Drug Delivery Technology®

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The SAINT™ Technology: Ideal for DNA, RNA & Proteins?

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

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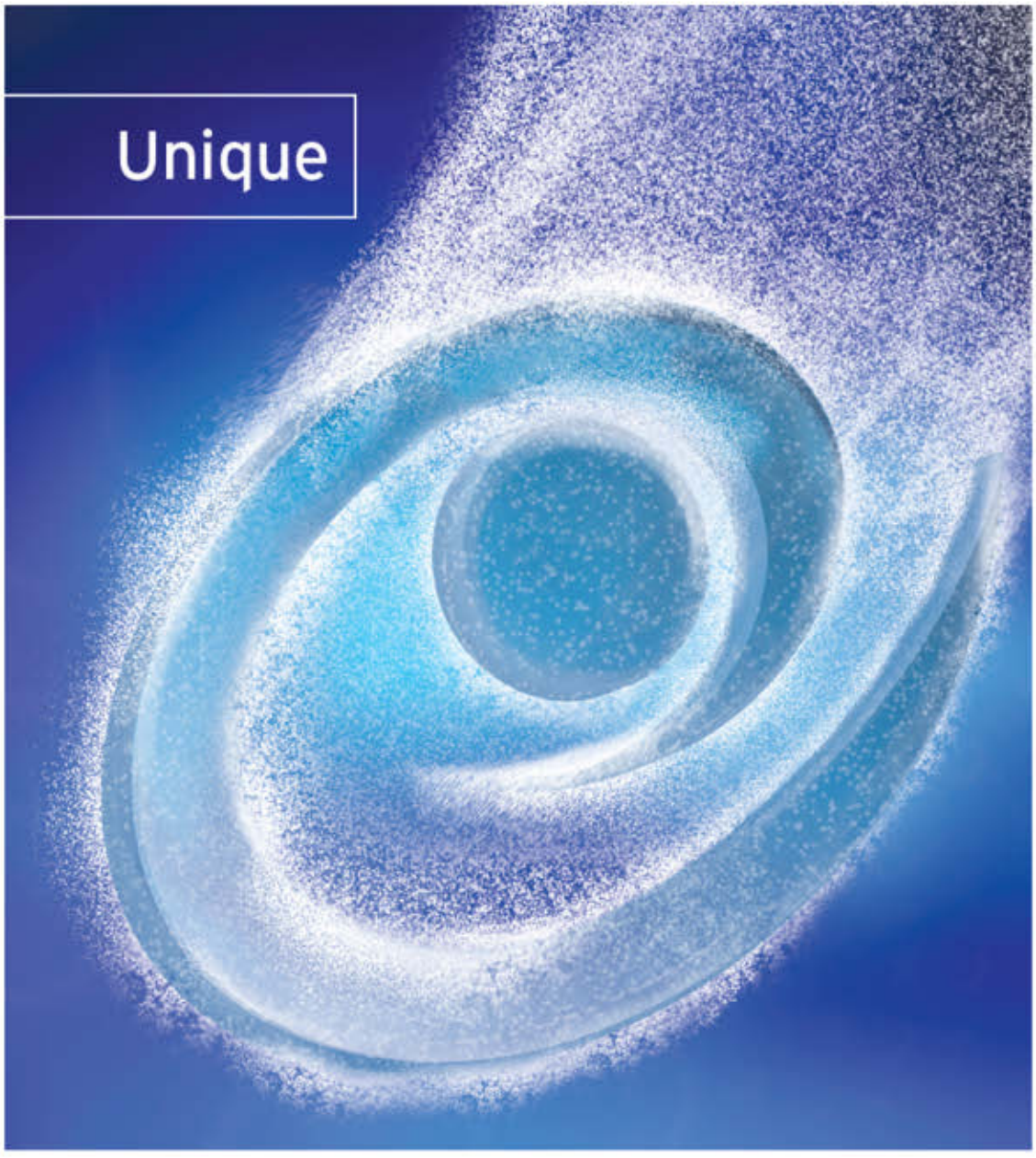

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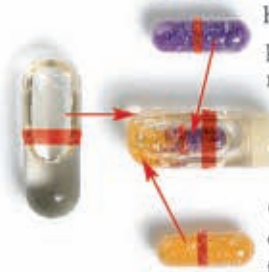
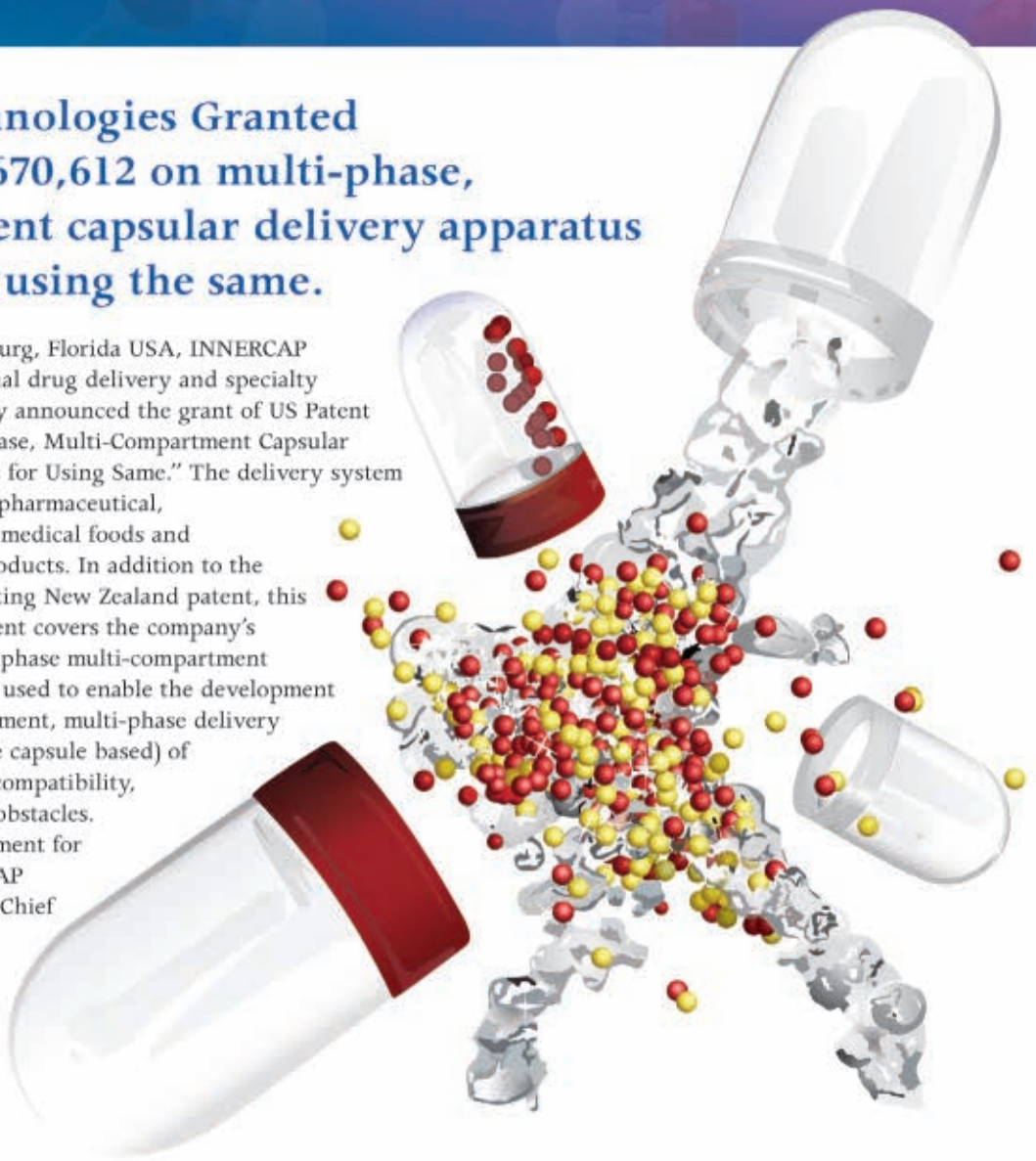
INNERCAP® Technologies Granted US Patent No. 7,670,612 on multi-phase, multi-compartment capsular delivery apparatus and methods for using the same.



March 23, 2010, Saint Petersburg, Florida USA, INNERCAP Technologies, Inc., an international drug delivery and specialty pharmaceutical company, recently announced the grant of US Patent No. 7,670,612 entitled "Multi-Phase, Multi-Compartment Capsular Delivery Apparatus and Methods for Using Same." The delivery system has uses for bio-pharmaceutical, pharmaceutical, medical foods and nutraceutical products. In addition to the existing New Zealand patent, this patent covers the company's multiphase multi-compartment delivery system used to enable the development of multicompartment, multi-phase delivery forms (two piece capsule based) of combination products that have compatibility, formulation or targeted delivery obstacles.



"This is a significant development for INNERCAP Technologies NOVACAP technology," said Fred H. Miller, Chief Executive Officer at INNERCAP. "The continued growth of our patent portfolio establishes INNERCAP as one of the leading companies in this space."

The delivery system and combinations covered by the patent have the ability to deliver therapeutic entities that have never been combined previously and now can be administered together, via an oral, implanted, or suppository capsule, in the most advantageous pharmacokinetic profile, utilizing different physical phases. This technology can therefore be used to enable capsule administration of compounds that are not normally administered as a combination product. The efficacy, safety, and side-effect profiles of drugs can be substantially improved using this delivery technology. It will also provide very significant quality-of-life improvements for patients and substantial economic savings for hard-pressed healthcare systems.

"INNERCAP's multi-phase, multi-compartment technology has been commercially manufactured and validated in several products, demonstrating that INNERCAP's delivery system creates real value to consumers and branded manufacturers," added Mr. Miller.

INNERCAP was represented by Cliff Davidson, Esq. of the patent firm Davidson, Davidson & Kappel, LLC (www.ddkpatent.com) based in New York City.

For more information contact us at the telephone number and email address below:

INNERCAP® TECHNOLOGIES, INC

United States Patent No. 7,670,612
US and International Patents Pending

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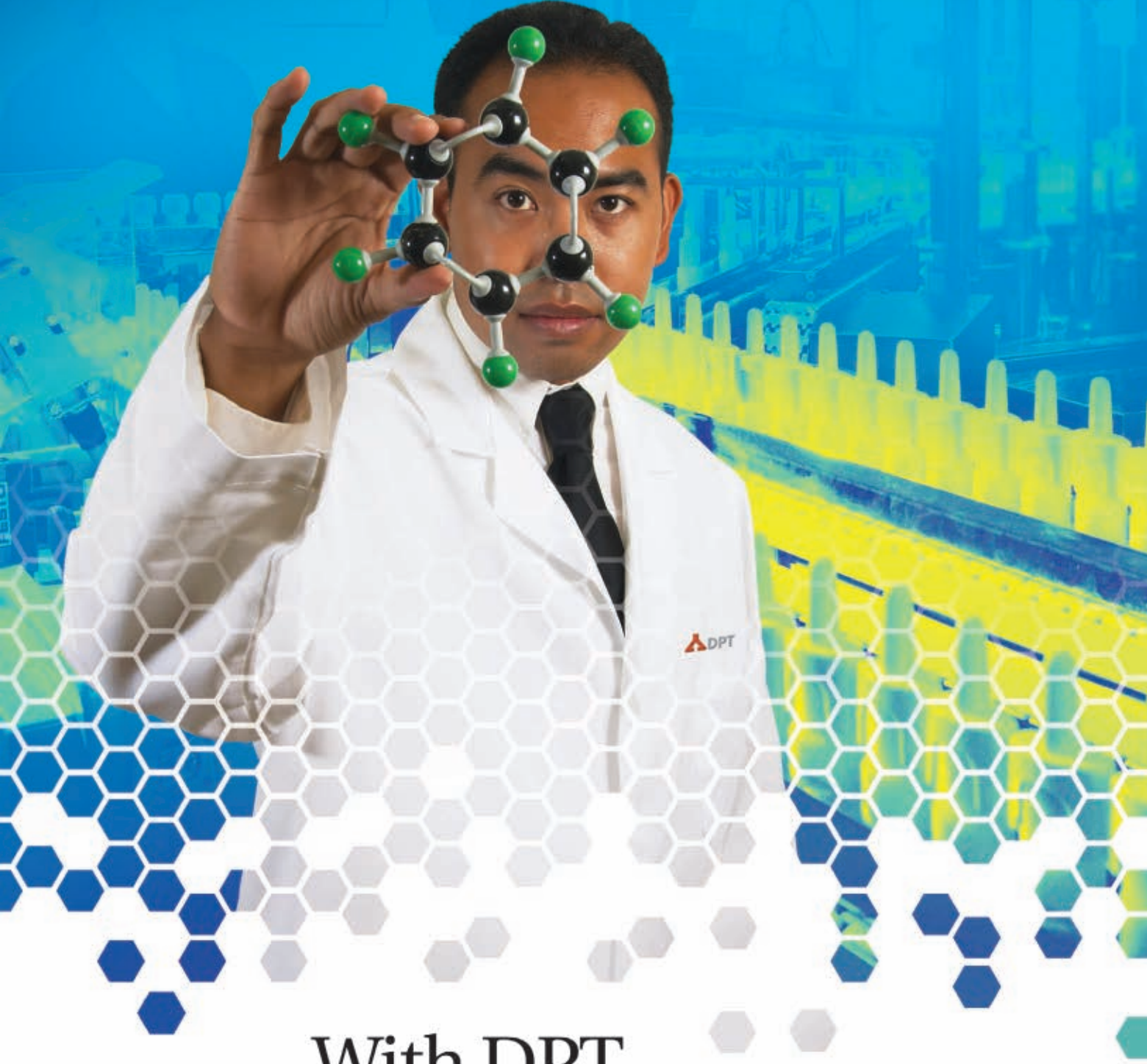

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Battling Bone Metastases

"In an Orazol Phase II study completed last year, patients reported much quicker pain relief. Unlike the kidney deterioration associated with zoledronic acid infusion, by taking a weekly dose, the peak drug load the kidney has to process is reduced. And, the flu-like side effects associated with the intravenous delivery don't seem to be present in the Orazol tablet taken weekly."

p.30

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TRANSDERMAL TRANSCENDENCE

That's the promise of Aveva Drug Delivery Systems, combining innovation and unparalleled industry experience to advance drug delivery and pioneer new frontiers in transdermal drug delivery for new chemical entities and life cycle management opportunities to enhance existing products.

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Market News and Trends

Encompass Announces Exclusive World-Wide Rights to Ocular Delivery System

Encompass Ophthalmic Development, Inc. recently announced it has secured the exclusive worldwide ophthalmic rights to PROLOC Bioadhesive Ocular Drug Delivery System from the Transdermal and Transmucosal business of Henkel Corporation.

PROLOC features long-lasting drug release and high bioavailability compared to traditional eye drops, ointments, and gels. It is a preservative-free polymer matrix in uniquely formed ocular mini-tablet form that is applied to the fornix. Upon insertion, PROLOC adheres rapidly to the ocular mucosa and transforms to a comfortable gel-like substance that will remain in place until fully eroded.

The PROLOC Bioadhesive Ocular Drug Delivery System permits high active ingredient loading and is compatible with hydrophilic or lipophilic active ingredients. PROLOC Bioadhesives are capable of residing over 8 hours during which time the active drug is gradually released. PROLOC is manufactured using USP ingredients, and clinical studies have been conducted to support ocular use.

The increased time that PROLOC remains in the eye may allow for lower concentrations of a drug to be administered over a longer period of time. This minimizes the inconvenience of frequent dosing, reduces the potential of related adverse side effects, and may lead to improved patient compliance.

The technology offers intellectual property protection, provides the opportunity to expand the lifecycle of current branded drugs, and opens new possibilities for new drug molecules and uniquely delivered therapies.

Encompass Development, Inc. is an Atlanta-based company focused on the development and out-licensing of ophthalmic pharmaceuticals and drug delivery systems. Encompass Pharmaceutical Services, Inc provides a full range of analytical, stability, and consulting services for the global pharmaceutical industry. One of its core competencies is ophthalmic development and formulation services from preformulation through manufacturing scale-up and quality systems. Services include preclinical support, drug formulation, drug delivery development, clinical supplies, and manufacturing support.

West Introduces Insert Needle Syringe System

West, a global leader in innovative system and component solutions for injectable drug administration, has recently introduced the Daikyo Crystal Zenith 1-mL long insert needle syringe system. The syringe system was introduced to the market at the Parenteral Drug Association's Universe of Pre-filled Syringes and Injection Devices Conference in Las Vegas this past October.

"The introduction of this unique delivery system for injectable drugs ushers in the future of prefillable syringes," said Graham Reynolds, Vice President, Marketing and Innovations, Pharmaceutical Delivery Systems. "In view of recent market recalls caused by glass breakage, delamination, and particles, this product provides a timely solution to problems that could adversely affect the health of patients and create a serious financial burden on the drug manufacturer."

A drug's safety and efficacy are impacted by its packaging and delivery system. Choosing a packaging solution that ensures the stability of a drug and eases administration is a complex process. Potential interactions between closure systems, primary drug contact materials, and processing aids must be held to an absolute minimum or, preferably, eliminated.

The industry has a growing need for prefillable syringe systems that are break-resistant, minimize interaction with the drug product, and provide options for use in self-administration devices, such as auto-injectors. Syringes manufactured from Daikyo Crystal Zenith, a cyclic olefin polymer developed by Daikyo Seiko, Ltd., provide market-proven solutions for the safe, effective delivery of biologics.

West manufactures the 1-mL insert needle syringe at its facility in Scottsdale, Arizona. The manufacturing process features automated vision inspection at several stages and includes an x-ray analysis of the needle to eliminate defects that may cause injection pain.

West's innovative system, device, and component solutions help improve the safety and administration of injectable drugs. West's proprietary materials science, formulation research, and manufacturing technologies advance the quality, therapeutic value, development speed, and rapid market availability of pharmaceuticals, biologics, and vaccines. West supports its customers from facilities in North and South America, Europe, Asia, and Australia.

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Althea Announces Installation of High-Speed Prefilled Syringe Line

Althea Technologies, Inc., a leading provider of development and manufacturing services for biopharmaceuticals and parenteral drug products, recently announced it has completed the installation of a new INOVA H3-5 high-speed syringe filling line. This line is located in Althea's large-scale and commercial manufacturing facility in San Diego. The expanded capacity complements existing prefilled syringe manufacturing for clinical supplies and allows Althea to provide its clients with drug product in prefilled syringes from early development through commercial supply.

The INOVA H3-5 syringe line operates within a Restricted Access Barrier System (RABS) and incorporates the ability to fill under vacuum, which facilitates handling of viscous products and products that require minimal head space. The line accommodates nested syringes from a variety of suppliers and can produce batch sizes in excess of 100,000 units. The system incorporates non-destructive, in-process weight checks to minimize product loss.

"We've been filling syringes for clinical use for over 8 years, and the addition of this new line allows us to continue to meet client requirements as they progress from late-stage development through commercialization," said Rick Hancock, President of Contract Manufacturing Services at Althea Technologies.

The prefilled syringe market is rapidly expanding as it provides numerous benefits relating to patient compliance and product differentiation.

"With our existing expertise in formulation development and protein analytics, we can now offer clients an integrated solution to quickly develop, register, and launch their products in prefilled syringes," added Dr. Shabbir Anik, CEO of Althea Technologies.

The line will be available for production of GMP batches in Q1, 2011.

Althea Technologies is a fully integrated, contract development and manufacturing organization that provides services for plasmid DNA, recombinant proteins, and sterile products. Located in San Diego, Althea offers cell banking, process development, cGMP protein & plasmid production, analytical development, formulation and lyophilization development, and aseptic filling in vials and prefilled syringes for clinical development and commercialization. Althea's technology platform for protein formulations employs crystalomics that can be applied to a variety of peptide and proteins for high concentration or sustained release formulations. For more information, visit www.altheatech.com.

Market News and Trends

DuoCort Pharma & Recipharm Start Innovative Collaboration

DuoCort Pharma recently announced it has concluded an agreement with Recipharm under which Recipharm is set to scale-up the manufacturing of DuoCort's tablets to commercial scale as DuoCort Pharma prepares for market entry with its orphan drug for the treatment of Addison's disease.

The scale-up agreement represents an innovative risk-sharing collaboration in which Recipharm, one of Europe's leading pharmaceutical Contract Development and Manufacturing Organizations, will co-invest in the scale-up along with DuoCort Pharma.

The Swedish speciality pharma company, DuoCort Pharma, took a step closer to the market earlier this year when it filed for marketing authorization in the EU for its new treatment for the rare and life threatening disease adrenal insufficiency, often referred to as Addison's disease.

Although cortisol replacement therapy for adrenal insufficiency has been around for a long time, several studies have recorded premature death, impaired quality of life, increased risk of cardiovascular diseases, and decreased bone mineral density in these patients. Existing replacement therapies, unable to mimic cortisol's normal diurnal release profiles, are viewed as the likely cause of these outcomes. The new treatment from DuoCort Pharma has a physiological release profile, which mimics the body's natural release of cortisol, thereby improving treatment outcomes.

"We are very pleased to be working with an organization of Recipharm's caliber to scale-up our tablet manufacturing process. It is a real endorsement of the quality and commercial potential of our drug development that Recipharm has chosen to co-invest in this with us," said Maria Forss, CEO of DuoCort Pharma.

"DuoCort Pharma is an industry innovator responsible for developing a new product for patients in great need of improved medical treatment. The agreement with DuoCort Pharma fits perfectly with our business model through which the Recipharm Venture Fund invests in projects in which we can make important contributions through our development and manufacturing capabilities, both in a short- and long-term perspective," added Carl-Johan Spak, Executive Vice President of Recipharm.

DuoCort Pharma is a drug development company focused on developing an improved glucocorticoid replacement therapy for patients with adrenal insufficiency, a rare disease for which DuoCort has orphan drug designations in Europe and the US. The new product is a once-daily dual-release hydrocortisone oral tablet. It has an outer layer that releases the drug immediately and an inner core that releases the drug over the day to mimic the body's own release profile of cortisol. The tablets come in both 5-mg and 20-mg.

Recipharm AB is a leading contract development and manufacturing organization based in Sweden with 2,000 employees. The company operates 12 development and manufacturing facilities in Sweden, France, the UK, Spain, and Germany and is headquartered near Stockholm. Recipharm supplies the global pharmaceuticals market with hundreds of different products in most dosage forms, including solid dose, granulates, powders, sterile liquids, and lyophilizates, semi-solids, beta-lactams, hormones, and inhalers.

PPD & Bend Research Enter Collaboration

PPD, Inc. and Bend Research, Inc. recently announced they have entered into a collaboration in the areas of formulation development, analytical testing, and clinical supplies manufacturing to provide pharmaceutical and biotechnology companies a full range of chemistry, manufacturing and controls (CMC) development services. As part of the collaboration, the two companies will refer potential business opportunities to one another in the areas of compound characterization, particle engineering, formulation development, clinical trial material (CTM) manufacturing, analytical development, stability programs, and GMP release and quality control testing.

A key area of collaboration will be inhalation formulation development and particle engineering for drug therapies. The two companies also plan to collaborate on opportunities that involve services provided by each company and to work together on client bids and projects.

Bend Research's strong formulation development and particle engineering expertise will strengthen PPD's ability to provide clients full-service CMC product development solutions. Through the collaboration, Bend Research clients will have access to PPD's state-of-the-art facilities in Madison, WI, Wayne, PA, and Athlone, Ireland.

"We continue to see strong global demand for our analytical laboratory services," said Magdalena Mejillano, PhD, Vice President of cGMP Lab Services for PPD. "The agreement with Bend Research allows us to expand our preformulation and formulation development expertise, enhance our strong CMC laboratory capabilities, and provide clients a more complete offering for small and large molecule testing."

"Working with PPD strengthens our position as a leading drug formulation resource for pharmaceutical companies," added Rod Ray, PhD, Bend Research President and CEO. "This collaboration with PPD offers a competitive advantage to biopharmaceutical companies looking for innovative drug delivery technologies."

PPD is a leading global provider of CMC testing across all phases of drug development with services ranging from early characterization and formulation and method development through commercial release and stability. Bend Research is a leader in drug formulation development and manufacturing technologies and currently works with more than 50 pharmaceutical and biotechnology clients worldwide.

Pharmaxis Announces Positive Phase III Results

Pharmaxis recently announced significant results of pooled data from its two large-scale 6-month Phase III trials of Bronchitol (inhaled mannitol) in people with cystic fibrosis. The two studies were of similar design and encompass 643 patients from 11 countries.

