Drug Development & Delivery

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Epicutaneous Immunotherapy With VIASKIN®

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

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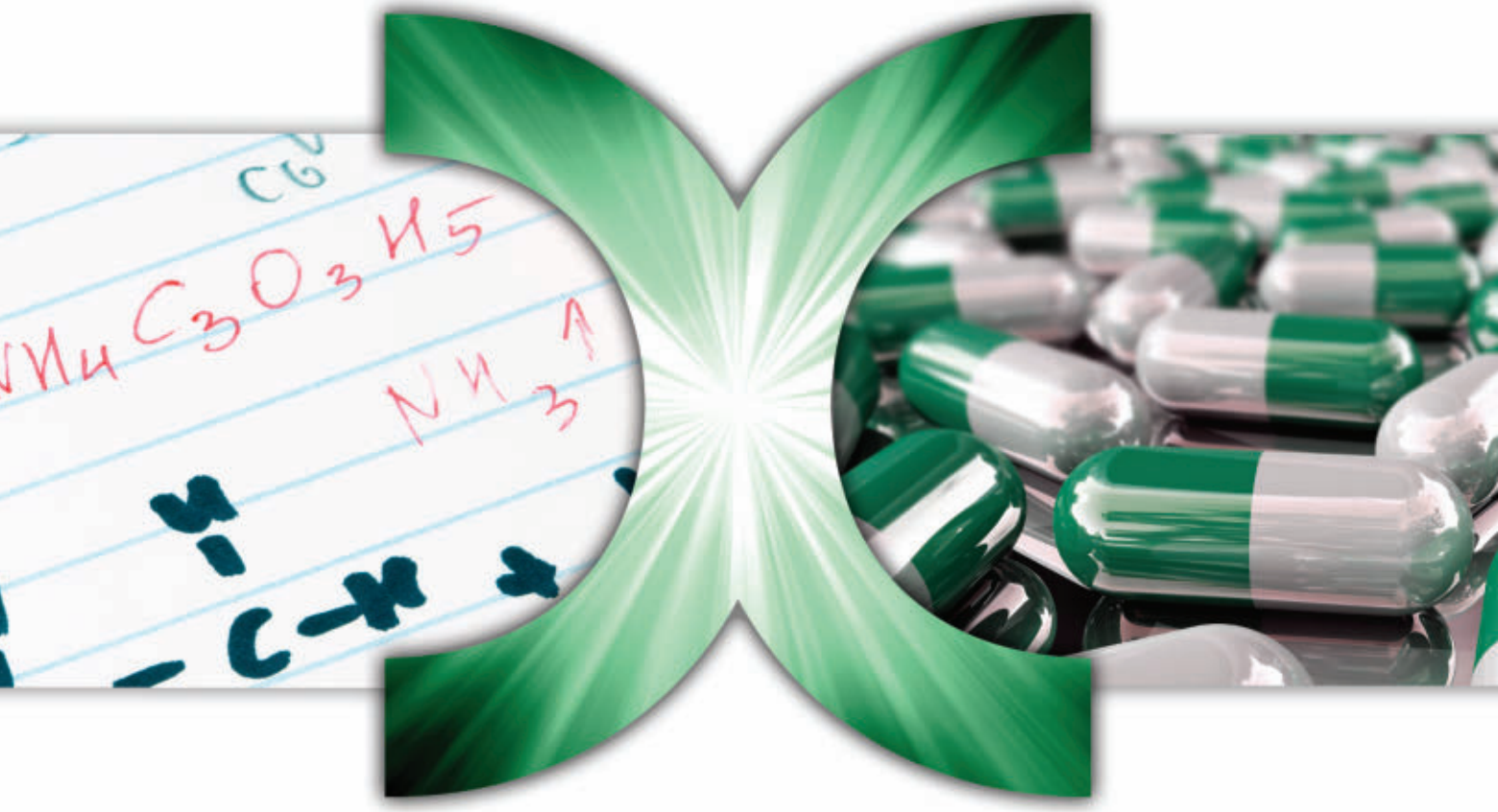

