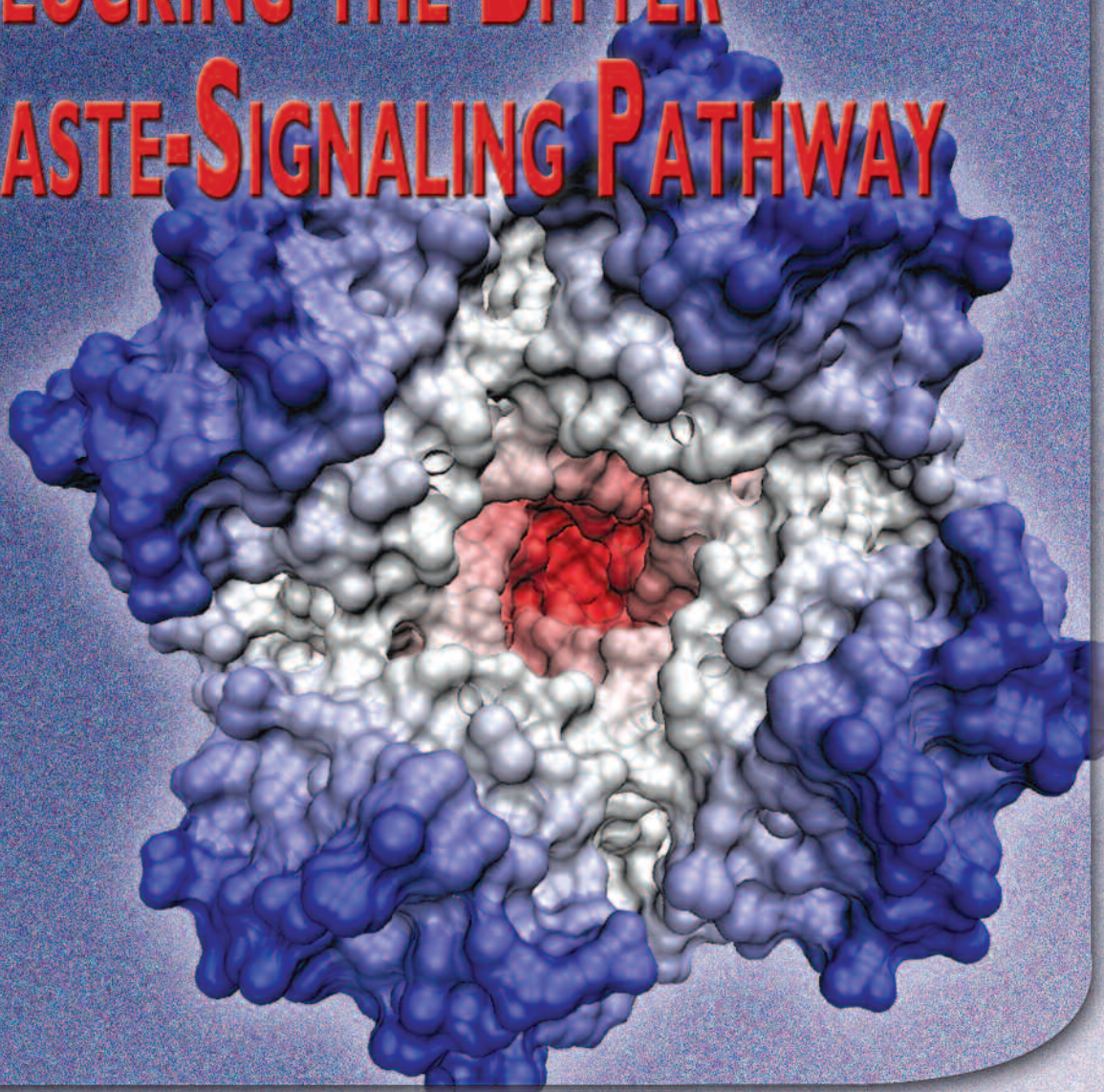
Drug Delivery Technology®

June 2008 Vol 8 No 6 www.drugdeliverytech.com

BLOCKING THE BITTER TASTE-SIGNALING PATHWAY



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

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Biochemical Bitter Blocking for New Drug Formulations

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MR. MARC HÄMEL

FEATURING

SPECIALTY PHARMA
Strategies For Business Development

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3M Drug Delivery Systems

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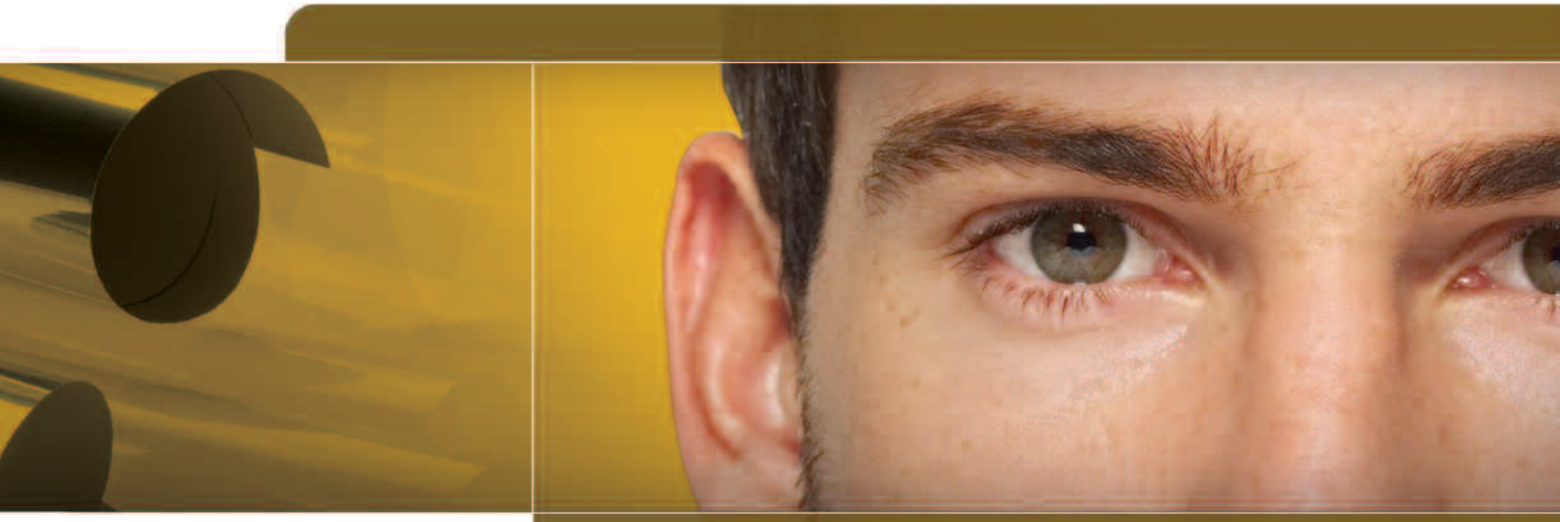

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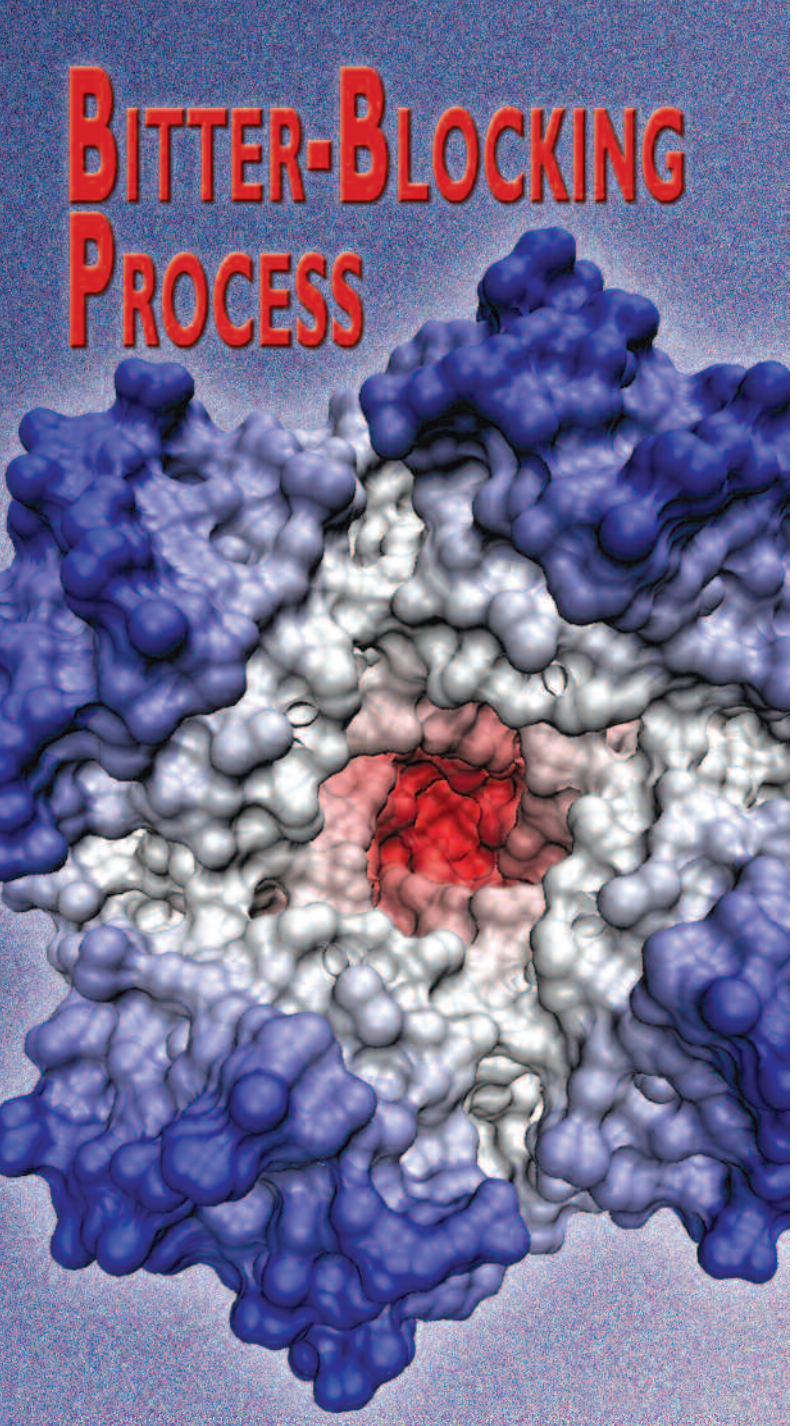

"An effective biochemical bitter blocker is anticipated to improve a wide range of pediatric, geriatric, OTC, and consumer products that currently have taste problems, and to enable new liquid formulations that have previously been technically challenging."

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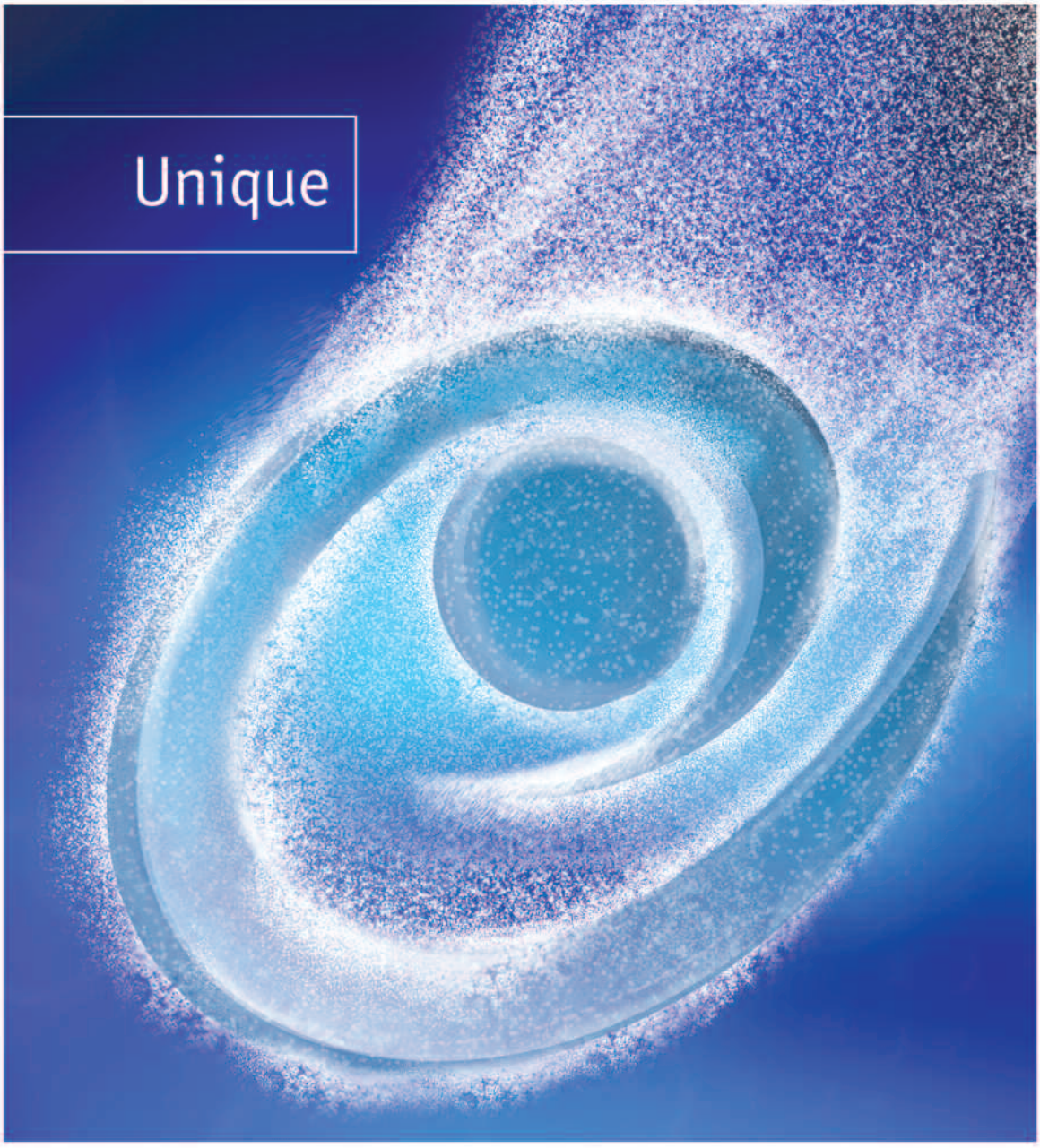

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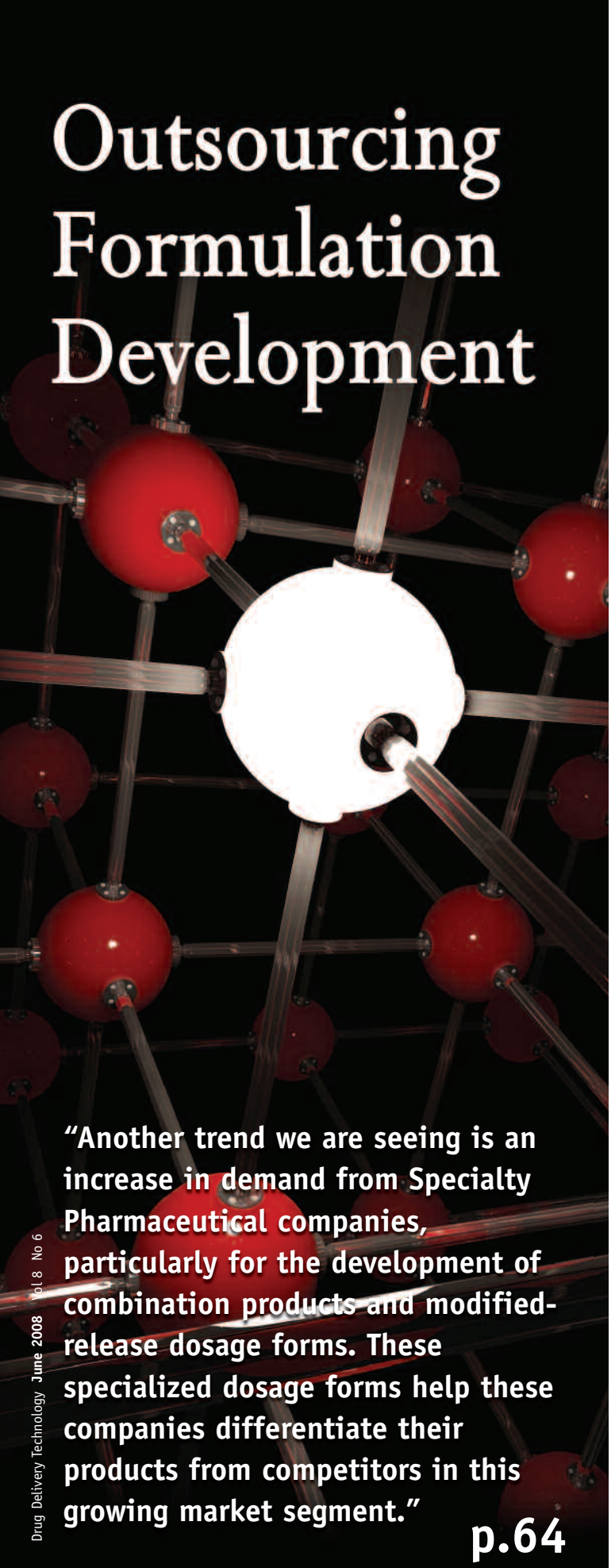

"Another trend we are seeing is an increase in demand from Specialty Pharmaceutical companies, particularly for the development of combination products and modified-release dosage forms. These specialized dosage forms help these companies differentiate their products from competitors in this growing market segment."

p.64

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Market News and Trends

NovaDel Pharma Announces European License Agreement for Ondansetron Oral Spray

NovaDel Pharma Inc., a specialty pharmaceutical company developing oral spray formulations for a broad range of marketed treatments, recently entered into a collaboration agreement with BioAlliance Pharma SA for the development and commercialization of NovaDel's ondansetron oral spray (OS) for Europe. Ondansetron is the leading 5-HT3 antagonist to prevent nausea and vomiting after chemotherapy, radiation, and surgery. Upon successful development and approval, NovaDel believes ondansetron OS could be the first antiemetic to be available in Europe in an oral spray form. BioAlliance and NovaDel anticipate collaborating in the completion of development activities for Europe, with BioAlliance responsible for regulatory and commercialization activities.

"This agreement expands the ondansetron OS opportunity into Europe, and we welcome the relationship with BioAlliance," said Steven B. Ratoff, Chairman and Interim President and CEO of NovaDel. "We continue to work closely on this product in the US under the potential brandname Zensana™ with our sublicensee Strativa Pharmaceuticals, the proprietary products division of Par Pharmaceutical, as they progress their clinical studies in preparation for a NDA filing later this year. Ondansetron OS is an excellent fit with BioAlliance and their strategy to commercialize products in the European oncology/HIV supportive care market. We are looking forward to working closely with our colleagues at BioAlliance to establish this product as an innovative alternative to patients having difficulty taking tablets and other forms of ondansetron."

"This first-in-class, spray drug system aligns well with BioAlliance's strategy to expand its presence in supportive care for oncology and hospitalized patients, and focusing on patient convenience," said Dominique Costantini, President and CEO of BioAlliance. "NovaDel's expertise designing spray formulations will allow us to bring this unique delivery system to market. Strativa is responsible for the clinical development of this product in the US, and BioAlliance will use their dossier for European registration."

Upon closing of the agreement, NovaDel receives a non-refundable license fee of $3 million. NovaDel is, under the terms of the agreement, eligible for additional development- and sales-related milestone payments totaling $24 million, consisting of a regulatory approval milestone of $5 million and sales-related milestone payments of $19 million as well as a royalty on net sales during the term of the agreement. NovaDel and BioAlliance will jointly develop ondansetron OS with BioAlliance paying 100% of the costs up to a certain amount after which the development costs are shared 50:50 between the parties. BioAlliance will be responsible for activities related to regulatory and pricing approvals as well as commercialization efforts throughout Europe. NovaDel will be responsible for supplying the product.

Ondansetron OS is NovaDel's proprietary, investigational oral spray formulation of ondansetron, the leading 5-HT3 antiemetic therapy indicated for chemotherapy- and radiotherapy-induced nausea and vomiting (CINV and RINV) and post-operative nausea and vomiting. NovaDel and Strativa are jointly developing ondansetron OS in the US under the brand name Zensana. Par recently initiated bioequivalence studies in man and is proceeding on schedule for their submission of a new drug application (NDA) to the FDA in the fourth quarter of this year. BioAlliance expects to file the European dossier in 2009-2010. Antiemetic therapies constitute the largest segment of the oncology supportive care market. According to IMS, in 2007, over 2 million prescriptions for ondansetron were written in the US, and in Europe, ondansetron unit growth was 19%, representing about 1 million prescriptions in Europe in retail and hospitals (800,000 prescriptions in the top five countries).

BioScreen Testing Services Instrumental in NDA From FDA

Spectrum Pharmaceuticals, Inc recently announced the approval to market Levoleucovorin for Injection from the US Food and Drug Administration (FDA). Approval was granted after the FDA reviewed application submissions supported by data from BioScreen Testing Services, Inc. BioScreen provides contract testing services to companies large and small and has contributed data to support many submissions to the FDA resulting in approval.

"We offer our sincere congratulations to Spectrum," said Bradford Rope, President of BioScreen. "BioScreen looks forward to a continuing partnership, providing release testing support during the manufacture of Levoleucovorin, as well as additional development support for the many drugs in Spectrum's pipeline."

BioScreen Testing Services is a quality-driven contract laboratory providing analytical chemistry, microbiology, and stability services to the pharmaceutical, biotechnology, medical device, and personal care industries. The Pharmaceutical Division is staffed with scientists that specialize in method development, validation, compendial testing, and contract research. BioScreen is FDA and DEA registered and ISO 9001:2000 certified. The company complies with current Good Manufacturing Practices (cGMP) and Good Laboratory Practices (GLP).

Please Join Us For This Special Event At The 2008 AAPS National Biotechnology Conference

Sensitive Drugs and Prefilled Syringes

Understanding The Mechanisms Of Compatibility Through Frontier Science

Hosted By BD Medical - Pharmaceutical Systems

OVERVIEW:

BD's Sensitive Drug Initiative (SDI) is a forward-looking effort aimed at developing novel and appropriate technologies to meet the current and future needs of the biotechnology and biopharmaceutical industries. Significant efforts are underway within BD Medical - Pharmaceutical Systems to optimize existing prefilled syringe solutions and to develop the next generation of highly compatible prefilled syringes. This dynamic session will highlight key areas of the SDI program and provide perspective on SDI's impact relative to the biotechnology and medical marketplace.

TOPICS TO BE DISCUSSED:

- Surface Science and Complex Molecules
- Protein Adsorption - Understanding Syringe Material Interactions
- Unlocking The Mechanisms Of Silicone-Induced Protein Aggregation

Please Note:
Due to the high level of response at last year's session, it is necessary that we limit attendance to pharmaceutical and biotechnology company representatives only. Thanks for your understanding.

A 2008 AAPS National Biotechnology Conference badge is required in order to attend this session.

TUESDAY, JUNE 24, 2008
2:00 - 4:30 pm
Room 809
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Convention Centre

Refreshments served before session.

All session attendees are invited to a Meet The Speakers reception, immediately following the presentation.

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For more information about BD's Sensitive Drug Initiative and this event, be sure to visit us at Booth #718.

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Xcelience Launches New Service to Enhance Preformulation & Formulation Capabilities

Xcelience, a leader in early drug development services, recently announced its expanded offering of X-ray Diffraction (XRD) capabilities to support clients' needs in the areas of preformulation and formulation development.

"At the urging of several of our clients, we have committed to the purchase of an XRD instrument to enhance our overall capabilities in formulation analysis, polymorph identification, salt screen and selection, and crystallinity determination," states Mark Cappucci, Team Leader for Preformulation and Formulation.

This information can be provided to aid early development activities with use of a small amount of sample, which is nondestructive to the sample being evaluated. The XRD is the key technique for solid state drug analysis benefiting all stages of drug development, testing, production, and stability.

"With the addition of the XRD, Xcelience improves its scientific prowess for early drug development support," states Derek Hennecke, President and CEO. "This new capability will help our clients make faster and smarter decisions on their New Chemical Entities and further enhance our scientific offerings to the science of drug development."

Xcelience, LLC is an early development contract research organization focused on formulation development, preformulation services, analytical services, and clinical trial manufacturing. The company has earned a solid reputation of accelerating early development activities to speed potential drugs to clinical trials while applying unparalleled scientific knowledge and experience. Xcelience is the premier source for unsurpassed quality in drug development services. The company brings together the industry's most experienced and talented scientists, consistently and efficiently moving compounds through the research and development continuum to regulatory approval. Since 1997, the Tampa-based laboratory has been developing formulations for clients throughout the pharmaceutical industry. Xcelience's unique corporate structure creates project teams that work intensively with each client, bringing an extension of their own organization into the Xcelience lab. The lab uses only state-of-the-art equipment, highlighted by the patented Xcelodose®, which fills API directly to capsules (Xcelodose is a registered trademark of Capsugel BVBA). This and other technologies give Xcelience unparalleled speed to market without compromising its absolute commitment to quality.

Osmotica Receives FDA Approval to Market Novel Forms of Extended-Release Venlafaxine HCl

Osmotica Pharmaceutical Corp. recently received notice of final approval for its Venlafaxine Hydrochloride Extended-Release (37.5-mg, 75-mg, 150-mg, and 225-mg tablets) NDA from the FDA for major depressive disorder and social anxiety disorder. The Osmotica product provides a controlled-release tablet form of venlafaxine HCl, including a previously unavailable 225-mg dosage strength. Equal doses of venlafaxine HCl Extended-Release tablets are bioequivalent to Effexor XR® capsules, a leading product marketed by Wyeth, when administered under fed conditions. Osmotica expects to launch the new product line for the two FDA-approved indications in the near future.

"We are excited about the approval and pending launch of this innovative product," said Forrest Waldon, CEO of Osmotica Pharmaceutical. "The combination of our Osmodex® controlled-release technology with the venlafaxine molecule has allowed us to bring a dosage strength not currently available to the marketplace. We are evaluating proposals from potential marketing partners and expect to make the final marketing decisions in the near future."

Osmotica Pharmaceutical is part of a multinational group of pharmaceutical companies (the Osmotica Group) specializing in neurology-based drug therapies and delivery technologies. The Osmotica Group has a portfolio of products in various stages of development focused in the treatment of Parkinson's disease. In addition, the Osmotica Group utilizes its well-established drug delivery technologies (including its Osmodex technologies) and its expertise to develop drug candidates for partner companies. The Osmotica Group has a track-record of successfully developing and commercializing products in the US, Europe, and other countries around the world.