Over the 26 weeks of the two studies, patients treated with Bronchitol had an average 7.3% improvement in lung function (FEV1) compared to baseline ($p < 0.001$) and a highly significant improvement compared to patients in the control group ($p < 0.001$). In the sub group of patients who were also on rhDNase, patients taking Bronchitol showed a 5.3% improvement from baseline ($p < 0.001$), that was again superior to the control group ($p = 0.020$). In the sub group of patients who were not on rhDNase, patients taking Bronchitol showed a 9.44% improvement from baseline ($p < 0.001$), that was also superior to the control group ($p = 0.009$). The overall rate per annum reduction in exacerbations for patients on Bronchitol versus those on control was 25% (NS), and the number of patients experiencing an exacerbation was 29% lower for those taking Bronchitol (NS). This result was achieved in a well-treated patient population who overall had a very low rate of exacerbations in the study.

"This comprehensive analysis of the pooled results provides an important insight into the overall benefits Bronchitol can provide to patients who are receiving current best standard of care," said Pharmaxis Chief Executive Officer Dr. Alan Robertson. "The number of exacerbations in the two studies was fairly low, reflecting the aggressive treatment with antibiotics that is now common practice in the clinic. Despite this, Bronchitol produced a clinically relevant reduction in exacerbations in patients completing the study, and together with recent data, showed sustained benefit in lung function out beyond 18 months."

Other results from CF302 underlined both the good safety profile of Bronchitol and patient adherence. Overall adverse events on Bronchitol were similar to those experienced on control with 7% of patients taking Bronchitol withdrawing due to adverse events compared to 4% of patients on control. There was no increase in the numbers of bacteria present in the lungs. The most commonly reported adverse event related to treatment was cough occurring in 6% of the Bronchitol group and 3.3% of the control group.

Bronchitol is designed to hydrate the airway surface of the lungs, which can then be cleared more effectively by ciliary clearance and coughing. It has received Orphan Drug Designation and fast-track status from the US FDA and Orphan Drug Designation from the European Medicines Agency. A marketing application has been submitted and is under review by the EMA.

Pharmaxis (ACN 082 811 630) is a specialist pharmaceutical company involved in the research, development, and commercialization of therapeutic products for chronic respiratory disorders. Its development pipeline of products includes Aridol for the assessment of asthma; Bronchitol for cystic fibrosis, bronchiectasis, and chronic obstructive pulmonary disease (COPD); PXS25 for the treatment of lung fibrosis; and ASM8 and PXS4159 for asthma.

DELIVERY REPORT

Decade in Review - Drug Delivery Transactions

By: Josef Bossart, PhD

What business deals of the past decade shaped drug delivery in the 2000s? How will these transactions impact business in this decade? In this Decade in Review series of articles, attention has focused on examining aspects of the business that can help us understand how we got to where we are now and where we are headed. For the most part, we have looked at the quantitative aspects of the business; product sales, product approvals, and company performance. This month, we'll move from the left side of our brain to the right side and take a more subjective look at the past decade through the lens of transactions.

And there are lots of transactions to consider. A query of the PharmaCircle database for deals and transactions involving drug delivery in the years 2000 through 2009 returned more than 3600 hits. These include technology, product, and service deals; mergers; acquisitions; and joint ventures - basically anything in which resources, assets, or money changed hands and drug delivery was involved. This amounts to more than 300 transactions per year and 25 per month; rather large numbers if you are trying to keep track of the teams, the players, and the scores.

The limited number of transactions selected for this article cannot properly represent the breadth of the events that shaped drug delivery in the past decade, either in quantity or theme. Many readers may believe critical transactions have been omitted. Some readers may regard the selected transactions as too Americentric. This US focus reflects the reality that the greatest proportion of drug delivery activities are conducted in America or with American companies, and the fact that there is greater transparency with respect to transactions, terms, and outcomes in the US. Or to put a twist on a popular slogan "what happens in America doesn't stay in America," a result of both mandatory regulatory filings and an investor demand for business transparency.

Let's see if a dozen or so transactions involving drug delivery can't help us understand how the business has developed and point to where it may be headed.

JOHNSON & JOHNSON (J&J) ACQUIRES ALZA CORPORATION - 2001

This wasn't the first transaction of the 2000s, but it certainly was the largest in terms of financial considerations ($10.5 billion) and importance in validating the potential of the drug delivery model. Unfortunately though, Alza was purchased more for its specialty pharma assets and product pipeline than its drug delivery capabilities. At the time of its acquisition, Alza not only had a recently approved specialty product with billion-dollar potential (Concerta) and high potential products in the pipeline, it was also collecting more than $200 million annually in technology-related royalties. It is easy to imagine the J&J bean-counters looking at the acquisition of Alza as a break-even proposition based on product sales and royalty savings with future drug delivery service revenue providing an upside.

This certainly seems to be the logic of how the company was run after the acquisition. The Alza products were folded into the J&J divisions, and the drug delivery business was left to stand on its own. The product call was a good one; since 2001, Concerta has recorded sales of about $8 billion with more to come. Unfortunately, there were problems with the drug delivery approach. The most obvious problem was the "maturity" of the revenue-producing drug delivery technologies. By the time of the acquisition, the core technologies (transdermal and oral sustained release) were getting long in the tooth and no longer enjoyed market exclusivity. Multiple companies by 2001 were offering me-too technologies, generally with lower price tags. And the Alza next-generation technologies being developed in the 1990s (E-Trans and Macroflux) were underfunded and required more time and investment to realize their potential; seemingly not something that interested J&J. The lead E-Trans product, Ionsys, was actually partnered with J&J but amounted to nothing. Finally approved in 2006, Ionsys was promptly discontinued. The Macroflux platform never made it at Alza but is getting a second chance at Zosano Pharma.

A second challenge faced by the Alza team as a service company was a potential conflict of interest with existing J&J products, and the simple fact that other Big Pharma companies weren't interested in subsidizing J&J by doing a deal with Alza. In the years following 2001, Alza executed less than a handful of deals with Big Pharma companies.

The Alza/J&J transaction validated many drug delivery company CEOs' dreams of high-value buy-outs, and it reinforced the emerging belief that the best way to make money with drug delivery was with a product pipeline you owned yourself.

CEPHALON ACQUIRES ANESTA (2000) & CIMA (2004)

If the Alza acquisition by J&J defined the upper limit of drug delivery company value, the acquisition of Anesta and Cima by Cephalon suggested it could happen to most any drug delivery-focused company (as long as it had an approved product or advanced product pipeline).

Cephalon showed considerable vision in its acquisition of Anesta in 2000 to access Actiq, a lozenge presentation of fentanyl for breakthrough cancer pain. Originally licensed to Abbot, Actiq and its predecessor Oralet were commercial disappointments in the hands of Big Pharma, and Abbott returned the rights to Anesta. Revenues were very modest, and the approved indication, the treatment of breakthrough cancer pain, was not widely considered to demand next-generation type medications. But in the hands of a smaller and more aggressive company like Cephalon, the transmucosal route of delivery and the breakthrough cancer indication (and off-label indications) proved to be a huge winner with Actiq recording sales in excess of $2.5 billion since 2000.

If a fentanyl lozenge was good, Cephalon imagined that a simpler transmucosal buccal product would be even better. This led to Cephalon's acquisition of Cima for more than $500 million in 2004. At the time of its acquisition, Cima not only had its transmucosal product (Fentora) in Phase III trials, it was also operating a successful and modestly profitable drug delivery business providing Big Pharma and Specialty Pharma companies with oral dissolve technologies (ODT) services and products. For Cephalon, the acquisition was a no-brainer; Fentora represented the leading threat to the Actiq business and offered the potential for a better product while extending Cephalon's market domination. As things have turned out, it's not clear that it was as big a winner as Cephalon had hoped. Fentora has been profitable but unremarkable in its sales, a little over $500 million since launch, and the ODT service business has been subject to fierce competition.

The net/net of these two transactions was the palpable evidence that the most attractive exit model for drug delivery companies was owning an approved product or an advanced product pipeline. Develop a product, take it into the clinic, and if it was done right your company, it might just be acquired for a much higher price than a technology service business could ever support.

SHIRE ACQUIRES NEW RIVER PHARMACEUTICALS (2007)

If there was any question in the drug delivery business that "it's the product stupid" prior to 2007, it was answered with Shire's acquisition of New River for more than $2.5 billion. It was New River's lead product Vyvanse, a novel pro-drug formulation of amphetamine for the treatment of ADHD in Phase III, that induced Shire to pull the acquisition trigger even though they already had licensed worldwide rights to the product in 2005.

While the New River pro-drug Carrierwave technology was potentially applicable to multiple molecules in reducing the potential for drug misuse, it was Vyvanse that mattered. Since US approval in early 2007, Vyvanse sales through the middle of 2010 are in excess of $1.2 billion. With the prospect of US market exclusivity through 2023, and approval in additional markets, the acquisition of New River will be profitable for Shire even if no additional products are approved using the Carrierwave platform.

CEPHALON LICENSES RIGHTS TO VIVITROL (2006) & RETURNS VIVITROL RIGHTS TO ALKERMES (2008)

Cephalon certainly has been consistent in their licensing of rights to drug delivery enhanced/enabled products (DDEPs) that are either approved or in advanced clinical development. Unfortunately, this deal did not

work out for Cephalon; credit Alkermes for playing the partnering game extraordinarily well and taking home a cool $300 million and regaining full rights to Vivitrol. As in life, you win some and you lose some.

Risk is part of the business in developing drug delivery technologies and products. Arguably, the risk of product development for a DDEP is lower than for a new chemical entity product, but it still exists given the current 24% approval rate for DDEPs that have entered clinical development. What is often forgotten is the market risk for any new product, whether it is entering an existing market with established competitors or is exploring a whole new market opportunity. Given their success with Actiq in the breakthrough cancer market, Cephalon certainly would have understood the challenges of building on the existing, but small, alcohol-dependence market. Cephalon did limit its development risk by deferring certain license fee payments until Alkermes received FDA approval for Vivitrol, but Cephalon still handed over about $300 million to Alkermes before the first sale was recorded. A back of the envelope calculation suggests that Cephalon was looking at overall sales of about $1 billion to $2 billion for Vivitrol to allow them to break even on the deal with anything above this profit.

Unfortunately for Cephalon and Alkermes, the alcohol-dependence market was much harder to crack, at least in the short-term, than either party thought. From approval in 2006 through the end of 2008 when Cephalon returned Vivitrol product rights to Alkermes, total cumulative sales were less than $50 million. By assuming development risk and costs, Alkermes was able to negotiate a very attractive up-front payment that more than covered their product development costs.

PFIZER RETURNS EXUBERA RIGHTS TO NEKTAR (2008)

There is little new to be said of the rise and fall of Exubera. The return of product rights in 2008 was critically important in pointing out that regulatory approval did not automatically translate into market acceptance. The market failure of Exubera and the return of product rights to Nektar had a huge ripple effect in the drug delivery field. Not only did almost every other inhaled insulin program get cancelled (MannKind being the exception), but so did many other inhaled protein programs as attention was brought to safety and the associated regulatory concerns with inhaled macromolecules.

NOVARTIS LICENSES ZALBIN (ALBUFERON) FROM HUMAN GENOME SCIENCES (2006)

This was a product deal that for the most part flew under the radar of most drug delivery executives. With the success of PegIntron and Pegasys, and validation of the benefits of extending interferon alpha residence time in the treatment of hepatitis C, it seemed reasonable that longer would be even better. Using albumin conjugation technology they had acquired in 2000, Human Genome Sciences developed an albumin conjugated interferon product. This led to the 2006 deal with Novartis for an effective $100-million up-front payment even though the product was still in late Phase II development.

This deal further validated the market value of DDEPs in advanced clinical trials and reinforced the notion that there was a significant business to be realized by improving the delivery performance of biological products.

Once again we saw that "it's the product stupid," especially if the buyer believes there is limited market and development risk. Well, development risk has come back to bite Human Genome Sciences and Novartis; Zalbin seems to have bitten the dust with Novartis recently announcing it had discontinued its development.

GLAXOSMITHKLINE LICENSES WELLBUTRIN XL FROM BIOVAIL (2001)

The market value of DDEPs was established early in the 2000s with this deal for a once-daily formulation of GSK's Wellbutrin. Biovail shrewdly decided to develop a once-daily formulation of bupropion, while the twice-daily formulation was delivering multi-billion dollar sales for GSK. Whether GSK had a similar formulation in development but behind the Biovail product, or they were caught with their pants around their ankles is not clear. Regardless, the deal proved to be a win-win for GSK and Biovail. GSK was able to start moving physician prescription and patients from their twice-daily Wellbutrin SR formulation to Wellbutrin XL before market exclusivity for the former expired and Biovail was able to capture a big piece of the action for a billion-dollar product.

This deal was perhaps a wake-up call to Big Pharma in letting them know that if they were not prepared to develop follow-on formulations of their products, others would. Biovail, which had a good track-record of developing oral extended-release formulations, proactively took on the challenge of a once-daily bupropion product and secured an effective royalty of greater than 30% as well as selected promotional rights to approved GSK products for its emerging Specialty Pharma group.

Biovail executed a similar transaction in 2006 for a once-daily formulation of tramadol with J&J, the product's original marketer. The terms once again included an effective royalty on the order of 30%. The commercial results for the two parties were not as positive. The once-daily formulation was launched well after generic products had established their presence in the market, and J&J was unable to convince physicians and payers that the dosing benefits of Ultram ER warranted the price premium.

Smart and experienced drug delivery companies it seemed no long provided partners with technology in exchange for minimal license fees and single-digit royalties, but rather took on the risk and cost of development in exchange for a much larger piece of the action, and in some cases, a premium take-out price.

INHALE ACQUIRES BRADFORD PARTICLE DESIGN (2001) & SHEARWATER (2001)

In separate transactions, Inhale acquired two technology-based companies, Shearwater (PEGylation) and Bradford (particle engineering), to complement its internal inhalation capabilities and provide Pharma partners with a one-stop shop for drug delivery technologies. This then led to the introduction of the new Inhale: Nektar Therapeutics, a multi-dimensional drug delivery service company.

This corporate strategy was consistent with the Alza model of the 1980s, which offered partners leading oral and transdermal

technologies under a service model. Nektar's one-stop service model failed to deliver the expected profits. In the case of Nektar, the reasons were too low technology prices and excessive overhead costs. While Nektar had many deals, a deep partnership pipeline, and several partner-approved products (notably Pegasys and Neulasta), it was never able to turn a profit. The issue was that the technology deals were providing only low single-digit royalties or minimal raw material supply prices. These results and the market withdrawal of Exubera by Pfizer led Nektar to reorient itself in 2008 to the development of proprietary DDEPs for out-licensing.

The technology deal as a profitable business model seemed to have failed its test with Nektar. With the disappearance of Alza, and the limited service activities of Alkermes and Nektar, there remain only a very few top tier companies offering premium drug delivery technologies, generally retaining manufacturing rights.

WATSON ACQUIRES ANDRX (2006)

The acquisition of Andrx by Watson for almost $2 billion closed the circle of its development partnership that began in 1994. It also put an exclamation point on the fact that oral drug delivery products were fully subject to generic competition. In the 1980s and 1990s, drug delivery products enjoyed some degree of protection because their technologies were covered by patents, and functionally equivalent technologies were not readily available. This changed in the 1990s with the efforts of Biovail and Andrx and their sustained-release oral products. While Biovail typically chose to sell its formulations as branded generics, not interchangeable with the branded products, Andrx went straight for the bioequivalent, substitutable AB generic market.

KING LICENSES ABUSE DETERRENT PRODUCTS FROM PAIN THERAPEUTICS (2005), ACURA (2007) & ACQUIRES ALPHARMA (2008)

This series of transactions was executed by King in an apparent bid to establish a leading position in the emerging opioid abuse-deterrent market. By the mid-2000s, it was clear that the abuse of prescription opioid products, particularly sustained-release formulations, was a significant medical and social issue and a business opportunity. The industry response was to develop novel formulations of these opioids with a lower potential to be repurposed and misused.

King kicked off its investment in this area with the licensing of Pain Therapeutics' (PTIE) abuse-deterrent formulation of oxycodone, Remoxy. Still in early Phase III development, King paid PTIE a $150 million up-front payment for marketing rights to Remoxy. This was followed in 2005 by King's deal for Acura Therapeutics' Acurox abuse-deterrent hydrocodone formulations for a $30-million up-front payment. King then increased its investment with the acquisition of Alpharma in 2008 for $1.6 billion, largely for its abuse-deterrent technology and portfolio, most notably Embeda.

There is no question that abuse-deterrent formulations will be important in this decade and beyond. It is not clear whether King has a winner with any of their investments to date. Remoxy is in development and regulatory limbo, and Acura has been sent back to the drawing board with Acurox following a negative FDA advisory panel review. While Alpharma's lead abuse-deterrent product, Embeda, was approved and launched in 2009, the sales to date have been modest, totaling about $50 million through June 2010.

More than a baker's dozen of transactions, these deals can provide a good idea of what to expect for this decade and beyond. One very obvious reality is that drug delivery technology is only as good as the products it can deliver. There is no magic, or value, in technology for technology's sake alone.

Thanks to Dr. Michael Crowley of Theridian Technologies for his helpful comments, and as always, thanks to Dr. Tugrul Kararli for access to his so very useful PharmaCircle database. ◆

BIOGRAPHY

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The material in this report is expanded upon in the upcoming Bionumbers report, DDEP 2010 - A Comprehensive Review of the Development and Commercial Parameters that Impact Drug Delivery Enabled and Enhanced Products.

New Devices for Dispensing Ophthalmic Treatments May Be the Key to Managing the Life Cycles of Established Products

By: Matthias Birkhoff and Degenhard Marx, PhD

According to the World Health Organization (WHO), about 314 million people worldwide suffer from impaired vision; 45 million of them are blind. About 82% of all individuals who are visually impaired are aged 50 or older, representing 19% of the world's population. An increasing number of people are at risk of age-related visual impairment as the global population grows and demographics shift to a higher proportion of older people, even in developing countries.[1]

These figures do not include people suffering from transient infections, dry eye syndrome, or allergic conjunctivitis. Based on these facts, it may be concluded that the majority of ophthalmic medication is and will be for chronic treatment, with a special focus on older people.

For chronic treatment, multidose containers are most useful and very cost effective. For ophthalmic use, few alternatives are available, and most current packaging concepts require preservatives in the formulation to warrant microbial stability. The following discussion will describe a targeted approach for the development of new preservative-free multidose devices for ophthalmic medications.

MATCHING PATIENT EXPECTATIONS WITH PHARMACEUTICAL REQUIREMENTS

New devices need acceptance from patients and consumers to become successful on the market. To access the opinion of patients, people from different areas of the world were asked to evaluate a range of different available devices as well as a few new concepts.

Though the interviewed population was comparably small, the users considered easy and intuitive handling of the packaging much more important than any other aspect. For at least one-fifth of people in the study, the presence of preservatives in the formulation was an issue. Any actuation in the direction toward the eye was totally unacceptable, and any spacer or distance holder was also judged to be unacceptable. Drops were much preferred to sprays. From this survey, it was concluded that a preservative-free squeeze dropper or side-actuated dropper would be most appreciated by patients.

Equally important stakeholders in the field are, of course, the manufacturers of ophthalmic medications. Important requirements here are compatibility of the packaging material with the pharmaceutical formulation and the manufacturing and filling processes. Production and filling of ophthalmic medications are highly sophisticated, so pharmaceutical manufacturers are reluctant to alter established processes or to invest substantially in new filling technologies that obviously require further process qualification.

The third stakeholder is the regulatory environment. Authorities need to make sure that no patient or consumer risks an eye. Agencies enforce guidelines on sterility of the product, absence of particles, and microbial stability. Typically, the observation of microbial growth in a product leads to rejection of the entire batch, which will impact the manufacturer significantly.

CURRENT STANDARD: PRESERVATIVES IN OPHTHALMIC PRODUCTS

Ophthalmic preparations have to be sterile. This requirement is in most cases met by a closely controlled aseptic manufacturing and filling procedure and by placing a suitable preservative or combination of preservatives in the products. The major non-preserved alternative established on the market is single-dose blow-fill-seal containers.

Benzalkonium chloride (BAC) is by far the most widely used preservative, but thimerosal, chlorhexidine, chlorobutanol and phenylethanol, and parabens can also be found in topical ophthalmic medications.[2]

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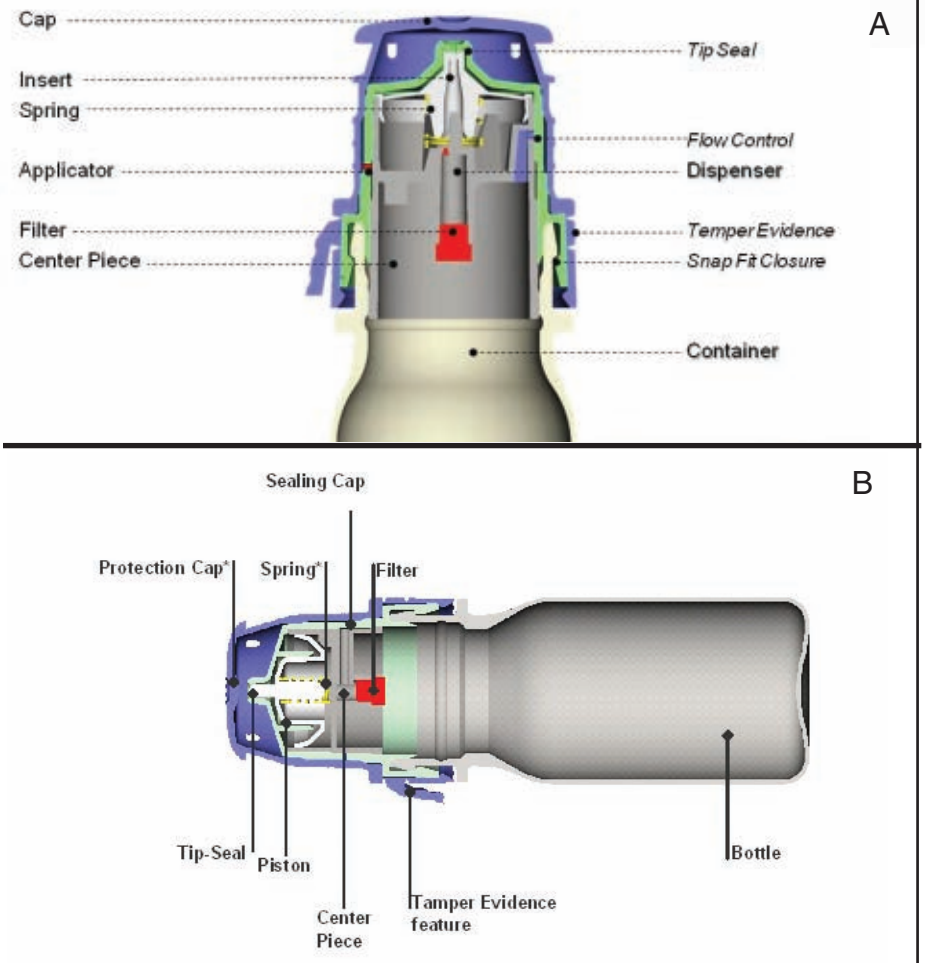
There are two general issues linked to the use of these preservatives, one of which is the choice of materials, which is important only for the manufacturer. Traditional glass containers do not interact with preservatives, but widely used plastic containers and dispensing devices pose problems such as permeation through the container or an interaction with it. Rubber also reacts with preservatives but is still used for components such as stoppers and closures. These have to be pre-treated with the preservatives they are to be in contact with to minimize subsequent uptake during storage.

The issue of significance for the patient and consumer, however, is the high incidence of local side effects attributed to preservatives. The discussion is controversial, and published preclinical and clinical studies are not always consistent. It seems to be clear that short-term use of ophthalmic preparations containing preservatives at low concentrations is well tolerated, but preservatives can cause serious inflammatory effects on the eye with long-term use in chronic conditions, such as glaucoma, allergic conjunctivitis, or dry eye. The responses may include chemical irritation, hyperreactivity, and true allergies.[2]

In response to these findings, manufacturers of ocular medications have developed new preserving systems as integral parts of their formulations in an attempt to limit these toxic side effects.[3]

Preservative-free multidose systems could solve some problems faced by pharmaceutical manufacturers and offer significant benefits for patients in need of chronic eye treatment. The crucial challenges are finding a patient-friendly device and providing convincing data on microbial stability during storage and use.

FIGURES 1A & B



Schematic drawings of the ophthalmic squeeze dispenser (OSD), which delivers a drop when the bottle is squeezed and the pressure forces the tip seal to open. The venting air for pressure equilibration within the system is forced through the sterile filter. Note that the tip seal spring is not in contact with the formulation and the device can be adapted to a certain viscosity range.

DEVELOPMENT OF NEW PRODUCTS FOR THE OPHTHALMIC MARKET

Currently for multidose systems, in most cases, preservatives are used to control microbial contamination during the regular use of the product. Only in this configuration are no further measures needed to prevent microbial occupation when in use. Regardless of whether a preserving agent is used, there are two pathways for microorganisms to enter the otherwise tight system: 1) via the orifice, when the tip or the remaining liquid attached to it comes into contact with infected tears or skin or with mucosal flora and 2) via the venting air when medication from the bottle is replaced by ambient air.

