50] Imaging is based on the unique optical properties of the particles, which include tunability from ultraviolet to infrared wavelengths, enhanced fluorescence, and experimental detection options such as optical coherent tomography.[5,6] Therapeutic approaches can utilize optical properties, such as infrared heating and photosensitization or drug delivery.[48,49] Thus, QDs or NSs can carry the drug or be the drug.

These activities portend the therapeutic nanomachines of the future, although

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commercialization of these advances for QDs and NSs has lagged. Nanospectra Biosciences is developing therapeutic applications of NSs, but the biological focus of the major QD companies, Evident Technologies and Quantum Dot, a division of Invitrogen, is analytical.[51-53]

Other solid-core nanoparticles built upon calcium phosphate, colloidal gold, titanium oxide, or iron centers, for example, can form the core of potential commercial products. Calcium phosphate, when judiciously precipitated and modified, can deliver a wide variety of therapeutics, including insulin, immunological adjuvant, and genes.[54-57] Colloidal gold, after specific modifications, carries either drugs for cancer chemotherapy or DNA.[58-60] Altairnano is developing TiNano Spheres for controlled drug delivery and as a phosphate binder (RenaZorb) for renal disease.[61] Magnetic nanospheres, partnered by a tumor-targeting antibody, heat and destroy the tumor via a magnetic field and are currently in preclinical development.[62] Ferumoxytol is in Phase III clinical trials as a unique, superparamagnetic iron oxide nanoparticle with improved iron delivery for the anemia of renal disease.[63] This group can easily be predicted to grow in diversity of composition, structure, and application.

Nanocrystals

Nanocrystals are crystalline, solid-core nanoparticles with a large exposed surface that can significantly improve stability, solubility, bioavailability, and pharmacokinetics. However, they were hindered in application by aggregation until important developments in formulation.[64] Aggregation is ameliorated by NanoCrystal™ technology to produce nanocrystals by media milling in an aqueous solution containing generally regarded as safe (GRAS) stabilizer.[65,66] The solid-dose tablet formulation of the immunosuppressant Rapamune® (sirolimus) from Wyeth Pharmaceuticals is the first drug on the market using NanoCrystal™ technology. It received its FDA approval on August 2000. Trivcor® (fenofibrate) from Abbott, Emend (aprepitant) from Merck, and Megace® ES from Par Pharmaceutical are other reformulated, FDA-approved drugs, which use the Nanocrystal™ technology. Recently, Roche and Johnson & Johnson have also licensed the technology.[66]

Other methods that produce nanocystals for pharmaceuticals include homogenization in water, such as in SkyePharma's Dissocubes® or Baxter's NanoEdge®; and homogenization in non-aqueous media or in water with water-miscible liquids like PharmaSol's Nanopure®.[67-69] Eurand also manufactures nanocrystal using its Biorise™ technology.[70] But nanocrystalization is more than a general method to improve bioavailability of poorly soluble drugs. Nanocrystalline silver, SILCRYST™, from Nucryst Pharmaceuticals is used in Acticoat™, an antimicrobial barrier dressing now licensed to Smith & Nephew. NPI 32101, which is in Phase III trials, is a cream formulation for the treatment of atopic dermatitis and other skin conditions.[71]

SUMMARY

These nanodrugs — liposomes, micelles, dendrimers, quantum dots, nanoshells, and other forms — are demarcated by size, differentiated by divergent structures, and extolled for convergent, seemingly magical, benefits. Inquiring minds, not only of scientist but also of the general public, want to know if these drugs will beat the hype, fail miserably, or merely be mainstream. Currently, we should remember that the vast majority is far from approval. Nanoformulations, such as liposomes and nanocrystals, can improve drug delivery and have yielded approved products. Other structures, such as dendrimers or polymeric micelles have yet to robustly prove themselves as drug delivery vehicles to meet the high standards of the FDA. But excitement in nanodrugs is in the multifunctional nanoparticles that aim to actively target, image, and eradicate a variety of diseases. Many of the structures discussed can support multiple functions and are in active development. However, they face the caveats of any drug development program before they might assume the role of the nanobot.

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BIOGRAPHIES

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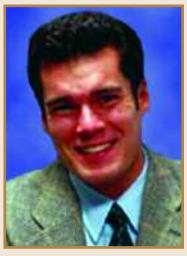

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INDUSTRIAL DESIGN

Industrial Design: The Secret Weapon Behind Drug Delivery Success

By: Andrew Pidgeon

INTRODUCTION

Industrial design might not seem like a secret weapon to many people involved in drug delivery device development, but it can be. So why is that? The profession has been with us for many decades and yet it is still generally undervalued. All too frequently, designers are only invited to participate in new product development once the technology and sometimes even the architecture of a device has been established. Their role is limited to tidying up the ergonomics and making a new technology look more attractive. When it is used in this way, the potential benefits are significantly reduced, and the major opportunities are already missed. Industrial design is not well understood by most engineers or marketers and consequently is often poorly managed. Designers are known for their visual creativity and their attention to detail, but they have another important skill, a user-focused viewpoint. With the FDA taking ever more interest in "use errors", ergonomic and human factors will increasingly come under the regulatory spotlight, but simply using design as a quick fix is missing the point. The more farsighted device manufacturers are now coming to the realization that marginalizing the industrial design component of the development cycle is an increasingly risky strategy. The reality is that today, design has never been more important in the creation of drug delivery devices as the sector grows increasingly crowded and product differentiation becomes more and more important. Far from just clothing the technology in an attractive package, good design can make a big difference in new product development and new product success.

INDUSTRIAL DESIGN'S BEST USE

Improving device aesthetics (bringing a device up to date), building brand equity, or sorting out poor device ergonomics, are common reasons for bringing designers into a project team. But these objectives are often poorly defined. It is probably more critical with industrial designers than most other professions that the original brief is well defined. Time should be spent to make sure the project objectives are clearly understood.

When bringing outside design consultants into a project, it is tempting to wait until the product architecture has already been settled upon in order to save on development costs. This is a common mistake as the development has already gone down an avenue that may not lead to the best final product. Instead, invite the designers in from the start, their perspective will be useful.

It should be standard practice for product ergonomics and user interfaces to be considered from the very beginning of the development cycle, but how many project managers ask their designers to take a lead in determining exactly what the product offering should be?

Good industrial design can simplify the complex and make difficult or threatening technology more appealing. The Dutch electronics giant Philips manufactures MRI scanners (Figure 1) that are consciously designed to have a friendly "domestic" aesthetic with warm homely color schemes to help the patients feel more at ease in what would otherwise be a very threatening environment. The same colors and details are used in Philips' kitchen equipment and medical devices, as part of its strategy to drive design to the heart of its new product development.

Developing a strong brand identity (even in companies with a single product) cannot be underestimated. Having your product easily recognizable is an important part of any marketing strategy, and this is particularly true as prescription medication and drug delivery devices become increasingly advertised in the mass media.

Design can make something inspiring out of the mundane, delight and stimulate customers, and achieve impact in a crowded market. Promoting "pride of ownership" might seem inappropriate for a drug delivery device, but is it really? People take care of items they value, they are more likely to use them correctly, abuse them less, and

recommend them to their friends or colleagues. If your customers are "delighted" by a feature of your new device, can this be a bad thing? If you have a superior technology, the product aesthetics should reflect this and sell it for you.

Nokia was one of the first companies to realize that cellular phones should be more than merely functional and so responded with designs that appealed to the lifestyle desires of their target markets. The industry has now moved from one in which models sell primarily by function to one in which style and image (Figure 2) are the primary selling points.

Product aesthetics are equally important to medical devices, perhaps more so. With a cellular phone, strong aesthetics can reassure you that the device is well made and reliable, that its technology is advanced, and that the company who manufactured it is world-class. These values should be equally important in a drug delivery device. The user or practitioner may be relying on this device, and as such, you need to reassure them that their trust is well placed.

Many drug delivery devices (inhalers for example) are carried around with a patient for much of the time; they become part of their lifestyle. If they have the opportunity to make a choice between two devices, aesthetics can be the deciding factor. This is equally true of medical practitioners whose equipment is seen as a reflection of their professionalism.

Another obvious use of industrial design is to reduce cost by rationalizing the component count or simplifying the assembly process. This can be an important project requirement, but unfortunately, it can become the sole focus of a design brief when a more successful approach might be to increase the perceived value of the device and allow it to compete at a higher price point with a better margin.

IS FASHION A FACTOR IN DRUG DELIVERY DEVICE AESTHETICS?

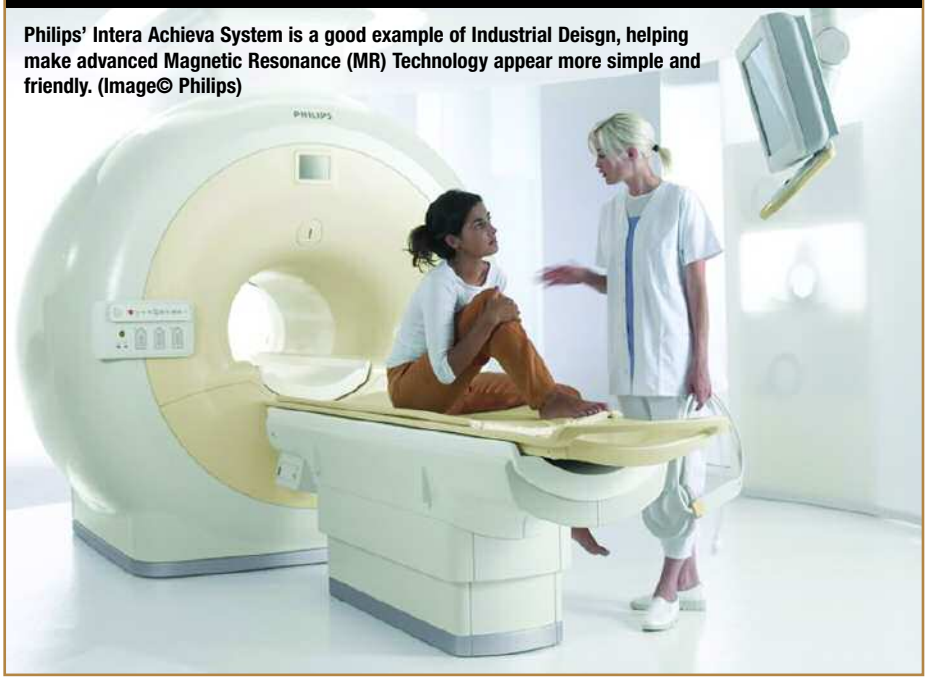
There are many influences on contemporary design. Even the most mundane products need to reflect the latest trends in their specific market segment. A common misperception, however, is that fashion has no place in the drug delivery device market. People cite that drug delivery devices take many years to reach the market (unlike the months it takes some high-street consumer goods), and FDA regulation makes change expensive and consequently products have to have long life expectancies. This is true; however, drug delivery devices do not live in a vacuum, and the fashion cycles that affect the world around them also impact on how we perceive these products. The people who use these devices (or specify them) drive contemporary cars, own MP3 players, and use cellular phones, and at a subconscious level, at least, they judge medical equipment by the same values. Indeed, products like inhalers or insulin pens may sit in a bag or pocket directly along side such devices.

This is not to say that a drug delivery device should try to emulate the latest high-street fashion (clearly this would be impossible as well as undesirable), but its design values should be consistent with it. Good quality design can be far more enduring than you might expect, while avoiding the pitfalls of emulating the latest design trend. For example, how many people are jumping on the iPod bandwagon just now? There are plenty of slower-moving trends that will filter through top-end consumer electronics into the mainstream marketplace.

A quick review of what medical devices looked like 10 or 20 years ago will reveal design trends that have come and gone (how much brown and cream plastic do we see these days?), but most current devices still look tired and dated compared

FIGURE 1

Philips' Intera Achieva System is a good example of Industrial Deisgn, helping make advanced Magnetic Resonance (MR) Technology appear more simple and friendly. (Image© Philips)



INDUSTRIAL DESIGN

to high-street products.

Influences on future design trends are diverse and not always easy to spot; however, the drug delivery sector does have the advantage that it is rarely at the cutting edge of these trends. A good example of this is the explosion of design influenced by Japanese Manga comic art. This might not seem an obvious influence until you consider the appeal of Sci-Fi graphic novels to the young Japanese designers now working for the big electronics giants who dominate the consumer electronics and gaming markets. Through their innovative approach to new products (ie, game controllers) and aesthetics, design concepts and influences have filtered down to other control devices throughout the West and ultimately into scientific equipment. This is in much the same way Paris couture fashion eventually finds its way into high-street stores.

As in high fashion, a talented industrial designer can identify, with a reasonable degree of certainty, the trends and fashions likely to hit a respective market in the near future. This is especially true of the drug delivery market.

It is interesting to note that some research asserts that aesthetically attractive designs are actually perceived as being easier to use than less aesthetically attractive designs, whether they are or not.

COLOR, A WHOLE LANGUAGE OFTEN OVERLOOKED

Product color schemes are frequently dismissed as a trivial part of a development program and left until near the end to be resolved. This can miss one of the best tools in a product's arsenal when it comes to self-promotion as a good color choice can express many useful things about a device.

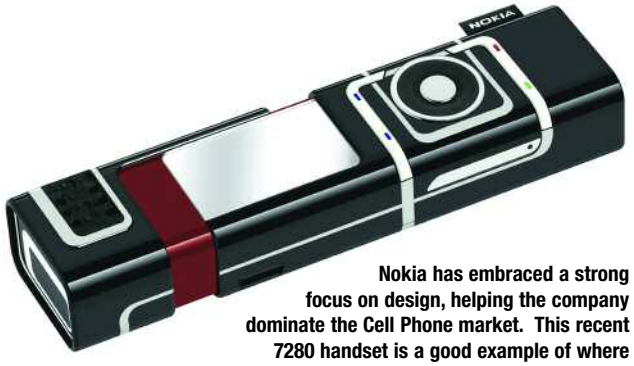
Color is profoundly affected by fashion cycles and in this way, most products visually age. While fashion trends often start on the high street (or in the car showroom), they ultimately filter down to business, scientific, and medical sectors.

If color can express how modern a product is (black for example was seen as very dated for cell phones a few years ago, but is now again very common), the fashion palette will also contain colors that date slower than others and a few that are almost timeless. Color can also imply how serious or competent a product is, which can be vital for drug delivery devices. It might even allude to how safe a product is. Color schemes can be very market dependant and as such, a color choice might give the observer a message about what type of device they are looking at or where it should be used. In the context of product ergonomics, color choice can also help explain how a device is used, particularly in combination with textures or graphic elements.

Once again, it is common to hear the view that fixed colors need to be used for regulatory or corporate branding reasons, but in reality, these rules are often more fluid than they at first appear.

The application of text and graphics on products can be even more neglected than the industrial design of a product and yet, this is an area where the best use of good design practices can make an enormous difference. In the case of some drug delivery devices, clarity and logical communication can literally save lives, it is important that this part of the program is not rushed.

FIGURE 2



Nokia has embraced a strong focus on design, helping the company dominate the Cell Phone market. This recent 7280 handset is a good example of where designers are pushing the boundaries. (Image © Nokia)

USER INTERFACES DESIGNED FOR USERS

In drug delivery devices, it would seem obvious that user interfaces should be designed to be easy to use, and yet this is so often not the reality. Cost sometimes has an impact here, whether it be a low priority in the development budget or a tight unit cost driving a less favorable display technology.

