Drug Delivery® Technology

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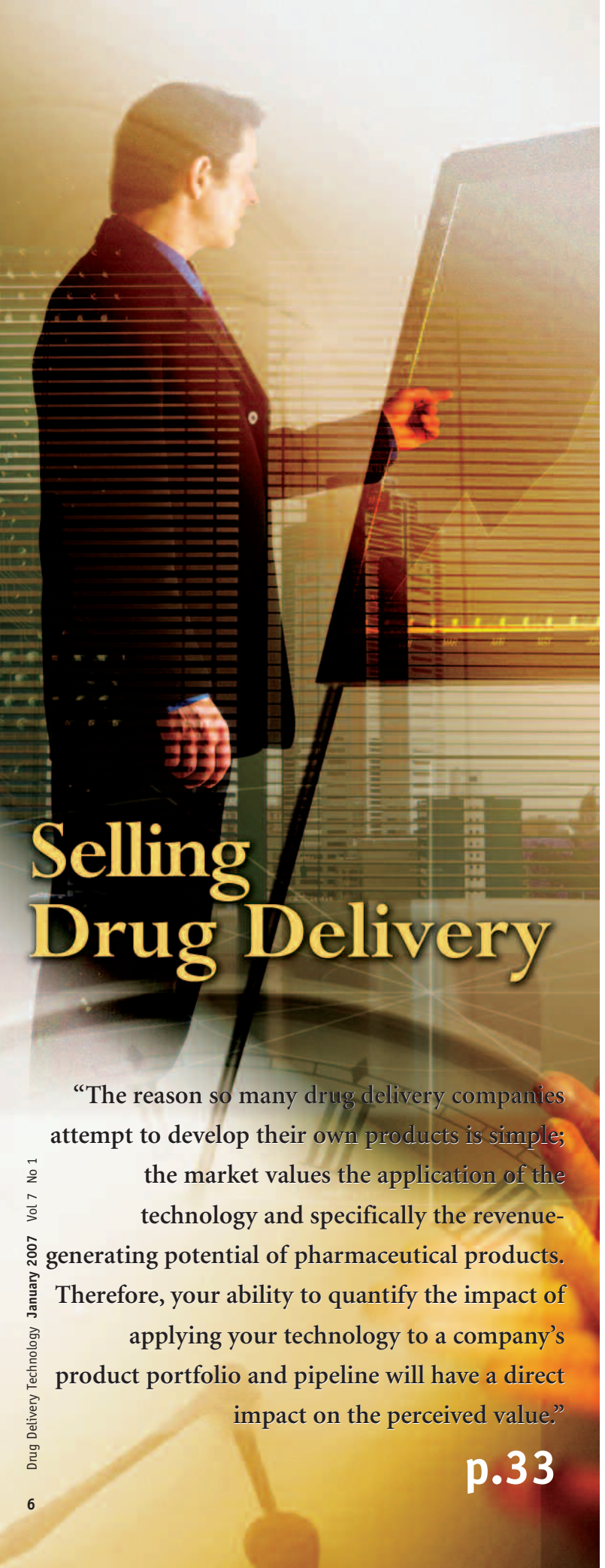

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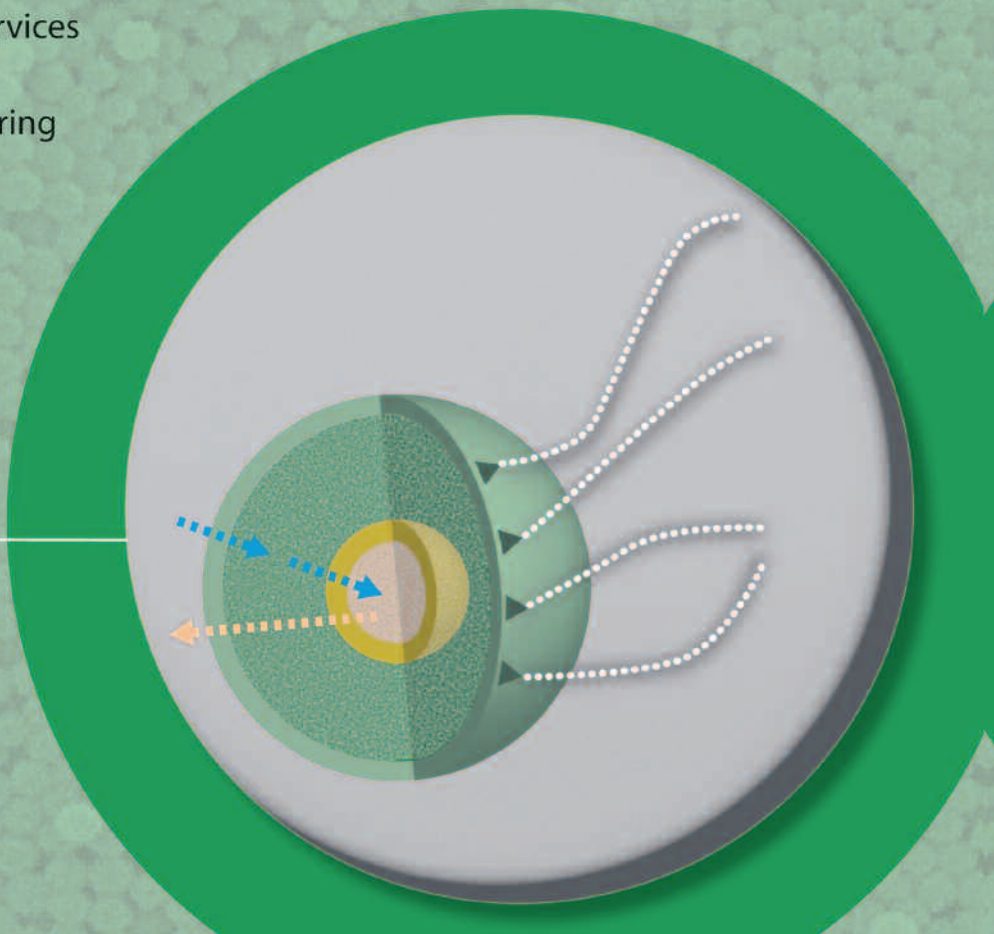

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Market News and Trends

Halozyme & Roche Enter Agreement for the Application of its Enhanze Technology

Halozyme Therapeutics, Inc. and Roche recently announced they have entered into an agreement to apply Halozyme's proprietary Enhanze Technology to Roche's biological therapeutic compounds. Enhanze Technology is Halozyme's proprietary drug delivery technology based on its recombinant human hyaluronidase (rHuPH20). rHuPH20 is an analogue of a human enzyme that temporarily clears space in the matrix of tissues such as skin. This clearing activity should allow rHuPH20 to improve drug delivery by enhancing the entry of therapeutic molecules through the subcutaneous space.

"Roche is a global leader in the development of biologics, and we are excited to be applying our rHuPH20 technology to this area with Roche compounds," said Jonathan Lim, MD, Halozyme's President and CEO. "We believe that our technology can enhance the clinical benefits that biologics have already been shown to provide. In every respect, both technically and commercially, this represents a landmark agreement for Enhanze Technology and for Halozyme."

"We are looking forward to working together with Halozyme using their rHuPH20 technology," said Peter Hug, Roche's Global Head of Pharma Partnering. "The potential to improve the administration and bioavailability of subcutaneous medicines presents an important advance to make a difference to patients' lives."

Under the terms of the agreement, Roche will pay Halozyme $20 million as an initial upfront payment for the application of rHuPH20 to three predefined Roche biologic targets. Throughout the next 10 years, Roche will also have the option to exclusively develop and commercialize rHuPH20 with an additional 10 targets. Pending the successful completion of a series of clinical, regulatory, and sales events, Roche may pay Halozyme further milestones, which could potentially reach a value of up to $111 million as well as royalties on potential product sales for the first three targets. For each of the additional 10 targets, Roche may pay Halozyme further upfront and milestone payments of up to $47 million per target. In addition, the Roche Venture Fund will make an $11 million equity investment, representing approximately 5% of Halozyme's outstanding common stock.

Under the collaboration, Roche will also obtain access to Halozyme's expertise in developing and applying rHuPH20 to Roche targets. Roche will obtain a worldwide, exclusive license to develop and commercialize product combinations of rHuPH20 and Roche target compounds resulting from the collaboration.

Headquartered in Basel, Switzerland, Roche is one of the world's leading research-focused healthcare groups in the fields of pharmaceuticals and diagnostics. As a supplier of innovative products and services for the early detection, prevention, diagnosis, and treatment of disease, the Group contributes on a broad range of fronts to improving people's health and quality of life.

Halozyme is a biopharmaceutical company developing and commercializing recombinant human enzymes for the drug delivery, palliative care, oncology, and infertility markets. The company's portfolio of products is based on intellectual property covering the family of human enzymes known as hyaluronidases. Halozyme's recombinant human enzymes may replace current animal slaughterhouse-derived extracts that carry potential risks of animal pathogen transmission and immunogenicity. The company has received FDA approval for two products: Cumulase®, the first and only recombinant human hyaluronidase for cumulus removal in the IVF process; and Hylenex for use as an adjuvant to increase the absorption and dispersion of other injected drugs.

Generex Biotechnology Selects Inyx to Produce Glucose RapidSpray for Worldwide Markets

Generex Biotechnology Corporation, a leader in treating metabolic diseases via drug delivery through the inner lining of the mouth, and Inyx, Inc., a specialty pharmaceutical company focused on niche drug delivery technologies and products, recently announced that the two companies have signed a letter of intent for Inyx to serve as the exclusive manufacturer of Generex's proprietary Glucose RapidSpray, its new confectionary glucose oral spray product.

The 3-year agreement, which is expected to commence in the first quarter of 2007, includes technical transfer, commercial manufacturing, packaging, and supply. Inyx will be the sole producer of Glucose RapidSpray for Generex in worldwide markets, with the exceptions of Canada and the Republic of Ecuador.

Glucose RapidSpray is an innovative alternative for people who require or want additional glucose in their diet. It delivers a fat-free, low-calorie glucose formulation that was developed using Generex's proprietary buccal drug delivery technologies. The formulation is delivered via spray to the inner lining of the mouth, with no lung deposition. Glucose RapidSpray is convenient to carry and simple to use. It provides swift, effective results without large tablets to chew or messy gels to swallow.

In making the announcement, Anna Gluskin, President & Chief Executive Officer of Generex, commented, "We are pleased to combine Generex's patented technologies with Inyx's drug delivery production expertise to bring to market a more efficacious product for responding to the symptoms of low blood sugar."

Jack Kachkar, MD, Chairman of Inyx, Inc., said, "We are very pleased that Inyx has been selected for the commercial production of Glucose RapidSpray, and we look forward to a long-term relationship with Generex, a new client."

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

Inyx, Inc. is a specialty pharmaceutical company with niche drug delivery technologies and products for the treatment of respiratory, allergy, dermatological, topical, and cardiovascular conditions. Inyx focuses its expertise on both prescription and over-the-counter pharmaceutical products, and provides specialty pharmaceutical development and production consulting services. In addition, Inyx is developing its own proprietary products.

Market News and Trends

Dow to Acquire Wolff Walsrode From Bayer

The Dow Chemical Company and the Bayer Group recently announced they have reached an agreement for Dow to acquire Bayer's Wolff Walsrode business group, which is primarily involved in cellulose products. The transaction is expected to close in the first half of 2007, subject to regulatory approval. Financial terms have not been disclosed.

For Dow, the agreement underscores the company's commitment to strengthen its performance businesses portfolio as part of its goal to dampen earnings cyclicality while driving growth.

"We continue to deliver on our strategy, and the acquisition of Wolff Walsrode is another step along our path to maximize long-term shareholder value from investments into advantaged technologies, growing end-use markets, and emerging geographies," said Andrew Liveris, Dow's Chairman and Chief Executive Officer.

Bayer announced in March 2006 that it would divest its subsidiaries H.C. Starck and Wolff Walsrode AG. "I'm pleased that following the sale of H.C. Starck, we've also found a buyer that offers promising perspectives for the future of Wolff Walsrode," said Bayer Management Board Chairman Werner Wenning. "As planned, the proceeds will help to finance the acquisition of Schering."

Wolff Walsrode, with 2005 revenues of more than $400 million, would become an integral part of Dow's Water Soluble Polymers business.

"The acquisition will create a $1 billion performance business for Dow. We will accelerate growth, ensure long-term supply, and offer a broad portfolio of differentiated solutions by expanding our collective expertise and capabilities," said Romeo Kreinberg, Dow's Executive Vice President for the Performance Plastics and Chemicals portfolio.

Dow and Wolff Walsrode are complementary, bringing different products, processes, applications and expertise to the combined business. "Dow is a good strategic fit for Wolff Walsrode, and our expertise is an excellent basis for further growth in cellulosics in particular," said Dr. Dieter Herzog, Managing Director of Wolff Walsrode.

The new business would combine Wolff's advanced production technology and proficiency in HEMC (Hydroxyethyl Methyl Cellulose) and CMC (Carboxymethyl Cellulose) chemistry with Dow's leading HPMC (Hydroxypropyl Methyl Cellulose) product brands and industry expertise. Cellulose derivatives produced by the combined businesses are used across a broad range of industry sectors, including construction materials, personal care, pharmaceuticals, food, and a number of specialty applications.

The global Water Soluble Polymers business is a $650 million business within the Performance Plastics and Chemicals portfolio of The Dow Chemical Company. It offers a wide portfolio of cellulose ethers and provides application and formulation expertise, products, and related technologies. The business employs nearly 700 people at 14 sites worldwide. Its brands include Amerchol, a global manufacturer and marketer of performance ingredients for personal care formulations; CELLOSIZE Hydroxyethyl Cellulose (HEC); Dow Dispersion Sciences, an advanced technology for the personal care industry; DOW Latex Powders; ETHOCEL Ethylcellulose Polymers; METHOCEL Cellulose Ethers; and POLYOX Water-Soluble Resins.

GlaxoSmithKline Signs Record $2.1 Billion Deal for Genmab A/S Drug

GlaxoSmithKline (GSK) and Genmab A/S recently announced a worldwide agreement to co-develop and commercialize HuMax- CD20 (ofatumumab), a fully human monoclonal antibody in late-stage development for CD20 positive B-cell chronic lymphocytic leukemia (B-CLL) and follicular non-Hodgkin's lymphoma (NHL) and in Phase II for rheumatoid arthritis (RA).

Under the terms of the agreement, Genmab will receive a license fee of DKK 582 million (approximately 52 million pounds Sterling and approximately $102 million), and GSK will invest DKK 2,033 million (approximately 183 million pounds and approximately $357 million) to purchase, 4,471,202 ordinary shares of Genmab. The total potential value of this agreement, in the event of full commercial success, in cancer and various autoimmune and inflammatory diseases, could exceed DKK 12 billion (approximately 1.1 billion pounds and approximately $2.1 billion), including the initial license fee and equity purchase, milestone payments, totaling DKK 9 billion (approximately 0.8 billion pounds and approximately $1.6 billion) and expected development, commercial manufacturing and commercialization costs. In addition, Genmab will be entitled to receive tiered double-digit royalties on global sales of HuMax-CD20.

GSK will receive an exclusive worldwide license to HuMax-CD20 as well as any other antibodies with affinity for the CD20 antigen, which Genmab may develop. GSK will also have an exclusive option to a CD20 UniBody to be developed in collaboration with Genmab. GSK and Genmab will co-develop HuMax-CD20. Genmab will be responsible for development costs until 2008, including costs of the two ongoing late-stage oncology studies after which development costs will be shared equally between GSK and Genmab. GSK will be solely responsible for the manufacturing and commercialization of HuMax-CD20.

Genmab will have an option to co-promote HuMax-CD20 in a targeted oncology setting in the US and in the Nordic region. Should this be undertaken, Genmab will also have the option co-promote Bexxar and Arranon in the US and Atriance in the relevant countries of the Nordic region. The agreement is subject to review by the US Government under the Hart-Scott-Rodino Act and will become effective after clearing review.

"We believe that this alliance is a significant step for GSK and Genmab," said Dr. Moncef Slaoui, Chairman of Research and Development at GSK. "By combining the skills and knowledge of Genmab in developing fully human antibodies, such as HuMax-CD20, and the substantial experience of GSK in clinical and commercial development, we hope to be able to bring this innovative and potentially valuable medicine to patients as soon as possible."

"This alliance puts the tremendous strength of GSK's development, sales, and marketing expertise behind HuMax-CD20," said Lisa N. Drakeman, PhD, Chief Executive Officer of Genmab. "We are looking forward to our collaboration and working together to maximize the value of this product that has the potential to benefit so many patients with different diseases."

Cardinal Health Announces Plans to Sell $1.8 Billion Pharmaceutical Technologies & Services Segment

Cardinal Health, the leading provider of products and services supporting the healthcare industry, recently announced plans to divest its Pharmaceutical Technologies and Services (PTS) segment, a business that manufactures or packages 100 billion doses of medication every year for pharmaceutical and biotech firms, employs approximately 10,000 at more than 30 facilities worldwide, and generates $1.8 billion in revenue. The company said the decision was made to focus Cardinal Health's capabilities and resources to better serve healthcare provider customers, such as hospitals and pharmacies.

"In the coming years, Cardinal Health will focus more on our products and services that help providers improve the safety and productivity of healthcare," said R. Kerry Clark, President and Chief Executive Officer of Cardinal Health. "While synergies clearly exist between PTS and our other businesses, we believe there is greater customer and shareholder value in the expansion of our supply-chain and medical and clinical products businesses domestically and internationally. These segments align with our core competencies and customers, and we see significant opportunities for future growth and improved return on capital."

The company expects to use the proceeds to repurchase Cardinal Health shares. In anticipation, the board has initially authorized an additional $1 billion, bringing the company's total repurchase authorization to $3 billion for fiscal 2007 and 2008. To date in fiscal 2007, the company has purchased approximately $500 million in shares and plans to complete a total of $1.5 billion by the end of fiscal 2007. Cardinal Health will also continue to invest in organic growth and tuck-in acquisitions to strengthen existing product and service offerings.

Cardinal Health will retain Martindale and Beckloff Associates, two businesses that support the generic pharmaceutical market. Martindale develops generic, intravenous medicine that is complementary to Cardinal Health's hospital business and generics strategy. Beckloff provides regulatory consulting services, including for Cardinal Health generic products. Combined, these businesses have approximately 400 employees at two primary locations in the United States and United Kingdom.

PTS is the leading contract manufacturing and service provider for the pharmaceutical industry. As a stand-alone company excluding Martindale and Beckloff, Cardinal Health estimates the business would generate in excess of $300 million in earnings before interest, taxes, depreciation and amortization. Among its core offerings, it develops and manufactures oral and sterile medication in nearly all dosage forms, and holds patents for softgel and Zydis® fast-dissolve technologies used in many popular prescription and over-the-counter medicine. The segment is also the largest contract packager of pharmaceuticals.

Cardinal Health said there would have been no change to its fiscal 2007 earnings per share (EPS) guidance had it not made the decision to sell PTS. However, based on the decision, results for PTS will be treated as discontinued operations in its financial statements, and the company issued new, consolidated EPS guidance for fiscal 2007. Non-GAAP diluted EPS from continuing operations for fiscal 2007 is now expected to be in the range of $3.25 to $3.40. All growth goals for the four remaining segments are unchanged from previous communications. Excluding the impact of any proceeds from the PTS divestiture, Cardinal Health reaffirmed its long-term financial goal of 12% to 15% growth in non-GAAP diluted EPS from continuing operations, and expects to be within that range for fiscal 2008. Depending on the timing of the divestiture, the company expects proceeds from the transaction should further add materially to fiscal 2008 EPS growth.

Market News and Trends

Nastech Announces Positive Phase I Clinical Results of Insulin Nasal Spray Compared to Exubera Inhalation Powder & NovoLog Insulin Aspart Injection

Nastech Pharmaceutical Company Inc. recently announced results from a placebo controlled, dose-escalation, cross-over Phase I study of Nastech's proprietary insulin nasal spray formulations, NovoLog insulin aspart (rDNA origin) injection, and Exubera (insulin human [rDNA origin]) Inhalation Powder in healthy subjects.

Twelve subjects participated in a six-treatment, cross-over study in which one treatment of a nasal placebo, three doses of a proprietary intranasal formulation of regular human insulin, one treatment of rapid-acting insulin aspart injection, a rapid-acting insulin analogue, and one treatment with insulin human inhalation powder. Plasma insulin and glucose levels were measured at 12 time points up to 6 hours, and pharmacokinetic parameters, including Tmax, Cmax, and AUClast, were determined.

With respect to time to maximum plasma level for insulin or Tmax, the three nasal doses had Tmax values of 16 to 19 minutes and were the fastest compared to the rapid-acting insulin aspart and inhaled insulin. With respect to plasma insulin levels, rapid-acting insulin aspart injection had the highest concentration, followed by the three nasal formulations, with inhaled insulin having the lowest. With respect to the extent of absorption, rapid-acting insulin aspart injection had the greatest total exposure or AUClast, with the highest dose of three nasal formulations next, followed by the inhaled insulin and then the lowest doses of two nasal spray formulations.

The pharmacokinetic-pharmacodynamic relationship demonstrated a high correlation between either Cmax or AUClast and the maximum glucose response. One subject was dropped from the study due to hypoglycemia after receiving insulin aspart injection; otherwise, there were no side effects, including clinically significant hypoglycemia.