One way to overcome this issue is the use

of oligodynamic compounds, such as silver wires in the tip, and/or collapsing bags to tackle the problems. Aptar Pharma decided to adapt an approach that is well established for preservative-free nasal spray systems: a mechanical seal technology combined with sterile filtration of the venting air. The spring-loaded tip seal keeps the system closed until a defined pressure is reached during actuation. The formulation is then forced through the orifice. When the pressure drops consequently, the tip seal immediately closes the orifice by an outward movement, which prevents any back-flow of contaminated liquid or particles.

For the venting air, Aptar Pharma uses a sterile filter (0.2-micron nominal pore size) to stop microorganisms from entering. The principle of sterile filtration is well recognized and widely used. As some ophthalmic formulations have compatibility issues with metal, it is advisable that, as in the nasal spray device, the ophthalmic system features a metal-free fluid path.

OPHTHALMIC SQUEEZE DISPENSER & OPHTHALMIC DROP DISPENSER

The development process resulted in two different devices: the ophthalmic squeeze dispenser (OSD) and the ophthalmic drop dispenser (ODD). Although both share the principles of tip seal technology and sterile filtration of the venting air, these devices have different properties.

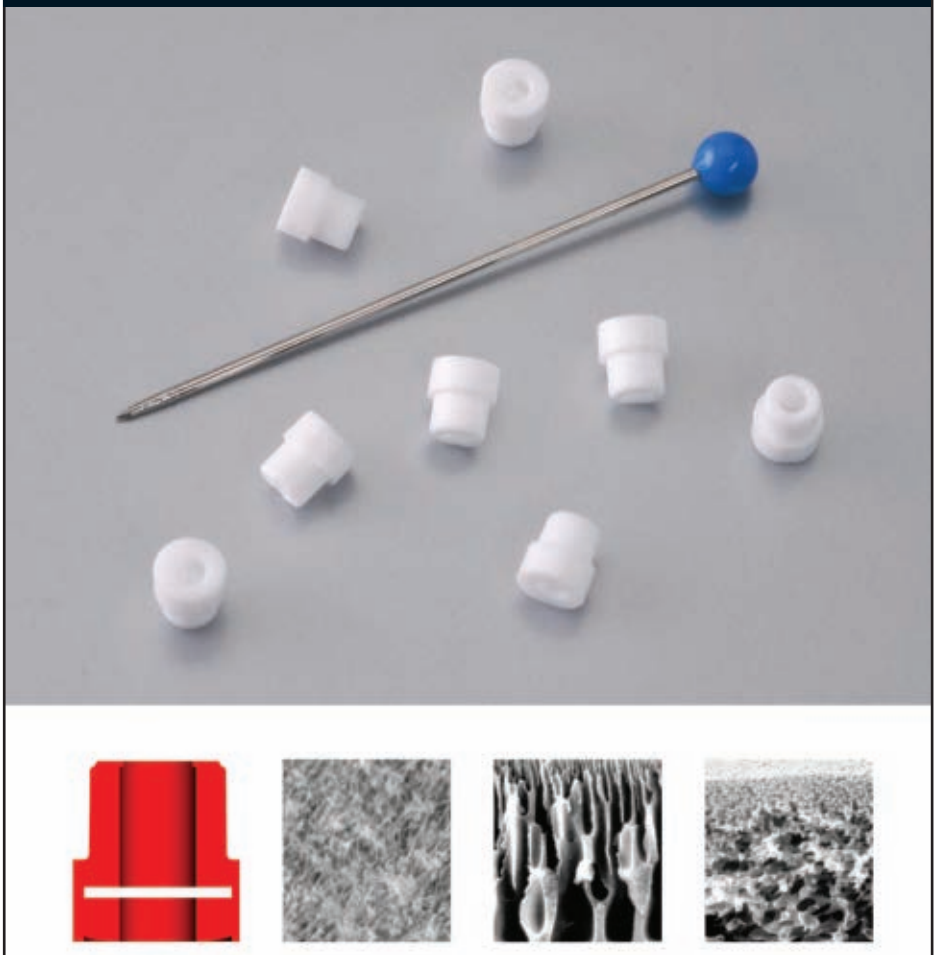
The OSD is actuated by squeezing the bottle, which restricts the choice of material for its construction. For this device, a modified 10-ml LDPE (low density polyethylene) bottle is used. The thickness of the bottle wall must be a compromise between minimizing water vapor loss and providing acceptable actuation forces. One limitation of this concept is that a higher viscosity of the product will increase the force needed to deliver a drop. The device can easily be adapted for a certain range of viscosity, however, to keep forces within a rational limit and to deliver a consistent drop.

The ODD works like a side-actuated pump and delivers drops in the range of 35 microliters. For this device, glass or stiff plastic bottles may be used to avoid interaction of the formulation with the material. The pump system can deal with a wider range of viscous products at low actuation forces.

MICROBIAL INTEGRITY TESTS

Although there are multiple guidelines in place for preserved multidose and preservative-free single-dose containers, there is no specific guideline on microbial testing of preservative-free ophthalmic devices. Aptar Pharma

FIGURE 2



Sterile filter for the venting air ready for assembly, schematic cross section, and microphotographs of the membrane (pore size of 0.22 microns) used for the production of these filters.

therefore collaborated with the Zwisler Laboratory in Constance, Germany, to create tests that ascertain microbial integrity under challenging conditions. These tests resemble those carried out on preservative-free nasal spray devices.[4] It should be clear that the tests protocols described here are very challenging to show the proper function of the device even under extreme conditions and not to mimic in-use stability. For this reason, we selected a very agile germ (*Pseudomonas aeruginosa*) for the tip seal test and the tiny and robust spores from *Baccilus subtilis* for the whole package integrity test. To provide optimum conditions for the germs to growth in the case of any contamination, we filled the devices with broth medium.

CHALLENGING THE FUNCTION OF THE TIP SEAL

Devices are filled with bacterial culture medium under sterile conditions. The devices are then dipped into a suspension of *Pseudomonas aeruginosa* (10^7 colony-forming units per ml) and actuated with submersed tips. This procedure is repeated twice daily for 5 days; subsequently the samples are incubated for another 5 days. At the end of the test, no bacterial ingress was observed, even when the challenge period was extended to 28 weeks.

CHALLENGING FILTER MEMBRANE & VENTING SYSTEM INTEGRITY

Again, the devices are filled with growth medium under sterile conditions. A rubber sleeve is mounted on the devices so that it covers the dropper (with exemption of the tip) and its connection to the bottle. Artificial dust containing spores of *Bacillus subtilis* (~10^9 spores per gram) is put into the sleeve. Subsequently, the device is vortexed at 2500 rpm to distribute the powder evenly in the sleeve. The dropper is actuated several times to deliver some drops, then gently shaken. The procedure is repeated until half of the medium has been dispensed and a sufficient amount of air has been allowed to ingress. Afterward, the devices are incubated for another 5 days to

FIGURE 3 A & B

Details of the automated assemly line for the OSD production under ISO class 7 clean room conditions and OSD ready for packaging. OSD will be delivered to customers after gamma radiation separate from the squeeze bottles.

monitor microbial contamination of the bottle content.

These procedures are much more exacting than what can be expected in normal use. A typical ophthalmic preparation will normally not support bacterial growth as the culture medium does, and the numbers of test bacteria far exceed the counts on skin or in ambient air. It is important, though, to test the devices under such harsh conditions to convince potential customers and the authorities, who ultimately have to approve the product device combinations.

PRODUCTION OF THE DEVICE

The ophthalmic devices utilize tip seal and filter technology very similar to the well-accepted preservative-free nasal spray systems marketed successfully by Aptar Pharma for 8 years, with more than 100 million pumps sold to date. Aptar Pharma is familiar with the industrialization of this technology. Molded components of the devices are produced at the company's German plant in Eigeltingen; the devices are assembled in ISO 7 clean rooms on state-of-the-art equipment. A 100% inline quality control for proper function of the tip seal and integrity of the sterile filter membrane is embedded into the manufacturing line. The bottles are purchased from an external supplier acknowledged for high-quality pharmaceutical packaging material. The dropper and bottles are sterilized using a validated gamma radiation procedure.

SUMMARY

The new ophthalmic devices of Aptar Pharma solve major current issues with ophthalmic multidose devices. They are suited to many liquid ophthalmic medications, in particular those for chronic conditions such as glaucoma or dry eye; and the simple intuitive handling is ideal for the target group. Preservatives can be omitted, which will be appreciated by the high number of patients experiencing eye irritation or allergic responses with preserved formulations. This positive benefit for patients is most likely going to increase medication compliance as prescribed. The new devices also offer advantages to the manufacturers of ophthalmic medications as there is no need for preservatives in the formulation that could potentially interact with other components of the formulation or the device, and the development and (later on) production process is less difficult. For the manufacturing of the OSD and ODD, substantially less material is used compared to that needed to pack the same number of doses with blow-fill-seal technology. The new devices can provide cutting edge technology for the life-cycle management of established products with low investments in filling technology. ◆

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BIOGRAPHIES

Matthias Birkhoff is Vice President of Marketing for Aptar Pharma. He joined former Ing. Erich Pfeiffer GmbH in 1998 and was Sales Director for the Asia Pacific region before getting involved in business development and marketing. After obtaining a nursing degree, he studied Medicine at the University of Düsseldorf in Germany.

Dr. Degenhard Marx is Director, Scientific Affairs for Aptar Pharma, formerly known as Ing. E. Pfeiffer, Pharma Division. Following the study of veterinary medicine and the successful completion of his thesis at the University of Leipzig, Dr. Degenhard joined the Arzneimittelwerke Dresden/Asta Medica co-operate research in 1992. In 2001, he took over a Senior Research position at Altana Pharma/Nycomed in Constance, Germany. During this time in the pharmaceutical industry, he collected ample experiences in the drug development of anti-inflammatory and cardio-vascular drugs.

RNAi
DELIVERY

Self-Delivering RNAi Compounds

By: James Cardia, PhD; Dmitry Samarsky, PhD; Tod Woolf, PhD

INTRODUCTION

Introduction of small interfering RNAs (siRNAs) into cells with transfection reagents results in potent and specific gene silencing by RNA interference (RNAi). While siRNA-based drugs represent a potentially significant therapeutic opportunity, the ability to apply this technology to drug development has unfortunately been impeded by the absence of efficient and non-toxic in vivo delivery systems. Currently, delivery is believed to be a major hurdle on the path to wide acceptance and utility of RNAi as a new class of therapeutic modalities. There are two major approaches to enhancing delivery: (1) formulation of oligonucleotides with particles/liposomes or (2) chemical modification of the oligonucleotide itself. RXi Pharmaceuticals has recently developed self-delivering rxRNA or sd-rxRNA™, which is a novel, covalently modified RNAi compound configuration that does not require a delivery vehicle to enter cells and has improved pharmacology compared to traditional siRNAs.

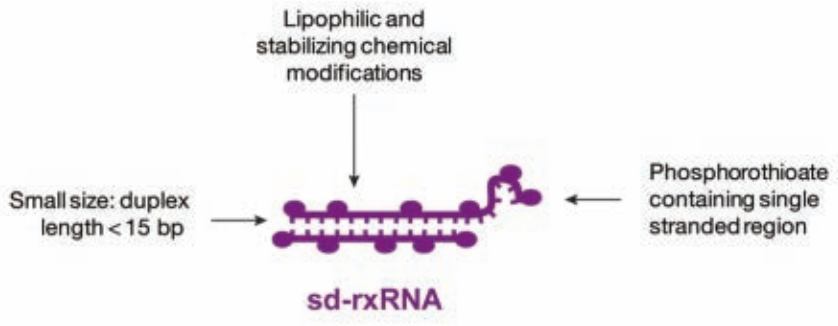
GENE SILENCING BY RNA INTERFERENCE

siRNAs are a promising new class of therapeutic oligonucleotides that target mRNA. In 1998, Andrew Fire and Craig Mello demonstrated that introduction of double-stranded RNA into the cells of a model eukaryotic organism, C. elegans, silenced the expression of complementary target genes by a process of post-transcriptional mRNA cleavage.[1] Introduction of siRNAs into mammalian cells also results in potent and specific gene silencing by the RNAi mechanism.[2] Properly designed RNAi compounds can be 100 to 1000 times more potent than traditional antisense compounds when transfected into cultured cells (EC50 of 5 to 50 pM for RNAi, compared to 1 to 50 nM for antisense).[3] RNAi compounds used in cell culture with cationic lipoplex transfection reagents have become one of the most widely used tools in research biology. In addition, a single administration of RNAi compounds to non-dividing cells results in long-term (up to 15 days) silencing, thus promising patient-friendly administration schedules.[4] Given the high potency of RNAi within the cell, it is generally agreed that RNAi will be broadly developed for therapeutic applications once issues of in vivo delivery are resolved.

CURRENT STAGE OF PARTICLE-BASED APPROACHES TO RNAi DELIVERY

Developers of liposomal and lipoplex formulations have focused on cationic lipid cocktails that mask the high charge-to-mass ratio of siRNAs.[5,6] While these formulations are highly effective in vitro, most are not fully optimized for in vivo applications.

FIGURE 1



sd-rxRNA Structure: Combination of Advanced Features of RNAi & Antisense Technologies
sd-rxRNA compounds have a shorter duplex (< 15 bp), a phosphorothioate containing single-stranded tail, and lipophilic and stabilizing modifications in both strands.

One issue is that the tissue distribution of siRNAs delivered in these formulations is predominantly confined to tissues with discontinuous endothelium, such as the liver. Some of these lipid-based formulations can be efficacious in vivo at very low concentrations (< 0.3 mg/kg) in animal models; however, potential immune-stimulatory side effects, especially upon repeat administration, can still remain an issue. To date, three INDs based on liposome-formulated siRNAs have been filed, one of which has been completed. Immune-stimulatory side effects observed in one patient in this clinical trial resulted in discontinuation of dosing and a revision of the formulation and siRNA.

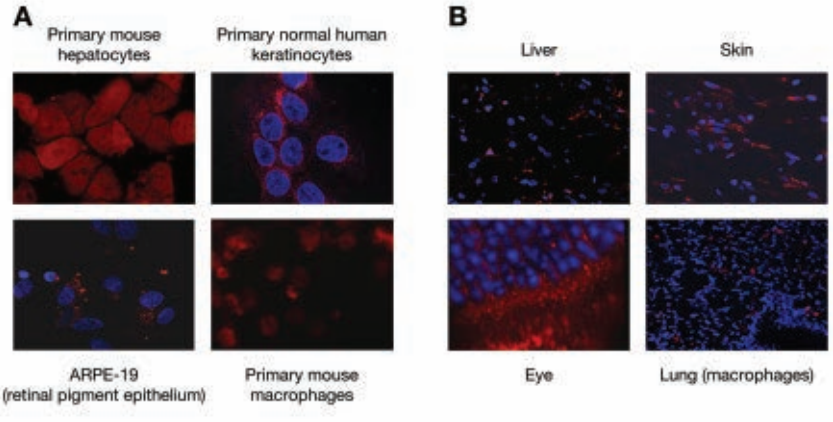
In an alternative delivery approach, significant progress has been achieved with a tumor-targeted, dextran-based siRNA formulation. Evidence of RNAi efficacy (mRNA knock-down) was seen in patients receiving repetitive, high doses (17 to 35 mg/kg) of this type of particle in a Phase I clinical study.[7] This work presented one of the first indications of RNAi compound efficacy in man and proved general applicability of RNAi technology for development of human therapeutics. While oligo formulation is one approach to achieve in vivo efficacy, development of siRNAs with improved drug-like properties will significantly expand RNAi clinical utility.

CHEMICALLY MODIFYING RNAi COMPOUNDS TO ENHANCE DELIVERY

In principle, it would be advantageous if chemical modification of the RNAi compound itself could facilitate delivery in a manner analogous to that achieved with antisense therapeutics. Early on, Alnylam Pharmaceuticals demonstrated that simple cholesterol conjugation to an siRNA compound improved PK/PD properties and enabled gene silencing in the liver.[8,9] Although the observed silencing effect required repetitive administration of high doses of oligonucleotide (3 x 50 to 80 mg/kg), this work provided the first evidence that medicinal chemistry can significantly impact in vivo efficacy of an oligonucleotide. RXi has recently developed a different type of chemically modified RNAi compound with improved drug-like properties. These chemically modified RNAi compounds are referred to as "self-delivering," defined as chemically modified RNAi compounds that do not require a delivery vehicle to efficiently enter target cells in vitro and in vivo.

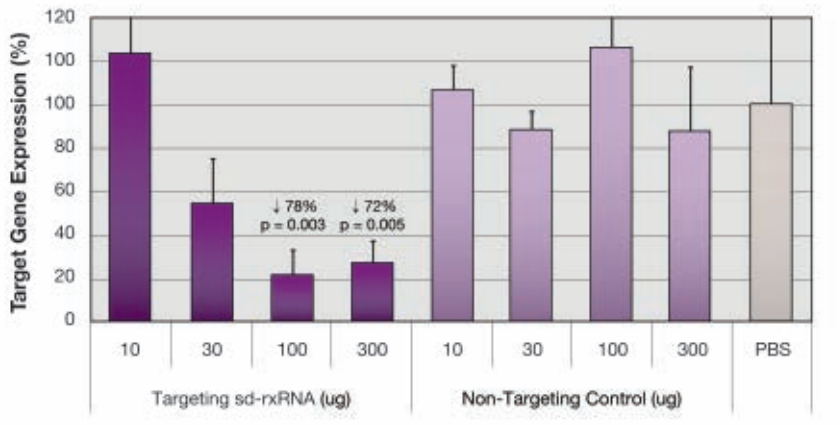
The self-delivering RNAi approach would obviate the need for potentially complex and toxic delivery vehicles. This approach should also reduce the expense and complexity of clinical development and commercialization because it requires the manufacture of the compound alone without the development of a complex formulation. Self-delivering RNAi compounds are much smaller than liposome or lipoplex complexes (~ 10 nm for sd-rxRNA compared to > 80 nm for liposomes or lipoplexes), and their reduced size may allow for broader tissue distribution, better tissue penetration, and the ability to use subcutaneous administration routes.

FIGURE 2



sd-rxRNA Uptake in Diversity of Cells & Tissues
A) DY547 fluorescently labeled sd-rxRNA (red) was added to cells in culture without a transfection reagent for 24 to 48 hours, nuclei were stained with Hoechst dye (blue), and cells were visualized with confocal microscopy. Silencing (> 90%) was observed by assaying MAP4K4 expression normalized to housekeeping genes PPIB and ACTB using a branched DNA assay (data not shown). B) DY547 fluorescently labeled sd-rxRNA compounds were administered by IV (liver); intradermal injection (skin), intravitreal injection (eye), and instillation (lung macrophages).

FIGURE 3



sdRNA In Vivo Efficacy

Intradermal injection of sd-rxRNA results in robust and potent silencing. 10 to 300 micrograms of a targeting or a non-targeting sd-rxRNA were administered by a single intradermal injection to the dorsum of a rat. At 48 hrs, 3-mm punch biopsies were harvested, and target gene expression was determined on the purified RNA by qPCR. Data are presented as target gene level normalized to a housekeeping gene and expressed relative to the PBS treated control group (± stdev).

sd-rxRNA COMPOUNDS

sd-rxRNA is a novel class of proprietary, lipophilically modified RNAi compound that does not require a delivery vehicle for cellular uptake and efficacy. It incorporates advanced features of both RNAi and antisense technologies (Figure 1). Traditional, single-stranded antisense compounds have favorable tissue distribution and cellular uptake properties; however, they do not have the intracellular potency that is a hallmark of double-stranded RNAi compounds.[3] Conversely, the duplex structure and hydrophilic character of traditional siRNA results in poor tissue distribution and cellular uptake. In an attempt to combine the best properties of both oligonucleotide classes, sd-rxRNA has a single-stranded region and a shorter duplex region and contains a variety of nuclease-stabilizing and lipophilic chemical modifications (RXi, Manuscript in preparation).[10] The combination of these features allows sd-rxRNA to achieve more favorable tissue distribution, efficient spontaneous cellular uptake, and potent long-lasting intracellular activity.

EFFICIENT CELLULAR UPTAKE IN VITRO & IN VIVO

Treatment of multiple cell types with fluorescently labeled sd-rxRNAs results in efficient and universal cellular uptake (Figure 2). In contrast to lipid-mediated delivery, in which transfection efficiency can be seen to be highly variable within a field of cells, sd-rxRNA is uniformly taken by cells upon contact. All cell types tested to date (including primary, neuronal, and non-adherent) internalize sd-rxRNA compounds efficiently, resulting in significant target silencing activity (data not shown). In addition to efficient cellular uptake in vitro, sd-rxRNAs demonstrate good tissue penetration and silencing activity following local and systemic administration in rodents. Efficient liver uptake has been observed with both IV and SC administration, in which high doses were required for silencing. While achievement of systemic clinically relevant efficacy requires further technology optimization, it is immediately applicable for gene silencing in tissues, where local administration is an option (Figure 2A). Local delivery to the desired site of action avoids the issues of kidney clearance and vasculature escape, allowing focus on the challenge of tissue penetration and spontaneous cellular uptake in vivo. As shown in Figure 2B, efficient in vivo cellular uptake can be seen in the liver following IV dosing, and in the skin, the retina of the eye, and alveolar macrophages following local administration.

EFFICIENT IN VIVO SILENCING UPON LOCAL ADMINISTRATION

Using intradermal administration as a model for local delivery, sd-rxRNAs were demonstrated to efficiently induce gene silencing. Maximum mRNA target level knock-down was achieved with a single administration of 100 micrograms. A minimal amount of compound was in the extracellular matrix, with the majority present in cellular cytoplasm 24 hours post-injection. Similar levels of silencing were demonstrated for multiple genes, and the effect persisted for more than a week (following 2 injections on days 1 and 2).

THERAPEUTIC POTENTIAL

Based on the promising data to date, sd-rxRNA and other chemically modified siRNA approaches may offer a key advance for use in future clinical development. These results may support clinical development in a number of dermatological indications, such as wound healing, scar reduction, and other indications where local injection is feasible or in which the skin is compromised. In addition, sd-rxRNA shows complete retinal penetration and efficient silencing upon intravitreal administration to the eye (data not shown), efficient delivery to alveolar macrophages (lung), and spinal cord, and may be applicable for treatment of a variety of ocular, respiratory, and CNS diseases. Thus, sd-rxRNA may have near-term clinical utility for local administation, with the potential for systemic therapeutic applications based on further technology optimization.

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BIOGRAPHIES

Dr. James Cardia is currently working as a Scientist at RXi Pharmaceuticals. His interests include applications of RNA biochemistry and chemistry to therapeutics. He was awarded the Donald White Teaching Award in 2004 and the Ruth Kirschstein National Research Service Award in 2007. He earned his PhD in Chemistry at Boston College in 2006 and performed his post-doctoral fellowship at Harvard University from 2006-2009.

Dr. Tod Woolf is a Scientific Advisory Board Member at RXi Pharmaceuticals. His research is focused on the use of chemical modifications to enhance oligonucleotides (synthetic DNA and RNA) for therapeutic and research applications. He co-founded and served as CEO of Sequitur and RXi Pharmaceuticals. He has co-authored over 50 scientific papers and patent applications. He served on scientific advisory boards of Signet Labs, ProNai, and TriLink Biotechnology. Dr. Woolf earned his PhD in Molecular Biology from Harvard University.

The SAINT™ Technology for DNA, RNA & Protein Delivery

By: Marcel H.J. Ruiters, PhD

INTRODUCTION

Since the human genome project has unravelled the human genes, the next step in research will be to study the functions of these genes and their proteins as well as the interaction between genes, RNAs, and proteins. From a clinical point of view, this will generate thousands of targets for therapeutic intervention - starting at DNA-mediated therapies (viral, plasmid, or plasmid derivatives like Midge-vectors) and epigenetic editing (histon modification or methylation) via RNA-transcription (siRNA) and translation regulation (zinc-fingers, tfo-constructs) toward protein replacement. Finally, combining these methodologies will result in the application of Technology for Recombination In Situ (TRIS).

Although all of these therapies hold great promise, the major hurdle in their development is the exclusive delivery in the targeted cells in the right organ.[1] Adequate drug delivery technologies are an urgent need, and huge efforts are made to solve the problem for specific applications. Unfortunately, each problem has its own solution, and general rules cannot be applied. Synvolux has identified four problems that should be tackled to bring a solution closer, indicating the delivery technology needs to be (1) applicable in vivo, (2) bio-safe and biocompatible at physiological needed concentrations, (3) targetable, and (4) highly efficient in intracellular release.

To address all these issues, the company has decided to build a modular system that can be adjusted to the specific requirements for any given application.