Amikacin Inhale Shows Promising Results in Phase II Study

Bayer HealthCare together with Nektar Therapeutics recently presented positive preliminary Phase II data on their unique drug-device combination Amikacin Inhale at the American Thoracic Society (ATS) annual meeting. Amikacin Inhale, currently being studied for the adjunctive treatment of Gram-negative pneumonia in intubated and mechanically ventilated patients, achieved over 1000 times greater lung exposure to the antibiotic amikacin as compared to intravenous route of administration. This shows that targeting antibiotic therapy to the site of infection might offer superior bacterial eradication and increased efficacy, which may result in a higher likelihood of the patient's survival. Currently, Gram-negative pneumonia carries a mortality risk as high as 50% in mechanically ventilated patients.

"Mechanically ventilated patients in critical care units are at particularly high risk of developing pneumonia. Most of them are already seriously ill because of severe underlying diseases," said Professor Michael Niederman, Chairman, Department of Medicine, Winthrop University Hospital, New York, and one of the lead investigators of the study. "Because of the high morbidity and mortality of Gram-negative pneumonia, fast and efficient treatment is essential. Intravenous therapies cannot always reach effective concentrations in infected lungs at tolerable doses. The new study data shows that the device successfully delivers the antibiotic directly to the site of infection, without reaching high systemic concentrations."

Amikacin Inhale is a unique drug-device combination being developed by Bayer HealthCare in cooperation with Nektar Therapeutics that combines a special liquid formulation of the aminoglycoside antibiotic amikacin with Nektar Therapeutics' proprietary Liquid Pulmonary Technology (LPT). It is designed to deliver amikacin deep into the infected lungs.

The device can be integrated into mechanical ventilation systems and can also be used as a hand-held off-vent device for patients no longer requiring breathing assistance. This allows for a unique full course of drug therapy in critically ill patients with Gram-negative pneumonia. Gram-negative pneumonia refers to pneumonia caused by a laboratory-defined group of pathogens, the Gram-negative bacteria. These account for a substantial proportion, if not the majority of pneumonias in intensive care units (ICUs).

Penwest Enters Into Development & Licensing Agreement With Cobalt Laboratories

Penwest Pharmaceuticals Co. recently announced it has signed a development and licensing agreement with Cobalt Laboratories Inc. to develop a formulation of an undisclosed compound utilizing Penwest's TIMERx® drug delivery technology. Under the terms of the agreement, Penwest will receive undisclosed fees and payments.

"We are pleased to have signed this development and licensing agreement with Cobalt," said Jennifer L. Good, Penwest's President and CEO. "This is the second collaboration we have entered into to license our proven TIMERx drug delivery technology outside our primary focus in neurology. These arrangements fit with our strategy of leveraging the value of our proprietary drug delivery technologies to provide additional financial benefit to Penwest while permitting us to focus our internal resources on building our own product pipeline."

Penwest is a drug development pharmaceutical company dedicated to bringing to the marketplace innovative products that help improve the lives of patients. The company's goal is to identify, develop, and commercialize prescription products that address unmet medical needs, primarily for disorders of the nervous system. Penwest is currently applying its drug development and drug delivery expertise to a pipeline of potential products that are in various stages of development and that it intends to commercialize independently or through third party alliances.

Cobalt Laboratories is the Canadian member of The Arrow Group, an international company focused primarily on generic pharmaceutical products. Cobalt is a fully integrated organization, with research and development, regulatory, manufacturing, and commercial operations. Currently the fastest growing generic pharmaceutical company in Canada, Cobalt began sales in 2002. The rapidly expanding product line is the result of robust R&D initiatives, and will continue to fuel sales growth for the coming years.

Halozyme Therapeutics Presents Findings on Combinations of rHuPH20 Enzyme With Bisphosphonates

Halozyme Therapeutics, Inc., a biopharmaceutical company developing and commercializing products targeting the extracellular matrix, recently announced new preclinical findings on the local tolerability and pharmacokinetics of bisphosphonates combined with rHuPH20 at the American Association for Cancer Research (AACR) conference.

The objectives of the presented studies were to investigate in animal models whether increasing the dispersion and absorption of bisphosphonates in the skin and subcutaneous tissues with rHuPH20 could modify injection site reaction (ISR) profiles from two intravenous bisphosphonate formulations, zoledronic acid and ibandronate. The pharmacokinetics of bisphosphonates in blood were also examined and compared to intravenous infusion. Key findings from the study include: (1) in rodent intradermal models, injection of bisphosphonates without rHuPH20 created ISRs characterized by erythema, induration, and ulceration in a concentration-dependent manner; (2) in rodent intradermal models, the maximal concentration of bisphosphonates that could be administered without producing ISRs was increased 3- to 5-fold when co-administered in combination with rHuPH20; and (3) in porcine pharmacokinetic models, absolute bioavailability by subcutaneous (SC) injection with rHuPH20 was comparable to IV infusion.

"Historically, hyaluronidase products have been utilized as an antidote to local extravasations of certain chemotherapy agents," said Gregory Frost, PhD, Halozyme's Vice President and Chief Scientific Officer. "We reasoned that if rHuPH20 hyaluronidase could rapidly disperse, dilute, and systemically absorb bisphosphonates, it could prevent local irritation and facilitate conversion from intravenous infusion to a more convenient subcutaneous route of administration. These preclinical findings support this program's objective of developing what would be the only SC bisphosphonate on the market, in the event of continued success."

The company plans to bring its SC bisphosphonate program into the clinic in the third quarter of this year. Bisphosphonates are a class of molecules that bind to mineralized bone matrix and inhibit bone resorption. Currently, there are oral and intravenous bisphosphonates. Oral bisphosphonates often cause gastrointestinal side effects and require a cumbersome dosing regimen. The gastrointestinal side effects of oral bisphosphonates is a significant cause of patient non-compliance to prescribed therapy. Certain bisphosphonates are indicated for the treatment of osteoporosis and skeletal metastases, but can only be administered today by intravenous infusion. As such, patients often have to travel to an infusion center or see a specialist to receive their intravenous bisphosphonate infusion. Subcutaneous injections of bisphosphonates are not considered feasible due to injection site toxicity in the skin and/or impractical injection volumes. The recombinant protein, rHuPH20, is a human hyaluronidase enzyme that increases the dispersion and systemic absorption of locally injected drugs by temporarily degrading hyaluronan under the skin.

Drug Delivery Success Rates & Development Times Defined in Report From Bionumbers, LLC

Bionumbers, LLC recently announced the publication of the first report in its Parameters of Performance series: *Drug Delivery 2008 – Product Success Rates and Development/Approval Times.* The report is based on an analysis of more than 430 products in development from 1993 to 2007 and evaluates the impact of multiple development parameters on success rates and development times for drug delivery products.

The Bionumbers report estimates the overall success rate for drug delivery development products to be 26%. This figure was found to vary by class from 0% to 90%, depending on definable parameters associated with the drug delivery product. The average time to product approval was 5.7 years with a range of 2 to 13 years.

"This report provides the first detailed analysis of the development times and success rates for drug delivery products and will be of interest to companies developing products in this sector, their partners, and investors," stated Josef Bossart, author of the report and Managing Director of Bionumbers. "The data provided in this report will play a critical role in refining the way companies forecast the development and approval performance of drug delivery products. The overall 26% success rate is surprising relative to the 20% success rate quoted by the Pharmaceutical Research and Manufacturers Association (PhRMA) for new chemical entity pharmaceuticals, and the sense among industry professionals that drug delivery products have a much higher success rate. The report finds that it is possible to improve the success rate to well over 50%; but only when the parameters are understood and appropriately managed."

In addition to an overall success rate, the report analyzes the impact of a wide range of variables on product approval success rates, and development and approval times. Both corporate status and technology platform validation status were found to have a remarkably high impact on success rates and approval times. The report includes an easy-to-use algorithm that permits companies to estimate their own product development and approval times based on the report findings.

The Bionumbers report *Drug Delivery 2008 – Product Success Rates and Development/Approval Times* is available for $8300 in Adobe Portable Document Format (PDF) by calling (512) 535-3613 or downloading an order form at www.bionumbers.com.

Bionumbers, LLC is a boutique research group based in Austin, TX, offering critical numbers and actionable insight into the parameters that impact the success and performance of products and companies in the biopharmaceutical sector.

QLT Reports Initial PoC Data for Punctal Plug Delivery Technology

QLT Inc. recently announced results from a proof-of-concept trial conducted by QLT's wholly owned subsidiary, QLT Plug Delivery, Inc., of its punctal plug drug delivery technology. The results demonstrated that QLT's drug-elution technology was effective in controlling intraocular pressure (IOP) and was well tolerated.

The proof-of-concept, open label study was initiated to determine if a sustained administration of latanoprost using the company's punctal plug drug delivery technology could lead to a reduction in IOP over 90 days when administered using a conventional plug design. Five patients (10 eyes) with glaucoma or ocular hypertension were enrolled at a single center. The primary efficacy endpoint was measurement of IOP. At baseline, the mean IOP was 23 mmHg for the 10 eyes treated. At 90 day follow-up, the mean IOP was reduced to 17 mmHg for the six eyes that remained. Data from two patients were excluded due to loss of plugs. No significant adverse events were reported.

"We are very pleased to report positive results from this preliminary proof-of-concept trial", said Bob Butchofsky, President and Chief Executive Officer of QLT. "Although the number of patients is small, we are encouraged by the clinically meaningful reduction in IOP that was observed and sustained for approximately 90 days. We look forward to providing you with additional details from this study at our Annual General Meeting."

The objective of QLT's punctal plug program is to demonstrate that the company's drug-elution technology leads to a statistically significant reduction in IOP for 90 days and that its proprietary punctal plug design can be retained comfortably in a high percentage of patients during that time period. The results presented are an early indication that QLT's drug-elution technology has the potential to provide a meaningful therapeutic benefit.

To generate proof-of-concept data for the company's proprietary punctal plug drug delivery system, QLT is currently enrolling patients in the CORE study, a Phase II, randomized, double blind trial to assess the safety and efficacy of its latanoprost punctal plug delivery system for the treatment of glaucoma and ocular hypertension at three different doses (low, medium, high). The medium dose of latanoprost in the CORE Study was used in the trial that is being reported.

QLT Inc. is a global biopharmaceutical company dedicated to the discovery, development, and commercialization of innovative therapies. Its research and development efforts are focused on pharmaceutical products in the fields of ophthalmology and dermatology. In addition, QLT utilizes three unique technology platforms: photodynamic therapy, Atrigel, and punctal plugs with drugs to create products such as Visudyne and Eligard and future product opportunities.

Morphotek Announces Collaboration to Facilitate Development of Human Monoclonal Antibodies for the Treatment or Prophylaxis of Infectious Disease

Morphotek, Inc., a subsidiary of Eisai Corporation of North America, recently announced it has signed a Cooperative Research and Development Agreement (CRADA) with the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health, for the development of human monoclonal antibodies for the treatment of infectious disease. Morphotek will apply its LibradomaTM technology to isolate and initially characterize candidate antibodies, and NIAID will further characterize the antibodies to identify candidates potentially useful in treating and preventing certain infectious diseases. Morphotek's Libradoma technology generates libraries of hybridomas that can be rapidly screened to identify monoclonal antibodies against disease-associated antigens.

"Morphotek is pleased to collaborate with NIAID on this important project," said Nicholas Nicolaides, PhD, President and CEO of Morphotek. "We remain committed to advancing candidates for clinical development in this therapeutic area, which if promising, may one day become available to patients with infectious disease."

Morphotek, Inc., is a biopharmaceutical company specializing in the development of protein and antibody products through the use of a novel and proprietary gene evolution technology. The technology has been successfully applied to a broad variety of cell lines and organisms to yield genetically diverse offspring that are suitable for pharmaceutical product development in the areas of antibody therapeutics, protein therapeutics, product manufacturing, drug target discovery, and improved output traits for commercial applications. The company is currently focusing its platform on the development and manufacturing of therapeutic antibodies for the treatment of cancer, inflammation, and infectious disease.

MBO Discussion Series

The Big Three – Employees, Managers & Customers

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

By: Derek G. Hennecke, MBA

The management buyout (MBO) is not just about money. Money is to the buy-out what walls and a roof are to your company. Money is the structure (the bones of the deal), but it alone will not make your success. What will make your success is your ability to bring with you the big three - employees, management, and customers.

Even if you are wallowing in cash, it won't do you any good if your employees are fleeing like rats from a sinking ship, or your managers are squabbling over turf. Great credit won't save you if your customers don't have faith that you will continue to hoist the corporate flag after the mother ship has left for distant seas.

Employees

If money is the bones of the buy-out, employees are the flesh and blood. In our case, they are even more vital than in most because we are a service business, creating a new, highly specialized product for every customer. We are only as good as the people we employ.

During our buy-out, this fact was even more pronounced. If we would have lost even one of a number of key people, the entire buy-out could have been scrapped. While it probably wouldn't have affected our ability to produce a great product, it would've sent a bad message to customers, and could've even triggered a landslide in morale within the organization itself.

During this period, employee morale was very sensitive because the mother company chose to make the sale of our plant a completely open process. I'm not criticizing this approach; it met with the company's policy of openness and integrity, which I greatly respect and am committed to continuing. In some ways, it made things easier for me because I didn't have to hide my feelings and thoughts from our customers or employees. We were an open book.

Most companies don't do it this way. It made for a long and difficult year of uncertainty for employees and saddled management with the task of maintaining employee loyalty at a time when management had little idea of what it was capable of giving in return.

Yet in other ways, the open process itself bore fruit. There was a certain amount of bonding that took place as we rode the waves of uncertainty together. And as the idea of an MBO began to take form, I sensed a genuine groundswell of support building from employees. In fact, by the time the buy-out was a sure thing, most of the employees were already solidly behind it. By contrast, when a buy-out takes place in secrecy, most of the work of bringing employees onside is still ahead of them.

Whether the buy-out takes place in secrecy or in the open, it's vital that everyone at every level of the organization know where they stand in the new organization as soon as possible. Employees need to believe that their future is secure and their career prospects are great.

Career prospects can be great in an MBO if you run your organization with a view to letting each individual take as much responsibility and initiative in their area as possible. The loss of that huge corporate overhead can reduce paperwork, lead times, and open the door to creativity.

At Xcelience, we further maximized employee input by holding larger group meetings than most companies, and encouraging

participation. Informal leaders were and are encouraged to work on informal projects, like specific equipment additions. Both seasoned and less-experienced chemists are given a chance to interact with sponsors.

You won't be able to retain everyone in a buy-out, and there are those who need to leave. It took me some time to realize that some employees, no matter how talented, are a negative influence and cannot be turned around. It is better to let them go. I regret that I didn't recognize this earlier, but it was an invaluable lesson to me. Morale shot up immediately after they left, and since then, our retention has been exemplary.

Management

The open process used in the sale of the company was hard on the staff, and perhaps even more so on management. Management saw every potential buyer that was dragged through the company. We were like the storybook princess in a movie I watched with my daughters the other night. Faced with the prospect of a forced marriage, she entertained a parade of suitors, with varying degrees of attractiveness. In the end, the experience served to convince her never to marry.

Again, openness and respect within the management team was essential. We talked about the buy-out together, and by the time it was official, the whole team was solidly on board, whether or not they were able to put some of their own skin in the game.

I hope that my other managers will agree with me when I say that we have become an incredibly tight and cohesive team. We respect each other and listen attentively. In a smaller company, it is even more important that you listen to every voice and entertain alternative ideas and opinions. I am immediately reminded of our Director of Project Management, Irene LoJacono, who constantly interrupts to remind me of our vision to stay small and focused. She is quick with pesky but necessary comments like, "Sure it's a great opportunity, but we don't want to become a jack of all trades."

On the flipside, the loss of a manager during a buy-out, while sometimes necessary, is not just a bad signal, but also a loss of valuable long-term experience at a time when you most need that corporate memory. What would we have done without the experience of Tom Kolessar, Director of Quality Assurance, who wrote the original SOPs back in 1997? Or Ted Koontz, Director of Operations, whom we brought back from a 2-year "sabbatical" up north. A mind like a steel trap, he remembered equipment that the rest of us had forgotten about.

And at the risk of returning to the theme of money, a lost manager results in a financial cost as well. Bear in mind that the average cost of replacing an executive, not including his/her salary, is over $80,000. You can add to that an average of 13 weeks to find a replacement and up to 70 weeks to make the new manager fully productive.

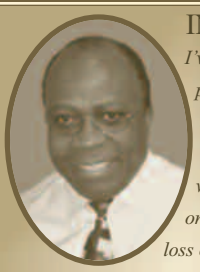
Customers

Before we launched the buy-out, we test ran the idea on our customers. If they were going to leave us, this whole exercise was pretty academic, right? Better to just walk away now. I worried. I fretted. What would they say? Would they stick with us? Would they trust us to stay afloat without a trusted mega-corporation?

Randy Guthrie, VP of Business Development, kept us calm. He claims there was never a doubt in his mind that the customers would see us through. At the time, I thought it was an act, but I went along with it. His cool confidence was contagious and had a real calming effect on others. I have learned to trust his instincts.

Maybe I should have had more faith, but it came as a surprise to me that we didn't lose a single customer because of the buy-out. In fact, we didn't lose a single customer throughout that entire period. We even had one customer remark offhandedly that we would most likely be able to do even better without a corporate yoke. They were looking forward to the change.

I had expected customer retention to be our number one problem, but it turned out to be the one thing we could have completely counted on. I credit this to our strong customer-centric operation. Because we literally re-invent our product for every customer, we know their wants, and they know our minds. We simply couldn't operate any other way. What I learned is that to our customers, it wasn't about the company. It's about our people. This was a huge lesson to me and continues to be central to the way Xcelience runs today. ◆



IN MEMORY

I've talked about our people as the flesh and blood of our company. So it is that we mark the loss of one of our own as the loss of a part of ourselves. Festus Hanciles, Director of Pharmaceutical Development Services, passed away unexpectedly on April 1, 2008. Festus was a quiet, contemplative man. He was a thinker; our corporate philosopher. He spoke little, but when he did, he was always worth listening to. His wisdom and leadership enriched us. We will miss him dearly.

BIOGRAPHY

Derek G. Hennecke, MBA
President & CEO
Xcelience

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

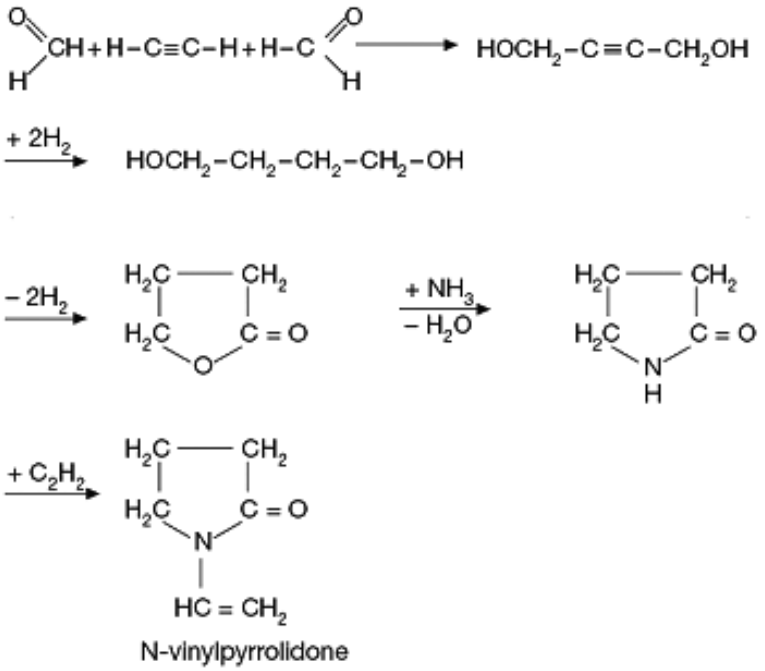
Polyvinylpyrrolidone (PVP) – One of the Most Widely Used Excipients in Pharmaceuticals: An Overview

By: Hubertus Folttmann, PhD, and Anisul Quadir, PhD, MBA

The chemistry of acetylene, developed at BASF in the 1920s by Walter Reppe, opened up numerous application possibilities, especially in the young field of plastics. In 1938, the year Nylon and Perlon were discovered, BASF succeeded in using acetylene chemistry to develop a highly interesting derivative: by reacting acetylene with pyrrolidone, vinylpyrrolidone was obtained, which in turn was used to form polyvinylpyrrolidone (PVP). The process patent was granted on January 1, 1939.

It soon became apparent that PVP was an all-around talent. It is readily soluble in water, physiologically compatible, non-toxic, essentially chemically inert, temperature-resistant, pH-stable, non-ionic, and colorless. This remarkable combination of properties predestined its use in numerous applications in medicine, pharmaceutical technology, cosmetics, and in the technical industry. Even as early as 1939, PVP was used as a plasma expander and was widely used in this form during World War II. During the 1950s, PVP replaced the schellac hitherto used in hair sprays. This article, however, deals with the applications of PVP in the pharmaceutical industry.

FIGURE 1



Reppe's Synthesis of N-vinylpyrrolidone

POLYVINYLPYRROLIDONE (POVIDONE)

Structure, Properties & Product Range

Soluble PVP products are obtained by the radical polymerization of vinylpyrrolidone, giving the structure in Figure 2. Drying is carried out either by spray- or drum-drying. This results in a white-to-yellow-white powder. Soluble PVP in aqueous solution has a very slight taste of its own.

The soluble PVP products of pharmaceutical quality are designated as Povidone in the USP. Today's range comprises products of different K-values. The K-value characterizes the mean molecular weight (eg, Povidone K 12, Povidone K 17, Povidone K 25, Povidone K 30, and Povidone K 90). BASF markets these products under the brand name Kollidon®; ISP is marketed as Plasdone®. As these products are widely used, they are monographed in numerous pharmacopoeias, eg, Ph Eur, USP, and JP/JPE. Table 1 lists the current pharmacopoeial requirements.

One of the outstanding properties of the soluble PVP products is their universal solubility in hydrophylic and hydrophobic solvents. Povidone, for

example, is practically infinitely soluble in standard pharmaceutical solvents, although at high concentrations, the solution becomes highly viscous. The mean molecular weight of the Povidone grades is characterized by the K-value in the European and US pharmacopoeias. It is always included as part of the tradename and is calculated from the relative viscosity in water. Povidone is hygroscopic, a particular advantage in its main application as a tablet binding agent.

The following M_w values (weight average molecular weight) were determined for different grades of Povidone in recent measurements: Povidone K 12 (2000-3000),

Povidone K 17 (7000-11000), Povidone K 25 (28000-34000), Povidone K 30 (44000-54000), and Povidone K 90 (1000000-1500000). With the exception of very few particles, the particle size distribution of the products is within the range 50 µm to 250 µm. The bulk density is approximately 400-600 g/l.

Povidone can form fairly stable association compounds or complexes with a number of active substances. The best-known example is PVP-iodine, one of the most important disinfectants in current use. The ability of Povidone to form a water-soluble complex with insoluble active substances can be used in pharmaceuticals to improve the release rate and solubility of drugs. It must be noted, however, that if Povidone is combined with strongly alkaline substances, such as lithium carbonate or sodium hydroxide, it can cross-link and become insoluble, particularly at elevated temperatures. In extreme cases, this can increase the viscosity of liquid presentation forms and delay bioavailability in solid forms.

Povidone possesses the following properties that make it ideal for numerous applications in drug manufacture:

- Solubility in all conventional solvents
- Adhesive and binding powers
- Film formation
- Affinity to hydrophilic and hydrophobic surfaces
- Ability to form complexes
- Availability in different mean molecular weights
- Thickening properties

TABLE 1

Specifications of the Povidone grades

	Povidone K 12	Povidone K 17	Povidone K 25	Povidone K 30	Povidone K 90
Colour (10% in water)	lighter than B6/BY6/R6	lighter than B6/BY6/R6	lighter than B6/BY6/R6	lighter than B6/BY6/R6	lighter than B6/BY6/R6
Clarity (10% in water)	clear	clear	clear	clear	clear
K-value	10.2-13.8	15.3-18.0	22.5-27.0	27.0-32.4	81.0-96.3
Nitrogen content (%)	11.5-12.8	12.0-12.8	12.0-12.8	12.0-12.8	12.0-12.8
Water (Karl Fischer, %)	≤ 5.0	≤ 5.0	≤ 5.0	≤ 5.0	≤ 5.0
pH value (5% in water)	3.0-5.0	3.0-5.0	3.0-5.0	3.0-5.0	4.0-7.0
Vinylpyrrolidone (ppm, HPLC)	≤ 10.0	≤ 10.0	≤ 10.0	≤ 10.0	≤ 10.0
Sulfated ash (%)	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1
Aldehyde (ppm)	≤ 500	≤ 500	≤ 500	≤ 500	≤ 500
Heavy metals (ppm)	≤ 10.0	≤ 10.0	≤ 10.0	≤ 10.0	≤ 10.0
Hydrazine (ppm)	≤ 1.0	≤ 1.0	≤ 1.0	≤ 1.0	≤ 1.0
Peroxides (ppm H_2O_2)	≤ 400	≤ 400	≤ 400	≤ 400	≤ 400
Microbial status (see Table 3)	passes test	passes test	passes test	passes test	passes test
Endotoxins (Ph.Eur.) (6% solution)	≤ 6 I.U./ml (≤ 0.1 I.U./mg)	≤ 6 I.U./ml (≤ 0.1 I.U./mg)	not tested	not tested	not tested
Residual solvents (Ph. Eur. 5.4)	≤ 0.5% 2-propanol	≤ 0.5% 2-propanol	≤ 0.5% formic acid	≤ 0.5% formic acid	≤ 0.5% formic acid
2-pyrrolidone (%)	≤ 3.0	≤ 3.0	≤ 3.0	≤ 3.0	≤ 3.0

The main applications of Povidone (including functions and dosage forms) in the pharmaceutical industry can be seen in Table 2.

As a Binder in Tablets, Granulates & Capsules

The main application area for Povidone K 25, K 30, and K 90 is as a binder in tablets and granulates (Table 3). The binding effect is achieved both in wet and dry granulation and in direct tablet compression.

While Povidone K 25 and K 30 are very similar, the binding effect of Povidone K 90 is considerably greater; this means that only about half the concentration of Povidone K 90 needs to be used. Due to their excellent solubility in water, the Povidone grades, in spite of their excellent binding qualities, have hardly any negative effect on the disintegration time of the tablets. Wet granulation with Povidone K 25, K 30, or K 90 results generally in hard granulates with excellent flow properties. Povidone can be used with all current granulation techniques. Povidone K 25 and K 30 are suitable for the manufacture of effervescent tablets as they, due to their high degree of solubility, rapidly form clear solutions. Interesting applications for K 25, K 30, and K 90 as binders are the wet granulation of excipients for direct tablet compression (eg, Ludipress®, Kollidon® SR) and the granulation of directly compressible active substances for tablets. Active substances marketed in pre-granulated form for direct tablet compression are usually those substances that are difficult to compress or that are subject to hydrolysis. Typical examples are vitamins and acetaminophen.