"The rapid absorption of a nasal product may have a unique value proposition compared with other insulin formulations on the market, especially in type 2 patients who have adequate insulin stores but a slow post-meal insulin response," said Dr. Harold E. Lebovitz, Professor of Medicine in the Division of Endocrinology at the State University of New York (SUNY) Health Science Center at Brooklyn. "A rapidly acting insulin may complement the remaining natural capacity in such patients."

"This study was designed to determine if Nastech's nasal spray formulations of regular human insulin would act faster than a rapid-acting injection formulation and would deliver more insulin than the recently approved, inhaled insulin and both of those goals were achieved with these initial formulations," stated Steven C. Quay, MD, PhD, Chairman, President, and CEO of Nastech. "We plan to conduct additional formulation work to increase both bioavailability and the duration of effect and will continue to develop insulin nasal spray based on its potential to become a safe and effective non-invasive insulin therapy for diabetes. The current study protocol has been expanded to include additional formulations and this study continues at this time."

Nastech is a pharmaceutical company developing innovative products based on proprietary molecular biology-based drug delivery technologies. Nastech and its collaboration partners are developing products for multiple therapeutic areas, including osteoporosis, diabetes, obesity, respiratory diseases, and inflammatory conditions.

Lipoxen Announces $75 Million Agreement With Baxter International to Develop New Blood Clotting Factors

Lipoxen PLC recently announced that the company has entered into an exclusive worldwide development and license agreement with a subsidiary of Baxter International Inc. to develop improved, longer-acting forms of blood-clotting factors. The signing of this agreement by Baxter triggers a $1 million payment to Lipoxen, and the agreement includes further clinical and regulatory milestone payments to Lipoxen potentially worth up to a total of $75 million, plus royalties on future product sales.

This announcement follows a 12-month research evaluation announced in August 2005 that focused on linking Lipoxen's PolyXen drug delivery technology with Baxter's proprietary proteins. Lipoxen's PolyXen protein drug delivery technology links therapeutic proteins, or peptides, to the naturally occurring polymer polysialic acid to prolong protein stability and biological half-life, and to improve solubility and immunological characteristics while maintaining biological activity and minimizing toxicity. Conjugating PolyXen to therapeutic blood clotting factors aims to improve pharmacokinetic profile and extend active life in order to reduce the frequency of injections required to treat blood clotting disorders, such as haemophilia

A.M. Scott Maguire, CEO of Lipoxen, said, "We are very excited to sign this significant agreement with Baxter, our second major development agreement in the past year. Over the course of the 12-month evaluation period, our PolyXen technology has indicated its potential for improving the delivery and effectiveness of Baxter's proprietary proteins and thereby represents an important validation of this protein drug delivery technology."

"Our agreement with Lipoxen furthers Baxter's legacy of scientific innovation and leveraging partnerships in the area of blood-free recombinant protein processing," said Hartmut J. Ehrlich, MD, Vice President, Global Research and Development, for Baxter's BioScience business. "Extending the duration of a blood clotting treatment in the body is important for both patients and physicians when evaluating haemophilia therapy."

Earlier this year at the American Society of Hematology 48th annual meeting, Baxter presented preclinical data from ongoing research studies aimed at developing a novel, longer-acting form of factor VIII, a protein essential for the normal clotting of blood. Baxter will continue to conduct preclinical research before moving these programs forward to clinical trials.

Lipoxen PLC is a biopharmaceutical company specializing in the development of high-value differentiated biologicals, vaccines, and oncology drugs. Potential products, which address markets in excess of $1 billion, currently under development include improved formulations of important biologicals, including EPO, G-CSF, insulin, and Interferon-alpha based on Lipoxen's proprietary PolyXen technology. This technology is designed to improve the stability, biological half-life, and immunologic characteristics of therapeutic proteins naturally. Lipoxen has two further naturally derived proprietary delivery technologies ImuXen and a related liposomal technology for the formulation of cytotoxic oncology drugs, which are being developed to enhance the efficacy and safety of various vaccines, such as hepatitis B and pneumococcal vaccines, as well as a number of anti-cancer agents like paclitaxel.

The company's proprietary delivery technologies are attracting significant interest and Lipoxen is already co-developing products with The Serum Institute of India, one of the world's leading vaccine companies. In addition, its technologies are being currently evaluated by leading biotechnology companies, such as Baxter, Amgen, Genzyme, and Genentech.

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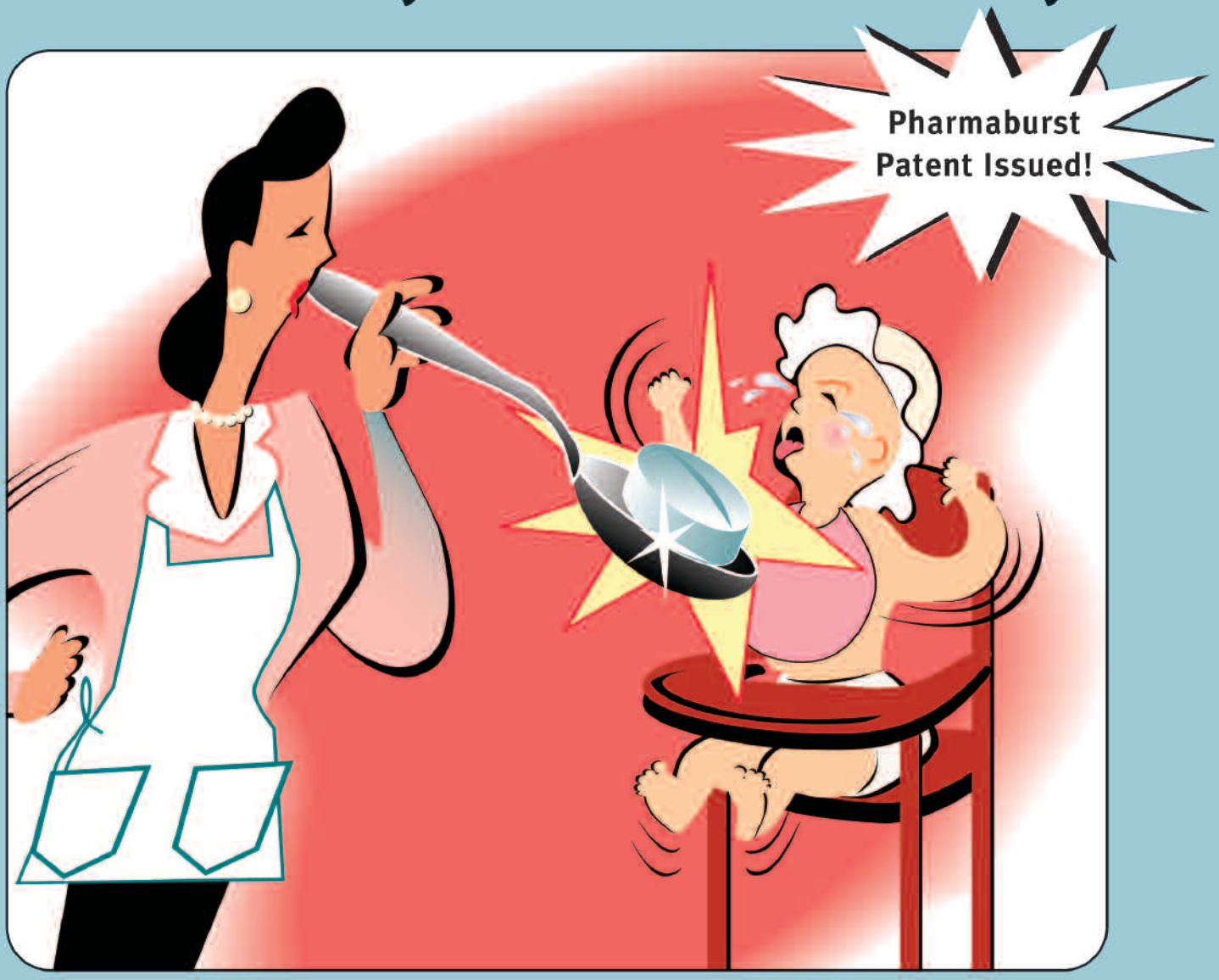

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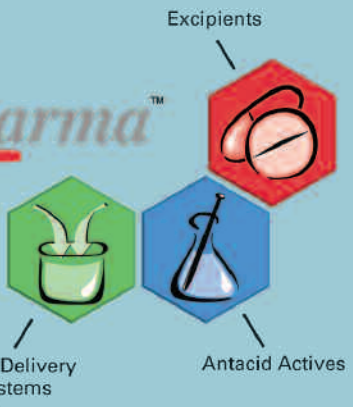

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Benchmarking Drug Delivery – Following the Money

By: Josef Bossart, PhD

INTRODUCTION

The question hit me while sitting in the audience at the recent keynote panel discussion titled Pharma's View on Drug Delivery, moderated by Ralph Vitaro (Publisher of *Drug Delivery Technology*) and hosted by the SRI Institute at its 11th annual *Drug Delivery Technologies & Deal-Making Summit.*

The panel featured an all-star collection of Big Pharma companies discussing their take on how drug delivery, in particular Drug Delivery companies, fit into their future plans and needs. The companies on the panel included Merck & Co., Roche, Pfizer, Lilly, Genzyme, and Bristol-Meyers Squibb. The panelists all had significant experience with the drug delivery initiatives in their companies and were equally positive on the future of drug delivery within their organizations.

That was why it was funny when they seemed to stumble when asked the simple question; what resources does your company dedicate to the discovery of novel drug delivery systems? One panelist positively indicated his company had about 30 people in its drug delivery division. But upon further questioning, it was revealed that all of these personnel were dedicated to applied drug delivery, rather than the discovery or development of novel systems. The rest of the panel said nothing.

The next question that went unasked was – who is taking home the money earned through investments in new drug delivery systems?

FOLLOWING THE MONEY

Company Figures

Following the money can be as complex or simple as you choose. For the sake of transparency, we'll take the simpler path. In particular, we'll take a look at the relative profitability of the two groups most deeply involved with drug delivery, Drug Delivery and Big Pharma companies.

Drug Delivery should not be considered adolescent in terms of development. Arguably, the commercial drug delivery sector was born simultaneously in California, Ireland, and Italy in 1969, with the founding of Alza, Elan, and Eurand. That was 38 years ago. This was followed in the next two decades by the birth of other leading companies, Ethypharm (1977), Debiopharm and SurModics (1979), Enzon and The Liposome Company (1981), Jago and Nastech (1983), Atrix and Cima (1986), Alkermes and Noven (1987), and Biovail (1989).

The fates of these drug delivery pioneers are varied. Alza, Atrix, Cima, Jago, and The Liposome Company have all been acquired or merged. Of the remaining 10 companies, only three (Ethypharm, Noven, and SurModics) still label themselves as Drug Delivery companies, in part or in whole. The remainder of the group have expanded or evolved their business models and adopted labels, such as specialty pharma, pharma development, bioscience, or biopharma. Regardless of label, all of them still rely in one way or another on their drug delivery assets to finance current activities.

Back to the subject of money, where do drug delivery product profits flow? Table 1 summarizes the individual and summed profitability for public Drug Delivery companies that have been in business for no less than 10 years and have at least one approved product. Excluded are adolescent-stage companies unlikely to be profitable because of their relative youth. The table also includes individual and summed profitability for the Big Pharma companies that participated in the SRI Drug Delivery panel mentioned earlier. Profitability figures (generally operating profit) are provided for 1995, 2000, and 2005. The figures for the Big Pharma companies provide more of a sense of their profit rather than firm

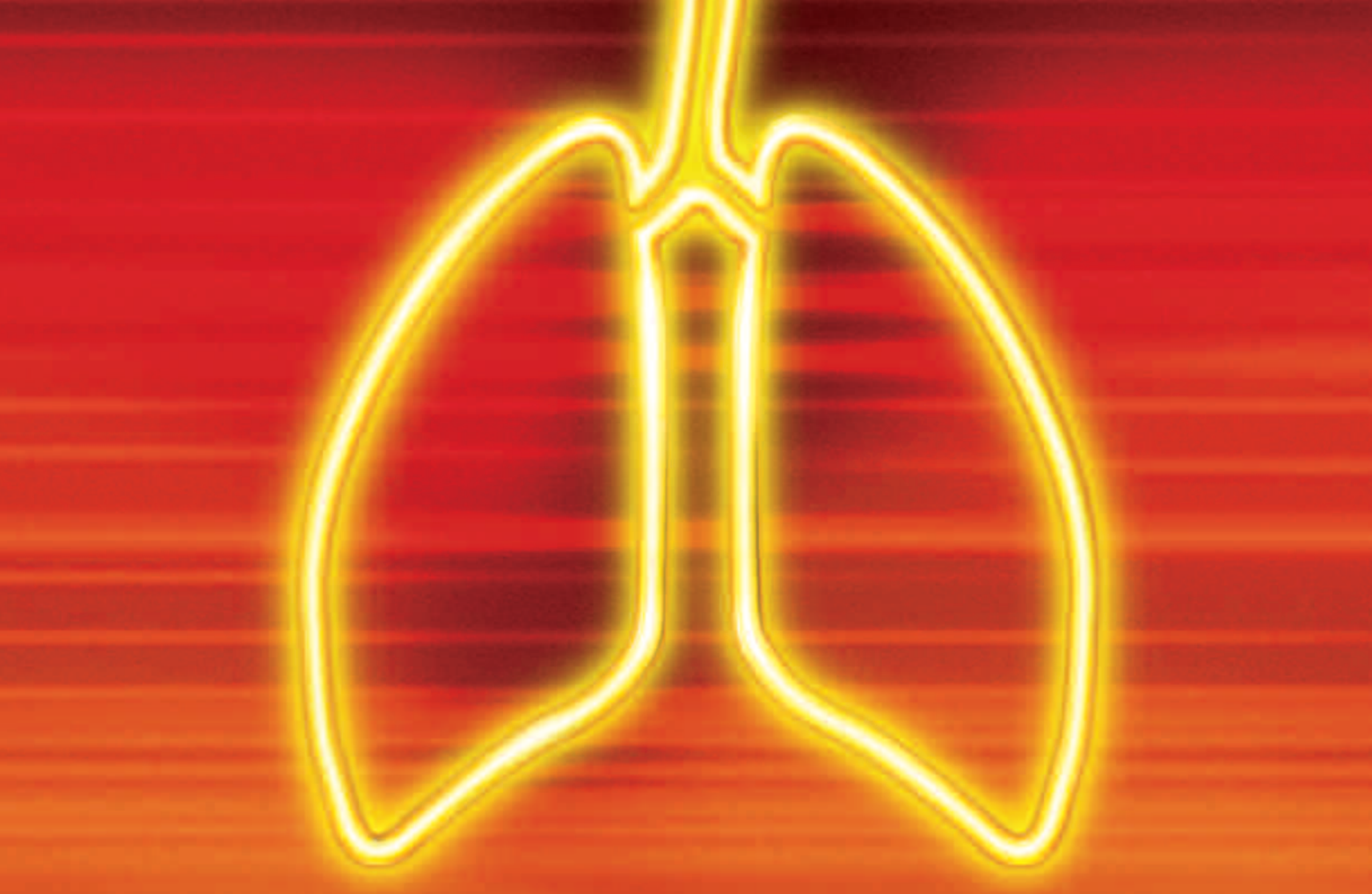

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TABLE 1

SECTOR	COMPANY	PROFIT (MILLIONS)		
		1995	2000	2005
DRUG DELIVERY	Alza (1969)	$72	$256	Acquired
	Elan (1969)	$39	$214	-$198
	Enzon (1981)	-$7	$12	-$12
	Liposome Company (1981)	-$35	$14	Acquired
	AP Pharma (1983)	-$9	-$4	-$8
	SkyePharma (1983)	-	-$27	-$68
	Atrix (1986)	-$14	-$5	Acquired
	Cima (1986)	-	$5	Acquired
	Alkermes (1987)	-	-$30	$14
	Noven (1987)	-	$12	$15
	Angiotech (1989)	-	-$11	$31
	Biovail (1989)	$3	-$148	$302
	SurModics (1990)	-	$5	$3
	Nektar (1992)	-	-	-$185
	DepoMed (1995)	-	-	-$26
	Total	**$62**	**$283**	**-$138**
	Average	$10	$22	$12
	Median	$2	$5	-$7
PHARMA	Bristol-Myers Squibb	$2,300	$5,478	$3,698
	Eli Lilly	$1,306	$3,858	$2,717
	Merck	$11,884	$9,824	$7,363
	Pfizer	$2,299	$5,781	$11,534
	Roche	n/a	$4,231	$7,259
	Total (excluding Roche)	**$17,789**	**$24,941**	**$25,312**

n/a – profit figures not readily available

figures. Some of these companies altered their reporting procedures (ie, including or excluding non-pharmaceutical operations) during this period, and in the case of Roche, the 1995 figures are not readily available.

Product Figures

Looking at selected product sales provides a different, and complementary, view of who pockets the money. For simplicity, we will take a sampling of Drug Delivery companies for which we can assemble reasonably reliable sales and profit figures. Biovail would have been interesting to include, but the forensic accounting required to separate its drug delivery and pharmaceutical operations is beyond the scope of this article. Table 2 summarizes product sales along with "rewards" earned by the partnering Drug Delivery company. These figures are presented with a few qualifications. The numbers are good "ballpark" figures based on the companies' regulatory filings. In almost all cases, partner product sales are underestimated because sales figures for a number of licensed products are not reported. Examples would include SkyePharma's partner sales of Madopar DR and Coruno, and Nektar's partner sales of Somavert, Definity, and DuraSeal. Alkermes product sales are closest to actual. In the case of Xatral sales (SkyePharma), an estimate was made of the split between the


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TABLE 2 - PRODUCT SALES & LICENSING INCOME (ALL IN MILLIONS)				
COMPANY	PARTNER PRODUCT SALES 2005	DRUG DELIVERY PARTNER REVENUES	GROSS ROYALTY RATE*	NET ROYALTY RATE*
Alkermes	$865	$81	9.4%	6.7%
Nektar	$4,352	$29	0.7%	<0.5%
SkyePhama	$535	$58	10.8%	1.5%
All	$5,752	$168	2.9%	1.6

* - See text for definition of Gross and Net Royalty Rate

immediate- and sustained-release sales. Nonetheless, the numbers provide a fair estimate of sales for the purpose of this analysis.

Drug Delivery company revenues are presented with fewer qualifications and include only sales and royalties. Milestones are excluded because individual product milestone figures cannot be reliably broken out, and because milestone payments are rarely applicable to marketed products. Gross Royalty Rate is calculated by dividing the Drug Delivery company partnership revenue by the total sales of its partners' products. Net Royalty Rate is calculated in the same fashion but after deducting any cost of goods related to the partnerships. In the case of Nektar, the appropriate cost of goods is not obvious, and no deduction is taken.

ANALYSIS

It seems drug delivery product dollars largely end up in the pockets of Big Pharma. For every dollar of sales for a drug delivery product, about $0.97 ends up in the pocket of Big Pharma. Even if we include milestones, we are hard pressed to see on average more than $0.05 ending up in the pockets of Drug Delivery.

Well it can be argued this is not really unfair; Big Pharma has all of the expense of manufacture, distribution, sales and marketing, as well as research and development. Let's challenge this assumption by teasing apart those figures and looking at how the dollars and cents drop to the bottom line. Table 3 provides a *pro forma* estimation of the contribution provided by a drug delivery product. The assumptions used are reasonable but do raise a number of questions. What about deducting for Big Pharma's R&D cost? Well, then we would have to deduct the Drug Delivery company's R&D costs for platform development and validation. Overall, the drug delivery company probably spends proportionately more on R&D; but we'll put in a 5% factor to cover the actual product development costs based on Pharma's 15% average spend on R&D and a 30% clinical success rate. We won't include a cost for administration because both companies have a proportionately similar expense. Let's ascribe a five percent royalty payable by Big Pharma to the drug delivery company. This is a bit higher than the figures calculated in Table 2, but we'll assume it takes into account licensing fees paid by Big Pharma. On the Drug Delivery side, we assume that all cost of goods are reimbursed and are included in the Big Pharma cost of goods. We'll add a five percent royalty payable by Drug Delivery on their revenues to academic institutions or peer companies for the underlying technology. And anyone who has ever done business development knows that it takes time and expense to establish and maintain a deal with Big Pharma, so we'll use a 10% figure for Drug Delivery sales and marketing expenses, again on their revenues, not sales. Overall then, Big Pharma and Drug Delivery can expect a margin of 60% and 85% respectively on their earned revenue.

Applying these figures to the $0.95 and $0.05 shares calculated earlier, we can take another look what's in each party's pocket. For every dollar of a drug delivery product sale, Big Pharma puts $0.57 in their pocket, while Drug

Delivery pockets a bit more than $0.04. The other $0.39 is paid out for expenses. The ratio of profit sharing is 14:1, in favor of Big Pharma.

TABLE 3 - ESTIMATION OF BIG PHARMA DRUG DELIVERY MARGINS

EXPENSE	BIG PHARMA	DRUG DELIVERY
Cost of Goods	10%	0%
Drug Delivery Royalty	5%	5%
Product Development Costs	5%	0%
Sales and Marketing	20%	10%
Net Margin	60%	85%

REFLECTIONS

So far, we haven't uncovered anything that will surprise any reader of this article. There may be some surprise in how skewed the figures really are. There was no question that Big Pharma was doing better; but a 14X factor? This is a figure that's worth bringing up in a negotiation when Big Pharma starts to plead poverty or complains that Drug Delivery is being greedy.