The basic rule is usually simple is best, keep it as intuitive as possible, and avoid icons or jargon whenever possible. Feedback needs to be appropriate to the function and level of expertise of the user; it doesn't always have to be complex, but it has to be right.

The interface should be developed in parallel with the device mechanism, even if it only consists of a physical button or counter, this is the part of the device the user relies upon to understand how to use it and if this is wrong, the device is worse than useless.

The FDA guidance states that the "frequency and consequence of hazards resulting from medical device use might far exceed those arising from device failures." Engineering teams spend many hours trying to avoid the possibility of device failures, but far less time tackling the more likely therapy failure resulting from an avoidable use error. The term "use" error is

used rather than "user error" as it is not the user who has made an error, it is the device that has led them to it. When you are designing devices, remember it's not about the technology, it's about the user!

To avoid graphical user interfaces (GUIs) being intimidating, they need to be thought through from a user's perspective. Too often, GUIs are driven by the system design and structured by engineers or clinicians. One of the core skills of an industrial designer is to look at products from users' perspectives as they will be the people on the development team who are constantly questioning how a new user will respond to the design.

Sometimes a design brief will specify the number of user steps required, the thinking being the fewer the better; this ignores the fact that more steps may be better if they follow a logical mapping, while a small number of illogical steps may be more confusing for the user.

The perception of quality should also be the aim. A good-looking GUI is usually judged to be a better interface, so its aesthetics are important.

DO YOU REALLY UNDERSTAND YOUR USER?

A frequent, and sometimes fatal, failing of device development programs is the basic lack of understanding of how a device is used or indeed what the user wants. It would seem obvious, but it is surprisingly common, for projects to be fairly advanced before any research is done into the user needs or perceptions.

The FDA advises that "addressing use-related hazards should be undertaken within the context of a thorough understanding of how a device will be used." An independent and early assessment of how a device might be used could be undertaken to look into the ergonomic constraints. It should also inquire into user perceptions and even other similar devices that the user might be familiar with, as there are many design languages out there that influence design in less than logical ways. An example of this is the QWERTY keyboard, which is not the best lay-out for keys; however, its universal familiarity would make it folly to design a keyboard with a different layout.

Inclusion of industrial designers in a new development project from the very start, at the point of writing the requirement specification, can be an effective way of avoiding some of the pitfalls that can lead to the development of the wrong product. Somebody within the team needs to be asking how any element of the design benefits the user and be there to fight the usability versus technology battles. It is important to remember that the best solution from a technological perspective may not be the best for a user (do you need a heavy battery pack capable of 2 days continual use if the device needs to be portable and occasional use?).

SUMMARY

Ultimately, it is the creativity that designers bring that can make the real difference. Device development programs need to check off a number of procedural boxes, but the best designs do not always come out of committees or focus groups, sometimes a spark of inventive creativity is the catalyst.

Mitigating risk is at the heart of any development program, but sometimes we can carry this too far. It is sadly not an uncommon stipulation that a device should be "as good as" the competition. How many project managers reading this article really ask their designers to break new ground in their design solution?

When considering product aesthetics, it is worth remembering that taking the safest route will guarantee that you don't stand out from the crowd and consequently won't make as much impact as your technology rightly deserves.

If your product is going to be used by a real person, you need to involve industrial designers in its creation. The product ergonomics and interfaces have to be right, and this can only be achieved by fully understanding the user. Good aesthetics are not just an extra option, your product must look like it is capable of doing what it is designed to do and it should be memorable (for all the right reasons) and be attractive. Remember, it may be a commodity to you, but it is part of the user's lifestyle.

BIOGRAPHY

Mr. Andy Pidgeon Mr. Andy Pidgeon is a Senior Industrial Designer in the Healthcare Business Unit of Cambridge Consultants, a technology innovation and development firm. Mr. Pidgeon has more than 20 years of industrial design experience across a wide range of market sectors.

PARENTERAL PACKAGING

Parenteral Packaging Concerns for Biotech Drug Products

By: Frances L. DeGrazio

INTRODUCTION

Biotechnology promises treatments, even cures, for many diseases previously thought to be intractable. Although the Biotech industry began just a quarter-century ago, since the late 1990s, the number of new Biopharmaceutical approvals has approximately equaled those for small-molecule drugs.

Despite a significant effort at delivering biotherapeutics peptides and proteins through non-traditional means, such as inhalation, transdermally, and by direct contact with mucous membranes, injection remains the principal delivery system for today's biotherapeutics.

The unit dose for injectible biotech products is the single-dose vial, with prefilled syringes a distant second. Product is provided either as a solution, or more commonly as a lyophilized cake that the caregiver reconstitutes and injects via syringe.

Requirements for product purity, activity, and shelf-life dictate a very high standard for injectible drug packaging, particularly for highly active peptides and proteins. However, with biopharmaceutical development, times averaging 7 to 10 years, and costs measured in the hundreds of millions of dollars, it is too easy for innovator companies to dismiss primary packaging as an afterthought.

Packaging represents the first line of defense for all formulated pharmaceuticals. A good package protects the drug product from the outside world and vice versa. At the same time, the package, including the vial, stopper, and seal materials, must be fully compatible with the product, whether in solution or lyophilized.

The FDA's requirements, as spelled out in the Container Closure Systems for Packaging Human Drugs and Biologics guidance, discuss understanding levels of extractables/leachables and test methods related to these contaminants. The Guidance, which addresses evaluation of packaging systems for pharmaceutical and biopharmaceutical drug products, requires that each NDA or ANDA contain enough information to demonstrate that a proposed package and its components are suitable for their intended use. The Guidance clearly indicates that all injectable products need to be evaluated for leachables that may have migrated throughout the product shelf-life during formal stability testing and beyond. In addition to addressing leachables/extractables, the Guidance also discusses evaluation of packaging components and related materials.

By placing much more scrutiny on stopper processing and handling, barrier films, and leachables/extractables, the FDA significantly raised the bar about what is expected from biopharmaceutical drug sponsors.

PACKAGING & PRODUCT: NOT ALWAYS PERFECT TOGETHER

Modern biopharmaceuticals are overwhelmingly proteins and peptides — molecules with unique chemical, physical, and mechanical properties. Protein function and activity is much more than simple linear chemical structure. Proteins are sensitive to heat, light, and chemical contaminants. Minute concentrations of metals, plasticizers, and other materials from biopharm packaging may deactivate or denature therapeutic proteins. The seriousness of chemical contamination is compounded by the extremely low concentrations of most protein drugs.

Whether in liquid or lyophilized form, biopharmaceuticals possess properties that make them more sensitive to their packaging or delivery system. Proteins and peptides have a tendency to adsorb onto the surface of packaging containers and closures, which due to the small amount of drug present, can essentially remove all active material from the drug formulation. In situations where the drug desorbs back into solution, the interaction could cause the drug to lose potency.

Lyophilized proteins are no less immune from the effect of packaging. Because most lyophilization cakes are sensitive to moisture, an inadequate seal could cause water and other contaminants to enter the package and deactivate the drug.

Many biopharmaceuticals are sensitive to silicone oil, a material commonly used to lubricate elastomeric stoppers during fill/finish to facilitate insertion of the

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PARENTERAL PACKAGING

FIGURE 1

During Phase I, a sponsor company should begin screening for vial closure designs and materials. Screening involves assessing packaging alternatives, generating preliminary data on leachables, and choosing one or several alternatives that provide the highest degree of product compatibility and the lowest level of leachables. By Phase II, sponsors should begin developing precise, validated methods for determining extractables and leachables.

stopper into the vial. Silicone oil has been associated with protein inactivation through nucleation of proteins around oil droplets. Recently introduced fluoroelastomer coatings on stoppers provide needed lubricity in addition to an added level of chemical inertness, barrier protection, and safety. Thus, fluroelastomers serve as both lubricant and a barrier to improve compatibility between product and the rubber closure.

Primary packaging should be a top priority with all drug products, even pills and tablets. These concerns are amplified several-fold with injectible biotech products due to proteins' chemical and physical unpredictability, and the fact that such products are injected.

SOURCES OF CONTAMINATION

Extractables are the most common source of leachables contamination arising from product coming into contact with package materials. An extractable is a chemical species, released from a container or component material, which has the potential to contaminate the pharmaceutical product. Extractables are frequently generated by interaction between product and package (including the glass vial and stopper) over time depending on solvent and temperature conditions. Extractables testing is recommended even if containers or components meet compendial suitability tests, and should be carried out as part of the qualification for the container and its components.

A leachable is a chemical that has migrated from packaging or other components into the dosage form under normal conditions of use or during stability studies.

Package component fabricators test for extractables from their materials as part of their development and qualification operations. More importantly, leachables tests are carried out at the point of use, in real-life situations in the presence of the actual drug product. The goal of testing is to determine that package materials are generally safe, compatible with the dosage form, and present acceptable risk of contamination for particular products.

The potential impact of extractables and leachables on drug products is significant, especially with highly active biopharmaceutical drug products that may contain just femptograms of active ingredient. Perhaps more important than these materials' toxicology is their potential to elicit serious immunologic responses, even at infinitesimal dosages.

MITIGATING THE RISK FROM RUBBER CLOSURES

Fluorocarbon film coatings provide the best combination of protection from extractables from the stopper material while providing a high level of barrier protection for the drug product, therefore, minimizing leachables.

When applied to stoppers, fluorocarbon films significantly reduce adsorption of the drug onto the stopper, which is critical for maintaining the product's potency and shelf-life. In addition, fluorocarbon films provide extra lubricity for proper vial sealing, without the need for silicone oil.

Fluoroelastomer films, which are made from highly inert materials, also significantly reduce the possibility of extractables migrating from the rubber stopper into the biopharmaceutical product.

Because the cost of specifying the wrong closure components and materials is so high, biopharmaceutical manufacturers need to devise a separate development plan for primary packaging, just as they do to molecule and clinical development. Normally, this separate activity is contracted out to firms that specialize in packaging components.

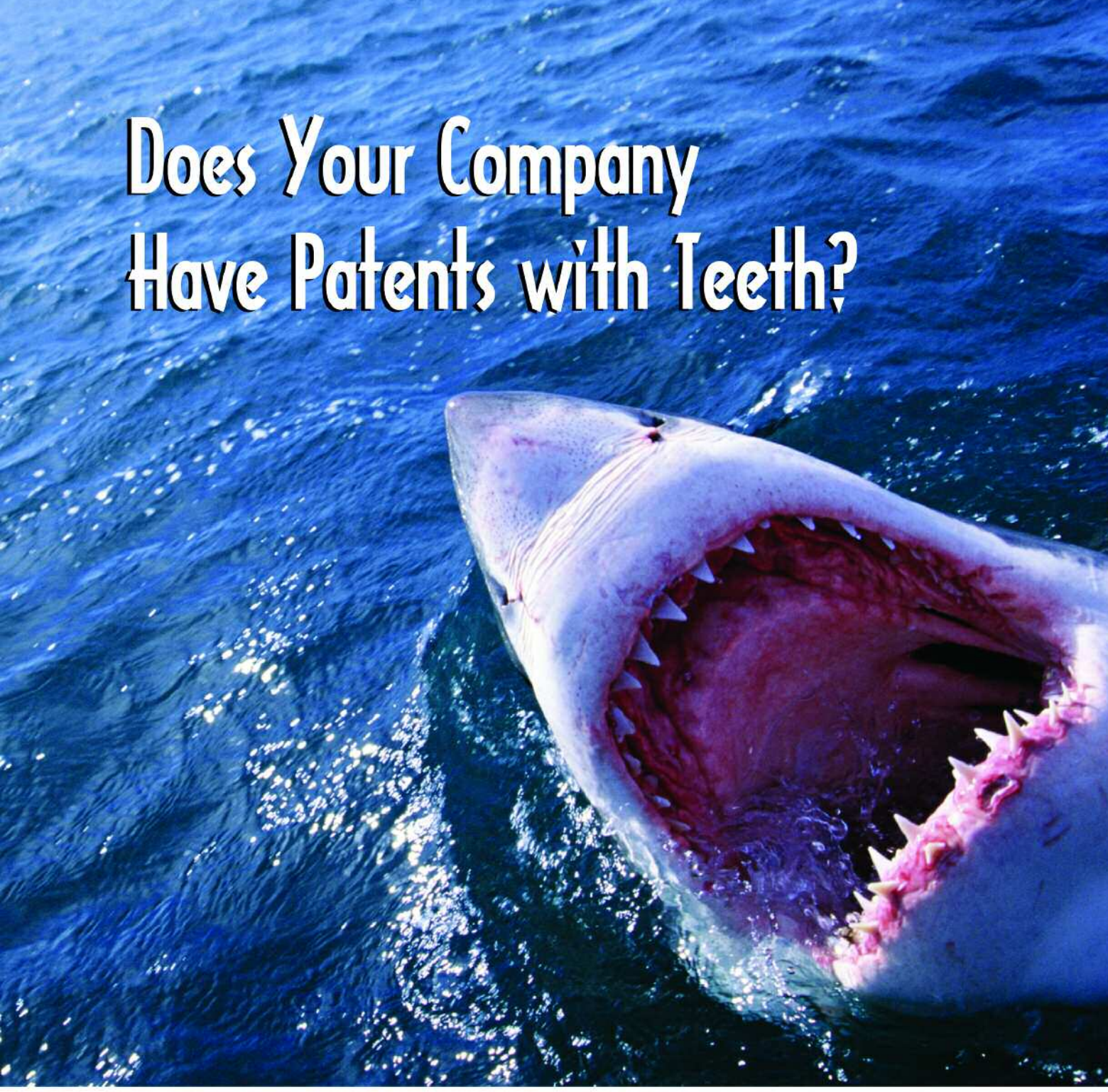
Some typical deliverables one could expect from such a relationship include:

- an understanding of the product;
- capability to work off-site on the product and proposed packaging;
- recommendations for components, especially for seals and stoppers;
- knowledge of the engineering and regulatory aspects of the packaging appropriate for that application;
- forewarning of potential problems; and
- support for package option evaluation through engineering and laboratory services.

These functions must be acquired, one way or another, by Phase I because this is the point at which sponsors and regulators get "serious" about product and package working together. During Phase I, a package component expert company will begin screening for closure designs and materials.

Screening involves assessing packaging alternatives, generating preliminary data on leachables, and choosing one or several alternatives that provide the highest degree of product compatibility and the lowest level of leachables.

By Phase II (earlier if possible), sponsors need to begin to develop precise, validated methods for determining extractables and leachables. For products that get this far, method development becomes almost a separate phase of stability testing. When method development and validation is com-



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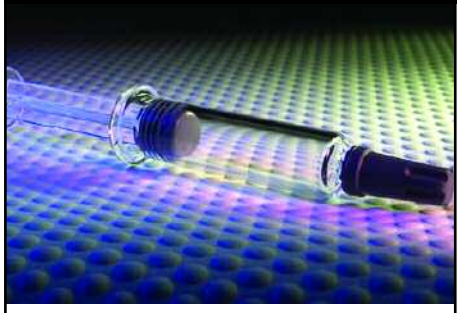
pleted, testing is carried out using samples stored under typical ICH conditions. Accelerated testing is typically done over 6 months at high temperature and humidity, whereas real-time testing uses standard 25°C and 60% relative humidity conditions over a 2- to 3-year period.

