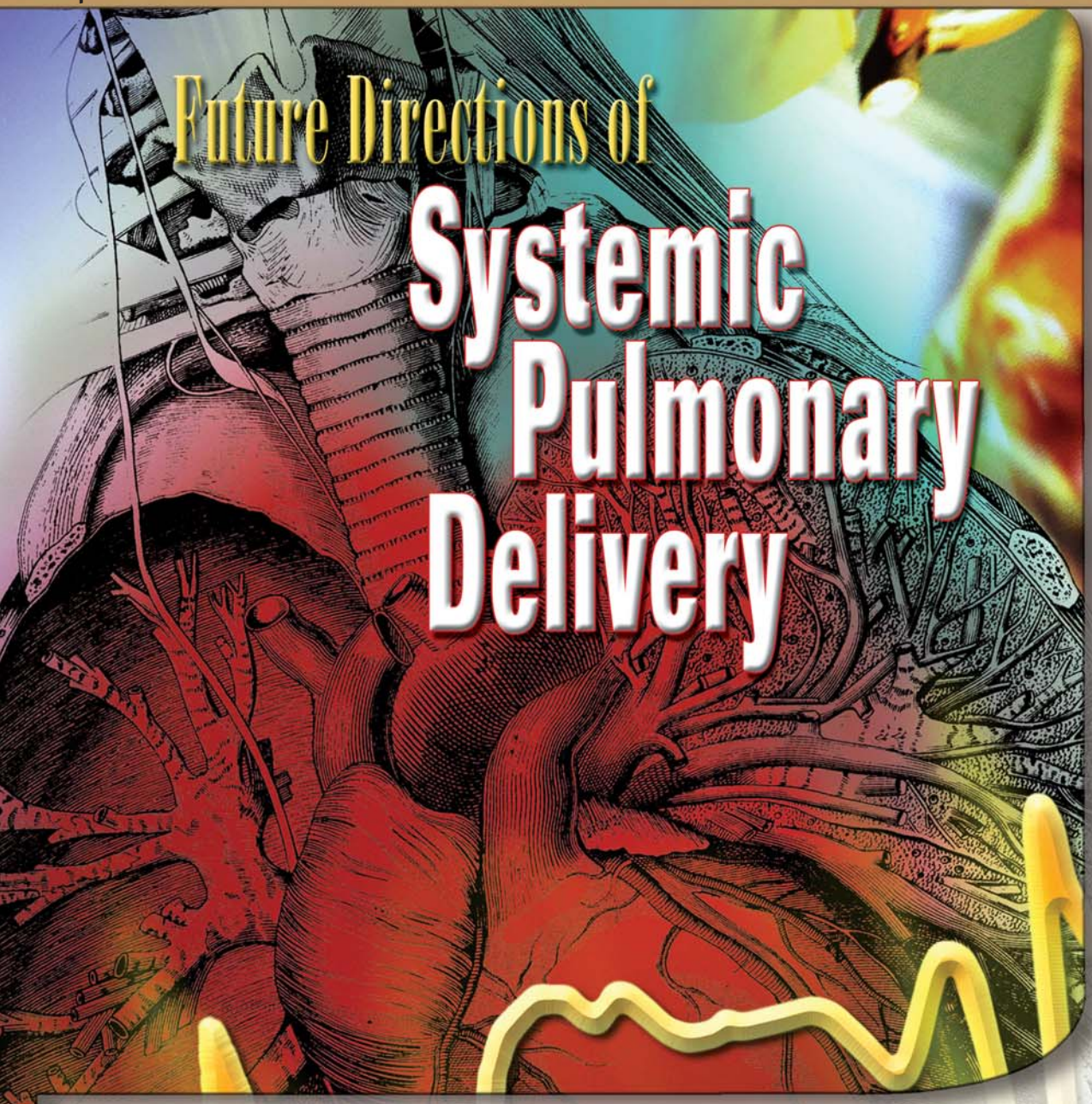
Drug Delivery Technology®

April 2006 Vol 6 No 4



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

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DR. ANDREW MUDDLE

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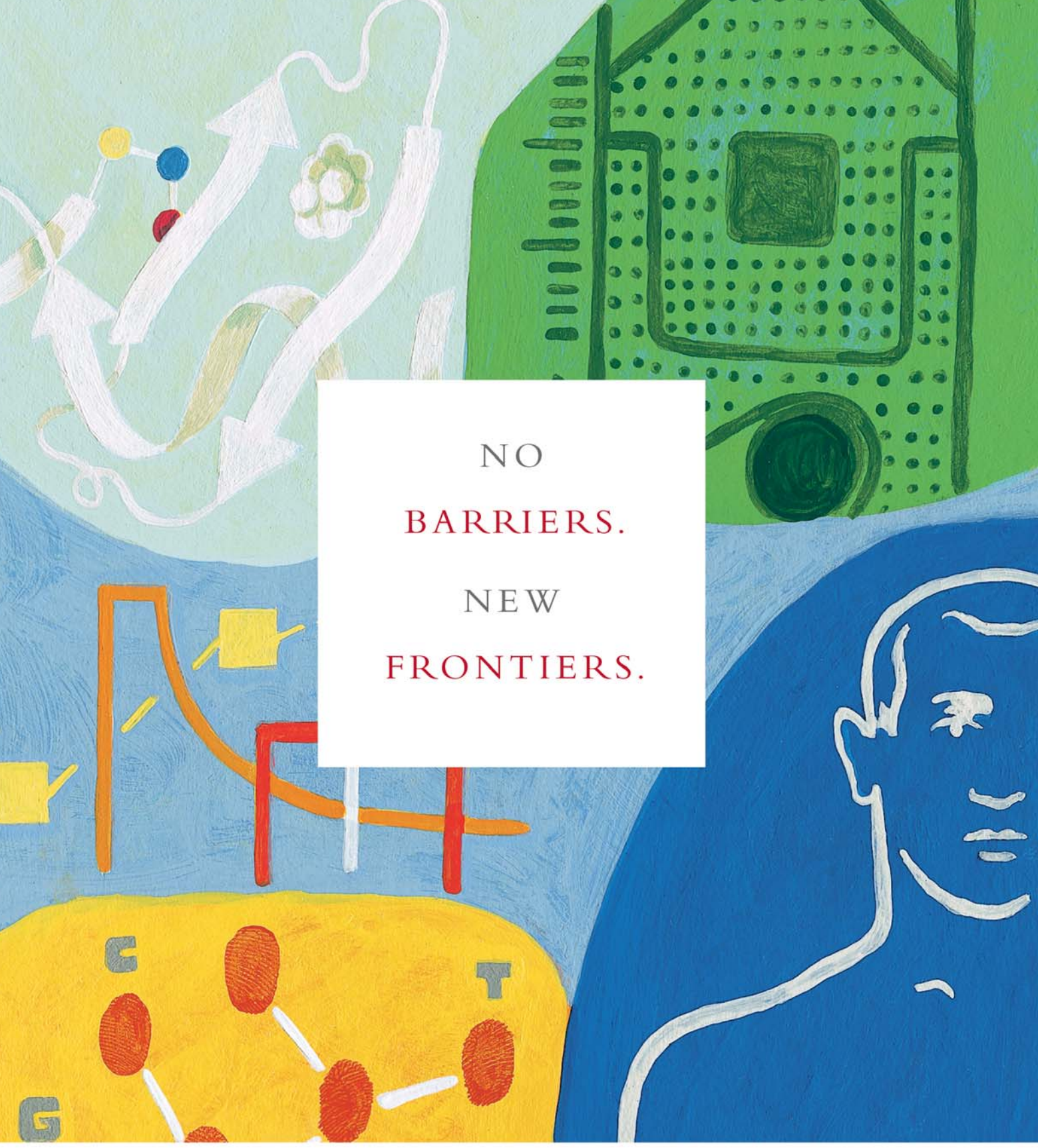

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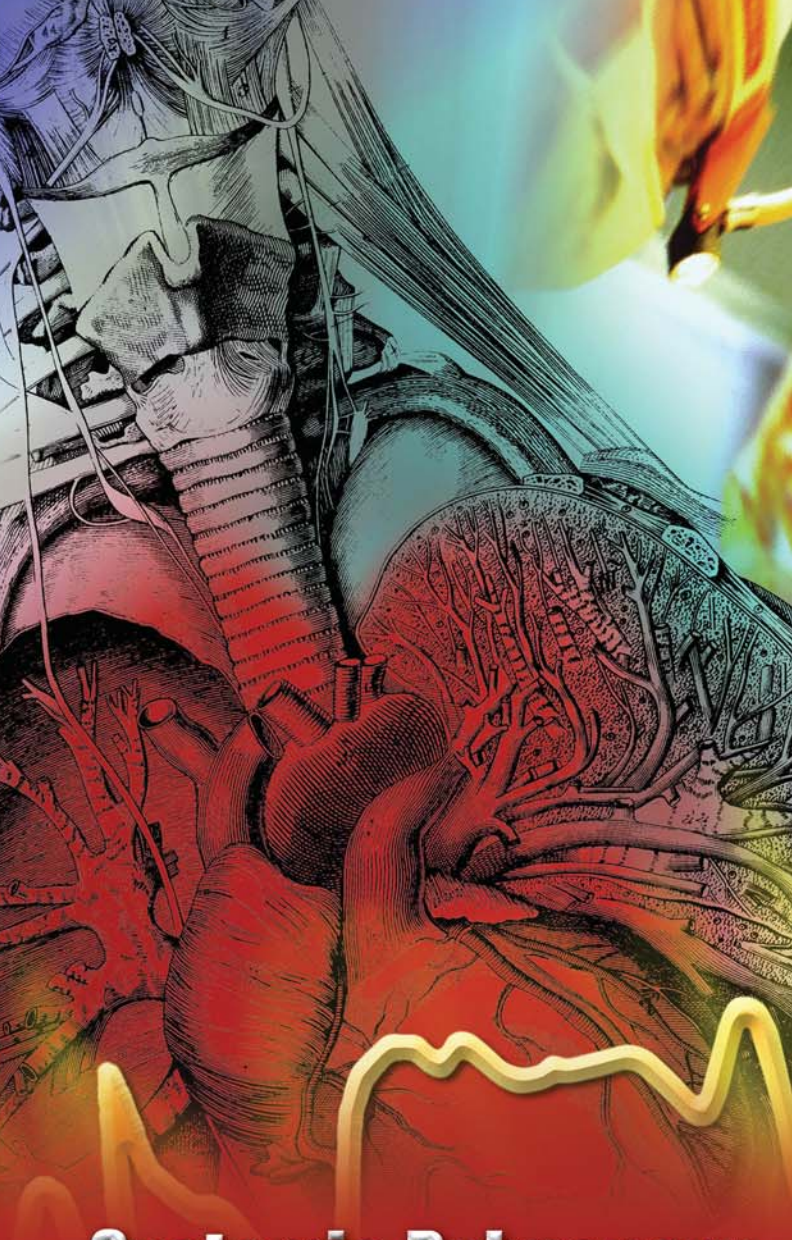

Systemic Pulmonary Delivery's Future

"Using the lung is a paradigm shift, and key to all of these new treatments will be the advantages (and disadvantages) of pulmonary delivery devices, such as safety, ease of use, consistent dosing, controllable dosing, lockouts, and monitoring capabilities."

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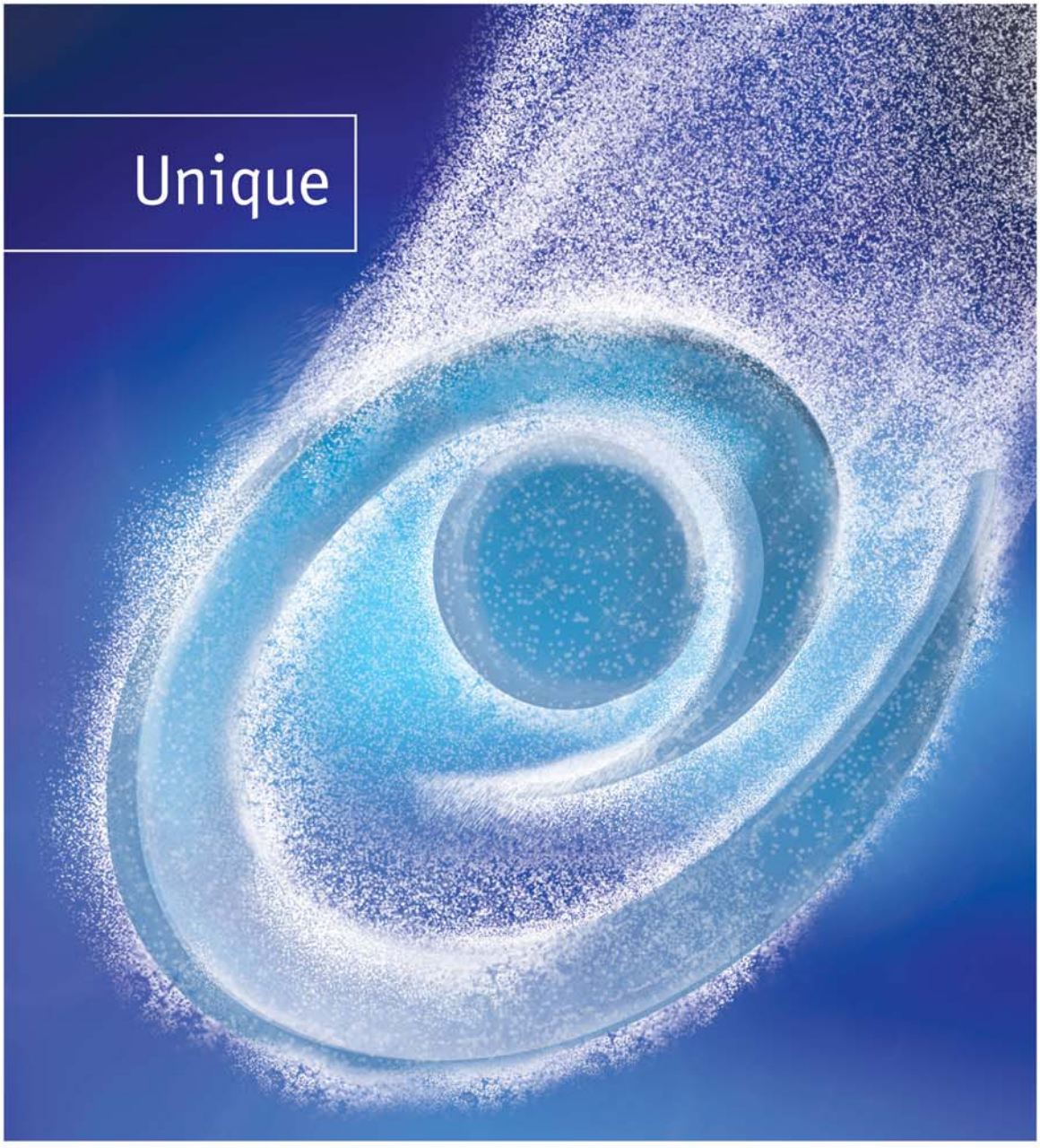

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Food-Formulation Concerns

"The food-formulation interactions, at a time, are spectacular but also problematic because the formulations will not be interchangeable. Nevertheless, formulation design based on food-formulation interaction is paramount to drug safety and efficacy."

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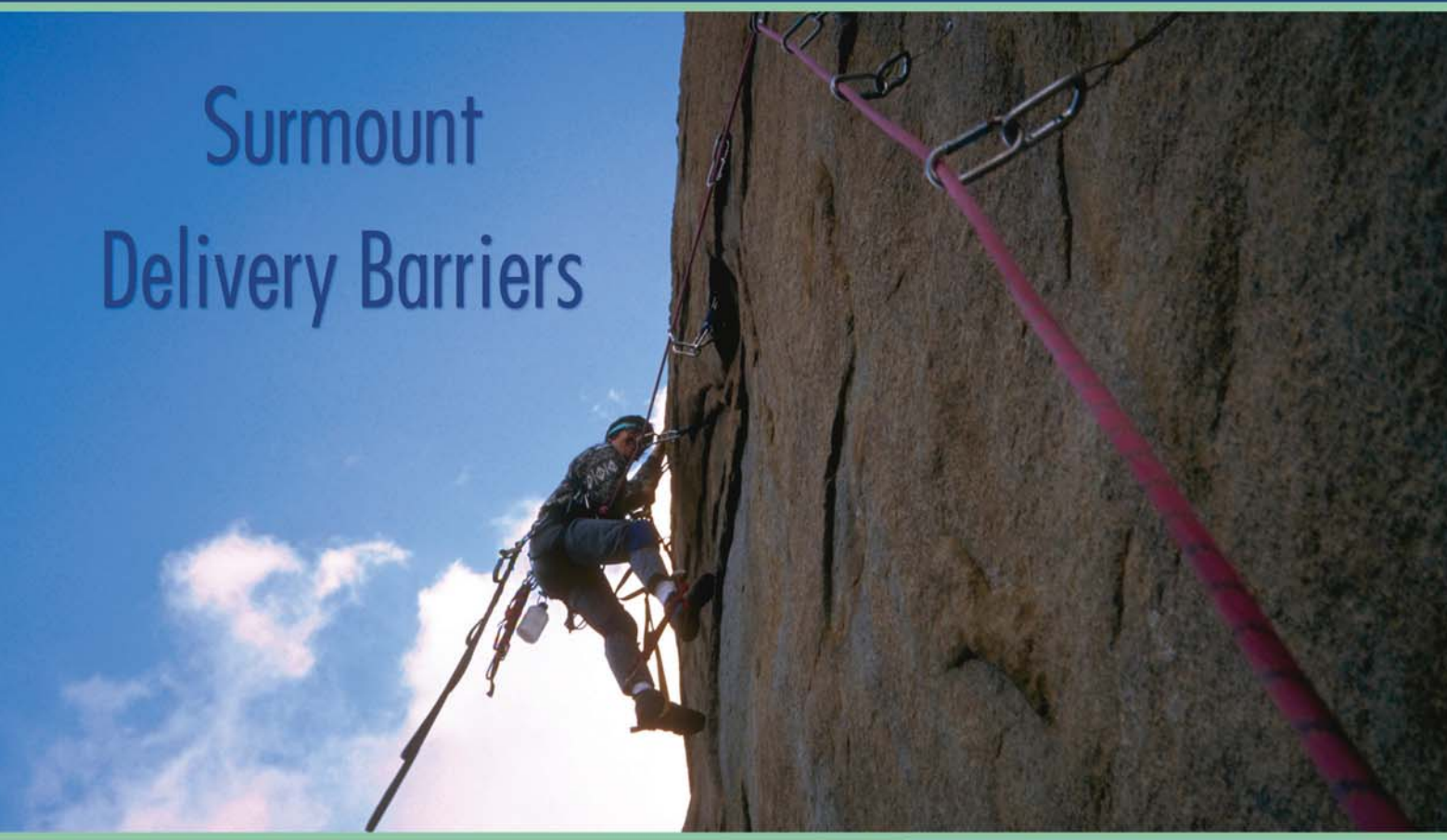

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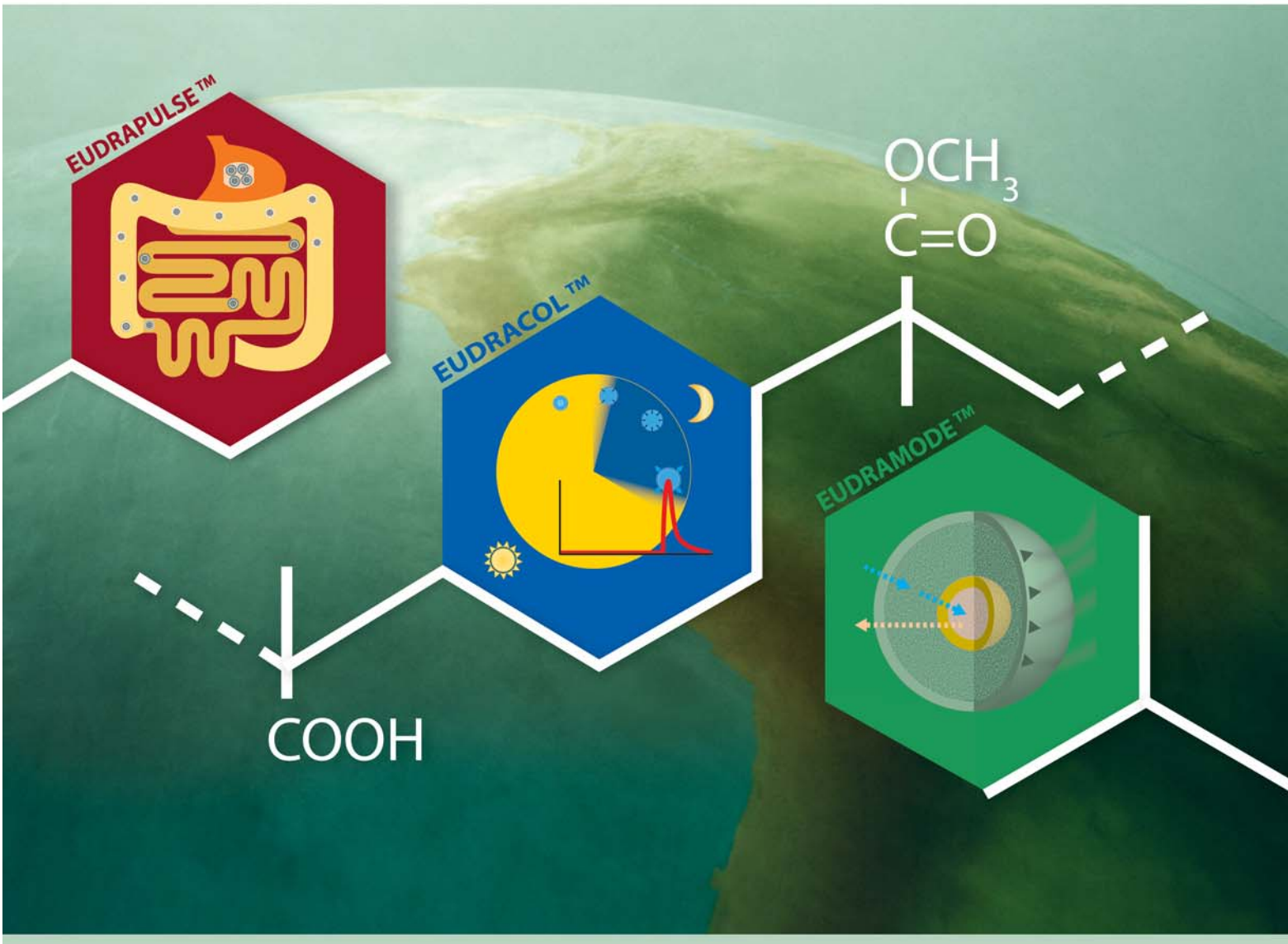

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MARKET NEWS and TRENDS

Nastech Presents Successful In Vitro & In Vivo Results With Its RNAi Therapeutics Program For Influenza; Announces Multi-Compound Agreement With Novo Nordisk

Nastech Pharmaceutical Company Inc., a leader in developing therapeutics using advanced molecular biology-based drug delivery technologies, recently announced the presentation of results demonstrating the effectiveness of the company's small interfering RNA (siRNA) therapeutics to broadly target and inhibit influenza viral production at the 8th International Symposium on Respiratory Viral Infections Conference.

In vitro and in vivo results were presented for siRNAs that are specifically designed to target conserved regions of the influenza viral genome. Nastech believes that targeting the conserved regions could enable an siRNA therapeutic to be effective against both current and future strains of the influenza virus, which is essential in stockpiling a treatment for rapid mobilization during an influenza pandemic. In vitro screening results identified highly potent siRNAs with IC50 values between 20 and 500 pM that were effective against representative human and avian influenza strains, including H5N1 avian influenza virus. Furthermore, in vivo results demonstrate that direct-to-lung and intravenous administrations of selected proprietary formulations of siRNAs effectively inhibit influenza viral production in a preclinical model. A 200-fold reduction of viral concentration in the blood was observed.

"Nastech's goal is to rapidly develop a safe and effective treatment that is broadly applicable against current and future influenza strains so that the medical community can be better prepared for an influenza pandemic, which has become an impending threat to worldwide public health," said Steven C. Quay, MD, PhD, Chairman, President, and CEO of Nastech. "The results presented by Nastech demonstrate the effective inhibition of influenza virus production by a siRNA therapeutic and further validate Nastech's advanced delivery technology and siRNA therapeutic development capabilities."

According to the World Health Organization (WHO), in a typical year, influenza infects 5% to 15% of the world's population, resulting in 250,000 to 500,000 deaths. The WHO and the Centers for Disease Control and Prevention are concerned about the potential for a major global pandemic, such as the 1918 Spanish Flu in which up to 50 million people may have died worldwide. Pandemic flu emerges from a sudden change in the influenza virus that results in a new flu strain, against which there is no immunity.

RNA interference, or RNAi, is a cellular mechanism that can be used to turn off the production of a protein. In the case of an RNAi directed against influenza, the target is one or more proteins critical for viral replication. By turning off the production of such proteins, the spread of infection is prevented or slowed. Nastech's RNAi research and development programs seek to develop safe and effective therapeutics by identifying key protein targets, designing the siRNA that will turn off the production of the targeted proteins, and developing a formulation for the systemic delivery of this potential new class of therapeutics.

Nastech also announced that it has entered into a multicompound, feasibility study agreement with Novo Nordisk A/S with respect to certain Novo Nordisk therapeutic compounds. Specific compounds and indications were not announced. Financial and other terms were not disclosed.

"Nastech is honored to be working with Novo Nordisk, a world-leader in therapies for metabolic disease. Novo Nordisk is known for its ethical standards and has participated in many innovative advances in medical practice," said Dr. Quay.

Generex Biotechnology Announces Additional Preliminary Results in a Trial of Generex Oral-lyn in Adolescent/Young Adult Patients With Type 1 Diabetes

Generex Biotechnology Corporation, a leader in the area of buccal drug delivery, recently announced additional preliminary results (10 weeks) of a long-term (6 month) clinical trial of Generex Oral-lyn, the company's proprietary oral insulin spray product, in adolescent and young adult patients with Type 1 diabetes mellitus. This data, which complements the positive data announced by the company on March 8, 2006, shows the variations of glycosylated hemoglobin (HbA1c), a very well-known marker for monitoring diabetes, during the first 10 weeks of the study.

Glycosylated hemoglobin (HbA1c) is considered by regulatory agencies and endocrinologists as the best long-term measure of metabolic control of diabetes.