No, the real surprise is that Big Pharma believes that this type of business arrangement can provide them with sustainable partnerships. Remember the panel session mentioned earlier where Big Pharma indicated that it did not conduct drug delivery discovery work? If Drug Delivery is financially unable or insufficiently rewarded to discover and develop these new technologies – who will? Does Big Pharma believe there will be no shortfall in the availability of novel technologies to deliver next-generation products? Perhaps Big Pharma is correct; there seems to be a never ending series of new drug delivery companies needing to validate themselves by executing "loss leading" deals.

If it has worked in the past why won't it work in the future? There are at least two reasons why not. The first follows a trend that has been developing for the last five years; drug delivery companies prefer to develop their own products rather then license out their technologies. Biovail has been traveling down this path for the last few years. Biovail's recent deal with J&J for extended release and ODT formulations of tramadol provides for a 25-35% transfer price. Plugging a middle of the road 30% transfer price number into our earlier analysis (Table 3) yields a $0.50 to $0.14 (about 3.5:1) profit split between J&J and Biovail, after deducting their expenses, and assuming a 10% cost of goods paid by Biovail. If the actual cost of goods paid by Biovail is 5% the split becomes $0.50 to $0.19, or about 2.6:1. This is a much more attractive deal for Biovail than those outlined in Table 3; but most of the money is still flowing to the Big Pharma company. For those of you doing your own calculations, the 5% R&D cost has been transferred to Biovail's side of the P&L estimation (see www.b4bio.com for the actual figures). Presumably Biovail felt that settling for a 30% share of the profits was offset by having tramadol's originator, and the clear market leader, promote the product. It is unlikely any other Big Pharma or Specialty company would be able deliver the gross sales figures volume that J&J can. For J&J it is a great deal; they will continue to harvest risk-free profits from their tramadol franchise instead of losing it all to generics or a next-generation product.

The second thing that can derail the Big Pharma drug delivery model is a retreat of investors from bankrolling new drug delivery companies. The biopharmaceutical business model depends on a promise of profit. If Drug Delivery companies continue to be bled by Big Pharma, albeit willingly, and the profit figures look like those summarized in Table 1, it seems unlikely investors will finance new technologies. The continuing movement of companies from a Drug Delivery to a Specialty Pharma model, due solely to poor economics, promises to leave a vacuum. New technologies will require more, not less funding than in the past.

So, should Big Pharma really care? There seems to be lots of drug delivery technology available in the public domain, or licensable for very low cost. Why worry about the technology if you have all you need?

Well there are huge therapeutic and commercial opportunities for novel drug delivery technologies. The whole area of biological agents, antibodies, vaccines, and cytokines, are yet to benefit from drug delivery. Beyond the obvious benefit of eliminating the needle, drug delivery can provide significant improvement in efficacy

and safety. Just look at the therapeutic and commercial opportunities offered by Pegasys and PEG-Intron. Where will Big Pharma look for next-generation technologies that will do the same and more for the challenging targets presented by antibodies and other macromolecules?

A couple of thoughts come to mind. The first is that the Big Pharma companies may choose to build their own drug delivery technology discovery programs, or to bankroll small emerging companies to the point of proof-of-principle. The economics of this is sound, but Big Pharma has a real issue with internal innovation. Moving to the development side of R&D, Big Pharma has left novel research to emerging entrepreneurial companies. Can Big Pharma enthusiastically take on the responsibility for drug delivery discovery? Another possibility is that the investment community will develop a general amnesia and continue to fund technology-focused Drug Delivery companies. At best there may be a revival of investment until the amnesia lifts. But once the business model realities surface, the investors will put their money elsewhere. Biotech companies may have a lower rate of "success" than Drug Delivery companies, but when they do succeed the payoff is much, much bigger.

There is a third possibility, and it follows a common theme of our times. Drug delivery technology discovery and validation may move offshore. There is no question that the greater part of drug delivery discovery and validation expenses are related to the cost of human capital. With the increasing technical capabilities of emerging markets and their lower cost structure, it is possible that money can be made by all concerned, even with the existing business model. The risk for Big Pharma is that these new markets are not ready to provide the types of technologies that address their biggest opportunities.

As long as Big Pharma focuses solely on the here and now and ignores a looming technology gap, and Drug Delivery believes that doing cheap validating deals will lead to larger deals later, we seem to be headed toward a crisis.

A last thought about net 5% royalty deals. If Nektar was able to earn even an effective 5% royalty on sales of existing products using its technology, Nektar would be able to erase its $185 million deficit for 2005 and show a modest profit. With an ongoing profit and the prospect of higher Exubera revenues, it's quite possible that Nektar's focus would be on developing new cutting- edge drug delivery technologies rather than heading toward the Specialty Pharma model. Are we lerning that what seems to be cheap and expedient in the here and now may lead to shortages in the future? Perhaps, but hey, that's someone else's problem. Isn't it? ◆

Biography

Dr. Josef Bossart is Founder and Principal at Bossart4 Bioconsult (www.b4bio.com), a business development services company that provides strategic and transactional advice to biopharmaceutical companies. Dr. Bossart has more than 25 years of global biopharmaceutical experience in the areas of business development, strategy, operations, as well as sales and marketing. His biopharmaceutical company experience includes, most recently, executive positions at Enzon Pharmaceuticals and GeneMedicine, Inc. Prior to that, he spent 15 years within the Rhône-Poulenc Rorer group, lastly as Vice President of Business and Marketing Development for the RPR Gencell division. Dr. Bossart earned his PhD in Medicinal Chemistry from The Ohio State University, College of Pharmacy, and his BSc (Hon.) in Chemistry from Carleton University.

Conix – A New Inhaler for Dry Powders

By: David Harris, Senior Consultant, Cambridge Consultants

The Dry Powder Inhaler (DPI) is becoming increasingly important within the respiratory field. Since the launch of the Fisons Spinhaler in the 1960s, pharmaceutical and device development companies have invested heavily in R&D to advance the alternative to the conventional metered dose inhaler (MDI). There are several reasons for this, in particular, the ease of creating novel formulations in powder form, and the avoidance of the complications associated with the development of an MDI.

However, there are numerous issues facing developers of DPIs – to produce an inhaler that is cost effective, simple to use, and has low technical risk, it must be passive – powered only by the energy available from the patient's inhalation. The key, therefore, is to design an inhaler that is able to take the greatest advantage of the available energy. This is not as straightforward as it may initially appear; the energy provided by patients will vary significantly. Designing an inhaler with a performance that is independent of this is extremely difficult, and perhaps one of the reasons why there are so many inhalers currently in development, yet relatively few products on the market.

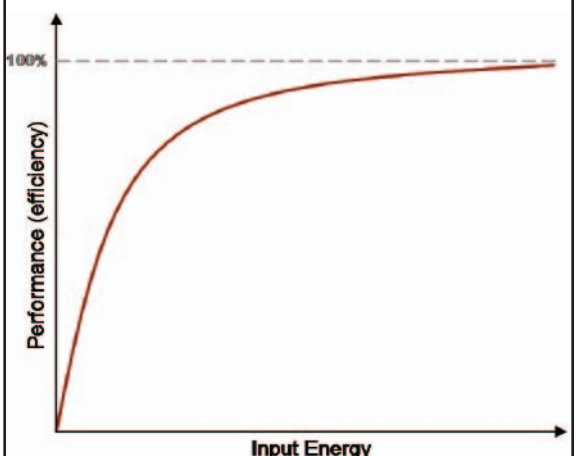
WHAT IS CONIX?

Most DPIs available today are passive, relying solely upon the power available from the patient's inhalation to create a fine, respirable aerosol. As a typical formulation is composed of micronized drug mixed with coarse, inert carrier particles (usually lactose), the purpose of the inhaler is to separate this mixture in order to deliver only the fine drug particles to the lung. To achieve this, inhalers use cleverly designed airway systems to accelerate the airflow provided by the patient's inhalation to create regions of high shear or turbulence, through which the formulation must pass. This high-velocity air serves to tear the micronized drug from the much larger lactose particles such that both fractions are separated as they exit the inhaler. As the patient continues to inhale, the heavier lactose particles impact upon the back of their throat, whereas the micronized drug particles remain airborne, and follow the airflow down into the patient's lungs.

All of this usually happens within a few hundred milliseconds, ie, at the very beginning of the patient's inhalation. Unfortunately, this only gives a very short window of opportunity during which energy can be applied to the formulation to create a respirable aerosol. Another significant factor follows the law of diminishing returns. Only a small quantity of energy is required to remove the most loosely bound micronized drug from the lactose. Conversely, it is almost impossible to remove all of the drug particles using aerodynamic forces alone. This means, crudely speaking, that even the very best inhalers will never be 100% effective as it becomes progressively more difficult to aerosolize the most tightly bound fraction, irrespective of the aerodynamic energy available (Figure 1).

One of the most interesting differences between the Conix principle and conventional DPI technology is that in Conix, the window of opportunity over which energy is put into the formulation is significantly extended. This means that even gentle inhalations impart sufficient energy to the formulation to achieve high performance. Conix

FIGURE 1



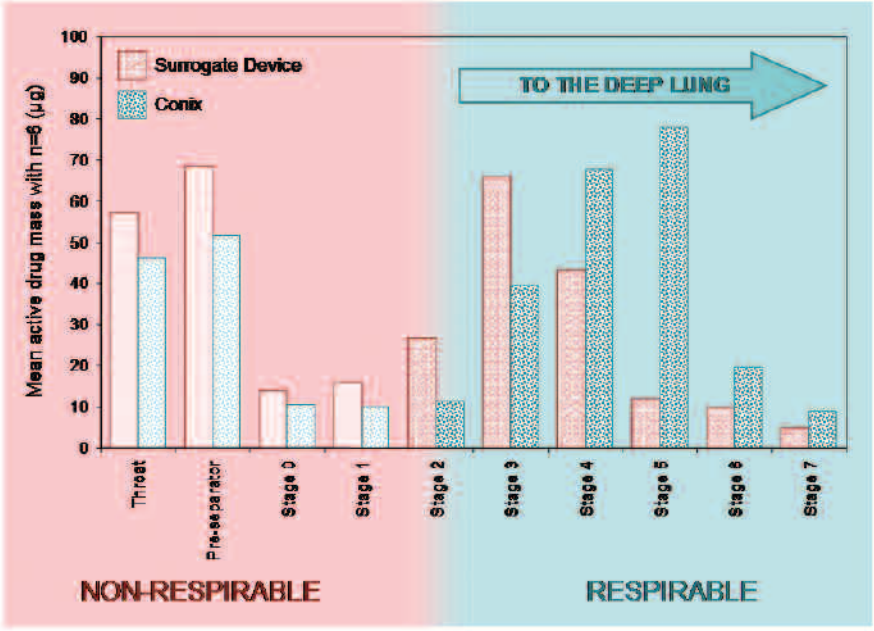
Schematic Illustration of Inhaler Performance

effectively operates on the flatter part of the curve depicted in Figure 1, and the performance is subsequently less dependent upon the strength of the patient's inhalation than conventional DPIs.

A second interesting feature is that Conix retains the lactose particles within the device throughout the inhalation event. Conventional DPIs deliver all the excipients of the formulation to the patient. This offers particular advantage for the administration of respirable medicines requiring large payloads, as the total mass of the emitted dose is reduced, and therefore, higher respirable mass can be delivered per inhalation.

Hence, Conix is a principle that increases the effectiveness of energy transfer from the patient's inhalation to the drug formulation, and it can be applied as a platform technology across a range of DPIs.

FIGURE 2



Example of Particle Size Distribution Data

HOW DOES IT WORK?

Owing to the current patent position, only a limited amount of information can be disclosed regarding the detailed mechanism behind the Conix principle. However, in broad terms, a variation of a "reverse-flow cyclone" is used to create a specific flow field within the device. Reverse-flow cyclones are a type of centrifugal separator and are used in a variety of industrial applications to separate airborne particulate matter from gas flows. A classic example is their use in wood mills to remove wood flour from the air expelled by the extraction systems. However, a standard reverse-flow cyclone is a very efficient mechanism for removing particulates from air flows, not exactly ideal for an inhaler, especially when our intent is to increase the window of opportunity over which energy can be applied to the formulation. However, by capping the exit at the cone of the cyclone chamber (which usually allows the collected material to flow directly into a hopper), the formulation cannot escape through the bottom of the cyclone. This forces the formulation to recirculate in a toroidal pattern within the cyclone chamber throughout the inhalation event. Only once particles are deagglomerated below a predetermined diameter can they escape through the circular outlet tube in the top of the cyclone chamber. Thus, a cyclone geometry can be designed such that, predominantly, only a respirable aerosol is emitted from the device.

PERFORMANCE

The modified reverse-flow cyclone embodied within the Conix inhaler is a particularly effective means to deagglomerate and aerosolize powder formulations. A simple experiment that demonstrates the efficiency of the Conix technology is a direct comparison with a conventional, marketed product. Drug formulation was harvested from three marketed DPIs (from the same batch) and loaded into a Conix inhaler. An Andersen Cascade Impactor was used in accordance with USP 29 to determine the particle size distribution emitted from both the Conix and marketed inhaler devices.[1]

Both inhalers were tested at the recommended pressure drop of 4 kPa.[1] Each test was repeated six times, and in

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FIGURE 3

Cross-section of the Conix Dry Powder Inhaler

FIGURE 4

Conix Dry Powder Inhaler

all cases, the mass of formulation filled in both devices was 12.8 milligrams, containing a nominal 200 micrograms of active drug.

The "respirable fraction" achieved by Conix is over 50% higher than the Surrogate device (Figure 2).[2] In addition, the aerosol emitted from Conix is significantly finer, as it has passed further into the cascade impactor, as can be seen by the higher quantities on stages 4 and 5 (Figure 2). The average particle size of the aerosol emitted from Conix is approximately 30% smaller than that of the surrogate device, which means that the drug particles will penetrate deeper into the patient's lungs, in typical use. In fact, the deagglomeration mechanism is so effective that in almost every case, the size distribution of the emitted aerosol is very close to that of the original formulation. This is a valuable factor, as it reduces the effort required by formulation scientists who typically have to develop formulations that account for the inability of conventional DPIs to fully deagglomerate the mixture and produce an aerosol that represents the premixed excipients.

MARKET APPLICATIONS

The Conix technology can form the platform for a variety of inhaler types, ranging from a single component, single use device (suitable for the administration of vaccines) through to a six-part multi-unit dose device (suitable for delivery of routine therapy, such as asthma and COPD).

Simplicity is crucial for the success of a DPI product, the combination of an inhaler and drug formulation. The technical risk associated with an inhaler under development increases with the complexity of the device. More time is usually required to develop a 20-component device, for example, than for a 6-component design. As the highest priority for a pharmaceutical company with a valuable NCE in its pipeline is minimum time to market, reducing the device development risk is an extremely attractive proposition.

Additionally, a device that offers greater tolerance of suboptimal formulations would also reduce the risk of the product development cycle. This, to some extent, avoids the classic scenario of optimizing (changing) the formulation whilst improving (changing) the design of the inhaler. If a platform technology can produce a sufficiently consistent aerosol with a suboptimal formulation, then clinical trials can commence earlier – again, reducing the time to market.

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1. United States Pharmacopeia (USP) 29, Physical Tests / <601> Aerosols, p. 2620-2621.
2. The respirable fraction is defined as the mass of drug below 5 micrometers as a percentage of the total delivered dose.

BIOGRAPHY

Mr. David Harris is a Senior Consultant at Cambridge Consultants, and works in the Drug Delivery Technology group. He specializes in aerosol science, including fluid dynamics, electrostatics, and the application to inhaler technology. Before joining Cambridge Consultants, Mr. Harris worked in the respiratory physics division of Rhone Poulenc Rorer.

COMBINATION UPDATE

Understanding the FDA's New Guidance for Early Development Considerations of Combination Products

By: Christine Ford, Event Director, PharmaMedDevice, Reed Life Sciences

Throughout the past decade, the FDA has been committed to ensuring the safety, effectiveness, and quality of the combination products industry. The general FDA definition of a combination product is a product composed of two or more regulated components that are physically, chemically, or otherwise combined or mixed and produced as a single entity.[1] These innovative products use cutting-edge technologies to merge the benefits of drugs, medical devices, and biologics to create opportunities for advancing patient care. Combination products have the potential to make treatments safer, more effective, and more convenient to patients.

Recognizing that rapid development in this area may widen the spectrum of scientific and technological considerations, the FDA issued a document in September 2006, titled *Early Development Considerations for Innovative Combination Products*. The document provides a framework for discussions, which may arise during the investigational and marketing research of combination products.

When a drug, device, or biologic are combined or used together, new scientific and technical issues emerge. These issues may arise especially during clinical trials, the manufacturing phase, or when evaluating preclinical safety in targeted areas of the body. This guidance describes general information on developmental considerations for products that combine devices, drugs, and/or biological products. The *Early Development Consideration Guidance* highlights key combination product and constituent part development points, which include the following topics: general development considerations, currently marketed product considerations, perspectives on the different consituents, clinical investigations, manufacturing investigations, and early interaction and communication with FDA.

GENERAL DEVELOPMENT CONSIDERATIONS

Combination products do not command a "one-size-fits-all" approach. The regulatory, manufacturing, and developmental considerations vary depending on the profile of the constituent parts and the combined product as a whole. As a great starting point, the FDA suggests that developers thoroughly research prior FDA approvals and/or clearances for each constituent part. This information can be used as a basis for the development of the final combination product. However, the final approval will depend on the safety and effectiveness of the combination product as a single entity. Recognizing challenges and issues presented by combining constituent parts will help developers identify any additional studies or information that will be required to establish the safety and effectiveness of the product.

PERSPECTIVES BY CONSTITUENT PARTS

The guidance specifically highlights development considerations for each of the constituent parts that may be used in a combination product. A constituent part is defined as an "article distinguished by its regulatory identity as a drug, device, or biological product." The concepts in this guidance are described in the context of a combination product composed of two constituent parts.

DEVICE CONSTITUENT CONSIDERATIONS

This consideration focuses on the safety and effectiveness of the device constituent and how it affects the combination product as a whole. The extent of preclinical testing required will depend largely on whether the device is already approved/cleared, or if it is a new device altogether. If the device is new, specific testing on the device alone will be necessary to establish its safety and effectiveness before it can be combined with another constituent. If the device constituent is already approved/cleared, testing will focus more on the new use of the device constituent as part of the combination product. The device may have to undergo new engineering and functional testing to establish its suitability for the new application or new environment in which it will be used.

The FDA also notes that it is important to give consideration to any potential physical or chemical interactions between the drugs/biologics and the device that may alter or change the functionality of the constituents. Some suggested studies to perform include the evaluation of any changes in drug stability when used with a device, any leachables/extractables of device materials into the drugs/biologics, any changes in delivered doses, or any effects a drug or biological product may have on the device. Based on the type of combination product, the Center for Devices and Radiological Health (CDRH) will adapt existing standards for the device constituent or in the case of a more innovative product, actually develop new methodologies for testing.

DRUG & BIOLOGICAL PRODUCT CONSTITUENT CONSIDERATIONS

As with device constituents, the considerations for drug and biologic consituents depend largely on whether the product is a new molecular entity (NME) or is already approved for another use. When an NME is a constituent part of a combination product, it may first be necessary to establish the safety of the NME alone. This may require standard pharmacology and toxicology studies to establish conventional parameters, such as genotoxicity, immunotoxicity,

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and local tolerance. It is also important to plan ahead for any reproductive or carcinogenicity studies that may also need to be submitted with the marketing application for the combination product.

When an approved drug/bioloic is used as a constituent in a combination product, the developers must supply supplemental safety data or new clinical studies if there will be a change in formulation, dosage, delivery method, or route of administration. Additional information may also be required if the combination product will be used for a new patient population or a new indication from what the drug/biologic was originally approved for.

With both NME and approved drug/biologic constitutents, the FDA suggests performing additional studies on the drugs/biologics once they are incorporated into the combination product as a whole. Some recommendations are supplemental studies on in vivo pharmacokinetics, dose ranging, dose toxicity, and specific monitoring on different patient populations. Developers are also encouraged to research previous agency findings which may provide relevant information.

CLINICAL INVESTIGATIONS

For most combination products, either an Investigational New Drug (IND) or an Investigational Device Exemption (IDE) is submitted. The regulatory guidance for these applications is generally flexibile when considering the related product issues. To help developers ensure that products are on the right regulatory track, the FDA recommends that combination product developers request an early discussion with the agency on matters of trial design, sample size, statistical methods, clinical end-points, appropriate number of clinical studies, and appropriate indications and claims during clinical investigations. The agency also recommends two guidance documents that specifically address questions and issues concerning clinical investigations; Exploratory IND Studies[2] and Guidance to Industry: *Changes or Modifications During the Conduct of a Clinical Investigation*.[3]

MANUFACTURING CONSIDERATIONS

The FDA encourages combination product developers to carefully assess the effects of manufacturing methods on each of the constituent parts, the interactions between the constituent parts, and the safety and effectiveness of the combination product as a whole. For example, sterilization techniques used for devices may alter or destroy some drug/biologic components. Also, any changes in the manufacturing processes that take place during premarket investigation or postmarket manufacturing need to be carefully evaluated for potential effects on the safety and effectiveness of the constituent parts or the product as a whole.