Apart from wet granulation, the Povidone grades are also used in dry granulation (eg, drum compression) or in direct tablet compression. However, for direct tablet compression, the more plastic and less hygroscopic Copovidone is the more suitable.

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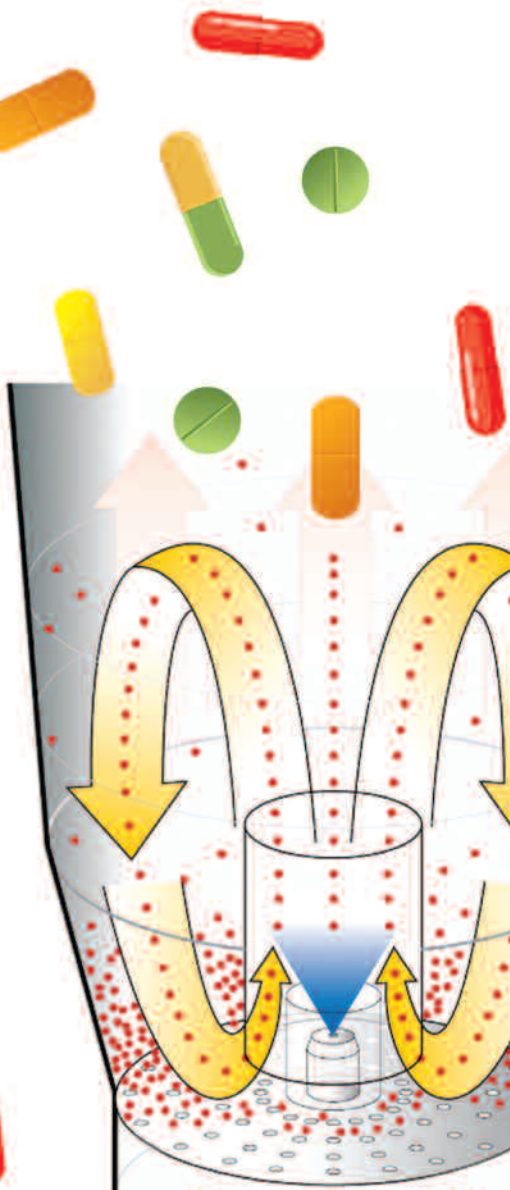

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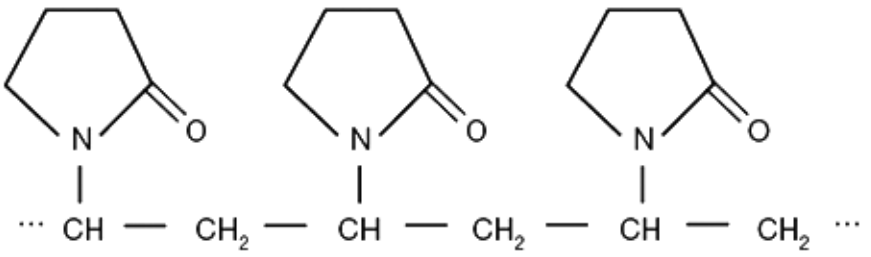
FIGURE 2



The Chemical Structure of Polyvinylpyrrolidone (Povidone)

TABLE 2

Function	Dosage Form
Binder	Tablets, Capsules & Granules
Bioavailability Enhancer	Tablets, Capsules, Granules, Pellets, Suppositories & Transdermal Systems
Film Former	Ophthalmic Solutions, Tablet Cores & Medical Plastics
Solubilizer	Oral, Parenteral & Topical Solutions
Taste-Masker	Oral Solutions & Chewable Tablets
Lyophilization Agent	Injectables & Oral Lyophilizates
Suspension Stabilizer	Suspensions, Instant Granules & Dry Syrups
Hydrophilizer	Medical Plastics, Sustained Release Forms & Suspensions
Adhesive	Transdermal Systems & Adhesive Gels
Stabilizer	Enzymes in Diagnostics & Different Drug Forms
Toxicity Reducer	Injectables, Oral Preparations, etc

Main Applications of Povidone

Improvement of the Release & Bioavailability of Active Substances

Two problems are frequently encountered with many active substances: their low degree of solubility in water and their limited bioavailability. One simple method to improve solubility is to add a solubilizer such as Povidone. With many active substances, Povidone forms soluble complexes. In some cases, a physical mixture of an API and Povidone is quite adequate. Apart from that, several methods have been used to increase the surface interface between active substance and solubilizer. In such cases, solid dispersions or solid solutions are suitable. In solid dispersions, the active substance is embedded in a hydrophilic carrier (eg, Povidone), possibly in fine crystalline form. In solid solutions, the active substance is in an amorphous, molecular-disperse form within the matrix (Povidone). Povidone is suitable for the manufacture of solid dispersions or solid solutions as it possesses hydrophilic properties, is available in various molecular weights and viscosities, forms water-soluble complexes with many active substances, and is almost universally soluble.

Suitable processes include mixing, co-milling, or melt-extrusion of the Povidone-drug mixture, co-precipitation, granulation onto a carrier, or spray-drying a solution containing the drug and Povidone. Numerous drugs are available on the market as solid dispersions or solid solutions. In some cases, a positive influence on bioavailability is described in the literature. The most frequently tested drug mentioned is most likely Nifedipine.

The low-molecular grades, Povidone K 12 and K 17, are used as solubilizing agents, dispersants, and crystallization inhibitors, particularly for injectables. This application is used in particular for antibiotics in solution or in lyophylized form. Povidones with higher K-values may not be administered parenterally as, due to their high molecular weights, they cannot be excreted by the kidneys and hence accumulate within the body. The use of Povidone grades K 12 and K 17 as solubilizers in parenteral applications is a frequent one for veterinary drugs; however, it has not been approved for use in humans in all countries.

Povidone K 25 and K 30 can be used as solubilizers in preparations for oral or topical applications in the same way as Povidone K 12 and K 17 are used in injectables. One typical example is the formulation of acetaminophen syrup, in which Povidone K 25 increases the solubility of the drug and also reduces its bitter taste.

Other Applications

STABILIZER OF SUSPENSIONS: The Povidone grades can be used in suspensions, dry granulates, and dry syrups as physical stabilizers. The most important function of these hydrophylic polymers in such cases is as a protective colloid; the individual solid particles are rendered hydrophylic and separated sterically. In this way, dispersibility is improved and the sediment volume can be increased. A further general function of Povidone is that it can prevent crystallization of the dissolved active substance by forming soluble complexes with it. The low-molecular Povidones K 12 and K 17 can also be used to stabilize parenteral suspensions.

OPHTHALMIC PREPARATIONS: Because of its solubilizing, film-forming, and

thickening properties, Povidone is used in ophthalmic preparations. This ensures that the preparation remains in the eye for a certain amount of time to lubricate it or to solubilize the active ingredient. This application requires between 2% and 10% Povidone. The bioavailability of some APIs in ophthalmic preparations can be improved by adding Povidone. Povidone is also used in cleaning fluids for contact lenses.

SUGAR COATING: In sugar coating, Povidone K 25 or K 30 is mostly used due to their following properties:

- Prevention of micro-cracks on the coating
- Adhesion of the sugar coating onto the core when hydrophobic active substances are being used
- Homogeneous distribution of the pigment or lacqueur in the coating
- Stabilization of the sugar suspension
- Slower and more homogeneous crystallization of the sugar

The prevention of micro-cracks is extremely important if large batches are to be prepared or if rapid drying is important. As most active substances are hydrophobic, Povidone helps to prevent the sugar coating from cracking.

FILM COATING: Due to its already mentioned film-forming and adhesive properties in sugar coating and its ability to form dispersions with pigments, Povidone is also used in film coating. However, it is never used as the sole film-former due to its hygroscopicity. Povidone, when added to other soluble film coatings increases the dissolution speeds of the other film-formers, resulting in the disintegration of the tablet and the release of active substance being accelerated.

MISCELLANEOUS APPLICATIONS: Apart from the aforementioned applications, the soluble grades of Povidone can be used for the following purposes:

- As adhesives in gels (eg, dentures)
- Stabilization of nitroglycerine in transdermal systems
- Regulation of the release of active substances in controlled-release preparations and transdermal systems
- Hydrophilization and pore formation in plastics for medical applications (eg, hollow fibers)
- Reduction of the toxicity of certain active substances
- Cryoprotection, lyophilization
- Enzyme stabilization (eg, diagnostics)
- Vitamin stabilization

TABLE 3

Povidone Grade	Concentration in Tablets/Granules
Povidone K 25	2%-5%
Povidone K 30	2%-5%
Povidone K 90	1%-3%

Usual Concentrations as a Binder

CONCLUSION

The unique properties of Povidone, such as its high solubility in solvents of differing polarities, its solubilizing and film-forming abilities, its suspension and emulsion-stabilizing effects and, last but not least, its binding properties, make it one of the most important excipients in pharmaceutical technology. Scientists keep working on numerous alternative applications of Povidone.

MORE LITERATURE

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Technical Information. Soluble Kollidon® Grades. BASF;June 2007.

BIOGRAPHIES

Dr. Hubertus Folttmann is a pharmacist by education. After 12 years of experience in different functions in the pharmaceutical industry, he joined BASF in 1998. His current position at BASF SE is the Head of Global Marketing, Pharmaceutical Excipients. His areas of expertise include binders, disintegrants, coatings, and solubilizers. He can be reached by email at hubertus.folttmann@basf.com.

Dr. Anisul Quadir is the Technical Development Manager of BASF Corporation in Roxbury, NJ. He earned his PhD in Pharmaceutics from the University of Rhode Island and his MBA from Rutgers University at New Jersey. In his current position, he leads the BASF Care Chemicals, North America development group for new applications of pharmaceutical excipients and to provide technical support to the pharmaceutical industry.The group developed various technologies like taste-masking, intra-oral film, soft gelatin coatings, floating technology, and drug solubilization, which can be used in different drug delivery systems. Before joining BASF, he worked at American Cyanamid and Catalytica Pharmaceuticals as a Development Scientist. He has been invited by the FDA to speak about the development of high-functionality excipients, is author of seven publications in peer-reviewed journals, and holds 5 patents. He can be reached by email at anisul.quadir@basf.com.

BITTER-BLOCKING TECHNOLOGY

Biochemical Bitter Blocking for New Drug Formulations

By: F. Raymond Salemme, PhD

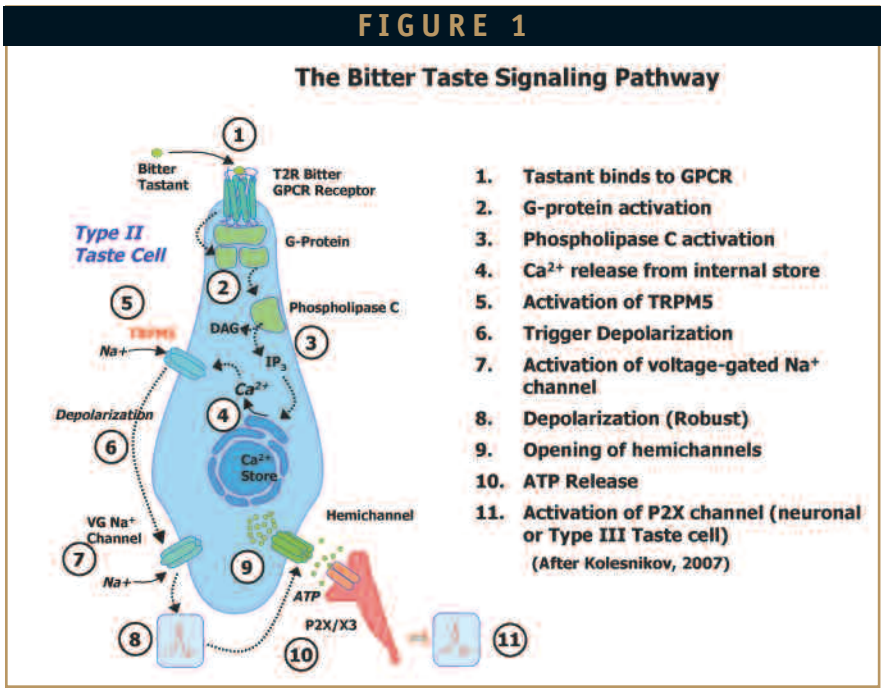
INTRODUCTION

The aversive taste of many active pharmaceutical ingredients (APIs) is a barrier to the creation of palatable liquid or other dosage forms that deliver the drug via absorption in the oral cavity. One commonly cited example is liquid pediatric formulations of antibiotics with poor taste, resulting in a lack of compliance and potential reemergence of resistant infections. Research studies have shown that palatability is particularly important to physicians prescribing liquid antibiotics for children. Other dosage forms, such as buccal delivery, lozenges, thin films, and orally disintegrating tablets, provide improved convenience and onset of action, as well as reduced hepatic drug metabolism for many APIs. However, in many cases, the aversive taste of the API is an impediment to their successful development and/or commercialization. The potential benefits of these improved formulation options motivate the development of new bitter blocking technology to overcome the aversive taste barrier.

CURRENT STRATEGIES FOR TASTE MASKING

The classic pill is typically coated and formulated to dissolve in the gut, thus avoiding most issues with aversive API taste. In contrast, most liquid or buccal delivery formulations typically incorporate some type of taste-masking. Numerous technologies have been developed for taste-masking, ranging from the simple addition of sweeteners and flavoring agents, to sophisticated methods of physical sequestration, such as API microencapsulation or complex formation with cyclodextrans or polymers. In many applications, substantial quantities of flavoring agents or sequestering agent are required to achieve effective taste-masking. In addition, many instances occur, due to the extreme bitterness of the API or the large quantities of API required for an effective dose, in which it is difficult to successfully mask the API aversive taste. There are over 100 commonly prescribed pharmaceutical and OTC products encompassing essentially all therapeutic areas that are known to have aversive API taste. Collectively, these products represent several billion dollars worth of annual sales.

FIGURE 1



"BIOCHEMICAL" BITTER BLOCKERS

An alternative approach to the creation of better-tasting liquid and orally absorbed drug formulations involves the development of topically active compounds that can be formulated in very small amounts together with the API to biochemically block the bitter taste-signaling system. This approach is enabled by a recently emerging understanding of the molecular biology of taste.

An ideal biochemical bitter blocker is intended to be effective in quantities of approximately 100 micrograms per drug dosage form, which is about 100- to 1000-fold less than the typical quantity of API dosage. As outlined in Table 1, there are numerous advantages to the

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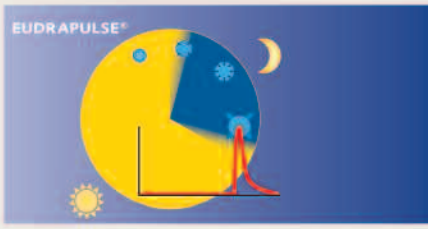

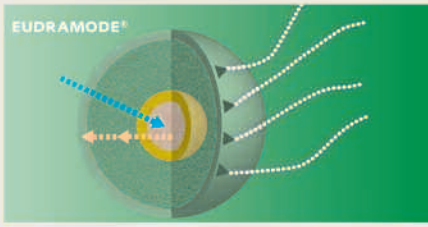

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BITTER-BLOCKING TECHNOLOGY

biochemical bitter-blocking approach that stem mainly from the very small amounts of compound required to transiently inhibit bitter taste perception in the oral cavity. There is also the potential for improved compatibility with orally absorbed drug delivery systems because there is no physical masking of the API to impede absorption through the oral mucosa. In addition, the small quantities of bitter blocker required can potentially reduce manufacturing complexity and lower overall formulation costs.

THE SCIENCE OF TASTE

Discovery of a novel biochemical bitter blocker follows a classical drug discovery paradigm based on inhibiting a specific molecular target in taste signaling. This strategy is enabled by the recent advances in understanding the molecular signaling processes underlying the sense of taste.

Generally, there are considered to be five basic tastes: sweet, umami (savory), bitter, salt, and sour. Sweet, umami, and salt are appetitive tastes that provide positive reinforcement for the intake of carbohydrates, proteins and nucleic acids, and minerals, respectively. Sour and bitter are aversive tastes, evolved to discourage intake of acidic substances (sour) or alkaloids or other compounds (bitter) that could be toxic if consumed indiscriminately. Recent advances in the molecular biology of taste now make clear that sweet, umami, and bitter tastants are sensed by G-protein coupled receptors (GPCRs) and that salt and sour are most likely sensed by ion channels. In addition to the five basic senses, there are several "spicy" tastes that appear to be sensed through ligand-gated ion channels of the extensive transient receptor potential ion channel (or TRP channel) family.

The bitter taste sense may have evolved in part to prevent the excessive ingestion of alkaloids (eg, natural compounds like caffeine, nicotine, etc) and other aversive compounds produced by plants as their own defensive mechanism to discourage consumption by animals. In fact, there is broad chemical diversity among the bitter compounds found in nature. Consequently, in contrast to the sweet and umami tastes, which are each sensed by a single heterodimeric GPCR, bitter taste is sensed by over 25 different receptors that have evolved to sense the diversity of plant defensive chemistry. Many drug APIs are more or less similar in

FIGURE 2

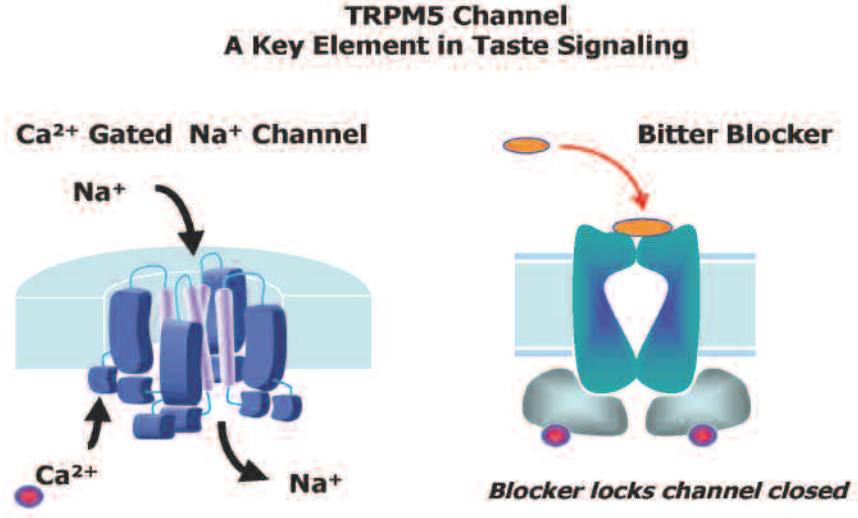

TABLE 1

Potential Advantages of a "Biochemical" Bitter-Blocker

	Conventional Taste Masking	Biochemical Bitter Blocker
Technology	Microencapsulation, Cyclodextrin carriers, Polymer resins	TRPM5 Inhibitor
Quantity Required	Typically equals API quantity	10^{-3} x API quantity
Oral Cavity Absorption Compatibility	Poor	Excellent
Manufacturing Complexity	High	Low
COGs	Variable	Very Low

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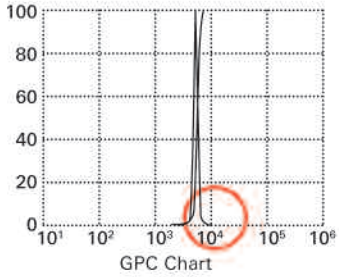

GPC Chart

Low Polydispersity: Mw/Mn=1.03
Low diol content

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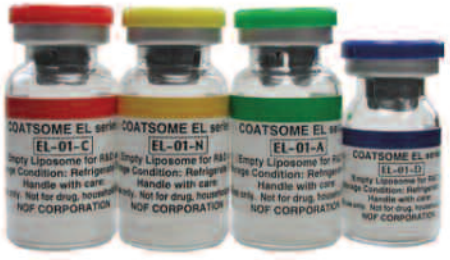

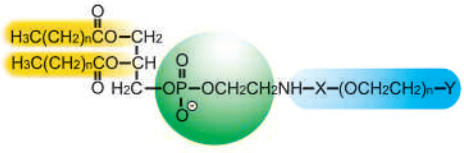

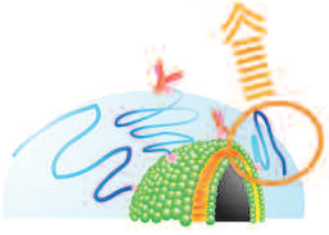

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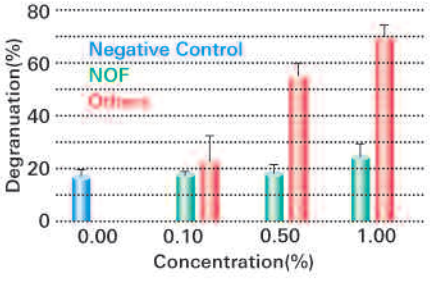

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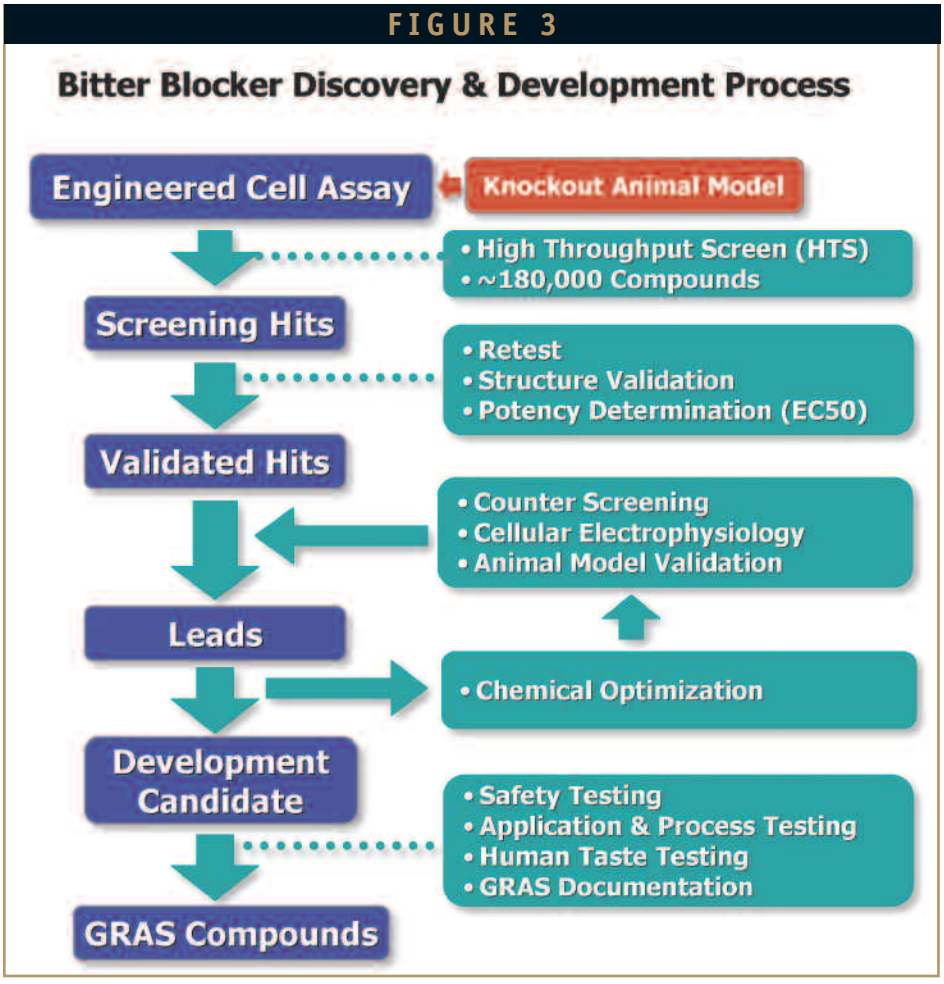
BITTER-BLOCKING TECHNOLOGY

FIGURE 3



chemical composition to alkaloids, and so are generally sensed as bitter.

Figure 1 outlines the bitter taste-signaling pathway.1 The taste-signaling pathway is initiated when a bitter molecule, such as a drug API, binds to a bitter GPCR receptor on the surface of Type II taste cells found in taste buds on the surface of the tongue (Figure 1 No. 1). API binding causes a conformational change in the GPCR that initiates a G-protein signaling cascade (Figure 1 No. 2), resulting in activation of phospholipase C (PLC 3) (Figure 1 No. 3). This in turn, causes mobilization of internal cell calcium (Ca^{+}) stores (Figure 1 No. 4). Released calcium binds to a trans-membrane ligand-gated ion channel called TRPM5 (Figure 1 No. 5). Calcium binding to TRPM5 causes the channel to open, admitting sodium into the cell interior. This produces a triggering depolarization that causes additional voltage-gated ion channels (Figure 1 No. 7) to open, admitting additional quantities of sodium and initiating a robust cellular depolarization (Figure 1 No. 8). Cell depolarization causes voltage sensitive hemi-channels to open, resulting in the release of ATP, which in turn activates P2X/X3 channels on neuronal or Type III taste cells (Figure 1 No. 9), ultimately initiating a "taste" nerve signal to the brain (Figure 1 No. 10).

Many of the aforementioned molecular components are highly specific to taste tissue.[2] The circuitry was principally worked out through the use of transgenic animals, in which specific genes are "knocked-out" so that they are ineffective in the expression of a functional signaling protein. The phenotype of animals with gene knock-outs of any of the key taste components is a greatly reduced capacity to taste bitter compounds. One of these signaling components, the calcium-gated channel TRPM5 in Figure 1 is an especially attractive target for pharmaceutical bitter blocking because it acts downstream of the 25+ bitter-sensing GPCRs. Thus, this target offers the potential to develop a single biochemical agent with the ability to broadly block bitter taste across a wide range of API chemotypes. Work carried out in Redpoint Bio's labs shows that TRPM5 knock-out animals are indeed deficient in their ability to taste a wide range of chemically diverse, bitter APIs, as suggested by the circuitry outlined in Figure 1.

Figure 2a shows a schematic of the TRPM5 channel, which is a homo-tetramer incorporating four identical protein subunits of MW~ 131,000 Daltons, including both transmembrane and intracellular domains. TRPM5 is believed to bind calcium at domains on the intracellular membrane surface, triggering the channel to open and allow the influx of sodium. As outlined in Figure 2b, a blocker is envisioned to physically block the transmembrane sodium channel, although it is equally plausible that a blocker could bind elsewhere on the channel and cause the channel to remain closed.

BITTER-BLOCKER DISCOVERY & DEVELOPMENT

The pharmaceutical industry has developed an extensive tool set to discover drugs directed to specific molecular targets. Redpoint Bio's bitter-blocker discovery process is outlined in Figure 3. The process begins much like a conventional therapeutic drug discovery campaign with the development of a high throughput screening assay and screening of a synthetic chemical or natural products compound library to find active "hits." Hits are then validated and begin iterative cycles of chemical diversification to optimize a continually expanding and more

rigorous set of evaluation criteria (eg, potency, selectivity, efficacy in animal models, etc) until a compound is selected as a development candidate. Computational chemistry tools are extensively employed throughout compound optimization to guide the process and to identify and correct potential liabilities with respect to compound efficacy and safety. Because taste is a characteristic shared in common with higher vertebrates, Redpoint makes use of operant animal models to evaluate its taste modulators throughout the optimization process. The company has developed novel approaches to traditional technology for animal behavioral testing that enable the in vivo testing of hundreds of compounds in usefully short timeframes.