APPLICABILITY IN VIVO & IN VITRO

The SAINT™ delivery technology has been validated in vitro as well as in vivo in a variety of cell lines, animals, and disease models, and SAINT products are being used by research groups all over the world.

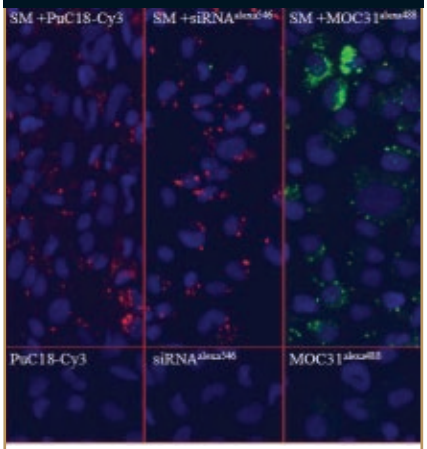
DNA-plasmids or plasmid-derivates ranging from 600 bp up to 102 Kbp are efficiently transfected. In collaboration with the German, Berlin-based biotech Mologen, Synvolux is developing a DNA vaccination technology for intradermal application. This developmental approach is funded under the Euro-Trans-Bio program.

Down-regulation of genes has been shown using minimal amounts of siRNA (0,3 pM). The off-target effects often seen with chemically (un)modified siRNA were minimalized by applying the SAINT technology. Furthermore, we have shown that complexing siRNA with SAINT-RED (RNAi-Enhanced Delivery) protects the siRNA from degradation. Stored at room temperature after 9 months, the complex is still highly efficient in transfecting cells, showing the same down-regulation as on the day of preparation.

Figure 1 visualizes the delivery of siRNA (RNAi), DNA, and proteins by using lipoplexes based on the SAINT synthetic amphiphiles in combination with helper lipids.[2,3]

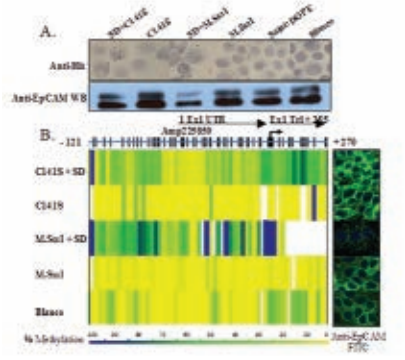
A more physiological way of

FIGURE 1



Delivery of 1 microgram of Cy3-labeled DNA, 1 microgram of Alexa^{546}-labeled siRNA, or 2 micrograms of Alexa^{488}-labeled antibody by 20 microliters, 75 nmol SAINT:DOPE (SM) 48 hours.

FIGURE 2



SAINT-mix mediates functional active protein delivery into the nucleus.
(A) Delivery of DNA-methyl-transferase M.SssI into SKOV-3 cells has been confirmed by staining the His-tag. The enzymatic almost inactive C141S mutant shows the wildtype is only delivered after profection SD. Without SAINT-MIX, no His-tags are detected. Westernblots show the protein expression was down-regulated with 48 hours only when the wildtype Enzyme was used in combination with the transfection-reagent.
(B) Down-regulation of the EpCAM has been confirmed by fluorescent staining with an anti-EpCAM FITC Ab. Bisulphite sequencing of the promoter region of the EpCAM gene shows that methylation at the promoter region corresponds with lower protein expression.

interference with the cellular metabolism and proliferation is with proteins directly. Compared with plasmid DNA delivery, which results in the almost unlimited transcription of the gene, profection (protein-transfection) results in a fast cellular response that is limited in time by the half lifetime of the protein. However, the effect of epigenetic interfering proteins like DNA methylases can have a lifetime effect on the cell lineage.[4] In the example in Figure 2, the immuno-histochemical stainings of the tumor marker protein EpCAM seems to be directly correlated with the methylation status of the EpCAM-gene, which is unravelled by bi-sulphite sequencing.

BIO-SAFETY & BIOCOMPATIBILITY

The basic biological safety has been demonstrated for SAINT-18. In the Ames-test and chromosomal aberrations test, doses could be reached that exceed the DNA amount of the viral load of adenovirus (Gelsinger dose) by a million-fold. In collaboration with different partners, we have shown bio-safety in mice, rats, guinea pigs, chickens, geese, rabbits, cats, dogs, goats, and horses. In total, more than a few thousand animals were tested.

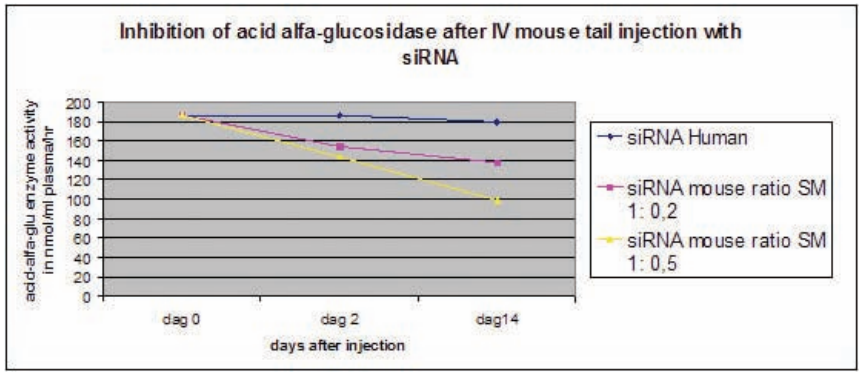
No acute toxicity due to SAINT complex injection (aggregates) with either DNA, siRNA, or protein could be found, and no signs of organ pathology or serological differences became apparent. Moreover, up to a dose of 5 mg of SAINT-MIX/kg body weight, no adverse effects were seen, while to achieve a biological effect with DNA delivery, only 5 micrograms of SAINT-MIX/kg body weight was required.

IN VIVO SIRNA DELIVERY

It has been shown that delivery of siRNA lipoplex with SAINT-MIX via the tail vein in a non-hemodynamic pressure application on a daily administration scheme of 50 micrograms siRNA results in down-regulation of the alfa-glucosidase enzyme activity by almost 50%.[5] Thus, one has to consider that the enzyme's half-life time is 10 days, and not all target cells (those cells producing alfa-glucosidase) are hit every time (Figure 3).

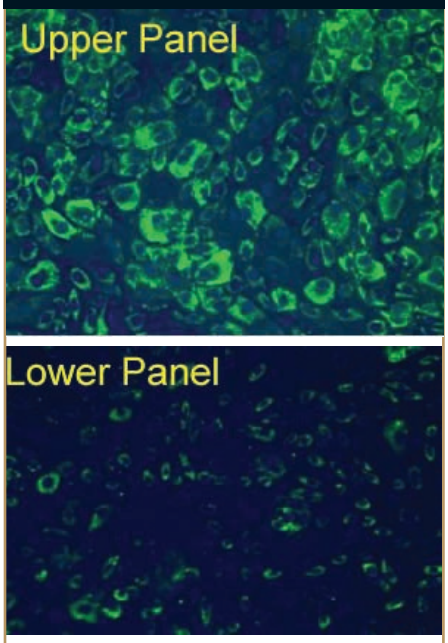
BL6 mice were daily injected with 50 micrograms of siRNA against GAA alone, or in complex with SAINT-RED (charge ratio siRNA:SAINT-RED, respectively 1:0, 2 and 1:0, 5) and sacrificed 14 days after the first injection (n = 2 for control group and n = 4

FIGURE 3



Down-regulation of GAA in plasma of mice after daily injection with siRNA complex with SAINT-RED.

FIGURE 4



TNF-alpha-activated Human Umbilical Vein Endothelial Cells were incubatred for 24 hours with liposomes with encapsulated calcein and E-selectin. After 24 hours, fluorescent microscope pictures were taken. If calceine is released form the liposome, its becomes green fluorescent.
Upper panel: Anti-E-selectin immunoliposome with 20% SAINT.
Lower panel: Anti-E-selectin immunoliposome without SAINT.

for SAINT-RED groups). Every other day, blood samples were collected and analyzed for down-regulation of GAA using the 4-MUG-assay and acarbose as inhibitor of maltase-glycoamylase as decribed in (Reference 5). Statistical analysis revealed a significant effect ($P < 0.05$) of siRNA treatment over the time in the siRNA-SAINT-RED (ratio 1:0.5) treated mice.

TARGETED DELIVERY

The major challenge in drug delivery is the development of targeted delivery devices. In general, most of the drugs that are injected intravenously end up in the liver macrophages or are excreted by the kidney within minutes. So enwrapment of the drug to ensure a longer circulation in the blood is a generally used strategy. Now, attempts are also made to deliver the drug in the rights cells, using for instance antibodies that are directed against a surface antigen of the targeted cells. Data available to date, however, show that all these solutions have to be fine-tuned for every application, and these adjustments might even be different per species (Alnylam, Silence Therapeutics).

Therefore, Synvolux decided to build a modular system that can be adjusted to every specific application. The SAINT-linker technology was developed to enable the formulation of drug delivery devices with targeting properties based on surface-recognition sides present on the targeted cells.

The basic structure of the SAINT molecule can be tailored to the specific needs. In addition, clients can apply their own ligand, peptide, antibody, or fluorescent tag by coupling it to the SAINT-linker device.

As previously mentioned, this technology is not limited to the use of antibodies; chemical ligands, peptides, or even lipids can be used to achieve targeting.

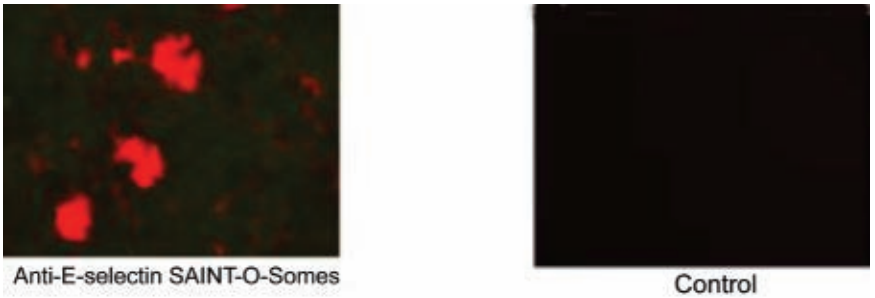
The modular system enables its use in lipoplexes or liposomal formulations.

It has been shown that E-selectin targeted delivery of siRNA against IL-8 results in a 60% down-regulation of the gene in hard-to-transfect human umbilical cord endothelial cells.[6]

HIGHLY EFFICIENT INTRACELLULAR RELEASE

Although targeted delivery devices theoretically improve the effect of the drug, it is obvious the delivery of the drug into the cell as such is not the only hurdle. Delivery of the drug into the cell generally means the drug is now trapped into the endosomal compartment of the cell where it is inactive and mostly degraded as fast as possible by the endosomal enzymes. Escape from the endosome, or bypassing the endosomal route, is needed to have the drug present at physiological levels in

FIGURE 5



DiI-labelled SAINT-O-Somes with e-selectin targeting devices we injected via the tail vein of mice and localized at the target organ, the endothelial cells of the inflamed kidney.

the cytoplasma and/or nucleus so it can become active. Much effort has been put into the pH-dependent switch release initiated after endosomal uptake; however, this does not yet seem to be the success strategy we are all looking for.

The liposome is a drug delivery system widely used across the pharmaceutical industry. Combining classical liposomes with targeting devices in combination with SAINT molecules results in the creation of so-called SAINT-O-SOMES. As shown in Figure 4, the ability to enhance uptake by using a cell-specific antibody as a targeting device has been demonstrated. More importantly, it has been shown that the release of the encapsulated chemical compound was enhanced by at least a 100-fold.[7]

The first attempts to use the high-release targeting devices in vivo made us optimistic that our chosen approach might be successful. We delivered anti-inflammatory siRNA at the glomeruli of an inflamed mouse kidney, making use of antibodies directed against E-selectin, an adhesion molecule that is up-regulated in inflammation.

Although Recombinant In Situ Technology (TRIS) seems to be far fetched, first proof-of-concept of this technology has been established in cell-line applications. By the delivery of a TFO-guided DNA-methyltransferase in SK0V-3 tumor cells, it has been it is possible to down-regulate the tumour gene EpCAM.[8] A second approach by the Mariane Rots group showed it is possible to increase homologous recombination by profection of a site-specific restriction endonuclease (triple helix-forming device, or zinc-finger-device) and co-transfection of a rescue promoter plasmid construct, resulting in restoration of a corrupt reporter gene.[5]

These two reports, in combination with the delivery technologies developed at Synvolux, will enable the application of TRIS, a completely different approach in the treatment of (at least) mono-genetic diseases.

SUMMARY

This discussion clearly shows the SAINT delivery technology meets all the requirements as an ideal delivery system for DNA, RNA, and proteins. We therefore believe the technology can greatly contribute to the removal of what today is still the biggest hurdle in DNA/RNA/protein-mediated therapies: delivery.

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BIOGRAPHY

Dr. Marcel H.J. Ruiters is CEO and Co-Founder of Synvolux Therapeutics. As a molecular biologist, he worked on unravelling gene regulation in *Drosophila* and *Schizophyllum commune*. In 1989, he moved towards preclinical research. Starting on mitochondrial diseases, he got interested in the field of DNA-mediated therapy and the delivery issues thereof. He is also Associate Professor of Medical Biology at the University Medical Center Groningen, the Netherlands.

SPECIALTY PHARMA
Strategies For Business Development

Therapeutic Focus

Weekly, Oral Zoledronic Acid Can Improve Quality of Life for Bone Metastases Sufferers

By: Cindy H. Dubin, Contributor

Patients suffering from late-stage cancer often learn that the disease has metastasized to the bones, which is a progression of their disease. The bone is a common site for metastasis. Bone metastasis or "bone mets" occurs when cancer cells from the primary tumor relocate to the bone. Cancer cells that have metastasized to the bone cause lesions to form and stimulate osteoclast activity, resulting in rapid breakdown of bone. This process of bone breakdown stimulates the tumor activity in the bone, causing a cycle of bone breakdown and tumor growth. Bone metastases or bone mets are a major clinical concern that can cause severe pain, bone fractures, spinal cord compression, hypercalcemia, and rapid degradation in the quality of life for patients. Types of cancer that most commonly metastasize to bone include prostate, breast, and lung cancers, although all types of cancer are capable of doing so.

Pain is the most common symptom and usually the first symptom that patients notice and is found in 70% of patients with bone metastases. Bone pain has been described as one of the most unpleasant types of pain by patients. Pain is most often felt at the site of the metastasis, which is referred to as localized pain, and usually results when a tumor impacts on bones, nerves, or other organs in the body. If left untreated, the bone mets patient is liable to suffer bone fractures or compression of the spinal cord. Often, the lesions created by the tumor in the bone have to be treated with surgery or radiation. The consequences of bone mets can have a significant affect on cancer patients and their Quality of Life.

Current Treatments for Bone Metastases

Approximately 1.5 million patients worldwide suffer from bone metastases, and the cost of managing bone metastases in the US is estimated at $12.6 billion annually. According to the University of Michigan Comprehensive Cancer Center, various cancer treatments are available to control the symptoms and the spread of bone metastases, and a variety of new agents are currently being developed.

Radiopharmaceutical therapy delivers radiation to tumor cells without harming normal cells. This type of therapy involves the injection of active metals that give off radiation particles in the patient. By providing radiation directly to the bone, these metals target and destroy the active cancer cells in the bone. Pain is also decreased or relieved entirely. This therapy has been shown to decrease platelet and white blood cell production in some patients as they undergo more treatments.

Radiation therapy, often called radiotherapy, involves the use of ionizing radiation–high-energy rays that are given off during treatment. The radiologist directs these rays to injure or destroy cancer cells in the area of the bone metastasis or tumor. Although some normal (non-cancer) cells are destroyed in the process, these cells can repair themselves and restore normal function. The goal of radiotherapy is to destroy cancer cells so that they cannot reproduce and grow.

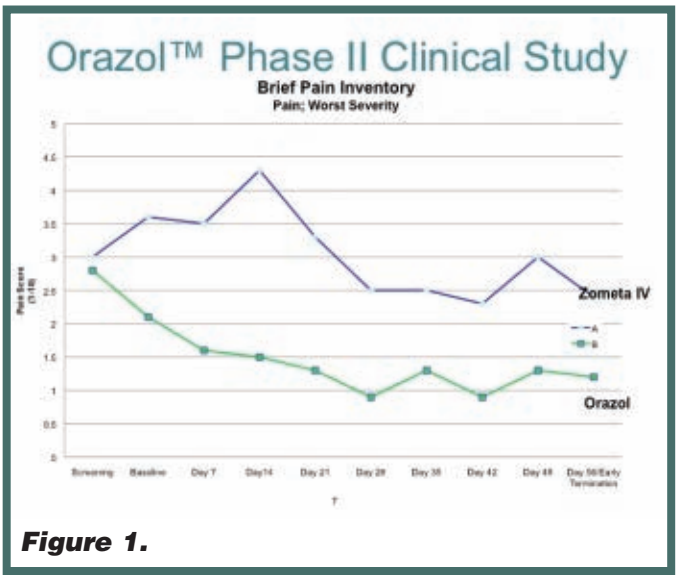


Figure 1.

In most cases, surgery can restore the function of the original bone. The type of surgery will depend upon the location and size of the bone metastasis tumor. Surgery usually involves removing all or part of the tumor and stabilizing the bone to prevent breakage. With fractures or impending fractures, surgery could include placement of metal plates, rods, screws, wires, nails, and/or pins or prostheses. The purpose of these tools is to strengthen or provide structure to the bone. Another option for surgery includes reconstruction of bones or joints. Reconstruction is a procedure in which metal, plastic, allografts, or a combination of these, replaces the damaged bone in the area of the metastasis. Over time, this piece becomes part of the human skeleton.

The current gold standard of treatment is intravenous bisphosphonates. Bisphosphonates are a class of medications shown to be effective in treating bone metastases in breast cancer, prostate cancer, multiple myeloma, lung, renal, and other solid tumor patients. The kind of bisphosphonates given for bone metastases is always given through an IV infusion. Specifically, they inhibit the breakdown of bone, decrease the risk of fractures, and decrease pain from bone metastasis. They also reduce the number of future radiation or surgery treatments for these patients. Commonly, patients take bisphosphonates along with other forms of treatment for their cancer.

"Without interventions like bisphosphonates, the consequences are fractures or spinal cord compressions, which together with surgery or radiation, are known as skeletal related events (SREs)," says John Lynch, CEO of Ireland-based Merrion Pharmaceuticals plc. "These SREs have been the endpoint for many studies assessing the effectiveness of bone metastases treatments."

The foremost biophosphonate in oncology is zoledronic acid, which has a known safety profile and has been shown to have anti-tumor effects when used as an adjuvant in cancer treatment. The

current leading zoledronic acid-based product on the market is Zometa® from Novartis. Bone metastases patients may obtain relief from a once-a-month trip to the infusion clinic for an infusion of Zometa, which is used to reduce and delay bone complications due to bone metastases. The IV infusion can delay progression of the metastases in the bone.

The monthly infusion of Zometa results in a high concentration that has been shown to cause kidney damage, says Mr. Lynch. And, patients may experience flu-like symptoms from the infusion for 24 to 48 hours called acute phase reaction (APR). Additionally, the treatment can be costly.

"From the payer's perspective, the cost of a monthly infusion has been calculated to be $359, and the drug costs more than $800 in the US, which can be a burden on the healthcare system." he says.

Nonetheless, 2009 worldwide sales of Zometa reached $1.5 billion.

About Orazol

Orazol™ is a tablet form of zoledronic acid developed by Merrion Pharmaceuticals that delivers the dosage on a weekly rate. Orazol is in development to treat bone metastases associated with prostate, breast, and other cancers. According to Mr. Lynch, the Quality of Life benefits offered by Orazol are exponential.

"Rather than having to visit a hospital for the infusion, the patient can conveniently take the tablet at home," he says.

In an Orazol Phase II study completed last year, patients reported much quicker pain relief (Figure 1). Unlike the kidney deterioration associated with zoledronic acid infusion, by taking a weekly dose, the peak drug load the kidney has to process is reduced. And, the flu-like side effects associated with the intravenous delivery don't seem to be present in the Orazol tablet taken weekly. Proof-of-principle for a weekly oral formulation has been demonstrated in a cancer patient population clinical study.

Orazol completed the Phase II trial with 30 patients, with equal efficacy in the primary endpoint, urine NTx, when compared to the monthly infusion of Zometa, as well as strong trends in secondary endpoints (Figure 2). Orazol patients didn't have to take 4 weekly tablets to get the same efficacy as the monthly infusion, but experienced similar effects after the first week. Merrion is planning a Phase III trial.

The multi-centre Phase II study, conducted in hormone refractory prostate cancer patients with proven bone metastases, took place at 13 sites in the US and Europe. The study examined the effects of treatment on four separate bone biomarkers: urinary NTx, serum CTx, serum bone specific alkaline phosphatise, and serum calcium. The published data presented at the American Society of Clinical Oncology (ASCO) shows a rapid response to treatment on

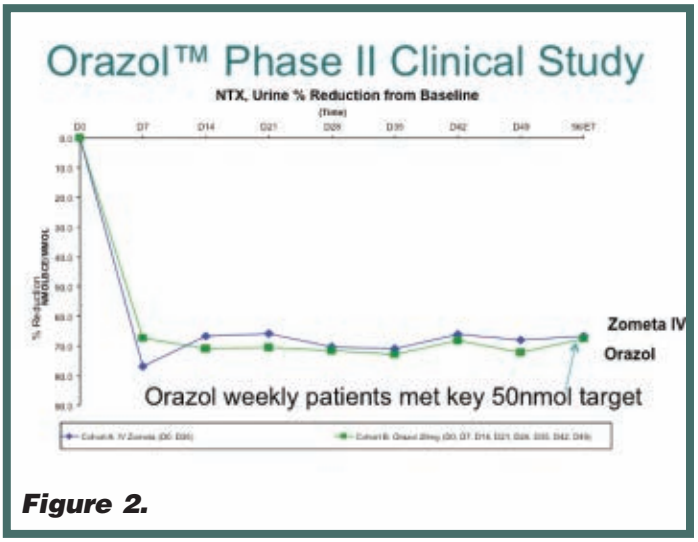


Figure 2.

biomarkers of bone resorption. These effects were noted at 7 days and were sustained throughout the study period. Preliminary results show that weekly therapy with 20-mg Orazol (tablet) appears to be as therapeutically effective as a monthly treatment with the intravenous drug Zometa (4 mg), based on movements in observed levels of critical bone biomarkers, from the first dose. Changes in bone biomarkers (urinary NTx) have been correlated with improvement in major clinical outcomes, such as SREs and morbidity. Zometa comes off patent in 2013 in the US.

"We hope to have our oral version available by that time," says Mr. Lynch. "We expect the market for oral zoledronic acid could be bigger than Zometa because a greater patient population will have access to it."

Merrion is also studying the effects of Orazol in early-stage breast cancer (pre-bone metastases). Trial studies show anti-tumor and disease-free survival benefits. For patients with breast cancer, a 40% reduction in baseline NTx from the median level was associated with an 11% lower risk of death.

"Orazol may help treat breast cancer by shrinking tumors and delaying progression of secondary cancer," explains Mr. Lynch. "Using Orazol in early-stage breast cancer has the potential to reach blockbuster status of around $1 billion."

The Orazol Drug Delivery System

Orazol uses Merrion's proprietary GIPET® technology (Figure 3), which allows the oral dosing of drugs previously only available in injectable form. Efficacy, safety, and side-effect profiles of drugs can be improved substantially using this delivery technology, says Mr. Lynch.

"Products developed with this technology have the potential to significantly improve the Quality of Life for patients, as well as providing greater access to the medication with substantial economic

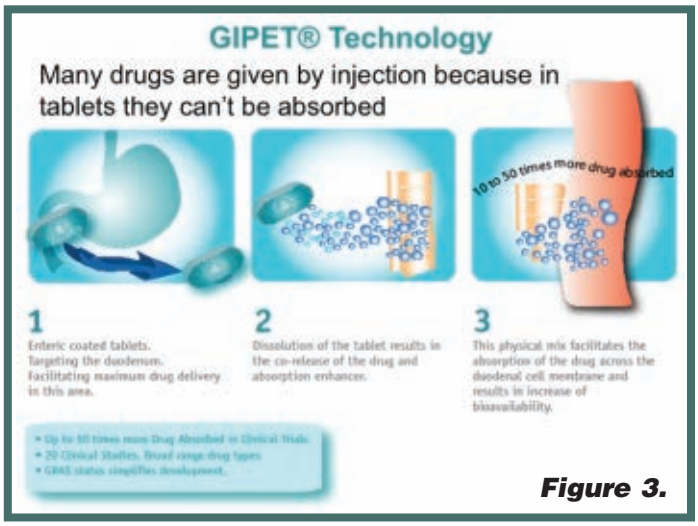


Figure 3.

improvements for hard-pressed healthcare systems."