EARLY INTERACTION & COMMUNICATION WITH THE FDA

Lastly, the FDA stresses the importance of early discussions initiated by combination product developers throughout the entire process. By creating lines of communication early on, the FDA believes that the approval and clearance process will operate in a more efficient manner and help manufacturers determine what kinds of preclinical and clinical testing may be needed. Pre-investigational and pre-marketing application meetings are key for identifying potential issues and challenges and providing helpful feedback on the development process. While meetings should be scheduled with the lead center after the primary mode of action (PMOA) is determined, developers are also encouraged to solicit feedback from consulting centers related to all product components. The Office of Combination Products (OCP) is also available to assist throughout the process or address specific concerns.

SUMMARY

The FDA's creation of the Early Development Considerations Guidance has opened additional channels of communication for combination product developers and the industry at large. The rapid growth of this sector is demanding a continual response with regard to every stage of development, including safety regulations and preclinical data. By breaking down each area of development into easily manageable steps, a smoother and more efficient system for approvals and clearances should evolve; this will in turn help the combination products industry to continue to thrive globally. ◆

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BIOGRAPHY

Ms. Christine M. Ford, is Event Director of PharmaMedDevice. Since joining Reed Exhibitions in 1991, Ms. Ford has been involved in a variety of conference and event management positions within a range of event portfolios, including technology, life sciences, and manufacturing. She served as Reed Exhibitions' Director of Business Development from 2000-2005, working on a variety of launch and acquisition projects. Since 2004, she has focused the majority of her business development work within the life sciences and healthcare industries, including the PharmaMedDevice launch. Ms. Ford earned her MBA from the University of Connecticut and her BS from Fairfield University. She can be reached at (203) 840-5391 or cford@reedexpo.com.

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Special Discussion

Key Considerations When Selling or Buying a Drug Delivery Business

INTRODUCTION

The Board of Directors and you agree that it is time to explore selling your drug delivery business, as the CEO, what are the critical issues that you must consider? As with any strategic activity, it is important to start with a prioritization of your objectives, which may include:

- Maximizing the after-tax return to shareholders
- Minimizing the time to a transaction
- Securing employment for the company's employees
- Ensuring continued investment in the drug delivery technology

In most cases, CEOs and founders would like to see all of the aforementioned objectives realized. The reality of the situation is that as a small company, likely dealing with a much larger acquirer, you do not have the opportunity to control all of the variables. It is imperative that you reach consensus with the key stakeholders (board, investors, and senior management) on the relative priority of after-tax return and timeframe. If you are operating with a deteriorating balance sheet and your investors have not committed to continued support, the CEO's ability to maximize after-tax return is greatly compromised.

Once you have support from your board and investors to maximize after-tax return, you can now focus on the issues that will be of most importance to a potential acquirer.

MARKET IMPACT OF THE APPLICATION OF THE TECHNOLOGY

The reason that so many drug delivery technology companies attempt to develop their own products is simple; the market values the application of the technology and specifically the revenue-generating potential of pharmaceutical products. Therefore, your ability to quantify the impact of applying your drug delivery technology to a company's product portfolio and pipeline will have a direct impact on the perceived value of your technology. Additionally, it is important to articulate why an exclusive ownership of your technology will offer competitive advantage in the marketplace.

APPLICABILITY OF THE TECHNOLOGY TO UNMET NEEDS

The value argument that you make is only credible if you are solving an unmet need. If there are multiple alternatives to your technology, it is unlikely that an acquirer will invest the effort to go the acquisition route. Focus on the key formulation challenges that the potential acquirer faces and how your technology provides the solution.

VALIDATION OF THE TECHNOLOGY

You have to be able to show a potential acquirer that you have made the investment to validate your drug delivery technology and that the results fully support your positioning. It is not imperative that you have brought products to market, but rather that you have solved multiple unmet needs by the application of your technology. Ironically, you will be best served by applying the technology to a proven molecule with known formulation issues. In this manner,

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all of the benefits associated with the new formulation will be attributed to your technology and not to the molecule.

DIFFERENTIATION OF THE TECHNOLOGY

You must have the answer to the question "Why is this different from the other drug delivery technologies I have seen?" It is just as important for potential acquirers to understand what your technology is not as to understanding what it is. Be mindful to delineate and if possible, quantify, the differences between your technology and other available and in-development technologies. Keep in mind, if an acquirer is serious about your technology, it is likely they have a formal evaluation process underway and are evaluating dozens of alternatives. Your technology needs to stand head and shoulders over all the others if you want to get the deal done.

STRENGTH & LONGEVITY OF THE INTELLECTUAL PROPERTY POSITION

The assumption will be that you have established a strong IP position and that the use of your technology will extend patent life and will facilitate the continued capture of returns only achieved by exclusive positions. What can set you apart from the other technologies is the manner in which you present the IP. Your ability to summarize the IP position, status, and strategy in a manner that can be easily understood will accelerate the process and help you build momentum early in your interactions with a potential acquirer.

SOME NOTES

Notably absent from the list of key issues are to WHOM will the business be sold and for HOW MUCH. The ideal answers to these questions can only be found by moving through a systematic process. Along the way, it will be important to evaluate each of the items identified earlier for each potential acquirer. Usually, the CEO and his/her advisors will often identify a short list of the most likely acquirers early in the process. In most cases, the ultimate acquirer is not on or at the top of the list. Valuation will be dependent on the CEO's ability to argue the value of the technology to the acquirer as it applies to their product portfolio and pipeline and the process' ability to generate multiple interested parties. If you successfully engage in a managed M&A process that results in a competitive bidding situation you and your shareholders will reap the benefits. ◆

BIOGRAPHY

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

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ROTATIONAL RHEOMETRY

Use of Rheometry in the Product Development of Semi-Solids

By: Charles Shaw, PhD, and Shravan Parsi, MS

ABSTRACT

The aim of this work was to evaluate whether rotational rheometry provides a more useful measurement of structural properties of an O/W emulsion system than conventional "Brookfield" viscosity measurements. To achieve this, three production validation lots of an O/W emulsion were evaluated. Although the three lots showed very similar "Brookfield" viscosity values, one of the lots exhibited a different spray pattern when sprayed from the same spray pump assembly. The ability of rotational rheometry to differentiate the rheological properties of the three lots was explored by performing characterization tests, such as yield point measurement, oscillation stress sweep, and oscillation frequency sweep studies. Through the rotational rheometry experiments performed, it was concluded that the rheological properties of the lot with the different spray pattern were different from the other two lots that exhibited the desirable spray pattern, even though the conventional viscosity values failed to distinguish between the three lots.

INTRODUCTION

The use of rheometry in the development of semi-solid pharmaceutical and cosmetic dosage forms has gained significant importance in recent years. Evaluation of physical properties like description/appearance, pH, and viscosity to monitor batch-to-batch consistency and to determine the physical stability (and hence the shelf life) of the product is not only the industry norm, but an FDA requirement for some pharmaceutical dosage forms. Viscosity determination conventionally consists of a single-point measurement, quantifying the resistance of a material to flow when exposed to a given level of applied stress. Determination of the rheological properties of semi-solid dosage forms, however, has a number of advantages. For example, it gives an accurate measure of changes in material flow characteristics, determines absolute viscosity rather than relative viscosity, and calculates dynamic properties (visco-elasticity) by evaluating measurements over a range of applied stresses.[1] In addition, the instrumentation available allows data analysis (models, calculations, graphics), provides good temperature control, and is fast and convenient.

In the present case study, three batches of an O/W emulsion manufactured with different level of energy inputs were evaluated. As part of the FDA guidelines, whenever a process for the manufacture of a pharmaceutical semi-solid dosage form/product is transferred from development to commercial scale, the process must be validated. For example, the same formula can be manufactured at three different levels

TABLE 1

Lot	Description	Bulk Viscosity (cP)	Finished Viscosity (cP)
A	Smooth Lotion	17400	20400
B	Smooth Lotion	16000	21867
C	Smooth Lotion	18575	20300

Description, bulk, and finished "Brookfield" viscosities for three lots of O/W emulsion.

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TABLE 2

Lot	Yield Point (Pa)	Mean Yield Point (Pa)
A (Target Batch)	Trial I = 16 Trial II = 12 Trial III = 16	14.7
B (Maximum Energy Batch)	Trial I = 19 Trial II = 13 Trial III = 15	15.7
C (Minimum Energy Batch)	Trial I = 7.2 Trial II = 9 Trial III = 8	8.1

Summary of rheology yield points for three lots of O/W emulsion.

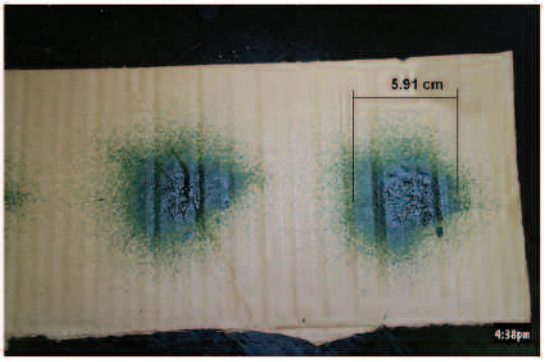
of energy input – a process with target parameters (optimum energy input), a process with approximately 25% lower than target parameters (minimum energy input), and a process with approximately 25% higher than target parameters (maximum energy input). In order for the process to be considered validated and robust, the three lots manufactured at different energy inputs should yield physical and chemical properties well within the set specifications. In the current study, lot A was manufactured with target process parameters, while lots B and C were manufactured with maximum and minimum process parameters, respectively. Although the physical properties (appearance, viscosity, and pH) along with chemical assay levels for the active ingredients were well within specifications for each of the three lots, the lot manufactured with minimum process parameters showed a different spray pattern when dispensed from a spray pump assembly. In this study, rotational rheometry was utilized to determine the rheological properties of each lot and to identify the difference in spray pattern.

EXPERIMENTAL

Materials

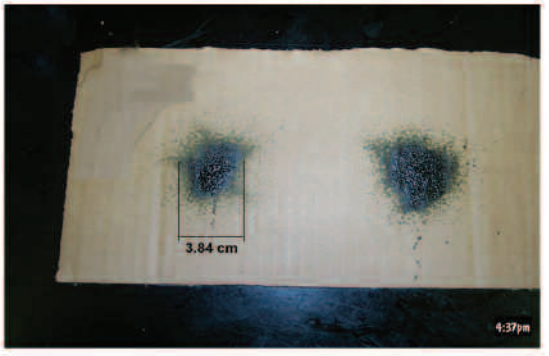
The materials characterized in this study were three different lots of an O/W emulsion. The O/W emulsion was comprised of three phases – an internal oil phase, a continuous water phase, and a suspended pharmaceutical active within the continuous phase. The oil phase and the water phase ingredients were heated to 70ºC to 75ºC. The oil phase was then added to the water phase under high shear mixing. The formulation was allowed to cool to 32ºC under constant low shear mixing. At this stage, the active phase was added and mixed under low shear until uniform. Each lot of the emulsion had the same

FIGURE 1



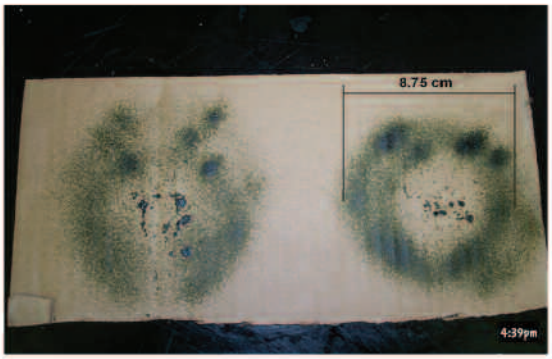
Spray pattern for lot A

FIGURE 2



Spray pattern for lot B

FIGURE 3



Spray pattern for lot C

TABLE 3			
Lot	**Rheology Crossover G' = G" (Pa)**	**Stress Value (Pa)**	**Linear Region of Rheology Plots**
A (Target Batch)	1. 210 2. 290 3. 210	1. 19 2. 21 3. 22	1. 0.1 - 4.0 Pa 2. 0.5 - 6.0 Pa 3. 0.1 - 6.0 Pa
B (Maximum Energy Batch)	1. 220 2. 310 3. 250	1. 21 2. 25 3. 21	1. 0.1 - 3 Pa 2. 0.1 - 7.5 Pa 3. 0.1 - 7.0 Pa
C (Minimum Energy Batch)	1. 72 2. 170 3. 240	1. 8.2 2. 13 3. 19	1. Not linear 2. Not linear 3. Not linear

Summary of rheology crossover/stress value and linear visco-elastic region for three lots of O/W emulsion.

composition, but was produced using a slightly different manufacturing process (different levels of energy input from temperature and shear). The three resulting semi-solid dosage lots were packaged and dispensed using a spray pump.

Conventional Viscometry

Conventional viscosity measurements (also called "Brookfield" viscosities) for the three lots were recorded using a Brookfield Model LVDVI+, spindle LV No. 3, at 3 rpm for 1 minute.

Typically, when developing methods for "Brookfield" viscosity measurements, the settings chosen (instrument, spindle, speed, and time) are such that the readings are stable and represent approximately 50% of the measurement range for that spindle and speed. This allows for any sample-to-sample or lot-to-lot variability to be captured using the selected settings. As "Brookfield" viscosities are "relative," the values obtained with one spindle and/or speed are not directly comparable to another spindle and/or speed.

Rheology

The visco-elastic properties of the three emulsions were investigated using a Thermo-Haake RS 300 Rotational Rheometer with stationary bottom plate and rotating top plate (PP 60 Ti) sensors.

About 4 to 5 g of the product were used for each experimental run. Each test was repeated three times to address experimental variability. In the first series of experiments, test methods for yield point, oscillation stress sweep, and oscillation frequency sweep were developed by optimizing the relevant parameters – gap size between the sensor plates, stress and frequency levels, run-time duration, etc.[2] Once test methods that gave reproducible results had been developed using a representative product lot, a second series of experiments were performed to determine the rheological properties of each of the subject product lots.

The test methods and parameters for the three characterization tests are summarized further. The data for each characterization test was plotted on a log/log scale to cover a wide range of experimental conditions and to enable detailed data analysis to be carried out at low levels of applied stress/low frequencies.

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TABLE 4	
Lot A Versus Lot B	p=0.675 (NS) (power = 5%)
Lot A Versus Lot C	p=0.01 (Sig) (power = 91.7%)
Lot B Versus Lot C	p=0.014 (Sig) (power = 85.1%)

Statistical Analysis of Yield Points

One-way Analysis of Variance (Anova): The difference in the mean values (n=3) among the three lots are greater than would be expected by chance; there is a statistically significant difference ($p < 0.05$) between lots A and B, and lot C.

Where: Lot A = target energy batch; Lot B = maximum energy batch; Lot C = minimum energy batch; NS = Not significant; Sig = Significant

Yield Point Measurement:

- Mode = Controlled Stress, Stress Range = 0.10 to 50 Pa, Frequency = 1 Hz, Gap Size = 1.0 mm, Time = 30 seconds, Data Plotting and Analysis = log/log scale

Oscillation Stress Sweep:

- Mode = Controlled Stress, Stress Range = 0.10 to 50 Pa, Frequency = 1 Hz, Gap Size = 1.0 mm, Data Plotting and Analysis = log/log scale, Number of Steps = 25

Oscillation Frequency Sweep:

- Mode = Controlled Stress, Frequency Range = 0.10 to 10 Hz, Stress = 1 Pa, Gap Size = 1.0 mm, Data Plotting and Analysis = log/log scale, Number of Steps = 9/decade

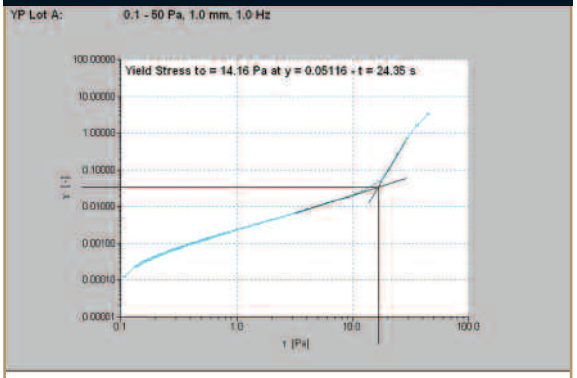
RESULTS & DISCUSSION

Description, bulk "Brookfield" viscosity, and finished (packaged product) "Brookfield" viscosity results for the three lots of O/W emulsion are listed in Table 1. The spray patterns obtained are shown in Figures 1 through 3.

The bulk and finished "Brookfield" viscosity values for each of the three emulsion lots were very similar (within the margin of experimental error). Although the spray pattern for lots A and B were reasonably uniform and desirable (Figures 1 and 2), lot C exhibited wide circles with a void in the center (Figure 3). In order to eliminate any variability in the spray pattern as a result of the type of actuator used, all the aforementioned lots were sprayed using the same spray pump.

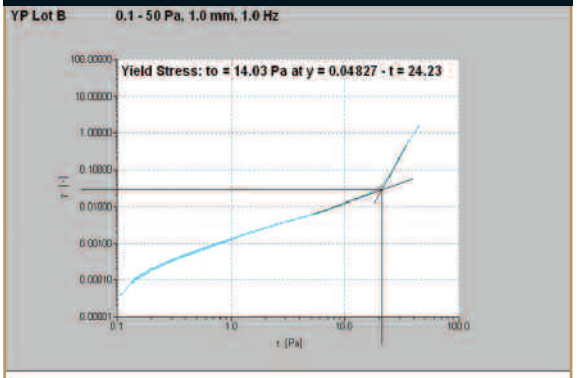
An understanding of the principles of viscosity measurements gives an insight into why different material spray/flow behavior can be obtained from product lots exhibiting similar viscosities. Conventional

FIGURE 4



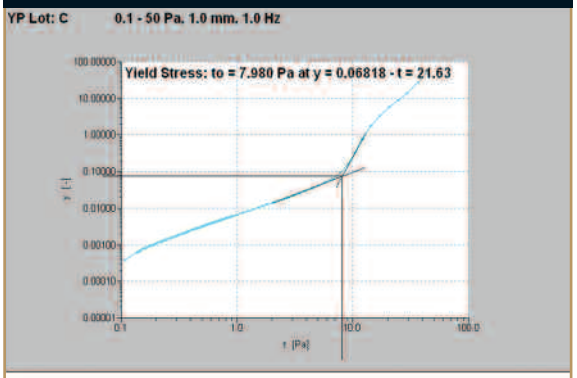
Yield point curve for lot A

FIGURE 5



Yield point curve for lot B

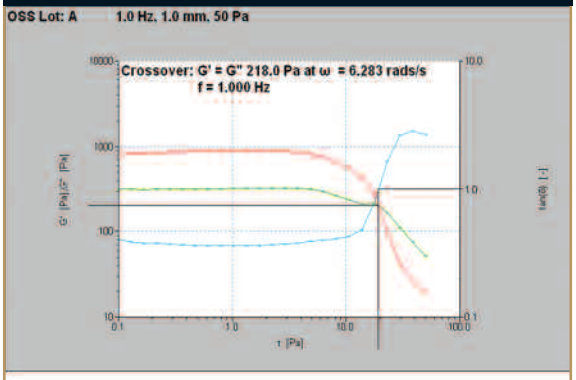
FIGURE 6



Yield point curve for lot C

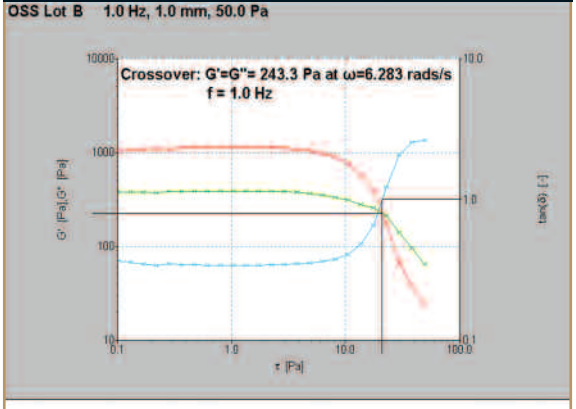
ROTATIONAL RHEOMETRY

FIGURE 7



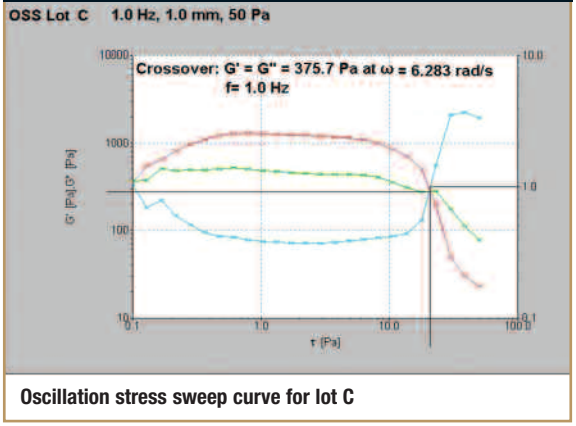
Oscillation stress sweep curve for lot A

FIGURE 8



Oscillation stress sweep curve for lot B

FIGURE 9



Oscillation stress sweep curve for lot C

viscosity defines the resistance to flow using a "one point measurement," where the semi-solid dosage form has been stabilized at a particular temperature. It does not define the effect of stress and/or shear on dynamic properties like visco-elasticity or deformation of the product. As a result, the more extensive principles of rheology were used to explain the undesirable spray pattern obtained with lot C.