Development candidates meeting initial selection criteria are scaled up for additional evaluation of safety, application suitability, and human taste testing. As noted previously, development compounds for pharmaceutical bitter-blocking applications are intended to be effective in quantities of approximately 100 micrograms per drug dosage form, which is about 100- to 1000-fold less than the typical quantity of the API dosage. Novel compounds used as flavor modifiers in foods and pharmaceutical products go through an extensive safety testing procedure, but are ultimately certified as safe for use through the Generally Recognized As Safe or GRAS approval process. GRAS is the category established by the 1958 Food Additive Amendment to the Federal Food, Drug and Cosmetic Act that applies to natural or artificial chemicals that can be added to food, beverage, and pharmaceutical products within a defined level of usage. New compounds can gain GRAS approval through a review of scientific material by an expert panel qualified by training and experience to determine safety. The current GRAS list contains approximately 2000 compounds, of which approximately 1400 are "nature identical" and 600 are synthetic. Many entries on the current GRAS list were reviewed and approved by the Flavor and Extract Manufacturers Association (FEMA) Expert Panel that has operated since the early 1960s. The FEMA expert panel requires a data package for GRAS status approval that generally includes extensive testing to demonstrate an adequate safety margin relative to the expected use level in any marketed product. GRAS Certification requires that the reviewing expert panel agree that the compound is safe at the anticipated use levels. Although FDA notification is not formally required, the GRAS data package is provided to the FDA so that the agency has the opportunity to review and/or challenge the GRAS status of flavor ingredients as determined by the FEMA expert panel.

PRODUCT APPLICATIONS

An effective biochemical bitter blocker is anticipated to improve a wide range of pediatric, geriatric, OTC, and consumer products that currently have taste problems, and to enable new liquid formulations that have previously been technically challenging. In addition, significant opportunities exist to create new dosage forms, such as lozenges, orally disintigrating tablets, and thin films, with bitter-tasting APIs. These formulations can offer improved convenience, more rapid onset of action, and potentially greater safety owing to bypass of hepatic metabolism. This technology is potentially applicable across numerous therapeutic indications, including pain, CNS, anti-infective, cardiovascular, gastrointestinal, genitourinary, and respiratory/allergy.

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2. Perez et al. A transient receptor potential channel expressed in taste receptor cells. Nat Neurosci. 2002;11:1169-1176.

BIOGRAPHY

Dr. F. Raymond Salemme is the CEO of Redpoint Bio, a biotechnology company leveraging recent discoveries in taste biology to discover and develop novel taste modifiers for the pharmaceutical, food, and beverage industries. Prior to Redpoint Bio, Dr. Salemme founded 3-Dimensional Pharmaceuticals, a company integrating structure-based design and combinatorial chemistry for drug discovery. Prior to 3DP, he worked in drug discovery at Sterling Winthrop and DuPont Merck Pharmaceuticals, and in basic materials science at DuPont CRD. Before joining industry, Dr. Salemme was Professor of Biochemistry at the University of Arizona. He earned his PhD in Chemistry from UCSD and his BA in Molecular Biophysics from Yale University. He is an inventor on 30 US patents and an author of over 90 publications.

PHARMACEUTICAL FILMS

Castable Edible Pharmaceutical Films

By: Ming J. Chen, PhD; Gloria Tirol, Charles Bass, Caroline M. Corniello, MS; Gavin Watson, and Ivonne Sanchez

INTRODUCTION

Commercial oral pharmaceutical film products have been used for sore throats, cough suppression, and vitamin supplements.[1,2] Retail sales of these types of edible films are expected to reach at least $350 million by 2008.[3] In this study, drug delivery via fast-dissolving and extended-release edible films was investigated for dissolution time, release profiles, and film strength. Three film delivery systems were evaluated to determine acceptable levels of benzocaine in which the active pharmaceutical ingredient (API) would not bloom to the surface of the film. The release profiles of model drugs benzocaine, caffeine, lidocaine, and diphenhydramine (DPH) in the polymer films were studied. Basic film-forming polymers employing hydroxypropylmethyl-cellulose (HPMC), methylcellulose (MC), and polyethylene oxide (PEO) were benchmarked with commercial films.

MATERIALS

The following water-soluble polymers from The Dow Chemical Company (Dow) were used for this study: METHOCEL™ methylcellulose A150 and A4M; METHOCEL™ hydroxypropylmethylcellulose E3, E5, E15, E50, K3, K100, and K100M; and POLYOX™ polyethylene oxide N-10, N-80, N-750, 60K, and 301.

Watson commercial films containing benzocaine or caffeine as API (or no API) were studied. Film Delivery Systems Nos. 1 and 2 were edible film systems containing polymers, plasticizers, benzocaine or caffeine, sweeteners, flavors, colorants, and processing aids. System No. 3 was a buccal film delivery system containing polymers, benzocaine, and colorants. These systems included both fast-dissolving and extended-release films. System No. 4 included cold pack and wound-dressing products that contained polymers, benzocaine (or no API), plasticizers, and processing aids. System No. 5 was a placebo film containing polymers, plasticizers, flavor, sweeteners, colorants, and processing aids with no API. Systems Nos. 4 and 5 were included in the study to compare the balance of mechanical properties. Other materials used in this study include the polymer pullalan, APIs lidocaine and diphenhydramine (DPH), and commercial Listerine oral strips.

METHODS

Visual observation was used to assess whether or not the API bloomed to the surface. The disintegration and dissolution times of cast films were based on a visual method.[4]

For the drug-release profile study, a standard USP dissolution apparatus I (Distek Dissolution System 2100B, North Brunswick, NJ) was used to evaluate drug-release kinetics from the prepared film formulations. In order to mimic the in vivo adhesion, each prepared film was affixed to a paper clip and put into the vessel at initial time (Figure 1). Deionized water (600 mL) at 25°C ± 0.5°C was used as the dissolution medium, and the dissolution apparatus was operated at 10 rpm. The samples were filtered through a 70-µm filter and then assayed for drug content using an Agilent 8453 UV-Visible spectroscopy system at 290 nm for benzocaine and at 273 nm for caffeine. The puncture strength was determined using a TA.XT2 Texture Analyzer. Tensile properties, percent elongation at break, and toughness of the film were determined at 23°C ± 1°C using

FIGURE 1

Active release profile set-up using the Distek dissolution system.

TABLE 1

System/ Composition	Theoretical % API in Film	Film Thickness (mil)	Visual Inspection for Blooming
1A	6.5% benzocaine	4.5	No
1B	9.8% benzocaine	3.5	No
1C	10.1% benzocaine	3.0	No
1D	10.4% benzocaine	3.5	Yes
1E	10.5% benzocaine	3.5	Yes
1F	10.8% benzocaine	4.5	Yes
1G	16.2% benzocaine	4.5	Yes
1H	27.7% caffeine	3.5	No
2A	6.0% benzocaine	3.0	No
2B	7.7% benzocaine	3.0	No
2C	8.4% benzocaine	3.0	Yes
3A (buccal)	17.2% benzocaine	15.0	No

Drug loading of film delivery systems.

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an Instron Universal Testing Machine (Model 1122, Instron Corp., Canton, MA) according to ASTM D882.

RESULTS & DISCUSSION

Drug Loading of the Film Delivery Systems

Table 1 summarizes the visual inspection results for blooming when loading various levels of API onto three film delivery systems. The maximum loading of API depends on the compatibility of the film-forming polymers with APIs and parameters such as pH of the system. In System No. 1, the maximum amount of benzocaine per film that could be delivered without blooming was 10.1%. For the film containing caffeine, 27.7% caffeine did not result in blooming. For System No. 2, the film could deliver 7.7% benzocaine without blooming; however, at 8.4% benzocaine, the API bloomed to the surface of the film. System No. 3 contained 17.2% benzocaine without blooming. The impact of film thickness on blooming was not investigated in this study.

Disintegration & Dissolution Times for the Film Delivery Systems

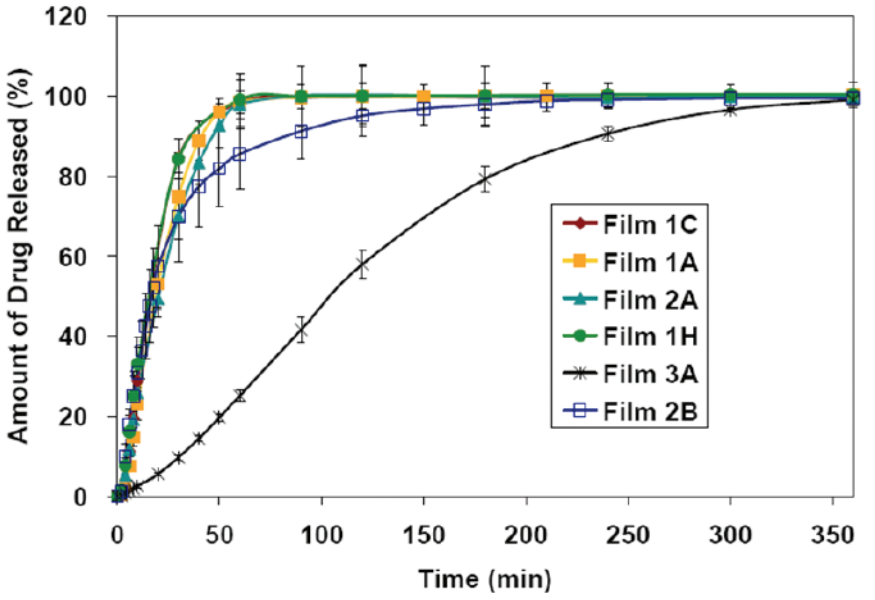
Table 2 summarizes the in vitro disintegration and dissolution time of pharmaceutical films determined by the visual method at 25°C and 37°C. Typically, as the film thickness increases, the disintegration and dissolution times increase. System No. 1 films containing benzocaine followed this trend. However, at the same thickness, a higher loading of the API decreased the disintegration and dissolution times of the films.

At the same film thickness, the dissolution times were faster for System No. 1 than for System No. 2. For the two films made using System No. 2, the dissolution results were quite different even though the film thickness was the same. This occurred because Composition 2B contained an ingredient that lowered the system's pH and, therefore, resulted in a carboxymethylcellulose (CMC) matrix that was less water soluble.[5] In general, disintegration and dissolution times decreased with increasing temperature.

System No. 3 was the thickest film and, as expected, this system had the slowest disintegration time at 25°C. However, due to the highly cross-linked carbomer network in the polymer blend in System No. 3, the solubility was poor, and dissolution incomplete.[6] Surprisingly at 37°C, the disintegration time was similar to that of the thinner films of Systems Nos. 1 and 2, which is probably due to the lower molecular weight PEO in the blend.

Due to the low pH in Composition 2B, this 3.0-mil film showed residual film after 4 hours similar to the results of the 15-mil thick film made from

FIGURE 2



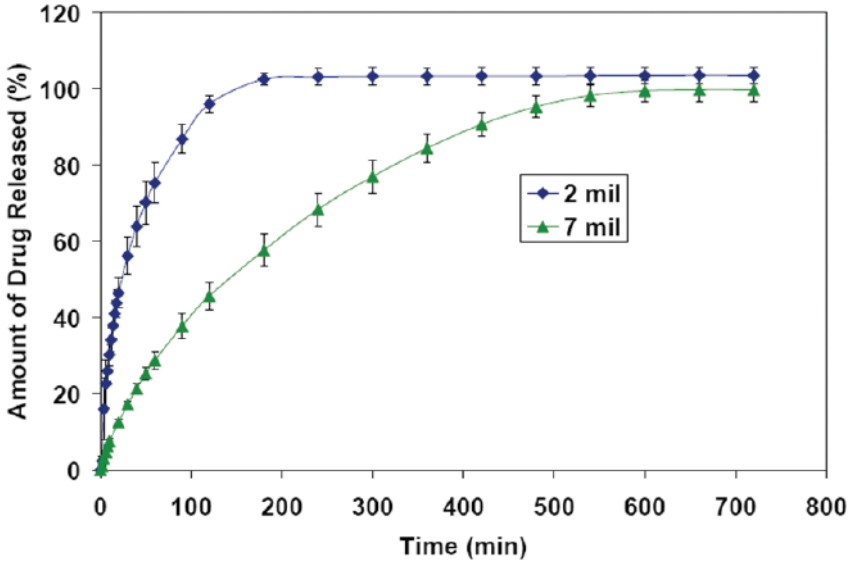
Release profile of fast- and extended-release films.

TABLE 2

System/ Composition	Theoretical % API in Film	Film Thickness (mil)	Disintegration at 25°C (s)	Dissolution at 25°C (s)	Disintegration at 37°C (s)	Dissolution at 37°C (s)
1A	6.5% benzocaine	4.5	28 ± 3	290 ± 11	10 ± 2	93 ± 15
1B	9.8% benzocaine	3.5	24 ± 1	158 ± 9	12 ± 2	100 ± 11
1C	10.1% benzocaine	3.0	7 ± 2	99 ± 4	4 ± 1	48 ± 3
1H	27.7% caffeine	3.5	27 ± 3	85 ± 5	20 ± 2	81 ± 10
2A	6.0% benzocaine	3.0	29 ± 5	370 ± 19	8 ± 2	215 ± 5
2B	7.7% benzocaine	3.0	5 ± 1	residual film after 4 h	3 ± 1	residual film after 4 h
3A (buccal)	17.2% benzocaine	15.0	322 ± 13	residual film after 4 h	10 ± 2	residual film after 4 h

In vitro disintegration and dissolution time for various Watson film products determined by visual method at 25°C and 37°C.

FIGURE 3



Release profile of benzocaine films based on HPMC E50 polymers.

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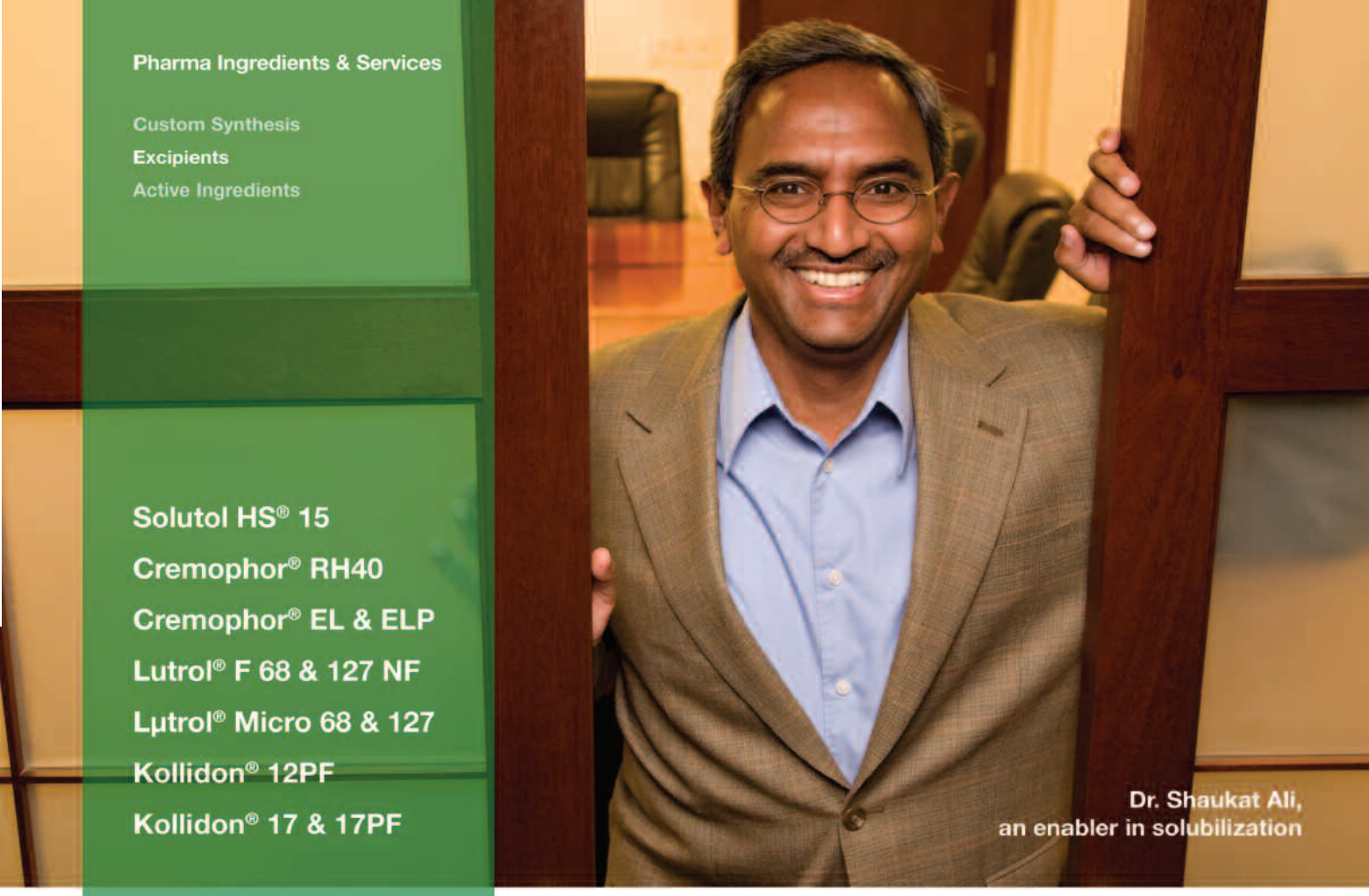

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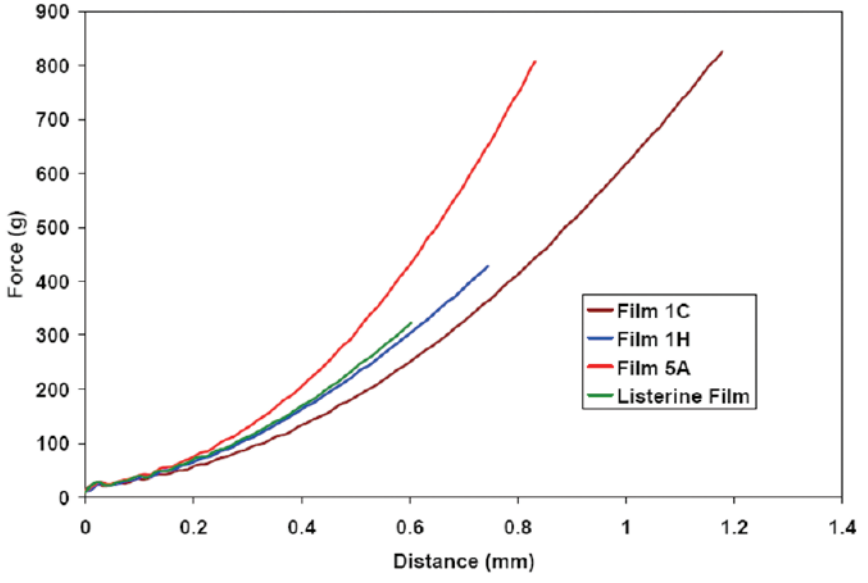
Composition 3A. Films containing DPH (10%), propylene glycol (9%), and polymer based on pullulan, PEO N-10, or PEO N-750 were studied for disintegration and dissolution times. All three films disintegrated instantly and were fast-dissolving. Table 3 shows that the dissolution time for DPH in pullulan was between that of the PEO N-10 and N-750 films. The dissolution time for films containing the API varied by the nature of the film-forming polymers. Films containing lidocaine (5%), glycerine (10%), and polymer HPMC K15M were studied for disintegration and dissolution times. Table 4 shows that the disintegration and dissolution times of the lidocaine films extended from 31 minutes to 4 hours, and from 46 minutes to 6 hours, respectively, when the thickness of the films was increased from 4 mil to 20 mil. This high molecular weight polymer is a carrier for APIs in controlled-release applications.

TABLE 3

Film Forming Polymer	Disintegration Time (s)	Dissolution Time (s)
Pullulan	6	46
PEO N-10	3	9
PEO N-750	3	159

Disintegration and dissolution times for diphenhydramine films based on pullulan, PEO N-10, and PEO N-750 at RT.

FIGURE 4



Puncture strength of Films 1H, 5A, 1C, and Listerine vs. distance.

TABLE 4

Film Thickness (mil)	Disintegration Time	Dissolution Time
4	31 min	46 min
7	1.5 h	2 h
20	4 h	6 h

Disintegration and dissolution times for lidocaine films based on HPMC K15M polymer in various thicknesses at RT.

Release Profiles of Fast- & Extended-Release Films

The release profiles of the APIs in commercial films were studied. Figure 2 shows the drug released as a function of time for various formulations of Watson films. For fast-dissolving films 1A, 1C, 1H, and 2A, the release rate was high at the beginning and then monotonically decreased with time, which follows the typical behavior for diffusion-controlled drug delivery systems. The API, benzocaine or caffeine, was released in 1 hour, based on the current designed method. On the other hand, for the buccal controlled-release film 3A, benzocaine was continuously released over 5 hours. As expected from the dissolution rate results, due to the lower pH in the Composition 2B, its release profile was slower than that of the Composition 2A.

Films based on 15% benzocaine in HPMC E50 polymer base were studied. Figure 3 shows the release of benzocaine films at two different thicknesses, 2 mil and 7 mil. The release rate followed a diffusion-controlled drug-release profile in which the diffusion pathways increase over time. The physical erosion of the 7-mil film is illustrated in Figure 1.

Film Strength of the Film Delivery Systems

Table 5 summarizes the puncture strength test results of the commercial films studied. The puncture strength of Films 1C, 1H, 5A, and Listerine is depicted in Figure 4. Film 1H had the most similar puncture strength to the Listerine strip; however, the film thickness was much greater for this film (3.5 mil) compared to Listerine (1.7 mil). The placebo film 5A (5.5 mil), which contained pullalan, was more brittle than Listerine (1.7 mil) due to the increased thickness. However, the strain was better (Table 5), which could be the effects of plasticizers and other additives.

Films 5A (5.5 mil) and 1C (3 mil) had similar force at break; however, the distance to break was quite different. It is interesting that the thinner film had more elongation to break than the thicker film. Pullulan (5A) is more brittle than HPMC, PEO, and sodium alginate in nature.[7]

The puncture strength of Films 2A, 3A, 4A, and 4B is illustrated in Figure 5. The puncture strength and % elongation at break significantly increased in Films 4A and 3A compared to others in Figure 5, and the behaviors of the strength are quite different. Film 4A was very strong due to HPMC while Film 3A was very tough due to the combination of PEO and carbomer. Compared to a similar PEO film, the puncture strength of 3A is more indicative of the carbomer. The incorporation of HPMC in Film 4A markedly increased the film strength, while incorporation of cross-linked carbomer in Film 3A increased the flexibility.

Generally, films made using pullulan or sodium

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alginate can have similar puncture strengths; however, the film thicknesses may be very different in order to achieve similar properties. HPMC and carboxymethylcellulose (CMC) films have similar puncture strengths; however, again, the film thicknesses may be very different in order to achieve similar properties.

Mechanical Properties of Various Water-Soluble Polymer Films

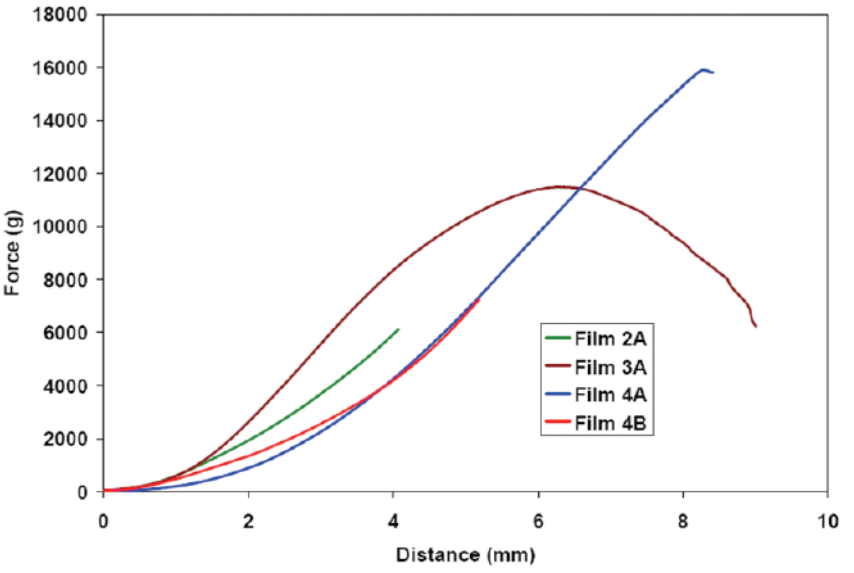
Various water-soluble polymer films were prepared and studied for puncture strength by the Texture Analyzer puncture test (Table 6). There are different grades of METHOCEL cellulose ethers that are classified by their chemistry. For example, METHOCEL A products are methylcellulose and METHOCEL E, F, J, and K products are hydroxypropylmethylcellulose with different ratios of hydroxypropyl group to methyl group. The tensile strength, percent of elongation, and toughness of Dow polymer films as determined by the tensile test are listed in Tables 7 and 8.

The MW of HPMC E3, E5, E15, K3, K100, K100M, and MC A15 and A4M are reported to be approximately 20.3, 28.7, 60.3, 19.3, 117.5, 720.2, 50.6, and 295.4 kDa, characterized by size exclusion chromatography (SEC) with LS-DP-RI detectors.[8] For the HPMC E series, the maximum puncture strength of the E series increased when the molecular weight of the polymer increased: E3 < E5 < E15 < E50. The polymer films from HPMC K and MC A series showed a comparable phenomenon, K3 < K100 < K100M and A150 < A4M.

The mechanical strength of POLYOX (PEO) products also consistently showed that N-10 < N-750 < WSR 60K < WSR 301, where the corresponding molecular weights are approximately 100,000; 300,000; and 2,000,000; and 4,000,000.[9] However, due to the nature of poly(ethylene oxide) chemistry with lower Tg and more flexibility, the puncture strength of PEO is much lower than that of cellulose-based MC and HPMC polymers. The maximum puncture strength of PEO films was up to 550 g/mil, while that of HPMC films ranged from 1400 to 4400 g/mil. High molecular weight PEO WSR-301 resulted in high toughness valued at 7056 ± 1196 psi and 522 ± 62% elongation.