One cannot overestimate the importance of carrying out these studies for the full testing period. In our experience, some product-package combinations that show little or no degradation during the first few months may lead to significant inactivity, due to adsorption onto the glass vial, prior to expiration of a 2-year shelf-life. Similarly, leachables that do not appear for the first several weeks may emerge later on, well within the product's specified shelf-life.

FIGURE 2



Fluorocarbon film coatings provide the best combination of protection from extractables from the component material while providing a high level of barrier protection for the drug product, therefore minimizing leachables. When applied to stoppers and syringe plungers, fluorocarbon films reduce adsorption of the drug onto the component, which is critical for maintaining the product's potency and shelf-life. Fluorocarbon films provide extra lubricity without the need for silicone oil and reduce the possibility of extractables migrating from the component into the biopharmaceutical product.

STRATEGIES FOR MINIMIZING RISK

Drug developers who do not understand the impact of packaging on their biopharmaceutical products are courting an unnecessary level of regulatory and product-related risk. Problems arise when a contract manufacturer tries to convince a sponsor that a particular stopper, vial, or other closure is appropriate because it has been validated with the contractor's fill line. That is all well and good, and even necessary. However, stoppers need to be validated with the product first, and only then with the filling machinery.

It is far more prudent, and in the long-term much more cost-effective, to test and validate packaging within the context of the drug product.

Submissions that lack properly generated data on product stability within the proposed package are very likely to be held up until such data are provided. Often, the information is generated, and that is the end of the problem. Occasionally, when rigorous testing uncovers leachables/extractables, product inactivation,or other packaging-related problems, approvals can be held up for months. Very few biotechnology companies are willing or prepared to gamble significant delays in clinical programs for the sake of a minor short cut.

LYOPHILIZATION – A SPECIAL CASE

Many biotech products are lyophilized in the package, usually a vial, before the stopper and seal are introduced. Lyophilization presents its own peculiar process and packaging requirements.

As with solution-phase biopharmaceuticals, packaging can make or break final formulation for lyophilized products, particularly with respect to the product's long-term stability and compatibility with package. Vials that are not designed specifically for lyophilization, for example with convex rather than flat bottoms, make the lyophilization process less efficient, leading to an extended lyophilization cycle. Rubber closures can also hinder freeze drying if they do not permit adequate venting during sublimation.

Stopper rubbers adsorb and desorb water at different rates. Under storage conditions, stoppers that were not properly dehydrated can release water into the lyophilized product, affecting product stability over time. This can be especially problematic with lyophilized biopharmaceuticals, which tend to have very small cake weights when compared to traditional pharmaceuticals following lyophilization. Because their weight is often in the range of milligrams or less, these cakes are significantly more sensitive to moisture, pH changes, and extractables that migrate from the rubber closure.

A small difference in moisture in the lyophilization cake can make the difference between an active and denatured protein. pH differences as well, which may be caused by contaminants, can seriously affect protein structure and activity. The wrong rubber closure can easily shift pH units in a small volume of product or a diluted lyophilization cake. Fluoroelastomer-coated stoppers eliminate the rubber closure as a source of the leachable that could impact pH because of its barrier properties. Glass vials, however, can also leach ions, which can impact pH.

Whatever precautions are taken with solution-phase preparations are doubly applicable to lyophilized biopharmaceuticals. During lyophilization, all the primary package components must work together without interfering with either the product or the process. Some packaging issues to be aware of for lyophilized products include:

- closures that allow adequate sublimation rates and cleanly insert into the vial without "back out" or sticking to the lyophilization chamber shelves;
- glass vials that provide adequate contact between the base of the vial and the lyophilization shelf; and
- compatibility during lyophilization between vial and elastomeric closure.

EXAMPLES FROM WEST'S EXPERIENCE

The globalization of the pharmaceutical supply chain presents new challenges for biomanufacturers. One West customer, a large pharma manufacturing an injectible US orphan

FIGURE 3

Fluorocarbon film coatings reduce stopper clumping during autoclave sterilization and help prevent stoppers from sticking to the shelves in lyophilization chambers. The film is applied during the molding process and is conformable to complex-shaped closures, which are typically required for dry powder and lyophilized applications. Lyophilization closures with fluorocarbon film are available in a single-vent igloo design that is proven effective in eliminating mechanical twinning, the interlocking of double-vented stoppers during processing.

drug product in Europe, had difficulty obtaining validated presterilization washing services for rubber stoppers produced by one of West's European subsidiaries. To save time, this customer utilized local washing services, which resulted in the FDA rejecting the US regulatory application. Curiously, this customer had had a similar experience with a different product. The approval delay cost the company tens of millions of dollars in lost revenues and considerable prestige. Even more seriously, for several months, patients were denied the only effective treatment for their chronic condition. The problem eventually was resolved by shipping the stoppers to West's Pennsylvania facility for washing, then reshipping to the finishing plant in Europe. Today, this product treats 15,000 patients per year.

Seemingly trivial changes in formulation can affect drug-package compatibility. A West customer had received European approval to market a protein drug, but was asked by European regulators to eliminate an additive stabilizer, human serum albumin (HAS). The sponsor found a surfactant stabilizing agent that worked as well as HSA with this drug. Unfortunately, the company did not pay close attention to potential interactions between the new stabilizer and the rubber plunger in the prefilled syringe used to deliver this medication. Initial data showed acceptable levels of leachables, so the product gained European approval, only to be recalled several months later due to serious adverse events related to leachables. This manufacturer's error was assuming that the plain rubber stopper would provide the same level of compatibility in the new formulation as in the old one. This problem could have been avoided by careful stability and leachables testing and by employing a fluoroelastomer coating for the syringe plunger, which is eventually what the manufacturer did, but not before a debacle that cost the company many millions in lost sales and opportunity.

SUMMARY

The high-value, clinical efficacy, and price tags for biopharmaceuticals, coupled with injectible delivery in most cases, demand a high level of awareness of primary packaging. Biotech companies entering the clinical stage need to take the same science- and risk-based approach to packaging materials as they exercise with molecule development. Where that expertise is lacking in-house, developers of biotherapeutics must look outside their organizations for the know-how and experience to ensure smooth transition from lab to clinic to market.

Specifying advanced coatings, such as fluoroelastomers, for most stoppers or plungers used with lyophilized or solution-based therapeutic proteins and peptides may seem like an extravagance. In reality, given the long development times and consequences of being wrong, these measures are actually prudent and will lower costs in the long run.

BIOGRAPHY

Ms. Fran DeGrazio is Vice President, Quality Assurance and Regulatory Affairs for the Americas Region of West Pharmaceutical Services. Ms. DeGrazio is responsible for Quality Assurance and Quality Control for all of West's rubber, metals, and plastics manufacturing facilities in North and South America. She is also charged with directing the Regulatory Affairs function for West, along with the management of West Monarch Analytical Laboratories. Ms. DeGrazio has been with West for 21 years, with past management responsibilities in Quality Assurance, the Analytical Labs, and Technical Customer Service. She earned her BS in Chemistry from Cabrini College.

DRUG DELIVERY Executive

Eric Tomlinson, PhD
President & CEO
Altea Therapeutics

"Conventional transdermal systems are limited to potent, lipid-soluble drugs with a molecular weight of less than 500 daltons. The PassPort System achieves continuous delivery of highly water-soluble proteins and low-molecular weight drugs that cannot be delivered via the skin using conventional passive transdermal patch systems."

ALTEA THERAPEUTICS: CREATING HIGHER STANDARDS OF PATIENT CARE

Altea Therapeutics has made a key scientific and commercial breakthrough in the delivery of drugs and vaccines via the skin. The PassPort™ Patch, a cost-effective and easy-to-use skin patch, uses short bursts of focused thermal energy to create hundreds of tiny channels in the surface of the skin. The new transdermal delivery technology achieves what existing transdermals are unable to do, namely the continuous delivery of highly water-soluble drugs and proteins through the skin – compounds typically administered by often repeated painful needle injections. Drug Delivery Technology recently interviewed Dr. Eric Tomlinson, President and Chief Executive Officer of the Atlanta-based company to learn more about Altea Therapeutics and how its proprietary PassPort™ System is able to expand the universe of transdermal patch products by delivering drugs and proteins that cannot be delivered using current transdermal patches.

Q: Can you tell us a little more about Altea Therapeutics and its pipeline? What is the business model?

A: Altea Therapeutics' initial strategy is to develop its technology for water-soluble drugs and proteins that are already approved for marketing and off-patent (or available for licensing). This approach both avoids the costs and risk of drug discovery and bringing a new compound to market and provides a significant pipeline of potential products. The product pipeline can expand as other molecules, developed by the pharmaceutical industry, are approved. The Company's product portfolio has been developed through analysis of several factors, including market opportunity, clinical need, cost and time to market, technical feasibility, and clinical chances for success. These products include:

- Daily hydromorphone hydrochloride patch for the rapid management of moderate to severe chronic pain and some acute conditions;
- Daily fentanyl citrate patch for the rapid management of moderate-to-severe chronic pain;
- Night-time and daily round-the-clock insulin patches providing basal levels of insulin for people with type 1 or type 2 diabetes;
- Daily apomorphine hydrochloride patch for the convenient management of late-stage Parkinson's disease; and
- Influenza vaccine patch for needle-free delivery of antigens.

Our business plan is to out-license our transdermal patch products currently in development while developing other pipeline products for future commercialization by Altea Therapeutics itself.

Q: Please describe your PassPort System technology and how it works.

A: The PassPort System both prepares the skin surface for effective delivery of water-soluble drugs and proteins and then provides a convenient dosage form for the delivery of these compounds. First, the PassPort System forms multiple tiny aqueous channels (micropores) through the stratum corneum, the outer dead surface layer of skin. This takes typically between 2 and 5 milliseconds. Water-soluble proteins and low-molecular weight drugs can then enter the body through these aqueous micropores from a transdermal patch reservoir for either local or systemic effect.

The PassPort System is composed of a single-use disposable PassPort Patch and its re-useable handheld Applicator. The PassPort Patch consists of a regular transdermal patch attached to a film of metallic filaments (a porator). To initiate dosing, a patient first clips a PassPort Patch onto its Applicator and places the PassPort Patch onto the skin. Pressing the activation button of the Applicator sends a pulse of electrical energy to the porator, which converts this into thermal energy. The rapid conduction of this thermal energy into the surface of the skin painlessly ablates the stratum corneum under each filament to create micropores. The Applicator places the transdermal drug patch on the skin, and a simple fold-over design aligns the transdermal patch with the newly formed micropores.

The aqueous channels formed in the stratum corneum using the PassPort System typically have a depth of about 30 to 50 micrometers, sufficient to impinge into the viable epidermis while avoiding the dermis and any thermal pain receptors. After dosing, when the transdermal patch is removed from microporated skin, the barrier function of the stratum corneum is quickly restored. The Applicator is easy to use and ensures accurate and reproducible patch application. It also provides verifiable dosing information and dose control, including optional programmed lock-out features and time and date stamping.

Q: What differentiates Altea Therapeutics in the transdermal drug delivery marketplace?

A: Conventional transdermal systems are limited to potent, lipid-soluble drugs with a molecular weight of less than 500 daltons. The PassPort System achieves continuous delivery of highly water-soluble proteins and low-molecular weight drugs that cannot be delivered via the skin using conventional passive transdermal patch systems. It can thus provide rapid onset of therapeutic effect, alongside constant delivery of the drug and rapid drug elimination upon removal of the patch. Moreover, using the salt form of the drug precludes the drug from dissolving in the skin and forming a depot, which is an important feature, as dosing can be terminated by removing the PassPort Patch in case of an overdose or an adverse reaction. The PassPort Patch by itself will not deliver drug into the body without a prior microporation event using an Applicator; this serves as an added safety feature.

As discussed previously, the Applicator can be programmed to ensure dosing control and monitoring. It can store a time and date stamp for each application that can be provided to the physician for diversion or compliance monitoring. The Applicator can be further programmed with physician controlled lock-out features to prevent drug misuse or abuse

In addition to the various features of the Applicator, we have developed novel formulations that result in rapid and sustained delivery of therapeutic amounts of proteins and low-molecular weight drugs through aqueous micropores. These formulations lead to high utilization of drug during the dosing period. For the hydromorphone hydrochloride and fentanyl citrate patches, the availability of little to no drug in the patch post-therapy lowers the probability of abuse, misuse, or diversion of these opioids.

Q: Can you give us an update on your transdermal basal insulin project and how this product may be used in the marketplace?

A: Our insulin patches are designed to meet basal insulin needs by providing a constant delivery of insulin. We have a 12-hour night-time patch and a 24-hour

daily patch. Basal insulin products are the fastest growing sector of the insulin market. Everyone with type 1 diabetes and most people with type 2 diabetes ultimately require exogenous basal insulin therapy. Basal levels of insulin in the bloodstream are necessary to assist the effective transport of glucose into cells. In type 2 diabetes, the use of basal insulin enables the pancreatic beta cells to be spared and to respond better to meal-time demand for endogenous insulin. Basal insulin is regarded as an effective new modality for the treatment of type 2 diabetes, and evidence supports that people with type 2 diabetes should be placed on basal insulin early in the development of the condition to prevent the functional decline of their beta cells.

The ideal insulin therapy regimen for both type 1 and type 2 diabetes is one that mimics normal physiological insulin secretion. Such regimens are typically referred to as "basal/bolus" or "basal/prandial" regimens wherein the goal is to provide a constant, low level of insulin between meals (the basal component), and supplement as required with additional peaks of insulin at meal times (the bolus or prandial component).

The basal insulin patches of Altea Therapeutics are designed to provide equivalent or better glycemic control than long-acting injectable insulins, such as insulin glargine (Lantus®) and insulin detemir (Levemir®), and equal or lower incidence of hypoglycemia, but without the formation of an insulin depot in the body. Furthermore, they will enhance compliance, all of which could lead to better adoption than injectable basal insulins. The novel insulin film formulation allows for convenient storage at room temperature.

We have demonstrated transdermal delivery of clinically relevant basal levels of insulin in humans. We have also demonstrated that the delivered insulin retains its expected glucose-lowering effects. We are currently completing Phase I studies to optimize insulin delivery rates, duration, and efficiency of delivery to demonstrate the desired glucose-lowering effects and to confirm product safety.

Q: Can you also give us an update on transdermal hydromorphone and how you think this product will compete in the more than $6-billion annual opioid market?

A: The hydromorphone patch is in development for the rapid management of moderate-to-severe pain, and for use by both opioid-tolerant and non-opioid-tolerant patients. Principal indications are in chronic pain (arthritis, lower back pain, and cancer pain) with some opportunity for treating acute pain. We have completed a multicenter Phase II dose-ranging clinical study in acute pain following hip or knee replacement, and we are preparing for definitive clinical trials in chronic pain.

The hydromorphone hydrochloride transdermal patch will compete primarily with transdermal patches delivering fentanyl base (eg, Duragesic®) and oral controlled-release oxycodone and hydromorphone hydrochloride in the chronic pain market. Our hydromorphone patch offers several key advantages over current therapies used in chronic pain. With the hydromorphone patch, analgesic levels are reached quickly and at a steady state in a few hours. The absence of a skin depot of the hydromorphone salt, unlike for fentanyl base, allows for rapid elimination from the body within a very few hours after patch removal. The unique features of the hydromorphone patch differentiate it as a product that enables rapid and flexible dose titration. Also, hydromorphone itself is associated with good patient-to-patient consistency in effect, less dysphoria and pruritis than morphine, and lower potential toxicity than other opioids.