"HbA1c correlates with the level of risk for diabetes complications," said Dr. Gerald Bernstein, the company's Vice-President for Medical Affairs. "The continuous and dramatic reduction seen in these preliminary results bode well for patients with diabetes, and society generally, in reducing the burdens of diabetes and its complications."

The investigators concluded that, during the first 10 weeks of this ongoing 6-month trial, replacement of subcutaneous injections of regular insulin by Generex Oral-lyn at lunchtime in adolescent and young adult patients with Type 1 diabetes was associated with overall adequate glycemic control and similar glycosylated hemoglobin (HbA1c) concentrations.

Generex is engaged in the research and development of drug delivery systems and technologies. Generex has developed a proprietary platform technology for the delivery of drugs into the human body through the oral cavity (with no deposit in the lungs). The company's proprietary liquid formulations allow drugs typically administered by injection to be absorbed into the body by the lining of the inner mouth using the company's proprietary RapidMist device. The company's flagship product, oral insulin (Oral-lyn), which has been approved for commercial sale in Ecuador for the treatment of patients with Type 1 and Type 2 diabetes, is in various stages of clinical trials around the world.

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Egalet Secures $27.6 Million Through International Financing Co-Led by Atlas Venture & Index Ventures

Egalet a/s, a drug delivery company focused on the development of oral controlled-release products, recently announced the successful closing of a $27.6 million financing in a private placement led jointly by new investors Atlas Venture and Index Ventures. Current investors, Bio Fund (Finland), Dansk Kapitalanlæg (Denmark), Danske Bank (Denmark) and QueQuoin Holdings Ltd. (New Jersey), also participated in the financing.

The proceeds from the offering will enable Egalet a/s to take its leading proprietary drug candidates in the therapeutic areas of heart diseases and pain management through final pivotal studies. Furthermore, the proceeds will be used to strengthen Egalet's product pipeline by leveraging its Egalet and Parvulet technologies. These formulation and controlled-release technologies offer a unique platform for the development of more advanced therapies for patients.

"Securing this major new funding and attracting leading international investors, such as Atlas and Index, demonstrates the significant opportunity inherent with Egalet. The support shown by our new and existing investors positions the company extremely well for future commercial success," said Jan Quistgaard, Chief Executive Officer of Egalet a/s.

"Egalet has been very successful in leveraging a pipeline of products from its technology platform. With two lead products in late clinical development and multiple future opportunities arising from its unique drug delivery technologies, Egalet is well positioned for its transformation to a product development and commercialization entity," added Dr. Regina Hodits of Atlas Venture.

"We are very excited about participating in this financing round. The company has made great strides in developing an attractive portfolio from their controlled-release technology. We believe this foundation will enable Egalet to evolve into a global player in the drug delivery sector," said Francesco de Rubertis of Index Ventures.

Concurrent with the closing of the financing, Seppo Mäkinen, Senior Partner, Bio Fund, was appointed Chairman of the Board of Directors. In addition, Dr. Hodits of Atlas Venture and Francesco de Rubertis of Index Ventures will take seats on the Board. Danske Markets Corporate Finance acted as financial adviser to Egalet a/s.

Egalet a/s is a drug delivery company focusing on formulation and development of oral controlled-release products using its proprietary drug delivery Egalet and Parvulet technologies. The company has four products in clinical development, two of which are entering into late-stage pivotal studies. The Egalet tablet incorporates almost any pharmaceutical into a polymeric matrix that is eroded by body fluids at a constant rate. The tablet is made by a simple, unique injection moulding technique, which breaks new ground because it can be used for virtually any type of medicine and provides controlled release with unusual precision and reliability. The Parvulet technology is a novel approach for pediatric drug delivery combining improved consumer acceptance with highly competitive development and production costs. The Parvulet technology is dispensed as a dry powder or tablet that, upon exposure to a small amount of water, turns into a tasty soft mass in seconds. Any undesired taste of medicine is completely avoided and so repeat dosing becomes less of an issue for the child.

Egalet aims to become a preferred partner for the pharmaceutical industry with its strategy for controlling drug development efforts from product formulation to clinical testing, regulatory submissions, and manufacturing. The company is based in Copenhagen, Denmark.

Emisphere Technologies Announces Oral PTH License Agreement

Emisphere Technologies, Inc., recently announced that Novartis has executed its license option for the development and commercialization of an oral parathyroid hormone (PTH) using Emisphere's eligen delivery technology. Emisphere is eligible for milestone payments totaling up to a maximum of $30 million, plus royalties on sales of the product.

"We are very pleased that Novartis has indeed elected to execute its option to develop oral dosage forms of PTH using our technology," said Michael M. Goldberg, MD, Chairman, and Chief Executive Officer of Emisphere. "The overwhelmingly favorable decision by the court in our litigation with Lilly will now mean that this product can at last move forward with a committed and capable partner."

This license agreement marks the third between the two companies: In 2000, Emisphere and Novartis entered into a license agreement for the development of oral salmon calcitonin, and a second agreement followed in 2004, for the development of oral human growth hormone.

The decision to execute the license follows the January 6, 2006, US Federal Court decision in Indianapolis favoring Emisphere in its litigation with Eli Lilly and Company. The Court agreed with Emisphere that Lilly had indeed breached the agreement in multiple areas and that the PTH agreement between Lilly and Emisphere was indeed terminated. In exchange for the option right, Emisphere received from Novartis in 2004, $10 million in the form of a convertible note. Repayment can be in cash or stock, at Emisphere's option. The stock price will be set at the time of conversion.

PTH1-34 is a fragment of the naturally occurring human parathyroid hormone that is an important regulator of calcium and phosphorus metabolism. When given by daily injection, PTH1-34 has been shown to increase bone mineral density and significantly reduce both vertebral and non-vertebral fractures in postmenopausal women. For example, subcutaneous PTH1-34 given with calcium and vitamin D reduced the risk of vertebral fractures by 65% compared to calcium and vitamin D alone. With respect to bone mineral density (BMD), daily subcutaneous PTH1-34 produced a 12% increase in lumbar spine BMD after 18 months of treatment. Studies will investigate whether the nasal formulation will produce the same results. Daily injections of PTH1-34 are approved for the treatment of postmenopausal osteoporosis. Osteoporosis is a major public health issue. According to the National Osteoporosis Foundation, 10 million Americans suffer from osteoporosis, with an associated annual national health expenditure of more than $17 billion.

Kurve Technology Signs Agreement With Schering-Plough Corporation

Kurve Technology, Inc., a leader in nasal drug delivery devices, recently announced it has entered into an agreement with Schering-Plough Corporation.

"We are delighted to partner with a global pharmaceutical leader," said Marc Giroux, Chairman and Chief Executive Officer of Kurve Technology, Inc. "The value of our Controlled Particle Dispersion™ technology platform and ViaNase™ device line continues to grow, and we are excited about working with the team at Schering-Plough."

Incorporating patented Controlled Particle Dispersion and intelligent nasal drug delivery technologies, Kurve Technology'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 potential delivery to the paranasal sinuses. In addition, ViaNase limits peripheral deposition of pharmaceutical formulations into the lungs or stomach. Kurve Technology'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.

Kurve Technology, Inc., offers pharmaceutical companies innovative nasal delivery systems for local and systemic medical therapies. Kurve's Controlled Particle Dispersion (CPD) technology intranasally delivers formulations with far greater efficacy and efficiency than traditional methods. The ViaNase product line of intelligent atomizers incorporates CPD to deliver a wide range of compounds, aiding the more than 200 million patients who suffer from such medical conditions as allergic rhinitis, chronic rhinosinusitis, sexual dysfunction, migraine headache, obesity, and CNS disease. Kurve Technology is headquartered in Bothell, Washington, with an office in Research Triangle Park, North Carolina.

MARKET NEWS and TRENDS

TransPharma-Medical Reports Promising Clinical Trial Results of its hPTH (1-34) Transdermal Delivery Product for Osteoporosis

TransPharma-Medical Ltd., the Israeli-based specialty pharma company that develops pharmaceutical products based on its unique RF-MicroChannels transdermal drug delivery technology, recently announced promising results of its first human clinical trials demonstrating transdermal delivery of human Parathyroid Hormone 1-34 fragment, (hPTH 1-34) for the treatment of osteoporosis.

The results of the study prove systemic delivery of therapeutic dosages of bioactive hPTH (1-34) with relative bioavailability in comparison to subcutaneous administration of over 50%. These results show the ability to deliver the required hPTH (1-34) dose via TransPharma's pen-size system incorporating a $1cm^2$-small patch.

The patch utilized in the study is TransPharma's proprietary dry protein patch developed particularly for the ViaDerm system. Scientists at TransPharma have formulated hPTH (1-34) into a stable printed dry-form patch that allows for the hPTH (1-34) to deliver into the patients' systemic circulation with a peak blood profile. Analysis of two biomarkers (ionized calcium and phosphorus) confirmed that the bioactivity of the delivered hormone was fully maintained.

The ViaDerm delivery system incorporates a device, which creates microscopic passageways through the outer layer of the skin allowing for therapeutic administration of a wide variety of drugs from a patch. This device, designed to deliver the Teriparatide, is a hand-held pen-size unit, which provides a painless, very low-cost, easy-to-use application.

"The results of this trial demonstrate TransPharma's ability to deliver transdermally a state-of-the-art peptide molecule for osteoporosis treatment with our proven ViaDerm delivery system, thus improving patients' quality of life," said Dr. Daphna Heffetz, CEO of TransPharma.

Throughout the next 5 years, the osteoporosis population is xpected to reach 52 million, with an anticipated market potential of $10.4 billion by 2011. The hPTH (1-34), which is the only anabolic (capable of bone building) osteoporosis drug molecule is currently being administered by injection only and is expected to reach $3 billion in sales by 2010. The osteoporosis market is underserved and is open for emerging products to provide better efficacy and more patient-friendly administration routes.

Dr. Heffetz believes that the the very high bioavailability of the drug together with a low-cost system has great potential to lead to extremely high gross margins when the product reaches the market.

Currently, TransPharma plans to continue the development of hPTH (1-34) to late-stage clinical trials when it plans to strategically ally with a major pharmaceutical company that can bring the product to the market. Parallel to its own development pipeline, TransPharma plans to continuously develop products in collaboration with other companies similar to the collaboration agreement it signed with TEVA Pharmaceuticals in 2004.

Watson Pharmaceuticals to Buy Andrx Corporation for $1.9 Billion

Watson Pharmaceuticals, Inc., recently announced a definitive merger agreement to acquire all outstanding shares of common stock of Andrx Corporation in an all-cash transaction for $25 per share, or a total price of approximately $1.9 billion. Andrx, whose capabilities complement those of Watson, is considered a leader in formulating difficult-to-replicate products and developing best-in-class drug delivery technologies, offering a unique portfolio of difficult-to-replicate generic products.

The transaction will be financed with Watson cash reserves, and committed bank financing, net of cash acquired from Andrx. The deal is expected to be accretive to 2007 earnings with estimated 2007 revenues of $2.8 billion, based on historical revenues. Watson will become the third largest generic pharmaceutical company in the US, based on prescriptions dispensed. Watson also expects savings from synergies in the first year post-closing, largely from reduced selling, general, and administrative expenses. The Boards of Directors of both companies have approved the transaction. The consummation of the acquisition is subject to customary closing conditions, including approval of the transaction by Andrx stockholders and the receipt of applicable US regulatory approvals. The transaction is expected to close within 6 months. Following the close of the transaction, the combined company will have more than 60 ANDAs in its pipeline, creating opportunities for growth in future years.

"Our acquisition of Andrx significantly supports our long-term goal of expanding our existing product portfolio and pipeline, while strengthening Watson's position in high value, specialized sustained-release technology," said Dr. Allen Chao, Watson's Chairman and Chief Executive Officer. "The combined revenue stream will fuel further product development and sales, while allowing Watson the flexibility and financial resources to continue building its brand and generic businesses through internal product development and product in-licensing."

Thomas P. Rice, Andrx's Chief Executive Officer commented on the opportunity presented by the agreement. "This transaction provides excellent value to our shareholders while also opening new business avenues for Andrx in terms of geography, product offerings, and technologies. The combined assets, product portfolio, and capabilities of the two companies position us strongly for the highly competitive pharmaceutical market. Andrx's manufacturing, R&D, controlled-release technology, distribution network, and employees, in combination with Watson's excellent team and capabilities, create a significant vertically integrated company in the specialty pharmaceutical industry."

Following the close of the transaction, Watson will have three operating divisions: Brands, Generics, and Distribution. Anda, Andrx's generic distribution business, will operate and be managed as an independent division offering quality generic products from manufacturers around the world and providing excellent service to valued customers.

Watson Pharmaceuticals, Inc., headquartered in Corona, California, is a leading specialty pharmaceutical company that develops, manufactures, markets, and distributes branded and generic pharmaceutical products. Watson pursues a growth strategy combining internal product development, strategic alliances and collaborations, and synergistic acquisitions of products and businesses.

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Genzyme Pharmaceuticals

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

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

BIOGRAPHIES

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.

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.

"The art of life lies in the constant readjustment to our surroundings." -Kakuzo Okakura (1862-1913)

Readjustment to our surroundings. I believe this message holds special meaning for many of the drug delivery companies in attendance at last January's IIR Drug Delivery Partnerships conference in Phoenix, Arizona. Speaker after speaker echoed similar taglines: "The industry is in transition." "Capital markets are placing increasingly greater value on products." "For small companies considering exit strategies, both IPO and acquisition valuations are driven by (no surprise here) products." OK then, so, how has this affected pure-play drug delivery technology companies?

For starters, it appears that more and more of the key players are beginning to incorporate internal product development into their corporate strategy. A quick poll of the audience showed that only a few of the companies in attendance still identified themselves as drug delivery pure-plays. Most associated themselves as either a specialty pharmaceutical company or transitioning toward this model. And who could blame them? Unless financial security can be achieved by other means, such as contract manufacturing or development services, small companies are at the mercy of the capital market conditions.

Given this backdrop, the subject of this two-part series on the topic of *Sourcing a Specialty Pharmaceutical Pipeline* is timely. This first installment addresses the need for a clear strategy and business process for setting a portfolio and sourcing a strategy. While these principles are applicable to larger companies, this column is specifically targeted to companies with novel drug delivery technologies that are wrestling with many of the critical issues related to making the transition to specialty pharmaceuticals. The second article in this series will address the tactical process of sourcing and ultimately vetting product opportunities and should help answer such questions as 1) Where do we find innovative product opportunities? and 2) How do we screen the pool of opportunities to select only the best?

Working in tandem, these two elements (one strategic and one tactical) provide the basic foundation for solid pipeline development. The information will provide a high-level framework, which companies can use to address these questions and many others along the way.

FOCUS ON STRATEGY FIRST

"Obstacles are those frightful things you see when you take your eyes off your goal." - Henry Ford (1863-1947)

Small companies transitioning to specialty pharmaceuticals face numerous strategic challenges in balancing extreme financial, technical, and development risks. From a pipeline perspective, you may ask the following:

- In what therapeutic area(s): commercial, regulatory, or geographic market niches should we compete?
- How many product opportunities can we effectively balance?
- How do we prioritize our opportunities to ensure the best are selected and true value is realized from the next tier?
- Should we partner our products? If so, which ones and when?

The key to meeting the pipeline sourcing challenge is to begin by first setting a clear strategic direction, which includes answering the aforementioned questions. We are often asked by clients to help them identify novel product concepts for their technologies. In doing so, only a few enter the process with a clearly defined vision of what opportunities would ultimately be viable. Answering these aforementioned questions will allow your company's resources to focus on specific opportunities that best match its technical capabilities, competitive positioning, and overall business strategy.

To illustrate this point of strategy, I'd like to first relate a quick anecdote excerpted from Lewis Carroll's *Alice's Adventures in Wonderland*. This example has been the subject of numerous management strategy discussions of late, and I believe it is equally applicable to pipeline sourcing. In the story, Alice and the Cheshire cat had the following conversation:

"Would you tell me, please, which way I ought to go from here?" asked Alice. "That depends a good deal on where you want to get to," said the Cat. "I don't much care where… so long as I get SOMEWHERE," Alice added. "Oh, you're sure to do that," said the Cat, "if you only walk long enough."

To paraphrase, if you don't know where you're going, then any road will take you there. Without a clear vision, your business development and scientific resources will be spread too thin scouring the globe for opportunities, chasing butterflies, and likely polishing their resumes in frustration. On the flip side, constant focus on the goal removes distracting obstacles, allowing your great people to do even greater things.

A PORTFOLIO MANAGEMENT PROCESS

If we buy in to the strategy first approach, then the next pressing question is how do we best accomplish this goal? Building on substantial lessons learned in the Big Pharma industry, I believe this is best accomplished via an internal management decision-making infrastructure charged with managing portfolio strategy and prioritization of opportunities.

Large pharmaceutical and device companies typically use structured portfolio management processes to manage go/no-go decisions and resource trade-offs and priorities among their pipeline products. This process generally includes the following key elements:

- A cross-divisional decision-making body of senior executives who are responsible for aligning strategy and making go/no-go decisions;
- Clear criteria for prioritizing pipeline opportunities and making go/no-go decisions;
- A single point person responsible for driving the process (eg, channeling opportunities, improving the process, and driving results);
- A defined process for product development and opportunity evaluation to drive progress and ensure informed decision-making; and
- Metrics for measuring success and determining areas for improvement.

While often seen as bureaucratic, these "stage-review" or similarly designed portfolio processes are essential for managing resources and the complexities surrounding the development risks of multiple pipeline products. Their philosophy is to "kill" troubled products quickly, providing more resources to apply to higher potential products, and spreading the risk over a larger product pool.

Drug delivery companies in transition would similarly benefit from a clearly defined portfolio process. The reason that this is so beneficial is that it forces management to make the tough strategic decisions that are necessary to focus the company resources on the right product opportunities. A tiered list of opportunities also helps provide a clear path forward in the event of pipeline product failures. Partners, investors, and employees will all appreciate the clarity this process brings.

Some might argue that many technology companies are too small to benefit from the portfolio view; after all, do one to three pipeline products represent a truly diverse "portfolio" in the true sense? On the contrary, while the number of products in the portfolio may be small, it is the aggregate number of resource-diverting opportunities that must also be managed. Small companies cannot afford to waste business, scientific, or financial resources on mediocre opportunities. They cannot source their pipeline by searching for the "needle-in-a-haystack." Nor can they afford to be caught without a clear risk-mitigation plan in the event that a key pipeline product fails. The fact that both human and financial resources are limited in small companies makes prioritization of opportunities an even more critical goal.

SUMMING IT UP

The good news is that the "start with strategy" and "portfolio management approach" I suggest in this column is a tried-and-true process with complexity that is ultimately under your control. A small company portfolio process need not be bureaucratic. Nor is it particularly difficult to design and implement under experienced guidance. It simply needs to be systematic, clear, and fast. So never fear the readjustments and transitions! Simply set strategy first, promote the infrastructure for success… and then follow the advice of childhood author, Dr. Suess, who said "Today is your day! Your mountain is waiting, so… get on your way!"♦

The Next Big Inventor

By: Patricia D. Granados, Attorney

BIOGRAPHY

Patricia Donovan Granados is a Shareholder at Heller Ehrman LLP, and is a member of the Patents & Trademarks practice group and the Life Sciences & Technology practice group, in which she works closely with FDA attorneys. As an intellectual property practitioner, she counsels clients in pharmaceutical and biotechnology patent-related matters, including patent prosecution, freedom to operate and infringement opinions, interferences, and litigation worldwide. She also assists clients with licensing and other technology transfer-related activities. She is a member of the Licensing Executives Society and Association of University Technology Managers. Ms. Granados earned her BA in Biology from Boston University, her MS from Johns Hopkins University, and her JD from the University of Maryland. She served as Law Clerk to the Honorable Philip B. Baldwin on the U.S. Court of Appeals for the Federal Circuit. Prior to attending law school, she spent several years in pathology research at Johns Hopkins Medical Institutions.

Reality television shows have covered everything from dancing competitions to worm eating. Now, two different networks have shows about inventors and inventions, Made In USA (USA) and American Inventor (ABC). The race is on: who is going to be the next big inventor? But don't expect the competing inventions in either show to involve new formulations for treating irritable bowel syndrome. No, the inventions are more in the line of simple consumer products, like salt shakers that can be located with a beeper or ladders that can fold into a hand bag — the kind of things you can sell on TV, of course. It all seems straightforward enough: competing groups of people have good, useful ideas, and someone is willing to buy the best idea, manufacture it, and sell it. The best idea is the one that will sell the most. It's all so entertaining.

Patent lawyers already know how entertaining inventorship issues are. This is particularly true in the United States where the first-to-invent, rather than the first-to-file a patent application, gets the patent. Competitions to determine who invented something first, called "interferences," can come as a complete surprise to a US patent applicant or US patent owner. One day, after a lengthy and seemingly successful prosecution, a patent applicant receives an action from the patent Examiner stating that all prosecution is suspended pending the declaration of an interference. Or, in the midst of celebrating a long-awaited and hard-earned Letters Patent, a patent owner receives a notice that it is now a party to an interference and needs to get a lawyer quickly. On the other hand, the interference may not be a surprise to one of the parties. The US Patent and Trademark Office (USPTO) has rules that dictate how an applicant can "provoke" an interference, if one is warranted.

Although the rules governing interferences are complicated, the basic idea is that two different entities present the same invention to the USPTO at the same time. The Board of Patent Appeals and Interferences decides which entity invented the common invention first, and that party wins the interference. However, at one stage of the proceedings, both parties have an opportunity to destroy or limit the other party's patent or application for reasons unrelated to who invented first. At this stage, one party might argue that the other party should never have gotten its patent in the first place for a variety of reasons. It might argue that the other party didn't have data to show that the claimed drug formulation works; that the claims are too broad; or that the invention is only one species, not the whole genus of compounds. Alternatively, one party may voluntarily surrender subject matter that overlaps with the other party's invention to pursue an invention that doesn't overlap and is patentable over the common invention. The idea is that if the inventions don't overlap, there is no basis for an interference. The goal might be to get just what one needs and walk away as quickly and cheaply as possible. Another option is to argue that neither party should have a patent because the invention is already in the public domain. This last option might appeal to the party that knows it would lose anyway and doesn't want to be dominated by the winner. Strategies vary with the facts of each case and the business objectives of the parties. Because interferences are complicated and therefore expensive and time-consuming, many parties are motivated to settle as early as possible.

In order to understand how the priority of invention contest part of an interference works, one needs to understand what it legally means to have invented something or better yet, how to prove it. In sharp contrast to the happy scenario on the TV invention reality

shows, pinning down who invented what, when, and where is one of the most difficult exercises there is for a patent attorney. Start with this type of judicial guidance:

"…the man who first reduced an invention to practice is prima facie the first and true inventor but that the man who first conceives, and, in a mental sense, first invents a machine art, or composition of matter, may date his patentable invention back to the time of its conception, if he connects the conception with its reduction to practice by reasonable diligence on his part, so that they are substantially one continuous act."[1]

Although this confusing quote is an excerpt from an 1893 case, it is still the law applied today in determining which inventor invented first.[2] Clearly, there is more than one concept to understand in order to apply this law. An invention is a "conception" and a "reduction to practice" of an idea. The party who wins the contest is the first one to reduce to practice the invention, unless the other party conceived the invention first and then diligently worked toward reducing the invention to practice. The legal meaning of "conception" is the mental formation of a definite and permanent idea of the complete and operative invention as it is applied in practice.[3] An invention is "complete" when all that would be necessary to reduce to practice the invention would be ordinary skill without extensive research or experimentation.[4] "Reduction to practice," is the act of showing that the invention will work as intended; if the inventor never got around to proving that something actually worked, the filing of a patent application is a constructive reduction to practice,[5] which is as good as an actual reduction to practice under US law.[5] "Diligence" means continuous activity toward reducing to practice the invention. Case law on diligence indicates that although it is not necessary to show daily activity toward the invention, there should be good excuses for any lapses in activity.[6]

And if understanding all of the aforementioned were not fun enough, once the concepts are clearly understood and corresponding milestones recognized, the next hurdle is to find evidence in the record that supports such milestones. Generally, evidence must be corroborated, although the nature and sufficiency of such corroboration varies depending upon the purpose of the evidence and the particular facts of the case.[7]

Interferences are not the only place where inventorship issues entertain patent attorneys. Disputes arise about the listing of inventors. Many people can contribute to an invention but not everyone is necessarily an inventor. Inventors must contribute to the conception of the invention, not just the testing or making of it. Contributors who believe they should have been listed as inventors can and do go to court. In a recent case, *Stern v. The Trustees of Columbia University*, (Slip op. 05-1291) (Fed. Cir. January 17, 2006), the Federal Circuit considered whether a medical student should have been named a co-inventor on a patent for a method of treating hypertension and glaucoma. The medical student believed that his experiments showing that topical application of a single dose of prostaglandin reduced intraocular pressure in a rhesus monkey rendered him a co-inventor. He also argued that his notebooks, that had been destroyed by the listed inventor, would have proven his claim to inventorship. The court disagreed. It noted that the medical student simply carried out an experiment previously done on a different animal by the named inventor. And, because the medical student's notebooks had not been witnessed, the notebook entries were uncorroborated and therefore would have been insufficient to support his claim anyway.

The lesson here is that it is important to get inventorship right for a variety of reasons and it is equally important to be able to prove it is right. A patent that lists improper inventors is invalid. Although it is possible to correct inventorship if someone is mistakenly included or excluded as an inventor, it is fraud on the USPTO to deliberately list the wrong inventors and fraud renders a patent unenforceable.

In the pharmaceutical and drug delivery industries, interferences are not uncommon, as patent fields are very crowded. Also, claims to inventorship rights are always more likely when there is commercial product involved. Finally, any business that relies on collaborations for creating or testing drugs has to be careful about inventorship issues. Collaborations may be very efficient and may spawn great ideas, but they also spawn hotly contested inventorship disputes. Consequently, every institution should have a reliable system for recording ideas and all the work related to such ideas. It is equally important that witnesses be a part of such system. The stakes are high, and the reality is that there is usually only one winner. It's not a game you want to lose.♦

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Preformulation & Dosage Form Selection: Choose Wisely!

By: Contributor Cindy H. Dubin

One of the early areas of focus in development is directed toward transforming the pure drug substance into a reproducible dosage form that can be safely and effectively administered to humans in a clinical trial, says John D. Higgins III, Research Leader, and William L. Rocco, Senior Research Investigator at Sanofi-Synthelabo Research.[1] According to the researchers, up until the 1960s, new drug substances were formulated by pharmaceutical scientists into seemingly good dosage forms, which often turned out to degrade chemically during storage. Surprises regarding changes in the drug's solid-state form (polymorphism) and subtle changes in physical form often led to serious issues regarding bioavailability and stability. It became apparent that considerable investigation was required before the formulation of the clinical dosage form to identify key problems. This early drug substance and dosage form characterization work became known as preformulation.