In March 2010, a patent was issued in the US for GIPET technology combined with bisphosphonates, of which zoledronic acid is a member, and a patent covering the GIPET technology, including its use with bisphosphonates, has been granted in Europe. The latest issued US patent to date gives protection to 2027.

By using its GIPET technology, Merrion has been able to formulate a sufficiently bioavailable oral dosage to make a once-per-week tablet. And, infusion chairs are freed up at the hospital to give chemotherapy or other treatments.

Using a technology purchased from fellow Irish pharmaceutical group, Elan, 6-year-old Merrion uses GIPET to convert parenteral drugs into oral tablet/capsule forms, as well as improve the absorption of current oral drugs. GIPET uses specifically designed oral formulations of patented absorption enhancers that activate micelle formation, facilitating transport of drug and substantially increasing absorption with good reproducibility and a strong safety profile.

In a database comprising more than 40 compounds having poor permeability, GIPET has shown the ability to improve their absorption by as much as 200 times, achieving excellent intersubject reproducibility, explains Mr. Lynch. This database covers a range of compounds with varying physio-chemical properties and molecular weights, and includes small molecules as well as biopharmaceutical peptides and proteins, making GIPET a platform technology with very broad applicability.

"GIPET uses Generally Regarded As Safe (GRAS) rated ingredients, permitting the development of low-risk new oral products, which can be brought rapidly and inexpensively to market [505 (b) (2)] to address major unmet clinical and patient needs," says Mr. Lynch.

Bone Metastases & Beyond

Orazol has the potential to make an impact on patient care in the years ahead, and the market opportunity for Orazol is substantial and presents compelling potential for major growth. Analysts from Edison Investment Research have estimated Orazol could be on the market in 2013, although Merrion will only move forward with the Phase III trial once it has secured a partner.

A partner license might also enable Merrion to pursue the osteoporosis and Paget's disease markets, both of which put patients at risk of bone breakages and are well treated by zoledronate acid. The US osteoporosis market is valued at $3.6 billion with an estimated 10 million Americans suffering from the disease, and 34 million more are at risk.[1]

Mr. Lynch expects that Orazol will become the preferred method of treatment for bone breakage over Zometa and the recently approved Prolia from Amgen, which is a new monoclonal antibody. Prolia, a twice-monthly subcutaneous injection, is likely to be more expensive ($825 per injection) than Orazol.

For the majority of bone metastasis patients, it is still possible to maintain a good Quality of Life. "The economic and treatment benefits of Orazol will be felt widely in the clinician and patient communities," says Mr. Lynch. "No longer will costly, rigid, and potentially unhealthy infusions dictate treatment decisions, but instead Orazol opens the potential for doctors to treat more patients more efficiently while limiting adverse impact on the patient's Quality of Life." ◆

Reference

1. Datamonitor, Commercial Insights: Osteoporosis, July 21, 2010.

BIOGRAPHY

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

Executive Summary

Brian Leuthner
CEO & President, Edge Therapeuitics

Edge Therapeutics: Transforming Off-Patent Drugs Into Targeted, Locally Delivered Therapies for Unmet Medical Conditions of the CNS

Founded in 2009, Edge Therapeutics Inc. is a private, New Jersey-based, specialty pharmaceutical company headquartered at the New Jersey Institute of Technology Enterprise Development Center (NJIT-EDC) Incubator. The company focuses on transforming proven, off-patent drugs into targeted, locally delivered therapies that address unmet medical conditions of the central nervous system (CNS). Typically, current treatments for CNS diseases are given orally or intravenously and are only marginally effective in part because standard delivery methods do not provide adequate and sustained doses of protective drugs at the injury site in the brain. Higher doses that may be more effective cause side effects outside the brain and are unsafe. For many CNS diseases, a new method of delivery is greatly desired.

The Edge Management team brings unparalleled scientific and commercial expertise to the field of neurocritical care. Under the scientific leadership of R. Loch Macdonald (CSO, Co-Founder, and a world-renowned brain scientist and neurosurgeon) along with the commercial leadership of Brian Leuthner (a neurocritical care marketing expert), Edge is developing four preclinical acute care products.

Edge's lead product, NimoGel™, is being developed in collaboration with SurModics, Inc. (Nasdaq: SRMX) to prevent a complication called delayed cerebral ischemia (DCI). DCI is a catastrophic delayed series of events which typically occurs days after subarachnoid hemorrhage (SAH) which is the result of a ruptured brain aneurysm or head trauma. NimoGel is a locally delivered, sustained-release formulation of the calcium channel blocker nimodipine, designed to provide consistent and sufficiently high concentrations in the brain to prevent DCI. Edge has recently completed a proof-of-concept large animal study and expects to enter clinical studies in 2011. *Specialty Pharma* recently caught up with Mr. Leuthner to discuss how Edge Therapeutics plans to translate its preclinical therapies into life-saving medicines by streamlining its path toward clinical efficacy and how the recent Healthcare Reform act may impact Edge's products and the industry.

Q: ***How was Edge Therapeutics founded?***

A: It's often by chance how businesses get started, and that's the story with Edge. I was at an International Stroke Meeting when a mutual neuro-intensivist friend introduced me to my Co-Founder and current Edge Chief Scientific Officer Dr. R. Loch Macdonald. This colleague was aware of my commercial expertise in the neurocritical care marketplace and knew about Dr. Macdonald's 20 years of research exploring the causes and potential cures for secondary brain injury and thought we would be a good match. Little did I know that Dr. Macdonald's research had resulted in almost 500 peer-reviewed published articles. So after a few phone calls and a few years later, Edge was born. Shortly thereafter, Co-Founder Carl Soranno, Esq. brought a business development and contract negotiations background to round out the team.

Q: ***Can you please describe Edge's products and the needs they address?***

A: Despite major advances in medical care throughout the past few decades, there are still many acute CNS diseases in which patient outcomes could be improved if there was an effective way to overcome the limitations of systemic drug delivery. The most

common limitation of systemic delivery is the inability to get appropriate and sustained drug concentrations at the injury site without causing unwanted side effects in other parts of the body. Lack of effective treatments continues to cause death, disability, increased hospital costs, and increased cost to societies around the world.

Edge believes that local, sustained-release delivery of medicine directly to the injury site would prevent certain delayed complications, improve patient outcomes, and significantly reduce healthcare costs.

The first CNS disease Edge is addressing is the aforementioned delayed cerebral ischemia (DCI), which starves the injured brain of oxygen.

The clinical course of DCI all too often ends with catastrophic consequences. For example, a not uncommon situation is exemplified by a 40-year-old mother of three small children who arrives at the Emergency Department describing a "thunderclap headache," the worst headache of her life, similar to how television personality Bret Michaels recently described his subarachnoid hemorrhage. Shortly after her arrival, doctors perform an angiogram and discovered a ruptured brain aneurysm. Despite this bleeding, cerebral blood flow is still sufficient to serve the oxygen needs of her brain. After undergoing neurosurgery to secure and stop her bleeding aneurysm, she begins recovery. Three to four days following surgery, she is progressing well and talking to her family. On day 7, things take a turn for the worse and later, depicted in her angiogram, this woman developed cerebral vasospasm, despite doctors' best efforts to save her, she dies, leaving her husband and three small children. That's why DCI is so devastating; patients and their families might believe they are out of the woods, and this terrible delayed complication arrives with devastating effect.

Today, current treatment to improve patient outcome consists of giving a drug called nimodipine either orally or intravenously. Unfortunately, oral nimodipine treatment is only marginally effective because it does not achieve appropriate concentrations at the site of injury to prevent DCI. Higher doses that might be more effective cause dangerous side effects in other parts of the body, such as low blood pressure (hypotension) and fluid pooling in the lungs (pulmonary edema). Despite current improvement in medical care, nearly two-thirds of patients die or suffer permanent brain damage by day 30. However, it appears that the problem is not the drug nimodipine; it is a drug delivery problem.

Edge is overcoming systemic limitations of oral nimodipine with NimoGel. NimoGel consists of the generic calcium channel blocker nimodipine formulated in a proprietary biodegradable polymer carrier composed of FDA-approved materials. It can deliver apprpriate and sustained nimodipine concentrations to the site needed in the brain, without causing unwanted side effects in other parts of the body. The medicine is delivered during standard brain surgery, so the change in neurosurgical practice is minimal.

Q: ***What is the potential market size for NimoGel, and how does Edge plan to address it?***

A: According to the World Health Organization and estimates from other brain injury organizations, 2 million people each year are at risk of DCI, generally caused by a ruptured brain aneurysm or head trauma. Typically, these at-risk patients are younger adults in their 30s, 40s, and 50s in the prime of their lives, and many will be dead or permanently brain damaged within 30 days. Blast vasospasm, another type of vasospasm caused by blast waves from improvised explosive devices, is also a major concern for military doctors and an area of intense interest for the Department of Defense.

Because all of Edge's current products target well-defined patient populations that are already stabilized and under the care of neurosurgeons or neurointensivists at major urban hospitals, this affords easy access with a small specialty sales force.

Q: ***What other products does Edge have in the pipeline?***

A: In addition to NimoGel, Edge has a robust pipeline. Upon obtaining additional funding, Edge plans to advance EG-1964 into preclinical development. EG-1964 is another locally delivered treatment to prevent another type of secondary brain injury after a subdural hematoma. EG-1960 is a locally delivered treatment to prevent hematoma expansion, another secondary complication following another type of brain hemorrhage. All products have worldwide sales forecasts in excess of $500 million.

Q: ***How is Edge funding clinical development?***

A: To date, Edge has raised almost $1.5 million from private investors and through grants. In late 2009, Edge was awarded a $500,000 grant from the New Jersey Commission on Science and Technology, and another $100,000 in a convertible note from the New Jersey Economic Development Authority and is currently awaiting results from NIH and State grant applications. We also recently spoke to physicians at the Department of Defense (DoD) and received high interest for all of our products and will be pursuing DoD funding later this year. In the future, Edge will rely on private investors, non-dilutive financing, strategic investments, and venture capital investments to fund clincal development.

Q: ***What role is there for partnerships and licensing in Edge's business model?***

A: Edge's business strategy has been clear since its inception: develop products alone or in partnership with other companies through Phase II clinical trials and generate significant value for its shareholders by (1) acquisition or collaboration with a larger pharmaceutical company, (2) a structured deal via private equity, or (3) through a public offering. So to answer that question, partnerships and licensing will play a significant role for Edge Therapeutics and at the end of 2012 or early 2013, we expect to have proof-of-human efficacy and safety information in approximately 50 patients with NimoGel.

Edge is well positioned to take advantage of the patent cliff that many larger pharmaceutical companies will be approaching in 2014 and 2015. The fact that our business model takes a streamlined regulatory and clinical path, and the way in which our products are already de-risked, with proper funding, Edge could have three different $500-million specialty products ready for US launch in 2015 or 2016.

Q: ***What has Edge accomplished in the 18 months since its inception?***

A: In the short time since its founding, we have accomplished several meaningful milestones including the folowing:

- Demonstrated proof-of-concept for NimoGel in a large animal model of subarachnoid hemorrhage.
- Raised $600,000 in non-dilutive grant funding.
- Established SurModics to be our formulation development company in February 2010.

Since signing the agreement in February, Edge and SurModics have successfully achieved important development milestones including:

- Encapsulated nimodipine in polymer microspheres.
- Developed multiple formulations optimizing initial and sustained-release of drug.
- Demonstrated that nimodipine microspheres can be terminally sterilized by gamma irradiation.
- Manufactured initial scale-up batches.

Following NimoGel optimization and additional scale-up, Edge expects to complete its IND-enabling study in 2011.

Q: ***What is the long-term objective of the company?***

A: Edge's vision is to be a drug development company. We believe there is a need for small companies to translate promising ideas into potentially life-saving therapies. Right now, we are extremely focused on advancing NimoGel into the clinic, and depending on the results, will consider its options, including early licensing of its products or selling of the entire company.

In the future as we grow and continue to demonstrate to others our ability to rapidly and cost-effectively advance products through Phase II and then sell or license the products to larger pharmaceutical companies, we believe our product development opportunities will grow.

Edge knows drug development is a risky business, but we also know there are patients and families who are depending on companies like Edge to come up with new treatments to change the way medicine will be practiced in the future.

Q: ***What impact might the new healthcare reform legislation have on Edge?***

A: What this new bill says to me is that spending research dollars on incrementally better drugs will stop. I believe the FDA and payers have already begun to set the bar higher for pharmaceutical manufacturers with regard to FDA approvals and also with an eye on reimbursement. I believe in the future, there will be significantly more scrutiny on costs, getting closer to the European markets, where getting a drug approved by the regulatory agencies is the first step, and getting the drug reimbursed is the most important step. At Edge, all of our products address large, unmet medical needs that cost society billions of dollars annually in direct healthcare costs. The indirect healthcare costs, such as loss of productive work years and long-term care costs, may be as much as four times direct costs as several of the conditions our drugs target strike people in their 30s, 40s, and 50s and leave 70% to 80% dead or permanently brain damaged within 30 days.

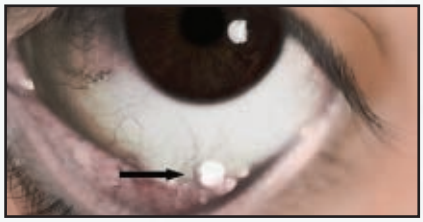
One recent study published in August 2010 out of Duke Medical Center concluded that patients who suffer severe vasospasm (part of just on the biochemical pathways that leads to DCI) have approximately $40,000 in additional direct hospital costs. Applying their numbers to the different severities of vasospasm, annual US direct costs of vasospasm exceed $1.3 billion. If NimoGel could just prevent 50% of the cases of vasospasm, it could save over $600 million annually in direct US healthcare costs and obviously improve the outcomes of many patients and their families. ■

Technology Showcase

Commercial Syringe Filling Solutions

Althea has been filling prefilled syringes for our clients' clinical needs for years, and has recently expanded capacity for large-scale manufacturing of Phase III and commercial supplies. Our commercial line produces over 100,000 syringes per day and features "bubble-free" filling, 100% in-process control weight checks, and a fully automated system for greater speed and efficiency. Coupling prefilled syringes with our portfolio of integrated services, Althea is a true strategic partner for your drug program. For more information, contact Althea Technologies at (888) 425-8432 or visit **www.altheatech.com**.

Ocular Delivery System



Henkel's PROLOC Bioadhesive Ocular Drug Delivery System features long-lasting drug release and high bioavailability compared to traditional eye drops, ointments, and gels. A preservative-free polymer matrix in uniquely formed ocular mini-tablet form that is applied to the fornix, PROLOC Bioadhesive adheres rapidly to the ocular mucosa and transforms to a comfortable gel-like substance that will remain in place until fully eroded. The PROLOC System permits high active ingredient loading and is compatible with hydrophilic or lipophilic active ingredients and are capable of residing over 8 hours during which time the active drug is gradually released. Encompass Ophthalmic Development, Inc has secured the exclusive world-wide ophthalmic license for Henkel's PROLOC Bioadhesive Ocular Drug Delivery System. For more information, visit **www.encompass-ophtha.com**.

Combination Capsule Technology

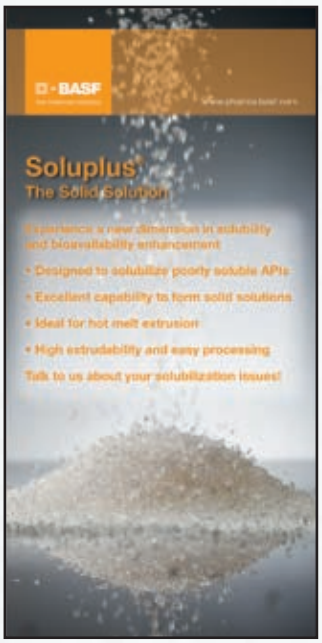
InnerCap offers an advanced patent-pending multi-phased, multi-compartmentalized capsular-based delivery system. The system can be used to enhance the value and benefits of pharmaceutical and biopharmaceutical products. Utilizing two-piece hard shell capsules, the technology offers the industry solutions to problems affecting pharmaceutical companies, patients, and healthcare providers. The delivery system will be licensed to enhance pharmaceutical and biopharmaceutical products. It is a very effective way to deliver multiple active chemical compounds in different physical phases with controlled-release profiles. The delivery system provides the pharmaceutical and biopharmaceutical industries with beneficial solutions to the industry's highly publicized need to repackage and reformulate existing patented blockbuster drugs with expiring patents over the next 5 years. For more information, contact InnerCap Technologies, Inc., at (813) 837-0796 or visit **www.innercap.com**.

Knowledge Management

PharmaCircle is an innovative knowledge management company specializing in the drug delivery, pharmaceutical, and biotechnology fields, with a current client base ranging from start-up life science companies to world leaders in Big Pharma. Clients choose PharmaCircle's services and content for its comprehensive technical (pipeline, products, molecule, and technology) and business (deals, acquisitions, royalty, licensing, drug revenues, market information, etc) related information and analysis, which are ideal for all segments of small and large companies. PharmaCircle helps facilitate product life cycle management (LCM), partnering, licensing, and competitive intelligence efforts as well as supplements internal efforts and costs at a fraction of the cost if performed internally. For more information, contact PharmaCircle at (847) 729-2960 or visit **www.pharmacircle.com**.

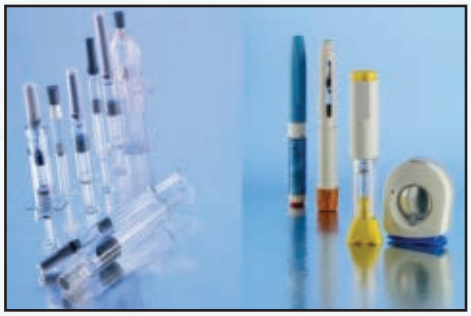
Technology Showcase

Solubility/Bioavailability Enhancement



Soluplus® is a graft copolymer composed of polyethylene glycol, polyvinylcaprolactam, and polyvinylacetate. It is designed to solubilize poorly soluble drugs and increase their bioavailability. It is ideally suited for preparation of solid solutions or solid dispersions by hot melt extrusion, spray drying, melt granulation, and co-precipitation processes. Soluplus is highly soluble in water at low and high pH and organic solvents. It is significantly less hygroscopic than many other polymers. Its low glass transition temperature (70°C) allows it to be extruded over a wide temperature range without the need for plasticizers. For more information, contact BASF at (800) 443-0627 or visit **www.soluplus.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. BD offers a range of products, including glass and plastic prefillable syringes, a nasal spray system, and a variety of self-injection systems. We deliver cost-effective alternatives to conventional drug delivery methods, which differentiate pharmaceutical products and contribute to the optimization of drug therapy. With a broad range of innovative systems and services, BD provides pharmaceutical companies with support and resources to help them achieve their goals. Our worldwide presence, market awareness, and pharmaceutical packaging know-how allow us to propose suitable solutions for all regional markets and parenteral drug delivery needs. Only BD offers the range and depth of expertise and packaging solutions to guide your drug from early phase development through product launch and beyond. For more information, contact BD at (201) 847-4017 or visit **www.bd.com/pharmaceuticals**.

Specialty Pharma

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Development & Manufacturing

DPT®

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**.

Technology Showcase

MDI Components

Enabling your success

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AN **ABF** INGREDIENTS COMPANY

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Innovative Platforms

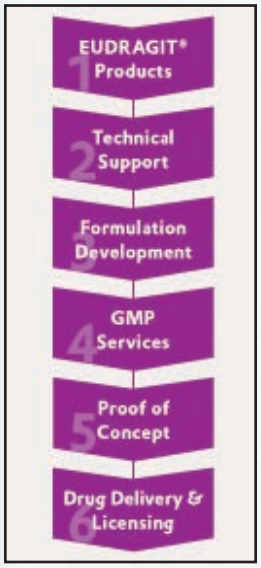
Adhesives Research has over 20 years of experience manufacturing pressure-sensitive adhesive systems for the pharmaceutical industry. Adhesives Research's custom development capabilities include polymer synthesis, adhesive mixing, compounding, coating, and release liner design, supported by analytical capabilities. The company integrates these capabilities to formulate and manufacture unique products to meet customers' specifications. The company's Pharmaceutical division provides skin-friendly adhesives and laminate for active and passive transdermal delivery systems and pulmonary delivery applications. ARx, LLC (a wholly owned subsidiary of Adhesives Research) addresses the growing global need for innovative delivery of active drug-containing systems. ARx develops and manufactures innovative pharmaceutical products, including adhesive laminates and dissolvable films, for customized drug delivery platform technologies. For more information, contact Adhesives Research at (800) 445-6240 or visit **www.adhesivesresearch.com**.

Licensing Opportunities

Aveva has numerous products for license from its development pipeline along with a full compliment of R&D capabilities to produce transdermal drug delivery systems that fortify R&D pipelines and maximize product life cycles. Aveva Drug Delivery Systems is one of the world's largest manufacturers of and a pioneer in transdermal drug delivery systems of providing pharmaceutical partners with fully integrated, controlled-release transdermal products that fulfill unmet market needs. Products for licensing include Sufentanil, Fentanyl, Clonidine, and Nicotine. For more information, contact Robert Bloder, VP of Business Development, at (954) 624-1374 or visit **www.avevadds.com**.

Technology Showcase

Pharma Polymers



Evonik Industries is a global market leader in specialty chemicals, offering a broad portfolio of products and services to meet the drug delivery challenges of the pharmaceutical market. Evonik Pharma Polymers manufactures EUDRAGIT® acrylic polymers used for enteric, sustained-release, and protective formulations. The unique functionality of EUDRAGIT polymers can also meet high sophisticated drug delivery requirements (eg, pulsed drug release). We have adapted our services to meet the requirements of the pharmaceutical industry's value chain. As a result, we are able to support our customers in the development process to bring products safely and quickly to the market. From excipients supply to the development of custom tailored drug delivery solutions, our customers benefit from our knowledge and expertise. For more information, contact Evonik Degussa Corp., Pharma Polymers at (732) 981-5383 or visit **www.eudragit.com**.

Analytical Testing Services

Gateway Analytical provides analytical testing and consulting services to the pharmaceutical, forensic, and material science industries. By pairing innovative technologies with conventional methods, Gateway Analytical utilizes a forensic strategy to scientific problem-solving. With more than 15 years of experience, you can rely on our expertise in regulatory affairs, product and process development, non-conformance and failure investigations, foreign particulate identification, and more to help solve your toughest challenges. Trust Gateway Analytical to be an extension of your own lab, providing personal attention, high-quality results, scientific talent, and technical expertise to help you get the job done. For more inforation, contact Gateway Analytical at (724) 443-1900 or visit **www.gatewayanalytical.com**.

Excipients & Technology

The MEGGLE Group's Excipients & Technology Business Group supplies the pharmaceutical industry with carrier substances, such as pharmaceutical lactose. With outstanding product quality and intelligent innovations, we have gained a leading global position in the field of lactose and compounds. MEGGLE pharmaceutical lactose, for example, serves as a carrier substance in medicines. It behaves completely neutrally in the human organism and causes no undesired effects due to interaction with other components of the medicine. We also have developed a diversified product portfolio in the more than 50 years that we have been active in the market that contains excipients for granulation and capsule-filling as well as special modern products for direct compaction and dry-powder inhalers. Our customers are predominantly manufacturers of pharmaceutical products and dietary supplements. For more information contact the MEGGLE Group at (914) 682-6891 or visit **www.Meggle.com**.

Development & Delivery Solutions

Founded in 1991, Particle Sciences is an integrated provider of both standard and nanotechnology approaches to drug development and delivery. Through a combination of preformulation, formulation, analytic, bioanalytic, and manufacturing services, Particle Sciences provides clients with a powerful, integrated solution to most efficiently take a drug from discovery to the clinic. Each project has a dedicated team and leader to manage the project from start to finish. With years of experience to draw upon, Particle Sciences can confidently handle difficult APIs, complicated intellectual property terrains, and challenging delivery goals to arrive at the simplest, most efficient solution to the client's needs. For more information, contact Particle Sciences at (610) 861-4701 or visit **www.particlesciences.com**.