The subsequent sections of this paper outline the rheological characterization tests performed, the analysis of this data using graphical models, and data interpretation to explain the differences in the spray properties of each emulsion lot.[2]

Yield Point

The yield point of a semi-solid dosage form is the minimum force required to cause the material to start flowing. On a controlled stress ramp using a rotational rheometer, this is represented by a change in the gradient of the deformation versus stress curve plotted using log/log axes (Figures 4 through 6) (Table 2).

Whereas lots A and B exhibited comparable yield points (lot A = 14 +/- 2 Pa, lot B = 16 +/- 3 Pa), lot C exhibited a statistically significant lower value (8 +/- 1 Pa). (Table 4). The effect of this lower yield point for lot C may have contributed to the observed different spray pattern due to the internal pump pressure generated on actuation of the spray pump assembly being high enough to deform the emulsion.

Oscillation Stress Sweep

Oscillation stress studies allow the product strength and stability to be characterized from dynamic measurements of the visco-elasticity of the material at different stress levels. The parameters of interest are the stress range over which the visco-elastic properties (storage modulus, G' = "elastic" component; and loss modulus, G" = "viscous" component) are linear, the stress value where the visco-elastic curves for G' and G" cross over (ie, where G' = G"), and the ratio of the viscous (G") and elastic (G') moduli when measured within the linear portion of the visco-elastic curve (G"/G' = Tan δ). (Figures 7 through 9) (Table 3).

Whereas lots A and B exhibited linear visco-elastic regions characteristic of stable formulations and relatively consistent crossover/stress values, lot C exhibited neither a linear visco-elastic region nor consistent cross-over/stress values.

In addition, it can be seen that the

values of Tan δ are less than 1 for lots A and B when measured within the linear visco-elastic region. Although there is no linear visco-elastic region for lot C, the value of Tan δ is also less than 1 when measured at low stress levels. A value of Tan δ < 1 shows that the "structural element" (storage modulus, G') is greater than the "fluid element" (loss modulus, G") and is indicative of structural stability within a semi-solid material.[3]

Oscillation Frequency Sweep Curve

Oscillation frequency curves allow the structural conditions of the sample to be determined. The data can be used to distinguish between particle solutions, entangled solutions (pastes), or three-dimensional networks (gels). Furthermore, based on the appearance of the visco-elastic curves, along with dynamic viscosity versus frequency profiles, it is possible to determine if the particles in a semi-solid system are non-associated, weakly associated, or strongly associated. Figures 10 through 12 show characteristic oscillation frequency curves for non-associated, weakly associated, and strongly associated particle systems, respectively. Figures 13 through 15 show the measured oscillation frequency curves for lots A, B, and C.

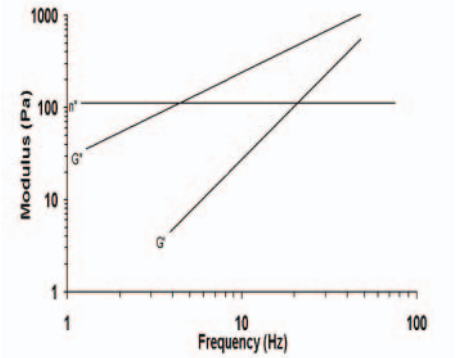
The modulus versus oscillation frequency and dynamic viscosity versus oscillation frequency profiles for the three emulsion lots exhibited the profile characteristic of strongly associated particles, indicating that all three emulsions are structurally stable (Figure 12).[4]

CONCLUSION

A series of rotational rheometry experiments have been performed on three different lots of an O/W emulsion – each of the emulsion lots having been manufactured with different energy inputs. The results of these experiments have shown that the lot that exhibited a different spray pattern, when dispensed from a spray pump assembly, had a significantly different yield point compared to the other two lots (Table 4). One point "Brookfield" viscosity measurements, on the other hand, were unable to distinguish any differences between the three emulsion lots.

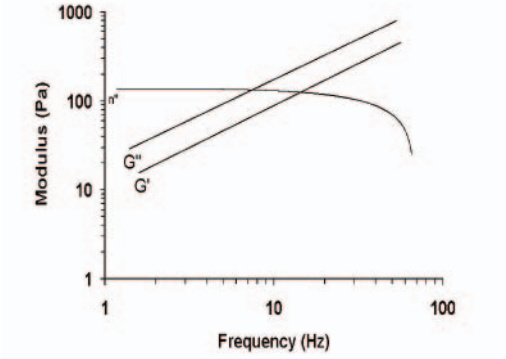
This case study has applied the principles of rheology to help understand the differences observed on spraying a pharmaceutical semi-solid dosage form. The same characterization tests can be utilized to help

FIGURE 10



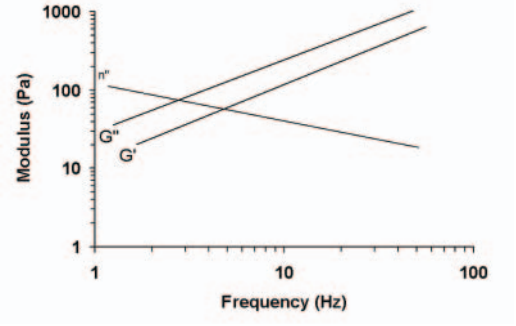
Oscillation frequency sweep curve for non-associated particles[2]

FIGURE 11



Oscillation frequency sweep curve for weakly associated particles[2]

FIGURE 12



Oscillation frequency sweep curve for strongly associated particles[2]

develop stable semi-solid formulations in the research phase – for example to compare and select prototypes, and to predict long-term stability (in conjunction with other physical properties). Rheological experiments can also be used to help evaluate the successful transfer of manufacturing processes from the laboratory to pilot and commercial scales, and to help understand and develop practical "Brookfield" viscosity methods for routine use.

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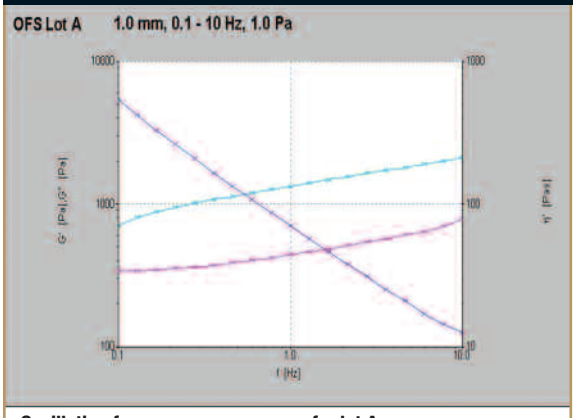
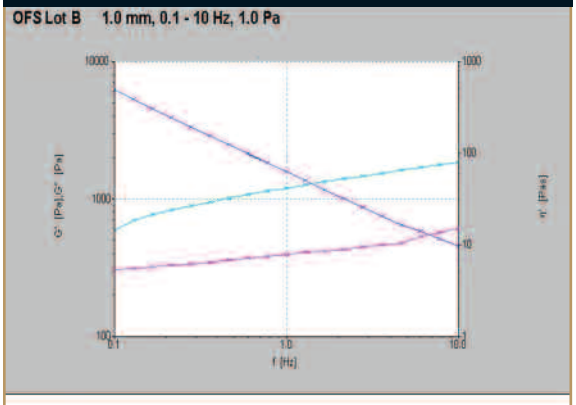
FIGURE 13



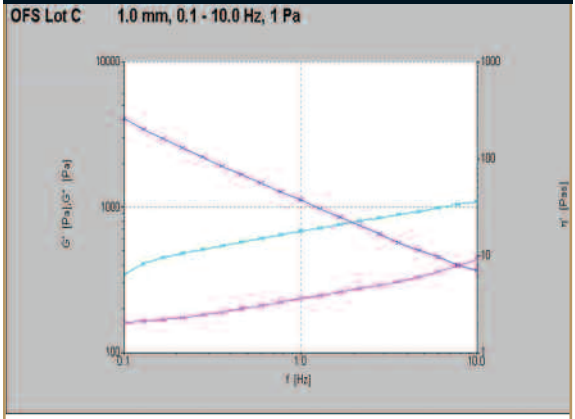
Oscillation frequency sweep curve for lot A

FIGURE 14



Oscillation frequency sweep curve for lot B

FIGURE 15



Oscillation frequency sweep curve for lot C

BIOGRAPHIES

Dr. Charles Shaw is Senior Manager of Formulation Services and Formulation Development and Manager of Research & Development at DPT Laboratories, Ltd., a DFB company. His responsibilities at DPT include managing departmental resources to ensure relevant scientific execution and timely completion of projects; ensuring compliance with relevant internal/external rules and regulations; assisting with the development of the R&D area in line with the strategic direction of the company; and training, development and performance of staff. Dr. Shaw has more than 20 years of experience in pharmaceutical and medical device development and manufacturing, and holds board certifications that include Chartered Scientist; Chartered Chemist; Fellow of the Royal Society of Chemistry, London; and European Chemist. Before joining DPT in 2004, he was a Product Development and Technical Services Manager with Smith & Nephew. He earned a Ph.D. in Chemistry and a BS in Chemistry with honors from the University of Hull, England.

Shravan Parsi until recently was a Formulation Development Scientist at DPT Laboratories, Ltd., a DFB company, on a team responsible for product development of pharmaceutical ointments, creams, lotions, gels, and other semisolids. He is a member of the American Association of Pharmaceutical Scientists and the Indian Pharmaceutical Association. He earned a MS in Industrial Pharmacy from St. John's University in Queens, N.Y., and a BS in Pharmacy from the College of Pharmaceutical Sciences in Manipal, India.

MULTI-TARGETED INHIBITORS

Beyond-Steroids: A Unique Biotech/ Specialty Pharma Approach to Rethinking Respiratory Treatments

By: G. John Mohr and Thomas K. Garver

INTRODUCTION

Chronic Respiratory Diseases (CRD) are disorders of the airways and other structures of the lung largely related to the presence of persistent inflammation. Some of the most common diseases are asthma, chronic obstructive pulmonary disease (COPD), respiratory allergies, and occupational lung diseases. The development and approval of inhaled corticosteroids in the 1970s and 80s introduced a new age of therapy in treating chronic inflammatory lung diseases. This was the first time that an anti-inflammatory product was available to reduce lung inflammation in airways and the associated obstruction ("swelling"), inflammation, hyper-responsiveness ("twitchiness") characteristic of asthma. Fast forward 30 years — corticosteroids are still the mainstay of treatment for inflammatory lung disease, largely defined as asthma and COPD. Unfortunately, these drugs never lived up to their early promise of reversing lung disease. New drug therapies in this category have been largely measured by improvements to older medications; the use of combination therapy for additive effects; and improved "user-friendly" delivery devices for better compliance. While these step-wise improvements are welcomed by patients and commercially successful for drug manufacturers, the pace of innovation has been slow, and a large number of patients still suffer from uncontrolled symptoms and disease progression.

A novel approach to designing and developing new medications for chronic respiratory disease is being pursued by TOPIGEN, a specialty biopharmaceutical company. TOPIGEN is developing therapies that have improved anti-inflammatory properties for targeting the source of lung inflammation — drugs that go beyond the anti-inflammatory properties of today's corticosteroids. It's a unique business approach that combines the development skills of a Specialty Pharma company with the innovation of biotechnology.

INFLAMMATORY LUNG DISEASES — ROLE OF CHRONIC INFLAMMATION

Inflammation is a natural process of our body's defense designed to protect us from physical damage and infection from foreign substances, such as bacteria and viruses. The primary objective of inflammation is to isolate, localize, and eradicate foreign substances and repair damaged tissues. Chronic inflammation is an inflammatory response lasting often for weeks, months, and years. The nature and extent of chronic inflammation varies greatly, and often depends on a balance between the agent causing the inflammation and the attempts of the body to remove it. In many diseases, the presence of chronic inflammation leads to severe complications of disease, such as damage, narrowing, and remodeling of lung tissue. In recent years, the role of chronic inflammation has become widely recognized in pulmonary diseases.

Airflow obstruction and airway inflammation are features of asthma as well as COPD. Both diseases are chronic respiratory diseases with complicated abnormal biological response to inflammation at the cellular level in lung tissue. Each involves different inflammatory mediators. While bronchial asthma is predominantly characterized by an

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Add up all the advantages. Expect higher sales...and high margins!

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

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

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

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

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

Compounds
Deliver Pharmaceutical, bio-pharmaceutical and nutraceuticals in a single dosage form.

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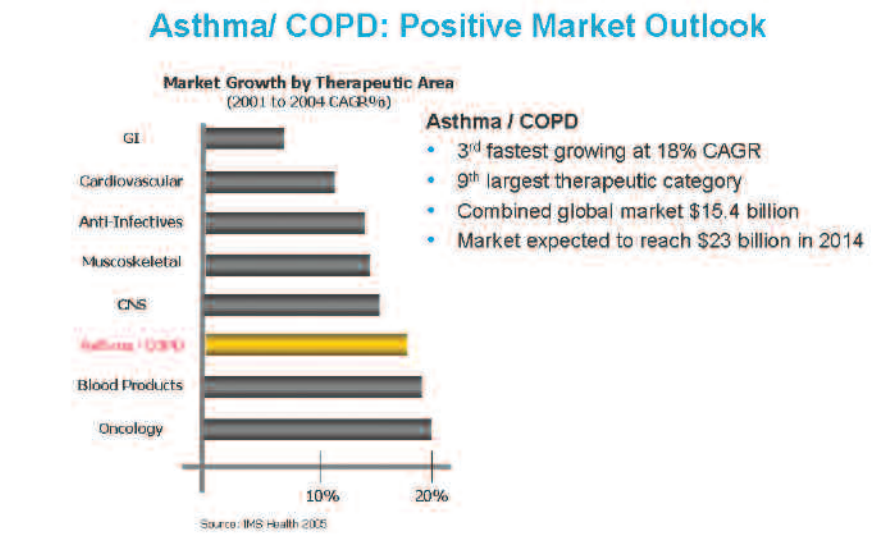
eosinophilic inflammation, neutrophils are believed to play a major role in the pathogenesis of COPD. In asthma, obstruction and intermittent episodes of bronchial hyperresponsiveness are present. Air flow is obstructed to a varying degree, but it is reversible. COPD is a disease characterized by persistent and progressive airflow reduction that makes it difficult to move air in and out of lungs. Unlike asthma, airway obstruction is not reversible in patients with COPD. The disease is classified as a combination of chronic bronchitis and emphysema. Emphysema is primarily caused by tobacco smoke reducing elasticity of tissue in the lung, increased airway resistance, and an inability expel air from the lungs. As the disease progresses, the airways of the lungs become inflamed and obstructed. Chronic airflow limitation is believed to be a consequence of an abnormal recruitment of inflammatory cells, such as neutrophils (cells releasing enzymes that destroy lung tissue) and response to exposure to cigarette smoke. Acute exacerbations are the most common complication and a primary contributor to morbidity and mortality.

MARKET LANDSCAPE

The incidence of both asthma and COPD has been described as epidemic. Across the seven major drug markets, it is estimated that 53 million individuals suffer from asthma. Similarly, it is estimated that 57 million people suffer from COPD in the top seven markets. The incidence of these two diseases is increasing at an alarming rate. Net growth in the rate of prevalence for these two diseases is projected to be in excess of 10% through 2011 (Source: NHIS 2003, LAIA 2003). More concerning are the upward trends in diagnosis of these two diseases in select patient populations. In the US, pediatric asthma has increased in many locations at a rate of more than 20% annually.

FIGURE 1



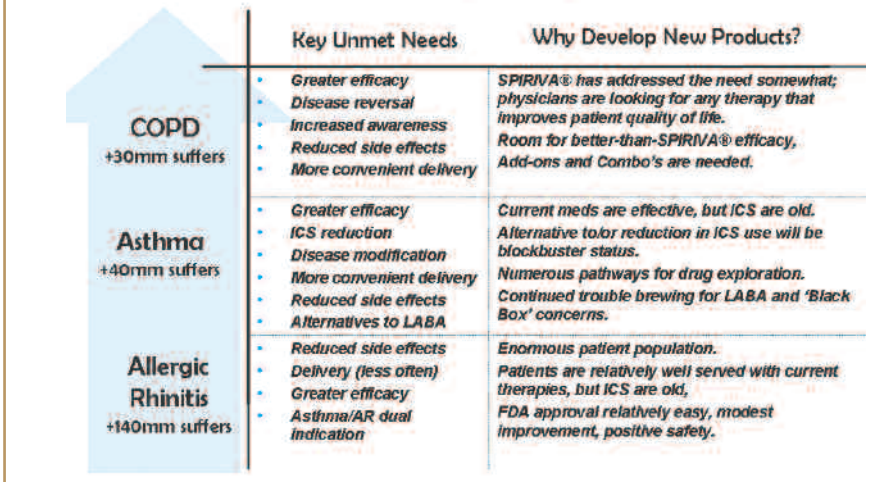
The market for asthma and COPD is now the third fastest-growing market in revenues, growing at a rate of 18% annually. The category is the ninth largest worldwide at $15.4 billion in revenue, expected to reach $23 billion by 2014.

UNMET MEDICAL NEEDS

Despite the widespread use and commercial success of inhaled corticosteroids, there remains significant medical need for improvement to drug therapy. In the US, the need can be measured in terms of lost days to work — now totaling 15 million days annually for asthma alone at a cost of $2.5 billion. In COPD, the need for improved drug therapy is far greater. Approximately 10% of the US population over age 45 now suffers from COPD, and the disease is projected to be the third most common killer in the US and the developed

MULTI-TARGETED INHIBITORS

FIGURE 2



Significant unmet needs exist in respiratory disease market. Companies with innovative and effective products will likely benefit from pricing power over competitive products.

world by 2020.

The science and understanding of cellular mechanisms underlying the inflammatory process in CRDs have significantly improved since the introduction of inhaled corticosteroids. Today, there are validated cellular pathways of inflammation and novel chemistries for better targeting inflammatory response cells (such as eosinophils, mast cells, T-lymphocytes, and neutrophils). The mono-target era of designing "one target for one disease" has evolved. Complex diseases require multiple approaches to circumvent the cellular signaling redundancy underlying inflammatory conditions. Most experts agree that in order to treat chronic inflammation, a single drug targeting multiple targets and pathways would be better at arresting progression of respiratory diseases and be an important advancement in current therapy. Moreover, there is a need for innovative products with a novel mechanism of action to complement today's inhaled products, particularly for patients who grow resistant to available steroids.

STATE-OF-THE-ART TREATMENT OPTIONS

Corticosteroids — Steroids are the hallmark of treatment of the inflammatory process as is expressed in their ever-increasing share of market as a therapeutic agent (used alone or as fixed combinations with long-acting beta agonists). For years, the use of steroids by the inhaled route was controversial due to fear of untoward long-term side effects. In addition, steroid-resistant patients are fairly common in clinical practice, and steroids are not effective in controlling the long-term progression and reversal of chronic respiratory diseases.

Leukotriene Receptor Antagonists — LTRAs competitively block leukotriene receptors, which are a subset of a large number of chemical mediators of asthma on bronchial smooth muscle, thus inhibiting or retarding inflammation. The first LTRAs introduced were associated with significant side effects and compliance issues. However, the introduction of Merck's SINGULAIR® (montelukast), with its superior safety profile and oral once-a-day dosing, has significantly expanded the use of this class of drugs for most patients. Efficacy, though, is still far from optimal, and montelukast is typically used concomitantly with corticosteroids in order to more fully mediate the inflammatory process.