The tensile and elongation properties of Watson film delivery systems are reported in Table 9. Generally for Systems Nos. 1 and 2 that contained benzocaine, as the amount of API in the film decreased, the tensile strength increased. Containing no API, Compositions 4A and 5A had the greatest tensile strengths. For Composition 4A, the film matrix contained HPMC, and for Composition 5A the film matrix contained pullulan. For Composition 1H that contained

FIGURE 5



Puncture strength of Films 2A, 3A, 4A, and 4B vs. distance.

TABLE 5

System/ Composition	Theoretical % API in Film	Film Thickness (mil)	Strain (mm)	Stress (g)	%RSD
Listerine	Listerine	1.7	0.6	322	2
1C	10.1% benzocaine	3	1	787	1
1H	27.7% caffeine	3.5	0.8	454	2
2A	6.0% benzocaine	3	4.4	6620	3
3A	17.2% benzocaine	15	6.7	11643	5
4A	No active	10.1	7.8	14880	10
4B	20% benzocaine	2.8	5.2	7190	1
5A	No active	5.5	0.8	660	4

Puncture strength test results for commercial films.

TABLE 6

Polymer	Maximum Puncture Strength (g/mil)
HPMC E3	1410
HPMC E5	2400
HPMC E15	2970
HPMC E50	4000
HPMC K3	1120
HPMC K100	2200
HPMC K100M	3120
MC A150	3300
MC A4M	4360
PEO N-10	13.8
PEO N-750	401
PEO WSR 60K	519

Maximum puncture strength of various water-soluble polymer films.

27.7% caffeine, the tensile strength was similar to Composition 1A that contained only 6.5% benzocaine. Therefore, it appears that caffeine has less negative impact on tensile strength when comparing films made using the same film delivery system. Composition 4B contained the highest load of benzocaine (20%) and had the lowest film thickness (2.8 mil); however, this film matrix had the highest tensile strength of all the films that contained API. It appears that System No. 4, made with HPMC, produced the strongest API containing film.

CONCLUSIONS

The loading of API onto a film delivery system without blooming was controlled by the compatibility of the API with the polymer ingredients. The disintegration and dissolution times of the pharmaceutical edible films reflected the fast-dissolving and extended-release applications, and varied by the nature of the film-forming polymers. Higher molecular weight and cross-linked film-forming polymers enhanced the film mechanical performance as well as the controlled release of APIs. In addition, thickness and formulations with plasticizers and other additives can further optimize the edible film functions.

ACKNOWLEDGEMENTS

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TABLE 7

Film Type	Stress at Break (psi)	Stress at Max. Load (psi)	Elongation (%)	Toughness (psi)
PEO N-10	154.0 ± 82.6	236.5 ± 55.4	1.4 ± 0.2	1.8 ± 0.6
PEO N-80	380.3 ± 113.8	714.3 ± 136.8	2.8 ± 0.6	13.3 ± 5.6
PEO N-750	501.6 ± 17.8	1238.0 ± 150.9	37.7 ± 8.7	346.5 ± 101.9
PEO WSR 301	1147.8 ± 186.4	1659.6 ± 66.6	521.7 ± 62.0	7056.0 ± 1195.7

Tensile, toughness, and elongation properties of various POLYOX water-soluble polymer films.

TABLE 8

Film Type	Stress at Yield (psi)	Stress at Max. Load (psi)	Elongation (%)	Toughness (psi)
HPMC E-3	4484.1 ± 703.1	4484.1 ± 703.1	2.0 ± 0.3	46.7 ± 16.6
HPMC K-3	3916.8 ± 214.3	5657.4 ± 516.9	2.6 ± 0.3	81.9 ± 20.8
HPMC E-15	5507.6 ± 72.6	7414.3 ± 472.2	15.4 ± 3.1	901.3 ± 227.9
HPMC E-50	6074.1 ± 170.7	7720.2 ± 665.2	15.3 ± 3.8	937.1 ± 295.9
HPMC K-100	5476.0 ± 598.2	7443.1 ± 598.2	16.0 ± 1.6	932.0 ± 137.4

Tensile, toughness, and elongation properties of various METHOCEL water-soluble polymer films.

TABLE 9

System/ Composition	Theoretical % API in Film	Film Thickness (mil)	Av. Tensile Strength (psi)	Av. Elongation (%)
1C	10.1% benzocaine	3.0	468	4
1H	27.7% caffeine	3.5	781	3
1B	9.8% benzocaine	3.5	445	15
1A	6.5% benzocaine	4.5	889	4
2A	6.0% benzocaine	3.0	827	39
2B	7.7% benzocaine	3.0	441	53
3A (buccal)	17.2% benzocaine	15	502	29
4A (cold pack)	no API	10.1	***	74
4B (wound dressing)	20% benzocaine	2.8	1283	28
5A (placebo)	no API	5.5	***	3

***Response above the detection limit of the instrument.

Tensile stress and elongation properties of Watson film delivery systems.

BIOGRAPHIES

Dr. Ming Jang Chen is Senior Applications Development Specialist at Dow and works in the Dow Wolff Cellulosics pharmaceutical group at Bound Brook, New Jersey. Dr. Chen earned her MS and PhD in Physical Organic Chemistry from the University of Chicago and was a Research Assistant Professor at Baylor College of Medicine. She has extensive experience in the pharmaceutical, healthcare, and biotechnology industry. Her experience has been in oral solids, drug delivery systems, formulation, and parenteral product development. Dr. Chen worked in the pharmaceutics R&D of Baxter Healthcare, genomic/proteomic biochips at PharmaSeq, and was R&D Manager of coatings and performance polymers at Rhodia.

Caroline M. Corniello is the Director of Product Development in the Film Technology Division of Watson Inc. She earned her Master of Science in Polymer Science from the University of Connecticut and her Bachelor of Science in Chemistry from Southern Connecticut State University. Ms. Corniello joined Watson in December 2002 with multiple years experience in developing and manufacturing water-soluble films in a commercial environment. She worked on projects for the food, medical device, oral care, pharmaceutical, and cosmetic industries. At Watson, she is currently researching the application of pharmaceutical-grade films in cosmetics and drug delivery, as well as broader-range medical applications.

DELIVERY CHALLENGES

Current Challenges in Drug Delivery

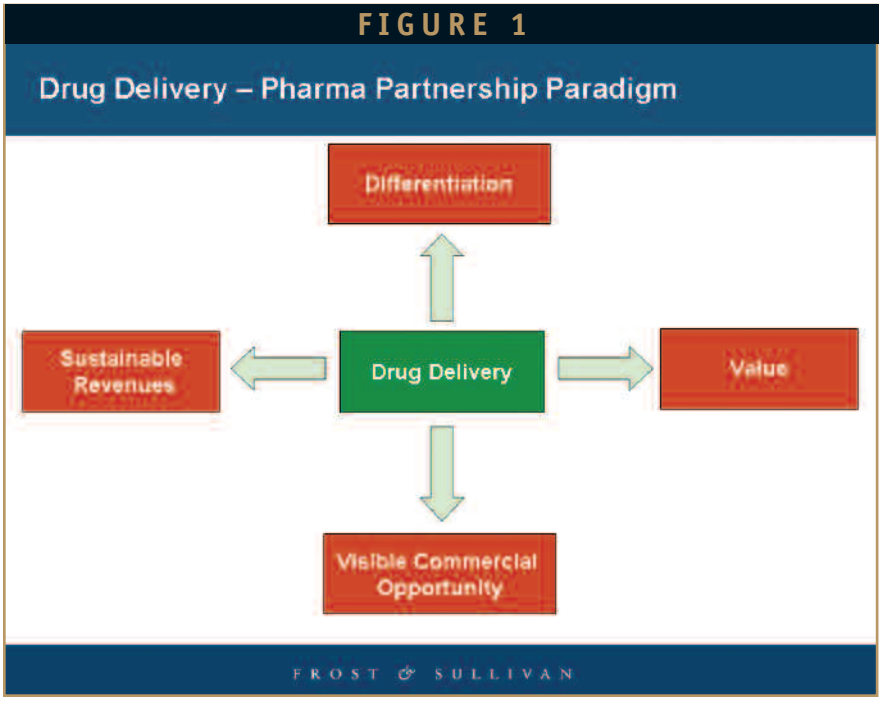
By: Daniel Ruppar, Industry Manager, Pharmaceuticals & Biotechnology, Frost & Sullivan

INTRODUCTION

Drug delivery is currently a hot area of interest in drug development. With the pharmaceutical industry facing a variety of challenges, including lower numbers of FDA approvals, pipeline problems, and overall contraction of discovery-to-market transitional productivity, companies are seeking new opportunities to support their future growth objectives. Within drug delivery, there are many challenges companies are facing as they seek to develop technologies and products. In addition, understanding both market and end-user factors for drug delivery technologies can provide companies with a clearer picture of the true commercial opportunity for a delivery technology-enabled drug in the marketplace.

In many areas of drug development, the evaluation of drug delivery technologies is seen as a solution platform for products. Not only can this aid in extension of IP or for use in life-cycle management strategies, it can also lead to improvements for existing products, better differentiation in the marketplace, new indication potential, or other portfolio development opportunities for drug companies. Within this area, companies are facing a variety of challenges as they seek to grow their businesses. These include operational model issues, the need to capture and demonstrate value, and the ability to fully understand the commercial opportunity for a delivery technology-enabled drug.

FIGURE 1



CHALLENGE: BUSINESS MODEL EVOLUTION

The drug delivery industry is facing changes and evolutionary pressures. Many companies are moving from a technology to product focus as they seek to transition and evolve their business models. For example, in February 2008, Nektar Therapeutics announced corporate restructuring from a technology-focused company to a product-focused company. With the low return sales execution and program halt for Exubera by Pfizer, this could be in the best interest of Nektar as they would hold differentiated revenue opportunities over a traditional technology provider-partner model. Even though many drug delivery companies are looking to a product-focused business, the technology-focused drug delivery company is still a needed commodity by the pharmaceutical industry. For example, with interest of the industry in biotechnology, improvements in expanding the delivery technology options for large molecule drugs are needed. Also, continued improvements

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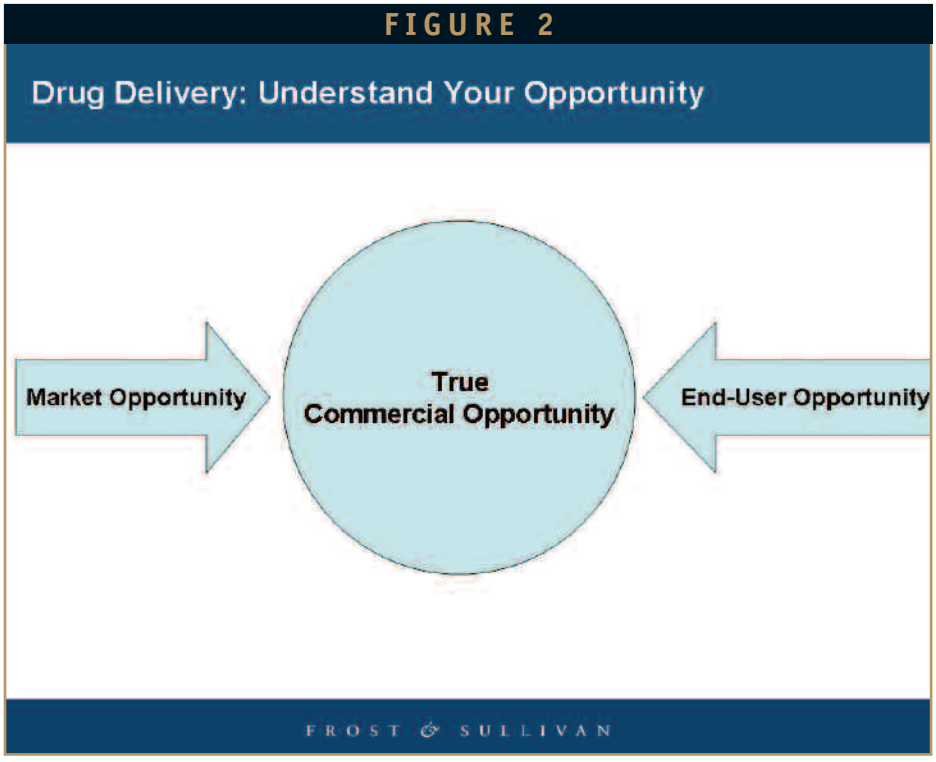
in products for many disease areas could also benefit from the continued optimization of non-oral approaches, such as intranasal or transdermal. Furthermore, as part of this process, the development of portfolios of technology, product, and hybridization of offerings by the drug delivery company is a way that firms are moving to spread and engineer their overall risk to their business.

CHALLENGE: CAPTURING VALUE & RETURNS

For those who are actively engaging in technology partnership opportunities with pharmaceutical firms, it is important to showcase factors above pure technology or science. Often, there are many technology platforms available to developers that could reach the same potential product endpoint. Therefore, positioning a drug delivery technology as being a central part of the overall value proposition is important for the technology partner to gain in returns.

In order for the drug delivery company to maximize the opportunity from partnership activities, it is important to be able to justify the importance of the technology platform and its value to the final product. Additionally, from the beginning product concept, the ability to understand the commercial opportunity, sustainable revenue opportunity, and enabled differentiation characteristics versus current or future prospective competitors are key points of evaluation for drug delivery partnerships. All of these points are areas in which the presentation and development of supportive content as to benefits of the drug delivery technology can ease the justification of revenue share for the drug delivery company in the overall partnership deal with the pharmaceutical developer.

FIGURE 2



CHALLENGE: UNDERSTANDING TRUE COMMERCIAL OPPORTUNITY

For product development, it is important to understand the full opportunity that exists for that drug in the market. Much of valuation, due diligence, or other business process scoping for product opportunities focuses on market side information in terms of assessment. In the drug delivery area, companies often use this as part of the investment justification process. For example, Nastech's intranasal Parathyroid Hormone (teriparatide) program (partnership was recently terminated by Procter & Gamble and returned to Nastech) for osteoporosis was compared to current daily injection therapy with an approximate market opportunity of $600 million (2006 sales comparison from injection form). That $600 million was used as a sizing opportunity by Nastech in justification that there was a revenue opportunity for their product. In addition to market value in terms of revenues, how those products or delivery technologies are viewed by end-user groups, such as patients and physicians, is also a key part of evaluating the true commercial opportunity for a drug in the market (Figure 2).

Even if there is a market opportunity for one drug delivery technology for a certain molecule, how that same molecule could be valued by end-users in a different delivery form is also important to understand. These factors could guide

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companies down development pathways they might not be considering or cause them to rethink or alter programs already in progress. For some technologies, patients or physicians could highly value or anticipate products using that approach to reach the market. Alternatively, for others, even if there could be a potential benefit to currently existing products in issues like compliance by changing the delivery; other factors for that same technology could drive end-users away from the product when viewed in the context of that new delivery form. Therefore, to understand the true commercial opportunity for a delivery technology-enabled drug, it is important to understand both the financial side market opportunity, and end-user opportunity.

END-USER RESEARCH

Recent Frost & Sullivan research in the area of drug delivery was conducted in four disease areas assessing a variety of patient and physician factors. Key focus points for this research were understanding challenges, adoption/non-adoption drivers, prescribing trends, compliance, and other important evaluation parameters for drug delivery technologies. Disease focus areas for this evaluation were diabetes, chronic pain, inflammatory diseases, and neurological disorders.

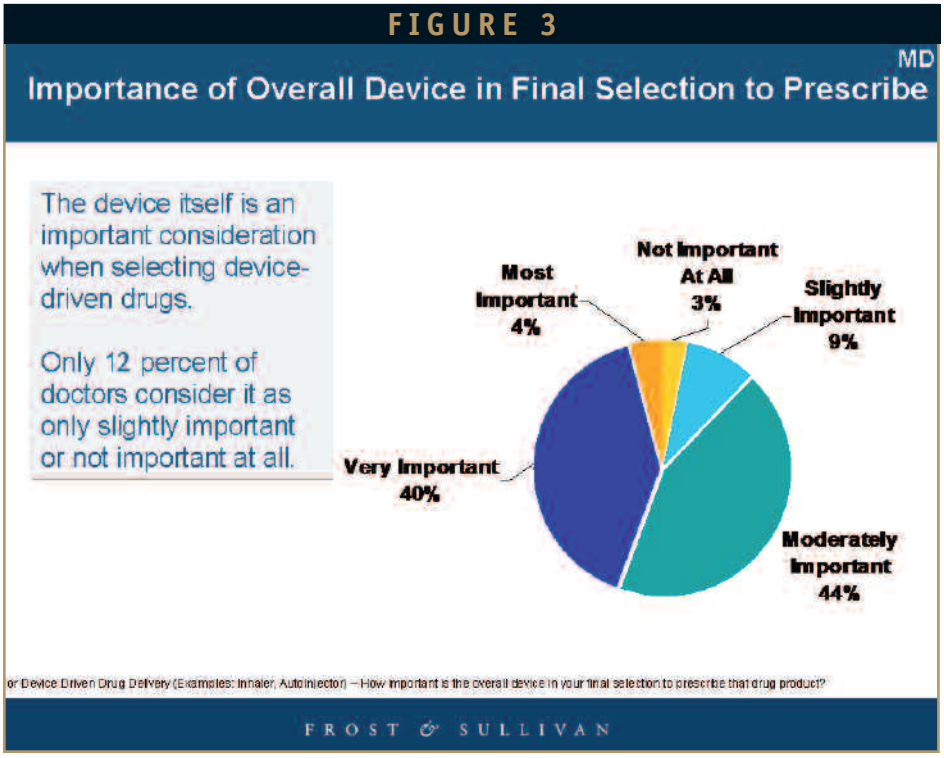
A key point of understanding for companies with device-driven drug delivery technologies is the importance of the overall device in the physician's decision to prescribe a particular drug (Figure 3).

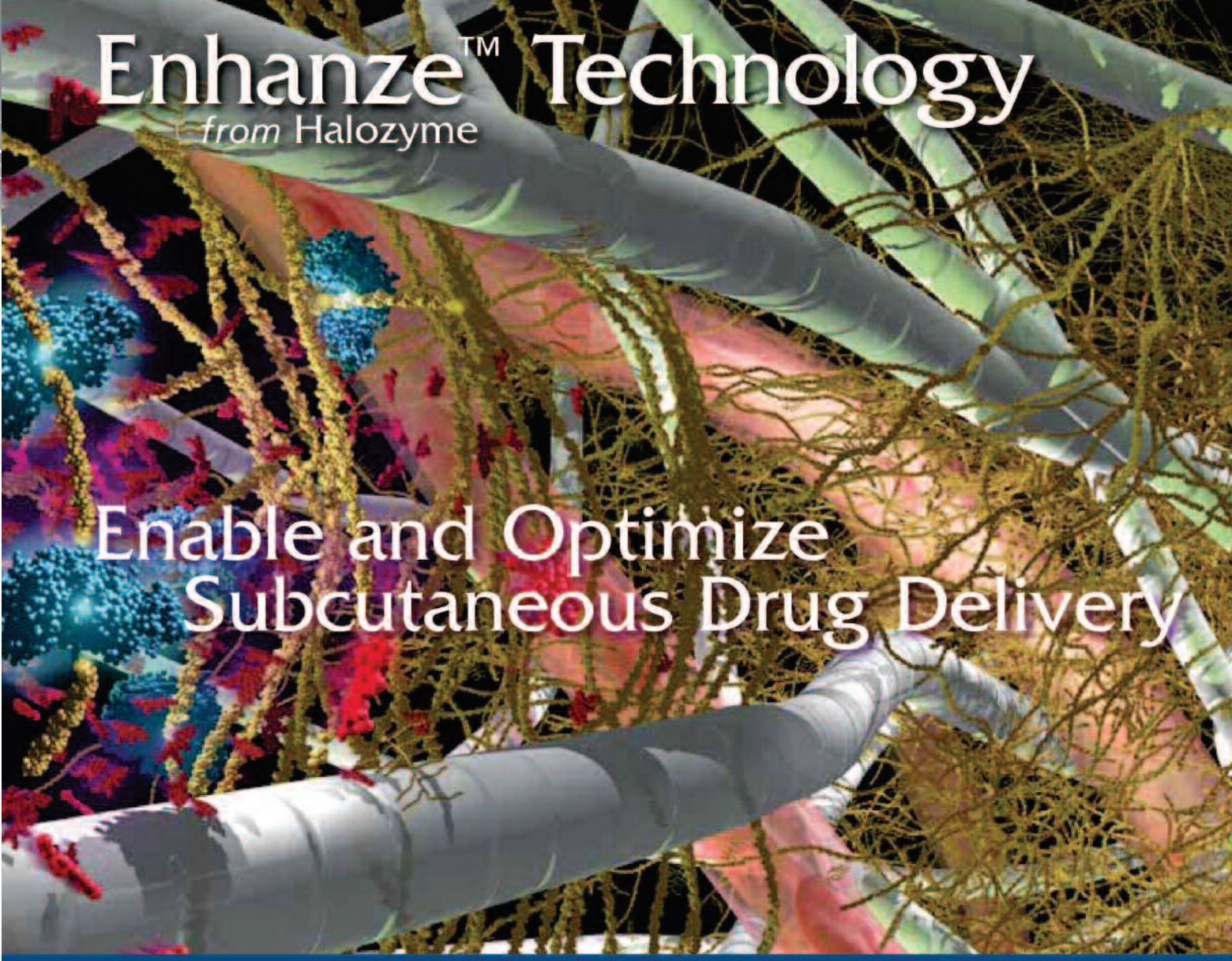
If the device itself is an important consideration, then that could greatly impact how a product is differentiated or evaluated in relation to the other drugs used to treat that disease. For both pharmaceutical companies and drug delivery companies, this is a key point to understand in the development of drugs as well as the partnerships in this area. What was found when this issue was posed to physicians, was that the device is an important consideration when doctors are selecting device-driven drugs. Only 11% of physicians (all disease types combined) considered the drug delivery device as only slightly important or not important at all.

What this reveals is that companies should pay particular attention to the characteristics of their drug delivery device both positive and negative. What in concept could be a beneficial approach to therapy could face problems in the market if the device has negative characteristics in the mind of physicians or patients. Exubera is a good example of this point. A multitude of data was obtained about pulmonary delivery from diabetes patients in recent Frost & Sullivan research. When the question of what patients would like to change about their usage experience with Exubera was investigated by Frost & Sullivan, improvements in the delivery device were desired by 60% of patient-user respondents (Figure 4).

In this case, users expressed dissatisfaction over the device used by Pfizer/Nektar to administer inhaled insulin. While the concept of inhaled insulin captured the minds of those involved in diabetes for some time, it is evident that the "convenience" of not using a syringe is not as great a driver as many thought. For those still interested in inhaled insulin development, it is important that they differentiate their

FIGURE 3





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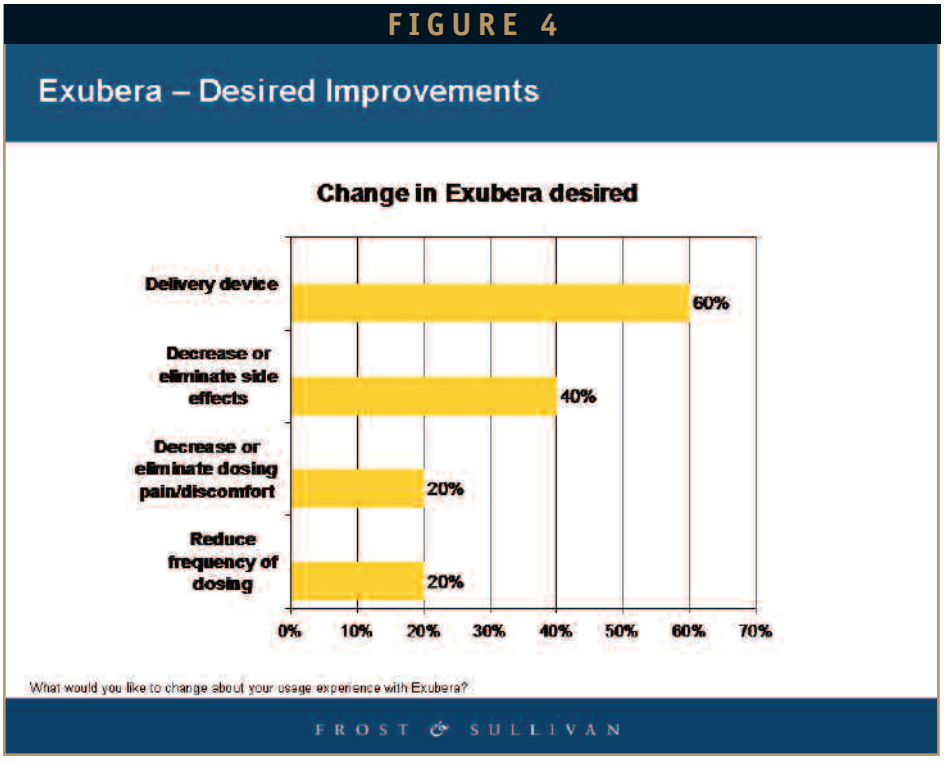
products from Exubera, and develop materials and data to show multiple points of benefit to patients and physicians, especially in terms of user-friendly devices and lack of side effects. Other programs have already been cancelled in the wake of Exubera, by Novo Nordisk and Eli Lilly for example, due to the recognition that people will not wait for a second-generation version of these products to optimize a drug, and would like a device with a high level of patient and physician centric optimization upfront.

SUMMARY

Overall, the challenge of assessing and understanding a product's true commercial opportunity is a daunting one. Conceptualizing value in terms of the potential revenue opportunity of a product is only one of the necessary points in the market value process. An understanding of both physician and patient views of drug delivery and its role in products can play a major part in how new drugs are being accepted by end-users. As biopharmaceutical and specialty pharma products expand importance for companies in the future, continued investment in new and further optimized drug delivery technologies is expected to be an important factor in the ability to create innovative products. In a changing industry, drug delivery companies are expected to continue to face challenges in terms of how they define and grow their business model and operate in their partnerships with developer companies. How drug delivery companies deal with and overcome these challenges is expected to make the difference in their long-term market success and future standing in the industry.

FIGURE 4



BIOGRAPHY

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

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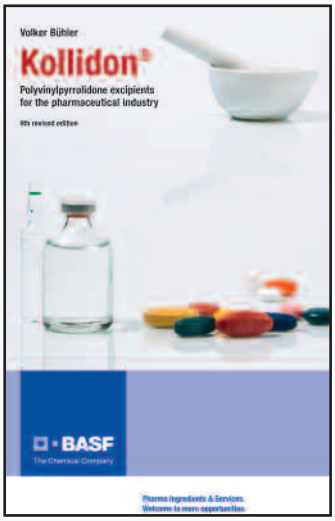

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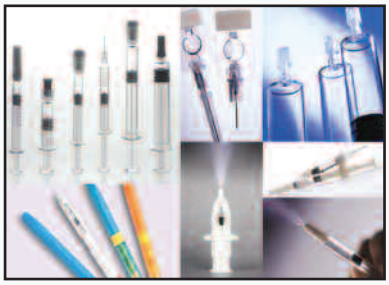
Technology Showcase

Prefillable Delivery Systems



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

Clinical Services & Supplies

Bilcare Global Clinical Supplies serves the Americas, Europe, and Asia with clinical trial materials support, services, and complete project management. Our services for solid, semi-solid, liquid, DEA (CI-V), and biotech clinical trial materials (CTM) satisfy a broad range of requirements from preformulation research and development, analytical services, and clinical supplies packaging and labeling to IVRS, controlled temperature (cold and frozen chain) CTM storage, distribution worldwide, and returns and destructions accountability. Our integrated approach provides you with seamless service throughout your entire project. We combine our industry experience and our total clinical supply chain service and delivery to provide smart, efficient, and innovative solutions. For more information, contact Bilcare Global Clinical Supplies at (610) 935-4300 or **www.bilcaregcs.com**.