Preformulation is a branch of pharmaceutical sciences that utilizes biopharmaceutical principles to determine the physico-chemical properties of a drug substance. The goals of preformulation studies are to choose the correct form of your drug substance, evaluate its physical properties, and generate a thorough understanding of the material's stability under various conditions, leading to the optimal drug delivery system. Pharmaceutical preformulation studies need to be performed routinely to establish which dosage form suits the drug substance.

According to Harry G. Brittain at the Center for Pharmaceutical Physics in Milford, NJ, an adequate formulation can only be developed by fully understanding the physical and chemical properties of the drug substance. Considering the physico-chemical characteristics of the active in relation to the proposed dosage form and route of administration is an essential element of preformulation.

"I am often surprised when drug developers skip preformulation studies and rely on expensive trial-and-error to create effective, stable dosage forms," said Gordon Marr, Principal Scientist, Analytical and Preformulation Services at MDS Pharma Services. "It really is a simple, pay-a-little-now-or-a-lot-later type of decision and yet, many dosage form development companies just don't realize how much strategic information can be gained prior to formulation. Hence, they end up paying much more due to reformulation, process changes and stability failures, while extending the time required to obtain regulatory approval."

Examples of physical characteristics that may need to be examined include solubility, water content, particle size, crystal properties, etc. Solubility can affect the choice of formulation and the choice of analytical method; water content can affect crystal properties and particle size, as well as influence stability; particle size can affect bioavailability, content uniformity, suspension properties, solubility and stability; and crystal properties may affect solubility, bioavailability, or stability.

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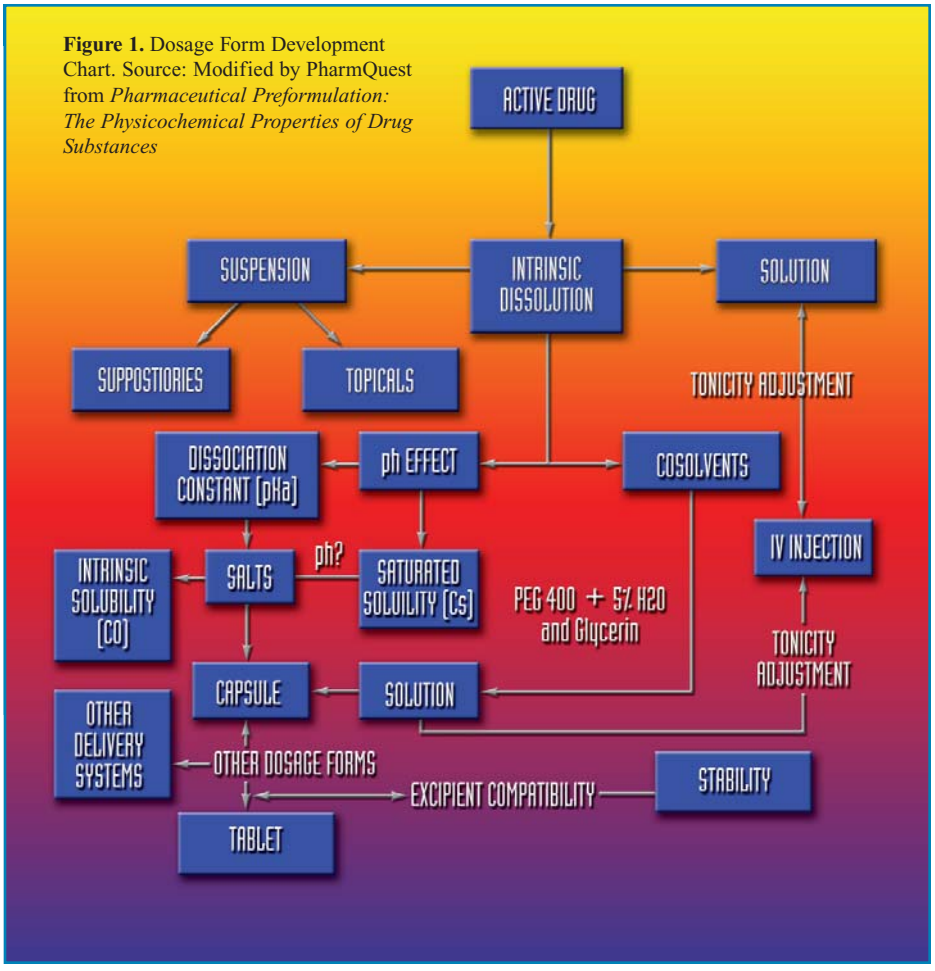


Figure 1. Dosage Form Development Chart. Source: Modified by PharmQuest from *Pharmaceutical Preformulation: The Physicochemical Properties of Drug Substances*

DOSAGE FORMS

Obviously, there are a variety of dosage forms, but what follows are typical dosage forms and what their preformulation study might entail.

Solid Dosage Forms

Preformulation studies need to be performed to determine chemical incompatibilities or instability in solid dosage forms, such as diluting or mixing the dosage form with drinks prior to administration. Differing physical properties of actives and excipients may also lead to an uneven distribution and alteration in drug delivery to the target site. A performance test — disintegrating the preparation and dissolving the active in a suitable medium — should be performed to help indicate the delivery of a drug from the dose form to the target site.

Transdermal Patches

These varying-sized preparations contain one or more active ingredient. Drugs intended to be incorporated into transdermal systems require an appropriate combination of physiochemical properties, potency, biocompatibility, and clinical need. Particular attention should focus on the active's compatibility with the matrix reservoir and adhesive materials.

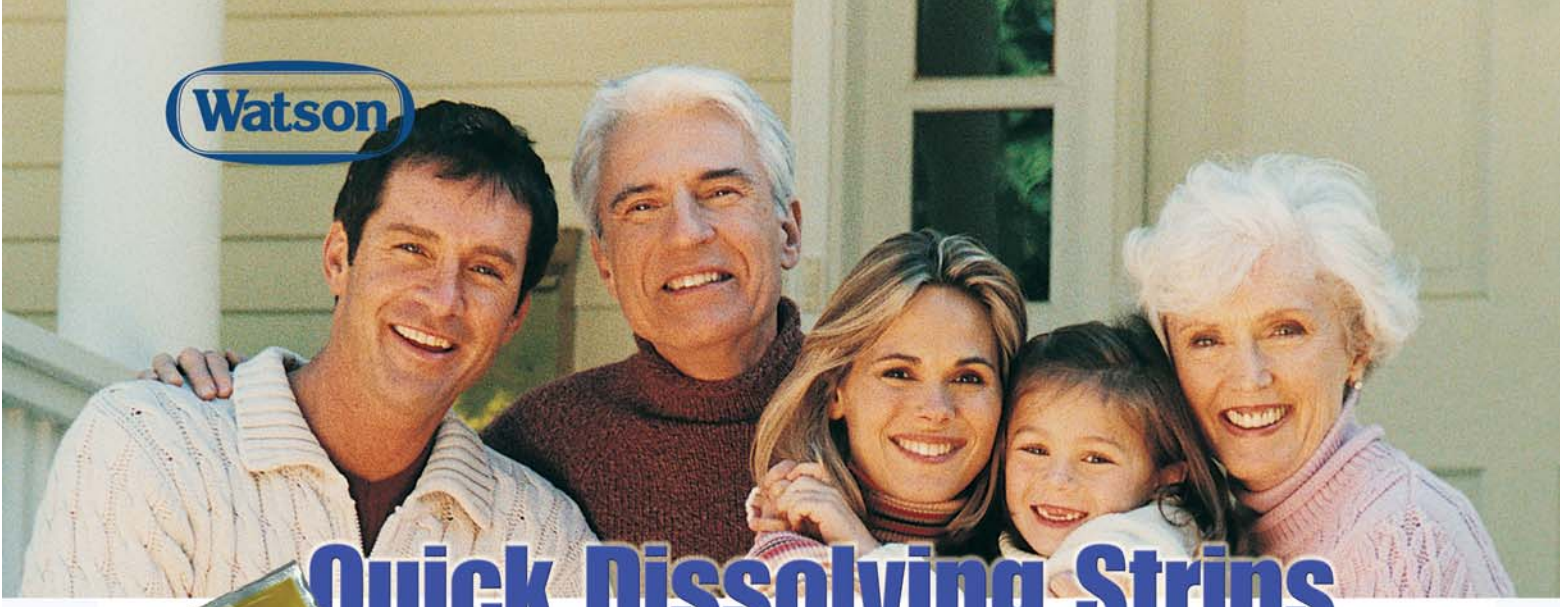
Pressured Metered Dosage Inhalers

Particle size and quality of the proposed propellant co-solvent and surfactant should be examined carefully. The propellant may interact with the active, altering the physical/chemical properties.

Dry Powder for Inhalation

Particle characteristics such as size, shape, rugosity, and charge may need to be addressed as should the flow properties of the drug. *In vitro* and *in vivo* tests should be used to investigate the dependence of dose delivered on air flow rate. Deposition of the drug in the mouthpiece and water content of the drug/excipient mix should also be addressed. According to the National Institute of Health, factors to be studied in dosage form design include:[2]

Elimination Half Life — Drugs with long elimination half lives are generally undesirable for prolonged-release dosage forms unless designed to prevent toxic effects due to a peaking effect or to reduce the dose.



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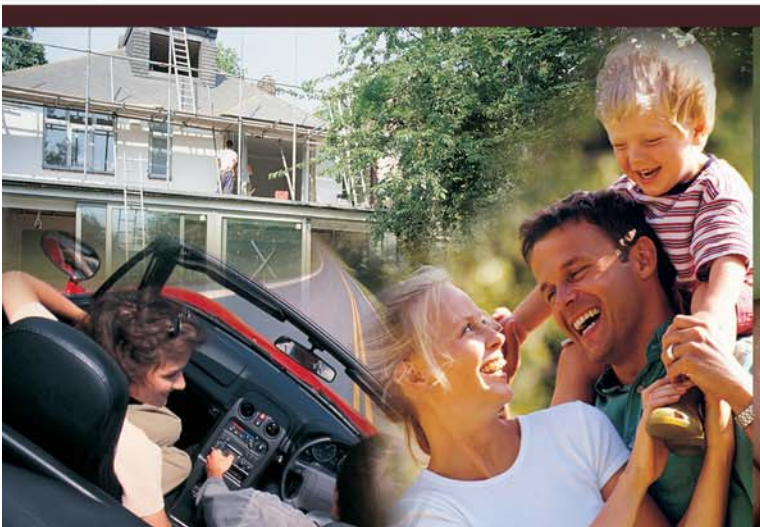

The First-Pass Effect — Bioavailability may be significantly impaired if the release rate is retarded for drugs that suffer from an extensive first-pass effect.

The Absorption Site — If the absorption site is limited, absorption is likely to decrease, and variable bioavailability will occur for typical prolonged-release dosage forms.

Adverse Reactions — Undesirable adverse reactions may develop by using prolonging drug release.

It is also desirable to clarify the correlation of clinical response with blood-drug concentrations or tissue concentrations at the site of action; induction or inhibition of drug metabolizing enzymes by the prolonged blood concentration, casual change of pharmacological response, and the possibility of tolerance or addiction for the drug; and interactions with other drugs due to protein binding.

STAGES OF PREFORMULATION

Higgins and Rocco separate preformulation activities into four distinct stages that involve selecting the appropriate salt form of the drug, characterizing the drug substance's solid-state and solution properties, and determining its compatibility with excipients. What evolves is a process for selecting the best form of the drug substance and the best excipients for formulating the drug substance into a final clinical dosage form.

Salt selection provides a means of altering the physio-chemical and biological characteristics of a drug substance without modifying its chemical structure. The main objective of a salt selection study is to identify the salt form that is most suitable for development.

Although each drug company has its own strategy for salt selection, Higgins and Rocco claim that the following general approach often applies: A few grams of the neutral form and several salts of the drug substance are synthesized in preparation for a salt selection study. The compound's molecular structure, purity, and sate of hydration are confirmed by standard analytical methods. The partition coefficient — the measure of how well a substance partitions between lipids and water — can help predict how well a compound will pass through cell membranes. High-throughput screening is used, such as microplate technique, to allow for a large array of counter-ions and crystallization solvents to be evaluated using as little as 50 mg of drug substance. After the optimum drug substance form is selected, compound synthesis is scaled up to a few hundred grams, and other stages of preformulation can begin.

Drug substance solid-state properties, such as crystallinity, particle size, and morphology, can affect processing. Various techniques can be used to evaluate these attributes, including polarized light microscopy (PLM), X-ray powder diffraction (XRPD), and differential scanning calorimetry (DSC). Data obtained via these techniques will help characterize the drug substance's solid-state properties and will serve as a benchmark for all subsequent drug substance lots.

Solubility is measured in aqueous media over a range of pH values and temperatures. The final dosage form should disintegrate and dissolve in aqueous media in a short amount of time.

Finally, drug substances are often combined with excipients to enable the formation of free-flowing spherical granules via a wet granulation process. Higgins and Rocco explain that the excipients required for this include diluents, binders, disintegrants, lubricants, and surfactants. Too often, the excipients used produce unexpected chemical degradation effects. A myriad of approaches are used to evaluate drug-excipient compatibility, ranging from evaluating simple drug-excipient

binary mixtures to applying statistical formulation matrices, which allow researchers to evaluate the maximum number of potential interactions.

One drug-excipient compatibility screening model was studied by the pharmaceutics R&D department at Bristol-Myers Squibb Pharmaceutical Research Institute. The model involved storing drug-excipient blends with 20% added water in closed glass vials at 50°C and analyzing them after 1 and 3 weeks for chemical and physical stability. The total weight of drug-excipient blend in a vial was usually kept at about 200 mg. The amount of drug substance in a blend was determined on the basis of the expected drug-to-excipient ratio in the final formulation. Potential roles of the chemical nature of the excipient, drug-to-excipient ratio, moisture, microenvironmental pH of the drug-excipient mixture, temperature, and light, on dosage form stability could be identified by using the model. Certain physical changes, such as polymorphic conversion or change from crystalline to amorphous form, that could occur in drug-excipient mixtures were also studied. Selection of dosage form composition by using this model at the outset of a preformulation program could lead to a reduction of surprise problems. At this point, a thorough preformulation study has been completed and the formulator can proceed on development of a stable, reproducible clinical dosage form. ♦

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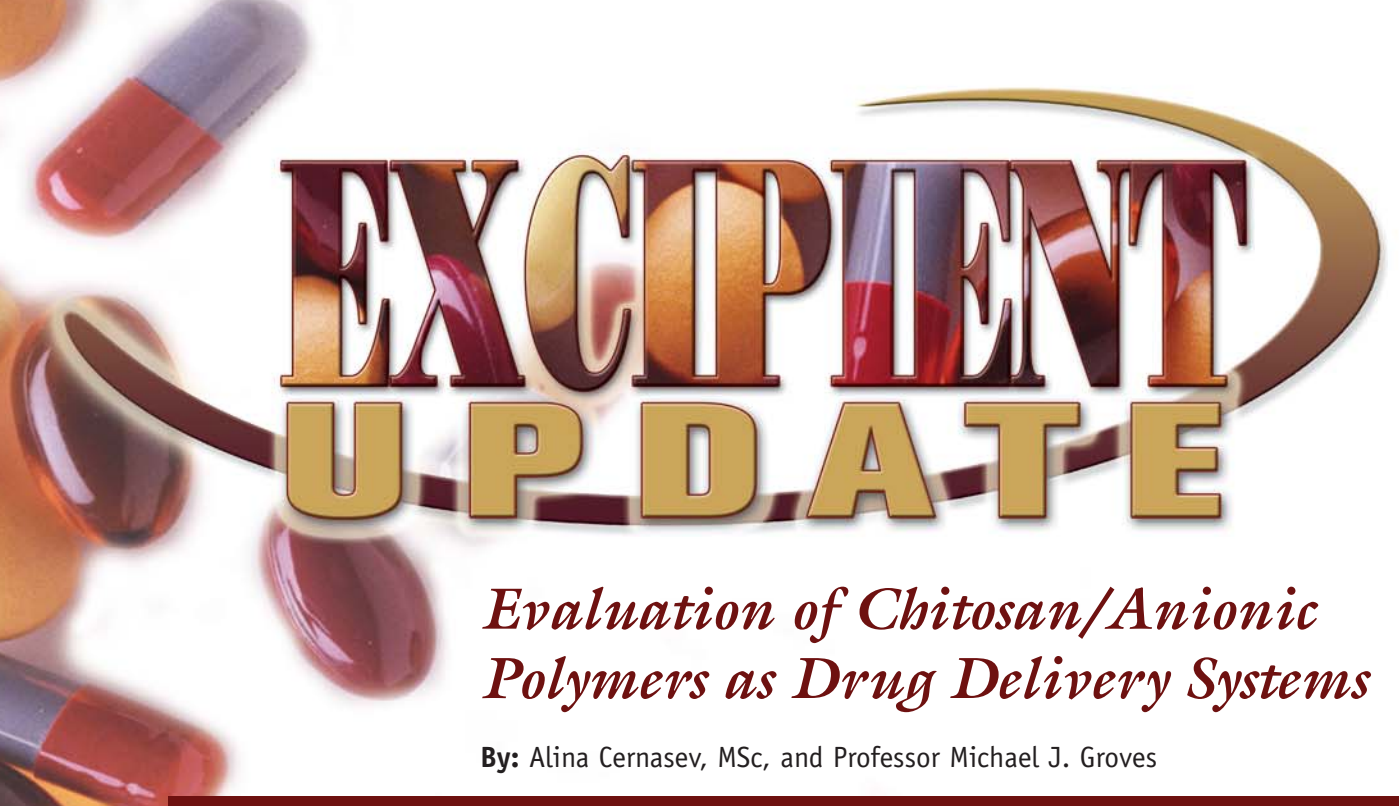
BIOGRAPHY

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



Evaluation of Chitosan/Anionic Polymers as Drug Delivery Systems

By: Alina Cernasev, MSc, and Professor Michael J. Groves

INTRODUCTION

In 1994, Luessen et al suggested that chitosan should be capable of interacting with anionic macromolecules, such as alginic acid or hyaluronic acid.[1] However, this suggestion does not appear to have been followed up. This present investigation confirms that chitosans are indeed capable of interacting with macromolecules and demonstrates that in principle, the separated adducts can act as drug delivery systems.

Chitosan adducts were formed between chitosan and various polymeric anions, such as alginic acid, dextran sulfate (various molecular weights), heparin, and sodium dodecyl sulfate. Conditions for the formation of these adducts were influenced by factors, such as concentrations of the two reactants, time, and pH. The data proved that this process was controlled principally by the concentration of the two reactants. After finding the conditions for forming adducts, they were characterized by measuring the particle size (light scattering), charge, and pH and visualized by optical and electronic microscopy.

Bovine serum albumin (BSA) was used as a model drug and precipitated adducts containing BSA could be prepared. The reaction mixture was centrifuged or filtered, and the supernatant and sediment were separately analyzed for BSA using a BCA kit. This demonstrated that the BSA was preferentially incorporated into the precipitated adducts. Dissolution tests showed that the BSA could be released rapidly at a pH in excess of 7.0 but more slowly at lower pH.

CHITOSAN: ORIGIN, STRUCTURE & PROPERTIES

Chitosan is a natural biopolymer produced by the hydrolysis of chitin, obtained from the shells of crustaceans. Chemically, chitosan is a polysaccharide with the structure poly [β- (1-4)-2-amino-2-deoxy-D-glucopyranose].

Chitosan was introduced to the market in the 1990s. Attention has been drawn to its unique properties, such bioadhesion, biodegrability, and low toxicity, which suggested it might form the basis of drug delivery systems.[2,3]

Commercial chitosans have average molecular weights between 3.8 and 2,000 kDa and are from 66% up to 95% deacetylated.[4] These two characteristics are relevant to the physico-chemical properties of chitosan and hence, have a principal influence on its biological properties.

It is well known that chitosan can interact with various polyanions. Luessen et al suggested that chitosan might form matrices with complex macromolecular polyanions such as gelatin, alginic acid or hyaluronic acid.[1] This is the first study to demonstrate factors involved in the formation of particulate systems that have the potential to act as drug delivery systems. In this research, the following polyanions were selected for evaluation: alginic acid, dextran sulfate (various molecular weights), heparin, and sodium dodecyl sulfate.

EXPERIMENTAL

Materials

Chitosan: low (Mr~150), medium (Mr~400, and high molecular weight (Mr~600 with degree of deacetylation 96%; dextran sulfate sodium salt: low (Mr~5,000), medium (Mr~500,000), and high molecular weight (Mr~1,000,000); alginic acid sodium salt; sodium dodecyl sulphate; heparin sodium salt from bovine intestinal mucosa (195 U/mg); and Tween 80 were all obtained from Fluka Chemie GmbH, Buchs, Switzerland. Bovine serum albumin (BSA), glycine, sodium hydroxide, sodium acetate, boric acid, potassium chloride, hydrochloric acid, and glacial acetic acid were all obtained from Sigma Chemicals, Cambridge, UK.

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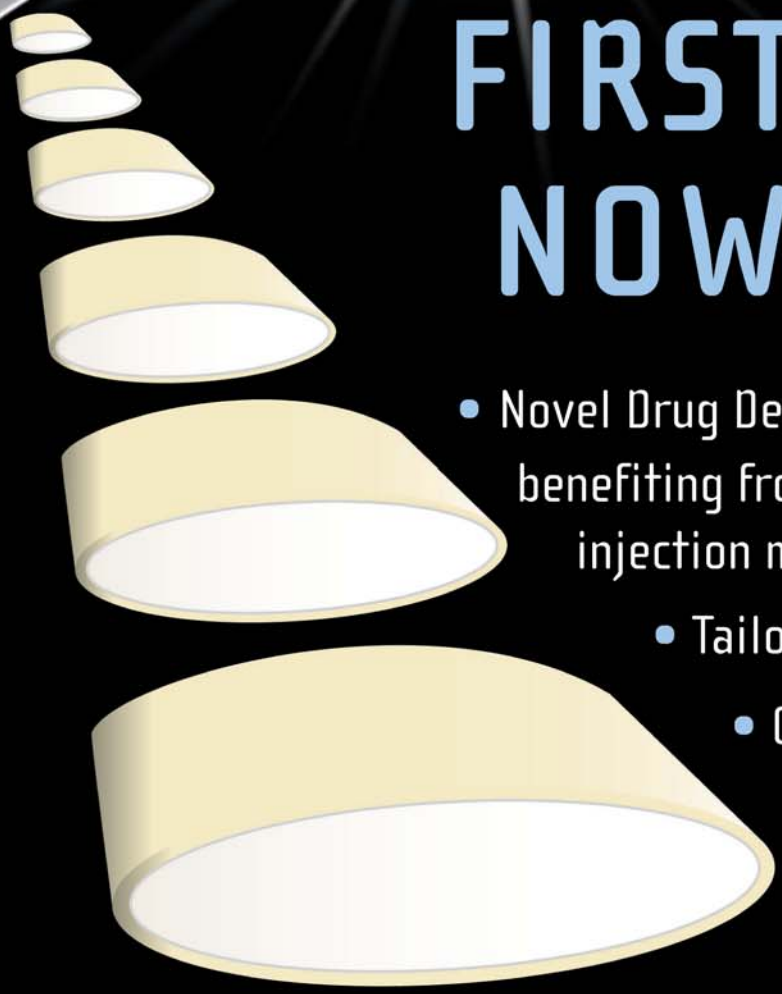

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METHODS

Preparation of Chitosan & Reactant Solutions

Chitosans with different molecular weights (low, medium, and high) (0.1% and 0.25%) were dissolved in distilled water containing Tween 80 1% and glacial acetic acid 1%. Addition of Tween 80 was necessary to stabilize the initial suspension. The solution was stirred with a magnetic stirrer for 90 minutes and sonicated for an additional 5 to 7 minutes by using a sonication bath. Sodium dodecyl sulfate (SDS) (0.1%, 0.2%, 0.5%, 1%) was dissolved in distilled water with a magnetic stirrer until a clear solution resulted.

Dextran sulfates (DS) (0.1%, 0.2%, 0.5%, 1%) with different molecular weights were dissolved in hot distilled water with a magnetic stirrer until a clear solution resulted and allowed to cool to ambient temperature prior to use.

Heparin (0.01%, 0.1%, 0.2%) was dissolved in distilled water with a magnetic stirrer. Alginic acid powder was added to water with stirring, and NaOH 0.2 M was added drop by drop. The solution was stirred for another half an hour or until a clear solution was obtained.

Preparation of Chitosan Adducts

To obtain the right conditions for obtaining chitosan microparticles, chitosan solution was added to reactant and vice versa. Preliminary results (data not shown) enabled approximated concentrations to be determined and procedures to be evaluated.

ANALYTICAL PROCEDURES

Centrifuge

Polyanions solutions, with or without BSA, were added to the chitosan solutions when a precipitate resulted in all cases. The precipitate was centrifuged for 1 hour under the following conditions: 15.000, 4ºC, by using a Sigma Laboratory centrifuge (3k30, Germany).

The supernatant was collected and analyzed. The sediment was redissolved using (5 or 10 mL) of alkaline borate buffer at pH = 8.6. It was observed that, contrary to literature reports, chitosan was soluble at this pH in this buffer, an observation confirmed later by Beaudoin et al who separated a mixture of chitin and chitosan using an 80-Mm borate buffer at pH=8.4.[5]

Filtration

Using Whatman filters with a pore size of 0.22 µm, a diameter of 13 µm or 35 µm, and a low protein binding in a polypropylene housing, the precipitate resulting from the reaction of chitosan and various polyanions was collected by filtration. After filtration, the sediment was redissolved in 1 to 2 mL of alkaline borate buffer USP pH = 8.6. The supernatant was measured for BSA content in all cases as described further. Both filtrate and retentate (dissolved) were analyzed as appropriate. In some cases, the retentate was lyophilized to enable a yield of solid material to be estimated.

Particle Diameters

The particle size was determined by using the Malvern MasterSizer S (Malvern Instruments, UK). One or two drops of the suspension was dispersed into the cell, which contained distilled water. All sizes are expressed as mean volume diameters, the diameter of spheres that would have the same volume as the particles.

Morphology

Scanning electron microscopy of lyophilized precipitate (Philips XL 30 Eindhoven, Netherlands) demonstrated that morphologically the precipitated adducts consisted of small primary particles, generally stuck together in larger aggregates.