Technology Showcase

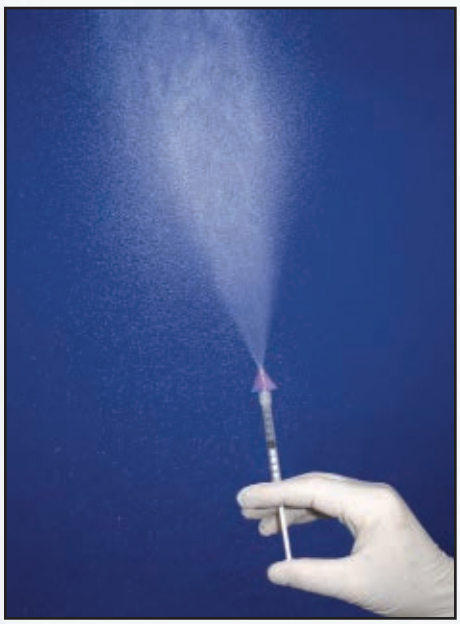
Manufacturing & Development

Patheon is a leading global provider of contract dosage form development and manufacturing services to the pharmaceutical and biotechnology industries. Employing more than 4,700 highly skilled staff, Patheon's network of modern manufacturing facilities located in North America and Europe offer more than 3 million sq ft of best-in-class capacity. With three facilities in the US, three in Canada, and four in Europe (including two in Italy, one in France, and one in the UK), Patheon is able to meet the international requirements of its customers. Patheon's development and manufacturing capabilities cover prescription (Rx) products in solid, semi-solid, and liquid dosage forms, as well as specialized capabilities in high-potency, cephalosporin, controlled/sustained release, and sterile manufacturing, including aseptic filling and lyophilization. For more information, contact Patheon at (888) PATHEON or visit **www.patheon.com**.

PFS Solutions

You need prefillable syringe systems and components designed to compete in an evolving industry. You need the management, expertise, and support of a manufacturer capable of creating systems and components that will mitigate risk and differentiate your product. You need West. Pharmaceutical and biopharmaceutical customers trust West to provide prefillable syringe systems and components that help bring products to market safely, reliably, and with the integrity you've come to expect from West. Our global technical expertise and services provide solutions that are true to our core goal of reducing regulatory risk while ensuring quality and patient safety. So you can rest easy. For more information, contact West at (800) 345-9800 or visit **www.WestPFSsolutions.com**.

Intranasal Vaccine Device



The new VaxINator™ Intranasal Vaccine Delivery Device offers a rapidly effective method to deliver vaccines or other medications to a patient without the need for a painful injection. The device features a precise 30- to 100-micron spray, has low dead space, attaches to any luer lock syringe, is ideal for lyophilized and liquid drugs, and is latex free. For more information, contact Wolfe Tory Medical at (801) 281-3000 ext. 101 or e-mail mdenton@wolfetory.com, or visit **www.wolfetory.com**.

Drug Development

Xcelience® Formulation Development

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

3M Drug Delivery Systems
3M Center, Bldg. 275-3E-10
St. Paul, MN 55144-1000
T: (800) 643-8086 F: (651) 737-5265
Website: www.3M.com/DDS

3M Drug Delivery Systems

Inhalation and transdermal drug delivery solutions that enable your success.

For more than 50 years, pharmaceutical companies worldwide have looked to 3M Drug Delivery Systems for ingenious transdermal (microneedle and drug-in-adhesive) and inhalation (dry powder inhaler and metered-dose inhaler) solutions to help their products meet the needs of the market. With proven international success in technology, development, manufacturing, and regulatory, partnering with 3M helps ensure critical speed to market and the technical success of your project.

Inhalation Systems & Components

With a successful 50-year history that includes development of the first metered-dose inhaler (MDI) and first CFC-free propellant pressurized metered-dose inhaler, 3M Drug Delivery Systems is a leader in inhalation technology. More than just systems and components, 3M delivers the expertise, efficiency, and flexibility you need to gain a competitive advantage.

Transdermal Systems & Components

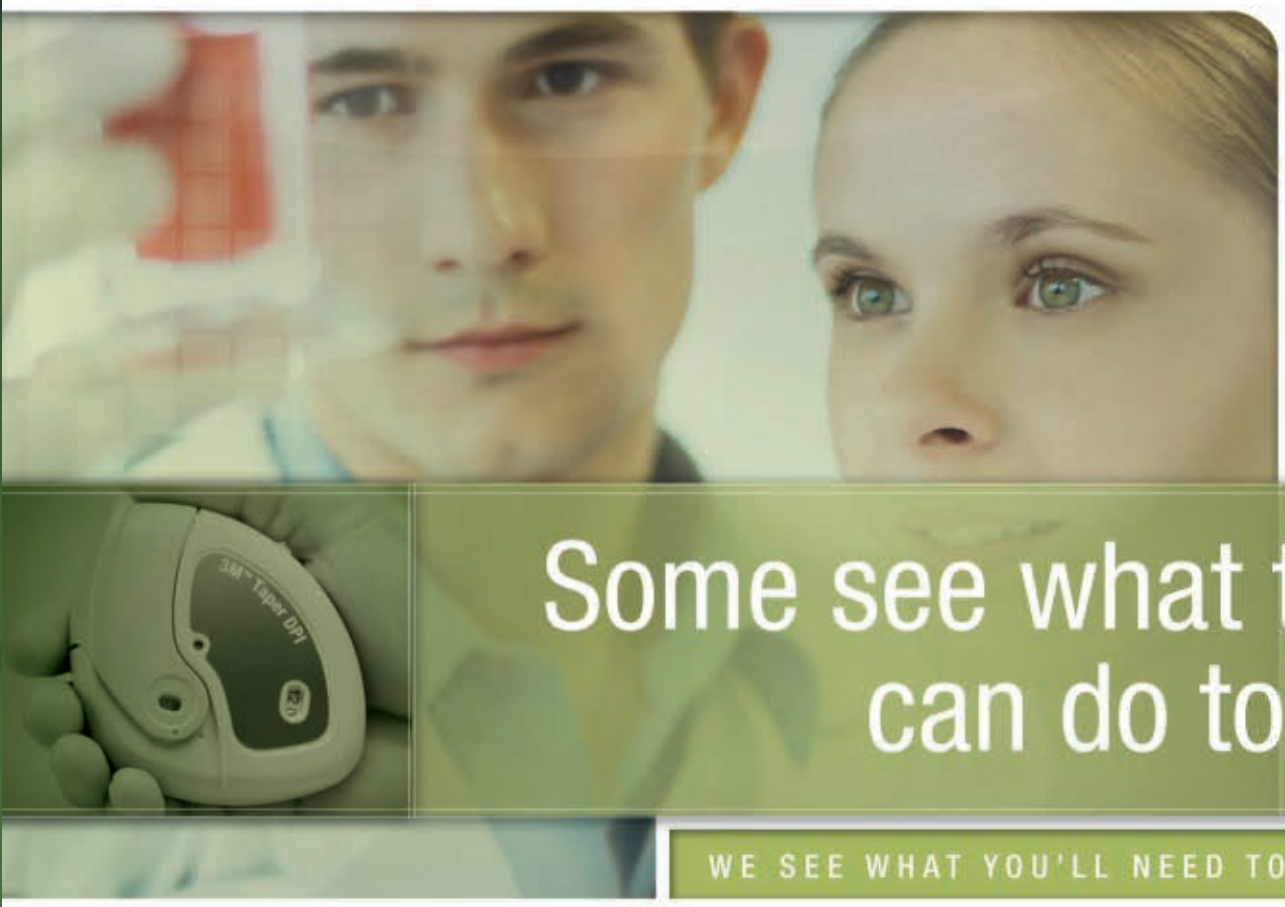
When you work with 3M, we leverage the collective resources of the 3M scientific community to find the best transdermal delivery solution for your molecule. 3M can fulfill both your passive and active transdermal needs, including individual components, full system development, and manufacturing.

Manufacturing Services

With our global pharmaceutical manufacturing experience, 3M is the reliable choice to satisfy both your inhalation and transdermal manufacturing needs, including controlled substance (CII-CV) and filling capabilities. With our new dry powder and microneedle technologies, 3M can fulfill DPI and MDI inhalation needs as well as both passive and active transdermal manufacturing. With five strategically located and cGMP-compliant facilities capable of producing the necessary volumes from clinical through commercial supply, we have the capacity and flexibility to meet your needs.

At 3M, it's all about your success. That's why more than 50% of all MDIs worldwide and 80% of all transdermal systems in the US utilize 3M drug delivery technology.

3M DRUG DELIVERY SYSTEMS
INHALATION SYSTEMS



Some see what they can do today.

WE SEE WHAT YOU'LL NEED TOMORROW.

Innovative DPI solutions help you capitalize on opportunities now and in the future.

3M continues to move inhalation technology forward with innovative Dry Powder Inhaler (DPI) products designed to overcome challenges associated with DPI delivery.

- Patient-friendly designs that are also efficient, reproducible and value-driven
- Innovative drug aerosolization technology customizable to your application
- Single and multi-dose applications

3M can provide you with both pMDI and DPI solutions for your molecule, supported by a full range of manufacturing services and backed by our proven track record of performance. Find out more at 3M.com/DPI.

US: 1 800 643 8086
UK: 44 (0) 1509 613626
ASIA: (65) 6450 8888

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ENABLING YOUR SUCCESS.

3M

Company Profile

Insight®
Adhesives Research®
Taking your products further.

Adhesives Research, Inc.
400 Seaks Run Road
Glen Rock, PA 17327
P: (717) 235-7979 Toll-Free: (800) 445-6240
F: (717) 235-8320
adhesivesresearch.com

Adhesives Research Ireland Ltd.
Raheen Business Park
Limerick, Ireland
P: +353 61 300 300 F: +353 61 300 700
adhesivesresearch.com

It all starts with a partnership approach to product development. With more than 20 years of experience manufacturing high performance pressure-sensitive adhesive (PSA) systems for the pharmaceutical industry, Adhesives Research is known for its custom solutions and unique components for transdermal, oral and topical drug delivery. We are one of the world's leading independent developers of high-performance custom PSAs, tapes, coatings, specialty films, dissolvable films and laminates.

Insight® drives our technology.

Adhesives Research offers custom polymer synthesis, adhesive mixing, compounding, coating and release liner design, supported by comprehensive analytical capabilities. It's through this Insight that we have pioneered the use of many adhesive and coating technologies to enable the world's leading pharmaceutical and drug delivery companies to launch innovative products for applications in:

- Passive transdermal delivery systems
- Device-assisted transdermal delivery systems
- Pulmonary delivery systems
- Oral thin film delivery systems

Quality is our first thought.

Our cGMP segregated manufacturing and ISO 9001 and 13485 compliant quality systems help us manufacture world-class adhesive tapes and coated products. We offer diverse manufacturing capabilities to produce pharmaceutical and medical device components under the appropriate Code of Federal Regulation requirements and ISO standards to support our customers in their FDA approval process, including:

- More than 20 coating lines in our state-of-the-art U.S. and European manufacturing facilities.
- Five isolated manufacturing lines for the production of components used in pharmaceutical, medical device and consumer applications under ISO 9001 and 13485.
- Two manufacturing lines dedicated to our ARx, LLC division incorporate active pharmaceutical ingredients into dissolvable films and adhesive coatings under 21 CFR 211.

Custom formulations for each application.

Based upon proven PIB, acrylic and silicone polymer technology platforms, Adhesives Research's skin-friendly adhesives are available with conductive, porous, occlusive, hydrophilic, hydrophobic, gentle or long-term adhesion functional properties to meet the unique needs of our clients' applications.

Where to find us.

Founded in 1961, Adhesives Research is headquartered in Glen Rock, Pennsylvania. Our global expansions have included the opening of a manufacturing facility in Ireland; sales and marketing offices in Great Britain and Singapore; a representative office in Shanghai, China; and sales representation in Japan, Korea and Taiwan. Additionally, Adhesives Research operates two technical centers for the design and development of custom adhesives, coatings and film components; one in Pennsylvania, and the other in Ireland.

Insight® is a registered service mark of Adhesives Research, Inc.

Adhesives Research® is a registered trademark of Adhesives Research, Inc., for engineering and design services of pressure-sensitive adhesive systems.

ARx, LLC is a wholly-owned subsidiary of Adhesives Research, Inc.

Our product development starts with you.

It all begins with a partnership. With more than 20 years of delivering proven technologies to the pharmaceutical industry, Adhesives Research has pioneered the development of adhesive and coating technologies to enable the world's leading pharmaceutical, drug delivery and consumer companies to innovate, launch products, and enter new markets.

We share our resources, giving clients exclusive access to our research and development teams so they can count on us to create a custom component for their transdermal, oral or topical drug delivery system. Contact us to discuss how Adhesives Research can partner with you.

Ask about our capabilities.

- Custom pressure-sensitive adhesives and tapes
- Specialty coatings and films
- Dissolvable films
- Laminates

Insight®
Adhesives Research®
Taking your products further.

800-445-6240 • adhesivesresearch.com

Insight® is a registered service mark of Adhesives Research, Inc.
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AVEVA DRUG DELIVERY SYSTEMS, INC.
3250 Commerce Parkway
Miramar, FL 33025
T: (954) 430-3340 F: (954) 430-3390
Website: www.avevadds.com
Contact email: Robert.bloder@avevadds.com

Aveva Drug Delivery Systems, a Nitto Denko company with revenues in excess of $6.4 billion, is one of the world's largest manufacturers of, and a pioneer in, transdermal drug delivery systems. Nitto Denko has a 40-year history of providing pharmaceutical partners with fully integrated, controlled-release transdermal products that fulfill unmet market needs or are high-quality, low-cost brand equivalents. Leveraging this experience, Aveva offers a full range of research, development, and manufacturing capabilities using a number of sophisticated technologies to produce proprietary and generic transdermal drug delivery systems.

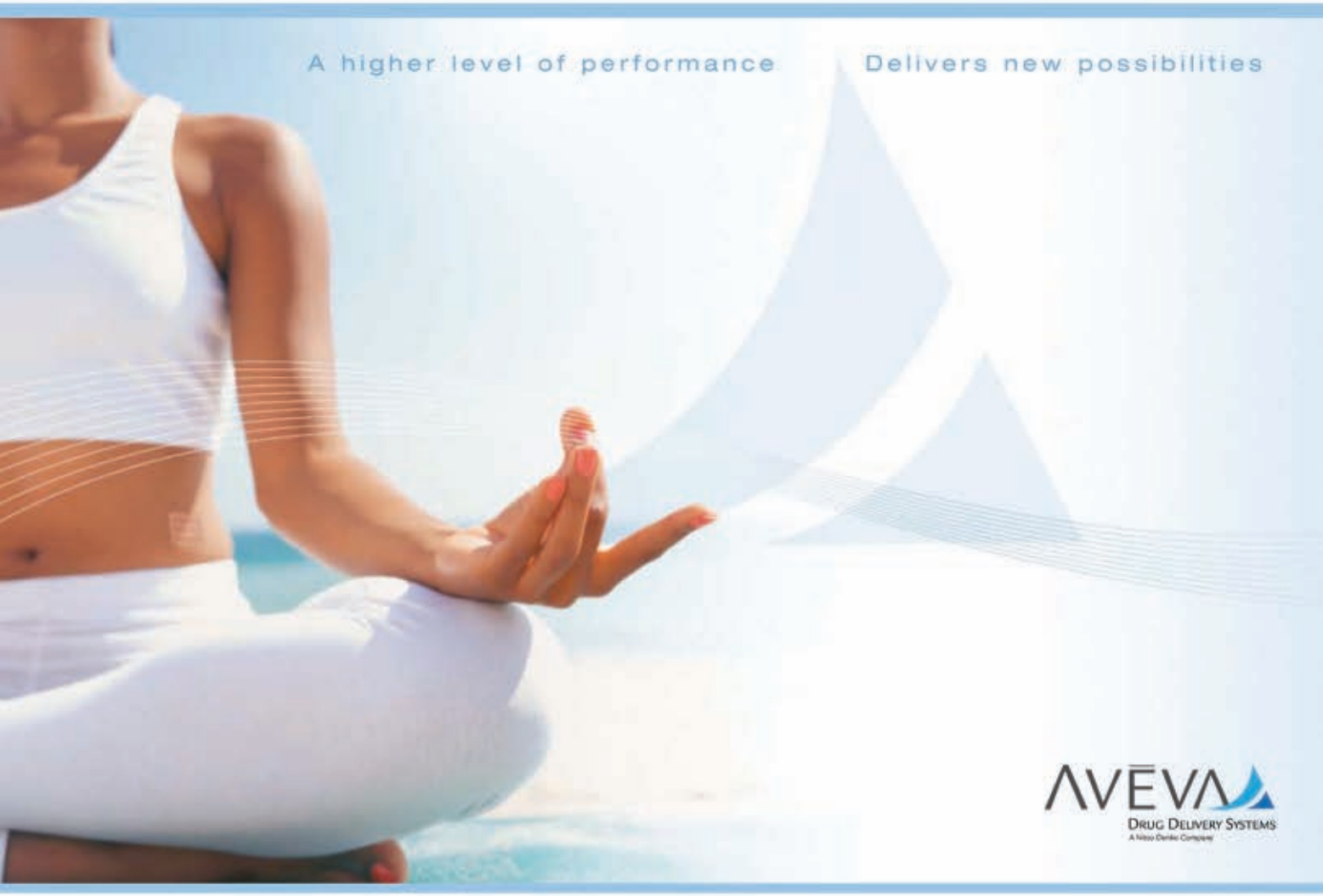
Aveva offers:
- Global licenses for Aveva's approved products and development pipeline
- Transdermal candidate assessments of APIs in as little as 4 weeks
- Extensive expertise in polymer synthesis and adhesive formulation technologies
- A full range of research, development, and manufacturing capabilities
- Creative solutions & sophisticated technologies to overcome formulation challenges

Proprietary Gel Matrix Adhesive Technology

Aveva DDS and Nitto Denko have produced the first and only marketed transdermal patch using a revolutionary Gel Matrix adhesive system for an unequaled balance of adhesion reliability and gentleness. Because the Gel Matrix adhesive minimizes the disruption of the stratum corneum (skin) during removal, these patches can be removed and reapplied with minimal skin irritation, resulting in a desirable patient experience. This technology also contributes to increased patient compliance and enhanced persistency, which are critical for patients with chronic conditions.

NITTO DENKO

TRANSDERMAL TRANSCENDENCE



That's the promise of Aveva Drug Delivery Systems, combining innovation and unparalleled industry experience to advance drug delivery and pioneer new frontiers in transdermal drug delivery for new chemical entities and life cycle management opportunities to enhance existing products.

As one of the world's largest manufacturers of transdermal patches offering a full range of research, development and manufacturing capabilities, Aveva transcends traditional limitations of patch technology and business partnerships to achieve new levels of product and corporate performance.

- Customizing solutions to the unique characteristics of each drug
- Masterfully balancing the patch properties of adhesion reliability and gentleness that lead to an enhanced patient experience.
- Managing a higher drug concentration in a smaller patch

A flexible, customer-oriented business philosophy that adds value to projects and exceeds customer expectations.

To license a product or to see how we can add value to your project, call Robert J. Bloder, Vice President Business Development, at **954.624.1374** or visit **www.AvevaDDS.com**

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COMPANY PROFILE

Baxter Healthcare Corporation
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Round Lake, IL 60073
US: 1-800-4-BAXTER International: 1-847-948-4779
F: 1-847-948-4770 E: biopharmasolutions@baxter.com
Website: www.baxterbiopharmasolutions.com

BioPharma Solutions

The Promise of Science Realized

BioPharma Solutions, a business unit of Baxter, partners with pharmaceutical companies to support your commercialization objectives by providing scientific expertise, sterile manufacturing solutions, parenteral delivery systems, and customized support services needed to meet the unique challenges that parenteral products face.

Experience Makes the Difference. With nearly 80 years of parenteral expertise, we can help to navigate the pathway of success for your molecule. Our long-standing history puts unique expertise at your fingertips.

We Understand Parenterals. As a parenterals specialist, BioPharma Solutions offers unique delivery systems and a wide variety of manufacturing solutions to meet complex and traditional sterile manufacturing challenges. In addition, we offer a broad spectrum of support services including formulation and development to help solve the high-stakes challenges in today's complex parenteral marketplace. Our areas of expertise include:





Parenteral Delivery Systems
- -Prefilled Syringes
- -Liquid Vials
- -Lyophilized Vials
- -Cartridges
- -Frozen Premix Systems
- -Liquid Premix Systems
- -BIO-SET Luer System
- -Diluents for Reconstitution
- -Ampoules

Drug Categories
- -Small Molecules
- -Biologics; including Monoclonal Antibodies & Therapeutic Proteins
- -Vaccines; both Adjuvant & Conjugate
- -Cytotoxics
- -Antibody-Drug Conjugates (ADCs)
- -Highly Potent Compounds
- -Cephalosporins/Penicillins

Extensive Network. With more than 50 manufacturing facilities across six continents, Baxter's global presence provides opportunities for unique manufacturing collaborations to provide the most value for our partners. The power of an extensive global network lies in the coordination of, and efficiencies resulting from, a systemic approach to cGMP manufacturing.

We Take Partnering Seriously. As a partner to over 60 pharmaceutical clients, we realize that successful alliances are critical in this extremely competitive environment. BioPharma Solutions has developed strong organizational capabilities to ensure our partnership provides the value you deserve and expect. Because of this we have been honored with various global distinctions by the industry including "Best Contract Manufacturing Organization" at the Vaccine Industry Excellence Awards and European Outsourcing Award winner for Most Effective Scale-up/Technical Transfer, to name a few.

Ultimately, our goal is to make you feel confident and secure choosing BioPharmaSolutions as a partner - helping you to avoid the unexpected and guiding you through marketplace complexities so you can achieve the full potential of your molecule.

BioPharma Solutions provides our clients with confidence of delivery, service, and integrity - we know the work we do is ultimately vital to the patients you serve.

Baxter

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BioPharma Solutions

The Promise of Science Realized

Experience Makes the Difference

With nearly 80 years of parenteral expertise, we can help to navigate the pathway of success for your molecule. We offer a broad spectrum of parenteral resources from formulation and development to sterile manufacturing solutions for traditional and complex molecules. BioPharma Solutions provides our clients with confidence of delivery, service, and integrity—we know the work we do is ultimately **vital to the patients you serve.**

For more information, visit
baxterbiopharmasolutions.com
or e-mail us at
biopharmasolutions@baxter.com

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BD Medical - Pharmaceutical Systems
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Franklin Lakes, NJ 07417
T: (800) 225-3310 F: (201) 847-4847
E: BDPS_marketing@bd.com
Website: www.bd.com/pharmaceuticals

BD Medical - Pharmaceutical Systems provides high-quality, customized, clinically-proven drug delivery systems and technologies to help pharmaceutical and biotechnology customers' injectable drugs reach their full potential.

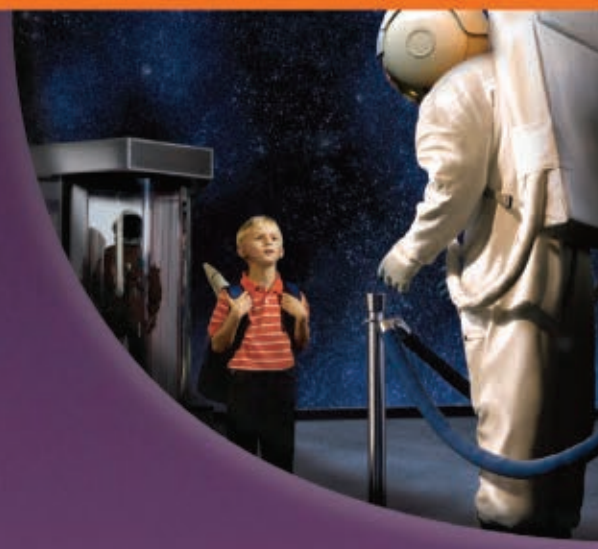
BD has over 100 years of experience in manufacturing and processing technology for parenteral drug delivery systems and has developed an in-depth understanding of the pharmaceutical industry's requirements. BD has leveraged this experience when developing advanced drug delivery systems that span from small scale clinical through large scale commercial programs.

BD offers a range of products, including glass and plastic prefillable syringes and a variety of systems for the self-administration of injectables. With a broad scope of innovative systems and services, BD Medical - Pharmaceutical Systems provides pharmaceutical companies with support and resources to help them achieve their goals.

BD is committed to building partnerships to develop product solutions that meet evolving customer needs by leveraging innovative technologies, extensive global manufacturing and advanced technical and scientific expertise.

Only BD offers the range and depth of expertise and packaging solutions to guide your drug from early phase development through product launch and beyond.

BD Hypak SCF™
Glass Prefillable Syringe System



Help your product reach its full potential

Only BD offers the range and depth of expertise and solutions to guide your drug from early phase development through launch. That's why hundreds of pharmaceutical and biotech manufacturers have chosen BD Hypak SCF Glass Prefillable Syringe Systems for their drugs.

Get more than a safe delivery system– gain a strategic advantage.

BD

Helping all people live healthy lives

Contact a BD expert today.
Call 800-225-3310 or e-mail
BDPS_marketing@bd.com.