Anti-IgE — Or XOLAIR® is a genetically engineered protein that blocks the inflammatory immune response and has been cited as one of the major breakthroughs in asthma and allergy treatment throughout the past 30 years. It is different from other treatments because it actually stops the allergic reaction before it begins by blocking the IgE antibody, an

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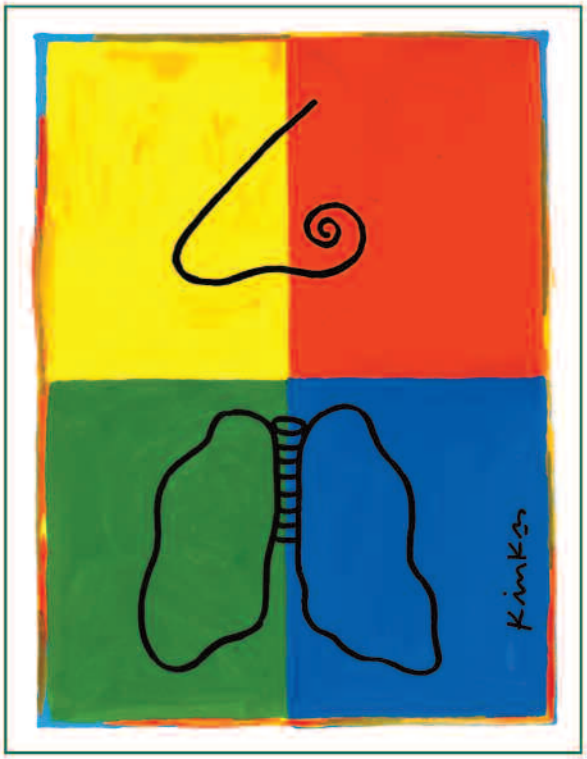

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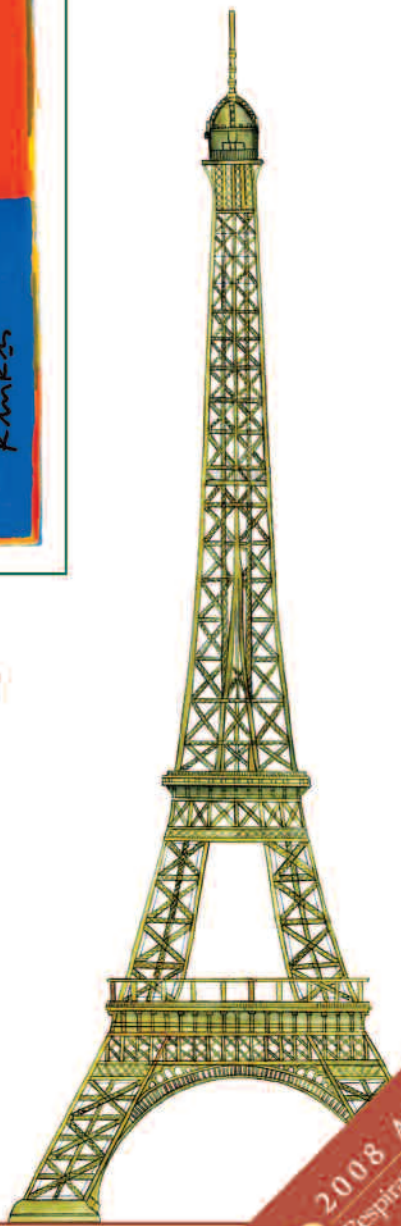

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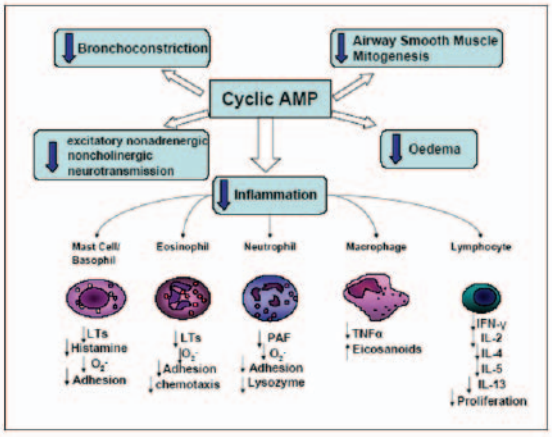
underlying cause of allergic asthma. However, the drug is not practical for most patients due to its administration by injection every 2 to 4 weeks and a cost of therapy upward of $13,000 annually for severe cases.

PDE Inhibitors — Nonselective inhibitors of cyclic nucleotide phosphodiesterase (PDE), such as theophylline, have been used for the treatment of obstructive airways diseases for several decades. Renewed interest in the pharmacology and clinical effects of this class of drugs is based largely on advances in the knowledge and understanding of the PDE isoenzymes, which represent one of theophylline's biochemical targets. PDEs are a family of enzymes that catalyze the degradation of cAMP and cGMP. PDE4 refers to an immunologically and pharmacologically distinct family of enzymes that, in humans, are encoded by four genes (PDE4A, PDE4B, PDE4C, and PDE4D). Inhibitors of these enzymes have absolute specificity for up regulating cAMP and are considered potential therapeutic targets for the treatment of chronic inflammatory disorders (Figure 3).

The development history of PDE4 inhibitors has been one of high hopes followed by great disappointment. PDE inhibitors act by inhibiting various enzymes involved in the inflammatory process in lung disorders. Most attempts at development have been in oral formulations and, unfortunately, side effect profiles have been such that many of these compounds have been abandoned. A number of products continue in development, but the history would indicate moderation in enthusiasm for success. Some physicians believe that PDE4 inhibitors are a case study in support for local lung delivery of therapeutics rather than the systemic delivery of oral compounds.

FIGURE 3

Effects of Elevating Cyclic AMP (cAMP) in Asthma and COPD



Effects of cAMP elevation by selective PDE4 inhibitors with relevance to the treatment of bronchial asthma and COPD.

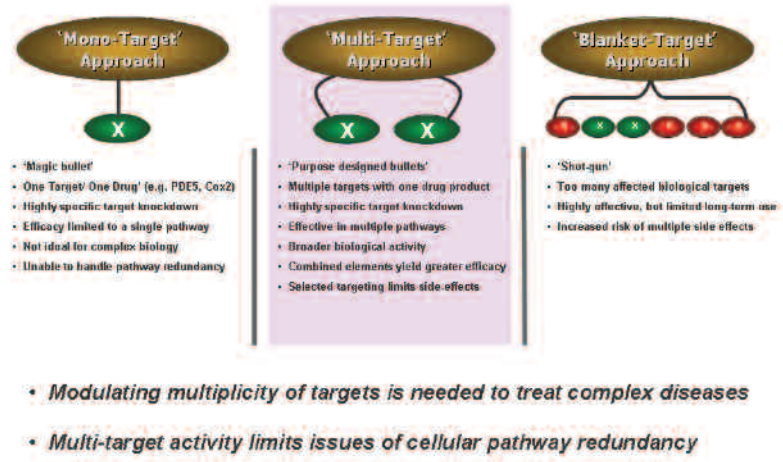
EMERGING TREATMENT OPTIONS

Importance of Topical Delivery

The advent of pulmonary delivery of compounds and new improved inhaler devices to better deliver drugs directly to the site of local activity in lungs has revolutionized the treatment of asthma and COPD. Through a combination of new more potent chemistry, improved formulation capability, and highly efficient devices, better inhaled products are projected to significantly improve outcomes in CRD. The lungs are a unique portal for topical absorption of drugs. Delivered properly, inhaled drugs are easily taken up by cells in the lung lining and make their way to inflammatory receptor sites directly in the epithelial layer. In the case of many new potent therapies, drugs can act locally, minimizing systemic distribution and the potential for adverse effects.

MULTI-TARGETED INHIBITORS

FIGURE 4



The era of designing a "magic bullet" to knock-out or treat chronic diseases is ending. A multi-targeted strategy is a more rational approach to drug targeting and treatment of chronic inflammatory conditions. Advances in chemistry and the use of RNA-targeting drugs allows "purpose-designed bullets" in CRD thereby minimizing untoward systemic side effects.

New & Better Multi-Targeted Approaches

In the past decade, new and potentially better cellular pathways have emerged for targeting drugs in the inflammatory process. The ability of drugs to inhibit the inflammatory response of specific mediators in multiple pathways has also been shown to be "synergistic" in arresting the cycle of chronic inflammation. Why? Once activated, certain mediators will recruit additional inflammatory mediators to the lung. Therefore, the ability of a treatment to inhibit multiple specific mediators is more likely to show improved anti-inflammatory activity over compounds that are narrowly focused on one inhibitory pathway.

At TOPIGEN, discovery efforts in CRD are uniquely focused on inhibiting multiple pathways of inflammatory cell activation and recruitment in the lungs. This multi-targeted approach (Figure 4) to drug development has shown highly specific target knockdown, often resulting in broader biological activity over mono-targeted drugs without the off-target effects associated with "blanket-targeted" corticosteroids.

Examples of several promising multi-targeted drugs currently being pursued are discussed further.

NITRIC-OXIDE (NO) DONATING BUDESONIDE (TPI-1020)

One novel inhaled drug approach that combines the benefits of corticosteroids with the specificity of a neutrophil inhibitor is TPI-1020, a nitric-oxide (NO) donating form of budesonide (Figure 5). NO is a well-known intra- and extra-cellular messenger that mediates diverse signaling pathways in target cells and is known to play an important role in modulating inflammatory responses underlying COPD and asthma. Budesonide (marketed by AstraZeneca as PULMICORT®) is a widely prescribed off-patent corticosteroid. Chemically linking NO-donors to budesonide can be performed to create an entirely new drug with known properties of budesonide plus the added benefits of NO. The resulting new compound has a distinct pharmacologic profile with pronounced anti-inflammatory effects targeting an important pathway for neutrophil influx in lung tissue. Such modified compounds are attractive commercial candidates, particularly for Specialty Pharma companies that can quickly develop these improvements on well-known drugs while lowering the unknown development and toxicology risks associated with totally new compounds.

RNA-TARGETING OLIGONUCLEOTIDES

RNA-targeting oligonucleotides are chemically modified molecules that are designed to bind to a specific sequence of a messenger RNA(mRNA)'s target through base-pairing interactions, thereby interfering with expression of the protein encoded by the mRNA.

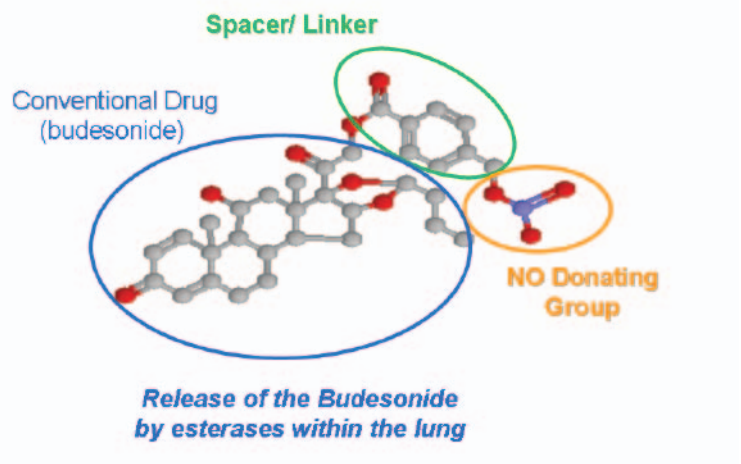
MULTI-TARGETED INHIBITORS

TOPIGEN's scientists are using RNA-targeting oligonucleotides to design new, more effective drugs to inhibit gene expression and production of abnormal levels of cell proteins involved in inflammatory diseases. The rationale for designing drugs with synthetic oligos is the ability to generate specific inhibitors for select target genes and to combine multiple sequences in one drug product to knock down several distinct and overlapping pathways. These drugs are easily inhaled and taken up in lung tissue without reaching levels in systemic circulation, often with potency and duration of activity to support microgram dosing levels in CRD.

One such novel RNA-targeting drug candidate for asthma is TOPIGEN's inhaled TPI-ASM8. The drug candidate consists of two modified RNA-targeting oligonucleotides designed specifically to reduce the recruitment and persistence of chronic inflammatory cells, key components underlying the cause of the disease. Using a proprietary antisense chemistry designed for the lungs, TPI-ASM8 targets two distinct cellular pathways involved in allergic airway inflammation by inhibiting the recruitment of allergic inflammatory cells (eosinophils) via the CCR3 receptor and reducing the persistence of allergic inflammatory cells via inhibition of a common beta sub-unit for the receptors of interleukin (IL) 3, 5, and GM-CSF. In a recent proof-of-principle allergen challenge trial, TPI-ASM8 has shown protection against early- and late-stage allergic responses in patients with asthma with substantial reductions of eosinophil cell levels and suppression of target gene expression. The drug was deemed safe and well tolerated.

FIGURE 5

Phase II Compound: TPI-1020
(New Inhalation Drug Candidate for COPD)



TPI-1020 is a nitrate oxide moiety linked to another active structure (budesonide). In vivo, the drug releases NO to provide synergistic anti-inflammatory effects beyond budesonide alone. The compound was designed by NicOx S.A., a leader in the field of creating hybrid NO-releasing molecules that harness the beneficial effects of NO.

TPI-ASM8 has a unique profile for respiratory products with potential to address a significant unmet need in the category, notably:

- First RNA-targeting inhibitor to demonstrate efficacy in respiratory disease
- Designed to inhibit multiple inflammatory cytokines
- Unique mechanism of action, different from available treatments
  - Non-steroidal
  - Non-biological
  - Non-immunostimulant
- Inhaled once-a-day dosing
- Potential alternative or complement to inhaled corticosteroids

TOPIGEN is planning an expanded Phase II study to further investigate TPI-ASM8 in 2007.

Another emerging therapy is TOPIGEN's inhaled TPI-1100, a selective and dual-acting RNA-targeting oligonucleotide inhibitor of phosphodiesterase isoforms PDE4 and PDE7. TPI-1100 targets validated genes for inhibition of PDEs known to be linked to progressive airway inflammation and remodeling in COPD. Delivered topically via aerosol

to the lungs, the drug is expected to provide local anti-inflammatory effects without the dose-limiting systemic side effects widely associated with known small molecule inhibitors of PDE. Clinical studies are expected to begin in 2007.

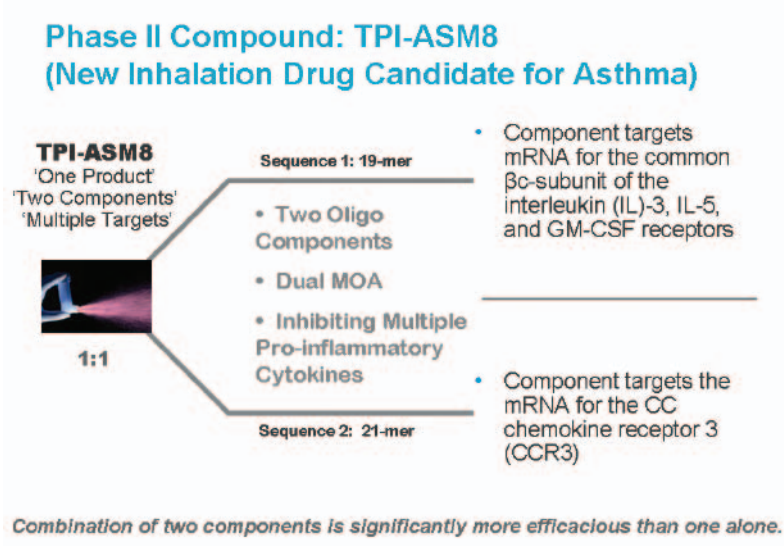
USING THESE EMERGING DRUGS

The rationale for developing these new specific and multi-targeted inhibitors is to provide a new class of anti-inflammatory agents that act more broadly on the underlying inflammatory triad: recruitment, activation, and potentiation of processes in chronic respiratory diseases. While designing replacements for inhaled corticosteroids is the challenge for drug developers, it is likely that these novel multi-targeted inhibitors will also enhance the efficacy of conventional respiratory therapies particularly for advanced stages of disease. Such novel approaches offer the promise of moving beyond steroids in CRD by reducing the abnormal, persistent, and damaging effects of inflammatory conditions underlying asthma and COPD.

ACKNOWLEDGMENTS

Special thanks to Dory Valiquette at LaVoie Communications Group for assistance in preparating this manuscript.

FIGURE 6



TPI-ASM8 is the leading RNA-targeting drug currently in man for the treatment of asthma. The drug blocks multiple gene pathways involved in recruitment and activation of chronic inflammation. Delivered by inhalation, the drug has shown efficacy in an allergen challenge proof-of-principle trial.

BIOGRAPHIES

G. John Mohr is Chief Business Officer at TOPIGEN Pharmaceuticals, Inc., a Montreal-based biopharmaceutical company focused on the discovery and development of innovative respiratory products for asthma and COPD. Mr. Mohr has more than 20 years of industry experience in the life sciences area. Before joining TOPIGEN, he served as Officer and Vice President of Licensing and Business Development for Atherogenics. Previously, he was Head of US Operations for Fournier Pharma, where he held responsibilities for US commercial and development activities, including the successful partnering and introduction of TriCor®, a billion dollar cardiovascular agent. Prior experience includes executive management positions at Merck & Co., including Worldwide Head of Marketing for Pepcid®. He has substantial experience in managing and licensing advanced biopharma technologies as both operating executive and commercial strategist. He currently serves as a member of the Business Development Roundtable for the Biotechnology Council of New Jersey (BCNJ) and a member of the Licensing Executive Society (LES). Mr. Mohr earned his BS in Finance/Accounting from Drexel, and he is a Certified Public Accountant.
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Mr. Thomas K. Garver, a 30-year veteran of the pharmaceutical industry, is the owner of Thomas K. Garver HealthCare Consulting, located in Rochester, New York. His background includes marketing research, product management, business development, and licensing experience with CIBA, Bristol Myers Squibb (both at the Westwood Dermatology and Bristol Laboratories divisions), Armour Pharmaceuticals, Pennwalt Pharmaceuticals, and Fisons Corporation. Beginning in 1981, he held executive positions at Pennwalt and its successor Fisons in marketing, business development, and licensing. In 1995, he founded his consulting business, from which he took a hiatus, in mid-2004 until mid-2006 as the Vice President Commercial Development for MAP Pharmaceuticals, which he co-founded. He has now reopened his consulting business. Mr. Garver earned his BA from Drew University and his MBA from Columbia University. He can be reached at 585-467-8797, or at tgarver@rochester.rr.com

TOPICAL DELIVERY

Utilizing Topical Delivery for Topical Diseases

By: Craig Dees, PhD

INTRODUCTION

The current trend in treating a number of serious, chronic skin conditions like psoriasis and eczema is to deliver the drug via a systemic route. I think this may be cause for concern. Perhaps because of my early experience in the area of biologics and vaccine production, I have a heightened awareness of the potential dangers posed by selecting the wrong route of delivery. I may also be focused on how efficacy can be enhanced by judicious choice of route of delivery.

I remember very clearly what happened a number of years ago when the company I worked for was in a race against a much bigger competitor to produce a vaccine against Canine Corona Virus (CCV). Our sales force couldn't match the resources of the larger competitor. We also couldn't afford the pricing and other incentives a large company could offer to capture market share. The first one to market would likely capture the greatest market share and maintain it, so getting the vaccine out first was critically important. Our problems were compounded by our research and development efforts starting about a year after the big company started their project.

It's important to understand a few points about CCV to appreciate why route of delivery was critically important. The disease causes a mild gastroenteritis that generally lasts about 3 days. Therefore a vaccine was needed that has virtually no risk associated with its use. Unfortunately, killed-virus vaccines, which provide such risk profile, usually don't provide the protection afforded by more complicated, modified-live vaccines. Because CCV usually isn't life threatening, I chose an easy and quick formalin-killed CCV vaccine that could be safely delivered by intramuscular injection. My competitor chose to make a modified-live vaccine. If I had made live CCV vaccine, I would have delivered it orally. The competitor attenuated the live virus and delivered it by intramuscular injection. It turned out that even the weakened CCV, when delivered IM, caused encephalitis and a huge liability problem. In contrast, my vaccine worked well and caused no problems. The CEO took notice of this at the yearly manager's meeting and complimented me, saying, "It's a heck of an accomplishment to make a great selling vaccine for an insignificant disease." His statement was a bit of hyperbole, but this case illustrates how selection of the proper route of delivery can make a huge difference in the safety, effectiveness, and value of a pharmaceutical product.

It doesn't matter if it's a vaccine, a biologic, or a small molecule pharmaceutical – it's critical that the route of delivery is carefully chosen to provide the highest levels of safety and efficacy. The best way to do this for skin conditions seems to be exactly opposite current trends. Most often, topical diseases are best treated by direct topical application to the diseased tissue.

COMMON SENSE THEOREM FOR DRUG DELIVERY

A central theorem for drug delivery should be, "No matter how safe the medicine, if it's delivered systemically, the associated risks will be higher than if delivered directly to the site of the problem." Alternatively stated, the chance of something going wrong, even if improbably low, increases with the dose of the medicament applied and/or the amount of tissue to which it's applied. Mathematically, this would look something like theorems governing chance and probability, whereas X tends toward infinity, and any Y tends toward 1. Change the X value to concentration of drug or put in an ever-increasing value for the body area affected and voila, the chance of any adverse event happening becomes significant. You can take your choice on what type of adverse event occurs. It's poor drug design to hope the magnitude and consequences of the event Y are low. Thus, even a very good drug, when delivered systemically at a high dose, may cross a threshold where rare adverse events become commonplace.