BSA Analysis

BSA was determined by using a bicinchoninic acid (BCA) protein assay kit (Pierce, Rockford, IL, USA,), in accordance with the manufacturers instructions. The concentration of protein in the sample was calculated using the calibration curve prepared from protein standards treated in the same way as the samples. The concentration of the sample was calculated using the equation of the calibration curve.

Zeta Potential

The electrophoretic motility of the particles in an electrical field was measured using ZetaSizer (Malvern Instruments, UK). Microparticles (1 to 2 mL) were suspended in 1-mM potassium chloride to produce a dilute suspension. The average zeta potential (mV) was determined over three readings for each sample. It was operated according to the manufactures directions.

Dissolution Tests

Reactant [5 mL of heparin, dextran sulfate (low molecular weight), or SDS], all with incorporated BSA, was added to the chitosan solution (100 mL). The resulted precipitates were centrifuged at 15,000 rpm and 4ºC, by using a Sigma Laboratory centrifuge 3k30. The supernatant was separated from

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Table 1. Dissolution Tests of Various Adducts

Abbreviations: CH L (chitosan low molecular weight), CH M (chitosan medium molecular weight), CH H (chitosan high molecular weight), DS L (dextran sulfate low molecular weight, DS M (dextran sulfate medium molecular weight), DSH (dextran sulfate high molecular weight), SDS (sodium dodecyl sulfate)

	REACTANTS (1.0%)			REACTANTS + BSA		
	Size (µm)	Zeta (mV)	pH	Size (µm)	Zeta (mV)	pH
SDS/ CH L	130.4	65.5	3.7	50.0	48	3.3
SDS/ CH M				100.1	23.8	3.4
DS L/ CH L	34.5	12.4	3.5	184.5	31.3	3.4
DS L/ CH L	40.1	57.5	3.5	42.1	33.2	3.4
DS L/ CH M	46.4	ND	3.4	229	33.9	3.4
DS L/ CH M	48	-4.4	3.5	ND	ND	ND
DS L/ CH H	68.4	66.5	3.4	ND	ND	ND
DS L/ CH H	77.2	28	3.5	ND	ND	ND
DS M/ CH L	28	ND	3.4	ND	ND	ND
DS M/ CH L	33.4	-22.5	3.4	ND	ND	ND
DS M/ CH L	34.5	ND	3.5	77	22.5	3.5
DS M/ CH M	42	ND	3.3	125.5	34	3.5
DS M/CH M	50	-19.6	3.4	ND	ND	ND
DS M/ CH H	61.0	ND	3.5	46.7	26.2	3.4
DS M/ CH H	75.03	ND	3.5	ND	ND	ND
DS M/ CH H	143.2	-23.2	3.3	ND	ND	ND
DS H/ CH L	35.1		3.4	483.8	30.1	3.4
DS H/ CH L	37.0	32.3	3.4	370.3	28	3.4
DS H/ CH M	41.2	ND	3.4	ND	ND	ND
DS H/ CH M	58.8	32.6	3.4	490.8	34.3	3.4
DS H/ CH H	78.8	38.8	3.4	ND	ND	ND
Heparin (0.1%)/ CH L	30.5	60.8	3.7	280.2	41.5	3.5
Heparin (0.1%)/ CH M	43.8	62	3.5	110.2	31.5	3.5
Heparin (0.1%)/ CH H	319.5	65.5	3.7	84.5	35.8	3.5

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Table 2. Dissolution Tests of Various Adducts

Abbreviations: BSA (bovine serum albumin), CH L (chitosan low molecular weight), CH M (chitosan medium molecular weight), CH H (chitosan high molecular weight), DSL (dextran sulfate low molecular weight

System	pH	%BSA Release
CH L/ Heparin/ BSA	5.5	1 hr 0 6 hr 9.2% 24 hr 23.5%
CH L/ Heparin/ BSA	3.9	1 hr 2.72%
CH M/ DS L/ BSA	7.5	1 hr 75.0%
CH M/ Heparin/ BSA	3.9	2 hr .5% 5 hr .6%
CH H/ Heparin/ BSA	8.2	1 hr 9.8% 2 hr 10.3%

sediment, and the sediment was filtered though a Millipore filter GP with a pore size 0.22 mm and 45 µm). The sediment was collected from the filter, frozen over night, and dried on the following day for 3 or 4 hours. The yield was weighed. The dissolution tests were carried out using a Caleva (Silchester, Berks) rotating paddle operating at 50 rpm, and temperature of 37ºC, according to the BP.

Four experiments were carried out at the same time using the following 200-mL medium: a) water; b) acetate buffer (pH = 3.9, USP); c) TRIS-Glycine (pH = 8.2, BP); and d) water and NaOH (pH = 8).

Samples (1 mL) were collected immediately, and then after 1, 2, 3, 4, 5, and 6 hours. The sample volume was replaced each time with the same volume of medium. The samples were filtered using a Whatman filter with a 0.22-mm pore size and 45-mm diameter. The filtrate was analyzed for BSA by using the BCA Kit as described earlier.

RESULTS

Formation of Adducts

By the way of a preliminary screen, adducts were formed by the addition of aqueous solutions of polyanions to chitosan solutions. Under some conditions, only opaque solutions resulted, and in others, only flocculate or gels could be observed. BSA was incorporated into some of the more pronounced chitosan adducts. This had a significant effect on the particle size, which was increased, and also on the zeta potential, which was generally decreased (Table 1). Yields of various adducts were measured, and dissolution data etermined (Table 2). The ratio of BSA in supernatant over that in the precipitate was determined and proved that the BSA was mainly in the sediment.

DISCUSSION

This systematic study focused on adducts formed with various selected polyanions. The selection criteria for these polyanions were their availability, their known approximate molecular weights, and their structures. Data suggested that there is an overall smooth progression in the precipitation process, controlled by the following concentration:

CLEAR SOLUTION > SMALL PARTICLES > LARGE PARTICLES > FLOCCULATED PARTICLES > AGGREGATED PARTICLES > GEL

All the experiments were carried out at room temperature. Another factor that probably influences the formation of adducts is time. Direct titration of anions and chitosan solution could not be carried out because the precise time for the reaction was not known.

The usual loading dose of heparin as an anticoagulant is approximately 10,000 units.[6] At a potency of 140 units/mg (the USP standard), this corresponds to a dose of 71 mg, well above the dose of heparin administered in formulations based on this present approach. In practice, therefore, if the heparin/chitosan formulations were developed further, the actual dose of heparin would be very low, depending on the incorporated drug.

The particle size is evidently of great importance. It is generally recognized that only small particles, dispersed as simple entities and often in the

micrometer or nanometre range, are transported across the intestinal wall and absorbed into the systemic circulation.[7] More specifically, these small particles are able to reach a specific target that can lead to improved drug absorption. The route of administration determines if the particle size can reach a specific target or not. For most routes of administration, the rate of absorption, the speed of effect onset, and the duration of therapeutic response might be determined by particle size. The particle size has also an influence on bioavailability.[6]

Morphological studies (not shown) revealed that most aggregates were of small particles (Table 1) with sizes of approximately 0.3 to 1.3 micrometers in diameter. It has to be mentioned that although the measured particle diameters varied from 40 to 360 micrometers, the larger particles probably consisted of aggregates of smaller particles (0.7 micrometers in diameter). These delivery systems could therefore not reach systemic targets. The particle size increased with increased molecular weight of chitosan. Given an improvement in preparation conditions, it seems reasonable to anticipate that smaller aggregates or even separated primary particles may be prepared and characterized more completely. However, it is clear that the larger aggregates of primary particles could be suitable as drug delivery systems to tissues, such as the nose or gastrointestinal tract.

As a model drug, BSA was used because it is a protein with a well-characterized structure and known molecular weight. A preliminary experiment evaluating interactions between chitosan and BSA solutions showed that there were no interactions between chitosan and BSA up to a concentration of 5% of BSA, because in all cases, the mixed solutions remained clear.

The pH is another factor that was taken into consideration because it has an important effect on the solubility of chitosan, the mucoadhesive properties of chitosan, and therefore adducts. These delivery systems have been intended to be administered to various parts of the body at different ambient pH.

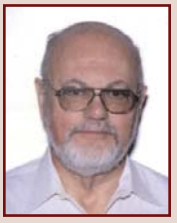
The charge was measured as zeta potential to determine if adducts could still have potential mucoadhesive properties. Before adding the BSA to these adducts, the zeta potential was positive with one exception, (dextran sulfate, medium molecular weight).

When the BSA was added to this system, the charge was decreased but remained positive.

In the case of dextran sulfate (medium molecular weight), the charge was reversed and became positive. These data are presented in Table 1 and suggest that there might be enough positively charged surfaces on the chitosan to interact with mucin *in vivo*. ♦

BIOGRAPHIES

Ms. Cernasev is a Romanian pharmacist (Iasi, 2002) and worked for a Master degree in Drug Delivery at the School of Pharmacy, University of London, 2004.



Dr. Groves worked initially in industry (Smith & Nephew, Boots) and was a Lecturer in Pharmaceutics, Chelsea College, University of London before coming to America in 1978 as an Associate Director (Travenol, G.D. Searle) in the drug delivery area especially involved with lipid emulsions. He moved to the Pharmaceutics Department, University of Illinois at Chicago, in 1983, first as Head of Department and, later as Director of the Institute for Tuberculosis Research. He retired in 2004. He has published 400 articles, papers, patents, and book reviews. His latest book is "Pharmaceutical Biotechnology", Taylor & Francis, 2005.

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CONTROLLED RELEASE

Controlled Release Technology – Necessity or Compulsion?

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

INTRODUCTION

Pharmaceutical products have traditionally been administered orally or through injections, without much complication. Three decades back, the industry reached a phase where drug molecules were being discovered that held the potential to revolutionize the industry, but met with difficulties due to poor absorption and solubility. The earliest form of modified drug delivery was offered in the 1970s, with the usage of lactic-acid-based polymers. Polymers continue to be used in the present day in controlled-release (CR) formulations.

Drug delivery technology is currently a rapidly growing market with several companies offering in-house technology solutions for pharmaceutical and biotechnology companies to enhance their products and competitiveness. The field of oral CR formulations is an emerging field that seeks to provide improved patient compliance through enhanced convenience, reduced dosing, and a minimal side-effect profile. However, the use of expensive materials and/or complex manufacturing processes has resulted in premium pricing of existing oral CR therapeutics.

CHALLENGES

Oral delivery of peptides and vaccines using CR technologies continues to remain the top challenge for researchers. Commonly, drug molecules are embedded in a matrix, which aids in controlling the release of the drug. Microencapsulation, nanoencapsulation, and emulsion polymerization are other CR technologies currently used. There are several proprietary technologies available to drug delivery companies, which could be extended to existing products to effectively extend the life-cycle and protect them from competition.

One of the key challenges that researchers encounter in the development of oral CR therapeutics is the measurement of *in-vivo* release rates of the formulation, which are extremely complex to determine, versus *in-vitro* release rates. *In-vivo* release is typically determined in a laboratory setting, using a variety of synthetic and organic membranes, while *in-vitro* release is determined by the ability of the drug molecule to cross various biological barriers, interact with various types of cells, and its distribution in organs, etc.

ADVANTAGES

Oral CR technologies provide pharmaceutical and biotechnology companies with innumerable advantages, including:

- Reproducible drug-release profiles and uniformity of dosage;
- Increased durability of product, which extends shelf life;
- Improved palatability and patient compliance;
- Improve dissolution of poorly soluble drugs; and
- Intellectual property protection.

Pharmaceutical and biotechnology companies are looking to derive maximum "bang for the buck" from their products, and improvised drug delivery is a top strategic option to achieve that. Having already invested millions into research and marketing, adopting technologies like CR would serve to benefit the patients as well as the companies. As a result, second or third generations of existing blockbuster drugs are likely to become a common occurrence in the future.

A CONTROLLED "FUTURE" RELEASE & APPLICATIONS

Most successful CR formulations are polymer-based due to ease of processing and easy control of physical and chemical properties. Typical polymer-based CR formulations are of two types:

- Encapsulation – The drug molecule is entrapped in a polymer shell.
- Matrix Form – The drug molecule is embedded in a polymer matrix.

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The release of the drug from the polymer is through diffusion in both cases. By controlling the degradation of the polymer, the release of the drug into the biological system is controlled.

A large percentage (> 65%) of the new chemical entities (NCEs) has problems of poor solubility and limited bioavailability. Oral CR platforms enable pharmaceutical companies to overcome these problems and design an effective therapeutic solution.

Insulin Delivery

One of the key future applications of CR platforms for oral therapeutics is insulin delivery for diabetic patients, utilizing glucose-sensitive hydrogels. A built in pH trigger is incorporated, which would release the insulin using a trigger - the body's own glucose.

Targeted Controlled Release

Targeted controlled release of a drug is likely to be achieved through the use of multiple polymeric networks, created through the polymerization of hydrophilic and hydrophobic monomers, which have the specificity to target certain cells. This could have a wide range of applications, especially in delivery of anticancer agents to a specific tumor site.

Drug Transport Devices

Electroactive polymer matrices, which have conducting ability, are likely to be used as a drug-releasing system. By controlling the movement of counter-ions in and out of the membrane, the release of the drug molecule from the matrix is achieved. This system could be extremely helpful for the formulation of cardiovascular therapies, in which precise control of the drug-release rate is extremely critical.

SPECIALTY PHARMACEUTICAL COMPANIES

The specialty pharmaceutical market, which comprises some companies that focus on drug delivery, is a burgeoning market, and oral CR platforms are a prime focus for these companies. Several large companies, such as Cardinal Health have designed successful CR platforms and entered into partnerships with other pharmaceutical companies. The role of these specialty pharmaceutical companies in the value chain is anticipated to rise in absolute terms for their contribution in reviving late life-cycle compounds, increasing intellectual property right protection, and creating a unique selling proposition (USP) for products.

Some of the other companies in the news recently for oral CR formulation development include the following:

- **Penwest Pharmaceuticals Co.**, which is developing a CR tablet formulation of Nalbuphine ER to be used as a pain killer, competing against drugs, such as Tramadol. Nalbuphine is currently available only as a sterile solution for injection.

- **DURECT Corporation**, which is developing a novel long-acting oral formulation of oxycodone based on its ORADUR technology.

SUMMING IT UP

The specialty pharmaceutical market is likely to witness increased fragmentation from the emergence of boutique drug delivery and research units. The partnerships between these units and pharmaceutical and biotechnology companies are poised to rise, which is likely to augur well for the pharmaceutical industry, which has been facing pressure from dwindling pipelines and rising research and development costs.

Oral CR technologies are thus poised to enter a new, exciting phase in which the integration of specialty pharmaceuticals with mainstream pharmaceuticals and biotechnology is expected to play a major role. With further emphasis on newer technologies gaining ground, oral CR therapeutics are expected to revolutionize therapies in areas, such as diabetes and cardiovascular therapeutics.

BIOGRAPHY

Mr. Barath Shankar joined the Pharmaceutical and Clinical Diagnostics group of Frost & Sullivan as a Research Analyst in October 2004. He focuses on tracking and analyzing various products, technologies, and markets in these industries while providing sophisticated quantitative forecasting. His prior work has included research on areas, such as cost-benefit analysis of R&D of the top 10 pharmaceutical companies and correlating stock volatility with underlying business volatility to find sources of perception in the Indian Stock Market. He also completed an internship with a leading generic drug company in Mumbai, India, that involved an individual assignment for the development of a generic drug for the EU Market. In addition to writing extensive research services, Mr. Shankar is also responsible for up-to-date articles on issues that affect the healthcare industry today. As an analyst, he brings an invaluable amount of analytical and quantitative experience to his position, giving him a keen perception into the functioning of technology in the healthcare industry. He earned a Bachelor of Pharmacy (Honors) degree from the Birla Institute of Technology and Sciences in Pilani-Rajasthan, India.

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OUTSOURCING

Improving Strategic Outsourcing Relationships

By: Elizabeth N. Treher, PhD

INTRODUCTION

How many of us have worked on teams that we knew we could be more productive and effective if we were all on the same page? If we were clear about our own goals before involving others? Research shows that failure rates of strategic alliances and outsourcing agreements have remained at about 50% for the past decade. Isn't it time to recognize that the soft side of outsourcing relationships really is the hardest and therefore devote the time and resources to address and prevent these issues?

Research indicates that North American companies are preoccupied with economics and neglect the cultural, organizational, and human aspects of outsourcing agreements.[1] Most efforts to select pharmaceutical, contract research, and manufacturing outsourcing partners go to evaluating technical abilities, resources, and performance metrics. Those elements that are harder to quantify, but affect the relationship and drive success, are often neglected or ignored.

The time it takes to understand subcontractor abilities and culture, and to build mutually beneficial relationships, is critical. In today's regulatory and legal climate, sponsors can be held liable for unethical or fraudulent business practices, even when they are unaware of them.

Directing time, money, and expertise toward the elements that promote collaboration, build relationships, shorten a project, and ultimately determine success (or survival for small companies) is essential. It is important that ad hoc approaches are not used to select, manage, and build outsourcing relationships. Even in well-studied joint ventures, where greater management resources are typically dedicated, only 53% are considered successful, compared to 51% a decade ago.[2] The Gartner Group reports failure rates of about 50% for outsourcing projects.

Time constraints and a sense of urgency to move forward quickly can explain why more effort isn't made to develop better-working outsourcing partnerships. Another reason may also be our traditional, almost ingrained, assumptions and experiences with vendor relationships. In the more transaction-based vendor arrangements, there is less need, value, or return on investment placed on building long-term, collaborative relationships. The majority of outsourcing relationships today are not transaction-based and require greater effort to manage and build. Trusting and knowing how to work well with colleagues in contracted organizations is an intangible return on investment that can streamline future collaborations, lead to greater profits, and create a superior competitive position. In addition, it makes for less stress and a more enjoyable work environment.

PARTNER SELECTION

Finding the right partner (Table 1) is key to achieving outsourcing success. Taking extra time to select the right partner has both short-term and long-term benefits. Prior experience with a service provider is one of the greatest predictors of success according to a National Science Foundation-sponsored study.

Three key criteria to improve the process are self-analysis; personal rapport between key executives; and historic, philosophical, and strategic compatibility.[3] Partner selection should balance human, technical, and business aspects — the fundamentals to establish and sustain a long-term partnership.

CONTRACT NEGOTIATIONS

When your outsourcing partner is selected, it is time to create the contract. This is the cornerstone of a successful, long-term relationship. The contract provides legal protection and written agreement of what was negotiated. Having an equal opportunity to structure the agreement or contract gives both parties a sense of partnership from the outset. People support what they help create. Some report that the source of most outsourcing problems is the way deals are conceived and set up initially.[4] A good contract is mutually beneficial, motivates partners to work collaboratively, and provides sufficient detail to define expectations, legal rights, roles, and responsibilities. It also satisfies those who consider contracts to be less important than

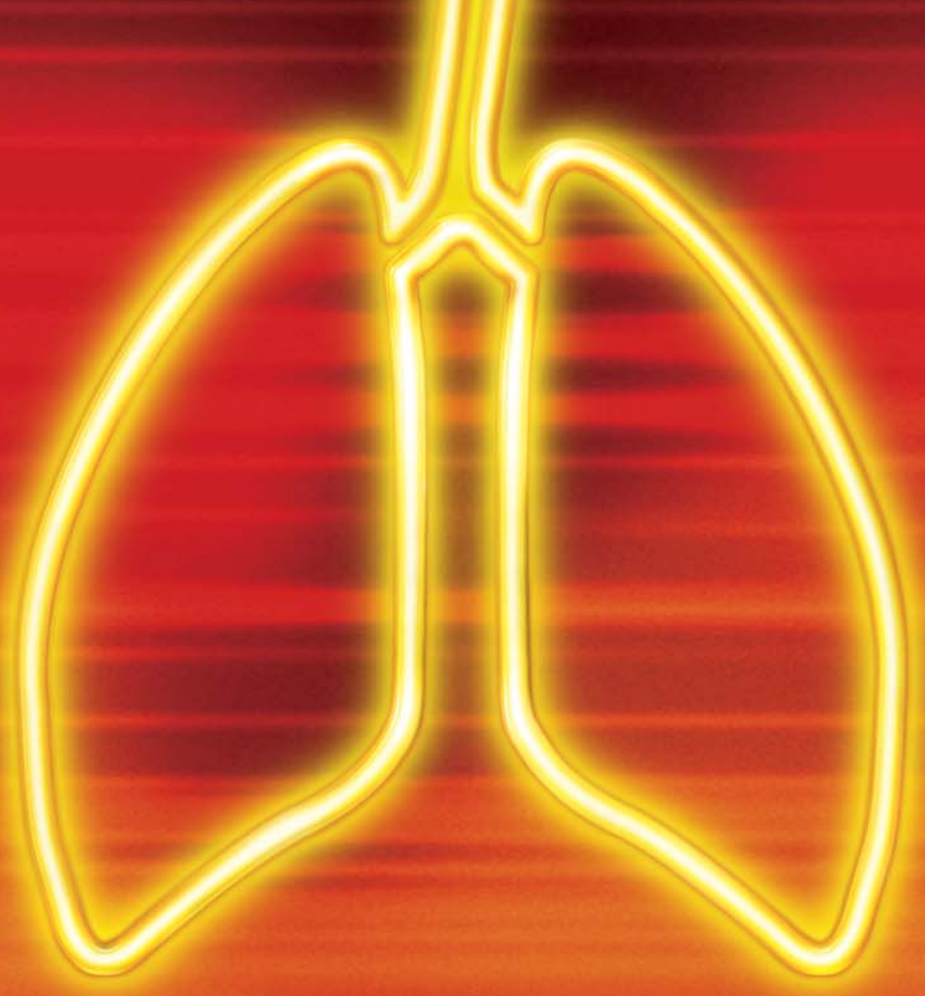

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Table 1. Key Steps in Partner Selection

- **Build an internal cross-functional core team to manage the selection, contracting, and implementation processes.**
- **Select project(s) to be outsourced.**
- **Define the scope of the work to be outsourced.**
- **Identify potential partner organizations.**
- **Narrow the list to a few strong candidates based on pre-determined criteria.**
- **Develop a request for proposal and submit it with a confidentiality agreement to candidates.**
- **Compare proposals, identify the two top candidates, and network to check references using pre-determined selection criteria to reduce "gut-feel" decisions.**
- **Invite candidates to present to your core team and explore experiences.**
- **Conduct QA audit, site visits, interviews and assess details.**
- **Select partner.**

establishing trust and personal relationships between the contracting parties.

To develop opportunities for mutual gain, the contract negotiation steps (Table 2) provide both structure and substance to the negotiation; by incorporating a well-defined, change-control process in the contract, they also build in flexibility.

PROJECT LAUNCH

Insufficient attention and management of the launch is a critical reason for alliance failure.[5] The productivity of a kick-off meeting can be enhanced significantly by assessing team member perspectives in advance. In planning for a launch meeting:

- Use a questionnaire to collect data on individual perceptions of expectations, concerns, goals, roles, and responsibilities. Summarize questionnaire data for use during the meeting; and
- Collect input from attendees on the contract, including their questions and comments; summarize this input for discussion at the meeting.

At the launch meeting, begin with an informal activity to break the ice and help participants get to know each other. Clarify meeting expectations and outcomes and use the data collected ahead of time to streamline discussion and focus on issues needing resolution. Include time to:

- Develop an agreement for operating norms;
- Establish communication plans for routine and crisis situations;
- Review key contacts and decision-making authority;
- Formalize a process to replace or add new team members; and
- Review the change control process and rationale.

PROJECT ENHANCEMENT

After forming, structuring, and launching a partnership, the challenge in implementation is to gain momentum, continue building trust and mutual respect among team members, and to enhance project management effectiveness. Continuous growth and development, rather than maintenance, is the goal here. Despite the best planning — the scope, complexity, and the large numbers of people involved in most outsourced projects make them vulnerable to problems and changes. As more people become involved, early relationships can be diluted. Staff may not feel as personally committed and may have less experience working outside their own culture. Some may oppose the relationship and try to undermine it. Usually most aren't dedicated full time to the partnership, and other responsibilities often take priority. Decision-making approaches, levels of authority, and reporting structures can all serve to create differences. Mechanisms to foster active collaboration are essential.