Pharmaceutical Solutions

Designed to allow formulation scientists the ability to better exploit the potential of lipid-based formulations for poorly soluble compounds, the CFS 1200 helps accelerate the development timeframe and achieve Faster Time to First in Man. A fully automatic cGMP-compliant machine, it fills and seals up to 1,200 capsules per hour with liquid or semi-solid formulations without banding. It is designed for ease-of-use and high reliability, with the ability to quickly clean and change capsule sizes with available change parts. Product integrity is ensured with gentle handling of capsules before sealing and during the drying cycle. Other features include a robust filling pump with highly accurate temperature control, improved capsule manipulation before sealing and during drying using new "Cap-edge" handling system, and improved design of filling and sealing process that ensures better control and cleanability. Fore more information, contact Capsugel at (888) 783-6361 or visit **www.capsugel.com**.

Pharmaceutical Solutions

Catalent™

Catalent Pharma Solutions' services include a full range of development services, such as preclinical support, API development, analytical services, drug delivery development, clinical manufacturing, and packaging services. We have expertise in inhalation development and can offer innovative biologic cell-line development using our proprietary GPEx™ technology. Catalent's drug delivery systems include soft gelatin and Vegicaps® Soft capsules; Zydis® fast-dissolve dosage form; oral modified-release technologies, including EnCirc®, EnVel®, and EnSolv®; and a range of inhaled technologies. Along with our proprietary dose forms, we also manufacture traditional oral, sterile, topical, and inhaled dose forms. We also produce biologics for preclinical and clinical studies. Globally positioned, our packaging services include commercial packaging for all dose forms and the supply of printed components. For more information, contact Catalent Pharma Solutions at (866) 720-3148 or visit **www.catalent.com**.

Technology Showcase

Orally Disintegrating Technologies

CIMA LABS INC. is a drug delivery technology company specializing in the development and manufacture of prescription and OTC medication based on proprietary, orally disintegrating technologies (also referred to as fast dissolve, fast melt, and fast disintegrating). OraSolv® and DuraSolv® orally disintegrating tablets (ODTs) disperse quickly in the mouth without chewing or the need for water. OraVescent® is an oral transmucosal tablet that can be administered buccally or sublingually. CIMA's ODTs provide a wide range of benefits to products, including differentiation, life cycle management, overcoming formulation challenges, convenience, and ease of administration. The company also works with partner's products and also develops proprietary products. CIMA is a subsidiary of Cephalon, Inc. For more information, contact CIMA LABS INC. at (952) 947-8748 or visit **www.cimalabs.com**.

Topical Formulations

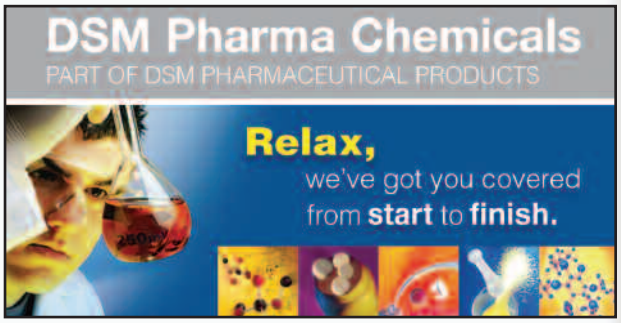
Dow Pharmaceutical Sciences, Inc.
The D in Topicals R&D
Since 1977

When you work with Dow, you can feel comfortable in knowing that your product is in very experienced hands because we focus only on topical formulations. After 31 years, we know how to prevent the unique problems that often occur during topical formulation development, analytical method development, scale-up, and long-term storage. In just the past 3 years alone, we helped 65 clients develop stable, elegant, scalable formulations that are disease compatible and penetrate the skin or ocular tissue as required. This is accomplished by a team of formulation, analytical, and drug transport scientists using Dow's unique formulation development process. For more information, contact Dow Pharmaceutical Sciences, Inc. at (707) 793-2600 or visit **www.dowpharmsci.com**.

Development & Manufacturing

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

Custom Manufacturing



DSM Pharma Chemicals, a business unit of DSM Pharmaceutical Products, is a global provider of custom manufacturing services to the pharmaceutical industry. Services include advanced intermediates, such as unnatural amino acids and derivatives, registered materials, and active pharmaceutical ingredients. Our technologies include biocatalysis, homogeneous catalysis, fermentation, and chiral technologies. DSM delivers comprehensive custom manufacturing services to the spectrum of pharmaceutical companies, including emerging pharmaceutical companies and large pharmaceutical companies. From clinical to commercial services, DSM focuses the right resources on providing the highest level of service and quality, while applying innovative solutions to satisfy customers' unique manufacturing needs. For more information, contact DSM Pharma Chemicals at (973) 257-8011 or visit **www.dsmpharmaceuticals.com.**

THE NUMBERS ARE OUT. WILL YOU BE READY TO RESPOND?

Announcing publication of the first in the Parameters of Performance Series from Bionumbers: Drug Delivery 2008 - Product Success Rates and Development/Approval Times.

Drug Delivery 2008 - Product Success Rates and Development/Approval Times for the first time quantifies drug delivery product success rates and development times. The results will surprise you.

Based on an in-depth analysis of more than 430 clinical stage drug delivery product candidates, Bionumbers provides critical insight into development and approval times for drug delivery products along with their success rates. More than an estimation of times and rates, the report analyzes product performance in terms of multiple variables including therapeutic area and delivery mode that yield insights into how they influence approval performance.

These numbers will reshape how everyone looks at the drug delivery business.
Will you be ready to take advantage?

Bionumbers™
Critical numbers. Remarkable insight.

The report is available at www.bionumbers.com.

Technology Showcase

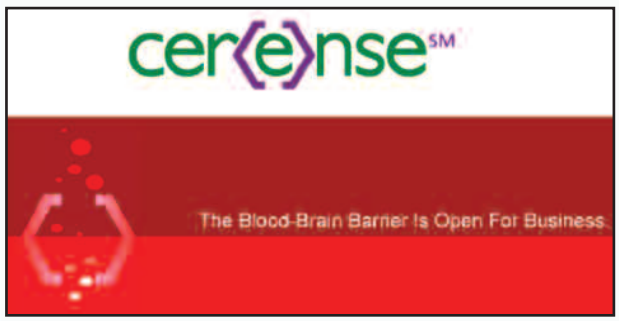
Orally Disintegrating Tablets

AdvaTab® is a new generation of ODT technology that offers distinct advantages and unique applications – unparalleled taste, flexible dosing, modified release, and a robust tablet. AdvaTab can be combined with Eurand's leading Microcaps® taste-masking technology to provide an ODT with superior taste and mouth-feel. AdvaTab tablets dissolve rapidly in the mouth within 15 to 30 seconds, and the smooth mixture of carrier excipients and taste-masked drug granules is suitable for delivering high drug doses. Modified-release drug granules can also be incorporated into the AdvaTab dosage form to provide a fast-dissolve tablet with sustained-release properties. AdvaTab tablets can be packaged in either bottles or push-through blisters. For more information, contact Eurand at (937) 898-9669 or at **partners@eurand.com**.

Polymers & Delivery Technologies

Pharma Polymers is one of the world leaders in the manufacturing and supplying of functional coatings for the pharmaceutical industry. EUDRAGIT® polymers are ideal for enteric delivery, controlled release, and protective coatings. Based on more than 50 years of experience in EUDRAGIT polymer design and formulation know-how for pharmaceutical applications, Pharma Polymers has developed intellectual property on advanced oral drug delivery technologies. The different brands of EUDRAPULSE®, EUDRACOL®, and EUDRAMODE® are the achievements of this intensive research and development effort so far. Pharma Polymers' business models for commercialization of these drug delivery technologies range from the development of customer-specific solutions to out-licensing strategies. For more information, contact Evonik Degussa Corporation at (877) 764-6872 (option 4) or visit **www.pharma-polymers.com**.

CNS Drug Assessment



Cerense℠ is the world's first integrated solution to release the value of your CNS portfolio by unlocking the blood-brain barrier (BBB) and measuring brain penetration. This is achieved through the combination of Genzyme Pharmaceuticals' patented CNS drug delivery technology and the unique expertise of Pharmidex to determine neuro-pharmacokinetics. Two major obstacles are recognized to inhibit the successful development of CNS medicines: (1) difficulties in getting compounds across the BBB and (2) difficulties in successfully measuring BBB penetration and neuro-pharmacokinetics. Cerense brings together a patented CNS drug delivery technology with world-class expertise in neuro-pharmacokinetics to overcome these twin obstacles and thus release the value of your CNS portfolio. For more information, visit Genzyme Pharmaceuticals or Pharmidex at **www.cerense.com**.

Pharma Systems & Packaging

The Gerresheimer Group ranks worldwide among the leading manufacturers of pharmaceutical primary packaging and drug delivery systems made of glass and plastic. In the field of injections, this international Group is regarded as a technology and quality pacemaker, particularly with sterile RTF® (Ready to Fill) syringes and intelligent accessories. Today, Gerresheimer supplies the pharmaceutics industry primarily with syringe systems in the completely prepared RTF® version. Innovative design options range from baked-on-siliconization to product labeling by means of laser encoding and multicolor printing via the heat-transfer process. The application-oriented accessory range comprises, for example, the Rigid Needle Shield with thermoplastic elastomer (RNS/TPE) and the Tamper Evident Luerlock Closure with a twist-off function (TELC). For more information, visit the Gerresheimer Group at **www.gerresheimer.com**.

CRS Opportunities for You

35th Annual Meeting & Exposition of the Controlled Release Society
July 12–16, 2008 • Hilton New York • New York, New York

The CRS 35th Annual Meeting & Exposition in New York City is pleased to bring you cutting-edge science, over 100 exhibitors, and many networking opportunities whether your interests are in pharmaceutics, consumer products technologies, or animal health.

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Member Meeting
Vet Get Together
Closing Reception/Banquet
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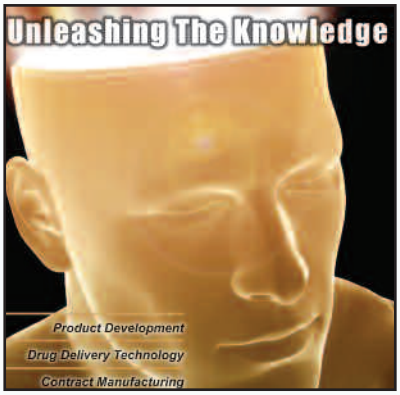
CRS Delivering Bioactives

www.controlledreleasesociety.org/meeting

Technology Showcase

Pharma Development Services



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

Enable & Optimize Subcutaneous Delivery

Would you like to convert your drugs from IV to subcutaneous (SC) delivery or enhance the dispersion and absorption of your existing SC compounds? With Enhanze™ Technology, microgram quantities of a fully human recombinant enzyme act as a "molecular machete" to clear the subcutaneous "jungle." Based upon this mechanism of action, co-delivery with Enhanze is anticipated to permit the SC administration of large volumes of antibody or other large molecule drugs, increase systemic bioavailability, speed onset of action relative to SC delivery without Enhanze, and improve patient tolerability. Learn how Enhanze Technology might revolutionize your drug delivery by contacting Igor P. Bilinsky, PhD, Vice President of Business Development & Special Operations, at ibilinsky@halozyme.com or (858) 794-8889, or by visiting **www.halozyme.com**.

Manufacturer & API Specialist

Hovione is a fine chemicals company that specializes in the process development and manufacture of active pharmaceutical ingredients and regulated intermediates. Dedicated to solving the problems associated with the industrial production of complex chemical entities, the company's expertise in process chemistry and regulatory compliance to cGMP standards is based on more than 40 years of experience. Over that time, its ability to provide customers with timely solutions that are dependable and economical has given them a worldwide reputation for superior customer service. Hovione's business is 50% custom synthesis for large pharma and biotech companies and 50% generic products. More than half of today's sales consists of products launched less than 5 years ago. For more information, visit Hovione at **www.hovione.com**.

Sorbent Technologies

MULTISORB Technologies

Multisorb Technologies has been an innovator in sorbent technology for over 40 years, and today, the company is the world leader in active packaging components. Multisorb delivers sorbent technologies with an unmatched commitment to leadership, innovation, and product solutions. Its products protect countless others in every industry from moisture, oxygen, odors, liquid spills, and more. Multisorb brings its partners the broadest line of sorbents in the world combined with a unique ability to invent and create innovative solutions that ensure freshness and stability. There is more to Multisorb Technologies than just desiccants; the company also offers a full breadth of active packaging technology. For more information, contact Muiltisorb Technologies at (800) 445-9890 or visit **www.multisorb.com**.

Technology Showcase

Central Lab Services

Pacific Biometrics, Inc. (PBI) is announcing new Clinical Biomarker Services, which are designed primarily to support clinical development of biotherapeutics. These include validation of ligand-binding assays for immunogenicity testing by ELISA and MSD and multiplexing for novel biomarkers, in a regulatory-compliant environment. Established in 1989, PBI is a Specialty Central Laboratory with an established reputation as the premier lab with scientific expertise, reliable results, and outstanding client services for cardiovascular risk, diabetes, osteoporosis, arthritis, and inflammatory diseases. For more information, contact Pacific Biometrics, Inc. at (800) 767-9151 or visit **www.pacbio.com**.

Delivery & Specialty Pharma

Penwest has a clear, well-defined growth strategy: to leverage its strength in drug delivery and drug formulation to develop a portfolio of products targeting disorders of the nervous system. The company's current development pipeline includes products for the treatment of pain, epilepsy, Parkinson's disease, spasticity, and edema. It is continually evaluating new growth opportunities, both internally and externally. During 2006, Penwest made important progress in pursuit of that strategy. Its key accomplishments included the approval and launch of Opana ER® by Endo Pharmaceuticals, development of its internal pipeline, and enhancement of its organizational capabilities and processes. For more information, contact Penwest at (845) 878-8400 or visit **www.penwest.com**.

Pharmaceutical Product Development

Licensing opportunities for PharmaForm's patented transdermal and transmucosal delivery systems are available. PharmaForm's proprietary delivery platform is a versatile polymeric delivery system that can be applied to many drug candidates and product applications. The company's Drug Delivery Technology team is integrated with formulation development, analytical, materials, and manufacturing groups to develop and optimize transdermal systems. The Formulation and Product Development and Analytical groups work closely to plan and execute the numerous facets of system development activities. After formulation development, clinical assessment, and final formulation selection is complete, PharmaForm can scale-up your product for commercial manufacture. PharmaForm will combine its pharmaceutical expertise, formulation chemistry, and long history of know-how to develop a high-quality transdermal drug delivery system for your market application. For more information, contact PharmaForm at (512) 834-0449 or visit **www.pharmaform.com**.

Controlled Delivery Platform

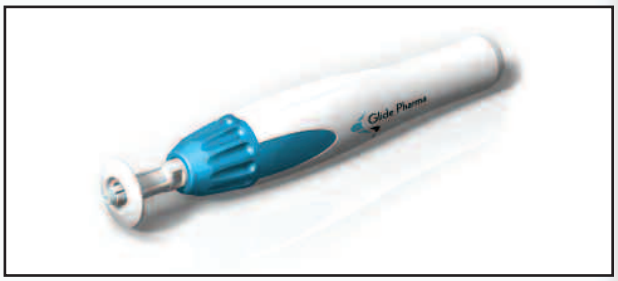
SCOLR Pharma applies its patented CDT® Controlled Delivery Technologies to develop formulations for companies with pharmaceutical, OTC, and nutraceutical products. These elegantly simple technologies can be used for controlled-release periods for up to 24 hours and can be manufactured using readily available standard materials and conventional production equipment. SCOLR Pharma partners with companies under contractual arrangements that include licensing fees, royalties, manufacturing contracts, or other mutually agreed upon financial arrangements. SCOLR Pharma's CDT® has the many distinct advantages, including highly programmable (capable of a wide range of release profiles), easy to manufacture (employs conventional manufacturing equipment), cost effective (utilizes standard tableting excipients), higher payload (when compared to other technologies), and strong patent protection (full patent life and easy enforcement). For more information, visit SCOLR Pharma at **www.scolr.com**.

Technology Showcase

Formulation Technology

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

Solid Dose Injector



The Glide SDI™ (Solid Dose Injector), developed by UK-based specialty pharma company, Glide Pharma, represents the next generation of needle-free injection technologies. With the Glide SDI, the dose itself is the delivery vehicle, allowing the easy, solid-dose injection of biologicals, small molecules, and vaccines. A solid dosage in the form of a tiny rod with a pointed end is simply pushed through the skin in a smooth, Push 'N' Click™ action using a spring-loaded, hand-held actuator, which resembles a pen. The dosage subsequently dissolves or degrades, releasing the drug or vaccine at the desired rate. The solid-dose formulation enhances thermal stability compared to liquid formulations, thus potentially removing the requirement for refrigeration simplifying storage and transportation. For more information, visit Glide Pharma at **www.glidepharma.com**.

Blow/Fill/Seal Machine

The Asep-Tech® Model 628 Blow/Fill/Seal machine features a two-piece stepped-base design for easy maintenance and convenient product discharge. All existing Model 624 tooling (molds, fill systems, parison heads) can be used on the Model 628, making it an attractive upgrade for current users. The versatile Model 628 has the flexibility to produce sterile, liquid-filled, tamper-evident containers ranging in size from 0.5 mL up to 250 mL in full-scale production quantities. Several other machine models are offered to fulfill higher output and/or larger container size requirements. The Model 628 comes complete with an integral product buffer tank designed to meet tight fill tolerances and all digital controls interfaced to a Data Acquisition System that features Wonderware® software. For more iformation, contact Weiler Engineering, Inc. at (847) 697-4900 or visit **www.weilerengineering.com**.

Drug Development

Xcelience is the premier source for unsurpassed quality in drug development services. The company brings together the industry's most experienced and talented scientists, consistently and efficiently moving compounds through the research and development continuum to regulatory approval. Since 1997, the Tampa-based laboratory has been developing formulations for clients throughout the pharmaceutical industry. Xcelience's unique corporate structure creates project teams that work intensively with each client, bringing an extension of their own organization into the Xcelience lab. The lab uses only state-of-the-art equipment, highlighted by the patented Xcelodose®, which fills API directly to capsules (Xcelodose is a registered trademark of Capsugel BVBA). This and other technologies give Xcelience unparalleled speed to market without compromising its absolute commitment to quality. For more information, contact Xcelience at (608) 643-4444 or visit **www.xcelience.com**.

Is Your Organization Effectively Positioned for Growth in the Drug Delivery Market?

As a result of developments in the pharma industry, the drug delivery market is poised to undergo rapid expansion. Pharma, Specialty Pharma, and Biotech companies will continue to seek partnerships with Drug Delivery companies that expand their product development options. Is your company positioned to take advantage of these opportunities for growth?

Frost & Sullivan's Pharmaceutical & Biotechnology group provides market intelligence and consulting support to identify and take advantage of the best growth opportunities in the Drug Delivery market.

Our expert Healthcare analysts:

- Provide objective, 3rd party analysis
- Identify a range of growth options
- Evaluate which options will produce the best Return on Investment
- Work with clients to develop effective implementation strategies

For more information on growth opportunities in the Drug Delivery market, please contact Melina Trevino at melina.trevino@frost.com.

FROST & SULLIVAN

DRUG DELIVERY
REXAM Executive

REXAM PHARMA: FULLY FOCUSED ON CREATING CUSTOMER VALUE

Marc Hämel
Managing Director
Rexam Pharma

"With the ever-increasing complexity of drugs and their administration, packaging has become as important as the product itself. We are business partners to many of the world's most famous and successful consumer brands as well as young, entrepreneurial start-ups. From unmet market needs to fully validated drug delivery solutions, we implement new ways to improve patients' lives."

Rexam is the No. 2 global consumer packaging company. It is the leading global beverage can maker and a major global player in rigid plastic packaging. With 22,000 people in more than 20 countries, Rexam's sales from ongoing operations are approximately £3.6 billion. Rexam Pharma is part of the Rexam group's Plastic Packaging business. It specializes in rigid plastic packaging solutions; intricate drug delivery systems; and medical devices for pharmaceutical, medical, and biotech industries. Drug Delivery Technology recently interviewed Marc Hämel, Rexam Pharma's Managing Director, to discuss his organization's strategic direction.

Q: Can you provide our readers with a little background and history on Rexam Pharma?

A: In 2003, Rexam made the strategic decision to seriously enter the market for pharmaceutical packaging and devices with the acquisition of Risdon Pharma from Crown. We already had a small pharmaceutical spray pumps and MDI valves business, and we merged this into the highly successful Risdon company to create Rexam Pharma. This provided us with a comprehensive product portfolio from ENT (ear, nose, and throat) spray dispensers to eyedroppers, pill jars, and medical devices.

The following year, Rexam acquired Plastic Omnium Medical, focusing on medical diagnostics and strengthening our position on drug delivery devices, which gave us a very strong position in Europe. We were still missing however a global footprint.

In 2005 and 2006, Rexam reinforced its leadership in healthcare packaging and became a global player with the acquisition of Precise Technology Inc, based in Buffalo Grove, IL, and Truepack India Pvt Ltd. Precise Technology had a strong presence in medical and drug delivery devices with state-of-the-art clean room manufacturing. Truepack was a leading manufacturer of plastic primary pharmaceutical packaging based in Bangalore, India. Rexam was the first global player in pharma rigid plastic packaging to enter India.

Most recently, Rexam acquired the plastic packaging unit of O-I and further demonstrated its intention to serve the pharmaceutical and medical companies in all their key markets worldwide. Rexam Pharma now has a strong presence with four European manufacturing plants, two in the US, and a facility in India from which we can service the needs of our global and regional customers.

Q: Please give us an overview of your products portfolio.

A: Our expertise in plastic injection and high-speed automated assembly enables us to offer high-quality products for all delivery routes and a broad range of packaging services and solutions for different industries, using different materials and technologies. We manufacture a wide range of products, such as advanced asthma inhalers, metering pumps and valves, eyedroppers and ophthalmic devices, nasal sprays, pill jars, tablet dispensers, parenteral devices, diagnostic disposables, and medical device components.

Q: What do you believe are the core strengths of your business?

A: In the past few years, we have managed to grow organically and integrate new businesses all the while maintaining and further cultivating our original culture, that of strong teamwork, passion for what we do, enthusiasm, and high sense of dedication. Our vision is to develop our people to deliver quality and innovation for the benefit of our customers and patients.

We believe that people are the key to any successful business strategy. Our vision is only made possible through a shared approach and by speaking the same language throughout our division. In doing so, we can respond to our customers, suppliers, and colleagues faster and better.

We have standardized global processes based on best practices, and this gives us a strong and common way of working worldwide. When it comes to GMP standards and ISO 9001:2000 guidelines, we have implemented standard validation in all our plants. All employees are trained for compliance with GMP. We commit to the ISO 13485:2003 certification for medical devices and have comprehensive experience in DMF and Clean Room manufacturing environments designed to meet Class 8 to Class 5 A GMP requirements. Validation and real-time in-process monitoring as well as change control are at the core of the quality system.

We commit to operational excellence, including Six-Sigma and Lean Enterprise programs to ensure the best performance for the benefit of our customers and patients.

A strong focus on Design for Manufacturing and a widely recognized know-how in Project Management and industrialization are the foundations of our ambitious growth strategy. We provide our customers with comprehensive custom manufacturing services, including extensive product design and value-added finishing services

Q: What makes Rexam Pharma attractive and unique on the market?

A: With the ever-increasing complexity of drugs and their administration, packaging has become as important as the product itself. We are business partners to many of the world's most famous and successful consumer brands as well as young, entrepreneurial start-ups. From unmet market needs to fully validated drug delivery solutions, we implement new ways to improve patients' lives.

As a partner, our goal and responsibility is to continually produce innovative products that provide enhanced quality at every level and focus on the patients' safety. Our global manufacturing capabilities, technologies, innovations, end-use applications, and geographical presence enable us to deliver even further value to our customers.

Above all, what makes us really unique is the quality and level of commitment of our team. We are strongly focused on excellence and customer value. People really are a

core part of what we call The Rexam Way values and our strategy.

Q: Tell us about the business strategies that have contributed to your success?

A: We stay focused on embracing and anticipating regulatory, GMP changes as a pharmaceutical company. Acting as a leader is important in a fast-changing market. More and more, we intend to be ahead of regulations. Anticipating market trends is also a must for product development.

Being global enables us to offer world-renowned expertise and capabilities to our customers wherever they may be. We partner with our customers as a single team, providing close cooperation from a product's very early concept design to pilot phase, industrialization, or full-scale production. We also develop a strong project management culture of "on-time, in-cost" expertise.

Rexam Pharma has earned a worldwide reputation as a leader in producing its own patented technologies and innovative products. Innovation is a core strength of our company. We have integrated Technology Centers in France, the US, and India to actively support our customers in their product developments. Our mission is to develop Innovative Concepts and project delivery in Quality, Cost, and Time.

Q: Talking about innovations, what products are you currently developing?

A: We are in the final stage of a new-generation pump at the leading edge of innovation and meeting new market requirements. Our patented Advancia pump will answer new demands in the drug delivery market, thus limiting the use of preservatives in order to reduce the risks of allergy or irritation. Our technology has been completely redesigned in order to meet the regulatory expectations and to deliver high-performing solutions for patients.

One of our latest launches concerns the MLx rigid plastic multilayer, injection blow-molded technology, designed to optimize barrier performance as well as strength, clarity, and pharmaceuticals compatibility. It is especially suitable for biotech drugs that require the best protection and for products that could endanger users in case of accidental exposure.

We have recently launched fully integrated radio frequency-enabled plastic pharmaceutical bottles that allow compliance with FDA recommendations with a fully traceable life cycle and counterfeiting prevention.

Rexam Pharma has also designed and patented a fully passive safety device for prefilled syringes, called Safe'n'Sound. It provides the healthcare industry and patients with full protection from needlesticks. The Safe'n'Sound is both a concept (integrated in customized devices for specific uses) and a product (suitable for use with standard prefilled syringes on the market).

In every case, Rexam's development teams are able to support specific customer requirements for these products and technologies.