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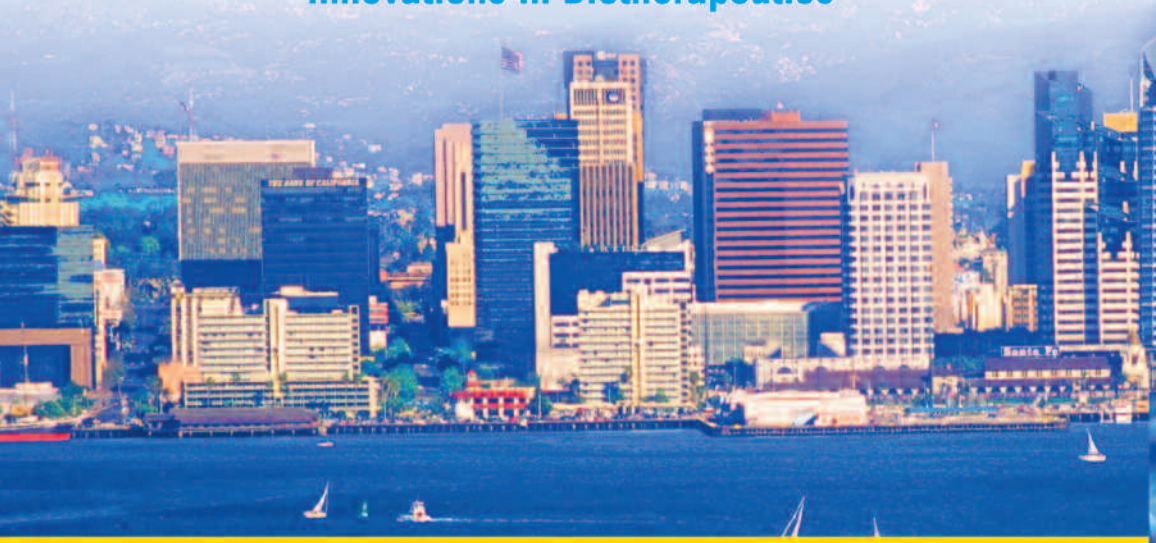

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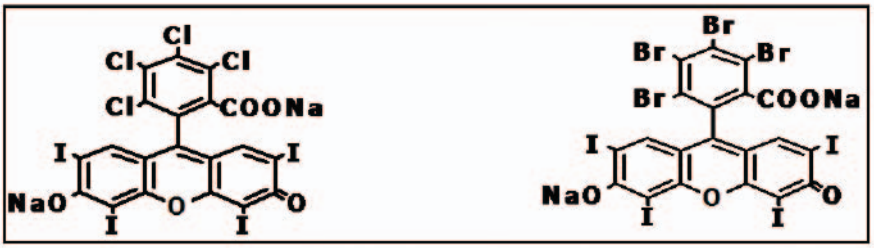
TOPICAL DELIVERY

If a drug is delivered only to the affected area, one might also predict that there will be a corresponding increase in efficacy. The combination of increased safety and efficacy certainly should make localized delivery a method of choice for drug delivery. However, despite the common sense maxim that the best and safest method for treating topical disease is achieved via a topical route, current trends in care for topical diseases like psoriasis and eczema are predicated on systemic delivery. For example, a common treatment of psoriasis is photodynamic therapy wherein psoralen is activated by ultraviolet light. Psoralen can be delivered to the body by systemic or topical administration. Without debating the relative efficacy of topical verses systemic administration, the relative safety of delivering psoralen via the systemic route is likely to be much lower than delivering it topically only to affected areas. Psoralen, when activated by ultraviolet light, creates a covalent bond between opposing strands of DNA. The effects of psoralen are not confined to diseased tissue. Promiscuous cross-linking of the genetic material can occur wherever the drug is present in skin. Therefore, a predictable, and unfortunately more common than necessary, side effect of photodynamic therapy using psoralen is development of cancer as a result of damage to genetic material.

FIGURE 1



Two halogenated xanthenes useful for treating topical diseases, including psoriasis, eczema, and infections of the skin. PV-10 (left) and PV-12 (right) target only diseased tissue or infectious agents. PV-12's photodynamic yield is greater than that of PV-10, as is its radiodensity with ionizing radiation. Therefore, PV-12 may have more utility as a topical agent activated by ambient light and as a diagnostic agent.

SIDEBAR 1

"Those that forget history are doomed to repeat it." Whoever made this statement wasn't specifically targeting the warning to those of us in medicine. However, he could have done so. The current trend in the delivery of medicaments for topical diseases is ever more often to do so via a systemic route of delivery. Systemic delivery is considered to yield more uniform delivery and enhanced patience compliance. Further, the mechanism of action of a number of new dermatologic medicaments is based on selectively "knocking out" certain elements of the immune system. However, even if confined to certain subsets of the immune system, these elements may ultimately prove critical to the body's defense from a wide variety of attacks.

Previously, it was in vogue to surgically remove elements of the immune system. For example, because the thymus gland undergoes involution throughout life, it was thought to be "vestigial," and it became popular to surgically remove it. However, whether it's involuted or not, it's now clear that the thymus plays a critical role in sorting immunocompetent cells produced by bone marrow, and it is central to sorting clones for self-and non-self reactions and affinities. Therefore, over time, it was noted that people who had been thymectomized had a higher incidence of viral, fungal, and neoplastic disease.

Though we are not performing these surgeries today, we are attempting to accomplish similar goals using chemical or biotechnological means. Results similar to those of the cruder surgical methods are likely.

THE TREND FOR TOPICAL DISEASES IS SYSTEMIC DELIVERY

The problems associated with systemic delivery are further amplified if the agent doesn't selectively target diseased tissue or cells. The treatment of psoriasis or eczema has long been predicated on delivery of a potent immunosuppressive agent. These agents, like hydrocortisone, are potent broad-spectrum inhibitors of the immune system. Generally, they act by inducing lymphocytes to commit suicide (apoptosis). Unfortunately, the suicide command that they give to lymphocytes isn't confined to those subsets of cells involved in the disease alone. All lymphocytes, classes and subclasses, may be affected to a greater or lesser extent depending on their type and state of activation. Therefore, steroidal immunosuppressive agents act by inducing a widespread state of immunosuppression not confined to the diseased tissue or even to the cells involved in the disease. Thus, the agents can induce generalized immuno-incompetence to bacterial, viral, fungal, and neoplastic diseases.

New systemic approaches for treatment of topical diseases are intended to limit action to certain immune system components. These medicaments can be small molecule agents or of biotechnology origins. For example, systemically delivered monoclonal antibodies are being used against certain lymphocyte subsets attempting to modify a specific immune response. Even if the resultant

SIDEBAR 2

Recently, I was asked by a neighbor about a recommendation to remove her 15-year-old daughter's tonsils. The first thing that gave me pause was that the recommendation for surgery had come from a relative who worked for the child's pediatrician. This particular person is a vocal advocate of any type of surgery imaginable and has had just about every surgical procedure needed or elective (with some debate about what was needed). I had a short discussion with the mother explaining that the tonsils were an integral component of the immune system and just cutting things out of the immune system wasn't a good thing to do. I suggested she get a second opinion from an unrelated physician before proceeding. Unfortunately, the child's father took the advice of the relative and allowed the child's tonsils to be removed.

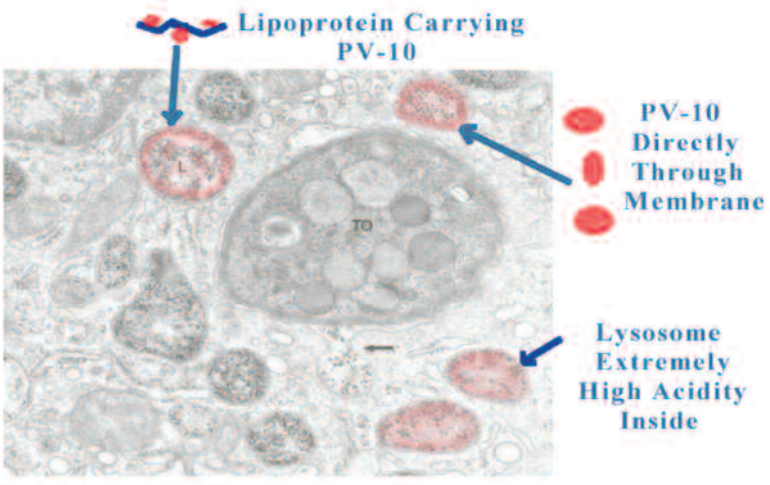
Just before the surgery, I received a second call. The mother said the child had a cold and asked if they should proceed with the surgery. I recommended that she wait due to the risk of spreading a virus through the lungs if certain anesthetic procedures were used. I also suggested once more not to heed my opinions, but to seek the advice of another pediatrician. The surgery took place anyway and the child proceeded from a slight upper respiratory infection to a generalized viral pneumonia compounded by a secondary bacterial infection. The child became severely ill and spent weeks in the hospital.

The specialist in infectious disease that treated the pneumonia did his best not to criticize his colleagues. However, on several occasions, he commented on the bad choice to perform a tonsillectomy, and the criticism was interlaced with numerous deprecations of intelligence and character of those who put the child at risk with an ill-advised surgery.

The first error causing this cascade of adverse events was the decision to surgically remove part of the child's immune system. Several of the physicians brought in to treat the pneumonia were very vocal about the bad decision to remove the tonsils and especially during the course of an upper respiratory infection. Fortunately, the adverse effects due to poor decisions about the immune system were detected immediately. Otherwise, they might have cost the 15 year-old honor-student-athlete her life.

This example is heuristic for the pharmaceutical industry: both systemic delivery and destruction of immune system components for treatment of topical diseases can pose unnecessary risks of serious adverse effects that may not be noticed for years.

FIGURE 2



One of the potential pathways used by PV-10 and PV-12 to enter diseased cells and be delivered into the lysosomes.

immunosuppression could be confined only to the desired subset of lymphocytes, these cells have an important function in maintaining the body's defenses against a wide variety of attacks.

As was the case with indiscriminant removal of the tonsils, appendix, and thymus, we may find that there are long-term consequences of removing parts of the immune system via chemical or biotechnological means. One might predict that just as we found a higher incidence of cancer and infection in thymectomized patients, in the future, something similar may be noted in patients treated with "high-tech" removal of parts of the immune system. In fact, black box warnings have already been applied to a number of the new medicaments for topical diseases based on increased incidence of certain cancers.

DISEASE-SPECIFIC MEDICAMENTS FOR TOPICAL DISEASES

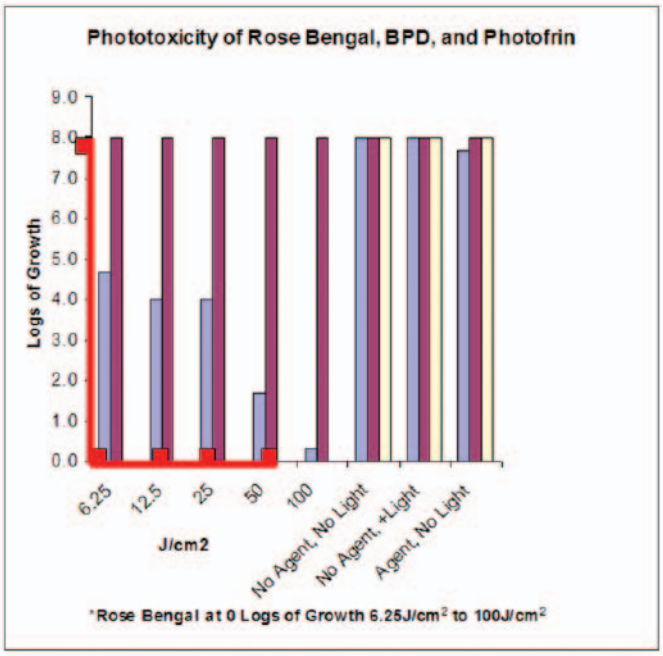
One of the most pressing problems in the treatment of chronic skin diseases like psoriasis or eczema is that current drugs do not specifically target only the diseased tissue. Compound this by delivering the drug systemically, and the adverse effects associated with any drug's use will increase, and life-threatening consequences may result. To solve these problems, the drug must affect only the diseased tissue or cells. Limiting the tissue exposed to the drug is a simple and effective way to achieve this.

A standard treatment for psoriasis utilizes photodynamic therapy (PDT) with psoralen. Although a large number of new photodynamic agents have been developed, use of these new agents has been limited due to a wide variety of problems, and none are likely to displace psoralen in the foreseeable future. Poor penetration of light into tissue (no matter what wavelength), dependence on uniform tissue oxygen levels, and poor cross-section for light are among the problems that have limited PDT's general acceptance. However, these problems are dwarfed by the failure to design PDT agents that act only on diseased tissue.

The first and foremost problem is that all currently available PDT agents for topical or systemic diseases are similar to current treatments for cancer – their effects are not adequately localized to diseased tissue. This limits efficacy (because they can't be used at levels capable of delivering maximum therapeutic effect) and creates unacceptable levels of adverse effects.

One example is the recent attempt to treat actinic keratosis with agents not specific for the diseased tissue. One compound used to treat this disease had to be applied using a device resembling a magic marker with instructions that it should be applied to affected areas only. In some cases, physicians wanting to treat the margins of a lesion ignored the instructions and applied the agent in a wide circle around the affected area. Because the agent was not specific to diseased tissue, serious photodynamic damage occurred in the normal tissue exposed to the drug. Another problem with most non-specific PDT agents has

FIGURE 3



Killing of antibiotic-resistant Staphylococcus aureus. Photofrin failed to kill S. aureus at all light exposures (purple columns). Benzoporphyrin reduced the number of S. aureus (blue columns) but wasn't equal to killing produced by PV-10 (red lines).

been extreme pain or prolonged photosensitivity. Treatment with one agent was reportedly so painful that "patients jumped out of the light booth."

TREATING TOPICAL DISEASES WITH A DISEAED TISSUE-SPECIFIC PDT AGENT

To gain maximum effect for the treatment of topical diseases with improved safety, it's necessary to combine a disease-specific agent with site-specific topical delivery. Topical delivery of the disease-specific agent potentiates efficacy and provides an additional margin of safety. Provectus Pharmaceuticals has developed a suite of compounds whose effects are almost completely confined to diseased tissue (Figure 1). Because the mechanism of targeting diseased tissue is known, Provectus can rapidly screen pre-existing compounds with known human safety profiles and determine which ones will afford desirable targeting characteristics.

Even though we have a suite of "new drugs" that only target diseased tissue, to get a product to market rapidly, we have chosen to initially advance a pre-existing compound (PV-10) for a variety of applications, including psoriasis, eczema, treatment of skin infected with antibiotic-resistant bacteria, and tumors.[1] Our lead topical drug candidate is XANTRYL™, a 0.001% hydrogel solution of PV-10.

MECHANISM OF ACTION

Both PV-10 and PV-12, when properly formulated, confine their effects almost exclusively to diseased tissue. PV-10 concentrates in diseased tissue when delivered topically, intralesionally, or systemically, and is rapidly eliminated from normal tissue (30-minute circulatory half-live). Because PV-10 penetrates the membranes of diseased cells only, its effects are confined to those cells at the cellular level. The changes that occur in the membranes of diseased cells making them selectively permeable are not fully known. However, increased membrane fluidity and hyperactivity of various membrane transport mechanisms are thought to be responsible for PV-10 and PV-12's selective uptake.

One possible route could be via increased uptake of these molecules when they become associated with lipoproteins (Figure 2). A previous study has demonstrated selective uptake and killing of neoplastic cells using toxic, oxidized high-density lipoproteins.[2] Lipoprotein receptors are often elevated in neoplastic cells and in other cells whose rate of division is abnormally increased. This is believed to be due to increased demand for lipids as cellular building materials. Intracellular drug concentrates in the lysosomes of these cells, becoming trapped at the membrane interface, and eventually leading to lysosomal

disruption and cell death.[3]

This lysosomal rupture mimics the normal cascade of events that occur in cells undergoing apoptosis. Therefore, the death of cancer cells is like the normal cell "suicide" process. Further, PV-10 and PV-12 do not enter the nucleus or work by damaging genetic material, and thus are not likely to be carcinogenic, mutagenic, or teratogenic, especially when delivered by a topical route. These factors make the likelihood of long-term sequela, such as treatment-induced tumors, remote.

EFFECTS OF PV-10 IN PSORIASIS

The effects of PV-10 in treating psoriasis were first tested by Dr. Peter Bjerring of the University of Aarhus in Denmark. Patients with moderate-to-severe plaque psoriasis were treated using topical PV-10 and green light illumination. On follow-up 90 days after a single treatment, patients exhibited a durable 60% reduction in plaque thickness. This Phase 1 trial and several subsequent trials have established that the effects of this topical regimen are confined to diseased tissue, with no evidence of systemic drug uptake or side effects. Phase II/III studies are scheduled to begin shortly to assess potential for this local treatment to produce remission of the disease. Additionally, future clinical studies are contemplated to evaluate performance against eczema.

KILLING OF ANTIBIOTIC-RESISTANT BACTERIA

PV-10 and PV-12 may have potential to treat antibiotic-resistant infections of the skin via a topical route of delivery. One of the most serious and difficult problems to treat are nosocomial infections caused by methicillin resistant Staphylococcus aureus (MSRA) or vancomycin resistant enterococci (VRE). As shown in Figure 3, PV-10 at the same concentration in XANTRYL™ kills large numbers of these bacteria within a few minutes when activated by ambient light. Further studies are required to evaluate the killing of such bacteria on skin. However, these results look promising, suggesting that XANTRLY may have additional utility in treating difficult infections caused by antibiotic-resistant agents, and in other difficult conditions in which infectious agents play a large role, such as diabetic and decubital ulcers. These areas represent major market sectors not well addressed by products currently in use.

SUMMARY

Maximum safety and efficacy in the treatment of dermatological disease can be achieved by topical applications as opposed to current trends based on systemic routes of delivery. Performance is further enhanced when the topical agent's therapeutic effects are directed solely against diseased tissue or an infectious agent while sparring normal tissue. Thus, short- and long-term adverse sequela are avoided, and the effects of the drug are focused only on resolution of the disease.

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BIOGRAPHIES

Dr. Craig Dees is the Chief Executive Officer of Provectus Pharmaceuticals, Inc. He has spent more than 20 years in Senior Management positions at Photogen Technologies, Inc.; the Oak Ridge National Laboratory; LipoGen, Inc.; and TechAmerica, Inc. Dr. Dees was a Founder, Senior Scientist and Founding Director of Photogen before Provectus was formed. His responsibilities have included product design and development in the fields of ethical vaccines, cosmetics, human diagnostics, and over-the-counter pharmaceuticals. His development record includes the first live viral vaccine produced by recombinant DNA technologies and the first recombinant antigen human diagnostic assay. Dr. Dees has also successfully licensed a number of proprietary cosmetic products. In addition to design and development activities, he has been responsible for business and market applications, regulatory affairs, and commercialization of human and veterinary medical products. Awards include an R&D 100 for an industrial enzyme, an Inventor's Forum New Product Award for a skincare product, and a First Saber Award for outstanding research in virology. Dr. Dees earned his PhD in Molecular Virology from the University of Wisconsin, Madison, his MS in Immunology from Auburn University, and his BS in Microbiology from Brigham Young University.

DRUG DELIVERY
bespak Executive

BESPAK PLC: HELPING 1,000 PEOPLE EVERY SECOND TO BREATHE

Bespak, a leader in devices for inhaled drug delivery and anesthesia, develops delivery systems for the pharmaceutical industry and disposable airway management products for critical care settings. Bespak's product range includes metered dose inhalers (MDIs) and dry powder inhalers (DPIs), actuators, inflation valves, breathing circuits, disposable face masks, and laryngeal tubes. The group, which has facilities in King's Lynn and Milton Keynes in the UK and Indianapolis, Indiana, and Kent, Ohio, in the US, is quoted on the Official List of the London Stock Exchange (LSE: BPK). Drug Delivery Technology recently interviewed Scott Kellogg, Commercial Manager at Bespak plc, to discuss Exubera®, the relative merits of MDIs and DPIs, Bespak's unique valve technology, and some of the key challenges facing delivery device manufacture.

Scott Kellogg
Commercial Manager
Bespak plc

"Bespak has been instrumental in the industrialization of the delivery device, employing its proprietary planning tool – Bespak Product Introduction Process (BPIP) – to deliver the most effective mode of manufacture and ensure the most appropriate utilization of its facilities."

Q: Can you provide a brief overview of the products and services Bespak offers?

A: Bespak is a global leader in specialty medical devices, developing delivery systems for the pharmaceutical industry and, through King Systems Inc., disposable airway management products for critical care settings. For more than 40 years, we have developed value-added services that assist customers in getting their products successfully to market, offering them expertise at every stage of the development life cycle from concept creation to manufacturing. Bespak has developed MDI valves for more products currently marketed with hydrofluoroalkane (HFA) formulations than any other manufacturer and has industrialized more DPIs than any other company. Every second, 1,000 people rely on a Bespak device to help them breathe.

Q: What are your main responsibilities within the company?

A: I am responsible for creating new business development opportunities for our device division with current and new US based customers. In essence, any organization that requires high-volume molding and product assembly within a regulatory compliant environment is a focus for me. Because of our manufacturing heritage, technical expertise, and advanced services planning, companies looking to develop technically challenging and complex

devices really should be contacting us.

A key focus for me is to encourage US prospects to visit our facilities. The cleanroom controls, organization, equipment, and processes in place are truly world-class and will undoubtedly impress any visitor. Any visit will include a tour of our facilities to showcase our GMP-compliant manufacturing, cleanroom facilities, molding, and high-speed automation equipment – part of the reason why companies like Nektar Therapeutics Inc, the originators of the Exubera inhaler, chose Bespak to manufacture its device.

Q: Can you tell us more about Bespak's role in the Exubera program?

A: In conjunction with Nektar, Bespak has been developing the inhaler's manufacturing process and supply chain since July 1999, and the company's Milton Keynes facility in the UK is exclusively geared toward the high-volume production of products like the Exubera device.

Bespak has been instrumental in the industrialization of the delivery device, employing its proprietary planning tool – Bespak Product Introduction Process (BPIP) – to deliver the most effective mode of manufacture and ensure the most appropriate utilization of its facilities. I play a key role in managing the company's ongoing relationship with Nektar here in the US.

Q: Many in our industry believe that a DPI is the best and perhaps only delivery mechanism for their formulation. What are the benefits of using MDI technology?