Project enhancement is an ongoing process that includes reviewing project status and achievements, milestone status, problems, and red flags (such as turnover, missed deliverables, growing frustration). Other activities include developing, initiating, and perhaps modifying actions to achieve the outcomes; determining how to measure success; obtaining feedback to assess how well it's going; devising new approaches and/or strengthening areas needing development; and finally creating new outcomes. This process can be supported with a series of facilitated sessions, often held in conjunction with regularly scheduled project update meetings or at other intervals as needed. An open forum is most important — one in which all parties contribute, feel free to share good and bad news, and have the opportunity to discuss project status, problems, necessary changes,

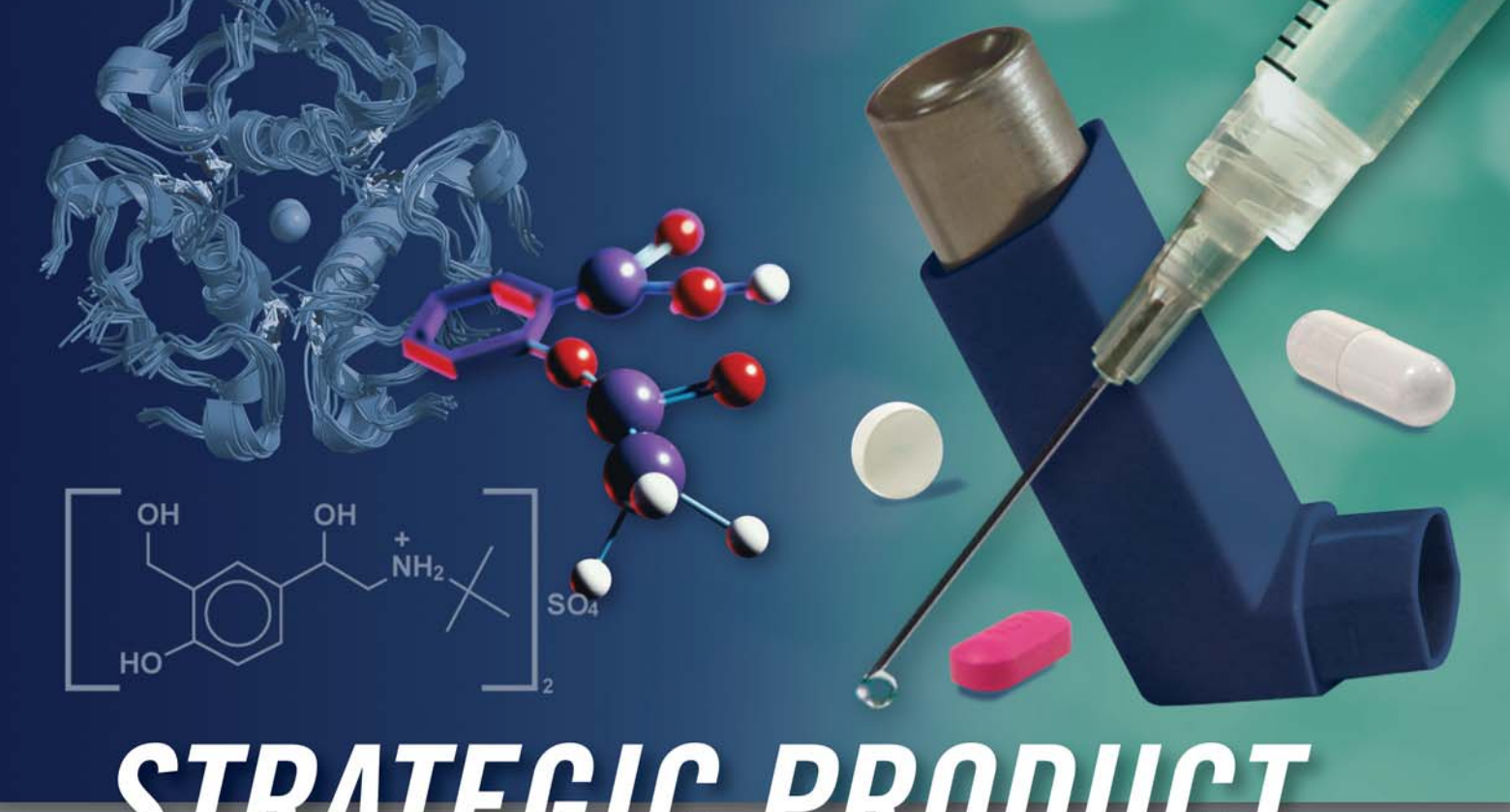

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Table 2. Contract Negotiation Key Steps

- **Review legal input and constraints on contract form and structure.**
- **Determine what form the contract should take.**
- **Establish and agree on outcomes for the contract negotiation; adopt a mutually beneficial strategy.**
- **Define the outsourcing relationship, including clear deliverables, milestones, activities to be completed by each organization, time lines, rules of conduct (norms), etc. Clarify key assumptions and expectations.**
- **Clearly define roles and responsibilities—the same title in different organizations does not necessarily mean the same role.**
- **Identify an individual in each organization to manage the relationship, mediate conflict, and pursue resources. This individual may represent a larger governing body, but should provide a single point of contact.**
- **Create and document communication expectations, strategies, and processes.**
- **Include mechanisms to monitor and measure progress; develop an appropriate audit process.**
- **Identify critical factors to guide progress and serve as a basis for go/no-go decisions.**
- **Incorporate a change-control process with methods to report deviations and manage scope creep.**
- **Review the contract with the responsible senior managers and all those in both organizations who will work on the project in the review process.**

action items required to keep the project on track, and pertinent issues, such as performance, relationships, communication, and processes.

LESSONS LEARNED

When the project or product is delivered or the project is terminated early, bring team members together to discuss and document lessons learned. Often, team members are busy with new projects, and this stage is postponed or ignored. Whether using face-to-face or virtual communication techniques, it is important to conduct a facilitated end-of-project meeting with each organization involved. Even in situations where teams have worked well together, a neutral third party can often surface additional opportunities. Even if the project did not go well — perhaps it went so poorly that you have no intention of working together again — maintaining respect and being open to others' perspectives can provide important lessons. Consider these questions:

- Did the majority of problems stem from one person, group of individuals, or specific communication barriers?
- Was the original contract itself flawed?
- Are relationships so strained that a neutral, external third party should be asked to collect data and facilitate the session?

Goals for the end-of-project meeting are to determine, document, and communicate:

- What worked well?
- What did not work well and how might these areas be improved next time?
- How were the results achieved?
- What were the best practices put forth?
- What individual or team development activities would be beneficial for future projects?
- How will lessons learned be leveraged to enhance other teams and/or projects?
- What will be done differently in the future, with this partnership or new partnerships?

SUMMARY

Many of us have worked on teams where we knew we could be more productive and effective — if we were "all on the same page," if we took the time to plan instead of jumping in to implement and then needing to redo, if… In organizations today, as we work with contractors who provide key strategic services for our businesses, we can't afford not to take the time to learn to work more collaboratively and effectively.

Such relationships are imperative, not optional. In the pharmaceutical industry, even a one-day delay to market for an "average" pharmaceutical product can cost about $1 million. For a blockbuster, it is

Table 3. Project Enhancement

- **Update communication plan for team meetings including schedule, decision-making strategies, process to use, and ways to handle urgent vs routine communications.**
- **Conduct reality check on alignment; analyze and reconcile differences between sponsor's and contractor's goals, values, and approaches.**
- **Acknowledge interim milestones.**
- **Update gap analysis and examine risk status.**
- **Identify potential opportunities for improvement.**
- **Assess team effectiveness (e.g. trust and communication, responsiveness, innovation, leadership).**
- **Address areas identified for improvement with developmental activities.**

many times that amount. Thus, the "simple" actions of reducing time spent in meetings while retaining or increasing output, streamlining communications, or developing a culture where issues are discussed early and openly can have a profound impact on the business. Fundamental to this is a clear foundation for approaches, methods, and tools to work with contractors and to capture lessons learned for continued refinement.

No matter where you are — whether initiating a new outsourcing relationship or well into implementation — it is not too late to take appropriate steps to improve your collaborative process.

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BIOGRAPHY

Ms. Elizabeth Treher has held positions in industry, government, and academia, including Los Alamos National Laboratory, E.R. Squibb & Sons, and Bristol-Myers Squibb. She led the teams that patented and developed a radiopharmaceutical imaging agent before developing and leading a corporate university for 22,000 employees. A graduate of Washington University in St. Louis with an MA and PhD in Nuclear and Radiochemistry, she was an NSF Post-doctoral Fellow and an invited member of the first U.S. delegation to China on HR Training & Development. For the past 15 years, she has consulted to the pharmaceutical industry and also developed team-based learning tools, including *The PHARM Game®*, *GMPWorks®*, and *Partnering Success*.

SYSTEMIC PULMONARY DELIVERY FINDS ITS FIRST STEPPING STONE

By: Contributor Cindy H. Dubin

INTRODUCTION

In our May 2005 issue, we told our readers that Systemic Pulmonary Delivery was in a make-or-break situation. The pending approval of Exubera® at that time had companies (that are developing other technologies and formulations of insulin) eagerly awaiting what would be, to a certain extent, a green light and validation to the invested expense and time of a highly complex device and formulation. Although individual applications showing that subsequent inhaled insulin products meet the required standards would of course need to be filed, the principle concern about whether it is safe to deliver insulin through the lung would be a far less worrying issue with the first-in-class product already on the market. The approval would also bolster the confidence of companies developing systemic pulmonary products for other therapeutic indications in which delivering the compound is relatively easier to deliver to the deep lung.

Of course, since then, there have been significant developments in the treatment of diabetes, especially with Pfizer's Exubera [insulin human (rDNA origin)] Inhalation Powder being approved by the US FDA for the treatment of adults with type 1 and type 2 diabetes. The following update is meant to highlight some areas that may be of key interest.

CURRENT STATE OF AFFAIRS

The pulmonary drug delivery industry let out a huge sigh of relief when the FDA approved Exubera Inhalation Powder for the treatment of adults with type 1 and type 2 diabetes. The baby of a collaboration between Pfizer and Nektar Therapeutics, Exubera, which is expected to be available for patients by mid-year, is the first inhaled form of insulin and the first insulin option that does not need to be administered by injection in the United States.

"Exubera is a major, first-of-its-kind, medical breakthrough that marks another critical step forward in the treatment of diabetes, a disease that has taken an enormous human and economic toll worldwide," said Hank McKinnell, Chairman and Chief Executive Officer of Pfizer, in a printed statement.

One of the more exciting aspects of Exubera's approval is that it sets the stage for systemic pulmonary drug delivery. As deep lung penetration is essential for systemic delivery, Exubera meets this challenge. But it's not just Pfizer and Nektar patting themselves on the back. Executives at companies considered competitors of Exubera's developers are also excited about the inhaler.

"This is indeed a major breakthrough for using pulmonary inhalation for treating systemic disease," says Leslie J. Williams, RN, BSN, MBA, President and CEO of Ventaira Pharmaceuticals. "It has set the stage for inhaling systemic drugs and opens the door for the rest of us in the space." "Exubera represents the first approval of delivering a drug to the lung to treat systemic disease versus focal lung disease."

Tony Garramone, President of Epic Therapeutics, a wholly-owned subsidiary of Baxter Healthcare, agrees "The approval of Exubera is a boon for pulmonary formulation technologies in general and holds promise for the future of pulmonary delivery."

ENOUGH OF THE NICE QUOTES... WHAT DOES IT MEAN?

Competitors being competitors, major players in the space are quick to point out that Exubera is a first-generation pulmonary delivery system and that the products that will come after it will feature significant improvements.

Some estimate that if an inhaler can prove that it can deliver drug deep into the lung and thereby deliver systemic drugs, the market for such an inhaler could reach in excess of $25 billion per year. The key is satisfying unmet needs.

Using pulmonary delivery for systemic diseases is evolving rapidly. Initial treatments, as we have seen, have been developed for type 1 and type 2 diabetes. Almost 21 million Americans have diabetes and approximately 95% of these people have type 2 diabetes.

But systemic delivery is not just for insulin. The next therapeutic area will likely be pain management. There are many drugs in

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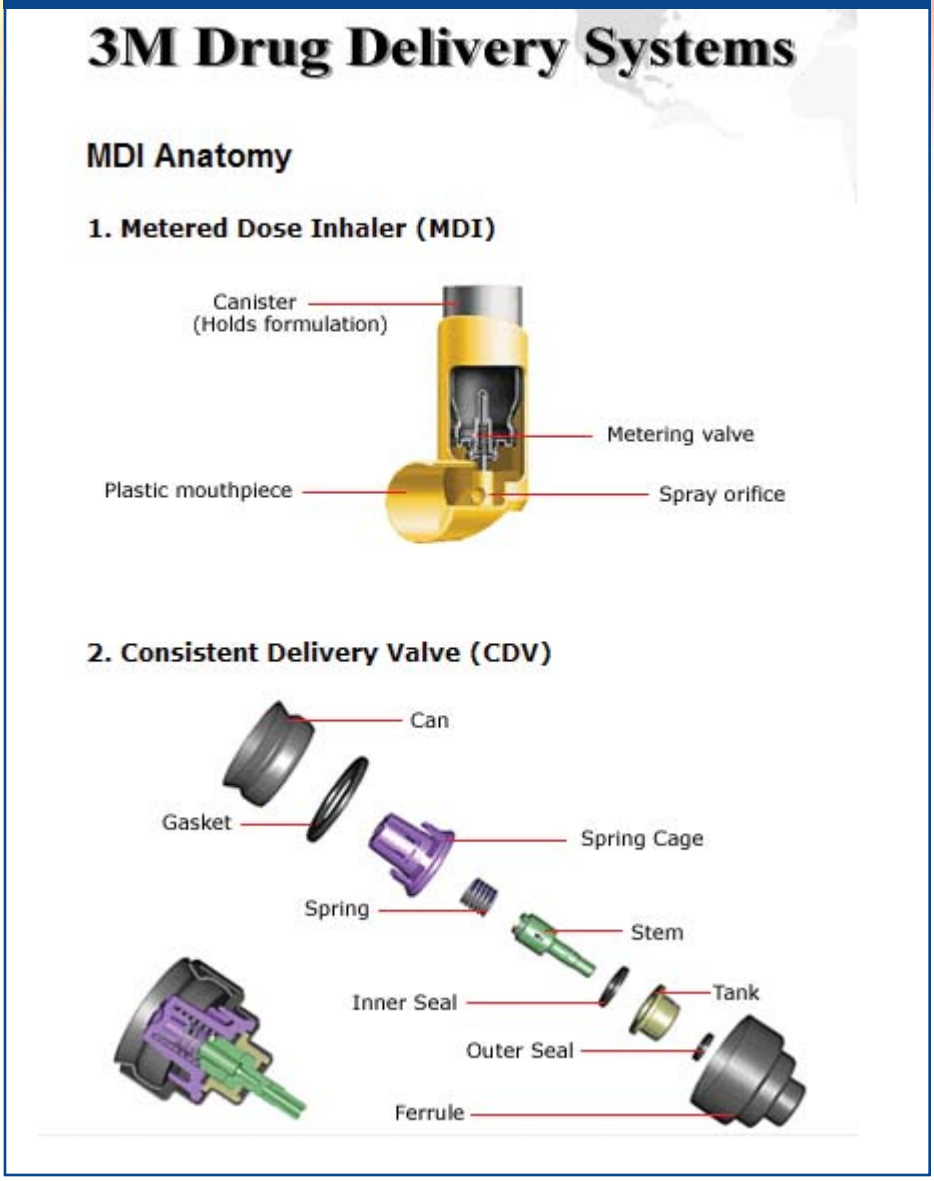
FIGURE 1



development, and inhalable forms of morphine, fentanyl, etc, offer quick onset of action. Next will be drugs to treat nausea and vomiting. Finally, we will see hormone treatments. A list of drugs in development can be seen in Table 1.

Using the lung is a paradigm shift, and key to all of these new treatments will be the advantages (and disadvantages) of pulmonary delivery devices, such as safety, ease of use, consistent dosing, controllable dosing, lockouts, and monitoring capabilities.

BUILDING A BETTER MOUSETRAP

Now considered a first-generation inhaler, Exubera will find itself among a crowd of next-generation inhalers. Here is an updated review of some of the technologies currently in development. The stages of development for the following technologies and products can be seen in Table 1.

3M's MDI

James Stefely, PhD, MBA, Senior Research Specialist at 3M Drug Delivery Systems, believes the recent approval of Exubera will have a significant impact on the systemic pulmonary delivery market throughout the next 5 years as their success increases the market's confidence in pulmonary drug delivery. As the threat of generic competition for some of the leading biotech molecules becomes more imminent, biotech companies are more likely to consider pulmonary delivery as a way to extend the life of their brand. Though Exubera is a dry powder inhaler, the concerns it addressed and the lessons learned apply equally to MDIs. The use of MDIs is still high, particularly in the US, and I believe we'll see more MDI formulations of large molecules in the pipeline.

3M has taken a broad approach to addressing the main issues that have slowed mainstream acceptance of inhalation delivery of systemic compounds. For instance, says Mr. Stefely, the company has taken two approaches to improve the dosing consistency to levels required by many systemic drugs having narrower therapeutic windows. First, it has been continuously improving its metered dosing valves to ensure consistent delivery (Figure 1). Second, it has focused on improving the formulation's consistency by developing several proprietary excipient families to improve the dose consistency and the dosing range. 3M's functionalized-PEGs family was specifically developed for use with biopharmaceutical compounds.

"3M scientists are demonstrating the feasibility of utilizing our proprietary MDI technology to deliver biopharmaceuticals. Investigations to demonstrate protein stability in HFA propellant systems, compatibility with MDI container closure systems, and delivery performance studies have shown promising results. Additional work in the area of particle size reduction has resulted in a novel, stable process for obtaining protein particles in the respirable range," says Dr. Stefely.

Epic's PROMAXX

PROMAXX dry powder microsphere technology enables the creation of uniformly sized microspheres that can be tailored to formulate many types of drugs, including protein drugs that are ideally suited for pulmonary delivery. "We are making microspheres using the PROMAXX technology that get delivered into the deep lung, and we can form these microspheres without excipients (Figure 2). This keeps the

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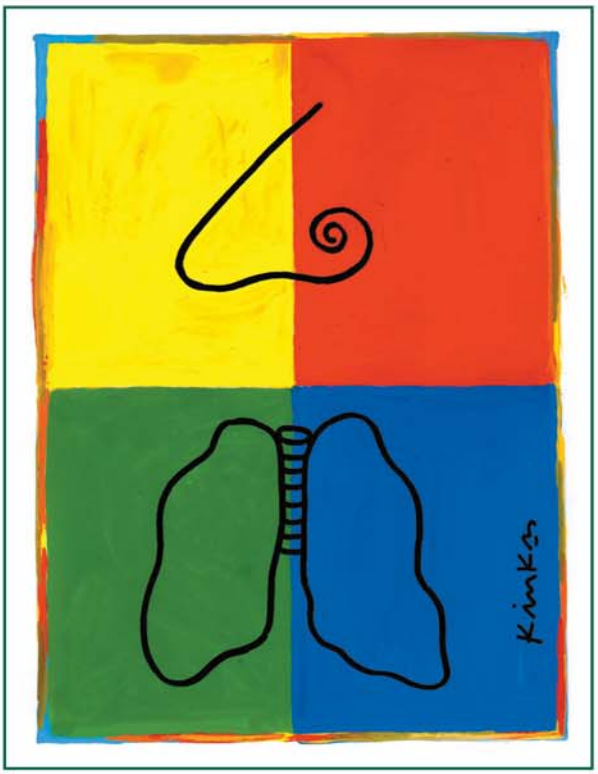

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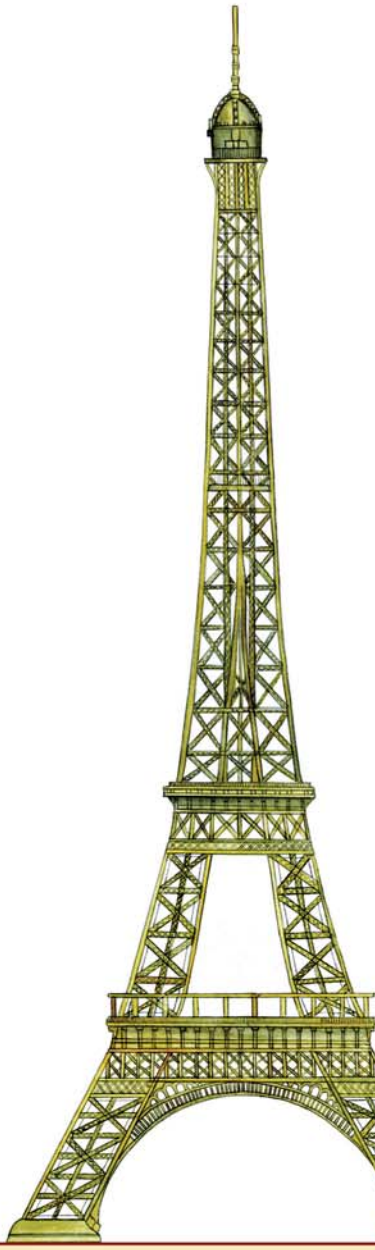

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FIGURE 2

Inhalable PROMAXX Microspheres

Suitable for Deep Lung Penetration by Andersen Cascade

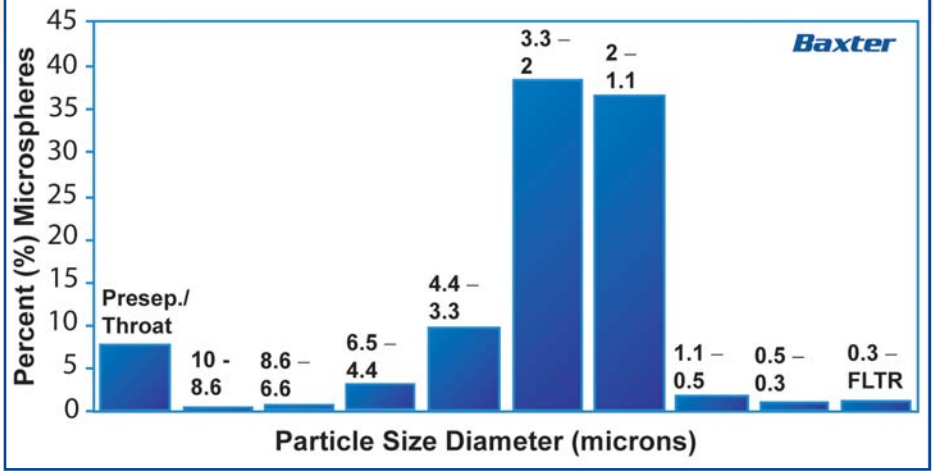

FIGURE 3

Inhalation Product Pipeline

Product	Indication	Pre-Clinical	Phase I	Phase II	Phase III	Projected sNDA/NDA
KI03216 Azmacort HFA (EDC)	Asthma					2H 07
KI02212 Insulin (BAI/VNA/EDC)	Diabetes					TBD
KI03218 Undisclosed	Endometriosis					2011
KI03219 ICS/LABA Combo	Asthma/COPD					2011
KI04204 ICS (Aero Device)	Asthma/Pediatric					2011

Kos Device References:
(EDC) Electronic Dose Counter
(VNA) Vortex Nozzle Actuator
(BAI) Breath Actuated Inhaler

KOS

formulation simpler and will likely result in a more clear-cut approval process. There are always zigs and zags in pharmaceutical development, but coming behind Exubera, we have a more straightforward path," explains Mr. Garramone.

PROMAXX microsphere technology offers narrow control of the microsphere size and the ability to vary drug-release profiles. The PROMAXX manufacturing process consists of a robust, gentle process that is water-based whenever possible to preserve the drug's protein structure and activity. The technology provides multiple options for solving drug delivery problems. High-load, high-yield formulations may provide the potential to develop safe, efficacious, and competitive therapeutic products.

To date, the company is currently in Phase I to study PROMAXX for insulin delivery, and feasibility studies are being performed to determine the potential of PROMAXX dry powder microspheres to deliver growth hormones.

Kos' MDI

Dr. Ralf Rosskamp, Executive Vice President, R&D, Kos Pharma, explains that Exubera's FDA approval was held up (putting Pfizer back into trials for another 2 years) because patients were experiencing reduced lung function. He attributes this reduced lung function to the fact that Exubera contains excipients and preservatives in addition to insulin. He says that Kos' product for inhaled insulin, which is currently in Phase II trials, contains only insulin.

"Exubera users will have to undergo an initial lung function test before using the product and will then have to undergo such tests every 6 to 12 months," says Dr. Rosskamp. "Insulin is natural to the body, but the added preservatives and excipients are not common to the body. By not incorporating those additions into our pure insulin product, we expect that users of our product will not have to undergo lung function tests."

Another difference that Dr. Rosskamp believes sets Kos' product apart from Exubera is that the actual device is different. Kos' inhaler boasts a reservoir system that contains 120 puffs of insulin, similar to an asthma inhaler.

Leveraging its aerosol formulation expertise, Kos formulates several proteins for delivery via the lungs using a proprietary metered-dose inhaler (MDI) device. As cogent *in vitro* and *in vivo* data demonstrating the performance and efficacy of such systems is developed, Kos is seeking to attract development partners skilled in developing biotherapeutic compounds to complete clinical development of these systems.

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FIGURE 4a

FIGURE 4b

FIGURE 5

Alkermes®

AIR® Insulin: Profile

- An important alternative to insulin injection
  - AIR technology provides the potential for improved therapeutic outcomes
- Multiple clinical trials successfully completed
- Large-scale manufacturing facility in place
- Easy-to-use inhaler design finalized
- Partnered with Eli Lilly

Complementing the formulation capabilities, Kos is developing a line of proprietary, state-of-the-art inhalation devices for delivering small and large molecules (Figure 3). To date, the focus is on a breath-coordinated inhaler, a breath-actuated inhaler (BAI), and a spacerless MDI device that generates low plume force.

Ventaira's Mystic

Ventaira's pulmonary devices, which are based on electrohydrodynamic (EHD) aerosol delivery, enable efficient, safe, and consistent delivery of drugs to and through the lungs. Ventaira inhalation devices utilizing Mystic™ technology (Figure 4a and 4b) deliver a low-velocity, soft (isokinetic) cloud of uniformly sized particles with more than 80% of the drug getting to the lungs. This is accomplished without the need for liquid propellants or other pressurized systems.

Ventaira has developed a portfolio of drugs from multiple chemical classes for treating both local lung and systemic diseases. "Uniform and consistently delivered and controlled particles are difficult, but critical", says Ms. Williams. "As the drug gets deeper into the lung, airways become narrower and narrower."

Small particle size is essential to ensure that compounds for systemic disease do not deposit in the upper airways and do indeed make their

SYSTEMIC PULMONARY DELIVERY FINDS ITS FIRST STEPPING STONE

Table 1. Commercially developed insulin technologies through oral route.