Q: Where do you see the company in 5 years and beyond? What are the long-term goals?

A: We believe our innovative products and technologies give us the recipe for a bright and successful future. We are positioned to become a leader in ophthalmic, injection, and inhalation products and devices. We also want to be increasingly involved in the early development design of devices, as well as providing more services to our customers. We will continue, as always, to cultivate strong customer relationships in order to fully meet their needs. We will also continue to capitalize on globalization opportunities (Japan, China, South America) building on Rexam's global footprint and seeking out new potential applications and markets together with our customers. ◆

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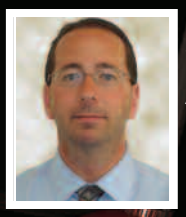

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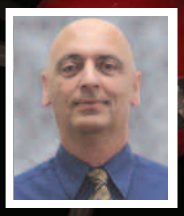

Frank Santillo, PhD
Senior Director of Research Services
Bilcare

Outsourcing Formulation Development

Strategic Partners in Today's Development Climate

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

Contract Resource Organizations, especially those in formulation development, have grown quickly, evolving from "an extra pair of hands" into strategic business partners, purveyors of innovation, and proprietors of novel drug development technologies, according to Goliath Business Knowledge. Industry formulators note several trends shaping CRO-Specialty Pharma relationships in terms of formulation development: more preformulation testing on the active pharmaceutical ingredient (API) and increasing requests for reformulation. *Specialty Pharma* magazine recently asked some of the industry's top companies to discuss the formulation development market and how that CRO–Specialty Pharma relationship can be maximized. Participants in this forum include Shabbir T. Anik, PhD, MBA, President (Global Pharmaceutical Development Services), and CSO, Patheon; Steve King, Senior Vice President, PII; Phil Meeks, CEO, Azopharma; Frank Santillo, PhD, Senior Director of Research Services, Bilcare.

Q: *Please discuss any pressing issues in outsourcing formulation development our readers, your potential clients, should know.*

Dr. Shabbir: There are a number of pressing issues companies are currently facing in formulation projects. These issues tend to differ by phase of development. Some of the most pressing issues include:

EARLY PHASE I & II: Molecules are increasingly becoming more challenging, and simplistic approaches, such as drug-in-bottle or powder-in-capsule, may not be able to accommodate the more complex delivery requirements for First Time in Human studies. Outsourcing development companies have an opportunity to help their customers understand risk/benefit of simple formulations versus more robust formulation approaches. These can have timeline implications for project advancement and potentially impact their transition to Phase II/IIB and Phase III projects.

PHASE III/MARKET FORMULATION: Robust approaches to formulation development are essential here. Quality by Design using statistical Design of Experiments can potentially result in a more highly optimized formulation developed in a more cost-effective way. In addition, by utilizing a single outsourcing partner experienced with these approaches in an integrated formulation framework can pay dividends with regard to overall speed of development.

Mr. Meeks: The classification and handling of high-potent and cytotoxic compounds for early clinical trials is forecasted to continue to increase in the coming years. Formulation processes and handling procedures for these molecules takes specialized expertise and infrastructure that are not common in many service providers. Fortunately, Azopharma has invested significant time and resources in the training and infrastructure required for these types of molecules and have capacity to handle this specialized category of formulation development.

Dr. King: Formulation development is outsourced as much as other process steps. To handle this need, PII can develop products faster and more cost effectively than developing and building your own formulations group. Outsourcing through a company, such as PII, provides companies with expertise and capacity that would take years to develop internally and be extremely expensive to maintain for a small pipeline of drugs. Typically, Specialty Pharma may only have three to four compounds in its pipeline at a given time. In addition, outsourcing through a reputable, established service provider provides solutions that can be a "best fit" for the compound rather than attempting to apply one or two dosage forms or processes. Specialty Pharma can also obtain access to a broad range of equipment, delivery solutions, and dosage forms without a large capital investment or overhead. Last but not least, working with the contract development organization early on in development stages ensures that formulations and processes can be easily transferable for scale-up to larger batches and equipment without changing the facilities for commercial production.

Dr. Santillo: Outsourcing the development of a formula is a more common practice now than it was 20 years ago. Development of a formula ties a number of technologies and sciences into a single project. Development of a formula is also an iterative process resulting in a number of prototypes before establishing the final formula. Equipment, instrumentation, and technical expertise are prerequisites for a successful development facility. Communication, although cliché, is one of the most critical requirements for the process. Not only does the developer need to be in frequent communication with the client with updates and timing, but the client needs to follow the development, know when key decision points are to be made, and participate in the decision-making process. With the time-to-market timeline becoming ever shorter, quick and accurate development is expected. Consequently, there is more responsibility on the side of the client to ensure he is placing the development in the right hands. The client needs to ask lots of questions and take a look around. Is the staff knowledgeable? Do they have the right experience base? Is the right equipment available?

Q: *What are some of the most common formulation development services currently sought after, and what trends are emerging?*

Dr. Santillo: The common formula development projects that are outsourced focus on the more common formulation types — tablets and capsules. Dry blend direct-compression

tablets or simple dry blend capsule manufacturing is common and typically the first approach to making that dosage type. Also common is the development of a parenteral product. Following solid dose and parenteral products, semi-solid formulation development (ie, creams, gels, ointments, etc) is also frequently outsourced. Regardless of the form the dose takes, these development services share the goal of identifying the ingredients in the proposed formula and the processing parameters to make that product reproducible.

There are some new dosage forms or variations of existing dosage forms that have emerged and are being requested by clients seeking formulation development services. Mini-tabs and pellets are an ideal dosage form for clinical trial material. They provide a way to deal with the increasingly potent drugs and allow for a simple means to accommodate changes to dose level (by adding more mini-tabs to a capsule) or to accommodate multiproduct dose (using two different mini-tabs in a single capsule). Orally disintegrating tablets (such as Zofran ODT) and oral thin film drug products are also being requested in formula development. These forms are especially useful for pediatric medication and medication for the elderly.

Nanotechnology, although not directly a dosage form, is a current and novel process in the pharma industry. Nanoparticulate formulas provide a unique way to increase bioavailability by reducing the particle size of the API to nanometers region. Bilayer tablets (in such products as Ambien CR) offer the ability to provide either an immediate-release drug and a controlled-release drug or possibly two different drugs in a single dose.

Mr. King: Formulation development (including reformulation) and the associated manufacturing is the core of PII's business. Reformulation usually occurs for several reasons, including (1) the formulation was not scaleable, (2) the PK end-point was not met, (3) the dosage or drug load needs to be changed, (4) product life cycle management, and (5) early Phase I formulation was not "final formulation."

Clients come to PII to tap into our broad experience, large portfolio of dosage forms, and state-of-the-art facilities. They also come to us for our expertise in troubleshooting formulations or compounds that have failed or not met endpoints in previous formulations. PII can offer both fee-for-service formulation expertise as well as patented, proven technologies to solve difficult drug delivery challenges for newer compounds. These drug delivery challenges include solubility, permeability limitations, site-specific absorption, poor bioavailability, and first-pass effects, as well as controlled-release profiles.

Specialty Pharma considers outsourcing formulation development for many reasons. They either don't have the resources or the expertise in house or don't want to build internal development capabilities. They could also need a specialized process or technology, seeking IP protection through formulations, having depleted their own internal expertise to solve a problematic formulation challenge.

Dr. Shabbir: The most sought after formulation services outsourcing suppliers are seeing tend to differ by phase and the customer company type. Early-phase development projects have become increasingly critical to a large number of clients. Being able to bring a new molecule to clinic for First Time in Human studies as quickly as possible enables companies to confirm proof-of-concept and therefore make informed decisions about the potential of molecules and further investment in their development. This is not only critical for small biotechnology companies, but also for Big Pharma, which has large numbers of candidate molecules emerging from discovery activities. In addition to the speed of the development process, the conservation of API in formulation is of prime importance in early development. This is particularly true for some of the new biologics, which are available in limited quantities and are quite expensive.

Patheon started offering Quick To Clinic™ early-phase development services in 2006 to meet this need. We utilize a toolbox, which can include Statistical Design of Experiment, miniaturization, and the application of nanoparticle technologies and simplified dosage forms to meet these needs. We recently opened a flexible development center in Milton Park, UK, which is dedicated to supporting early phase rapid development projects. At this location, they also emphasize the use of disposable technologies to help accelerate development projects to meet our customer's rapid development timelines.

Another trend we are seeing is an increase in demand from Specialty Pharmaceutical companies, particularly for the development of combination products and modified-release dosage forms. These specialized dosage forms help these companies differentiate their products from competitors in this growing market segment. As a result, there is a greater need for contract formulators to be able to offer specialized technologies and development approaches that can be applied to more complex formulations.

Mr. Meeks: At Azopharma, we see continued increase in Phase I supplies and reformulation of products for life-cycle management. We are forecasting a continued increase in both of these important categories in addition to high-potent and cytotoxic compounds.

Q: ***What are the three most important factors your potential clients know before outsourcing formulation development to help alleviate any unrealistic expectations?***

Dr. Shabbir: In general, from the outsourcers' perspective, really understanding the scope and goals of a project can significantly help the outsourcing firm meet the required formulation timelines. Having all of the available information about the project from the customer enables the outsourcing

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company to accurately quote and schedule the project milestones to meet the expectations of the customer. These considerations will help an outsourcer to accurately quote the project so there is less chance of surprises along the way, and enable the supplier to meet all of the customer's timelines for crucial milestones throughout. This aids in delivering a robust, manufacturable formulation to the client.

Another factor potential customers should consider is understanding the influence of API properties on the formulation and therefore the criticality of integrating the API scale-up strategy with the formulation development activities for commercialization. The quantities of API needed significantly increase and must be planned for so that development can quickly continue to commercialization if approved.

Clients should also take into account marketing considerations early in the development process. Changes of dosage forms at late stage may not be easily accommodated and may require reformulation. Hence, scenario analysis of dose, marketing, regulatory, and manufacturing requirements is essential before initiating development work.

Mr. Meeks: At Azopharma, we advise our clients to first understand the chemical stability of the molecule as ultimately this is one of the most critical aspect for a potential marketed product. Second, timelines of the project from a clinical or market launch perspective must be addressed and understood so that both the outsourcer and outsource provider are on the same page. Third, depending upon the clinical phase of the project, it is important to understand that the developed formulation will be a work in progress that may need modification at a later time to achieve bioavailability goals.

Dr. Santillo: There are three key areas that one should consider when planning to outsource the development of a formula. These areas of consideration are not in themselves technical, but by giving thought to these areas, one can prevent downstream delays and disappointment. The three areas to address include the following:

TIMING: When is material needed? Is a project plan set up to include availability of components and excipients? Is there sufficient time for multiple prototype evaluation, scale-up, review, approval of documentation, inclusion of analytical development, and testing?

PRODUCT REQUIREMENT: Recognition of the different efforts required for protein-based versus small molecule products, knowledge of the dose level (is it a potent low dose drug or high dose load?), knowledge of release profile desired (IR versus SR dose significantly changes development times), decision on product aesthetics (size, color, and shape of the dose affects selection of tooling and excipients), and determination of batch sizes (determines equipment selection and room availability for manufacturing) are paramount.

PROJECT SCOPE: Will the project include analytical development? Will API characterization be included? Are large-scale batches needed? Will a full pharmaceutics development report be required? Is the product being used in the EU or Asia (where additional or unique requirements may exist)?

Q: ***There are many formulation development providers, and many specialize in the services they offer. So would you recommend a potential client contract with a different provider for each type of formulation, or look for a large provider that specializes in several different areas?***

Mr. Meeks: The client should assess the capabilities for the outsource provider to develop the type of dosage form desired. Demonstrated experience in that particular dosage form is of vital importance. It may be of interest that the provider has capabilities and experience with other types of dosage forms, but broad experience does not compensate for lack of experience in the particular dosage form being developed.

Mr. King: PII has a vast amount of experience. Having worked on over 300 NCEs, and 15 commercially developed products in the market, PII brings a level of experience and problem-solving that few can match. In addition to this, we have many dosage forms available for formulations that smaller firms or universities are just not able to access. There are multiple factors involved when selecting a CRO, which should not be limited to only size. First, they should seek out companies with a long-standing record in the industry as well as companies that are FDA inspected. Second, they seek out companies that maintain and operate under high-quality systems and SOPs as well as hold an excellent reputation for delivering quality products through commercialization. Additionally, they should seek out companies with the capacity and equipment to ensure timely operations and service across a broad range and scope of dosage forms and formulations. Last, they should seek out companies with a solid financial position and stability and access in the senior management positions. This will ensure participation throughout the entire development program and the ability to respond to changes by acquiring and expanding services according to client needs and newer technologies.

Dr. Shabbir: Although there are some very good, small, specialized suppliers, there are some distinct advantages to working with a large established formulator. A larger supplier will tend to have more scientific resources available representing a broad range of expertise and experience that can be drawn upon for any formulation challenge. They also will have additional in-house technical and infrastructure advantages that

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may not be available for smaller development services providers. Suppliers should be evaluated as early as possible to assess the long-term project needs and make sure they are a good match.

Dr. Santillo: The decision on the selection of a large broad development provider versus a specialty house is dependent upon the type of product and the unique features being sought. The more unique the dose or the requirements, the greater the level the sophistication the contract facility should have. Finding the right fit means asking the right questions. Here are some examples of potentially outsourced development projects and questions one might ask:

- If the product is a biologic (biopolymers/recombinant proteins/antibodies), it will require a special experience base in both the formulating and analytical testing areas. A typical small molecule contract facility may not have those abilities. Has the company worked and successfully developed biological type products?
- If the dose type is unique (ODT, OTF), the facility will need to have specialized equipment to deal with that product. Does that equipment exist in the company?
- If the drug is considered a potent compound, does the site have potent suite or lyophil equipment or what is needed for the job?
- If the client has little knowledge of drug development, is the contract facility flexible and attentive to your needs? Do they offer pros and cons for the various options that are available? Are they willing to have more frequent discussions to assist in the decision-making process?

Q: ***Is there something you would like to tell our readers about your company or formulation development in general that they have not read about before?***

Dr. Santillo: Bilcare knows what it takes to provide the type of service the client is seeking. The staff is composed of experienced scientists from both the pharma and contract world, so Bilcare understands well the needs of the client, and we know what it takes to provide a quality service in the shortest amount of time. To succeed in this business model, we focused not only in the technical field but also in the areas related to client relations. We do not have multiple layers of bureaucracy, and the staff is empowered so we can accomplish tasks rapidly. We offer the client direct lines of communication to the scientists, and scientists even participate in client project team meetings. We are flexible and can accommodate to quickly changing (read shortening) timelines; we offer the analytical, production, packaging, labeling, and distribution functions under one roof so the hand-offs between functions are invisible and there are no delays between hand-off (a significant savings of time - months in the case of transferring a developed formula to a site for scale up, and weeks in the case of transferring methods to another laboratory). The combination of a solid technical group coupled with a client-specific dedicated project manager to represent the client and spearhead activities on the client's behalf has proven to be a successful strategy.

Dr. Shabbir: Patheon really does offer the full range of dosage form development services from the earliest stages all the way through to scale-up and launch of products. We have continued to expand and optimize our development service offering to meet the evolving needs of our customers, which includes small flexible development services from units dedicated to rapid early phase development (like our recent Milton Park launch) to being able to handle larger late-phase development projects, including formulation, CTM manufacturing, as well as clinical packaging and distribution services all from one globally integrated supplier. We also are heavily involved in the development of dosage forms for large molecules (proteins, MAbs). Patheon has invested significantly in state-of-the-art sterile/lyophilization facilities and supporting analytical capabilities to efficiently develop these valuable new molecule types for customers. We also offer a growing range of technologies that can be applied to a customer's project should the more conventional approaches not apply.

Mr. Meeks: Azopharma has experience in developing formulations and manufacturing materials for all phases of clinical investigation, but has had great success in helping clients with their needs for total product development into Phase I clinical trials and beyond. For example, our Phase I Express™ allows for expedited post-discovery processing into clinical materials. This is due to our proprietary systems and breadth of services spanning medicinal chemistry lead optimization, preclinical assessments, formulations, and CTM manufacturing.

Mr. King: Drug delivery and Specialty Pharma has created a wealth of opportunities for new, novel, complex formulations. As compounds are screened and selected, they become increasingly targeted for delivery, structurally challenged for absorption, and difficult to administer as a simple tableted blend or granulation. Drug delivery systems can provide unique solutions to solve these challenges. However, the key is for the service provider to understand the formulation and the process. They must also have the resources and equipment to scale-up for either manufacturing or transferring the process for Phase III and beyond. If the formulation can't be scaled up, it isn't worth much. PII has the capability of manufacturing most oral solids, liquids, topicals, and even aseptic filling for larger molecules and injectables. Its portfolio of drug delivery solutions also creates a unique opportunity for the client to consider more novel, innovative approaches with patented technologies. ◆

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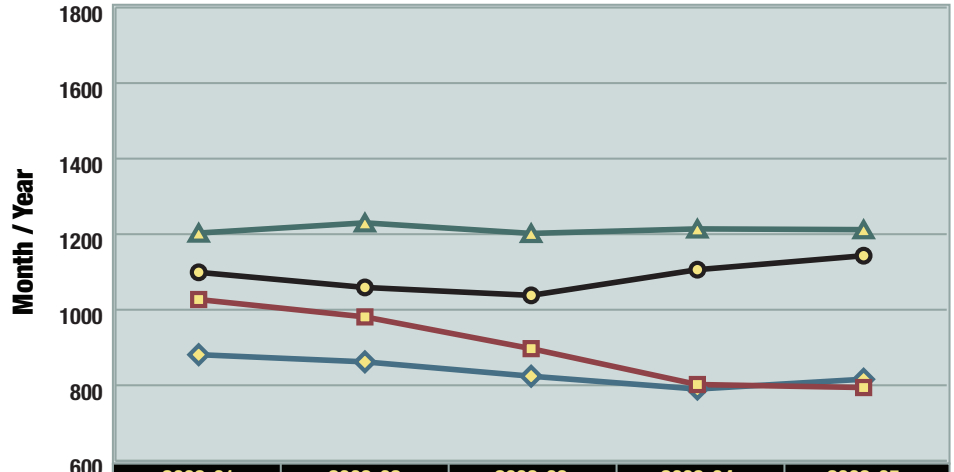

*The indexes refer to Market Capitalization rather than Share Price

	2008-01	2008-02	2008-03	2008-04	2008-05
CSPI	1,203	1,230	1,202	1,214	1,212
ESPI	1,027	981	897	802	794
DDI	81	862	824	790	816
NASDAQ	099	1,059	1,038	1,106	1,143

Index Value

CSP Index Value: 1212 | Change YTD: -6.1% | Change M/M: -0.0% | Total Index Capitalization: $50.5 Billion

Top 5 Capitalizations YTD Change		
Shire	$9.7 Billion	-24%
Hospira	$6.5 Billion	-4%
Warner	$4.4 Billion	-1%
Perrigo	$3.4 Billion	+4%
Endo	$3.0 Billion	-16%

Top 5 Gainers YTD Change	
Millbrook	+357%
Encysive	+182%
Columbia	+70%
Draxis	+48%
Vivus	+47%

Top 5 Laggards YTD Change	
Ista	-58%
Indevus	-37%
Barrier	-36%
Shire	-24%
Alkermes	-24%

ESP Index Value: 794 | Change YTD: -36.7% | Change M/M: -1.3% | Total Index Capitalization: $2.2 Billion

Top 5 Capitalizations YTD Change		
Nektar	$395 Million	-36%
Pain Therapeutics	$332 Million	-29%
Durect	$324 Million	-32%
Cadence	$251 Million	-42%
Javelin	$188 Million	+3%

Top 5 Gainers YTD Change	
NovaDel	+44%
AP Pharma	+67%
Javelin	+3%

Top 5 Laggards YTD Change	
Keryx	-94%
Elite	-74%
Epicept	-58%
Cadence	-42%
Spectrum	-38%

DD Index Value: 816 | Change YTD: -15.7% | Change M/M: -0.3% | Total Index Capitalization: $9.2 Billion

Top 5 Capitalizations YTD Change		
Biovail	$1.9 Billion	-11%
Alkermes	$1.2 Billion	-24%
Surmodics	$800 Million	-20%
Eurand	$651 Million	-6%
Momenta	$456 Million	+75%

Top 5 Gainers YTD Change	
Labopharm	+88%
Momenta	+75%
Psivida	+56%
Acura	+47%
NovaDel	+44%

Top 5 Laggards YTD Change	
Elite	-74%
CytRx	-69%
Vyteris	-69%
Nastech	-63%
Aradigm	-40%

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Executive Summary

Dr. S. Kumar Chandrasekaran
Chairman & CEO
InSite Vision

InSite Vision: Multiple Products, Minimal Risk

By: Cindy H. Dubin, Contributor

InSite Vision develops novel topical anti-infective products for eyes and ears. The company has created a platform for the development of multiple products that combine the antibiotic azithromycin with InSite's proprietary, patented, synthetic polymer-based drug delivery system, DuraSite®. The first product from this platform is AzaSite® (azithromycin ophthalmic solution) 1%, which was launched in the US by Inspire Pharmaceuticals for the topical treatment of bacterial conjunctivitis. InSite is also creating worldwide marketing and distribution channels for AzaSite through agreements with a network of leading international distributors. Now, InSite is in late stages of clinical development with its second topical ophthalmic antibiotic product, ISV-502(AzaSite Plus™). This product candidate, in Phase III pivotal trials, is directed against eye/eyelid infections and inflammation, currently an unmet need particularly prevalent among adults and particularly the growing elderly population. In addition, InSite is evaluating the use of its product platform for middle ear infections with the product candidate, AzaSite Otic™ in preclinical development. The company is also developing AzaSite Xtra™, a product for ocular infections designed to assist in penetrating international markets. *Specialty Pharma* recently interviewed Dr. S. Kumar Chandrasekaran, Chairman and Chief Executive Officer of InSite Vision, to discuss the role of drug delivery technology in transforming the company in a low-risk manner from an R&D organization to a sustainable, multiple products company.

Q: ***What role did drug delivery play in the success of your product AzaSite?***

A: First, it is important to understand the benefits of AzaSite, which is a topical antibiotic developed for bacterial conjunctivitis. AzaSite offers a reduced dosing frequency compared to currently available eye drops in the US for the treatment of bacterial conjunctivitis, and has a favorable safety and efficacy profile. A complete therapy of AzaSite requires a total of 9 drops, while the next lowest number of drops required is 21, which can make a difference in encouraging patient compliance, particularly among children who are the primary pink eye patients.

AzaSite contains the drug azithromycin, a broad-spectrum antibiotic formulated with our proprietary drug delivery technology (DuraSite) as eye drops. This is the first time azithromycin has been formulated successfully for use in the eye. DuraSite is a patented synthetic polymer-based formulation designed to extend the residence time of a drug relative to conventional topical therapies. It enables topical delivery of a

solution or suspension and can be customized for delivering a wide variety of potential drug candidates. The use of DuraSite enables the sustained presence of azithromycin in the infected eyes, thereby resulting in broadened bacterial coverage and shortened therapy requirements.

Q: ***Why did you select azithromycin? Is this the first time it's been successfully formulated for topical use?***

A: Azithromycin is a broad spectrum antibiotic widely used to treat bacterial infections as an oral drug. It was discovered in 1980 by researchers at a Croatian pharmaceutical company and licensed to Pfizer in 1986 for rights for the sale of azithromycin in the US and parts of Europe. In 1991, Pfizer introduced azithromycin under the brand name Zithromax®, which became the top selling antibiotic in the world. Given its broad spectrum, combined with its established safety profile in infants, children, adults, and geriatric patients, azithromycin is an excellent candidate for treating a variety of bacterial infections. Among its many applications, azithromycin has been used to treat bacterial infections of the throat, ears, and skin and for tonsillitis, laryngitis, bronchitis, pneumonia, sinusitis, and certain sexually transmitted diseases.

However, it was not until InSite Vision developed AzaSite that azithromycin was available for the topical treatment of eye infections. Until this formulation, azithromycin had been available only as an oral suspension, tablet, or intravenous injection. The use of azithromycin for the topical treatment of eye infections had been limited by a number of formulation challenges, specifically the instability in aqueous solutions and heat instability.

While other industry leaders were unable to overcome these formulation challenges, we saw azithromycin as an excellent candidate for ophthalmic applications. In 2001, we began using DuraSite to create a formulation that enabled the use of azithromycin for the topical treatment of ocular infections, particularly bacterial conjunctivitis. This formulation with DuraSite led to the development of AzaSite and our pipeline product candidates.

Q: ***What other products is InSite developing, and what part does your drug delivery technology play?***

A: Our strategy is to leverage the azithromycin-DuraSite platform to develop other products with less risk, yet targeted at significant markets. We know the topical antibiotic works. Our new product candidates are formulated to meet the specific needs of the indications they address.

Our next product is in Phase III pivotal trials and is directed at treating eye/eyelid infection and inflammation, which is a growing malady among the elderly population. As there is no approved product for the indication (blepharoconjunctivitis), we believe there is a significant market need and estimate that there is at least a $500 to $600 million market. This is an ideal product for InSite as it uses the technology developed for AzaSite and adds a corticosteroid, also formulated in DuraSite, to manage the inflammation caused by the eyelid infection.

Further, we are working on an ear infection product for middle ear infections. There is a need for a directly applied antibiotic to treat children with chronic middle ear infections. Approximately 6 of every 1000 children in industrialized countries require the insertion of tubes to drain the ear, and of these, 50% to 75% require antibiotic drops after tube insertion. These tubes can also be used to directly apply an antibiotic. We are in preclinical development of a topical product of azithromycin to treat the infection combined with a corticosteroid to treat the inflammation, both formulated in DuraSite.

Q: ***Is part of your plan in transforming to a multiple products company to sell these products yourself? Will you hire a sales force?***

A: Current plans are to partner our products, like we did for AzaSite. Inspire Pharmaceuticals has licensed AzaSite and is promoting and selling it in the US with rights to do the same in Canada once the product is approved there. In addition, we have signed license and distribution agreements for AzaSite in South America, Korea, and Turkey and plan to add other partners

worldwide. In exchange, we receive royalties on sales as well as some nominal upfront and licensing fees. We plan to remain a small company capable of developing multiple products. At this time, we are not intending to become fully integrated. Therefore, we will most likely license our products for commercialization.

Q: ***What makes InSite Vision an ideal partner?***

A: In the case of partnering product candidates, we are offering a complete product with little associated risk. In addition, we have developed contract manufacturing with a competitive cost-of-goods. In the case of AzaSite, we had already filed for regulatory approval with the FDA when we reached an agreement with Inspire Pharmaceuticals.

For partnering other DuraSite formulated molecules, we offer proven experience in formulation development and clinical trials; strong ophthalmic experience to expedite product development; and operational resources to accelerate commercialization opportunities.