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Franklin Lakes, NJ 07417
www.bd.com/pharmaceuticals

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www.theconferenceforum.org

Setting new standards in information exchange for the pharmaceutical, biotech & drug delivery industry

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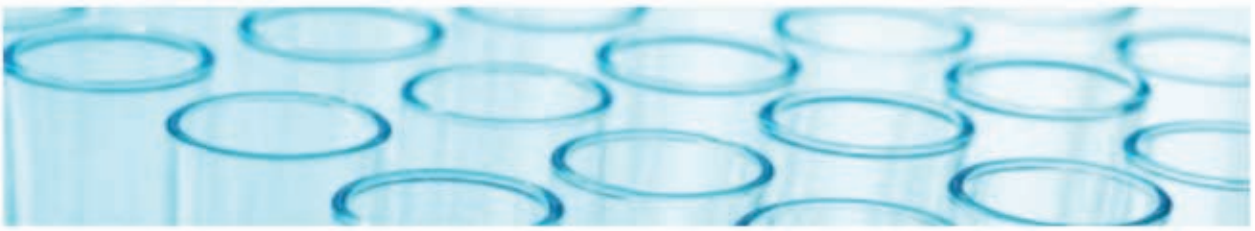
This new standard in information exchange is based on the quality of our research and our exceptional service. Our research team concentrates fully on in-depth market analysis to uncover the most relevant issues in the industry. Led by our Conference Research Director with more than 17 years of experience, our research team combines its detailed findings with penetrative insight from our Advisory Boards to create events that surpass industry expectations.

Quality research and information are the result of our commitment to providing outstanding service to our customers. Our job is to make you more successful in advancing drug development to enhance health and economic outcomes. We listen very carefully to the market, attendees, speakers and sponsors to ensure we continually improve our customer, networking and format experiences.

To suggest new topic areas or educational formats you would like to see us cover, please email us at Customer Service or call 646-350-2580.



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Dennis Purcell, Senior Managing Partner, **Aisling Capital**

Lori Rafield, PhD, LFR Advisors, former Partner, **APAX**

Greg Rossi, Vice President Global Pricing and Payer Strategy, **Genentech**

Greg Scott, Founder, **China Bio Investor**

David Shlaes, MD, PhD, President, **Anti-Infectives Consulting, LLC**

Daniel Spiegelman, previously CFO, **CV Therapeutics**

Bob Temple, MD, Director of the Office of Medical Policy, **CDER, FDA** (invited)

Bernice Welles, MD, CEO, **Alquest Therapeutics**

Travis Wilson, Morningside Group and CEO, **Stealth Peptides, Inc**

Fred Zheng, PhD, Research Scientist, Clinical Biomarker Group, Oncology Early Development, **AstraZeneca**

Wei Zhou, PhD, JD, President and CEO, **Centrillion**

Zhenping Zhu, MD, PhD, EVP, Global Biologics R&D, **Kadmon Pharmaceuticals,** President & CEO, **Kadmon China**

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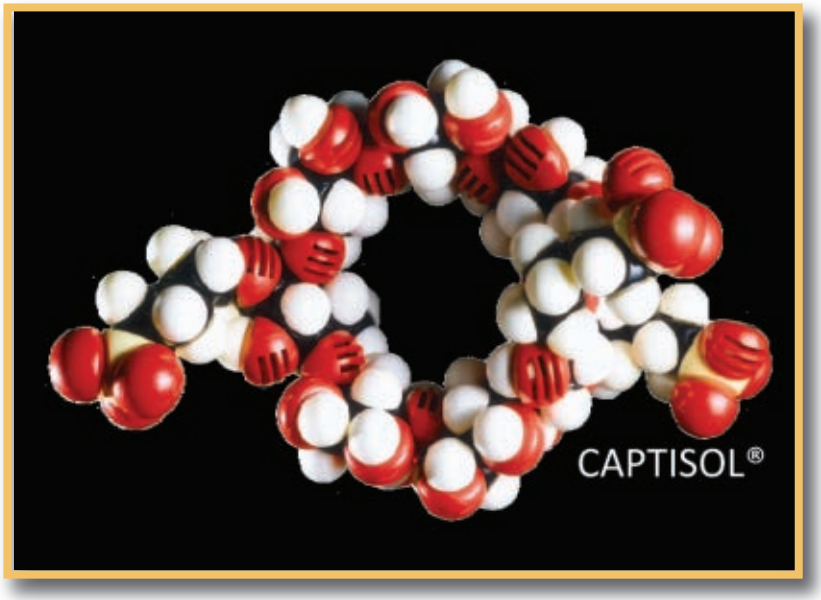
F: (913) 685-8856 E: cdinfo@cydexpharma.com
Website: www.cydexpharma.com



CyDex Pharmaceuticals, Inc., founded in 1993, is a specialty pharmaceutical company headquartered in suburban Kansas City. Our patent-protected drug formulation technology uses a specifically modified family of cyclodextrins called Captisol® to improve the solubility, stability, bioavailability, safety and dosing of active pharmaceutical ingredients, or APIs. Our business is focused on developing and commercializing new products that use Captisol to address the limitations of currently marketed drugs.

Our core strategy is to license Captisol to established pharmaceutical companies that are interested in using the technology to improve product candidates in their pipelines. Five FDA-approved, Captisol-enabled® medications are now being marketed by three CyDex licensees: Pfizer, Bristol-Myers Squibb and Prism Pharmaceuticals. Looking to the future, we currently have License and Supply Agreements (LSAs) in place with a number of pharmaceutical companies worldwide with Captisol-enabled product candidates in their pipelines. Routes of administration include injectable, topical, and oral.

In 2004, we began complementing our LSA program by providing Limited Clinical Use Agreements (LCUAs) that make it simple and cost-effective for pharmaceutical companies to use Captisol early in the process of developing new compounds. LCUAs grant a limited license to use Captisol in small Phase I human clinical trials, and CyDex agrees to supply a specified quantity of Captisol to the licensee for these trials. This approach has proven to be tremendously successful, and more than 20 companies around the world are currently using Captisol to develop their own products under LCUAs with CyDex.

In addition to licensing our Captisol technology to other companies, CyDex also performs formulation development activities with a variety of drug substances with poor solubility, inherent instability, or low bioavailability. Suitable formulations with Captisol, other cyclodextrins, or without cyclodextrins can be developed. Each project is tailored to meet the scientific needs and timeframes of our clients. Please call 913-685-8850 for additional information.

CyDex maintains patents in the United States and worldwide for its Captisol drug formulation technology and Captisol-enabled products, as well as comprehensive FDA Manufacturing and Safety Drug Master Files.

Captisol® and Captisol-enabled® are registered trademarks of CyDex Pharmaceuticals, Inc.

CAPTISOL®

&

CyDex® Contract Development Services

A Clear Solution

CYDEX
PHARMACEUTICALS
cydexpharma.com

CyDex Pharmaceuticals provides a wide range of services throughout the pharmaceutical product development process. Each project is tailored to meet the scientific needs and timeframes of our clients.

PRE-FORMULATION/FEASIBILITY ASSESSMENT • FORMULATION DEVELOPMENT • CONSULTANT SERVICES

Company Profile

DPT®
A DFB COMPANY

DPT Laboratories
318 McCullough
San Antonio, TX 78215
T: (210) 476-8100 F: (210) 829-8733
Web Site: www.dptlabs.com

Year Founded: 1990
Number of Employees: 1,000

Key Personnel: Paul Johnson, President; Paul Josephs, Vice President Sales & Marketing; Lyle Flom, Vice President, Development & Commercial Services

Who We Are

DPT, a DFB Pharmaceuticals, Inc. company, is a contract development and manufacturing organization (CDMO). DPT provides pharmaceutical, biotechnology, and consumer healthcare companies the best solutions to their drug development and manufacturing needs through innovation, technology, and service. Specializing in semi-solid and liquid dosage forms, DPT has a reputation for quality, unmatched technical expertise, extensive sterile and non-sterile manufacturing capabilities, and an exemplary regulatory compliance record.

Customers choose DPT as a strategic partner because of our ability to provide fully integrated drug development and manufacturing solutions. DPT customers have confidence that their projects, from concept to commercial manufacturing, will be handled by professionals with unparalleled knowledge and experience, using state-of-the-art equipment and processes.

The ability to develop, manufacture, and commercialize products in semi-solid and liquid dose forms makes DPT unique. To get your next product to market fast and with confidence, call DPT – The Industry Source for Semi-solids and Liquids®.

Comprehensive Drug Development Services for Sterile & Non-sterile Dose Forms

- Pre-formulation and formulation development
- Biopharmaceutical development
- Analytical method development and validation
- Stability studies
- Process development and validation
- Pilot and proof-of-concept batches from 0.3 kg
- Clinical trial materials phase I-III

Packaging Services

- Identification and sourcing of relevant packaging options
- Packaging specification development
- Formulation and package compatibility assessment
- Packaging equipment sourcing, design, and engineering services
- Turnkey sourcing services for unique and specialized packaging

Manufacturing Services for Sterile and Non-sterile Dose Forms

- Four cGMP facilities
- cGMP batch sizes from 0.3 kg - 25,000 kg
- Controlled substances Schedules II-V
- Extensive packaging capabilities for semi-solids and liquids
- Sterile manufacturing for pilot, clinical, and commercial scale
- Sterile batch sizes from <500 mL to 50 liters
- pMDI and aerosol manufacturing capabilities
- Specialized equipment installation, operational qualification, and validation services

Facilities

Headquartered in San Antonio, TX, DPT has four facilities there and one in Lakewood, NJ, with state-of-the-art development, manufacturing, packaging, and distribution space.

With DPT,
development and manufacturing piece together seamlessly.

DPT is the contract development and manufacturing organization (CDMO) that specializes in sterile and non-sterile semi-solid and liquid dosage forms. With unmatched technical expertise and fully integrated drug development and manufacturing services, we can help you successfully develop and commercialize your next product. Partnering with DPT gives you a seamless transition from pre-formulation to clinical supplies to commercial supply. After all, keeping it all together is what sets us apart. To get started, visit us at www.dptlabs.com or call 1.866.CALL.DPT.

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EURAND PHARMACEUTICAL TECHNOLOGIES
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Website: www.eurand.com

Eurand is a global specialty pharmaceutical company that develops, manufactures, and commercializes enhanced pharmaceutical and biopharmaceutical products based on its proprietary drug formulation technologies. Eurand has had six partnered and proprietary products approved by the FDA since 2001 and has a pipeline of product candidates in development for ourselves and collaboration partners.

Eurand is also a leading industry partner that provides one of the broadest, well-validated portfolios of proven oral drug delivery technologies for the development of Rx and OTC formulations. Our technologies can be as innovative and effective life-cycle management tools that can prolong the market life of products.

Breadth & Flexibility of Oral Delivery Platforms

Eurand has a strong track record of developing products using its proprietary drug formulation technologies. With integrated manufacturing and R&D facilities in the U.S. and Europe, Eurand has one of the broadest ranges of pharmaceutical technology platforms in the industry, including:

- Customized Drug Release
- Bioavailability Enhancement
- Taste Masking / Orally Disintegrating Tablets (ODT)

These platforms include eight distinct technologies and are covered by more than 700 granted and pending patents. Eurand uses these technologies to develop and expand the Company's own internal pipeline and to partner with pharmaceutical and biopharmaceutical companies to develop their products.

Product Licensing & Distribution Opportunities

Eurand is focused on the co-development of partnered products and the out-licensing of Eurand's products worldwide.

Eurand also has a number of Rx and OTC products available for licensing. We license these products to pharmaceutical companies for marketing throughout the world.

Currently more than 40 products, spanning a range of therapeutic categories, have been developed by Eurand and are commercialized by our partners in different countries around the world.

Turnkey Manufacturing Services

We manufacture all of the products that we develop for ourselves and our licensees. Our manufacturing processes and units are integrated with our R&D facilities thereby facilitating the scale-up and manufacturing process for products in development. Shared facilities, processes and development teams enhance this strategy.

Our facilities in the U.S. and in Europe supply products to many regions of the world, are operated to maintain compliance with cGMPs, have possess solvent processing capabilities, and are approved to process controlled substances.

Visit www.eurand.com to learn more about Eurand's oral drug delivery technologies and portfolio of products available for out-licensing.

Evonik Company Profile

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Pharma Polymers
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Evonik Industries is a global market leader in specialty chemicals, offering a broad portfolio of products & services to meet the drug delivery challenges of the pharmaceutical market. Evonik Pharma Polymers, a business line within the Chemicals Business Area of Evonik Industries, holds a leading position in the manufacture and supply of functional coatings for the pharmaceutical industry. EUDRAGIT® acrylic polymers are used for enteric, sustained release and protective formulations. The unique functionality of EUDRAGIT® polymers can also meet high sophisticated drug delivery requirements (e.g. pulsed drug release). We have adapted our services to meet the requirements of the pharmaceutical industry's value chain. As a result, we are able to support our customers in the development process to bring products safely and quickly to the market. From excipients supply to the development of custom tailored drug delivery solutions, our customers benefit from our knowledge and expertise. Pharma Polymers is committed to providing solutions to the pharmaceutical and biopharmaceutical industry in drug development, manufacturing and drug delivery, with products and services that meet requirements during the entire drug development process – from EUDRAGIT® supply via custom development support and GMP services to advanced drug delivery cooperation.

The process chain in formulation development consists of many single demanding steps which are often accelerated when carried out in strategic collaboration with specialists. Pharma Polymers is such a strategic partner, providing global support for local custom-tailored applications: from formulation development via enhanced formulation technologies to unique customer products with individually designed release profiles. Our international network of technical service centers gives you on-site support at every stage of pharmaceutical development, with the same high quality standard and flexible performance anywhere in the world. Benefit from our international team of experts that work for you as soon as you contact a local Pharma Polymers Laboratory. With EUDRAGIT® related products and technologies you gain speed to market, access to new drug delivery technologies, and drugs of enhanced value.

1 EUDRAGIT® Products → 2 Technical Support → 3 Formulation Development → 4 GMP Services → 5 Proof of Concept → 6 Advanced Drug Delivery

Pharma Polymers is committed to providing solutions to the pharmaceutical industry during the entire dosage form development process:

- **EUDRAGIT® Products** – excipients for targeted drug delivery
- **Technical Support** – feasibility testing, on-site scale-up and production support
- **Formulation Development** – matching desired release profiles by various process technologies
- **GMP Services** – clinical batch manufacturing
- **Proof of Concept** – added value formulations for life cycle management and generic developments
- **Advanced Drug Delivery** – unique proprietary solutions for advanced therapies, joint development of enabling technologies

Great results with less water.

Solubility enhancement with EUDRAGIT® polymers

Eudragit®

For innovative product opportunities, contact us at:

PHONE USA +1 732 981-5383

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www.eudragit.com/bio

www.evonik.com

1 EUDRAGIT® Products → 2 Technical Support → 3 Formulation Development → 4 GMP Services → 5 Proof of Concept → 6 Advanced Drug Delivery

A clever solution to bioavailability issues comprises a combination of functional excipients, know-how in process technologies (e.g. melt extrusion) and the right formulation expertise. Evonik provides all this. EUDRAGIT® polymers are a safe and robust formulation platform to face bioavailability challenges. And our global lab network supports your development projects at all stages: from excipient screening through formulation development up to clinical batch manufacturing and scale-up. Read more about our revolutionary MEMFIS™ (Melt Extrusion Modeling & Formulation Information System) which helps you to select lead formulations for bioavailability enhancement without API consumption.

Evonik. Power to create.

EVONIK INDUSTRIES

FROST & SULLIVAN

FROST & SULLIVAN
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San Antonio, TX 78229
T: (210) 247-3870
Contact: Johanna Haynes (johannahaynes@frost.com)
Website: www.frost.com

Frost & Sullivan, founded in 1961, has more than 40 global offices with more than 1,800 industry consultants, market research analysts, technology analysts and economists. Our mission is to research and analyze new market opportunities for corporate growth. We are the world leader in growth consulting and the integrated areas of technology research, market research, economic research, corporate best practices, training, customer research, competitive intelligence, and corporate strategy.

Frost & Sullivan employs 1,800 analysts, growth consultants, and visionaries in 40 global offices. We provide two critical services to our "partners" that support their growth strategies: Growth Partnership Services and Growth Consulting. The Growth Partnership Services (GPS) represent a subscription-based program that provides our clients with disciplined research to support the generation and evaluation of growth opportunities, and career-focused best practices to help implement growth strategies at best practice levels. Our growth consulting program provides our clients with customized consulting that supports a visionary understanding of the market, the development of growth strategies, and diagnostics to validate growth strategies.

Exclusively Focused on Growth	Actively engaged in identifying, researching, and developing opportunities, growth models, and strategies that enable clients to accelerate growth.
Industry Breadth	Cover the broadest spectrum of markets and technologies to provide clients with the ability to look outside the box and discover new and innovative ideas.
Global Perspective	40 global offices ensure that clients receive global coverage and perspective based on regional expertise.
Continuous Monitoring	Continuously monitoring markets, technologies, careers, and geographies for growth opportunities.
CEO's 360 Degree Perspective™	Disciplined research integrates all critical research methodologies to significantly enhance the accuracy of decision-making and lower the risk of implementing growth strategies.
Trusted Partner	Work closely with the clients' Growth Teams, helping them generate new growth initiatives and leverage all of Frost & Sullivan's assets to accelerate their growth.

www.frost.com

What do you *really* know about end-users of drug delivery technologies?

Drug delivery technologies are an important part of the changing Pharma & Biotech industry. Feedback from patients and physicians, in terms of factors such as perception, desired attributes, compliance, and drivers of adoption/non-adoption for different drug delivery types, is therefore vital to developers. Is your company positioned to understand and take advantage of these opportunities for growth?

Frost & Sullivan's Pharmaceutical & Biotechnology group can provide your organization with the research and support it needs to fully understand end-users of Drug Delivery Technologies, and to identify and take advantage of the best opportunities for growth in this market.

Our expert Healthcare analysts:

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

For more information on growth opportunities in the Drug Delivery market, please contact Johanna Haynes at johanna.haynes@frost.com.

FROST & SULLIVAN

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Website: gatewayanalytical.com

Gateway Analytical provides cGMP- and ISO-compliant analytical testing as well as consulting services. By pairing innovative technologies with conventional methods, our company utilizes a forensic approach to scientific problem solving.

With more than 15 years of experience in regulatory affairs, product and process development, foreign particulate identification, non-conformance and failure investigations, Gateway Analytical's pharmaceutical services support many facets of the drug formulation lifecycle. No matter what the phase of development, our goal is to provide reliable results with a quick turnaround.

Trust Gateway Analytical as an extension of your own lab, providing personal attention, high-quality results, scientific talent and technical expertise to help you get the job done.

Product/Process Development
- Content and Blend Uniformity Measurements
- Characterization and Identification of Polymorphs in Drug Products
- In Vitro Particle Characterization
- Study of Controlled Release Systems

Pharmaceutical Forensics
- Counterfeit Investigation
- Foreign Particulate Matter Identification
- Particle Contamination Characterization
- Product Return Analysis
- Source Determination

Deviations
- Failure Investigations
- OOS Investigations
- Non-conformance Investigations

Consulting
- Intellectual Property Support
- Legal Consulting
- Regulatory Guidance

Bridging the Service Gap–
Beyond the Expected

- cGMP-Compliant Laboratory Environment
- Analytical Testing and Method Development Services
  - Product and Process Development
  - Deviation Investigation
  - Forensic Investigation
- Regulatory and Legal Consulting

Meet Your Connection to Innovative Solutions

Whether you're a drug formulator or manufacturer, no two problems are alike. That's why we've created an inclusive client strategy. Before beginning any project, our goal is to understand your biggest hurdles—inside and out.

With more than 15 years of experience, you can rely on our expertise in regulatory affairs, product and process development, non-conformance and failure investigations, foreign particulate identification, and more to help solve your toughest challenges.

Gateway ANALYTICAL

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Drug Delivery to the Lungs 21

INNERCAP Technologies, Inc.
9216 Palm River Road, Suite 203
Tampa, FL 33619
T: (813) 837-0796 E: busdevelopment@innercap.com
Website: www.innercap.com

INNERCAP Technologies, Inc. offers NOVACAPS™, a multi-phase, multi-compartment single pill solution for difficult combination drugs. The proprietary NOVACAPS™ delivery system accommodates otherwise incompatible pharmaceutical agents, solid or liquid, in a single-dosage, combination product. The delivery system also provides the option of working with multiple release profiles for the actives administered in the delivery system. Surging worldwide interest in such combination formats is evidenced by the FDA's initiative to advance the development of single-dosage forms for delivery of multiple HIV/AIDS drugs.

With the INNERCAP delivery system, therapeutic entities that have never been combined previously can now be administered together, via an oral, implanted, or a suppository capsule, in the most advantageous pharmacokinetic profile, utilizing different physical phases. This approach maximizes bioavailability and, at the same time, addresses patient compliance issues that often plague multi-drug regimens.

The NOVACAPS™ delivery system can be used for all therapeutic classes, such as immunologic, cardiovascular, neurologic, psychiatric, oncologic, and pain management.

The INNERCAP delivery system also provides a solution to overcome the difficult development issues related to bi-layer tablets. This will provide companies with a quicker and efficient solution to transition innovations smoothly from development, through the clinical phase, and into commercialization — ultimately reaping the financial fruits of their labor.

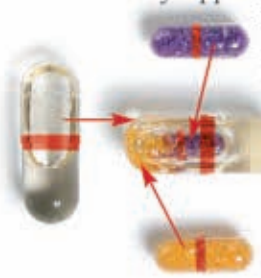
NOVACAPS™ offers a significant first-to-market advantage by minimizing valuable time in R&D when the product could be in clinical trials determining the patient response to a new combination product.

Companies interested in a novel solution for life-cycle management issues, patent protection, increased compliance, combination drugs, reduced counterfeiting, increased stability, multiple release profiles, increased bioavailability, barriers to entry, higher perceived value, and branding opportunities with difficult formulation issues can contact INNERCAP Technologies.

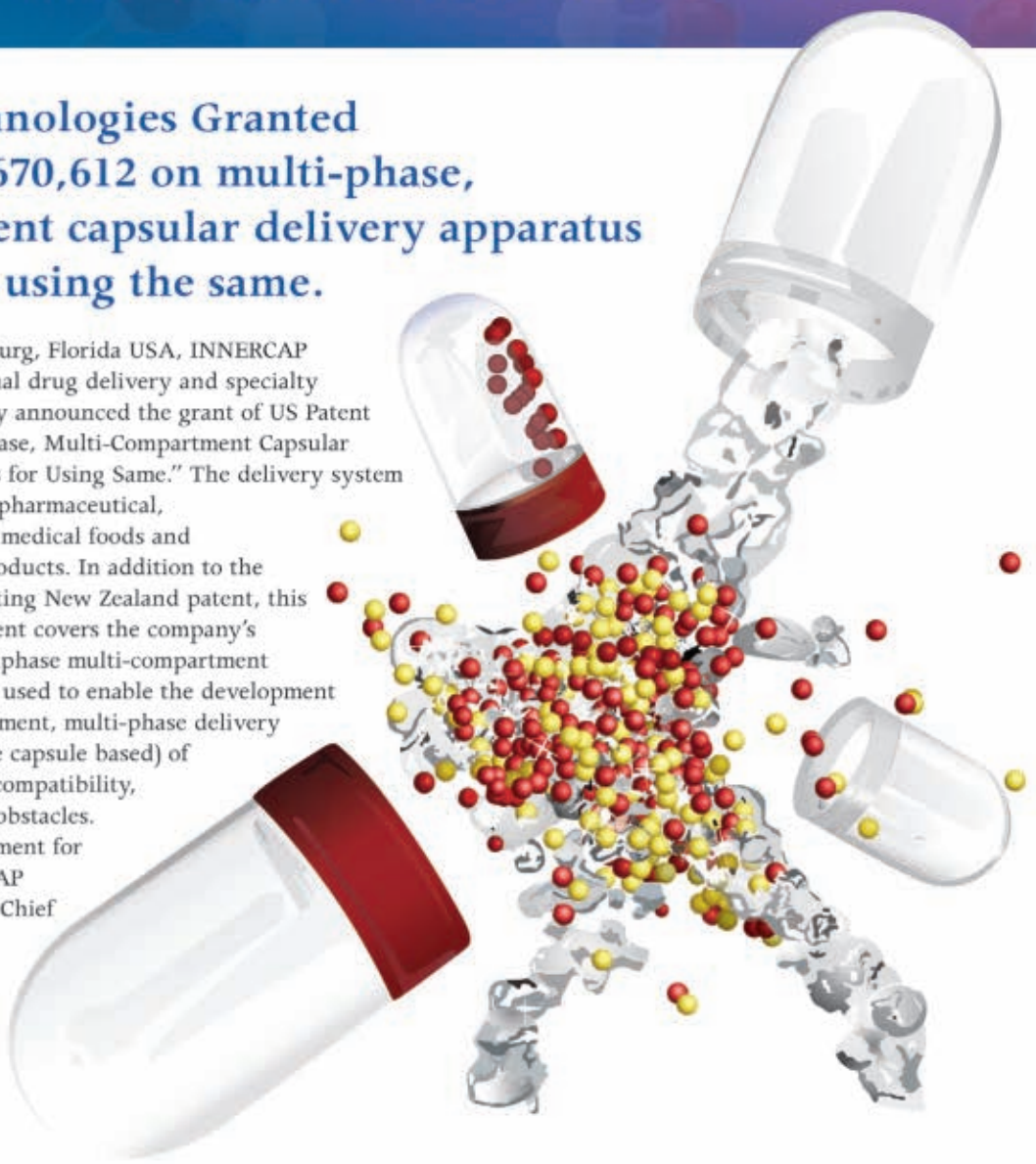
THE ADVANTAGES

OF MULTI-PHASE, MULTI-COMPARTMENT CAPSULES ARE CLEAR

INNERCAP® Technologies Granted US Patent No. 7,670,612 on multi-phase, multi-compartment capsular delivery apparatus and methods for using the same.