The hydromorphone patch is being developed with built-in safeguards to reduce the potential for drug abuse and misuse as compared to oral or transdermal dosage forms currently used to treat chronic pain. The novel formulation makes extraction of the drug difficult and enables high drug utilization leaving low amounts of drug in the patch after wear. As discussed in my previous answer, the Applicator also serves as a control device with potential to limit the number of successful patch applications per day and to record time and date stamps; this provides the pain management physician with a new and powerful tool for the management of

moderate to severe pain in patients, particularly given the current climate for prescribing opioids.

Finally, all fentanyl (base) patches in the marketplace are approved only for opioid-tolerant patients (predominantly due to safety issues relating to the pharmacokinetics of the fentanyl base). Our clinical development strategy is to also obtain approval for use in non-opioid-tolerant patients, which we believe can significantly expand the market opportunity for this product.

Q: Why is Altea Therapeutics developing another fentanyl patch, considering the availability of several generics on the market?

A: The world-wide market for transdermal patches containing the base form of fentanyl is in excess of $2.5 billion annually. Patent expiration of Duragesic® has led to the introduction of competing generic fentanyl patches, with others in the late stages of regulatory approval. As such, it would seem that the opportunity to compete directly in the transdermal fentanyl market is limited. However, events at the FDA throughout the past few months suggest that there is significant opportunity in development of an advanced fentanyl transdermal product. In July 2005, the FDA issued a warning related to transdermal fentanyl patches that have been associated with approximately 120 deaths.

The FDA primarily is concerned about the slow elimination kinetics (T1/2 approximately 17 hours) associated with current transdermal fentanyl delivery. This makes discontinuation of therapy difficult in the event of a severe adverse event (respiratory depression), which is a major aspect of the FDA concerns. Moreover, the slow elimination kinetics are mirrored by slow absorption and distribution kinetics. Following application of the initial patch, a period of 3 days is required to achieve steady-state plasma drug concentrations. This can give rise to misuse of the product in that a patient may apply a second patch due to inadequate pain relief during the protracted rise to steady state resulting in an overdose.

Existing fentanyl patches delay physicians' ability to titrate the dose for a patient (in case of inadequate pain control) by up to 6 days, which is significant considering approximately half the patients require an increase in dose after initial application. Additionally, the FDA expressed concerns relative to adverse consequences of dose-dumping from currently marketed fentanyl patches.

The recently developed Altea Therapeutics fentanyl citrate patch addresses the concerns with existing fentanyl (base) patches, especially by reducing the elimination half-life from approximately 17 to 7 hours, which is comparable to the elimination half-life following long-term fentanyl intravenous infusion. Additional advantages of a PassPort fentanyl citrate patch are the high drug utilization of up to 90% and reduced abuse/diversion potential. The use of drug salts precludes delivery through intact skin even if reservoir spreading were to occur.

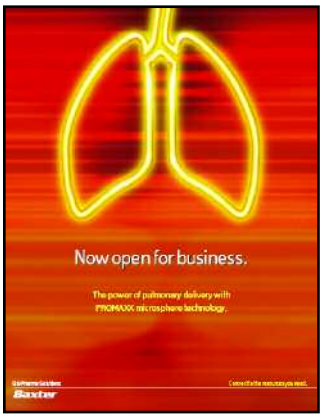
Similar to the hydromorphone patch, the Applicator can be programmed to provide dosing information and monitoring, providing control against misuse, abuse, and diversion.

Q: What partnerships do you currently have and what makes Altea Therapeutics PassPort System such an attractive candidate for future partnerships?

A: In January 2006, Altea Therapeutics and Teikoku Seiyaku Co. Ltd. of Japan signed an exclusive licensing agreement for Japan to develop and commercialize a transdermal patch therapy for the treatment of advanced Parkinson's disease. We are pursuing additional partnerships as we discussed in our business model. The PassPort System is a new transdermal patch that enables the affordable, non-invasive, and controllable delivery of a wide range of drugs that cannot be delivered using conventional patches, replacing painful injections for patients. It provides patients with freedom from needles and pumps and costly, complicated devices, enhancing their comfort and compliance. Also, the technology and formulation attributes, together with their manufacture at low cost using scaleable processes, provide for economically satisfying costs of goods, thus making the PassPort System an attractive candidate for future partnerships. ♦

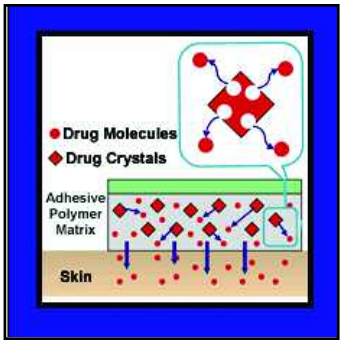
Drug Delivery Showcase

Pulmonary Formulation Brochure



Baxter Healthcare Corporation released a new 8-page, full-color brochure highlighting its proprietary drug delivery technology that can enhance formulation success. The PROMAXX protein microsphere technology offers narrow particle size distribution ideal for delivery to and through the lung. This versatile platform can be applied to a variety of drug classes and has the potential to improve stability of the starting material. Baxter's experience with technology transfer offers clients the option to integrate formulation processing equipment with their manufacturing process. The PROMAXX manufacturing process consists of a simple, robust, gentle process that is water-based whenever possible. This has been shown to preserve the drug's protein structure and activity. Pulmonary formulation challenges? Let Baxter help you overcome them. For more information, contact Baxter Healthcare Corporation at (781) 440-0100 ext. 281 or visit **www.baxterbiopharmasolutions.com**.

Crystal Reservoir Technology



An innovative advancement in transdermal technology, Aveva Drug Delivery Systems' Crystal Reservoir Technology results in greater efficiency in drug delivery and smaller patches. By oversaturating an adhesive polymer with medication, partial crystallization of the drug occurs, leading to a more controlled and sustained drug release. The combined presence of dissolved and crystal forms allows a considerably higher concentration of drug in the patch. As drug is absorbed into the skin, crystals redissolve to maintain a maximum thermodynamic driving force to sustain continued absorption. By modifying the crystals to a solute ratio, optimized patterns of drug release may be achieved, including Sustained Release, Burst Release, and Circadian (time of day) Controlled Release. For more information, visit Aveva Drug Delivery Systems at **www.avevadds.com**.

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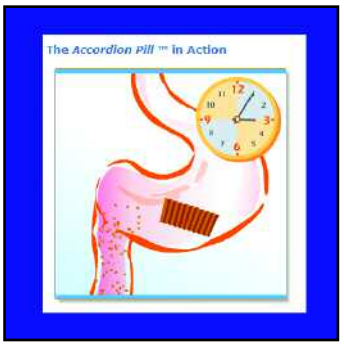
Drug Delivery Showcase

Liposomology/Drug Delivery

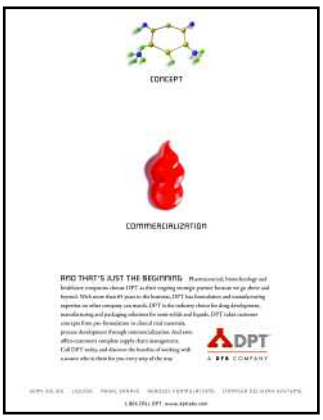
Polymun Scientific provides contract development and manufacturing and creates liposomal formats of drugs for partners. Revenues are invested in proprietary products and further development of technology platforms. R&D projects and technologies are open for co-development and licensing. Liposomes protect,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

Gastric Retention Dosage Form



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

Drug Delivery Services



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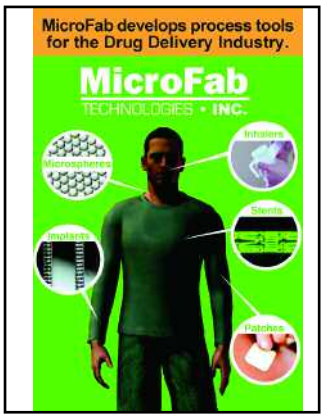

MicroFab Technologies, Inc., develops ink-jet microdispensing equipment and processes for the drug delivery industry. The technology enables precise digital control for microdispensing applications ensuing unsurpassed accuracy and repeatability. Printing drugs and drug-polymer combinations in complex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

NASAL DELIVERY

Nasal Delivery: A Boon for Analgesics

By: Michael T. Sheckler, MBA; Daniel B. Carr, MD; Fred H. Mermelstein, PhD; Douglas A. Hamilton, MBA

INTRODUCTION

The withdrawal of Palladone™ and several COX-2 inhibitors during 2005 resulted in negative press for pain management medications. These events have resulted in a short-term void in the analgesics marketplace. Overlooked in this spate of bad publicity was the more significant, long-term trend of under-treatment for chronic pain and the remarkable, decades-old success story of medical pain management.

Pain is now recognized as the fifth vital sign in addition to blood pressure, pulse, respiration, and temperature. This recognition should encourage physicians and patients to discuss and treat pain-related conditions. In turn, this will drive growth in the market for the management of pain. This market is projected to enjoy sustained growth through greater recognition of the need to treat acute, chronic, and cancer-related pain. The approvals of pipeline-stage drugs will propel the market for treatment of neuropathic pain, acute and breakthrough cancer pain, and postoperative pain from $21 billion in 2004 to $30 billion by 2008.

A good deal of this growth will result from development and approvals of novel delivery systems. Like the pain management market, nasal drug delivery is also projected to grow significantly throughout the next few years. Greystone Associates is forecasting 24% annual growth between 2004 to 2007. This will more than double the value of the nasal drug delivery market from slightly less than $2 billion to $4.3 billion. More specifically, the global 2007 forecast for analgesics delivered nasally is $535 million.

Numerous factors and mega-trends are driving the growth of the nasal market, among them the aging population in the US and abroad, the trend toward self-administration of medications, cost containment, and advances in technology. Large proteins and peptides, once thought undeliverable via the nasal route, are now under development as nasal sprays. Enabling this welcome development is the use of improved absorption enhancers and the ability to modulate the tonicity and pH of proteins and peptides.

Delivery devices are becoming much more sophisticated as well, having evolved well beyond simple nasal sprayers to high-tech devices whose spray characteristics meet increasing standards for precise delivery. Today nasal delivery devices come equipped with dose counters and lock-out mechanisms to prevent overdosing and abuse.

Yet, even with these technological advances, one may ask why anyone would bother to deliver drugs nasally in the first place. Oral delivery remains the primary (and some would say preferred) route of administration for most drugs, and oral delivery technology has also improved significantly. Still, for all of the improvements, oral delivery has its drawbacks, and is by no means optimal for all drugs and all patients. Onset of action for orally administered medicines is variable and not particularly rapid. Because of first-pass metabolism, oral doses need to be considerably higher than for an injectable or transmucosally delivered drug, which can lead to more GI side effects.

NASAL DELIVERY

Nasal drug delivery offers many advantages over other routes of administration. Among them are ease of administration, a more rapid onset of action, non-invasiveness, and avoidance of first-pass metabolism.

Nasal drug delivery is by no means new. For decades, patients have purchased over-the-counter antihistamines and cold preparations packaged in simple nasal spray bottles. More recently, systemically acting prescription drugs for bedwetting and osteoporosis, as well as a vaccine to prevent flu, have been available as nasal sprays. With nasal delivery technology advancing rapidly, more drug developers than ever are considering nasal delivery for vaccines, CNS/neurology drugs, growth and reproductive hormones, osteoporosis prevention, vitamin deficiency, and pain relief. Based on current development-stage products, the market for CNS/neurology drugs delivered nasally could reach $1.3 billion by 2007. In some cases, drugs are formulated as nasal sprays from their earliest development stage; in others, nasal delivery has been recognized as a way to enhance the value of existing drugs and even to extend patent life.

A number of small, innovative companies are now addressing the unmet need for nasal analgesics. The July 2005 update of BioPharm Insight cited 16 IND applications for nasally delivered pain drugs. This tremendous interest in the nasal delivery route speaks to its attractiveness. Compared with intravenous and intramuscular delivery, the nasal route is non-invasive and offers a high degree of safety. Compared to oral delivery, nasal delivery provides a more rapid absorption and onset of action, and relatively low dose requirements.

Morphine remains the gold standard of opioids and is often considered the prototype μ-agonist. Morphine has been used extensively to manage both acute and chronic pain. With its good safety profile, widespread usage, and historical record of efficacy, it is highly unlikely that morphine will ever be withdrawn from the market. Ketamine, a non-opioid N-methyl D-aspartate (NMDA) receptor antagonist, has been safely used as a general anesthetic for the past 30 years.

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NASAL DELIVERY

INTRANASAL MORPHINE

With morphine's successful track record for intranasal morphone and IV delivery (oral preparations are available, but have a slow onset of pain relief and variable bioavailability), one might ask why a new delivery route is needed at all for this drug. In fact, intranasal morphine offers several advantages over more conventional routes, among these the elimination of needles and syringes. Intranasal morphine also offers important pharmacokinetic benefits, approaching the bioavailability of intravenous administration, which provides the most rapid absorption and onset of action of all administration routes.

Both patients and physicians are familiar with morphine and recognize it as the gold standard in pain management. Nasal delivery further improves morphine's perception in the marketplace, making this delivery route ideal for large target markets, including orthopedic, postoperative, and burn pain. Intranasal delivery also carries a low risk of abuse.

A nasal morphine formulation, Rylomine™, from Javelin Pharmaceuticals is formulated with chitosan, a biodegradable cationic polysaccharide derived from crustacean shells, which when formulated with morphine, provides significantly higher mean plasma concentrations compared with unformulated morphine.

The anesthetic ketamine has a rapid onset of action (4 to 8 minutes), and its duration (up to 2.5 hours of analgesia) matches the timeframe for breakthrough pain and procedural pain episodes.

Approximately one-tenth to one-sixth of the ketamine dose required to induce anesthesia is effective in treating acute moderate to severe pain. Ketamine enjoys an excellent history of safety, is not physically addictive, does not cause respiratory depression, hypotension or GI/GU dysfunction, and at lower doses is not associated with dissociative side effects sometimes associated with higher doses. Like intranasal morphine, it is easily titrated for effective nasal dosing. Ketamine may be used as an alternative to opioids, or in combination to minimize opioid side effects, especially in opioid-intolerant patients.

With the documented success of ketamine as an anesthetic, one can ask the same question as that for morphine: Why create an intranasal dosage form? Consider a cancer patient taking an opioid to help manage baseline pain. More than likely, this patient also suffers from episodic, or breakthrough, pain brought on by a sneeze, cough, movement, or for no apparent reason. Today, the clinical choices for managing this type of pain include increasing the baseline opioid regimen to blanket the breakthrough pain, but at the expense of sedation, respiratory depression, and constipation. Delivery of a non-narcotic analgesic such as ketamine, through metered, nasal delivery systems offers such a patient the best of both worlds: pain relief on an as-needed basis without impairing the quality of life.

Endogenous opioid peptides may offer new opportunities for treating pain. The endogenous opioid system includes a large number of peptide ligands to opioid receptors. Some produce morphine-like effects and can be displaced from their binding sites by opioid antagonists.