Product Name (generic name)	Company Name	Indication	Dev. Status	Technology	Description
Exubera (insulin)	Nektar/Pfizer	Type 1 & Type 2 Diabetes	Approved January '06	Inhance	DPI
AERx iDMS (insulin)	Aradigm/Novo Nordisk	Type 1 & Type 2 Diabetes	Phase III	AERx	Electronic Aqueous Droplet
Technosphere/Insulin	MannKind Corp	Type 1 & Type 2 Diabetes	Phase III	Medtone Technosphere	DPI/FDKP Microsphere Formulation Technology
Insulin	Alkermes/Lilly	Type 1 & Type 2 Diabetes	Phase III	AIR	DPI
Morphine	Aradigm	Pain	Phase II	AERx	Electronic Aqueous Droplet
VR004 (apomorphine hydrochloride)	Vectura	Erectile Dysfunction	Phase II	Aspirair	DPI
Dronabinol	Nektar/Solvay	Migraine	Phase II	Inhance	DPI
Amikacin	Nektar (Aerogen)	VAP	Phase II	PDDS	OnQ Electronic MicroPump
AeroDose Insulin	Nektar (Aerogen)	Type 1 & Type 2 Diabetes	Phase II (on hold)	AeroDose	Electronic Aqueous Droplet
KI02212 (insulin)	Kos	Diabetes	Phase II	Proprietary MDI	Breath-actuated MDI with electronic dose counter and Vortex Nozzle Actuator
Undisclosed Small Molecule	Aradigm	Pain	Phase I	AERx	Electronic Aqueous Droplet
Human Growth Hormone	Alkermes/Lilly	Growth Hormone Deficiency	Phase I	AIR	DPI
Recombinant PTH	Alkermes/Lilly	Osteoporosis	Phase I	AIR	DPI
Epinephrine	Alkermes	Anaphylaxis	Phase I	AIR	DPI
Alveair (insulin)	Coremed USA	Type 1 & Type 2 Diabetes	Phase I	Alveair	Bioadhesive Polymer Technology
VR776 (off-patent marketed compound)	Vectura	Premature Ejaculation	Phase I	Aspirair	DPI
Technosphere/sCT (salmon calcitonin)	MannKind Corp	Osteoporosis	Phase I	Medtone Technosphere	DPI/FDKP Microsphere Formulation Technology
Technosphere/PTH (parathyroid hormone)	MannKind Corp	Osteoporosis	Phase I	Medtone Technosphere	DPI/FDKP Microsphere Formulation Technology
BioVant (vaccine adjuvants)	BioSante	Various	Phase I	CAP Particles	Formulation Technology
Testosterone	Aradigm	Undisclosed	NA	AERx	Electronic Aqueous Droplet
BioAir (insulin)	BioSante	Type 1 & Type 2 Diabetes	Preclinical	CAP Particles	Formulation Technology
AERx Liposomal Ciprofloxacin	Aradigm/Defense R&D Canada	Inhalation Anthrax	Preclinical	AERx	Electronic Aqueous Droplet
AERx (nicotine)	Aradigm/ US NIH	Smoking Cessation	Preclinical	AERx	Electronic Aqueous Droplet
AERx Liposomal Treprostinil	Aradigm/United Therapeutics	Pulmonary Arterial Hypertension	Preclinical	AERx	Electronic Aqueous Droplet
VR040	Vectura	Parkinson's Disease	Preclinical	Aspirair	DPI
KI03218 (active undisclosed)	Kos	Endometriosis	Preclinical	Proprietary MDI	MDI
Tempo Migraine (active undisclosed)	MAP Pharmaceuticals	Migraine	Preclinical	Tempo	Next-Generation PMDI
Undisclosed	Vectura	Migraine	Research	Aspirair	DPI
VR400	Vectura	Female Sexual Dysfunction	Early Research	Aspirair	DPI
Small Molecule Analgesics	DirectHaler A/S	Pain	Early Research	DirectHaler Pulmonary	DPI
Undisclosed	Chrysalis Technologies	Undisclosed	Early Research	Aria	Soft Mist
Undisclosed	MicroDose Technologies/3M	Undisclosed	Early Research	MicroDose	Piezo-Electric Aqeous Droplet
Undisclosed	Ventaira	Nausea/Vomiting	Early Research	Mystic (EHD)	Soft Mist
Undisclosed	Ventaira	Undisclosed	Early Research	Mystic (EHD)	Soft Mist
Undisclosed	Ventaira	Immunosuppression	Early Research	Mystic (EHD)	Soft Mist

SYSTEMIC PULMONARY DELIVERY FINDS ITS FIRST STEPPING STONE

journey into the alveoli for systemic delivery. Ventaira claims it can control the particle size characteristics of the aerosol can by adjusting a number of variables, such as physical and chemical properties of drug formulations, flow rate, operating conditions, and the electric field. This subsequently allows for targeted distribution in the lung.

"Our technology is highly differentiated based on our ability to control particle size, thereby tailoring drug delivery for the specific therapeutic need," Ms. Williams adds. "We also have the ability to provide programmable dose control. Now that Exubera is approved, the stage is set for using the lung to deliver drugs for systemic disease. The unique attributes of Ventaira's technology make it adaptable for the treatment of both acute and chronic systemic diseases. We are aggressively advancing development in this area."

The aerosol mist generated by Mystic technology is delivered using the patient's own breath, meaning that the patient can easily control the drug delivery. The breath triggers the device to deliver the right dose. This delivery mechanism is especially suited for use with young children, seniors, and patients with compromised respiratory function. The therapeutic mist dispersion delivers liquid solutions and potentially, suspensions. In the spray nozzle of a typical Ventaira device, fluid flows over an electric field, and a charge builds up on the fluid surface. When the fluid exits the nozzle, the repelling force of the surface charge overcomes the surface tension of the fluid, forming a soft mist droplet aerosol.

Alkermes' AIR

Rebecca Peterson, Vice President, Corporate Communications at Alkermes, says, the company views the recent approval of Exubera in both the US and Europe as a positive advancement for the diabetes field. There is now a clear, proven regulatory pathway to approval in both the US and Europe. "Our next-generation inhaled insulin product, AIR insulin, continues to advance in the clinic."

The AIR® Pulmonary Drug Delivery technology (Figure 5) offers a unique, proprietary delivery system for optimized drug delivery to the lungs. This system can provide efficient dry-powder delivery of small molecule, peptide, protein, and other macromolecule drug particles to the deep lung. Alkermes currently has ongoing large-scale trials with both protein therapeutics and small molecule drugs in a range of therapeutic areas.

In January 2006, Alkermes entered into an agreement with Eli Lilly to develop and commercialize inhaled formulations of parathyroid hormone (PTH). "This agreement underscores Alkermes' commitment to leverage our delivery technology platforms to bring forward innovative products in major disease areas, like osteoporosis," says Ms. Peterson. "Adherence is a problem with many current medications for osteoporosis, as they require patients to administer injections or stand for a period of time following administration. An inhaled formulation of PTH could potentially provide patients with a more acceptable treatment option."

LOOKING AHEAD

Although currently driven by the respiratory market, demand for inhalable drug delivery technology looks set to increase rapidly in the longer term if systemic inhalable therapies can achieve their full potential.

According to a new report from Greystone Associates of Amherst, New Hampshire, advances in drug formulation and inhalation device design are creating new opportunities for inhaled drug delivery as an alternative to oral and parenteral delivery methods. These developments are attracting new players and new investment, accelerating the pace and number of new pulmonary delivery candidates entering the drug development pipeline.

While inhaled insulin — with its demand profile, favorable market outlook, and quality-of-life implications — is the focus of media attention, more than a dozen other important disease therapies and treatment options have been quietly winding their way through the development and clinical trial process. These new combination products include inhaled drugs for the treatment of endometriosis, several forms of cancer, hemophilia, MS, neurological disorders, and pain management.

Several of these emerging drug products will have a significant impact in the therapeutic markets they target, states the Greystone report, improving patient compliance and effectively changing the way important illnesses and conditions are treated. ♦

BIOGRAPHY

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

ANALYTICAL SUPPORT

Analytical CMC Activities Involved in Phase I Clinical Trials: Enhancing Partnerships & Development

By: J. Blair West, PhD, and Kevin M. Kane, PhD

ABSTRACT

The successful advancement of a drug product through Phase I clinical trials relies heavily upon high-quality scientific preclinical studies that demonstrate that the product and its manufacturing methods do not yield components that are potentially harmful to the human subjects. The soundness of these supporting data is ensured only by appropriate analytical methods; a complete and thorough study of the API, formulation components, and manufacturing methods; and rigorous stability studies. Investment in robust preclinical studies to support a complete CMC package can result in fewer risks and delays of revenue caused by problems in Phase I trials. This overview gives the necessary elements that enable a successful execution of clinical trials beyond Phase I.

INTRODUCTION

Whether trying to advance a new drug candidate, a first-to-generic version of an existing drug, or a new drug delivery technology, a company is required to demonstrate to the FDA that its product or technology is safe and effective. This burden of proof must be demonstrated in a series of clinical trials in human subjects, during any of which a drug may fail because of human-specific toxicity or a lack of efficacy, inherent risks that must be explored. But before a drug or technology can be examined in the clinic, its "credentials" must be presented to show: that the drug is fully characterized; that it is identical to the substance used in prior animal toxicity studies; that the process feedstocks, methods, and equipment do not impart any hazards to clinical trial subjects; and that the analytical methods used to generate these supporting data are appropriate and specific to the entire history of the drug product.

Small drug delivery or discovery companies oftentimes cannot support full analytical resources internally, whereas larger firms may have their analytical teams dedicated to other projects. Generic companies may not have enough experience to adequately investigate the complexities of an expiring drug because limited data are in the public domain. In addition, virtual or small companies rarely find a partnership in which the larger company funds the required analytical effort. Phrases like, "we won't pay for your learning curve," are a common response to an otherwise successful presentation to a potential development and funding partner. In these cases, a development partner is needed who can provide the analytical proof — as a robust data set that is sufficiently broad — that a drug product is safe enough to be tested in first-in-human clinical trials.

To be sure, some companies will conduct or commission "just enough" analytical studies to support an application for clinical trials of their product or technology. But the financial risks to a company are astronomical if a poorly characterized impurity causes harm to a human subject, or a stability study incorrectly showed a product shelf-life. The effort and money not spent before going to the clinic will be dwarfed by the costs in lost or delayed revenue because of restarts or — even worse — harmed subjects. Clearly, it serves both the target patient population and the pharmaceutical company to fund robust and high-quality scientific preclinical studies that will support successful clinical trials and lead to an on-time product launch. Careful research into the capabilities and track-record of its analytical support partner can ensure a company that the supporting data for a submission for clinical trials will be complete, scientifically sound, and stand up to scrutiny by the FDA.

PHASE I CLINICAL TRIALS: OBJECTIVES & ACTIVITIES

The primary objective of a Phase I clinical trial is to provide a controlled introduction of a new drug into humans in order to assess its safety. To achieve this goal, the drug is administered to a small group of patients or normal volunteers, typically healthy adults. During the trial, subjects are monitored closely, drug levels measured, metabolism of the drug monitored, and pharmacological actions of the drug in humans assessed. Any side effects are closely watched and recorded, especially those that occur with increasing dose. A well-designed Phase I trial may also provide early evidence of drug effectiveness, and will provide the basis for design of well-controlled, scientifically valid Phase II studies, in which the effectiveness of the drug will be tested in a larger population.

TABLE 1

Examples of preformulation data. Salt screening of a basic compound involves formation of pharmaceutically acceptable salt forms and initial physico-chemical characterization. These data and additional information, such as API stability or aqueous solubility, are used to select the optimal salt form.

SAMPLE NAME	SAMPLE APPEARANCE	SOLUBILITY (mg/mL)	T_{melt} °C (at Peak)	Crystallinity (wt-%)	Equilibrium Moisture Content (wt-% @ 25°C/ 75%RH)	Polymorphism Yes/No/Suggested
Drug, free base	Coarse, tan powder	12.26	254.1	88	0.41	No
Drug , Sulfate	Coarse, tan powder	1688.44	120.9	70	14.52	Yes
Drug , Phosphate	Coarse, tan crystals	87.44	210.7	12	4.15 - 9.14	No
Drug , Sulfate	Fluffy white powder	671.22	274.6	15	7.96	Suggested
Drug , Sulfate	Bluish Crystals	522.88	176.2	60	14.66	No
Drug , Sulfate	Bluish Crystals	471.99	131.7	40	14.50	Suggested
Drug , HCl	Coarse, tan Crystals	491.81	143.0	70	5.28	Suggested
Drug , Mesylate	Fine, white powder	311.42	166.3	74	1.21	Yes
Drug , Besylate	Coarse, tan powder	188.21	241.7	82	0.65	No
Drug , Besylate	Coarse, tan Crystals	136.77	291.6	12	1.77	Suggested
Drug , Salicylate	Fine, white powder	62.61	143.0	70	3.11	Suggested

The CMC (Chemistry, Manufacturing, and Controls) section of any IND (Investigational New Drug) application should provide sufficient information to demonstrate that synthetic and manufacturing processes are understood and that analytical methods are in place to ensure the identification, quality, purity, and strength of the drug and drug formulation being tested. The information needed to comply with these requirements depends on a number of factors: the phase and duration of the study, the particular dosage form and route of administration, the novelty of the drug, existence of previous studies, the patient population, any known or suspected safety risks, the manufacturing processes involved, and other factors. In Phase I specifically, the analytical methods must provide adequate information to allow for the evaluation of the safety of subjects, and to relate the drug product in the clinical study to drug products used in any animal toxicology studies.

Analytical Data Required in the CMC

As outlined in 21CFR 312, the CMC section of an IND should contain descriptions of the nature of drug substance, drug product, related placebo, the analytical

methods used to assess the drug substance and product, a description of labeling procedures, and an environmental assessment for the manufacturing process.

For the drug substance, the required information includes a description of the drug substance (physical, chemical, and biological characteristics), identification of the manufacturer, description of the preparation methods, analytical methods for the drug substance, and information related to stability of the drug substance. The description of the method of preparation should include the synthetic method and a listing of reagents, solvents, and catalysts used. The section on analytical methods should describe the methods, outline the proposed criteria for acceptance or release, and provide any certificates of analysis that may exist for the drug substance. For both drug substance and drug product, a demonstration of the stability of the API — both alone and in the dosage form — must be presented. A brief description of a stability study should be given, including test methods used and preliminary tabular data.

Similar data for the drug product should be provided. A quantitative description of the composition of the dosage form, including a list of all excipients and their grade (ie, USP/NF or ACS) should be included. The manufacturer should be identified with the method of manufacture, including all processes. As with the drug substance, details of the stability study used to demonstrate chemical stability of the API in the dosage form is presented.

One visual model of the necessary steps to writing a solid CMC section for an IND submission is a pyramid. As shown in Figure 1, the pyramid constitutes the entire knowledge base of a CMC, and the analytical methods are the critical base upon which all other activities rest. Using appropriate and strong analytical methods, structural and chemical data relating to the API and the resultant formulations and underlying processes can be obtained. Any problems, such as impurities or degradants arising from stability studies, will need to be addressed by isolating or synthesizing the reference standards needed to qualify these related compounds. A well-built CMC section will then stand up to scrutiny by regulatory officials as they evaluate the safety of the proposed clinical trial material.

Soundness of Analytical Methods Used

As stated previously, the purpose of the CMC section is to demonstrate that the identity, strength, quality, and purity of investigational new drugs is ensured, especially as these characteristics relate to safety of the dosage form being studied. The analytical methods package supporting the drug product development ensures these targets are met and that a dosage form is free from safety concerns as it moves into clinical trial testing. For example, safety concerns arise when a drug product is made with unknown or impure components or in a processes where the sterility or apyrogenicity of the dosage form is not ensured (eg, for injectables). Stability of the API in the drug product must be demonstrated, typically for the time period equal to the duration of the clinical trial. Failure to do so may stop or delay the clinical trial because purity can no longer be guaranteed. Other concerns include situations where the drug strength or impurity profiles are insufficiently well-defined, or the impurity profile indicates a health hazard.

Characterization of the API

As soon as one or more sources for the API have been identified, the critical work begins on characterizing that API and related compounds. Isolation and characterization of reference standards of the drug is a primary task, followed by analyses of known or suspected process-related impurities and degradants. Bulk supplies of the API are needed in order to support salt selection and polymorph screening studies, and these supplies are used in the development and validation of analytical methods. Data collected from the analyses of multiple lots of API enables the establishment of release specifications for GMP supplies of the API and also provides baseline data for assessing the chemical and physical stability. Table 1 shows some examples of the data for a drug studied in a preformulation study.

Beginning with the reference standard, the characterization data collected include structural analyses (^{1}H and ^{13}C NMR, FTIR, mass spectrometry, etc); the confirmation of potency and purity using chromatographic methods; and the measurement of other properties, such as the contents of moisture, residual solvents, metals, and ash.

With the reference standard characterization data in hand, a full-spread analysis of the bulk API is performed, with additional tests conducted in order to provide data on representative samples of the materials used in manufacturing the drug product. Along with the chemical assay and purity data, physical properties, such as hygroscopicity and thermal behaviors for all polymorphs, are collected. Forced degradation studies yield physical and chemical stability data that are critical for downstream activities. Chemical synthesis of known degradants can be used as final confirmation of structure and provide material for reference standards for analytical methods, and be used for qualification purposes, if needed.

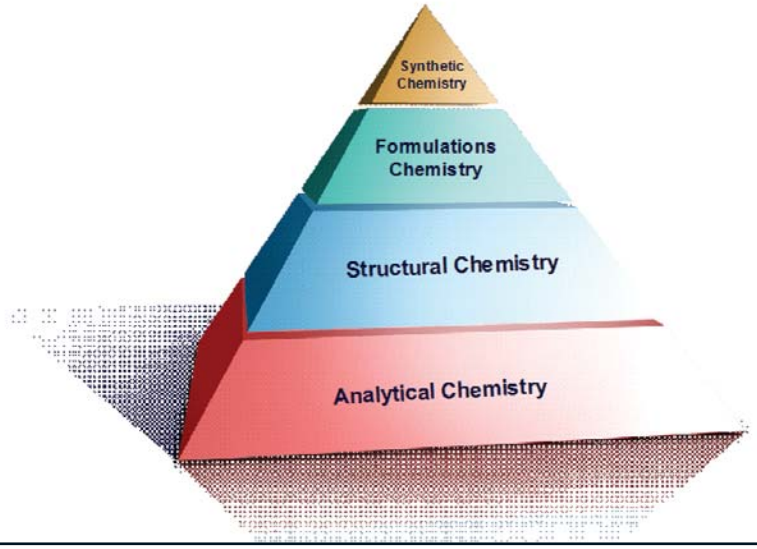
Characterization of the Drug Formulation

Collectively, these data are used in designing and selecting lead formulation prototypes. In fact, a design of experiments (DOE) approach can screen for and identify the most critical physical and chemical properties of the excipients that will yield a formulation with maximal performance and stability properties. For example, characterization data (such as degree-of-substitution or polymeric molecular weight) from many different lots and grades of an excipient measured against the performance or stability of prototype formulations can be used to establish specifications that ensure an optimized product. These same formulations data are then available to guide formulation selection for either a new dosage form or a new API. The same approach has been successfully applied to establishing process parameters that yield optimized drug formulations.

Salt selection and polymorph studies are increasingly important tasks in supporting CMC studies for clinical trials. The advantages of selecting a salt form with

FIGURE 1

Well-designed CMC activities involve the development and application of solid analytical techniques that support further studies into the chemistry of the API and its formulated products. Strong analytical methods can identify process impurities or degradants that will need to be isolated or synthesized for full characterization as reference standards.



increased aqueous solubility or better chemical stability are well-recognized. Equally important, though, are the molecular-scale chemical and physical properties of polymorphs that can affect solubility, stability, and bioavailability, but the bulk properties of polymorphs can greatly affect their manufacturability and formulation. Investigations on possible salts and polymorphic species can reveal potential risks and opportunities early in the development process when these studies are conducted in the context of likely manufacturing and processing conditions. These learnings can be transferred to scale-up teams early and reduce the chances and costs associated with correcting for incompatible process conditions that yield off-specification batches of API and/or drug product.

Method development and validation are critical tasks to providing reliable supporting analytical data on the API and subsequent drug product. The most common techniques developed and validated are assay and chromatographic purity methods for characterizing the quantity and quality of the API, as well as residual solvents methods. The potential presence of contaminants, degradants, or solvents requires the generation of these validated methods to determine the amounts of species that may pose health risks to clinical trial subjects and patients. Validation of an analytical method demonstrates that it is specific for the API in question, that it exhibits a linear instrument response over a given range of API concentration, that the method is accurate ("true") and precise ("repeatable"), and that limits of detection and quantitation have been determined and verified.

The Real Burden of Proof: How Do You Know What You Know?

The use of validated analytical methods enables one to reliably set manufacturing and release specifications for API and drug product because they are based on quantifiable data sets. In addition to visual inspection (appearance), the measurable attributes of drug assay and purity, and residual moisture, solvent, metals, and ash contents can be set; thus, each lot of API, excipient, and formulation is then evaluated against these specifications. Those lots meeting the specifications — supported by rigorous testing standards — can be released with the confidence that they contain no potentially harmful contaminants.

Oftentimes, additional release specifications are required that report properties having an impact on manufacturability (eg, particle size) or physical identity (eg, PXRD for polymorph verification). Release specifications also must be written for the finished product. For a liquid or semi-solid product, packaging and labeling specifications need to be defined, whereas for solid tablets or capsules, the expected appearance of these products must be set.

Product Safety & Lifetime From Stability Studies

Throughout this specification process, there is a rigorous and continuous assessment of the stability of the API, excipients, and finished drug product. Shelf-life determination for a product is again driven by safety of the clinical trial subject, in that there can be no chance of the inclusion or formation of harmful contaminants or degradants during the manufacture of the clinical supplies or over time during the course of the clinical study. Here, the stability data obtained during the forced degradation studies of the API and prototype formulations provide guidance on the storage method and duration of the formulation so that changes in chemical or physical composition are minimized. After exposure to accelerated (40°C/75% RH) and long-term (or ambient 25°C/60% RH) stability conditions, the API, excipients, and drug product are measured for appearance, assay, purity, and other physical attributes.

The stability data are compared to both time-zero and reference standard specifications so that stability effects of the formulation can be determined. For a poorly designed formulation (or a good formulation based on poor-quality data),

this means that a costly reinvestigation must be performed to address the underlying causes of failure or conflicting data. Even well-designed formulations sometimes yield surprises; however, a robust data set from preformulation and formulation studies can shorten the investigation time required to reformulate. For example, the appearance of a different polymorph in stability samples can quickly be investigated to confirm that the polymorph was absent before stability testing began, that it matches polymorphs already identified, and that its dissolution release performance may still meet the target profile. If a high-quality and sufficiently broad dataset is available, an opportunity now exists to either pursue a new formulation with that other polymorph at the outset or refine the excipient set to suppress polymorph conversion. Moreover, if the polymorph found in the stability samples is unique, the characterization data can support even broader patent protection for the API.

Know Your Packaging

Although the intrinsic stability of the formulation and its components must be measured, the packaging used for the drug product must also be shown to not adversely affect the quality and safety of the formulation it holds. Sources of packaging materials must be qualified as meeting specifications that are based on analytical characterization (stability testing) of the packaging materials in contact with the formulation. Vendors of packaging components can generate their own certificate of analysis (COA) from data collected using validated analytical methods. In many instances, the influence of a packaging material on a drug product is assessed using compendial or developed-and-validated testing methods specific to that drug product.

By the time a final drug product has been produced, the analytical methods outlined here will provide a large body of supporting analytical data that can demonstrate the identity, purity, strength, and quality of the product and support assurance of the safety of that product. These data come from the preceding analytical characterization performed during the preformulation studies, the formulation development, the analytical method development and validation studies, the specification generation and finished product release testing, and finally, the stability storage and testing of that finished product.

SUMMARY

In summary, well-defined and understood CMC aspects of a Phase I clinical study not only minimize the risk of regulatory deficiencies but enhance the facilitation of Phase II and beyond clinical trials through a keen understanding of the reactive and interactive properties of the API in the presence of its formulation components. Success in Phase I is enhanced by the careful development of high-quality analytical methods and subsequent validation of those methods for analyzing the API and resultant formulation, establishing the release specifications, and designing the packaging and labeling of the product. As a result, the data produced by these scientific studies can show with a high degree of confidence that the new drug product presents no known risk of harm to the clinical trial subjects, and with a positive outcome from Phase I, can lead to a rapid start of Phase II trials and beyond. The important first step, then, is to identify the development partner with the experience and capability needed to perform these high-quality studies.

BIOGRAPHIES

Dr. J. Blair West is the Technical Director for Azopharma. Prior to joining Azopharma, Dr. West worked in the areas of pharmaceutical process design, drug discovery technology development, novel drug synthesis technology, formulations research (drug solubilization, excipient design, formulations aids to improved absorption), drug delivery platform design (controlled release, triggered release). Dr. West earned his PhD in Bio-Organic Chemistry (Enzymatic Organic Synthesis) from Texas A&M University, and his AB in Biochemistry from Harvard University.

Dr. Kevin M. Kane is the Technical Manager at Azopharma. Before joining Azopharma, Dr. Kane was Senior Research Chemist and Team Leader for Hewlett-Packard's Drug Delivery program in Puerto Rico, developing solubilization, particle-size reduction, and formulation methods based on HP's thermal-inkjet technology platform. Prior to that, Dr. Kane worked for R&D firms in the Pacific Northwest on drug formulation and process development. Dr. Kane earned his PhD in Inorganic Chemistry from Ohio University, and his MS and BS in Chemistry from Texas State University, San Marcos.

Drug Delivery EXECUTIVE

MedPharm: Development Specialists Applying Innovative Delivery Technologies & Formulations to the Market

DR. ANDREW MUDDLE
Chief Executive Officer
MedPharm

"If you subscribe to the current theory of the industry being based on a relatively small handful of core drugs, then reformulation will be key to extending product pipelines, by widening the applications and improving the efficacy of old and well-respected drugs."

MedPharm is a private company that is building on its success as a contract formulation development services provider to rapidly becoming a recognized pharmaceutical development specialist of international standing. As well as a first-class service operation, focusing on topical skin, nail, nose, lung, and other mucous membranes drug delivery, the company now boasts a product development pipeline of its own based on delivery systems that is has developed. Throughout the past year, the company has announced two major new delivery technologies: MedSpray, a novel spray system for dermatological applications, and MedNail for enhancing delivery of drugs across nail. It is now looking to exploit these technologies through internal drug development programs and licensing relationships. Drug Delivery Technology recently interviewed Dr. Andrew Muddle, CEO of MedPharm, to discuss the exciting opportunities MedSpray and MedNail bring as well as the often undervalued importance of formulation development in turning compounds into medicines.

Q: Can you discuss the origins of MedPharm?

A: Back in 1999, colleague Dr. Marc Brown and I saw a major gap in the market for contract pharmaceutical development, particularly for alternative delivery routes. Pharmaceutical companies were cutting back on in-house formulation development teams, and there was a shortage of outsourcing alternatives. Those who remained concentrated mainly on traditional oral routes by tablets and capsules. We already had a wide network of contacts through my industry background and Dr. Brown's academic position at King's College London. Very quickly, we built a reputation for tackling unusual formulation requirements, for example by reformulating failed formulations. Thanks to a lot of hard work and good science, the clients we had secured kept coming back. They helped spread the word and the rest is history, as they say. Throughout the

past 5 years, the company's revenues have grown at an annual average of 38% mainly through projects concerning the topical route. By topical we mean skin, nail, nasal, buccal, vaginal, as well as via the airways; it's become our speciality for which we're now recognized all over the world. Currently, we deal with more than 55 companies worldwide, half in the US. These range from some of the largest Pharma companies to small, often virtual biotechs. We work with a lot of NCEs but are also getting more involved in reformulation. We now offer a full range of services from feasibility studies, dosage design, and optimization through to preparation of GMP clinical supplies for Phase I/II trials.

Q: Why do you believe formulation to be so important?