March 23, 2010, Saint Petersburg, Florida USA, INNERCAP Technologies, Inc., an international drug delivery and specialty pharmaceutical company, recently announced the grant of US Patent No. 7,670,612 entitled "Multi-Phase, Multi-Compartment Capsular Delivery Apparatus and Methods for Using Same." The delivery system has uses for bio-pharmaceutical, pharmaceutical, medical foods and nutraceutical products. In addition to the existing New Zealand patent, this patent covers the company's multiphase multi-compartment delivery system used to enable the development of multicompartment, multi-phase delivery forms (two piece capsule based) of combination products that have compatibility, formulation or targeted delivery obstacles.



"This is a significant development for INNERCAP Technologies NOVACAP technology," said Fred H. Miller, Chief Executive Officer at INNERCAP. "The continued growth of our patent portfolio establishes INNERCAP as one of the leading companies in this space."

The delivery system and combinations covered by the patent have the ability to deliver therapeutic entities that have never been combined previously and now can be administered together, via an oral, implanted, or suppository capsule, in the most advantageous pharmacokinetic profile, utilizing different physical phases. This technology can therefore be used to enable capsule administration of compounds that are not normally administered as a combination product. The efficacy, safety, and side-effect profiles of drugs can be substantially improved using this delivery technology. It will also provide very significant quality-of-life improvements for patients and substantial economic savings for hard-pressed healthcare systems.

"INNERCAP's multi-phase, multi-compartment technology has been commercially manufactured and validated in several products, demonstrating that INNERCAP's delivery system creates real value to consumers and branded manufacturers," added Mr. Miller.

INNERCAP was represented by Cliff Davidson, Esq. of the patent firm Davidson, Davidson & Kappel, LLC (www.ddkpatent.com) based in New York City.

For more information contact us at the telephone number and email address below:

INNERCAP® TECHNOLOGIES, INC

United States Patent No. 7,670,612
US and International Patents Pending

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T: (610) 861-4701
Website: www.particlesciences.com

For 20 years, Particle Sciences has been developing innovative drug delivery solutions. Clients range from startups to academic institutions to the worlds largest pharmaceutical and biotech companies. A full-service CRO, Particle Sciences provides complete formulation development, GMP/GLP analytic and bioanalytic methods development and testing, as well as clinical trial material manufacturing. Particle Sciences regularly works with highly potent compounds and is DEA and FDA registered. Particle Sciences specializes in nano-particulate, semisolid, and drug/device combination products, all aimed at optimizing the delivery of your API.

Our Approach

Drug delivery has advanced beyond dosage form specialization. Most APIs under development today have issues ranging from solubility to stability. Approaches to these challenges cross dosage form boundaries, and Particle Sciences is the leader in this API-centric trend. We believe a fundamental understanding of your compound and delivery goals is the key to success. At Particle Sciences, we use the most advance tools to ensure an efficient process, including our own solubility characterization paradigm, Design of Experiments and state-of-the-art equipment. Our clients' needs are thoroughly discussed and documented prior to initiating a project so that everything we do is on mission and makes the most of our clients' resources.

Technology

Our staff has extensive experience in drug delivery formats, including micro- and nano-particulates, emulsions, suspensions, encapsulated APIs, and controlled-release dosage forms. Fine-particle and nano-scale systems have been a focus of Particle Sciences since its inception in 1991. Particle Sciences employs technologies ranging from milling to controlled precipitation to polymeric solid solutions. Particle Sciences has all the necessary instrumentation and in-house expertise to produce and characterize these systems. Additionally, Particle Sciences is among the few in the industry with a dedicated drug/device combination-product team with full compounding, injection-molding, and analytic capabilities.

Client-Focused

Clients' projects receive individualized attention. Particle Sciences takes a collaborative approach to ensure positive project outcomes and the highest levels of client satisfaction. Projects are overseen and coordinated by a dedicated project manager in conjunction with a cross-functional team.

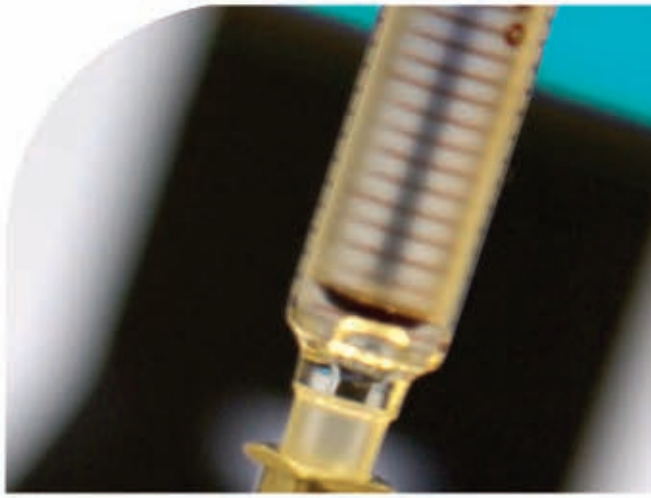
Integrated Process

Through a combination of preformulation, formulation, analytic, bioanalytic, and manufacturing services, Particle Sciences provides clients with a powerful, integrated solution to most efficiently take a drug from discovery to the clinic. With years of experience to draw upon, Particle Sciences can confidently handle difficult APIs, complicated intellectual property terrains, and challenging delivery goals and arrive at the simplest, most efficient solution to meet our clients' needs.

THE DRUG DELIVERY EXPERTS

Particle Sciences Inc. (PSI) is a fully-integrated analytic, formulation and clinical trial material manufacturing services provider. PSI offers a seamless drug development process that minimizes the time and risk going from discovery to the clinic. PSI brings unmatched experience in traditional and innovative approaches to drug product development. Expert in difficult-to-solubilize APIs, PSI works across a variety of dosage forms including: topical, mucosal, oral and parenteral and is a globally-recognized leader in the development of combination drug/device products. For more information, please visit www.particlesciences.com, email info@particlesciences.com or call (610) 861-4701.

AN INTERNATIONALLY RECOGNIZED LEADER



PARTICLE SCIENCES
DRUG DEVELOPMENT SERVICES

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Pharmacircle™ is a best-in-class knowledge management company that provides a one-stop source for all information needs within the Pharmaceutical industry. PharmaCircle provides a detailed analysis of drug delivery technologies, marketed products/pipeline, deals, acquisitions, and venture capital. PharmaCircle also provides detailed company related information, such as employee numbers, R&D spending, product sales, product development costs, royalties, and more. The data within PharmaCircle is searchable and exportable into user-defined charts and graphs.

Why PharmaCircle?

- Comprehensive technical (pipeline, products, molecule, and technology) and business (deals, acquisitions, royalty, licensing, drug revenues, market information, etc.) related information and analysis has utility for all segments of small and large companies.
- Facilitates product life cycle management (LCM), partnering, licensing, and competitive intelligence efforts.
- Supplements internal efforts and costs at a fraction if performed internally.

PharmaCircle Content

- Unique and comprehensive content on Drug Delivery (DD), pharmaceutical, biotechnology, and related fields.
- Drug Delivery technologies, pipeline/products, deals, patents, etc. are organized using 180+ Drug Delivery categories, as well as therapeutic fields.
- Extensive information on physical, chemical, and pharmacokinetic properties of molecules.
- Searchable information on formulation, dosing, and administration for marketed and development products.
- Comprehensive Reviews and Compare & Contrast Tables for all major Drug Delivery technologies.
- Information updated daily is based on public sources and PharmaCircle's own analysis.
- Extensive search capabilities on almost every data entry.
- The data base structure and presentation are designed and supported by dedicated and skilled IT professionals.

putting together all the pieces at your fingertips

PharmaCircle™ is an innovative knowledge management company specializing in the drug delivery, pharmaceutical and biotechnology fields. With customers varying from world leaders to start up companies, our web of content and customer support gives you the cutting edge advantage.

"I can now hand the customers something when I thought we'd have to say we couldn't."

-Customer Feedback

- **Products & Pipeline**
- **Regulatory**
- **Formulation & Excipients**
- **Drug Delivery**
- **Clinical Trials**
- **Deals & Acquisitions**
- **Life Cycle Management**
- **Sales**
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- **Paragraph IV**

PHARMACIRCLE™

Innovation in Pharmaceutical Knowledge Management

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760.436.1199

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Company Profile

Pharmanumbers

Forecasts and Pipeline Strategy
Drug Delivery Specialists

Pharmanumbers Services:

Product forecasts
Pipeline analysis and optimization
Risk and opportunity analysis
Product positioning
Drug delivery benchmarking including our annual DDEP report
Partnering strategy and program development

At Pharmanumbers we help companies formulate better product and pipeline strategies.

In addition to benchmarking thedevelopment and commercial performance of drug delivery products and companies we continuously distill the data to identify key elements that can help companies make better decisions.

Perhaps the only thing worse than a drug delivery product that fails in clinical trials is one that passes the clinical and regulatory hurdles but is unable to generate partner and market interest.

We can help you better align your drug delivery product, pipeline and technologies with real market needs.

Contact:

Josef Bossart

Tel: (512) 535-3613

jb@pharmanumbers.com

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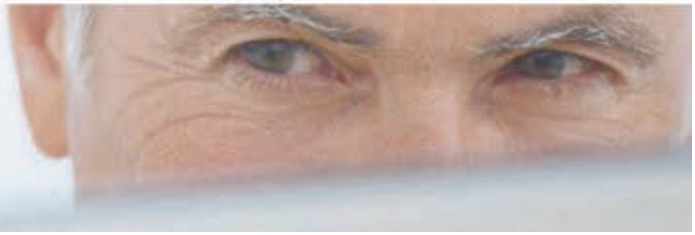

Pharmanumbers™
Forecasts & pipeline strategy

A GREAT FORECAST GOES BEYOND NUMBERS AND CAPTURES PRODUCT VISION.

A strong forecast suggests opportunities, and points to actions the whole company can understand. Pharmanumbers™ helps companies develop forecasts that connect the dots, and connect with development teams and investors.

Pharmanumbers provides emerging biopharma companies with the support and perspective necessary to better position their products and pipelines for market success. Pharmanumbers helps companies quantify the potential of their products and understand the qualitative issues that impact pipeline performance.

If the foundation of a successful company is an easily understood statement of objectives and strategy, the foundation of a successful product is a forecast that intuitively models the opportunity and translates it into clear strategies and tactics. As a strong plotline underpins a successful story, a strong forecast underpins a successful development program.

Pharmanumbers provides companies with business development and consulting support for enhancing product and pipeline value. Pharmanumbers also publishes custom reports on the parameters and strategies impacting the performance of emerging biopharma companies. Current reports examine the parameters underlying the product and pipeline success of drug delivery enabled and enhanced pharmaceutical products (DDEP).
Give us a call or go to our website for more information on our reports and consulting services.

Pharmanumbers™
Forecasts & pipeline strategy

Josef Bossart, Tel: 800-569-5724, Email: jb@pharmanumbers.com www.pharmanumbers.com

Pharmanumbers LLC – Forecasting and pipeline strategy consulting services.
Bionumbers – Reports and custom analysis that impact business decisions.

Patheon™
Performance the World Over

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Research Triangle Park, NC 27709
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E: doingbusiness@patheon.com
Website: www.patheon.com

Patheon is a leading global provider of contract development and manufacturing services to the global pharmaceutical industry. Patheon prides itself in providing the highest quality products and services to approximately 300 of the world's leading pharmaceutical and biotechnology companies. Patheon's services range from preclinical development through commercial manufacturing of a full array of dosage forms, including parenteral, solid, semi-solid, and liquid forms. Patheon uses many innovative technologies, including single-use disposables, liquid-filled hard capsules, and a variety of modified-release technologies. Patheon's comprehensive range of fully integrated Pharmaceutical Development Services includes preformulation, formulation, analytical development, clinical manufacturing, scale-up, and commercialization. Patheon can take customers direct to clinic with global clinical packaging and distribution services, and Patheon's Quick to Clinic™ programs can accelerate early phase development projects to clinical trials while minimizing the consumption of valuable API. Patheon's integrated development and manufacturing network of 15 sites across North America and Europe strive to ensure that customer products can be launched timely and confidently anywhere in the world.

What we do

- Over 40 conventional and specialized dose formulations
- The global leader in Pharmaceutical Development Services with the broadest range of dose forms from Early Development through Commercial Manufacturing
- Offer a broad range of Commercial Manufacturing capabilities and services
- Global network of world-class facilities that guarantee on-time delivery for every new commercial contract
- Offer significant available capacity

Facilities

Patheon operates 15 locations around the world. Our largest Development centers are co-located within our Commercial facilities.

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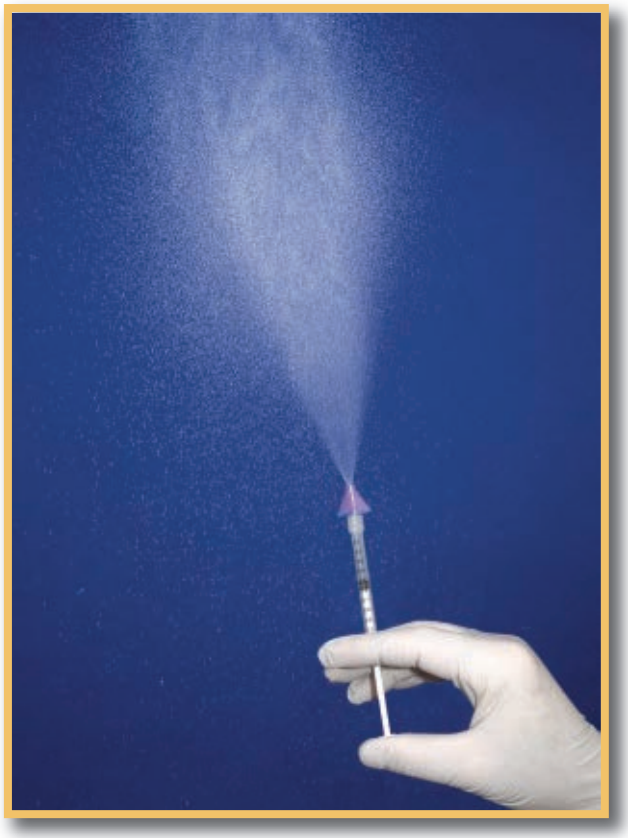

For more than 16 years, Wolfe Tory Medical has focused on new concepts in new markets. This strategic approach has allowed its two primary product lines, the atomization family of products (including the NEW VaxINator™ Intranasal Vaccine Delivery Device and the AbViser® Intra-Abdominal Pressure Monitoring System) to become leaders in its market segments with strong brand recognition. Both product lines emerged because practicing physicians recognized a unique clinical situation for which a new and innovative solution could enhance patient care.

The atomization devices emerged based on Dr. Tim Wolfe's observations of selected patients who were self-treating diseases (addiction) with nasally administered illicit drugs. Realizing the therapeutic potential of this treatment modality, Dr. Wolfe began experimenting with a variety of nasal medications, but noted numerous failures due to substantial inter-individual responses to the medications. Rather than abandon the idea, he teamed with an engineer, Marshall Denton, and they devised an elegant but simple method to fragment the drug into fine particles, allowing enhanced delivery and efficacy of any low-viscosity liquid medication. After more than a decade of persistent experimentation, teaching, and research, the idea has now become common knowledge with a rapidly expanding clinical potential. Wolfe Tory's atomization products are sold globally to hospitals, clinics, doctors, and pharmaceutical companies for dozens of therapeutic applications.

The Wolfe Tory atomization products have now been used in numerous clinical studies - firmly establishing its clinical utility and recognition as a leading delivery device in this rapidly emerging market. The new VaxINator device is Wolfe Tory's answer to a cost-effective solution for high-volume intranasal applications, including major vaccine delivery programs around the globe.

West Pharmaceutical Services, Inc.
101 Gordon Drive • Lionville, PA USA 19341 • 610-594-2900
www.WestPharma.com

Company Profile

Westar®
component processing

ConfiDose®
auto-injector system

Daikyo Crystal Zenith®
prefillable syringe systems

Prefillable Syringe Components
a solution for every need

West is a leader in developing and manufacturing packaging and delivery systems that enhance the administration of pharmaceuticals. The products and services we provide help improve health care for people around the globe. West supports its customers from locations in North and South America, Europe, Asia and Australia.

Providing Solutions for Global Health Care

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Prefillable Syringe Solutions – Prefillable syringe systems and components help bring products to market safely and reliably. West's products, technical expertise and services provide solutions that help reduce regulatory risk and ensure quality and patient safety. Visit www.WestPFSsolutions.com for more information.

Administration Systems – West develops and manufactures safety and administration devices for the reconstitution, mixing, transfer and administration of injectable drugs.

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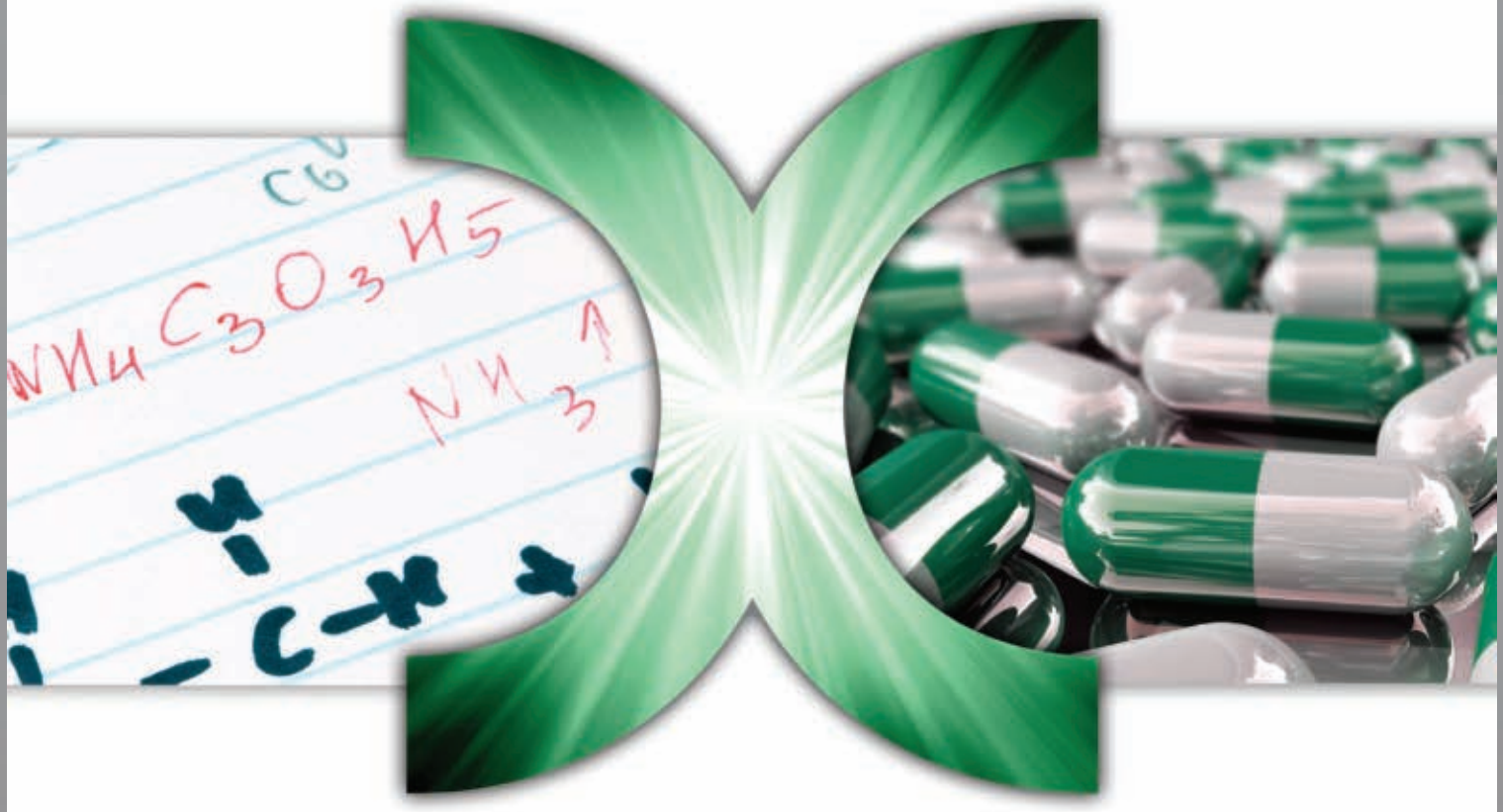

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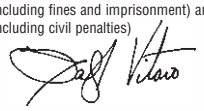

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Where's the Beef?

By: John A. Bermingham

First airing on January 10, 1984, the Wendy's commercial featured three elderly ladies examining an exaggeratedly large hamburger bun topped with a minuscule hamburger patty at the *Home of the Big Bun* fast food hamburger restaurant. The small patty prompts one of the ladies to angrily exclaim, "Where's the beef?"

Our current economic condition reminds me of this advertisement from the standpoint of "Where's the Strategy" to resolve our economic situation. When I join a distressed company as the turnaround CEO, two of the many things I immediately accomplish are to hold a Staff Meeting on day one and a company-wide Town Hall Meeting on day two.

I always ask the same question in both meetings: "What is the articulated strategy of the company?" Not what you think it is, but what you know it is. I offer $50 to the person who can answer that question.

In 10 turnarounds throughout 25 years, no one has ever answered that question, and I still have the $50. I hear things like, "more new products, more customers, increase fill rates, on-time delivery, raise prices, etc." Those are tactics, not an articulated strategy.

So I keep waiting for our government's articulated strategy for economic recovery to be made available to us so that we all know the strategy that will get us to where we need to get to and the tactics to get us there. "Where's the Beef?"

Throwing billions/trillions of dollars at the auto industry, banks, healthcare, student loans, higher taxes for the rich, and lower taxes for the middle class, small business incentives, clean energy incentives, plus other tactics seem to be more of a throw it against the wall to see what sticks rather than a strategy.

Now I am not so naïve as to think that any President and Congress can sit down and develop a highly effective and well-articulated strategy for the American economic recovery. Too many lawyers in the mix!

When I lead a strategic development process for a company, I bring in a cross-section of the company for three days to put that strategic plan together. We emerge with a vision, mission, and strategic plan with the supporting tactics to accomplish the strategic plan. I then make certain the new strategic plan and related tactics are well articulated across the entire company.

So what if the President brought in a cross-section of about 100 people (say only six from Congress) from all walks of life, led by a professional facilitator, to develop the strategic United States Economic Recovery Plan with supporting tactics. Sound crazy? Maybe…..maybe not.

I mean, can you tell me what the strategic economic recovery plan is for the United States? Not the tactics, the overarching strategic plan? No? Don't worry, no one else can either, me included. I could use the $50.

So let's form a committee to bring together the people to develop the strategic United States Economic Recovery Plan. The acronym will be USERP (Usurp!) and just take this over from the President and Congress. Who's in? Ralph, Dan, me? Who else? ◆

BIOGRAPHY

John A. Bermingham is the President & CEO of Cord Crafts, LLC, a leading manufacturer and marketer of permanent botanicals. Prior to Cord Crafts, he was President & CEO of Alco Consumer Products, Inc., an importer of house ware, home goods, pet, and safety products under the Alco brand name and through licenses from the ASPCA and Red Cross. He successfully turned around the company in 60 days and sold Alco to a strategic buyer. Mr. Bermingham was previously the President & CEO of Lang Holdings, Inc. (an innovative leader in the social sentiment and home décor industries) and President, Chairman, and CEO of Ampad (a leading manufacturer and distributor of office products). With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona Corporation, and Rolodex Corporation. He turned around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served 3 years in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes, earned his BA in Business Administration from Saint Leo University, and completed the Harvard University Graduate School of Business Advanced Management Program.

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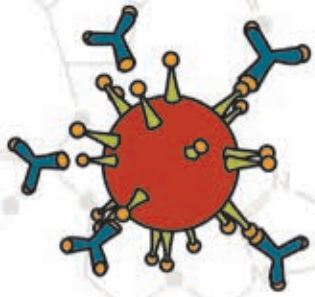

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