The three families of endogenous opioid peptides are the endorphins (derived from pro-opiomelanocortin), enkephalins (from proenkephalin), and the dynorphins (from prodynorphin). These agents have high affinity for μ opioid receptors and have produced potent and prolonged analgesia in animals.

As peptides, these agents cannot be delivered orally due to their hydrolysis in the gut. Because delivery by injection is limited to clinical settings, a very viable option for widespread adoption of these agents is a metered, easy-to-administer, patient-friendly delivery system with minimal potential for abuse. With the continuing advances in formulation technologies, proteins and peptides may well become more likely candidates for nasal delivery.

A CLOSER LOOK AT SAFETY & RISK MANAGEMENT

Safety, risk, and benefit must be balanced in the development of any analgesic product, and intranasally delivered morphine is no exception. Pharmaceutical developers have learned some valuable lessons from earlier work on the nasal delivery of butorphanol, a potentially addictive medication.

Sold in a multidose sprayer (up to 12 to

13 doses after priming) with no lock-out mechanism, butorphanol was easily abused. Regrettably, the death of the child drew public and regulatory attention to the dangers of an abusable drug sold in a multidose sprayer. While similar delivery vehicles remain on the market, potential drugs of abuse are more likely delivered in unit-dose sprayers similar to those that contain Imitrex® and Zomig® nasal migraine products.

This device is the same one chosen by Javelin Pharmaceuticals for its nasal morphine product (nasal ketamine will be delivered using a bi-dose device). Because it contains only 120 ml of drug and the delivered amount is 100 ml, there is very little residual material available after actuation. Intranasally administered drugs also possess an intrinsic physiologic safety mechanism in that each nostril holds only 150 to 200 ml of administered drug in solution, which requires approximately 15 minutes for absorbtion. Introducing additional drug before clearance results in drug dripping back down the throat, to be swallowed or discharged out the front of the nose. Both intranasal morphine and ketamine are non-irritating to the nasal mucosa.

SUMMARY

Pain management and nasal drug delivery are clearly growing, both in terms of market size and in their natural, symbiotic relationship, to the great benefit of the underserved pain relief marketplace. Helping to drive that growth will be the acceptance and approval of new nasal products for pain management, a trend toward self-administration, a desire for greater compliance and low addiction potential, the needs of an aging population, managed healthcare initiatives to control costs, and the growth of home healthcare and home hospice.

Although the convergence of pain management and nasal drug delivery will benefit pharmaceutical developers and managed care organizations, the major benefactors will be individuals suffering from acute moderate-to-severe and breakthrough pain who deserve analgesic products that are non-invasive, fast-acting, safe, and effective.

BIOGRAPHIES

Mr. Michael T. Sheckler brings nearly 20 years of pharmaceutical marketing experience to the company. Prior to joining Javelin, he served as Director of Business Development for Intranasal Technology, Inc., a nasal drug delivery company, and Kurve Technology, a nasal drug delivery device firm. His broad experience includes marketing, product management, product launches, and creating and building business streams while at Bespak, and sales and marketing research during his tenure at the Ross Division of Abbott Laboratories. Mr. Sheckler graduated from Indiana University and obtained his MBA from The Fuqua School of Business at Duke University in Durham, North Carolina. He serves as an Advisor on the Specialty Pharma Council for Specialty Pharma magazine.

Dr. Daniel B. Carr became CEO in September 2005, after joining the company as Chief Medical Officer a year earlier. Dr. Carr is a Founding Director of the MS Program in Pain Research, Education & Policy of Tufts University School of Medicine. A Principal Investigator on numerous clinical studies of pain and analgesia, Dr. Carr is also the recipient of many awards and honors from leading professional organizations and healthcare institutions worldwide. He is a sought-after advisor and speaker at Pain industry events. Dr. Carr has authored or contributed to over 300 articles, book chapters, and books on therapies for pain. He joined Javelin from the position of Saltonstall Professor of Pain Research in the Department of Anesthesia at Tufts-New England Medical Center. Dr. Carr holds an MD with honors (Alpha Omega Alpha) from Columbia University and an MS and BS (Honors) in Physics, also from that institution.

Dr. Fred H. Mermelstein has served on the Javelin Pharmaceuticals Board of Directors and as President from inception through July 2003. Formerly, Dr. Mermelstein served as Director of Venture Capital for Paramount Capital Investments, LLC. Dr. Mermelstein is a member of Orion Biomedical GP, LLC. He also serves as a Director of Cardiome Pharma, Inc.; Adherex Technologies, Inc.; and previously the Jordan Heart Foundation. From February 1997 until January 2000, Dr. Mermelstein served as a Director and the Chief Science Officer of PolaRx BioPharmaceuticals, an oncology-based biopharmaceutical company. Dr. Mermelstein holds a dual PhD in Pharmacology and Toxicology from Rutgers University and University of Medicine and Dentistry of New Jersey (UMDNJ) Robert Wood Johnson Medical School. He completed his Post-doctoral training supported by two grant awards; a National Institutes of Health fellowship and a Howard Hughes Medical Institute fellowship in the Department of Biochemistry at UMDNJ Robert Wood Johnson Medical School.

Mr. Douglas A. Hamilton was a Founder of Javelin Pharmaceuticals and previously served as Chief Financial Officer and Project Manager for Trisenox™ at PolaRx Biopharmaceuticals, Inc., which was acquired by Cell Therapeutics, Inc. Mr. Hamilton formerly served as Project Manager for Zithromax™ and Voriconazole at Pfizer, Inc., and as Project Manager for Epogen™, Aranesp™ and Stemgen™, among other products at Amgen, Inc. He brings extensive experience across numerous functional areas in the biopharmaceutical industry, including research at Connaught PMC, business development at Allelix Biopharmaceuticals, Inc., and sales and marketing at Pharmacia Biotechnology. Mr. Hamilton holds a BS in Molecular Biology and Molecular Genetics from the Department of Medical Genetics at the University of Toronto and an MBA from the Richard Ivey School of Business.

PROTEOLYTIC ENZYME INHIBITION

Human Insulin Stability With Proteolytic Enzymes: The Effect of Aqueous Soybean Extract in the Formulation

By: Antoine Al-Achi, PhD; Jiten Patel, MS; and Madhavi Anumandla, MS

ABSTRACT

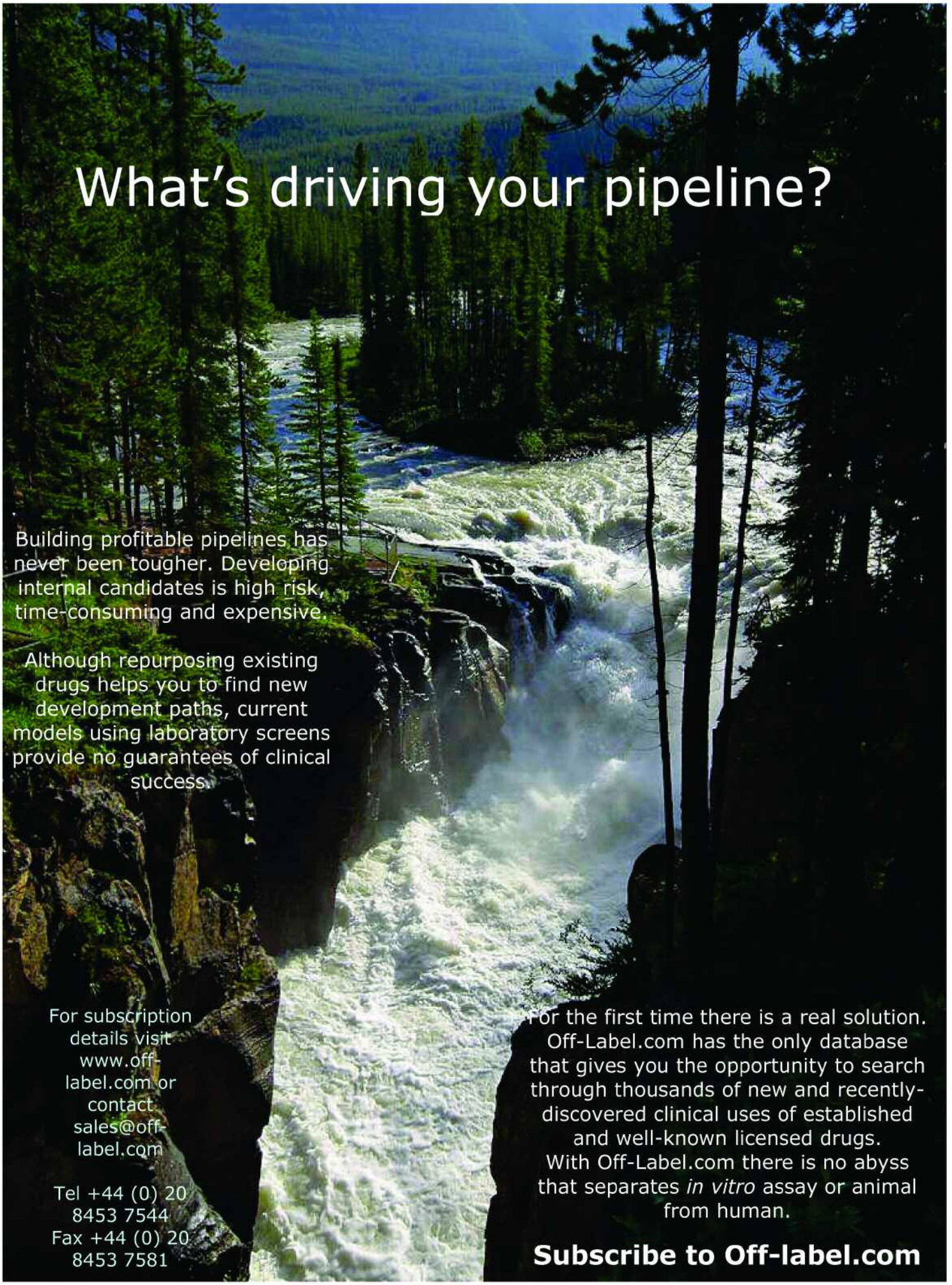
Human insulin is a hormonal drug used in the treatment of diabetes. The aim of this study is to examine the degradation of insulin in the presence and absence of an aqueous soybean extract. Soybean contains proteolytic enzyme inhibitors that can act on improving the stability of insulin in the presence of the enzymes. Human insulin (in the form of a solution or a suspension) was incubated with and without soybean extract with the enzymes at 37ºC for a minimum of 1 hour and a maximum of 7 hours. The degradation of insulin in preparations with simulated intestinal fluid (SIF, trypsin, and chymotrypsin) followed a first-order process with degradation rate constants of 0.0070 min^{-1} and 0.069 min^{-1} for solutions containing soy extract and without soy extract, respectively. Insulin in solution was degraded rapidly by a simulated gastric fluid (SGF, pepsin), and the addition of soy extract reduced this degradation significantly ($k = 0.056\ min^{-1}$). The formulation of insulin in suspensions (with or without soy extract) did not provide much improvement over that seen in solutions with pepsin. The addition of soy extract to the insulin suspension further improved the resistance to degradation by SIF. The results of this study demonstrate a protective effect for human insulin by soybean extract against proteolytic enzymes in vitro. The results obtained from this study warrant further in vivo investigations because the oral bioavailability of insulin will depend on a host of factors (including the effect of proteolytic enzymes), such as the presence of foods in the gastrointestinal tract (GI), the pH, the permeability of the GI tract mucosa to insulin, and the effect of intracellular peptidases on insulin following its absorption. The *in vivo* studies will also ascertain whether the protection of insulin by soy observed in the *in vitro* experiments is of pharmacologic or therapeutic significance when tested in diabetic experimental animal models.

INTRODUCTION

The use of human insulin in the treatment of diabetes is extensive. All type 1 (autoimmune) and some of the type 2 (non-autoimmune) diabetic patients depend on daily insulin injections to control their disease. The prevalence of diabetes is on the rise in Western countries. In Europe, it is expected to reach an epidemic magnitude, and in the US, the number of patients suffering from the disease exceeds 16 million.[1,2] Human insulin therapy usually involves multiple daily subcutaneous injections in order to control blood glucose levels so that they remain normal. It is now recognized that a fasting blood glucose level of 126 mg/dl or higher is indicative of diabetes.[3] Because of the discomfort associated with this daily injections regimen, other oral routes have been the subject of many investigations. Owens et al recently reviewed the various experimental routes for insulin administration as a substitution for the subcutaneous route.[4]

Among these potential routes of administration for insulin is the oral route. This route affords the patient an easy means of administering medications, and in the case of insulin, it is perhaps the most physiologically sound (allowing insulin to reach the liver first via the portal vein). However, obvious disadvantages of using this route for administering proteins and peptides are the presence of proteolytic enzymes, different absorption potential among the different segments of the GI tract, and the presence of foods and natural flora, among others. Perhaps the most important factor is the proteolytic enzymatic degradation of insulin into di-peptides. Several approaches have been suggested to overcome this degradation capacity of the enzymes. Among these methods is the use of enzyme inhibitors, chemical modification of the insulin structure, or encapsulating insulin in a carrier system (eg, nanoparticles, lyposomes, or erythrocyteghosts are the most common).

Soybean (*Glycine* max) is known to possess proteolytic enzyme inhibition, specifically against trypsin and chymotrypsin. In this study, we examined the effect of an aqueous soybean extract on the degradation of human insulin by three proteolytic enzymes *in vitro*, namely trypsin, chymotrypsin, and pepsin. The degradation profile of human insulin in the presence or absence of soybean aqueous extract is presented in two dispersed systems: a solution and a suspension. To our knowledge, this report is the first to examine the effect of soybean aqueous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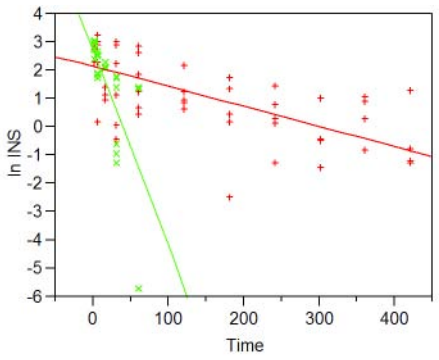
PROTEOLYTIC ENZYME INHIBITION

FIGURE 1



Human insulin (100 U/ml, 1 ml) was diluted with 3 ml of either DD water (x) or aqueous soybean extract (+) and incubated with 1 ml of SIF at 37ºC for 7 hours. Data points are actual observations.

extract on the degradation of human insulin by proteolytic enzymes *in vitro*.

MATERIALS

Soybean was obtained from a local store in North Carolina. Humulin R (Human insulin solution, Lilly, 100 U/ml) was from NC Mutual, North Carolina. Acetonitrile (HPLC grade) was purchased from Fisher Scientific (Pittsburgh, PA). All other chemicals were from Sigma, St. Louis, MO. Except for those that were used in the HPLC assay, chemicals were of analytical grade.