A: Far too often, formulation development is still left until the last moment and only allocated a fraction of the budget, which is amazing in my opinion because formulation is the key stage in which we actually turn the molecule into a medicine ready for trials. If the drug fails in clinical trials and the formulation is wrong or unsuitable, we don't know if it's the drug or the formulation to blame. We believe that getting the formulation right is very important indeed and in the grand scheme of things, it's a small price to pay. Most of our clients are beginning to recognize that, and by working with us, we'd like to think we have offered them a significant competitive advantage. I have lost count of the times I have seen a molecule with good efficacy that is totally unsuitable for the proposed delivery method and dosage. Furthermore, because the average formulation project takes approximately 12 months, any delay can be extremely costly in overall terms of bringing a drug to market. Formulation must be considered early on in the design of a development project and allocated sufficient budget. Having said this, whichever way you look at the pharmaceutical industry, I believe formulation will be a major factor in its continuing success. If you subscribe to the current theory of the industry being based on a relatively small handful of core drugs, then reformulation will be key to extending product pipelines, by widening the applications and improving the efficacy of old and well-respected drugs. On the other hand, correct formulation offers small biotechs greater chances of success with the thousands of APIs in development.

Q: Please describe your own delivery technologies MedSpray and MedNail?

A: As previously mentioned, the majority of our projects have been in the "alternative" delivery markets – dermal, ungual, nasal, and pulmonary. This has brought about its own special formulation challenges and led us to develop our own delivery technologies. The first technology is MedSpray, a spray technology primarily for dermatological for dermal as well as transdermal applications. Then there is MedNail, a novel system using known excipients to dramatically improve the penetration of drugs across the nail, for example fungal infections. Our plans for these technologies have two aspects. First, we have built our own product portfolio by reformulating existing drugs that are now off-patent for indications for which we strongly believe our delivery systems will offer a competitive advantage. Our first port of call is the dermatology market for which where we are developing novel sprays for acne and eczema, and a new topical treatment for onychomycosis (fungal infection of nail). Second, we are actively seeking to license the technologies, particularly MedSpray, to multiple partners on an indication-by-indication basis, and have recently announced our signing of an Evaluation Agreement that we expect will lead to the first of many licence deals.

Q: Tell us more about MedSpray and its potential in the dermatology market?

A: Spray technology is rapidly becoming the delivery method of choice in the dermatology market due to its increased patient acceptance and consumer appeal, and ability to deliver increased efficacy with lower dosage rates. We are convinced that our technology offers a significant competitive advantage over creams, ointments, and gels that together are losing favor amongst young adults in particular. By addressing these challenges, MedSpray will be attractive to all companies active in the sector. First, we can reformulate existing drugs and thus extend patent life. And second, we can offer more competitive products in a "Patch in a Can" format. We have already initiated a number of clinical development projects by reformulating existing, proven drugs that are now off-patent, and are now looking to license MedSpray on an indication-by-indication basis to interested parties. The first Evaluation Agreement was signed in January this year. MedSpray also has considerable potential in the transdermal sector, for example, for HRT and nicotine dependence, which we are exploring.

Q: Ungual delivery is another area with unmet needs?

A: That is for certain. The nail is one of the hardest barriers to penetrate, and again, formulation is the key for success. You might be surprised to learn that onychomycosis affects more than 10% of the population and is currently treated with drug-incorparated nail lacquers that are turning over good business but have poor success rates, or with oral therapeutics, which even though work, have significant side effects. Patients don't want to take a pill that could damage their livers are reluctant to take a pill to treat an infection of the nail. There's a clear need for a reliable topical treatment and that's where we can help. We have developed a series of unique in vitro screens and nail models, which have in turn enabled us to develop the MedNail ungual delivery platform that we strongly believe will help us to develop the first reliable topical treatment for onychomycosis. The product will be presented as a topically applied medicine and could be incorporated into a range of dosage forms (eg, lacquer, semi-solid spray).

Q: How do you see the future of MedPharm?

A: I see us continuing our dual business model of technology and product development together with a first-class service operation. Our contract services business is well developed and continues to generate good revenues. However, I see us being contracted more and more as overall development specialists with formulation just one element in a service stretching from project design to GMP manufacture of clinical supplies and beyond. These revenues will in turn enable us to develop the other side of the business, and in particular, our own product portfolio where we believe real value will be generated. Whilst we focused on dermal and ungual delivery in this interview, we are also for example involved in a joint venture with bidirectional nasal delivery specialists OptiNose with whom we are reformulating an existing, off-patent drug to develop a fast-acting sedative to treat insomnia. Therefore, the future looks extremely promising as the value of successful formulation becomes more and more evident. ♦

FOOD–FORMULATION INTERACTIONS

Food Effects on Drug Formulation Performance In Vivo

By: Rajeev Gokhale, PhD, Merck Research Laboratories

ABSTRACT

This review provides information of drug formulation performance in vivo in relation to food effect. Both immediate-release as well as modified-release formulations are considered. The fundamentals of food-drug interactions lie within the physicochemical and biopharmaceutical drug properties as well as food induced physiologic changes. However, food-drug interactions should be viewed as food-formulation interactions because different formulations perform differently when presented with food. There is mounting evidence that all the formulations of the same drug cannot be dosed under the same regime. The formulation food interactions, at a time, are spectacular but also problematic because the formulations will not be interchangeable. Nevertheless, formulation design based on food-formulation interaction is paramount to drug safety and efficacy.

INTRODUCTION

The influence of food on drug bioavailability has been elusive and intrigued the pharmaceutical scientists and the regulatory agencies throughout the past 4 decades. Formulation-food interactions attracted the media attention when several theophylline once-a-day formulations, introduced in late 70s, failed to produce equivalent exposures in fasted and fed subjects. The trend was clearly non-uniform. Some formulations showed increased absorption whereas others showed decreased absorption, with only one formulation showing no difference when co-administered with food. Dr. Aziz Karim had published an excellent article reviewing the food effect of theophylline formulations and emphasized the need to conduct food effect studies.[9] Theophylline melancholy has sparked numerous food effect studies to understand this phenomenon in greater details. The food effect studies are now conducted early in the program (Phase I) when the drug is administered with high-fat or low-fat meals at a certain time (before or after food) to measure impact on bioavailability. Outcome of food effect studies reveal the food-drug interactions and afford opportunity to address the problems with creative solutions. New formulations can then be developed to make commercial drug products out of active molecules.

Welling and co-workers have published numerous articles, dating back to 1977, to address the subject matter, Influence of food and diet on gastrointestinal drug absorption.[1-4] Charman and co-workers in a review article elucidated the effect of food and the role of lipids and pH in relation to physicochemical and physiological mechanisms for drug absorption.[5] More recently, Marilyn Martinez and Gordon Amidon have reviewed the fundamentals, paying specific attention to food and its effect on absorption.[6]

Fliesher and co-workers in their review article published in 1999 have focused on the drug and formulation physicochemical properties affecting drug absorption in the presence of food.[7]

Drug-food interactions are really the formulation food interactions, and there is a paucity of organized information to assess how different formulations of the same drug will interact differently with food. The objective of this article is to review the food-formulation interactions.

PHYSICOCHEMICAL & BIOPHARMACEUTICAL DRUG PROPERTIES & FOOD EFFECT

The following is a summary of key physicochemical and biopharmaceutical drug properties in relation to food effect, also tabulated with examples in Table 1. From the drug physicochemical stand point, in the perspective of food effect, pKa; solubility; stability; enzymatic hydrolysis; complexation with metal ions; and adsorption on to meal components, such as pectin and fibers, will be of importance.[7,8] The increased splanchnic blood flow will improve bioavailability for drugs absorbed from the upper gastrointestinal track having saturable first-pass effect. Certain foods are enzyme inducers, while certain others are inhibitors, and will affect drug absorption.[7]

FOOD–FORMULATION INTERACTIONS

Table 1. Physicochemical and Biopharmaceutical Drug Properties and Food Effect

Property	Influence of Food	Potential Food Effect
Weak acids, high pKa	Increased solublization in stomach due to delayed emptying, increased pH	+ Ve
Weak bases low pKa	Drug precipitation due to altered pH	- Ve
Acid labile drugs	Drug degradation in stomach due to delayed gastric emptying	- Ve
Class II and IV (poorly soluble drugs)	Improved solbilization, drug bile acid micelles are soluble	+ Ve , danzol[11], diethylstelbesterol[12], diazepam[13]
Class II and IV, in-soluble drug-bile acid complex	Decreased solublization	- Ve, neomycin, kanamycin, tubocurarine[10], large molecular weight antibiotics
Class II and IV high log P	Increased lymphatic flow and absorption	+ Ve, cyclosporine[14], narfetine[15], lipophilic vitamins[16]
Class III drugs with narrow absorption window	Decreased diffusivity due to high viscosity of food,	- Ve[17]
Complexation with metal ions	Unabsorbable drug-metal complexes (eg calcium in milk)	- Ve food effect, norfloxacin, Ciprofloxacin[20, 21]
Drugs binding to soluble fibres	Increased absorption	+ Ve food effect[53]
High first pass metabolism	Reduced systemic clearance	+ Ve, propranolol, metoprolol[18, 19]
Low first pass and high first pass drugs with absorption from upper duodenum and saturable metabolism	Increased splanchnic flow	+ Ve[6]
Substrates for enzyme inhibiton	Enzyme inhibition	+ Ve food effect
Substrate for enzyme inducers	Enzyme induction	- Ve food effect

pKa

A weakly acidic drug with relatively high pKa will have a positive food effect due to drug solublization in the stomach owing to delayed gastric emptying. On the other hand, weak bases with low pKa may precipitate and have a negative food effect.

Solubility

Poorly soluble compounds will show a positive food effect due to increased solublization in the presence of food and bile salts. Exceptions of poorly soluble drugs forming an insoluble bile acid complex impending the absorption are reported.[10] Soluble compounds may only undergo onset delay in the presence of food.

Stability

Acid labile drugs have the potential to undergo degradation in the presence of food, owing to increased stomach-emptying time, impacting absorption and bioavailability.

Complexation

Drugs binding to metal ions, such as calcium, will be influenced, as some of the food components, such as milk and yogurt, contain calcium.

Solubility & Permeability (BCS Classification)

The meal impact will be minimum for class I drugs (soluble and permeable) except for a possible delay in drug absorption. For class II (poorly soluble, permeable) and IV (poorly soluble and poorly permeable drugs), meals are expected to improve drug solublization and then absorption. For class III drugs (soluble and poorly permeable), issues related to drug permeability will affect drug absorption, increased viscosity in presence of food may impend drug absorption, especially if the drug has a limited absorption window.[6,17]

First-Pass Metabolism

Reduced systemic clearance may improve absorption of drugs undergoing first-pass metabolism.

Enzyme Substrates

Depending on induction or inhibition, bioavailability will be impacted.

FOOD–FORMULATION INTERACTIONS

FOOD-INDUCED INTERACTIONS

The effect of food components impacting drug bioavailability are listed in Table 2. The ability of meals to influence gastrointestinal pH; solubilization effects; and lymphatic absorption, motility, residence time, and blood flow would affect drug bioavailability.

High fat in food will improve bioavailability of poorly soluble drugs via improved solublization as well as transport to the lymphatic system. Food alters presystemic metabolism and can increase bioavailability of drugs undergoing first-pass metabolism. On the other hand, high-protein content in food may impede absorption of amino acid drugs by competing for absorption. Calcium and heavy metals in certain foods, such as milk and yogurt, may bind to drug and form insoluble complexes. Polycyclic aromatic hydrocarbons in smoked food, presence of enzyme inducers in certain spices, and cruciferous vegetables may decrease systemic bioavailability of enzyme substrate drugs.

FOOD-FORMULATION INTERACTIONS

Food-formulation selected interactions are illustrated in Table 3. Formulation excipients may impact the drug-release profile as well as bioavailability via different manifestations in the presence of food. Alteration in GI pH, as induced by food in the stomach, may reduce excipient solubility and retard drug release. Certain excipients may bind to drugs and retard disintegration of dosage forms when the pH in the stomach is elevated. Altered gastric retention time will cause single units to stay longer in the stomach and have adverse impact on stability for acid labile drugs. In general, multiparticulate systems produce a lesser food effect. Surfactants interact with enzymes and can potentially alter the metabolic profile and drug bioavailability in the presence of food. Oils and surfactants in the formulation will mimic the food effect via improved solublization and minimize food effect. Enteric coating polymers may release the drug prematurely with delayed gastric retention, compromising the stability of acid labile drugs. On the other hand, dose dumping may occur with polymers used in controlled-release formulations.

HIGHLIGHTS OF FOOD EFFECTS ON DRUG FORMULATION IN VIVO[122]

Food-formulation interactions can be significant and may affect safety and efficacy of drug products if a proper dosage regime is not followed. In the selected case studies below, the impact of food effect on formulations in relation to therapeutic areas are discussed. More information on influence of food on drug bioavailability is provided in Table IV.

Arrhythmia Treatment

Food or antacids do not alter Flecainide bioavailability; however, substitution of milk for dextrose in young adults produced ventricular tachycardia.[34] Other drugs in the class show variable food effects, amiodarone and encainamide (increased absorption), sotalol (decreased) betamethyl digoxin, and morcizine (onset delay).

Asthma Treatment

Bioavailability of several theophylline formulations in fasted and fed subjects was compared[9]: Theo 24®, pellets in capsules with pH dependent dissolution; Theodur®, pellets compressed in to tablets with pH-independent polymer; Theodur sprinkles®, pellets in capsules with pH-independent polymer; Uniphyl tablets®, cellulose matrix in pH-independent polymer; Theograd®, porous matrix-controlled pH-independent polymer; and Neulin retard formulation.

Theo 24®, Uniphyl® tablets, Theograd®, and Neulin® retard showed increases absorption whereas Theodur® sprinkle showed decreased absorption in fed subjects. Theodur® tablets showed no food effect. This example demonstrates the complexity of food effect where the exact reasons for formulation-dependent food effect were not well understood. However, in vitro methodology was developed to assess formulation-food interaction.[123] Each tablet is dipped in sunflower oil for 2 hours prior to dissolution testing. Excellent correlation was seen between in vitro dissolution and in vivo bioavailability after food.

Albuterol (used in the treatment of asthma) shows no food effect but onset delay. However, albuterol extended-release formulation; Vospire® EM shows positive food effect.

Diabetes Treatment

Metformin is coformulated with rosiglitazone maleate in Avadamate® tablets. In the fed subjects, a reduction of C_{max} but no effect on AUC were seen in comparison to fasted subjects.

Fortamet™ was developed as an extended-release formulation using the patented single-composition osmotic technology (SCOT™). The tablet consists of an osmotically active core formulation that is surrounded by a semipermeable membrane. Two laser-drilled exit ports exist in the membrane. The core formulation is composed primarily of drug and excipients. The semipermeable membrane is permeable to water but not to higher molecular weight components of biological fluids. Upon ingestion, water is taken up through the membrane and dissolves the drug and excipients in the core formulation. The dissolved drug and excipients exit through the laser-drilled ports in the membrane. The rate of drug delivery is constant. However, upon administration of food, both AUC and C_{max} increase significantly over fasted with prolongation of T_{max}. Fortamet™ should be given in the evening with meal.

Dislipidemia Treatment

Prevastatin is a high-extraction ratio drug (0.66). The systemic bioavailability of prevastatin may vary with food, but the efficacy is not compromised as the primary site for activity is the liver. After food administration in patients, C_{max} and AUC dropped, but efficacy was uncompromised.[35]

Table 2. Food Induced Interactions

Food Component	Influence on Absorption	Potential Effect
High fat breakfast	Secretion of bile acids, and pancreatic fluids, digestion of oils to fatty acids and mono- glycerides may improve solublization, temporarily enhance membrane permeability, visceral and lymph blood flow[27], alter pre-systemic clearance, delayed gastric emptying, increased gastric pH	Increased absorption of lipophilic drugs, delayed tmax, decreased absorption for poorly permeable water soluble drugs with narrow absorption window, decreased absorption of acid labile molecules
High Protein Meal	May impede absorption of amino acid drugs	Decreased absorption for some drugs, eg levodopa, carbidopa[22]
Diet rich in salt	Increase CYP3A activity [23, 24]	Decreased absorption
Smoked and Char-broiled food	Potent enzyme inducers[23, 24]	Decreased absorption
Water	Decrease in gut metabolism	Increased rate and extent of drug absorption due to solublization and decrease in gut metabolism, increased GI transit time[25, 26]
Yogurt and Milk	Contains calcium, some drugs may bind to calcium ion	Decreased absorption for some drugs[20, 21]
Red and Black Pepper	Capsaicin inhibits CYP1A, CYP2B, CYP2E1[23, 24], Piperine inhibits CYP1A and glucuronidation[23, 24]	Increased absorption of some drugs
WaterCress	Inhibitor of CYP2E1[23, 24]	Increased absorption of some drugs
Curciferous vegetables	Induce several enzymes	Decreased absorption for some drugs
Grapefruit juice	Inhibitor of PGP and CYP3A [23, 24]	Increase absorption of estradiol, felodipine, cyclosporine
Cholesterol, cocoa butter, olive oil	Induce hydroxylation and glucronidation in duodenum[27]	Decreased bioavailability for some drugs

Other drugs in the class, lovastatin, Altoprev® shows negative food effect whereas the lovastatin-niacin combination product Advicor® shows positive food effect.

Endometriosis Treatment

Danzol is a poorly water-soluble, high octanol-water coefficient (Log P), high-dose compound that exhibits highly variable bioavailability.[33] The commercial danzol capsules (Danocrine®, Winthrop) exhibits a three times difference in bioavailability between fasted versus fed subjects along with non-linear absorption in the 50- to 200-mg dose range. Two approaches to the danzol formulation appeared to improve bioavailability and minimize food effect.

In the first approach, danzol was dispersed in glyceryl mono-oleate to create a self-emulsifying drug delivery system.[33] The new formulation was compared (fasted versus fed subjects) in a human bioavailability study against the commercial capsule, Dancorine®, at 100-mg dose. The capsule study results indicated a three-fold difference in AUC and C_{max} between fasted and fed subjects. The emulsion formulation data showed a three- to four-fold C_{max} and AUC over the capsules in fasted subjects. Moreover, the C_{max} and AUC differences among the fasted and fed subjects receiving emulsion were insignificant.

In the second approach, danzol nanosuspension (0.17 micron) bioavailability in dogs was compared with a conventional (micron) suspension and cyclodextrin solution.[36] The BA of conventional suspension was 5% as compared to 82% and 106% with nano-suspension and cyclodextrin solution, respectively. Models developed by Jennifer Dressman showed good correlation between in vitro dissolution in simulated intestinal fluid, fasted (FaSSIF), and fed (FeSSIF), and in vivo bioavailability in humans.[37]

Epilepsy Treatment

Valproic acid is a weak organic acid and expected to show formulation-dependent food effect. Valproic acid in Depakene® capsule was formulated in corn oil, and Depakene® syrup in sorbitol. Depakote® formulations incorporate Divalproex sodium, a stable coordination compound composed of sodium valproate and valproic acid in a 1:1 molar ratio. Depakote® sprinkle capsules contain specially coated granules for sprinkle. Valproate ion absorption may vary with solid, liquid, or sprinkle formulation as well as fasting or fed conditions, but the differences are minimum. However, among various formulations, C_{max} and T_{max} could be crucial for initiation of anti-epileptic treatment and may have significant effect on efficacy. For example, the rate of absorption of Depakote® tablets in fed patients causes a significant delay in T_{max}, 4 to 8 hours, as compared to 3.3 to 4.8 hours for Depakot® sprinkle capsules. Other drugs in the class show variable food effect: Oxcarbazine (positive), Phenytoin (negative), and Oxcarbazine, Tiagabine, Vigabartine, and Topiramate (onset delay).

Hypertension Treatment

Enalapril is an ACE inhibitor, which acts by suppression of the renin-angiotensin-aldosterone system whereas felodipine is a dihydropyridine calcium-channel blocker.

Lexxel® is a combination product consisting of an outer layer of enalapril maleate surrounding a core tablet of an extended-release felodipine formulation. Felodipine is practically insoluble and has a positive food effect, whereas enalpril shows a negative food effect. The felodipine core in Lexxel® is composed of, apart from matrix-forming materials (Hypromellose), a surfactant, and Cremophor RH 40 to counter food effect. The formulation is administered QD w/o food. Felodipine is also a substrate for PGP and grapefruit products and will enhance absorption and thus should be avoided.[78]

Isosorbide mononitrate is an arterial and venous vasodilator. Imdur® tablets contain isosorbide mononitrate, an active metabolite of isosorbide di nitrate in the extended-release form. Although food does not significantly alter Imdur® bioavailability, the onset will be delayed, and isosorbide tablets should be taken on an empty stomach upon waking as onset of action will be critical for rapid relief and efficacy.

Bidil® tablets contains isosorbide dinitrate and an arterial dilator, hydralzine, in combination. The bioavailability of hydralazine is non-linear, and food may impact bioavailability upon metabolic saturation and changes in presystemic clearance. A clinical study with hydralazine with food reported a six- to seven-fold decrease in blood levels as compared to fasted.[38] Attention to time of food in relation to drug administration will be important.

Nifedipine food effect is formulation dependent. One study reports more than a two-fold increase in peak plasma levels in the presence of a high-fat meal, whereas another study indicated a significant reduction in peak plasma levels in the presence of food.[38,39] Moreover, nifedipine absorption is known to increase in the presence of grapefruit juice.[78]

The bioavailability of three controlled-release nifedipine formulations, Adalat OROS®, an osmotic mechanism, Coral®, and Slofedine®, a pH-sensitive polymer mechanism, was investigated in fasted and fed subjects.[40,41]

Adalat OROS® achieved a higher C_{max} and AUC in fasted subjects than the other two formulations. When C_{max} and AUC data in fed subjects were examined, Slofenidine® formulation showed significant release delay in 15 out of 24 patients, with 15 hours lag time after dosing. The Coral® formulation showed significant dose dumping in fed subjects with 11 out of 24 patients showing a four-fold increase in plasma concentrations. Adalat OROS® exhibited only minimum differences in AUC and C_{max} between fasted and fed subjects. In vitro dissolution data indicated uniform drug release in the pH range 1 to 8 for the Adalat® formulation, but pH-dependent release for Coral® and Slofenidine® formulations.

Thus, food can significantly alter onset and bioavailability of controlled-release formulations and should be carefully monitored. Moreover, these formulations are not interchangeable.

Verapamil is a calcium-channel blocker and has antihypertensive activity. Tarka® is a combination product of tandolapril and verapamil and shows reduction in verapamil C_{max} and AUC in the fed subjects as compared to fasted. Covera® HS is a once-a-day osmotically engineered verapamil formulation. Unlike Tarka®, it does not undergo food-related changes in bioavailability.

Verelan® PM utilizes the proprietary CODAS™ (Chronotherapeutic Oral Drug Absorption System) technology, which is designed for bedtime dosing, incorporating a 4- to 5-hour delay in drug delivery. This controlled onset delivery results in a maximum plasma concentration of verapamil in the morning hours. These pellet-filled capsules provide extended-release of the drug in the gastrointestinal tract. The rate of release is essentially independent of pH, posture, and food. Multiparticulate systems, such as Verelan® PM have been shown to be independent of gastrointestinal motility.

Other marketed products in the class show variable food effect: metoprolol succinate, Toprol XL® (no food effect); isardipine, Dynacirc® (negative); and nisoldipine, Sular® (positive). Other drugs in the class show variable food effect: buflomedil, dilitiazem (positive), and atenolol and nitredipine (negative).

Immuno-Suppressants

Cyclosporine is a poorly soluble, relatively large molecular weight peptide. The formulation design needed an excipient to create a food-like effect for improved solublization. The first-generation formulation (Sand immune®) is an emulsion, whereas the second generation (Neoral®) is a microemulsion. The second-generation formulations are more bioavailable than first generations. In a different approach, Gengraf® capsules improved cyclosporine solublization, which was achieved using a dispersed system containing polyethylene-glycol, propylene glycol, cremophore, and polysorbate. Each of the aforementioned

Table 3. Food - Formulation Interactions

Formulation Excipients	Food Influence	Potential Food Effect
Calcium phosphate salts (Filler)[28]	Insoluble at high pH, alterations in stomach pH may affect drug release and Ca++ available from nutrient supplement	- Ve
Sodium phosphate salts (Filler)	Will protect acid labile drugs by creating a high local pH	Food effect minimization
Croscaramelose Sodium (disintegrant)[29]	Has been reported to bind to weakly basic drugs in the pH range 2-8. Binding may affect drug release under fed conditions	- Ve
Single unit dose[30]	Transit of drug will be controlled by GI emptying	- Ve for acid labile drugs
Multiple unit system[30]	Solutions and pellets (less than 2 mm in size) emptied from stomach rapidly	Less likely to show food effect
Cremophore EL, Solbutol HS [15] (surfactant and solublizers)31	Modulator of MDR Resistance	Food effect minimization
Triton X-100 (surfactant and solublizer)[31]	Reverse MDR Phenotype	Food effect minimization
Pluronics (surfactant and solublizer)[32]	PGP inhibition[4,52]	Food effect minimization
Mono-glycerides, diglycerides, triglycerides (Solublizers)[33]	Will mimic food effect situation, secretion of bile acids, improved solublization, secretion of pancreatic fluids, digestion of oils to fatty acids and monoglycerides may temporarily enhance membrane permeability, and also facilitate lymphatic transport	Food effect minimization
Cellulose acetate phthalate, polyvinyl acetate phthalate, polymethyl acrylates (enteric coated polymers)	High stomach pH may cause premature release of drug, pH normalization and delayed gastric emptying may cause degradation of acid labile drugs	- Ve
pH sensitive polymers (controlled release,CR)	High stomach pH may cause premature drug release and dose dumping	+ Ve
pH insensitive polymers (CR)	Likely to have less potential for dose dumping	Food effect minimization
Wax matrices (CR), fatty acid esters	Hydrolysis rate changes subject to pH	+ Ve
Osmotic and laser drilled (CR)	Less potential for dose dumping	Food effect minimization

formulations interacts with food differently and are not interchangeable. The formulations should be administered consistent with time of day in relation to food. Cyclosporine is a substrate for PGP, and co-administration of grapefruit or grapefruit juice will enhance absorption, thus it should be avoided.

Infections Treatment

Clarithromycin: When children as well as adults were dosed with the drug postprandial, absorption enhancement was reported.[42,43] Biaxin Filmtab tablets and Biaxin granules (to be reconstituted in the suspension) produced higher C_{max} but no effect on AUC post-food administration. Moreover, both the exposures of plain clarithromycin and its active metabolite 14-OH clarithromycin exposure were comparable in patients taking either of the two formulations. These two formulations are interchangeable and can be administered without regard to food. The Biaxin XL FilmTab formulation is formulated with a cellulosic polymer for controlled release. Clarithromycin and its active metabolite 14-

OH clarithromycin play a role in driving efficacy and although the extent of metabolism is the same in fasted and fed, bioavailability of the parent drug is higher in fed subjects, which can be attributable to reduced presystemic clearance. Biaxin XL is to be administered with meals.