Q: ***Can you leverage the manufacturing and sales infrastructure from product to product given that they are based on the same drug delivery technology?***

A: We have envisioned central contract manufacturing for worldwide manufacture of AzaSite, which we plan to apply to our other antibiotic topical products. This will enable us to take advantage of economies of scale with the intent of reducing cost of goods. With regard to sales and marketing, the InSite brand should carry over to multiple groups of physicians. And if we should partner with the same company, we would experience a leveraged sales force.

Q: ***Can you formulate other molecules with DuraSite besides azithromycin?***

A: DuraSite is more than a vehicle for the delivery of azithromycin to the eye. Many conventional topical medications that last only a short time and require frequent dosing of a highly concentrated burst of drug to sustain therapeutic levels could benefit from the DuraSite drug delivery technology. The demonstrated compound advantage of DuraSite has the potential to provide a wide variety of proven drugs, like azithromycin, with an extended life cycle.

Potentially, the DuraSite drug delivery system can be customized to deliver small molecule and protein drug candidates to the ear, nose, throat, skin, and other sites. The unique properties of DuraSite may enable these drugs to be released gradually over a longer period of time. Increased residence time made possible by DuraSite could permit lower concentrations of a drug to be administered over a longer period of time, thereby minimizing the inconvenience of frequent dosing, reducing potential adverse side effects, and improving patient compliance. As with AzaSite, topical medications, such as eye drops delivered with DuraSite drug delivery technology, offer a compelling contrast to conventional approaches.

Q: ***What is next for Insite Vision?***

A: We recently completed a non-dilutive, non-recourse $60-million financing secured by the royalty stream from AzaSite. We anticipate that we have enough cash to continue our product development for the next 3 years — even without any infusion of cash from other sources. We do anticipate additional revenue as well. For example, revenue from international sales of AzaSite could begin the second half of 2009; and assuming that it gets approved, revenue from our second product, ISV-502, could start as early as the second half of 2010. As we expand our pipeline, we are creating additional sources of revenue. So we believe that we are developing a revenue stream that will enable us to build the company.

The next major catalyst is successfully completing Phase III trials for ISV-502 and successfully partnering that product. In parallel will be the completion of an additional two or three international partner deals for AzaSite. We also plan to initiate clinical trials for AzaSite Otic. By leveraging our drug delivery technology, we anticipate that in the next few years and with minimal risk, we will transform InSite Vision into a sustainable, multiple products company. ■

Cyclobenzaprine ER: Development of the First Once-Daily Muscle Relaxant

By: Troy M. Harmon, MS, MBA

Introduction

Muscle relaxants are commonly prescribed as an adjunct to rest and physical therapy for acute, painful musculoskeletal conditions. Typically, muscle spasm occurs at the site of an injury as part of the body's own efforts to stabilize the injured body part in order to prevent further damage. Common musculoskeletal conditions that cause tenderness and muscle spasm include low back pain (including sciatica), neck injuries, tension headaches, fibromyalgia, and myofascial pain syndrome (caused by trigger points). If muscle spasm is present in these conditions, it is related to local factors involving the affected muscle groups. These conditions are commonly encountered in clinical practice and can cause significant pain and disability in some patients, which can be mitigated with skeletal muscle relaxants.

Low back pain is one of the most common reasons for prescribing muscle relaxants. Approximately 15% to 20% of the US population suffers from low back pain in any given year, and according to the federal Agency for Health Care Policy and Research, about two-thirds have low back pain at some point in their lives. In fact, low back pain is the most frequent cause of disability in people under age 45. It is estimated that up to half of all working adults experience some form of back pain each year (which when including disability and lost days of work, accounts for > $50 billion in costs annually).

Muscle Relaxant Treatments

Muscle relaxants are not really a class of drugs, but rather a unique group of drugs that have different mechanisms of action. These drugs do not act directly on the muscles, instead they act centrally (in the brain). Muscle relaxants typically work by blocking nerve impulses (or pain sensations) in the brain. The most common drugs prescribed for muscle relaxation are the anti-spasmolytics cyclobenzaprine, carisoprodol, and metaxolone. However, with the exception of cyclobenzaprine ER, approved in 2007, all of these drugs are required to be dosed three to four times daily, a very inconvenient dosing regimen. Additionally, all of these drugs have

Figure 1. Plasma Levels of Cyclobenzaprine ER Versus IR Reference

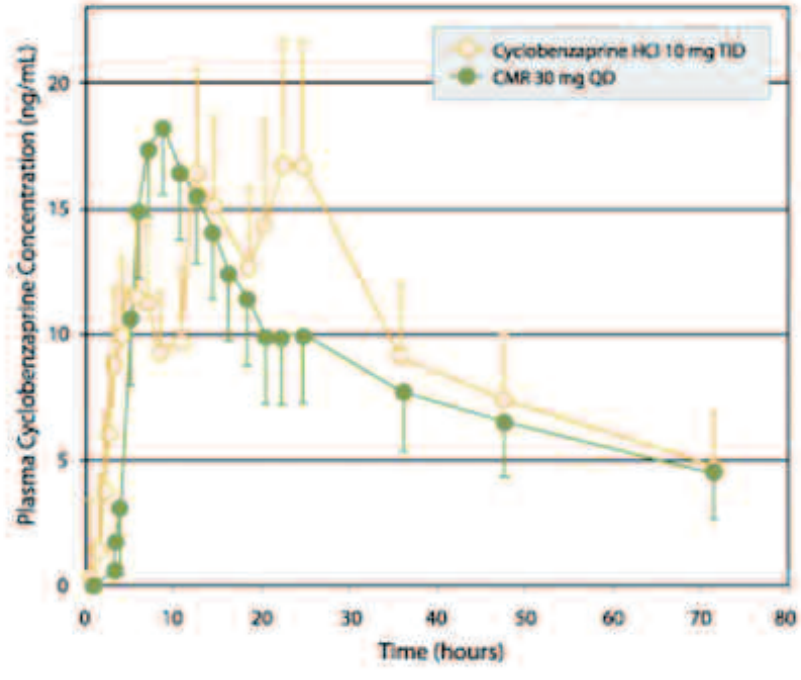


Table 1. 2006 Sales for Leading US Muscle Relaxant Brands

Product	Sales ($)	Rank (# of Rxs)
Cyclobenzaprine	230	34
Carisoprodol	207	76
Skelaxin	483	180

significant sedation as a common side effect, which decreases their acceptability.

Flexeril®

One of the earliest brand medicines in this category was Flexeril®. Flexeril, was developed by Merck's Merck Frosst Canada division in the late 1960s and arose out of the discovery that a compound called cyclobenzaprine hydrochloride, synthesized in a search for a psychiatric medication, was exceptionally effective in relieving muscle spasm, despite its ineffectiveness for psychiatric conditions. Flexeril was approved by the FDA in 1978 as a 10-mg strength with dosing required three times daily. It wasn't until 2003 that a lower 5-mg strength version of the drug was approved, at which point Flexeril was marketed by Johnson & Johnson's McNeil division. The effectiveness of Flexeril 5 mg was demonstrated in two 7-day, double-blind, placebo-controlled, randomized, multi-center clinical trials enrolling 1,405 patients with acute (< 14 days), physician-rated moderate or moderately severe painful muscle spasm in the lower back or neck. Compared to placebo, both the 5- and 10-mg strengths demonstrated an ability to relieve muscle spasm pain, but patients taking the 5-mg tablet reported less drowsiness than patients taking the 10-mg tablet (29% vs 38%, respectively; vs 10% for the placebo). Most patients who reported sedation developed it on the first or second day of dosing. Other side effects of Flexeril include dry mouth, fatigue, and headache. Despite these side-effects, cyclobenzaprine remains the most frequently prescribed muscle relaxant in the US and is available as a generic.

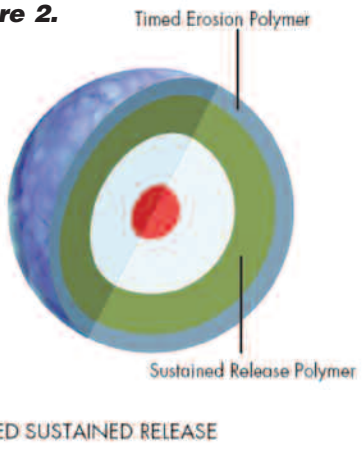
Soma®

Carisoprodol, the active ingredient in Soma®, has been marketed in the US since 1959 as a centrally acting muscle relaxant. Although the mechanism of action is unclear, carisoprodol is thought to act by sedation rather than by direct skeletal muscle relaxation. It is metabolized in vivo to hydroxycarisoprodol, hydroxymeprobamate, and meprobamate, and because meprobamate is a controlled substance, carisoprodol has abuse potential. In fact, in 2007, the European Medicines Agency recommended that carisoprodol be removed from the market due to an insufficient risk/benefit ratio. With prolonged use at high dosage levels, carisoprodol can lead to tolerance, dependence, and withdrawal symptoms in humans. Carisoprodol abuse has escalated in the past decade in the US, according to 2004 National Survey on Drug Use and Health (NSUDH) data. Soma is currently marketed by MedPointe Pharmaceuticals as a 350-mg tablet with recommended dosing of three or four times daily, and generic carisoprodol is frequently prescribed in the US. Despite the abuse-potential concerns, carisoprodol is one of the most frequently prescribed drugs in the US, according to a Drug Topics 2006 survey of retail pharmacy sales.

Skelaxin®

Skelaxin® is currently marketed by King Pharmaceuticals as an 800-mg tablet with recommended dosing of three or four times daily. Originally developed by Elan in a 400-mg strength, only the higher strength is available today. Metaxalone, the active ingredient in Skelaxin, is considered to be a moderately strong muscle relaxant, with relatively low incidence of side effects that may include nausea, vomiting, drowsiness, dizziness, headache, and irritability. There are two Orange Book-listed patents on Skelaxin with expiration dates in 2021, and no generic forms are available. Therefore, as a patented, branded medication, Skelaxin is the market leader in terms of dollar sales, although both cyclobenzaprine and carisoprodol are more frequently prescribed as shown in the comparison table (Table 1).

Figure 2.



Diffucaps® Timed-Sustained Release Bead

Cyclobenzaprine ER – The Product

In 2000, Eurand began a development program in collaboration with ECR Pharmaceuticals to create a once-daily dosage form of cyclobenzaprine. It was envisioned that such a product would provide the efficacy of immediate-release cyclobenzaprine, but with a much more convenient once-daily dosing regimen, and perhaps with less of the limiting side-effects of the drug (drowsiness, dry mouth, and dizziness). Eurand developed a novel multiparticulate formulation of cyclobenzaprine, produced clinical materials, and ECR conducted two multi-center, randomized, double-blind, placebo-controlled Phase III studies with the product. Results of patient ratings on the product's

helpfulness in reducing muscle spasm are shown in Table 2.

The cyclobenzaprine ER product demonstrated statistically significant differences in patient's rating of medication helpfulness versus placebo at day 4, and essentially equivalent helpfulness ratings versus the immediate-release reference product. Plasma levels achieved for the cyclobenzaprine ER product versus the immediate-release dosage form are shown in Figure 1. Cyclobenzaprine ER maintains a consistent plasma level over the 24-hour post-dosing period, without the peaks and troughs associated with t.i.d. administration of the immediate-release reference product.

Figure 3. Photograph of Amrix® Bottles

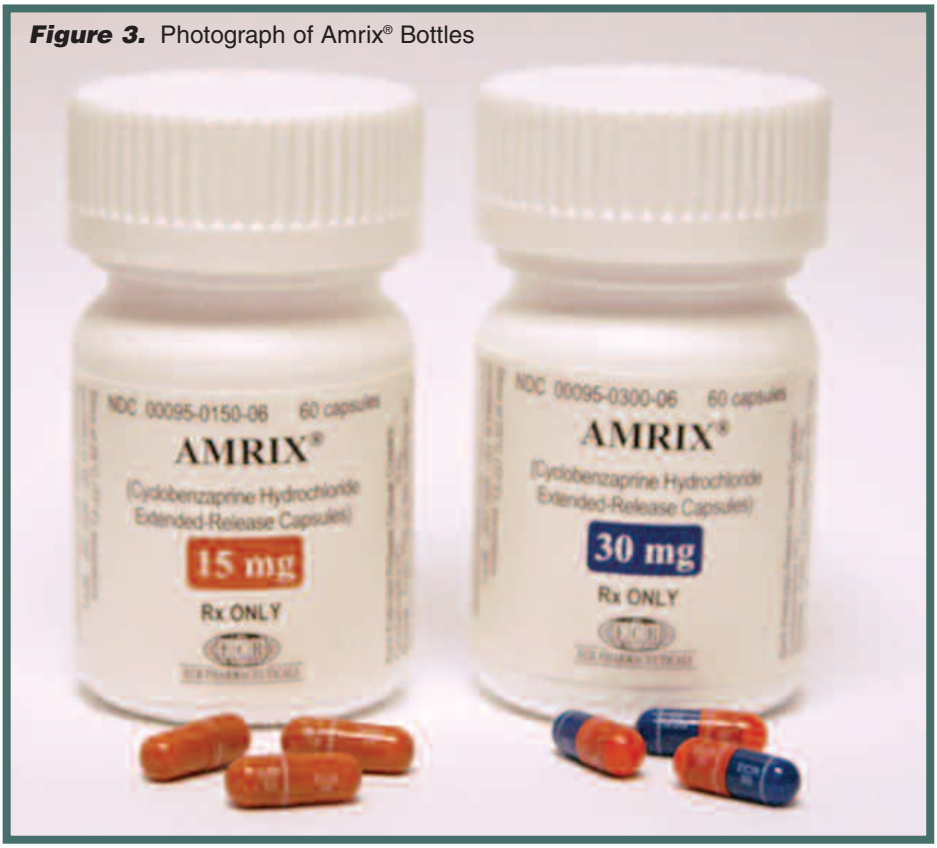


Table 2. Patient Ratings of Medication Helpfulness at Day 4

Rating	Cyclobenzaprine ER (15 mg qd, n = 127)	Cyclobenzaprine ER (30 mg qd, n = 126)	Cyclobenzaprine IR (10 mg tid, n = 123)	Placebo (n = 128)
Excellent	2%	5%	2%	2%
Very Good	16%	18%	17%	12%
Good	34%	32%	38%	23%
Fair	28%	31%	30%	31%
Poor	13%	10%	8%	23%
Missing Data	9%	5%	4%	10%

Table 3. Patient Ratings of Daytime Drowsiness at Day 4

Rating	Cyclobenzaprine ER (15mg qd, n = 127)	Cyclobenzaprine ER (30 mg qd, n = 126)	Cyclobenzaprine IR (10 mg tid, n = 123)	Placebo (n = 128)
Extreme	17%	19%	24%	9%
Some	28%	37%	44%	22%
Little	46%	40%	28%	59%
Missing Data	8%	4%	4%	9%

In addition to the compliance advantage of once-daily administration, the cyclobenzaprine ER product demonstrated less daytime drowsiness than the immediate-release product dosed three times a day as shown in Table 3.

The Technology in the Product

The technology used to develop cyclobenzaprine ER was Eurand's Diffucaps® technology. Diffucaps is a technology for creating small layered particles with tailored drug-release properties. Customized drug-release profiles are created by first layering active drug onto a neutral core (such as cellulose spheres) followed by the application of one or more rate-controlling, functional membranes. As shown in Figure 2, these particles (also known as beads) can have an outer layer that must erode before drug release initiates. This enables the development of products with delayed release of drug. Following erosion of the outer layer, an inner, sustained-release polymer can further control a steady release of drug for a set time.

Eurand has developed formulation technology that combines the customized drug release offered by Diffucaps with technologies that enhance the solubility of insoluble drugs in the gastrointestinal tract. The drug layering process can be conducted either from aqueous or solvent-based drug solutions, which increases the flexibility of the technology to work with a wide variety of compounds.

Customized Release Diffcuaps® Technology

Diffucaps beads are small, approximately 1 mm or less in diameter, and are filled into capsules to create the final dosage form. Beads of differing drug-release profiles can be easily combined in a single

capsule. This gives a remarkable level of control to create complex release profiles. Diffucaps beads of different drugs can be combined to make convenient single-dose units for combination drug therapies as well. Thus, the Diffucaps system offers significant flexibility by enabling the combination of different types of release profiles into one dosage form. As a result, Eurand can combine sustained-release, pulsatile-release, and immediate-release profiles, depending on the specific needs of the product. In addition, different dose-proportional strengths of a product can be easily manufactured by filling capsules with varying amounts of the Diffucaps beads.

For the cyclobenzaprine ER product, Eurand custom formulated a bead by spraying a solution of cyclobenzaprine onto an inert core followed by the application of multiple polymer layers to achieve the desired release profile. Eurand developed two strengths of the product, 15 mg and 30 mg. The same bead is contained in both product strengths, the higher strength simply contains twice the number of beads as the lower strength.

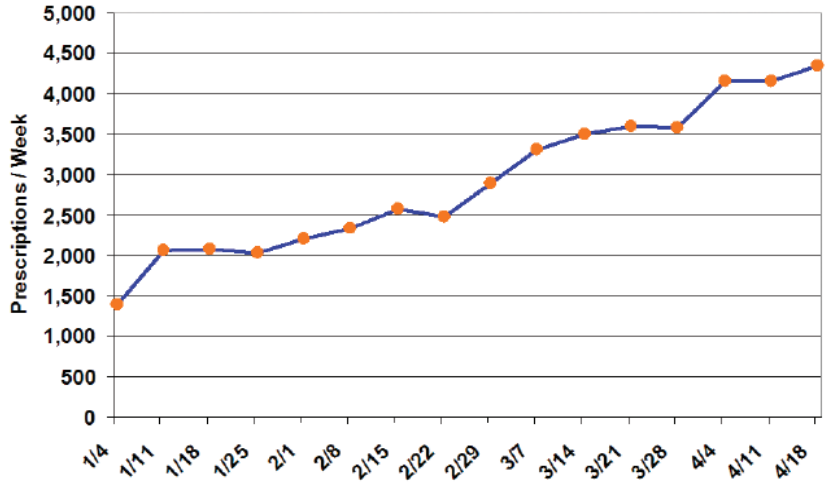
Cyclobenzaprine ER – Commercialization of Amrix®

ECR's NDA for the cyclobenzaprine ER product was approved by the FDA in 2007. However, instead of launching the product themselves, ECR sold rights to the product to Cephalon in August 2007. The tradename selected for the product was Amrix®, and Cephalon began promotion of the product in November 2007.

Despite the limited time to promote and sell the product in 2007, Cephalon achieved $8.4 million in 2007 revenues (source: IMS Health). Eurand is the exclusive supplier of cyclobenzaprine ER to Cephalon, and Eurand receives a royalty on Cephalon's net sales of Amrix. As 2008 progresses, Cephalon has expanded the sales force promoting Amrix, and weekly prescriptions have steadily increased as shown in Figure 4. Cephalon has reported that physicians are pleased with the clinical performance of the product and are typically prescribing the product for night-time administration.

Amrix is the first and only once-daily skeletal muscle relaxant available in the US. With the approval and launch of Amrix, physicians have the option to prescribe a more convenient dosing regimen for patients. Patients now have a more convenient option for administration of the market-leading muscle relaxant cyclobenzaprine, and may also benefit from a lower incidence of somnolence that has been associated with the immediate-release formulation of the drug. The development and commercialization of cyclobenzaprine ER is another successful example of the application of drug delivery technology to improving patient's lives. ◆

Figure 4. Growth of Amrix® Prescriptions in 2008 on Weekly Basis (source: IMS Health)



Troy M. Harmon, MS, MBA
Vice President, Business Development
Eurand, Inc.

Mr. Troy Harmon is currently Vice President, Business Development for Eurand, a specialty pharmaceutical company focused on the development of novel drug delivery technologies and products. Mr. Harmon joined Eurand in 2002, and his responsibilities include business development, marketing, and licensing efforts for Eurand in North America. Prior to joining Eurand, Mr. Harmon was Director, Business Development at Delsys Pharmaceutical in Princeton, NJ, where he was responsible for marketing and partnering the company's electrostatic powder deposition technologies worldwide. In addition, Mr. Harmon has served as Director, Business and Product Development at FEI Technologies, a company specializing in implantable drug delivery systems, and as Sr. Scientist at Summit Technology, an innovator in laser vision correction procedures. Mr. Harmon earned his BS from the University of Kentucky, where he was elected to Phi Beta Kappa and received the University's first prize for undergraduate academic research. He earned his MS in Physical Chemistry from Cornell University and his MBA from Villanova University.

June 2008

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EXTERNAL DELIVERY

Who's The Boss?

By: John A. Bermingham

One of the characteristics of a great CEO is a clear understanding of what effective leadership is and having the courage to stand alone on or make an unpopular decision for the good of the company and its shareholders or investors. Sometimes a CEO has to take the bull by the horns and push through what he or she believes is correct and convince others to get on the bus. Why? Because he or she is the boss, and a CEO accepts that responsibility when he or she accepts the position. So that brings me to the current situation in our country regarding gas prices. Who's the Boss? Heck, what I want to know is Where's the Boss?

The insane price per barrel of oil is not due to a supply/demand ratio. Oil inventories are at acceptable levels, and there are billions of barrels of oil in the ground that are yet to be tapped. Brazil, as one example, discovered an oil field off of their coast that appears to hold more than 30 billion barrels of oil. There are tens of billions of barrels of oil off our own coasts, not to mention huge deposits of natural gas. In fact, Royal Dutch Shell estimates that our continental shelf holds 100 billion barrels of oil. So why not go get it and decrease or eliminate our dependence on foreign oil?

But wait! There's more!!! We also have huge oil deposits in the Alaskan wilderness as well as massive shale oil deposits in Colorado, Wyoming, and Utah. It is estimated that these three states hold more than 1.5 trillion barrels of oil alone. Ready?

The reason we do not access these oil and natural gas deposits is due to our Congress (you know, those people we elect to represent our interests in government) declaring that 85% of our coast lines are off limits to drilling. Congress also passed a measure last December that prohibits spending that would establish a program to lease shale oil deposits on federal lands. And congress is also rejecting the building of additional pipelines to transport these deposits.

So as we approach $5.00 per gallon gas prices at the time of this writing, we sit on trillions, not billions, of barrels of oil. Now, I am firmly behind the belief that we must protect our natural resources to include our wildlife, be they fish or mammals. Not for a minute should we sacrifice these creatures for oil and gas deposits. But we certainly have now or can further develop technology that will allow us to tap these deposits and transport them to refineries. People in the know say that if we were to do this, the cost of a barrel of oil from these US deposits would be $30.00 per barrel.

So where is the boss (President), and why is he not taking control of this crisis? Where are our elected officials, and what are are they doing to gain control of this situation? Why does this not seem to be a top priority for them? In any company, a crisis of this level would have to be immediately addressed and resolved by the CEO and his or her executive staff, or the Board would quickly replace them with new executives who can get the job done. I guess we will see what happens between now and next November when we have the opportunity to begin replacing politicians. I would very much like to hear the presidential candidates tell us what their position is on this crisis without the typical political garbage speak. ◆

BIOGRAPHY

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

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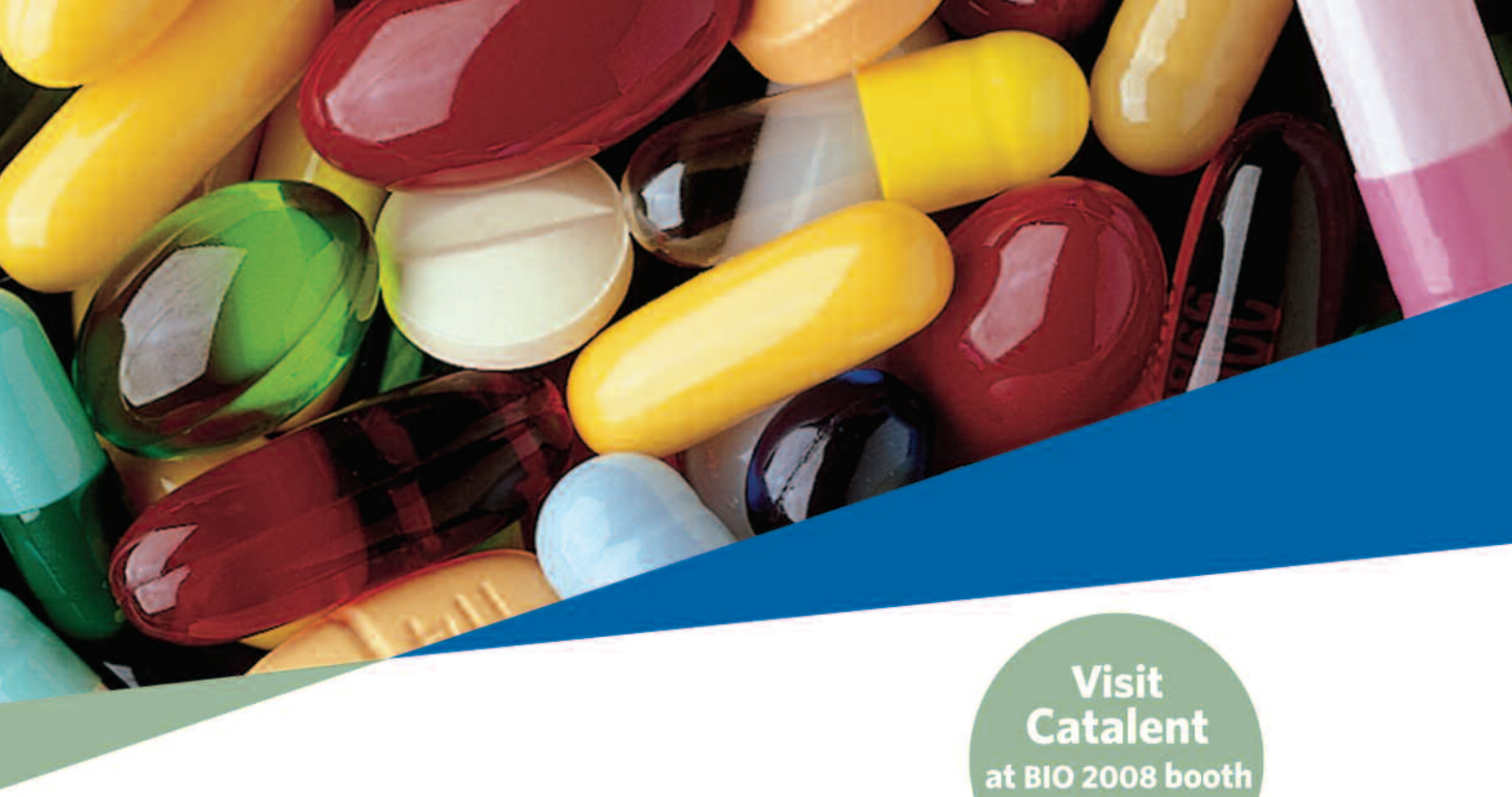

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