METHODS

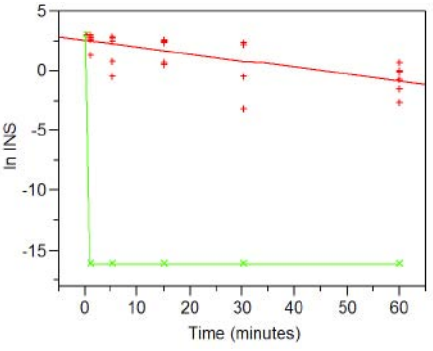
Preparation of aqueous soybean extract: The preparation of soybean powder was according to the method described previously.[5] Briefly, soybeans (approximately 57 g) were ground in a coffee grinder (Mr. Coffee, Sunbean Products, Hatiesburg, MS) to a fine powder. The resulting powder was characterized to have a volume-surface mean diameter (d_{vs}) and a volume-number mean diameter (d_{vn}) of 45.5 m and 31.6 m, respectively.[5] The aqueous extract of soybean was prepared by mixing 5 g of the resulting powder for 2 minutes with 25 ml of double deionized (DD) water. The mixture was incubated at 37ºC for 1 hour. To separate the powder material from the aqueous extract, the mixture was centrifuged for 20 minutes at 12,000 rpm and 4ºC. This centrifugation step was repeated twice for 20 minutes at 16,000 rpm each time on the supernatant fraction. Following centrifugation, the extract was filtered first with a 0.45-µm nylon filter followed by a 0.22-µm nylon filter. About 10 ml of aqueous soybean extract was obtained as the final preparation. The extract had a pH 6.5 to 7.0. Its viscosity, obtained by a capillary viscometer, was on average 1.39 centipoises. Because soybean powder contains about 40% by weight of proteins, we estimate the total protein concentration in the extract to be in the order of 80 mg/ml.[6] Assuming an average value for proteolytic enzymes inhibitors of 22 mg per gram of powder, the final enzyme inhibitors concentration in the extract can be estimated to be about 4.4 mg/ml.[6]

Preparation of simulated gastric fluid (SGF) & simulated intestinal fluid (SIF): These two solutions were prepared based on U.S.P. recommendations with some minor modifications. Simulated gastric fluid was made by dissolving 0.02 g of NaCl and 0.032 g of pepsin in 7-ml DD water. To the resulting clear solution, 0.07 ml of 12N HCl was added, and the final volume was brought up to 10 ml with DD water. If necessary, the pH of the solution was adjusted to 1.2 by the addition of a few drops (about 200 µL) of 12 N HCl. Simulated intestinal fluid contained 0.068 g of monobasic potassium phosphate, 0.05 g of trypsin, and 0.05 g of chymotrypsin. The potassium salt and enzymes were dissolved in 1.9 ml of 0.2N NaOH solution to form a clear solution. The final volume was brought to 10 ml with DD water. If necessary, the pH of SIF was adjusted to 7.5 with 50% NaOH (about 7 µL). All preparations were made fresh on the day of the experiment to minimize any enzyme degradation.

High performance liquid chromatography assay for insulin: Quantification of insulin in solution was made by an HPLC assay previously published.[4] The main components of this system included a Vydec Protein C4 column; ConstaMetric 4100 solvent delivery system; Waters 717plus Autosampler; Waters 746 Data Module; and a UV detector (Waters 2487 Dual λ absorbance detector). The mobile phase consisted of acetonitrile:water:trifluroacetic acid:hexanesulfonic acid-sodium salt (30:70:0.1:0.1). The flow rate was set at 1 ml/min; wavelength: 215 nm; and injection volume: 20 µL. Throughout the concentration range studied (0.5 to 50 U of insulin/ml), insulin absorbance in solutions exhibited a linear profile (r = 0.99). Components in soybean aqueous extract, SIF, or SGF did not show any interference with the insulin peak on the chromatogram.

Stability of human insulin solution in the presence & absence of aqueous soybean extract: Human insulin solution (Humulin-R, Lilly, 100 U/ml) was mixed with either DD water or aqueous soybean extract in a volume ratio of 1:3 (insulin:water or soy extract). To each of the resulting solutions, 1 ml of either SGF or SIF was added, and then the final mixtures (containing 20U/ml of insulin) were incubated at 37ºC. The concentration of insulin in solution was monitored over time (up to 7 hours). Immediately following the incubation, the pH of the mixture was adjusted with either 12N HCl or 50% NaOH; in the case of SGF, the pH was made approximately 8.0; in the case of SIF, the pH was adjusted to 2.5. All experiments were done in three to six replicates.

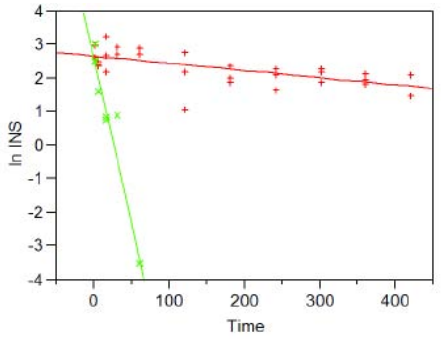
FIGURE 2



Human insulin (100 U/ml, 1 ml) was diluted with 3 ml of either DD water (x) or aqueous soybean extract (+) and incubated with 1 ml of SGF at 37ºC for 1 hour. Data points are actual observations.

PROTEOLYTIC ENZYME INHIBITION

FIGURE 3



An aqueous suspension of human insulin containing DD water (x) or soy extract (+) (1 ml, 50 U/ml) was diluted with 1 ml of the same vehicle (water or soy extract) and incubated with 0.5 ml of SIF at 37ºC. Samples were collected over time and analyzed for their content of insulin. Data points are actual observations.

Stability of human insulin suspension in the presence & absence of aqueous soybean extract: Human insulin solution (Humulin R, Lilly, 100 U/ml) was mixed with either DD water or aqueous soybean extract in a volume ratio of 1:1. The pH of the mixture was adjusted to 4.30 (± 0.05) using 6N HCl. Under these conditions, insulin precipitates out from the solution. The particle size of precipitated insulin particles was determined under different pH conditions using light microscopy. The particle size of precipitated human insulin particles reached a minimum at pH 4.0, 4.3, and 5.2. At pH 4.30, the d_{vs} and d_{vn} were 31.19 m and 29.60 m, respectively. The smaller the particle size, the slower the sedimentation rate is and the better the physical stability of the suspension. One (1) ml of insulin suspension (50 U/ml) was then mixed with either 1 ml of DD water (in the case of water suspension) or 1 ml of soy extract (in the case of soy suspension). Insulin stability in these mixtures was tested in the presence of 0.5-ml SIF or SGF at 37ºC for up to 7 hours. The final mixture with the enzymes contained 20 U/ml of insulin. All experiments were done in three to six replicates.

Statistical analysis: Values are reported as mean ± standard deviation. A Student's t-test was used to compare groups and for estimating the 95% confidence interval (95% CI) on the true difference between the groups. Estimated values of the first-order degradation rate constant (k_1) were statistically evaluated with the null hypothesis that k_1 equals to zero ($H_0 = 0$). A p value less than 5% was considered significant. JMP® Statistical Discovery Software (SAS Institute, Cary, NC) was used for the statistical analysis.

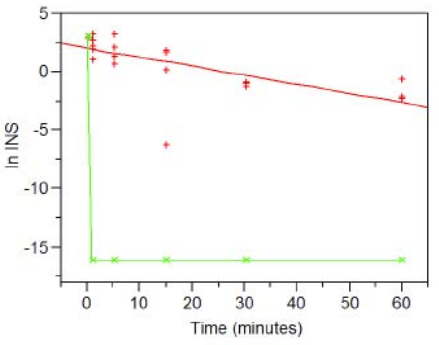
RESULTS & DISCUSSION

Human insulin is composed of 51 amino acids forming two chains, A and B, which are linked together by disulfide bonds (one bond links A7-Cys to B7-Cys and another bridges the two chains at [A20-Cys/B19-Cys]) (B or A refers to insulin chains followed by the location and the name of amino acid present). An additional disulfide bond is found on the A chain linking A6-Cys to A11-Cys. Insulin degradation by trypsin and chymotrypsin is the result of the ability of these two enzymes to cleave insulin at certain points at its A and B chains. Trypsin cleaves insulin at two locations, while chymotrypsin does its cleavage on eight sites.[7] The two sites for degradation by trypsin are B29-Lys and B22-Arg, while chymotrypsin cleaves insulin at B26-Tyr, A19-Tyr, A14-Tyr, B-16-Tyr, B25-Phe, B1-Phe, B15-Leu, and A11-Cys.[6] Pepsin can act on insulin in 15 locations; four are found in A13-A19 region, six in the B chain, and five are located in A2-A8 segment.[8]

Soybean (*Glycine* max) contains between 16.7 to 27.2 mg of proteolytic enzyme inhibitors per gram (Bowman-Birk and Kunitz types).[6,9] Morishita et al found that the oral administration of microspheres containing insulin along with Bowman-Birk inhibitors in rats significantly reduced serum glucose level.[10] A drug-carrier matrix containing Bowman-Birk inhibitor and insulin was shown to significantly reduce the degradation of insulin by proteolytic enzymes (98.7% of insulin degraded within 1 hour at 37ºC without inhibitors compared to 22.3% degradation in the presence of the inhibitors).[11] The relative efficacy of these microspheres to intravenous insulin injection was approximately 2.0.[12] The incubation of human insulin solution with SIF at 37ºC resulted in a rapid reduction in insulin concentration over time (Figure 1). The first-order degradation constant for insulin was calculated to be 0.069 ± 0.013 min^{-1} ($p <$ 0.0001). When the experiment was repeated in the presence of aqueous soybean extract (Figure 1), k1 was reduced to 0.0070 ± 0.00098 min^{-1} ($p < 0.0001$; 95% CI on the true difference = [0.059 – 0.065]). The presence of soybean extract resulted in a ten-fold increase in the stability of insulin in solution. This may be due primarily to the inhibition of chymotrypsin by soy extract because insulin degradation by chymotrypsin is more than eight times greater than that with trypsin.[7] In the presence of SGF, insulin degradation in aqueous solutions was fast and complete, with 100% of insulin degraded within 1 minute of incubation. However, upon the addition of soy extract to the medium, insulin degradation by SGF was reduced with a first-order degradation constant of 0.056 ± 0.0096 min^{-1} ($p < 0.0001$) (Figure 2). In both cases, SIF and SGF, insulin degradation by proteolytic enzymes was significantly reduced in the presence of soybean extract.

We further tested the effect of the proteolytic enzymes on insulin in suspensions. Drug degradation occurs primarily in solution, with little or no degradation occurring on the drug solid particles. Suspensions of insulin were prepared at pH 4.3 with and without soybean extract. Aqueous suspensions of insulin did not provide added protection with SIF when compared with aqueous insulin solution ($k_1 = 0.098 \pm 0.012$ min^{-1}; $p <$

FIGURE 4



An aqueous suspension of human insulin containing DD water (x) or soy extract (+) (1 ml, 50 U/ml) was diluted with 1 ml of the same vehicle (water or soy extract) and incubated with 0.5 ml of SGF at 37ºC. The incubation time lasted 1 hour at 37ºC. Samples were collected over a 1-hour period and analyzed for their content of insulin. Data points are actual observations.

0.0001). However, insulin stability in a soy extract suspension in the presence of SIF had a k_1 value of 0.0021 ± 0.00043 min^{-1} ($p < 0.0001$) (over three-fold improvement as compared to a solution containing soy; 95% CI on the true difference between the solution and suspension = [0.0045 – 0.0053]) (Figure 3). While insulin in a soybean extract suspension was much more resistant to the degradation by SIF than just a simple solution, insulin degraded rapidly in aqueous suspensions with SGF. However, soybean extract decreased this rate of degradation significantly with a characteristic k_1 of 0.072 ± 0.019 min^{-1} ($p = 0.0014$) (Figure 4). The results from this study suggest that soybean aqueous extract can reduce the degradation of human insulin by proteolytic enzymes *in vitro*. This protection by the soy extract is more pronounced against trypsin and chymotrypsin than against pepsin. Similar results were reported with microspheres containing insulin along with various protease inhibitors.[12] Insulin degraded rapidly and completely with pepsin, chymotrypsin, and trypsin without the presence of enzyme inhibitors; protease inhibitors significantly protected insulin from the enzymatic degradation.[12]

CONCLUSION

This study examined the protective effect of an aqueous soybean extract on human insulin in the presence of proteolytic enzymes. The extract improved the stability of insulin in solution in the presence of trypsin and chymotrypsin by about ten-fold. A suspension of insulin in water (ie, in the absence of soy extract) was as stable with SIF as a simple solution. Soy extract enhanced the protection of insulin in a suspension by SIF (over a three-fold increase in the stability as compared to a solution containing soy). The degradation of insulin by pepsin was reduced in the presence of soy extract; however, suspending insulin did not provide any added benefits to that of a simple solution.

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BIOGRAPHIES

Dr. Antoine Al-Achi is Associate Professor of Pharmaceutical Sciences at Campbell University School of Pharmacy. In this role, he teaches pharmaceutics and biostatistics in both the PharmD program and the MS (Pharmaceutical Sciences) major. Dr. Al-Achi earned his PhD in Biomedical Sciences/Pharmacokinetics from Northeastern University, Boston, Massachusetts. He completed Post-doctoral studies in Cancer Pharmacology at Dana-Farber Cancer Institute/Harvard Medical School. Dr. Al-Achi has published more than 100 scientific papers, reviews, and abstracts. His area of interest is in drug delivery systems of peptides and proteins.

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PURE DRUG NANOSUSPENSIONS

Impact of Nanosuspension Technology on Drug Discovery & Development

By: Rajesh Dubey, PhD, MPharm

ABSTRACT

Development of new molecular entities has become tougher in spite of emergence of new concepts in high throughput screening to accelerate the drug discovery process. One of the main problems responsible for the low turn-out is poor solubility and poor permeability of lead compounds. Looking at the new molecules launched in the market and profiles of the current molecules in pipelines, it is evident that the problem is getting severe. Nanosuspension technology can be used in drug discovery programs to increase aqueous solubility as well as to increase bioavailability during the preclinical and clinical development stage. The technology can be applied to all the drugs belonging to BCS classes II, III, IV. The present article provides a review of current methods that can be used to prepare nanosuspensions of pure drug. Also, the application of nanosuspension technology to improve bioavailability and to formulate intravenously injectable solutions has been described with pertinent case studies.

INTRODUCTION

Modern drug discovery has been revolutionized by new concepts in high throughput screening (HTS) that include in silico modeling for prediction of ADME-related characteristics of candidate drug; molecule microarray technologies for gene expression analysis; and screening libraries of proteins and small molecules, bioinformatics, and combinatorial chemistry leading to better and faster target validation and virtual screening.[1-3] The basic aim of these tools is to choose the promising molecules and reject the non-promising ones. The distinction that a molecule is promising or non-promising is made on the basis of the structure activity relationship (SAR) that predicts if the molecule is having "drug-like characteristics" or not.[4] Though the use of such techniques has made it feasible to evaluate a plethora of compounds in a very short time, the same has not resulted in discovering molecules, which satisfy both therapeutic as well as formulation requirements. The majority of drug candidates are selected on the basis of SAR that seldom takes into consideration the properties that influence formulation of the molecule. Various formulation parameters that play a crucial role for successful formulation of NMEs can be enlisted as aqueous solubility, stability at ambient temperature and humidity, photostability, compatibility with aqueous and nonaqueous solvents, and excipients etc. Of these, solubility remains the most important property, especially for developing formulations at the preclinical stage. At this stage, selected NMEs (also known as hits) are subjected to the lead selection and lead optimization studies using exploratory pharmacokinetic (PK) studies. To conduct these studies, an NME needs to be administered intravenously to the test animal. On the basis of the PK results (eg, $t_{1/2}$), a molecule is selected for further studies or is rejected. Thus, preclinical studies can be attributed as the first litmus test for the drug to be selected for further in vivo evaluation. A highly lipophilic molecule (ie, with log P > 5) may show excellent in vitro activity in the cell-based assay, but it may not be formulated for in vivo evaluation, leading to its rejection or downgrading. Interestingly, the number of such difficult-to-formulate molecules approved or filed for approval is steadily increasing. As per a recent report, 46% of the total NDAs filed from 1995 to 2002 were BCS class IV, while only 9% were BCS class I drugs, indicating that a majority of the approved new drugs were water insoluble.[5] The most surprising of all is the fact that 40% of the top 10 best-selling drugs are practically insoluble in water, while only two drugs are soluble or freely soluble (Table 1).