Azithromycin is a lipid-soluble compound degraded by acid-catalyzed hydrolysis.[44] Oral bioavailability of azithromycin is 30%, which can be reduced by almost two-fold with food. Each of the azithromycin formulations shows characteristic food effect. Zithromax® capsules, without a buffering agent in the formulation, showed a reduced C_{max} and AUC. Zithromax® capsules should be taken 1 hour before or 2 hours after the food. Zithromax® for oral suspension contains sodium phosphate tribasic and showed increased C_{max} (46%) and AUC (14%) in presence of food, whereas Zithromax® tablets contain calcium dibasic phosphate and showed increased C_{max} (31%) but no effect on AUC. The oral suspension and tablets can be taken without regard to food. These three formulations use the dehydrate API, whereas as Zmax® uses anhydrous API. Zmax® is designed for extended release and contains cellulosic polymers and showed increased C_{max} and AUC in fed subjects. However, Zmax® should be administered on an empty stomach. The Zmax® and Zithromax® for oral suspension products are not interchangeable.

Ciprofloxacin shows formulation-dependent food interactions. Ciprofloxacin apparently binds to heavy metals, such as calcium, and forms insoluble complexes. Ciprofloxacin bioavailability is reported to be reduced when coadministered with milk and yogurt.[21] For cefrozil and ceftbuten, the absorption appeared to be reduced in the presence of food as well.[45,46] However, commercial ciprofloxacin formulations, Cipro® Suspension, Ciprofloxacin® Tablets, and Cipro® XR, show unchanged bioavailability upon food administration. Ciprofloxacin formulations should be administered without regard to food. Antacids should be avoided because significant reduction (90%) in the presence of antacids was observed.

Zidovudine C_{max} was reduced as much as 50% post-administration of a high-fat breakfast.[47] Zidovudine is also administered in combinations with lamuvidine (Combivir® tablets), with lamuvidine and abecavir (Trizivir® tablets). Reduced C_{max} (28%) but with no effect on AUC of zidovudine was seen after the Trizivir® formulation was administered in fed subjects. However, efficacy is not impacted. Zidovudine formulations can be taken without regard to food. In fact, the reduced C_{max} after food may be beneficial, maintaining the efficacy with reduced toxicity.[47]

Didanosine (anti-HIV) is an acid labile molecule and undergoes degradation at acidic conditions. Chewable tablets of didanosine are subjected to reduced bioavailability in fed patients given a high-fat breakfast.[48] The timing of meal is crucial as well, drug administered 1 or 2 hours after a meal showed a 65% bioavailability reduction. However, fasting 30 min or 1 hour before administration of food had no adverse effects. The currently marketed formulation (Videx®) is composed of enteric-coated beads in a capsule. When the Videx® capsule is administered to fed subjects, a 46% reduction in C_{max} and 14% reduction in AUC was observed with an onset delay. Videx® capsules should be administered on an empty stomach.

Other drugs in the anti-infective class show variable food effects. Amocarazine, ceflamet, cefuroxime, sparfloxacin, itroconazole (positive); rufloxacin, norfloxacin, tetracycline, ceprozil, ceftibuten, and dideoxycytiden (negative), and cefidinir, doxycycline, erythromycin, fusidic acid, hydroxychloroquin, lomefloxacin, oflaxacin, pencicclovir, and rifabutin (onset delayed).

Inflammation Treatment

Delayed onset and decreased C_{max} after diclofenac beads formulation has been reported.[49] Diclofenac is a weakly acidic drug with poor solubility. Salts of diclofenac are soluble and have been used in the commercial formulations. Diclofenac sodium is formulated as Voltaren EC® (enteric-coated tablet) and Voltaren XL® (extended-release product), whreas diclofenac potassium is formulated in Cataflam IR® (instant-release product). The Voltaren EC® formulation, when administered with food, delays onset and reduces C_{max} but has no effect on AUC. The Voltaren XL® formulation appeared to be formulated with pH-insensitive polymers for controlled release but shows a two-fold increase in C_{max} with food. The Cataflam® formulation showed a 30% reduction in C_{max} and delayed onset in presence of food. Even though the extent of absorption is similar and the onset delayed, each formulation reacts differently with food. The IR and EC formulations showed a C_{max} reduction owing to increased gastric retention and pH effect. On the other hand, the XL formulation appears to release the drug from the matrix at a faster rate in presence of food, producing higher C_{max}. The Voltaren® formulations are not bioequivalent.

The Arthrotech® formulation is an enteric-coated core of diclofenac surrounded by a misoprostol (mucosal protective prostaglandin) mantle and expected to perform similar to Voltaren® EC.

Progesterone bioavailability increased two-fold in the presence of food with plasma levels increasing as much as five-fold.[50] The increase in bioavailability is attributed to direct drug-food interaction or reduction of presystemic clearance. The Prometruim® formulation contains micronized progesterone formulated in peanut oil and lecithin to mimic food effect and increase absorption. The formulation should be taken at bed time.

Some other commercial products in the class show no food effect: naproxen sodium (Naprelan®), nicotinamide (Nicomide®), whereas 5-amino salicylic acid (flubiprofen and salsalate) show onset delay.

Malaria Treatment

Aqueous solubility of atovaquone is 0.1 mcg/ml and increases to 100 mcg/ml in post-meal conditions in the stomach. The bioavailability increases three-fold with a five-fold increase in C_{max} in the presence of food.[51] The increased absorption of atavaquone can be attributable to bile salt solublization. Dressman

Table 4. Food interactions with different drug across the therapeutic areas

Compound	Food Effect	Compound	Food Effect
ALLERGY TREATMENT		**CNS DISORDERS TREATMENT**	
Repirinast[54]	+ Ve	Vinprocetin (celebral circulation improvement)[126]	+ Ve
ALZHEIMER'S TREATMENT		Vanoxerin (dopaminergic)[127]	+ Ve
Tarcine[55]	- Ve	**DEPRESSION TREATMENT**	
ANALGESICS		Brofaromine[90]	+ Ve
Tramadol[56]	-Ve	Gepirone[100]	+ Ve
Paracetmol[57,58,59]	+Ve, Onset delayed	Moclobemide[101]	+ Ve
ANTIHISTAMINIC		Zalospirone[102,103]	+ Ve, Onset delayed
Terfenadine[124]	Onset delay	Trazodone[104]	Onset delayed
ANXIETY TREATMENT		**DIARRHEA TREATMENT**	
Antiracetam[61,65]	Onset delay	Acetorphen (Racecadotril)[105]	Onset delayed
ANTI-PLATELET		**ENDOMETRIOSIS TREATMENT**	
Ticlopidine[62]	+ Ve	Danzol[33]	Positive
ARRHYTHMIA TREATMENT		**EPILEPSY TREATMENT**	
Sotalol[63]	- Ve	Phenytoin[106]	-Ve
Amiodarone[64]	+ Ve	Oxcarbazine[107]	+ Ve
Encainide[66]	+ Ve	Tiagabine[108]	Onset delayed
Betamethyl digoxin[67]	Onset delay	Vigabartine[109]	Onset delayed
Moricizine[68]	Onset delay	Topiramate[110]	Onset delayed
ASTHMA TREATMENT		**HYPERTENSION TREATMENT**	
Albuterol[69]	Onset delay	Atenolol[71]	- Ve
Theophylline[116]	Negative	Nitredipine[111]	- Ve
CANCER TREATMENT		Bluflomedil (vasoactive)[112]	+ Ve
2-chloro-2'-deoxyadenosine[70]	- Ve	Diltiazem[113,114]	+ Ve, action delayed
Methotrexate[72,73]	- Ve, onset delayed	Nifedipine[38]	Onset delayed
Navelbine[74]	- Ve	**INFLAMMATION TREATMENT**	
Fadrozole (breast cancer)[125]	Onset delayed	Naproxen	- Ve
Terazocin (Hytrin)[60]	Onset delayed	5-amino salicylic acid (Mesalamine)[132]	Onset delayed
CHOLESTEROL-LOWERING (anti-lipidemic)		Flubiprofen[92]	Onset delayed
Fluvastatin (Lescol)[75]	Onset delayed	Salsalate[93]	Onset delayed
Prevastatin[35]	- Ve	**ISCHEMIC HEART DISEASE**	
INFECTIONS TREATMENT		Nicorandil[94]	Onset delayed
Ceprozil[46]	- Ve	**MALARIA TREATMENT**	
Cefuroxime[79]	+ Ve	Atovaquone[51]	+ Ve
Ceftibuten[45]	- Ve	**POST-OPERATIVE NAUSEA & VOMITING**	
Cefdinir[76]	Onset delayed	Apripitant[52]	+ Ve
Doxycycline[77]	Onset delayed	**PSORIASIS TREATMENT**	
Erythromycine acistrate[129]	Onset delayed	5-methoxypsorlean[95]	+ Ve
Fusidic acid salts[130]	Onset delayed	**OSTEOPOROSIS TREATMENT**	
Hydroxychloroquin (anti-malarial plaquenil)[80]	Onset delayed	Monofluorophoshpate[96]	Onset delayed
Lomefloxacin[81]	Onset delayed	Alendronate Sodium[121]	- Ve
Loracarbef[82,131]	Onset delayed	**ULCER TREATMENT**	
Oflaxacin[84,85]	Onset delayed	Famotidine[97]	Onset delayed
Penciclovir (anti-viral)[86,83]	Onset delayed	**URINARY INCONTINENCE TREATMENT**	
Rifabutin[87]	Onset delayed	Oxybutinin[98]	+ Ve
Dideoxycytidien (anti-HIV)[88]	- Ve		
Troconzole[89, 91]	+ Ve		
Rufloxacin[115]	- Ve		
Norfloxacin[20]	- Ve		
Tetracycline[128]	- Ve		
Amocarzine[117,99]	+ Ve		
Ceftamet (piroxil)[118, 119]	+ Ve		
Sparfloxacin[125]	+ Ve		

Table 5. Selected Modified Release Products in relation to food effect[122]

Compound	Manufacturer	Presentation	Indication	Food Effect	Technology/Excipients Related to CR
Allergy Treatment					
Cetrizine hydrochloride and pseudoephedrine hydrochloride tablets	Zyrtec –D-12 hour, Pfizer	Cetrizine hydrochloride 5 mg and psuedoephedrine hydrochloride 120 mg, extended release tablets	Anti-histamine, nasal decongestant	No significant food effect psuedoephedrine, decreased Tmax and increased Cmax for Cetrizine, to be taken with or without food	Bilayer tablet, Cetrizine IR, and Psuedoephedrine ER
Fexofenadine hydrochloride 60 mg and psuedoephedrine hydrochloride 120 mg	Allegra-D12, extended release, Sanofi-Aventis	Fexofenadine hydrochloride 60 mg and psuedoephedrine hydrochloride 120 mg, extended release tablets	Treatment of seasonal allergies, rhinitis	Fexofenadine negative, approximately 50% decreased in AUC and Cmax, psuedoepinephrine no effect, to be taken with water on empty stomach	Double layer tablet
Analgesics					
Morphine Sulfate	Kadian SR capsules, Alpharma	20, 30, 50, 60, 100 mg capsules	Management of moderate to severe pain	None, to be taken with or without food	SR Pellets, polymer coated, (HPMC, Methacrylic acid polymers
Oxycodone hydrochloride	Oxycontin, Purdue Pharma	Controlled release tablets, 10, 20, 40, 80, 160, mg	Pain Management	Positive Cmax, no change AUC, to be taken on empty stomach	Methacrylic acid and HPMC excipients, release is pH dependent
Asthma Treatment					
Theophylline anhydrous	Thero 24 (Searle), Theodur Tablets (Key), Theodur Sprinkle cap (Key), Uniphyl, Purdue Fredrick*	Controlled release system, 400 and 600 mg	Chronic respiratory disease, asthma	Technology dependent	pH dependent and pH independent polymer use
CNS Stimulant					
Methylphenidate	Ritalin SR, Novartis Metadate, CellTech	5 and 20 mg tablets	Mild CNS stimulant	30-45 minutes before meal	Coated Tablets
Convulsions Treatment					
Carbamazepine	Carbatrol, Shire, US	100, 200 and 300 mg extended release capsules	Anti-convulsant	Positive, Tmax reduced , Cmax increased, beads to be sprinkled on food	IR, ER and DR beads mixed together
Decongestant					
Psuedoephedrine Hydrochloride, 120 mg	Contac, GSK	Non-drowsy timed release maximum strength 12 hour cold caplets	Relief of nasal congestion	None	IR and CR components, caplets
Depression Treatment					
Venlafaxine hydrochloride	Effexor XR, Wyeth_Ayrest	Extended release capsules, 37.5, 75 and 150 mg	Anti-depression	To be administered with food	EC coated spheroids, membrane diffusion
Dislipidemia Treatment					
Niacin extended release/lovastatin	Advicor, Kos	Tablets, 5500/20, 750/20, 1000/20	Treatment of dislipidemia	Niacin bioavailability increases with food, lovastatin bioavailability decreases with food, to be taken at bed time with low fat snack	Tablets containing Niacin ER and Lovastatin IR
Lovastatin	Altoprev, Andrx Labs	10, 20, 40 and 60 mg tablets	Ext release tablets	Negative, to be taken at bedtime	HPMC and methacrylic acid polymer
Expectorant					
Guaifensin	Mucinex, Adams Labs	600 mg Guaifensin extended release tablets	Expectorant	None	Carbopol 934, HPMC excipients
Hypertension Treatment					
Verapamil hydrochloride	Isoptin, SR, Abbott Covera, HS Searle	120, 180, 240 mg film coated tablets	Calcium channel blocker, anti-hypertensive	Negative, prolongation of Tmax None (Covera)	Alginate polymer Osmotic
Metoprolol succinate	Toprol-XL, Astra Zeneka	Extended release tablets, 25, 50, 100 and 200 mg	Anti-hypertensive, beta selective blocking agent	None	Multiple pellets in tablets, each separate delivery system
Isradipine	Dynacirc, Reliant	Controlled release tablets, 5 and 10 mg	Management of hypertension	Negative, with or without food	Gastro Intestinal Therapeutic System (GIST), Osmotic based
Nifedipine	Adalat CC, Bayer	Extended release tablets, 30, 60 and 90 mg	Calcium channel blocker, anti-hypertensive	Positive, Cmax increases, no change AUC, take without food, grapefruit products should be avoided	Coat as slow release, core as a fast release Nifedipine
Metformin Hydrochloride	Fortamet, Andrx Labs	Film coated extended release tablets, 500 and 1000 mg	Anti-hypertensive	Positive, take with the evening meal	SCOT (Single Composition Osmotic Technology)
Enalapril maleate-felodipine ER	Lexxel, Astra-Zeneca	Tablets: 5-5, 5-2.5	Calcium blocker and ACE inhibitor combination	positive feldopine, negative enalpril, take without food	Tablet
Nisoldipine	Sular, First-Horizon	Extended Release Tablets, 10, 20, 30 and 40 mg	Calcium channel blocker	Positive with CR, less with IR, avoid high fat meal and grape fruit products	Coat contain slow release and core contain fast release component

Table 5. Selected Modified Release Products in relation to food effect[122] (continued)

Compound	Manufacturer	Presentation	Indication	Food Effect	Technology/Excipients Related to CR
Inflammation Treatment					
Naproxen sodium	Naprelan CR Tablets, Elan Anaprox DS (Dealayed Release, Roche)	375, 500 mg CR tablets	RA, OA and Gout	None	Film Coated tablet with IR (35%) and CR (65%) erosion matrix type) components
Infections Treatment					
Ciprofloxacin	Cipro XR, Schering	Film Coated Extended release tablets, 500 and 1000 mg	Treatment of urinary track infection	None	IR and CR components
Nacrolepsy, ADD					
Dextro-Amphetamine sulfate	Dexedrine spansules capsules, GSK	5, 10, 15 mg capsules	Nacrolepsy, ADD	None	Time released pellets
Potassium Replacement					
Potassium chloride	Klor-Con, Upsher Smith	Extended release capsules, 1500, 1125 and 750 mg,	Potassium replenishment	With meals for tolerance	Microencapsulated with ethyl cellulose
Prostrate Hyperplacia Treatment					
Alfuzosin hydrochloride	Uroxatral, Sanofi-Synthelobo	Extended release tablets, 10 mg	Treatement of benign prostate hyperplasia	Positive, immediately after meal	Ethyl cellulose, HPMC
Smoking Cessation					
Bupropion hydrochloride	Zyban, GSK,	150 mg film coated tabs 150 and 300 mg Wellbutrin	Non-nicotine aid to smoking ceasation, anti-depressent	Positive but can be taken with or without food	
Stroke Treatment					
Aspirin extended release dipyridamole	Aggrenox,Boehringer Ingelheim	Aspirin 25 mg, dipyridamole 200 mg capsules	To reduce risk of stroke	Negative, but can be taken with or without food	Each capsule contain 25 mg aspirin IR and dipyridamole in ER forms HPMC Pthalate, Methacrylic acid
Urinary Incontinence Treatment					
Oxybutynin hydrochloride	Ditropan XL, Ortho-McNeil	Extended release tablets, 5, 10 and 15 mg	Control of overactive bladder	None	Osmotic system Drug layer and push layer

et al have shown excellent IV/IV correlation for atavaquone with data from in vitro dissolution in fassif and fessif and in vivo absorption.[36]

The formulation design was based on increased surface area and a dissolution rate utilizing microfine particles as well as surfactants for wetting and drug solublization.

Malarone® is a fixed-dosed combination of atavaquone and proguanil. The formulation contains a poloxamer surfactant to enhance wetting and solublization. The Meprone® suspension is formulated with a microfine drug wetted with a poloxomer. The BA of tablet and suspension were 23% and 46%, respectively and with meal, a two-fold improvement in BA was seen.

Osteoporesis Treatment

Alendronate ions appear to bind to food components impacting bioavailability. Fosamax® is available in potencies ranging from 5 to 70 mg. Following oral administration, bioavailability of alendronate is less than 1%, and food has significant impact on the bioavailability.[121] Caffeinated beverages, milk, yogurt, and juices alter the bioavailability adversely. Foso$_{max}$® tablets should be administered at least 2 hours before meals (preferably after overnight fasting) with water only.

Post-Operative Nausea & Vomiting Treatment

Apripitant, the API in Emend®, had shown extreme utility in the control of post-surgical nausea and vomiting.[52] Apripitant is a poorly soluble, unstable to oxidative stress, and poorly permeable compound that undergoes first-pass metabolism in the gut and liver and is a substrate for PGP. Absorption of the drug appears to be from the upper gastrointestinal tract with minimal absorption from colon. Apripitant shows a positive food effect; however, drug delivery of apripitant to patients undergoing surgery was a daunting task because patients could not ingest food to help absorption.

The Phase I formulation (with micronized material) in humans exhibited two to three times absorption enhancement in the presence of food. A non-linear PK associated with decrease in AUC was observed. A dog model was developed to mimic human food effect. A nanomilled (0.12 microns) supsension (4% HPMC, 0.08% SDS, and 20% sucrose) was administered to dogs (2 mg/kg) and compared with alpine-milled (5.49 microns), jet-milled (1.8 micron), wet-milled (0.48 microns) suspensions and drug pre-emulsion in an Imwitor-Tween vehicle. The nanomilled formulation boasted a four-fold improvement in AUC as compared to the alpine-, jet-, and wet-milled formulations. Moreover, the nanomilled formulation, as well as solution (pre-emulsion) achieved reduction in food effect with insignificant differences in exposure between fasted and fed animals. The solution formulation could not be further developed because of solubility limitations.

The nanomilled suspension was further formulated into capsules utilizing spray-coating technology. Thus, a bioavailability hurdle was resolved formulating a nanomilled capsule to overcome food effect, poor bioavailability, and dissolution. The Emend®

example illustrates how one can formulate a poorly soluble drug by increasing the surface area in the nanometer range to improve exposure for complete absorption and minimize food effect.

Parkinsonism Treatment

Levodopa absorption is not affected with high-fat food. However, levodopa is a small aromatic amino acid; its bioavailability is lowered in the presence of a high-protein meal owing to competitive amino acid absorption.[22] Levodopa bioavailability increases with a diet rich in soluble fibers.[53]

FOOD-CONTROLLED RELEASE FORMULATION INTERACTIONS

Selected controlled-release marketed product characteristics are presented in Table 5. Food effects on controlled-release drug formulation pose unique challenges. The controlled-release drug delivery systems contain significantly greater quantities of drugs to accommodate multiple doses compressed into one unit designed to release over the extended period of time. The premature drug release due to food effect can be a particular concern in terms of drug safety in response to higher circulating drug levels. On the other spectrum, reduced bioavailability from controlled-release drug delivery systems may have efficacy implications in response to reduced absorption rates and inadequate exposures. In Table 5, drugs in controlled-release formulations are catergorized according to therapeutic areas. Zyrtec®-D12 formulation (allergy treatment) contains psuedoephedrine (no food effect) with cetrizine (increased C_{max} and onset delayed); however, it can be taken with or without food. On the contrary, Allegra® allergy treatment contains psuedoephedrine (no food effect) and fexofenadine (decreased C_{max} and AUC) and has to be taken on an empty stomach. Carbatrol® (convulsions treatment) formulations contain carbamazepine (positive food effect), and the formulation is to be sprinkled on the food to get optimum effect. Advicor® formulations (dislipidemia treatment) contains niacin (positive food effect) and lovastatin (negative food effect), the formulation is to be administered at bed time with a low-fat snack. The number of formulations that can be taken without regard to food are also listed in Table 5.

CONCLUSIONS

The impact of food and food components on the drug physicochemical as well as biopharmaceutical properties was illustrated. Formulation excipients and manufacturing technologies will play an active role, some will create a food effect and have a negative impact on bioavailability, whereas some others will help overcome the bioavailability hurdles and afford improved drug delivery. Armed with the knowledge of food-formulation interactions, a skilled formulator selects the excipients and designs the manufacturing technologies to craft formulations addressing poor solubility, instability, and poor permeability issues. A review of several selected marketed products and respective formulations, composition, and technology was presented to emphasize how the different formulations of the same drug will interact differently when administered with food. The lack of interchangeability of formulations due to the food effect, and its impact on safety and efficacy, will be a topic of future interest.

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REFERENCES

All 132 references are available from Drug Delivery Technology, please e-mail the Editor at dmarino@drugdeliverytech.com.

BIOGRAPHY

Dr. Rajeev Gokhale is a Senior Research Fellow at Merck in West Point, PA, since July 2004. In his current job, Dr. Gokhale is responsible for solid formulation development of small molecules. He earned his BPharm from the University of Bombay, his MS from the University of Kansas, and his PhD from the University of Georgia. Upon graduating from Georgia, he joined the faculty of Pharmaceutical Sciences at Northeast Louisiana University (NLU), Monroe, LA. He was an Assistant and then promoted to an Associate Professor. At NLU, he was a Research Advisor to two MS and three PhD students. Dr. Gokhale joined Searle/Pharmacia in 1988 in the Advanced Drug Delivery Group and then gained a cross-functional experience in Solids Formulation, Preformulation, and Discovery Support. His last position at Pharmacia was Senior Research Advisor. After leaving Pharmacia in 2003, he was employed at Incyte Corporation, Wilmington, DE, from 2003-2004. Dr. Gokhale's research work has been in drug development, including oral solids and liquids, transdermal, and topical and ocular drug delivery. He has authored and co-authored nine patents, two book chapters, edited a book, published more than 15 manuscripts, and presented over 30 presentations at national and international meetings and symposia.

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Acquisition Let-Downs: It's Only Business!

By: John A. Bermingham

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.

I began my career in sales and have not stopped selling regardless of my later positions. I was taught early on that a sales person's job is to fulfill a need or to solve a problem for the customer. After many many years of selling, I have learned that this is not true!

Here's the truth: (1) Great sales people always ask for more than they really want; (2) Great buyers always offer less than they are willing to pay; (3) Great sales people have two ears and one mouth because they listen twice as much as they talk; (4) Great buyers always know when to shut up; (5) Sometimes a deal that the seller and buyer both want to put together does not happen; and (6) Buying and selling is never personal, it is just business.

Recently, I was working with a private equity firm to acquire a company that they owned in their portfolio of companies. It was a company in decline, and the private equity firm wanted to liquidate their investment in the company before it went down too much. They told me that we could begin discussions if I could quickly raise the financing.

In meetings throughout the following three days, four different private equity firms agreed to back me on the acquisition of this company. I chose one of them and called the selling private equity firm to inform them I was ready to proceed with due diligence if I could have a 30-day exclusive on the deal.

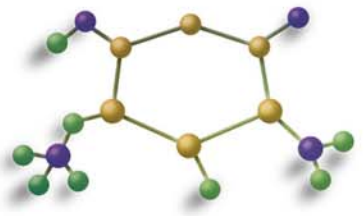
They finally called me back after four days to tell me they had signed a 30-day exclusive with another acquirer and I was out for the time being. I did some investigating and found that the selling private equity firm had signed a 30-day exclusive with another acquirer ***before*** they discussed the acquisition with me.

In my earlier days, my normal reaction to this situation would have been extreme anger for wasting my time, using me as leverage with the other interested acquirer, and being less than forthcoming on the actual situation. Not now! It's just business! That's just how it is in the business world! Nothing personal! Heck, another deal may surface with this private equity firm, and I do not want to burn a bridge.

There may come a day when you will be in a position to buy or sell a business, a division of your company, or be a part of a negotiation to buy or sell a business. When you make a transaction a personal issue, you are preparing to lose. I know that if this is a business that you started and grew, not making it personal is a tough go. But you have to do it. Making it personal significantly weakens your negotiation stance, and the advantage goes to the other side (and they will know this). That's why it is often to your advantage to have someone else negotiate for you who will not make it personal.

The other option to think about is when to walk away. I have seen many negotiations completed that never should have gone to closing. Sometimes a buyer and seller want the deal to go together so badly that they conclude a bad deal for both sides. Never put yourself in a position that you have to have the deal. Look at it as though you can always walk away and negotiate another day with someone else. When you take that attitude, the other side will feel it, which is to your advantage.

I expect that the private equity firm that owns the company I am interested in will conclude with the company that is conducting due diligence. What if they don't? Then the private equity firm will call me to see if I am still interested. I am already looking at another company to acquire and will let them know that while being as gracious to them as possible even after what they did to me. Why? Because this is business. Nothing personal. Oh yeah. When they find out from me, "Mr. Gracious," that I am looking at another company, guess who gains the advantage in the potential negotiation? ♦



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