A: MDI technology offers real benefits in terms of its cost effectiveness and historically, its speed through regulatory compliance to market. MDIs also offer dose flexibility; "active" dose delivery, and patient familiarity. MDIs have their drawbacks, but many are introduced as a result of poor patient training and compliance. Bespak has worked to constantly improve their design, and we have now developed an MDI valve, the BK361 Easifill, which eliminates Loss of Prime (LOP) and significantly improves shot-to-shot dose content uniformity.

Q: What are the key features and benefits of the Easifill MDI valve?

A: The BK361 Easifill valve is designed to have fast fill/fast drain characteristics that allow the metering chamber to fully refill just before actuation, eliminating LOP after extended storage or on first use and thus reducing dosing variability. Because the Easifill valve requires no priming, it presents consistently accurate doses with each actuation, improving compliance and creating the potential to offer 1-shot dosing regimes. Because the user does not need to prime the valve by firing it into the air before use, waste is reduced and, with the growing likelihood of more expensive molecules being delivered from MDIs, offers a significant economic advantage.

Q: The challenge for many generic therapies is creating a unique point of difference. How can the delivery device assist in creating such a USP?

A: We believe that in time, more and more regime assurance and assistance features will be

incorporated into everyday drug delivery devices, creating a unique point of difference through a marked improvement in patient compliance. The development of a range of dose-counting devices, our collaboration with Bang & Olufsen Medicom to develop The Assist Actuated Inhaler™ and other device enhancements show how differentiation can be achieved through improved aesthetics as well as better patient compliance. Other technologies, such as a Regime Assurance Device (RAD), can prevent access at "non administration" times and minimize the risk of accidental overdose, not only helping patients comply with the prescribed regimen, but also enabling prescribers to monitor usage and, of course, prevent easy access by unauthorized users.

Q: Another challenge for pharmaceutical partners is managing the product development phase of a device's life cycle. How is this best managed?

A: As mentioned earlier Bespak has created its own proprietary planning tool – BPIP – to guide and control product development from concept creation to industrialization, manufacture, and on throughout life.
The principles of BPIP enable a consistent, repeatable, and pragmatic approach to new product introduction. BPIP provides for open, fact-based planning with developer and manufacturer working alongside each other to govern the program at strategic and tactical levels. Replacing reactionary decision-making, BPIP leads to the most appropriate utilization of the available facilities. This methodology creates a platform for continuous improvement throughout the life cycle of the product, touching every aspect of the process from continually strengthening the supply chain to minimizing waste in both process and product. This is done within the prescriptive regulatory environment demanded by the pharmaceutical industry. Coupled with flexible manufacturing approaches and a company wide Six Sigma methodology, BPIP has delivered effective, measurable, and repeatable processes for every aspect of our customers' device development programs.

Q: What are the company's long-term goals?

A: Bespak is working to build itself into an even more significant company. We believe that in order to achieve this, we must continue to fulfill our three main goals:

1. Contribute to society. Every second, 1,000 people rely on a Bespak device to help them breathe, and our employees understand that what they do is significant and sometimes saves lives.

2. Achieve great performance for its customers and shareholders. Bespak strives to give the highest quality and responsiveness to customers and deliver steady increases in value to its shareholders. In addition to growth brought about through new product introductions and finding and keeping new customers, our growth strategy includes selective acquisitions.

3. Be a great place to work. Building a high-performance culture allows employees to realize their potential while making everybody feel like an owner. ◆

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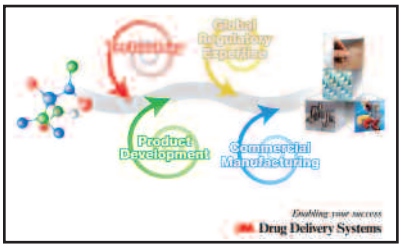
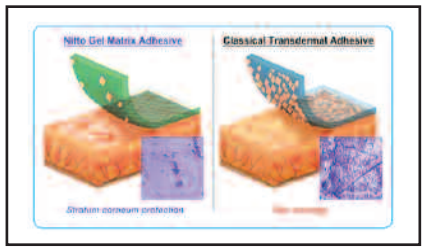
Drug Delivery Showcase

Inhalation & Transdermal Delivery



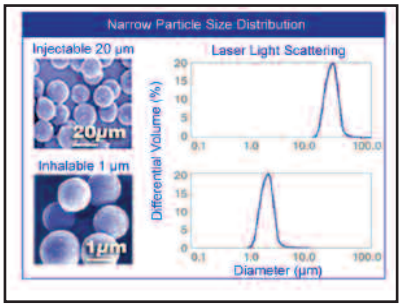
3M Drug Delivery Systems is a global leader and innovator for inhalation and transdermal drug delivery. From drug discovery to commercialization, 3M offers innovative and proven technology, product development services, global regulatory expertise, commercial manufacturing, and a broad range of customizable system components. 3M's technology, expertise, and experience can provide pharmaceutical and biotech companies with differentiated products, speed to market, and increased probability of technical and commercial success. 3M's proven track record includes development of the first MDI, HFA MDI, and the first stand-alone 7-day transdermal system. Products manufactured by 3M Drug Delivery Systems are currently sold in more than 60 countries on 6 continents. The company combines the agility of a leading drug delivery company with the resources of a major, multinational corporation, providing expertise in product development, regulatory, and manufacturing to get its partners to marker sooner. For more information, contact 3M Drug Delivery Systems at (800) 643-8086 or visit **www.3m.com/dds.**

Gel Matrix Adhesive Technology



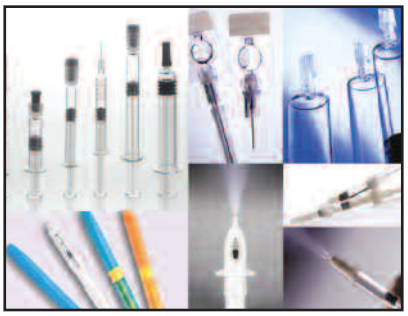
Conventional transdermal technology has relied upon traditional pressure-sensitive adhesives, which include primarily acrylate-, silicone-, and rubber- or polyisobutylene- based polymers, as the primary matrix to adhere the patch to the skin. With these traditional adhesive types, a significant amount of stratum corneum cells are removed and transferred to the adhesive surface, resulting in damage and irritation to the skin. The technology employed by Aveva and Nitto Denko is based upon a proprietary adhesive composition, which addresses these problems. This Gel-Matrix adhesive has unusual properties that allow for exceptional adhesion and wear to the skin without the removal of a significant amount of stratum corneum cells. This allows for unique properties, including the ability to reapply patches while reducing skin damage and irritation. For more information, visit Aveva Drug Delivery Systems at **www.avevadds.com.**

Pulmonary Formulation



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

Prefillable Delivery Systems



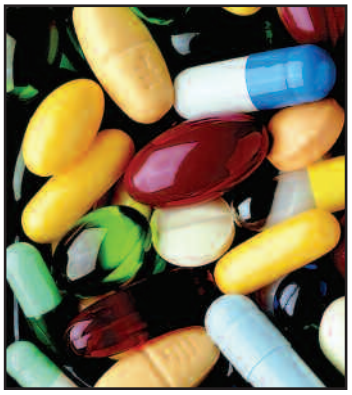
BD Medical - Pharmaceutical Systems is dedicated to developing prefillable drug delivery systems designed to fit the needs of the pharmaceutical industry. Whether a glass or plastic prefillable syringe, a nasal spray system, a dry drug reconstitution system, an injection or self-injection device, BD 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.**

Drug Delivery Showcase

Injectable Technologies

Founded in 1991, Safety Syringes, Inc. specializes in the development of anti-needlestick devices for the healthcare industry. Safety Syringes is actively marketing its UltraSafe® Delivery Systems for prefilled pharmaceutical glass syringes that are commonly used for vaccines, low molecular weight heparins, and other medicines, including many of the newer biotechnology drugs. The company's extensive line of UltraSafe Products combines simplicity, efficiency, and intuitive ease of use to offer its partners the very best and most preferred drug delivery and safety solutions. UltraSafe Services provide unmatched time-to-market capability to support rapid and efficient integration of the company's products with its clients' prefilled presentations. For more information contact Safety Syringes, Inc. at (760) 918-9908 or visit **www.safetysyringes.com.**

Advanced Delivery Technologies



Cardinal Health is the global leader in providing outsourced pharmaceutical development services, drug delivery technologies, contract manufacturing, packaging, and product commercialization services, serving the worldwide pharmaceutical and biotechnology industries. The company offers the broadest range of dose-form development and manufacturing options in the industry - from traditional and proprietary oral forms to sterile products, from inhaled forms to topicals. Cardinal Health holds more than 1,500 patents and patent applications for drug delivery systems. Technologies include soft gelatin capsules; Zydis® fast-dissolve dosage form; EnCirc®, EnVel®, and EnSolv® for oral modified-release products; lyophilization; inhaled technologies; and topical Microsponge® for timed-release and DelPouch® for unit dosing. For more information, contact Cardinal Health at (866) 720-3148 or e-mail pts@cardinal.com; or visit **www.cardinal.com/pts.**

Development & Manufacturing

Coating Place, Inc. is a privately owned drug delivery systems development and manufacturing company specializing in Wurster fluid bed microencapsulation of powders, granules, crystals, and beads. Other coating capabilities include softgels, hard shell capsules, and tablets. Our services include contract formulation development, technology transfer, scale-up, and commercial manufacturing in a GMP environment with analytical support. Applications include controlled oral delivery, such as enteric, delayed, or sustained release, moisture or oxygen barrier and taste-masking applications for Rx, OTC, and controlled substance products. Our facilities process solvent, aqueous, and hot melt formulations. Our creative and innovative staff is ready to take on your toughest projects. For more information, contact Coating Place, Inc. at (608) 845 9521 or visit **www.encap.com.**

Polymers & Delivery Technologies

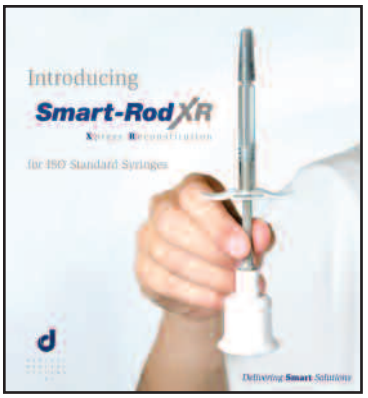
Pharma Polymers is one of the world leaders in the manufacturing and supplying of functional coatings for the pharmaceutical industry. EUDRAGIT® polymers are ideal for Enteric Delivery, Controlled Release, and Protective Coatings. Based on more than 50 years of experience in EUDRAGIT® polymer design 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 Degussa Corporation, Rohm America LLC at (877) 764-6872 (Option 4) or visit **www.pharma-polymers.com.**

Drug Delivery Showcase

Drug Development Services

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.**

Reconstitution Device



Duoject has recently introduced the new Smart-Rod XR: Xpress Reconstitution system for staked-in needle syringes. The system is designed to fit a wide range of syringes and pharmaceutical cartridges for pen-injector applications. The development of Duoject's technologies in reconstitution and drug delivery of solid-form injectables is driven by a commitment to achieve similar user advantages as found in liquid prefilled syringes. Streamlining the reconstitution process reduces the need to develop stabilized aqueous drug formulations. Duoject designs and develops transfer and delivery devices for injectable drugs. Its unique expertise is focused on solid-form drug reconstitution and suspension devices for a wide range of indications. Customized versions of its innovative and patented device platforms are made available for license to biotechnology and pharmaceutical clients. For more information visit Duoject Medical Systems Inc. at **www.duoject.com.**

Controlled Release Technologies

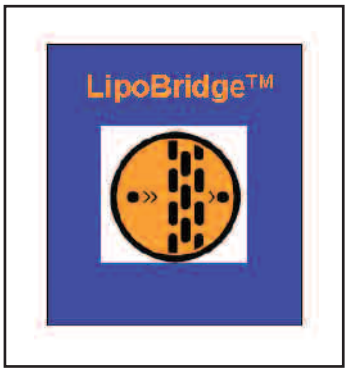
Egalet a/s is a drug delivery company focusing on formulation and development of oral controlled-release products using its proprietary drug delivery Egalet® and Parvulet® technologies. The company has four products in clinical development, two of which are entering into late-stage pivotal studies. The Egalet tablet incorporates almost any pharmaceutical into a polymeric matrix eroded by body fluids at a constant rate. The tablet, made by a simple, unique injection-moulding technique, can be used for virtually any type of medicine and provides controlled release with precision and reliability. The Parvulet technology is a novel approach for pediatric drug delivery combining improved consumer acceptance with highly competitive development and production costs. Egalet aims to become a preferred partner for the pharmaceutical industry with its strategy for controlling drug development efforts from product formulation to clinical testing, regulatory submissions, and manufacturing. For more information visit Egalet a/s at **www.egalet.com.**

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 **bizdev@eurand.com.**

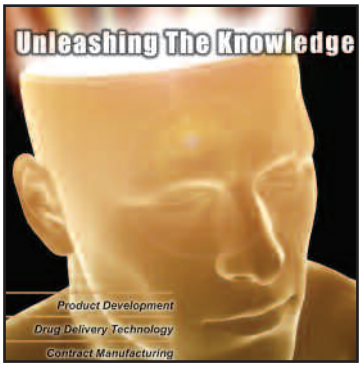
Drug Delivery Showcase

BBB Transporter



Lipobridge™ compounds facilitate transport of drugs across the blood-brain-barrier (BBB) and into the CNS. Short chain oligoglycerolipids have been shown to facilitate the delivery, distribution, and uptake of pharmaceutical actives into the CNS and thereby permeate the BBB. Data shows that some of these molecules can increase drug concentration reaching the CNS by a factor up to 100 without toxic side effects. Demonstrated in several laboratories, intracarotic injections of a simple mixture of Lipobridge and model compounds or pharmaceutical actives can be delivered into one or both hemispheres of the brain allowing for increased concentration in a selected hemisphere. This permeability has been shown to be reversible and has been demonstrated that the carrier itself is excreted unmetabolized. For more information, contact Genzyme Pharmaceuticals at (800) 868-8208 or visit **www.genzymepharmaceuticals.com.**

Pharma Development Services

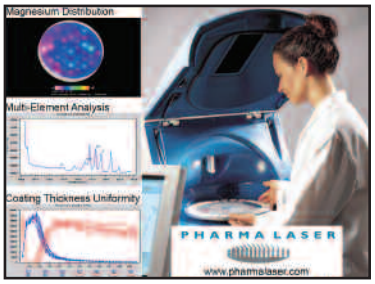


It is critical for a service provider to meet the technical, financial, and timing demands of projects and offer clients first-class expertise and capabilities throughout the world. The Glatt Group has been supplying solid dosage technology, equipment, integrated systems, and processing expertise to 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.**

Sub-Q Protein Delivery

Would you like to convert your drugs from IV to subcutaneous (Sub-Q) delivery or enhance the dispersion of your existing Sub-Q 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 Sub-Q administration of large volumes (up to 10 cc) of antibody drugs, speed onset of action relative to Sub-Q delivery without Enhanze, and improve patient comfort. For more information, contact Mark Wilson, Vice President of Business Development (Halozyme Therapeutics) at mwilson@halozyme.com or (858) 794-8889; or visit **www.halozyme.com.**

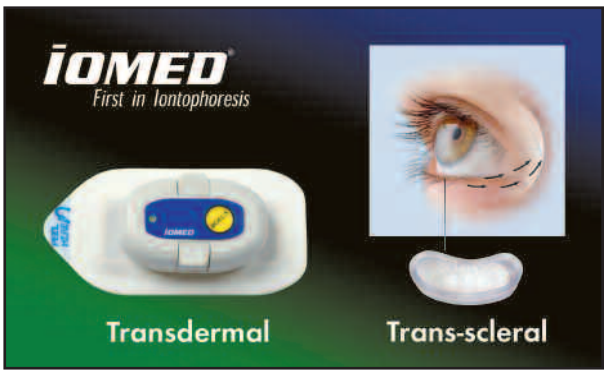
LIBS Technology



The Patented PharmaLIBS™ 250 (Laser Induced Breakdown Spectroscopy) qualitatively and quantitatively analyzes pharmaceutical solid-dosage forms in seconds. It provides site-to-site, tablet-to-tablet, and in-depth targeted analysis — evaluating coating thickness/uniformity, including API, lubricant, and disintegrant blend/tablet uniformity. The results are shown in graphs, tables, and revealing 3D Mapping. The PharmaLIBS 250 can easily and rapidly perform all these analyses in real-time, in one acquisition, directly on the tablets without sample preparation nor solvent required. The instrument can be used anywhere from product development to manufacturing and even for counterfeiting investigation. The powerful software of the PharmaLIBS 250 provides better understanding of processes — ideal for PAT implementation. For information, contact PharmaLaser at (212) 696-5284 or visit **www.pharmalaser.com.**

Drug Delivery Showcase

Iontophoresis Technologies



IOMED is a leader in the development, manufacture, and sale of active drug delivery systems that employ iontophoresis. IOMED's versatile transdermal and trans-scleral technology allows for custom delivery profiles for local and systemic applications. The company is actively pursuing opportunities to utilize its non-invasive drug delivery systems in combination with specialty pharmaceuticals to offer unique products designed to satisfy unmet medical needs. Licensing, co-development, and marketing agreements are available. For more information, contact IOMED at (801) 975-1191 or visit **www.iomed.com.**

Silicone Materials

When it comes to drug delivery, NuSil provides numerous solutions that fit a variety of device needs. And, with the acquisition of the Simethicone product lines, NuSil offers an even wider range of silicone material and compound options for transdermal, transmucosal, implanted intrathecal, and external delivery devices, as well as ingestible materials. While most silicone products are customized for individual delivery systems, all are developed with FDA regulatory concerns in mind. In addition to its role as a supplier, NuSil offers research and development capabilities for those looking for proprietary, custom formulations. Regardless of batch size, NuSil delivers quality, high-performance silicone materials based on your unique property requirements, as well as provides precise, custom formulations. For more information, contact NuSil Technology at (805) 684-8780 or visit **www.nusil.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.**

Formulation Solutions

SPI Pharma is a worldwide leader in custom formulation solutions for pharmaceutical and neutriceutical manufacturers. By offering raw materials, processing capabilities, and advanced application technologies, the company has become a valued source for complete custom delivery systems. This provides a competitive advantage for its customers' formulations. SPI's broad product line includes excipients, antacid actives, and formulated systems. All products are produced under cGMP manufacturing guidelines suitable for pharmaceutical and neutriceutical applications. Core processing capabilities include precipitation, hydrogenation, crystallization, spray drying, granulation, micronization, suspensions, and encapsulation. Some advanced applications include solid dosage formulation, viscous suspensions/blends, DC chewing gum, effervescent systems, chewable/quick-dissolve tablets, and customized granulations. For more information, contact SPI Pharma at (302) 576-8554 or visit **www.spipharma.com.**

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EXTERNAL DELIVERY

It's a Puzzle!

By: John A. Bermingham

I have to thank my neighbors Mimi and Ed again. They are the ones who came up with the idea that turnarounds are treasures. I wrote an article a while back based on their idea that *Turnarounds Are Treasures*. Now they have given me the idea that turnarounds are kind of like jigsaw puzzles too. Thanks gang.

It's true. Turnarounds are kind of like doing a jigsaw puzzle. Not exactly like putting a jigsaw puzzle together, just kind of. When a new CEO walks into a company to initiate a turnaround, he or she is looking at a fairly complex puzzle that has many pieces to put together. You don't have a picture on the cover of the box to look at while putting the pieces together. You have to imagine what you want the finished product to look like and hope that the right pieces (think people and products or services) are there. Otherwise, you have to go out and get new ones.

Sometimes you might make it up as you go and work hard to have a nice picture (think company) when you are finished. Often, a puzzle piece that looks like it will fit at the beginning of the puzzle process doesn't fit after all. Or it fits at the beginning and then doesn't fit later. Or it doesn't look like it will fit and then does. Sometimes you get the whole puzzle put together and the picture isn't exactly what you had expected it to be. So you have to quickly modify the pieces of the picture that are an issue and get the puzzle back together to make the picture look great. Sometimes you put the puzzle together and it looks great but nobody wants it because the market passed you by.

So what's a CEO to do? Well, first a CEO has to have a very clear picture of what the finished product (company) must look like. Not just an idea or a "make it up as you go" strategy. It has to be clearly defined in your mind and articulated to the people who are helping to put the puzzle pieces together. You also have to look very carefully at all of the puzzle pieces and use the ones that meet the requirements for the picture that you have clearly in mind and discard the remainder. There is no sense wasting time on a puzzle piece that does not fit your picture.

As you are putting the pieces together, make certain that your puzzle maker helpers are the right people. A bad puzzle maker helper can really hurt the finished product or really slow down its development. Sometimes they even sabotage the project. True! Sometimes a turnaround CEO gets only part way through the puzzle development and has to start over due to unforeseen complications. Also true! There are more issues that you face when you are a turnaround CEO but two things are for certain:

1. Turnarounds a kind of like putting a jigsaw puzzle together
2. Turnarounds are Treasures ◆

BIOGRAPHY

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

How to deliver your drug's best performance

Oral Technologies

You've invested heavily to get your product to this point. Now is the time to make the most of your investment. Cardinal Health can help identify the best technology to enhance your molecule's performance:

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- **For improved dissolution**—EnSolv® technologies

Contact us today to explore how our advanced delivery technologies can improve your drug's performance—in development, in the clinic, and in the market. Call toll-free: 866-720-3148.

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