Based on these trends, it will be prudent to expect that an increasing number of promising candidates that are selected "as hits" will be highly water insoluble. In such cases, formulation of a drug solution can be a daunting task, depending on the characteristics of the drug.

The compounds that are selected as hits can be classified as those that are difficult to dissolve (< 10 mg/mL) and those that are easy to dissolve (>10 mg/mL). Further, difficult-to-dissolve compounds may be practically insoluble in water (ie, <100 µg/mL) or those that are slightly soluble in water (< 10 mg/mL to > 100 µg/mL) and can be dissolved using solubilizing agents.

In general, a solution containing 3±1 mg/mL of the NME will suffice for its preclinical screening. There may be drug candidates that have poor solubility in water but can be dissolved by suitable conventional formulation strategies, eg, the use of

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PURE DRUG NANOSUSPENSIONS

co-solvents, pH adjustments, etc. This can be a challenging task as the process involves searching and optimizing critical factors like type and concentration of co-solvents such that a solution can be obtained using minimal quantity of the toxic excipients in order to reduce vehicle-related toxicity.[6] However, the real problem occurs when the use of such formulation strategies fails to give a desired solubility of the drug. Such drugs are either discarded for the lack of a suitable formulation or are formulated using unusually higher concentration of co-solvents, which sometimes may be as much as 100% of the vehicle composition.[6] Use of such ingredients at such concentrations not only creates severe toxicity, but may also give false results about drug toxicity profile during acute toxicity and/or chronic toxicity studies. The importance of the true mapping of toxicity is indicated by the recent spurt in the failure of drug candidates in advanced stages of clinical trials as well as failures after commercialization.

Thus in this era, when almost all the research-based pharma companies are facing a declining pipeline, the higher proportion of "practically-insoluble-in-water" compounds will further reduce the success rate unless there exists an enabling technology to make these drugs' in vivo evaluation feasible.

TABLE 1

S. No.	Brand Name	Generic Name	Solubility in Water
1	Lipitor	Atorvastatin calcium	Very slightly soluble
2	Prevacid	Lansoprazole	Practically insoluble
3	Zocor	Simvastatin	Practically insoluble
4	Nexpro	Esomeprazole magnesium	Slightly soluble
5	Zoloft	Sertraline Hydrochloride	Slightly soluble
6	Celebrex	Celecoxib	Insoluble
7	Zyprexa	Olanzapine	Practically insoluble
8	Neurontin	Gabapentin	Freely soluble
9	Effexor	Venlafaxine Hydrochloride	Soluble
10	Adavir	Fluticasone propionate	Practically insoluble
		Salmeterol Xinafoate	Sparingly soluble

PURE DRUG NANOSUSPENSIONS: THE PROMISING TECHNOLOGY

Pure drug nanosuspensions may help to provide a viable solution for formulating such practically insoluble drugs. "Nanosuspensions" can be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of suspended particles is < 1 µm in size. Nanosuspensions can help in drug discovery programs to achieve two objectives: (a) increasing aqueous solubility and (b) increasing bioavailability during the preclinical and clinical development stages. This is very desirable in drug discovery programs, where the molecules with poor solubility (ie, BCS II), poor permeability (ie, BCS III), or both (ie, BCS IV) pose a significant challenge to the formulation scientist at the preclinical as well as clinical development stages.

Pure drug nanosuspensions are different from drug polymer nanoparticles in which drug remains dispersed in (nanospheres) or encapsulated by a carrier polymer (nanocapsules). The details of these systems can be found elsewhere in the literature. The objective of the present article is to describe various methods of preparation, critical parameters of the formulation that needs to be characterized, and the application of nanosuspension formulations.

PREPARATION OF NANOSUSPENSIONS

The various methods reported in the literature for preparation of nanosuspensions can be classified into three basic techniques: (1) wet milling, (2) emulsification-solvent evaporation, and (3) supercritical fluid.

Wet Milling Methods

Many pieces of equipment are available that use different principles in mechanical milling of large drug particles to reduce them to the nano-scale range. This includes wet milling, high pressure homogenization, opposite stream collision, and ultrasonication.

Pearl/ball mills can be used to prepare nanoparticles by colloidal grinding. In this case, an aqueous suspension of drug is fed into the mill containing small grinding balls, which are made of ceramic sintered aluminium oxide or zirconium oxide with high abrasion resistance. As the pearls/balls rotate, they fly through the grinding jar interior and impact against the sample on the opposite grinding jar wall. The combination of frictional forces and impact forces thus produce a high degree of particle size reduction. Planetary ball mills (PM 100 & PM 200, Retsch GmbH & Co. KG) is one example of the equipment that can be used to achieve a grind size below 0.1 µm. Nanosuspension of an investigational compound (301029) has been prepared via the pearl milling technique in which the average particle size of the active compound was reduced from 7 µm to 280 nm.[7] In another report, a nanosuspension of Zn-insulin with a mean particle size of 150 nm was prepared using wet milling techniques.[8]

Instruments working on the principle of "high pressure homogenization" use cavitation forces for particle size reduction. In this case, the suspension of the drug is made to pass through a small orifice (called a valve) that results in reduction of local pressure below the vapor pressure of the medium. This leads to formation of small bubbles filled with vapor. When these bubbles go to an area where local pressure is more than the vapor pressure, they implode, and the surrounding part containing the drug particles rushes to the center, and in the process colloids, causing a reduction in the size of particles. This principle is employed in the APV Gaulin Micron LAB 40 homogenizer

(APV Homogenizer, Lübeck) and NS 1001L-Panda 2K high-pressure homogenizers (Niro Soavi S.p.A.).

This technique was used by Peters et al to prepare clofazimine nanosuspensions.[9] Here, an aqueous suspension of clofazimine was homogenized using an APV Gaulin Micron LAB 40 homogenizer. After subjecting the coarse dispersion of clofazimine to 10 cycles of homogenization at 1500 bar, a nanosuspension of clofazimine was obtained. Another piece of equipment that works using a similar principle is an Emulsiflex high pressure homogenizer (Avestin Inc.). Sudhan et al have reported the production of Monensin nanoparticle formulations with particles measuring < 200 nm in size using an Emulsiflex homogenizer.[10]

Another technique, called opposite stream (or nanojet) technology, uses a chamber where a stream of the suspension is divided in two or more parts, which in turn, colloid with each other at high pressure. The high shear force created during the process leads to a reduction of particle size. Equipment using this principle include the M110L & M110S microfluidizer (Microfluidics), and this microfluidzation-based process was used by Dearn to prepare nanoparticle formulations of atovaquone.[11] Microfluidizers have also been reported for reducing the size of liposomes to the nano-range. Vemuri et al have reported the use of microfluidizers (M-110 & M-210) to reduce the size of liposomes from 0.64 µm to 0.16 µm.[12]

Ultrasonication-based instruments use high-energy sonication waves generated from probes (also called sonotrodes) vibrating at very high frequencies and placed directly in the suspensions. These waves colloid with the suspended particles, breaking them into smaller pieces. UP50H/UP100H ultrasonic processors (Dr. Hielscher GmbH, Teltow) can be used for nanoparticle formulations.

Emulsification-Solvent Evaporation Technique

While the previous methods involved dispersing drug into the aqueous vehicle followed by particle size reduction by using high-shear forces, the emulsification-solvent evaporation technique involves preparing a solution of drug followed by its emulsification in another liquid, which is a non-solvent for the drug. Evaporation of the solvent (present in drug solution) leads to precipitation of the drug. Provided the crystal growth is controlled during the precipitation stage, nano-scale particles are obtained dispersed in the aqueous vehicle. Here, the drug solution needs to be prepared using a water-immiscible organic solvent with a boiling point near room temperature or lower (eg, dichloromethane). The solution can be prepared by adding the drug to a small quantity of the solvent with ultrasonication, if required. The solution thus obtained is then added slowly to an aqueous media with stirring at a high speed that leads to formation of small droplets (containing drug dissolved in organic solvent) emulsified in the aqueous vehicle. As the stirring progresses at high speed, droplet size is further reduced. The process is also accompanied by slow evaporation of the organic solvent from the droplets. Once the organic solvent is evaporated completely, pure drug particles are left behind suspended in the aqueous vehicle. High-shear forces created during the high-speed stirring prevent particle aggregation and Oswald ripening of the small particles, and thus prevent particle size growth. Provided the stirring is sufficiently high, nanosuspensions can be prepared using this process. The process is similar to those used for preparing polymeric nanoparticles.[13]

Hydrosol Method

This is similar to the emulsification-solvent evaporation method with the difference being that the drug solvent is miscible with the drug-antisolvent. The method, as described by Sucker and co-workers, involves dissolving drug into the solvent and mixing the solution with the antisolvent with high stirring.[14] The mixing results in a supersaturated drug solution. The supersaturation is further accentuated by the evaporation of the drug solvent. This leads to the precipitation of the drug. High-shear force prevents nucleus growth and Oswald ripening, thus ensuring that the precipitates remain smaller in size. Finally, when all the solvent gets evaporated, pure drug nanoparticles suspended in water are obtained.

Supercritical Fluid Method

Nanoparticles can be produced with supercritical fluids using various methods, such as rapid expansion of supercritical solution process, gas antisolvent process, and supercritical antisolvent process.

The rapid expansion of supercritical solution process involves expanding solution of drug in supercritical fluid through a nozzle. Upon expansion, supercritical fluid loses its solvent power, leading to precipitation of dissolved drug as fine particles. Cyclosporine nanoparticles in the size range of 400 to 700 nm were produced using this technique by Young et al.[15].

The gas antisolvent process involves pressurizing with CO_2 a solution of drug in common solvent. As the solvent is removed and the solution gets supersaturated, drug precipitates and forms fine crystals.

The supercritical antisolvent process uses a supercritical fluid in which drug is poorly soluble and a solvent for drug, which is also miscible with supercritical fluid. The method involves injecting solution of drug in the solvent into the supercritical fluid. As the solvent is extracted by the supercritical fluid, the drug solution becomes supersaturated, and finally the drug gets precipitated as fine crystals. Chattopadhyay et al have reported the use of this method to prepare naoparticles of Griseofulvin, an antifungal agent with poor aqueous solubility.[16] The particle size and morphology of the nanoparticles were further controlled by subjecting the drug solution to an ultrasound field generated by a vibrating surface inside the supercritical media. The frequency of the vibration can be varied to obtain particles with different size and morphology.

Thus, as discussed previously, many different techniques can be employed for particle size reduction to prepare nanosuspensions of drug substances.

However, each technique has its disadvantages. For example, the milling process can degrade thermolabile drugs due to the heat generated during the process. The supercritical fluid-based method and emulsification solvent evaporation method can lead to particle nucleation overgrowth due to transient high supersaturation. High supersaturation in these methods may also result in the development of an amorphous form or other undesired polymorph. This is particularly true in the case of organic molecular crystals, in which the forces holding the molecules together in the lattice are relatively weak.

PURE DRUG NANOSUSPENSIONS

CHARACTERIZATION OF NANOSUSPENSIONS

While characterization of nanosuspensions can be carried out in similar ways as those used for any conventional pharmaceutical suspensions (eg, appearance, color, odor, assay, related impurities, OVI - if used during the preparation - etc), which are widely described in literature and regulatory guidelines, particle size measurement of nanosuspensions is an additional and important parameter. The particle size distribution determines the physicochemical behavior of the formulation. Further, the particle size distribution is also a critical parameter, especially at the time of scaling up/site transfer of the manufacturing of the formulation. The particle size distribution of nanosuspensions can be carried out using various methods like laser diffraction (LD) (Malvern Mastersizer), photon correlation spectroscopy (PCS) (Malvern Zetasizer), and Coulter counter multisizer (Coulter Electronics). While the PCS method measures the particles in the size range of 3 nm to 3 µm, the LD method detects particles/aggregates with sizes in the micron range. The Coulter counter multisizer gives absolute number of particles as opposed to the LD method that gives relative particle size distribution. Some other techniques that can be employed to characterize the impact of the homogenization process on drug substances are differential scanning calorimetry/differential thermal analysis in combination with X-ray analysis to detect polymorphic changes and electrophoresis to measure development/change in the surface charge.

Nanosuspension formulations for intravenous administration is required to be sterile and pyrogen free in addition to complying with the required particle size (less than 5 µm).

APPLICATIONS OF NANOSUSPENSION TECHNOLOGY

Pure drug nanosuspensions can play a critical role as an enabling technology for poorly water-soluble and/or poorly permeable molecules having significant in vitro activity. Such molecules pose problems at any or both of the following during new drug development activities: (1) formulation of an intravenously injectable product for preclinical in vivo evaluation of the new molecule to measure its toxicity and other pharmacokinetic characteristics and (2) poor absorption of the drug candidate from the GIT resulting into poor bioavailability during preclinical as well as clinical development studies. Pure drug nanosuspensions can provide solutions to both of these problems.

A pure drug nanosuspension contains pure drug particles suspended in an aqueous media. As the particle size (usually below 400 nm) is way below the minimum particle size that can be administered intravenously (ie, 5 µm), a nanosuspension can be administered intravenously to conduct exploratory study with the candidate drug molecules.

Bioavailability Enhancement

The poor oral bioavailability of the drug may be due to one or more of following factors: poor solubility, poor permeability, and poor stability in the GIT conditions. Nanoparticle technology addresses the problem of poor bioavailability by solving the twin problems of poor solubility as well as poor permeability of the drug across the biological membrane.

As reported by Böhm et al, reduction of particle size of poorly water-soluble drugs in the nanometer range results in an increase in dissolution pressure as well as dissolution velocity.[17] The parameters affecting dissolution pressure and dissolution velocity are explained by Equations 1 and 2, respectively.

Equation 1.

$$P_r/P_\infty = 2\gamma M_r/(rRT\rho)$$

Where, P_r is the dissolution pressure of particle with radius (r), P_∞ is the dissolution pressure of an infinitely large particle, γ is the surface tension, M_r is the molecular weight, r is the radius of the particle, R is the gas constant, T is the absolute temperature, and ρ is the density of the particle.

Equation 2.

$$D_m/d_t = DA(c_s - c_t)/h_d$$

Where, D_m/d_t is the dissolution velocity, D is the diffusion coefficient, A is the surface area, c_s is the saturation solubility, c_t is the concentration in the vicinity of the particle, and h_d is the diffusional distance.

According to Equation 1, size reduction leads to an increase in the dissolution pressure. Higher surface area of the nanoparticles as compared to the microparticles leads to a higher rate of dissolution as illustrated by Equation 2. However, an increase in solubility that occurs with relatively low particle size reduction may be mainly due to change in the surface tension leading to increased saturation solubility. As explained by Muller, the energy introduced during the particle size reduction process (eg, homogenization) leads to an increase in surface tension (γ) and an associated increase in the dissolution pressure.[18]

Nanosuspension of 301029, a poorly soluble lead compound, was used to enhance its oral bioavailability.[19] To study the impact of particle size reduction, four different formulations containing the bulk drug material with different mean particle size were prepared. The particle size of the drug in the formulations prepared by alpine, air-jet, wet (without polymeric surfactants), and wet-media milling (with polymeric surfactants) methods were 5.49, 1.85, 0.85, and 0.12 µm, respectively. These formulations were dosed to dogs orally at a dose of 2 mg/kg. It was observed that the decrease in the particle size resulted in increase in the AUC. The increase in AUC with a decrease in the particle size showed good correlation with the formulation containing nanoparticles (120 nm), giving four-fold AUC as compared to the formulation containing microparticles (5.49 µm). The bioavailability (in terms of AUC) of the compound was found to be four times higher with nanosuspension formulation as compared to the microparticle formulation. The increase in the bioavailability was related to the higher permeation of the drug on the basis of an in vitro permeation study using Caco-2 monolayer cell line. Higher permeation of the drug also resulted in a faster rate of the drug absorption as the Tmax was found to be one fourth of that obtained with the microparticle formulation. Danazol nanosuspension containing particles with a mean diameter of 169 nm was reported to give much higher bioavailability (82.3 ± 10.1%) as compared to that obtained with conventional drug suspension (5.1 ± 1.9%).[20]

PURE DRUG NANOSUSPENSIONS

Bioavailability of a poorly soluble hepatoprotective agent, oleanolic acid, was improved using a nanosuspension of the drug that contained particles with an average size of 284.9 nm. The therapeutic effect of the drug was significantly enhanced, indicating higher bioavailability of the drug. This was explained to be due to the faster dissolution (90% in 20 min) of the drug as compared to the dissolution from suspension of coarse drug (15% in 20 min).[21]

The technology has also been patented for improved formulations of human immunodeficiency virus (HIV) protease inhibitor drug substances (eg, saquinavir, indinavir) also known as proteases.[22] These proteases provide an alternative of drugs that interfere with the HIV reverse transcriptase, eg, azidothymidine, didanosine, dithiothreitol, etc. However, the poor bioavailability of the proteases has created complexities in the development of many potential lead compounds. As disclosed in the patent, mechanical grinding of the drug particles dispersed in aqueous media can develop nanosuspension of these proteases. The resulting nanosuspension with the effective average particle size less than about 400 nm results in several advantages, such as increased rate of dissolution in vitro, an increased rate of absorption in vivo, a decreased fed/fasted ratio variability, and a decreased variability in absorption.

In addition to using nanosuspension as such, they can also be used to prepare solid oral dosage forms. Tablets prepared using nanosuspensions of the drug have been reported to give better bioavailability then those prepared with conventional drugs.

Tablets of aprepitant, a drug for the prevention of chemotherapy-induced nausea and vomiting, were formulated using nanodispersions of drug.[23] The nanodispersion of the drug was formulated using NanoCrystal Tachnology (Elan). The formulation has been reported to give higher bioavailability and less food effect on absorption. These effects were attributed to increased surface area, resulting in increased dissolution of the drug.

Abbott recently received approval for a new formulation of fenofibrate tablets available under the brand name Tricor. The reformulated product has been shown to have higher bioavailability and less fed-fasted variability as compared to the earlier formulation. The new formulation employs the nanoparticle technology in which an aqueous nanosuspension of the drug is prepared using either the wet-milling method or precipitation method.[24] The aqueous dispersions of a nanoparticulate drug and other excipients, such as polymeric surface stabilizer, dioctyl sodium sulfosuccinate (DOSS), and diluents, such as lactose or mannitol, are then spray dried to form a dry powder. The dry powder is then further processed by mixing with suitable required excipients and compressed to prepare solid oral drug products.

Nanoparticle naproxen ranging from 100 nm to 600 nm in size has been formulated as a tablet using suitable excipients like a filler (eg, lactose), binder (eg, L-HPC), lubricant (eg, magnesium stearate), etc.[25] The dissolution of naproxen from this new formulation was compared with tablets available as market products that were prepared from macro-sized naproxen (Aleve). For the dissolution study, the dissolution medium consisted of phosphate-buffer (pH 7.4) at 37ºC, the rotation speed of the paddle of the dissolution system was 50 rpm, and the detection wavelength was 332 nm. Dissolution of drug was found to be significantly higher from the nanoparticle formulation (64% to 92%) as compared to only 30% of drug release from the market product.

Intravenous Administration

One of the main applications of nanotechnology has been the formulation of pharmaceutical compositions that can be administered intravenously. For intravenous administration of a suspension, the particles in the suspension need to be less than 5 µm, which is the diameter of the smallest blood capillaries in the body. Intravenous administration of the nanosuspension may result in several advantages, such as the following:

- administration of poorly soluble drug without using higher concentration of toxic cosolvents,
- improving therapeutic effect of the drug available as a conventional oral formulation, and
- targeting drug to macrophages and the pathogenic microorganism residing in the macrophages.

Taxol, the market product of paclitaxel, contains Cremophor EL and ethanol (1:1) as the vehicle. The quantity of the Cremophor used in the formulation is higher than in any other formulation. This high concentration of the Cremophor has been attributed as the main cause of various side effects (eg, hypersensitivity reaction, nephrotoxicity, neurotoxicity, etc) associated with the intravenous administration of the Taxol.[26] In order to mitigate these adverse effects, Abraxane, a solvent free, intravenous formulation of paclitaxol, has been formulated using nanoparticles of paclitaxel. The particles in the size range of 20 nm to 400 nm present in the formulation are additionally coated with albumin, a biocompatible and biodegradable water-soluble polymer. The formulation, when administered intravenously to rats, resulted in higher level of concentrations of paclitaxel in the pancreas, kidneys, lungs, heart, bone, and spleen when compared to Taxol (market product of paclitaxel) at equivalent doses. More importantly, the new formulation was reported to be much safer than Taxol in the clinical studies.[27]

The nanoparticle technology is of tremendous help for poorly water-soluble drugs for conducting various screening studies at the preclinical stage. As the formulation does not contain any major cosolvent, results of such studies can be more precisely correlated with the candidate molecule. A preclinical study with a nanoparticle formulation of the tumor suppressor gene FUS1, a clinical development candidate of Introgen Therapeutics, Inc., has demonstrated that intravenous administration of FUS1 significantly suppressed tumor growth, inhibited metastasis, and prolonged survival in mice with metastatic lung cancer. Mice treated with INGN 401 survived almost 70% longer than untreated mice.

Injectable nanosuspension of the poorly soluble drug tarazepide has been prepared to overcome the limited success achieved using conventional solubilization techniques, such as the use of surfactants, cyclodextrins, etc to improve the bioavailability of the drug.[28] A stable intravenously injectable nanosuspension of omeprazole has been formulated to tackle the problem related to the acid degradation of orally administered omeprazole.[29]

Using nanosuspensions, it is possible to dose higher concentrations of drug with decreased adverse effects associated with the drug. A nanosuspension formulation of camptothecin, a camptotheca derivative,

containing particles in the size range of 20 nm to about 100 nm has been used for intravenous administration of larger doses of the drug as compared to existing methods of administration of the camptothecin analogs, allowing for higher blood levels of the therapeutic agent, yielding greater efficacy.[30]

The potential of nanosuspensions for targeting pathogenic microorganisms in macrophages has been demonstrated by Peters et al using clofazimine as the drug candidate.[31] Clofazimine nanosuspension was produced by homogenizing (APV Gaulin Micron LAB 40 homogenizer) a coarse aqueous dispersion of clofazimine containing stabilizing agents. The nanosuspension containing particles with mean size of 385 nm was administered intravenously to female C57BL/6 mice. Results of organ distribution of clofazimine after 2 hours of administration indicated the highest clofazimine concentration in the liver and spleen. The concentration in these organs was higher than MIC for *M. avium*. Further, the study also indicated that the tenedency of nanoparticle formulations to accumulate in the liver is higher than liposomal formulations, indicating better targeting potential of nanoparticle formulations as compared to liposomal formulations. Other intracellular pathogens that can be targeted using nanosuspensions of the drug are *Mycobacterium tuberculosis, Listeria monogyna, and Leishmania sp*.

CONCLUSION

Nanosuspension of pure drug offers a method to formulate difficult-to-dissolve drug and enhance the bioavailability of the poorly soluble and/or permeable drug. The method has many formulation and therapeutic advantages, such as a simple method of preparation, less requirement of formulation excipients, reduction in the toxicity of the candidate drug, significant increase in the bioavailability leading to decrease in the optimal dose, decreased fed-fasted variability, etc. The technology is gaining significance as the number of such problematic molecules are increasing, accompanied with a decrease in the number of new molecules with better therapeutic efficacy and rising cost of drug discovery. One of the pernicious problems in the pharma industry is life-cycle management of drug molecules nearing their patent expiry. Of the various measures currently being employed to achieve this life-cycle management goal, nanoparticle technology is one method that has already been used for the purpose. Recent launch of the TriCor tablet is one such example. Thus, naoparticle technology can play a major role in the successful development of a drug - from the initial stage of preclinical screening to the post market launch stage - as well as increase the life of the drug in market.

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BIOGRAPHY

Dr. Rajesh Dubey is currently working as an IP expert in Dr. Reddy's Laboratory, Hyderabad, India, where he is involved in the area of developing non-infringing formulation strategies. A PhD in Pharmaceutical Technology by qualification, he has more than 6 years of experience in academics, pharmaceutical industry, and project management. He has worked as a Senior Scientist (formulation development) in the area of conventional and controlled-release formulations. He has carried out extensive research in the area of particulate drug delivery systems, dissolution techniques, and solid oral dosage forms. His research works have been published in many international and national journals, including AAPS PharmSciTech, Drug Delivery Technology, Pharmaceutical Technology Europe, IJPS, etc. Dr. Dubey is also a life member of the Indian Pharmaceutical Association.

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EXTERNAL DELIVERY

Domestic Economic Terrorists

By: John A. Bermingham

Most of us learned in school the law of supply and demand. The law states that when the supply is high and demand is low, prices go down. And the inverse is that when supply is low and demand is high, prices go up. I get it. I remember really learning that law back in the early 1990s when my son wanted a Teenage Mutant Ninja Turtle doll for Christmas, Michelangelo to be exact.

I called our local Toys R Us and asked when the next shipment was scheduled in due to the doll being out of stock and back ordered everywhere. I arrived before the store opened on the appointed day, entered the store when it did open, and waited for the empty shelf to be restocked with Turtles. I was the only male of a group of about 15 people, all lying in wait. When the stock person brought out a large box of the high-demand Turtle dolls from the back of the store, he never made it to the display shelf. He and the box were attacked immediately with the box being ripped open by the others waiting with me. Cardboard was flying everywhere! I waited for the initial attack to subside and then eased in and rescued Michelangelo from the chaos.

Very high demand. Very low supply. Very very high price for Michelangelo at check out! So how is it then that, with oil inventories in the United States at their highest level in 8 years with demand rising at what could be considered a normal rate, crude oil just closed at $70 per barrel. In fact, May oil futures closed at $70.40 per barrel, and I expect over $71 per barrel shortly.

People smarter on these things than me (economists and analysts) say that high oil prices will cause a slowing of economic growth, which in turn will cause lower demand for oil, causing lower oil prices. They also say that another cause for the price run-up is investment flows into oil futures. Huh? So the only way to get oil prices down is to raise oil prices to the point of slowing the economy, lowering oil demand, and that will lower oil prices. Can you imagine presenting that as your hypothesis for an economics paper in price/demand ratios? In the mean time, the Mercantile Exchange boys and girls are betting that their investments in oil futures will continue to drive oil prices higher in, dare I say, collusion with Wall Street.

So my latest theory is that we are under attack by domestic economic terrorists. There are two groups of them: the oil company executive terrorists and the Wall Street/Mercantile Exchange terrorists. Much like the way the direction of the flow of the Chicago River was changed in the early 1900s, these guys have changed the supply/demand law that we have all known and loved for so many years.

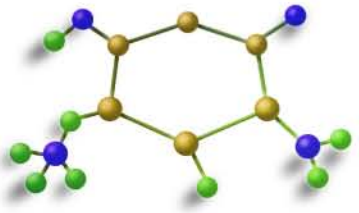
I agree that the soon to be higher price of gasoline will slow economic growth. When we are all looking at $3 to $4 per gallon of gas, you stop doing many things that you normally do. Like going to the mall, going out to dinner, going on vacation, not going anywhere but that where you must go to survive. Like to work, the doctor, and to the grocery store.

I remember talking to Lee Scott, the CEO of Wal-Mart, a while back and he told me that his number one concern was a $3 per gallon of gas. We may see $4 per gallon soon. Lee said that his customers would decrease their frequency of visits to Wal-Mart because of the gasoline cost, hence severely impacting Wal-Mart's cash flow. Lee is right, and what really concerns me is that the negative impact will not just be on Wal-Mart. It will be on all businesses, excepting of course the domestic terrorists' businesses. They'll be looking at record profits and record investment gains.

Now, I am not against the free enterprise system and fair competition. I am against executives, companies, and individuals gouging the people of this country on a necessity of life. I have heard all of the theories on why oil prices are continuing to escalate. Hurricanes, China, Iraq, Iran, Middle East unrest, Nigeria, India, OPEC, supply disruption, you name it. I view these as excuses with limited merit and little substance. Come on. Let's call a spade a spade. The reason all of this is happening is the domestic economic terrorists' quest for….$$$!

BIOGRAPHY

John A. Bermingham joined Ampad as President and CEO in August 2003 when Ampad was acquired by group of investors composed of an affiliate of Crescent Capital Investments, himself, and another private investor. He also serves as Chairman of the company's Board of Directors. Previously at the helm of numerous industry-leading companies, Mr. Bermingham brings more than 20 years' experience in guiding enterprises to new levels of performance. Most recently prior to joining Ampad, Mr. Bermingham held the positions of Chairman, President, and CEO of Centis, Inc., a diverse multinational manufacturer and marketer of office, storage, and human resources products. Prior to joining Centis, Mr. Bermingham successfully leveraged the potentials of two start-up companies, raising capital, forging key relationships, and establishing the structure and direction that would pave the way for future growth and achievement. Among his many career highlights in the role of President and CEO for companies serving the office products industry, Mr. Bermingham successfully reorganized Smith Corona Corporation, restoring the company's stability, profitability, and reputation. At Rolodex Corporation, he refocused operations and a strategic vision for a dramatic turnaround in corporate culture, and phenomenal increases in both revenue growth and cashflow. Mr. Bermingham's expertise in leveraging technology and optimizing resources for the business products/services markets has also been deployed at industry giants, such as AT&T Consumer Products Group, and by having served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served three years in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes. Earning a BA in Business Administration from Saint Leo University in Florida, Mr. Bermingham has also completed the Harvard University Graduate School of Business Advanced Management Program.



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