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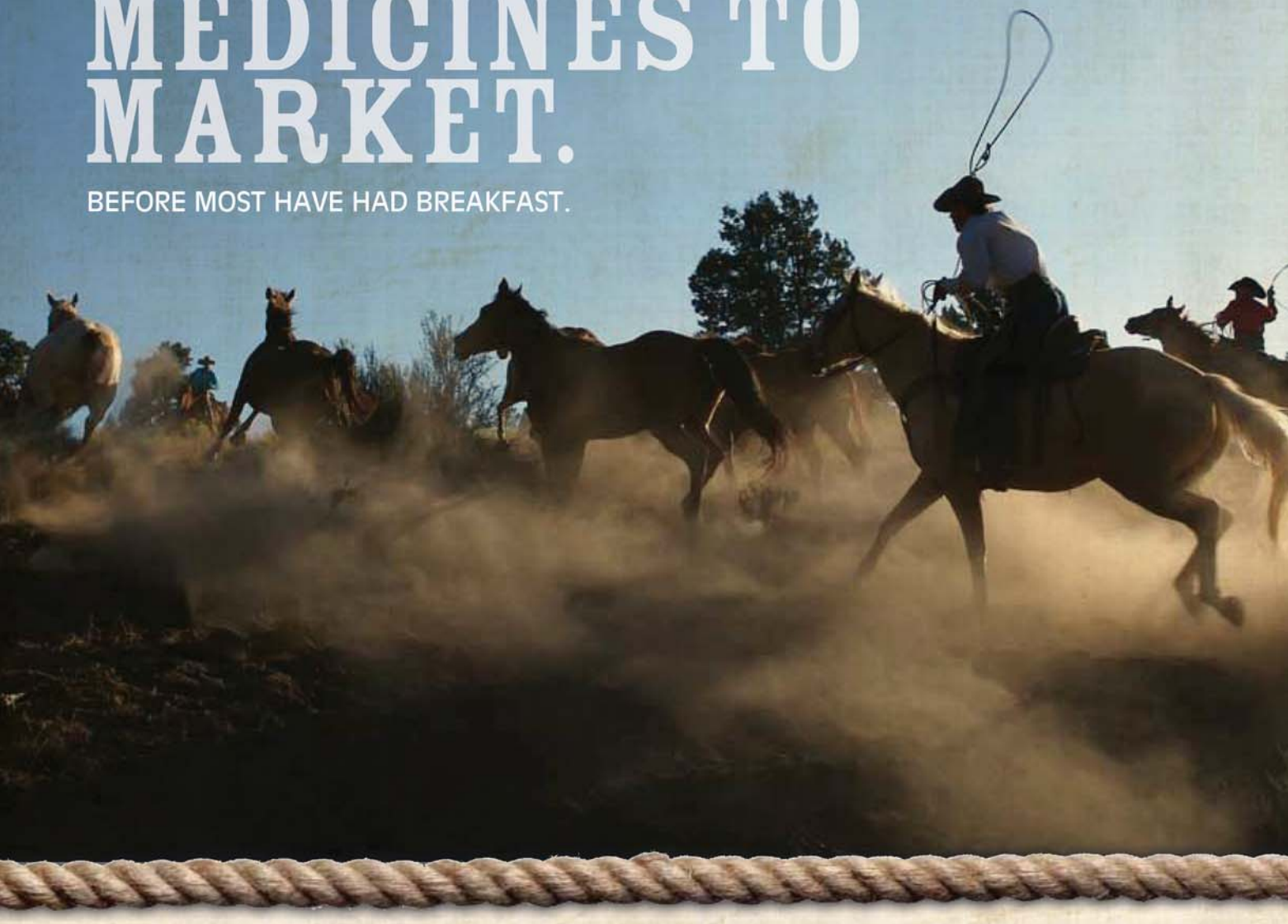

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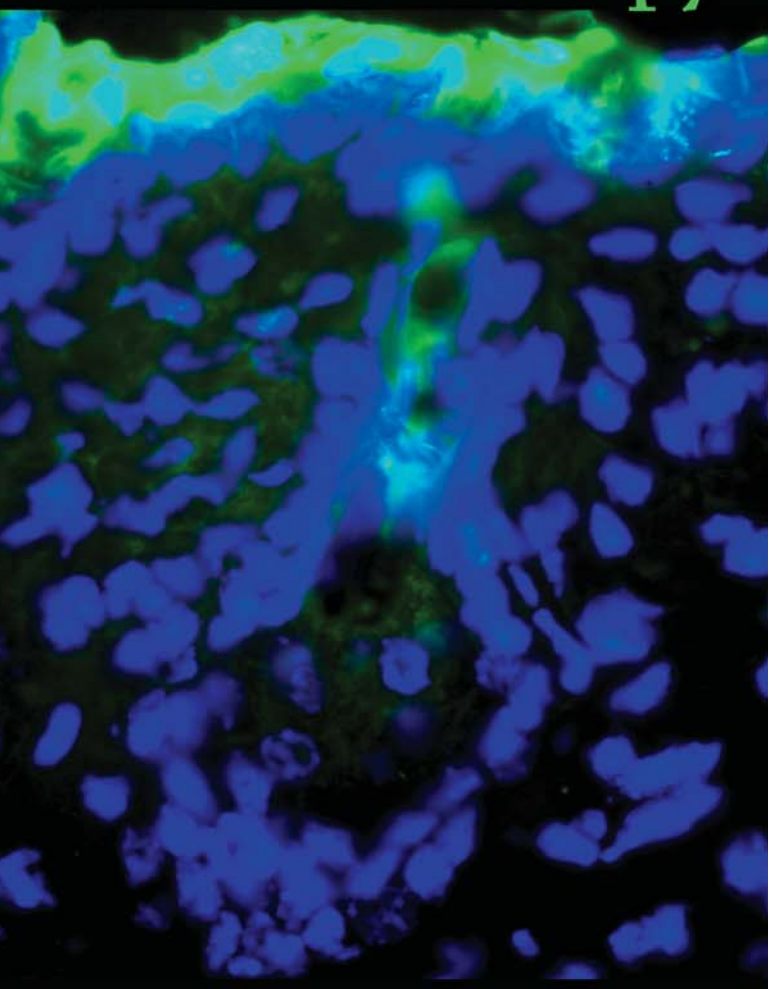
Epicutaneous Immunotherapy



"The VIASKIN epicutaneous delivery system includes a condensation chamber as a key component to deliver proteins to the epidermis. This condensation chamber achieves both solubilization of the proteins to be released for a direct contact to and hydration of the skin in order to facilitate the delivery through the stratum corneum to the epidermis."

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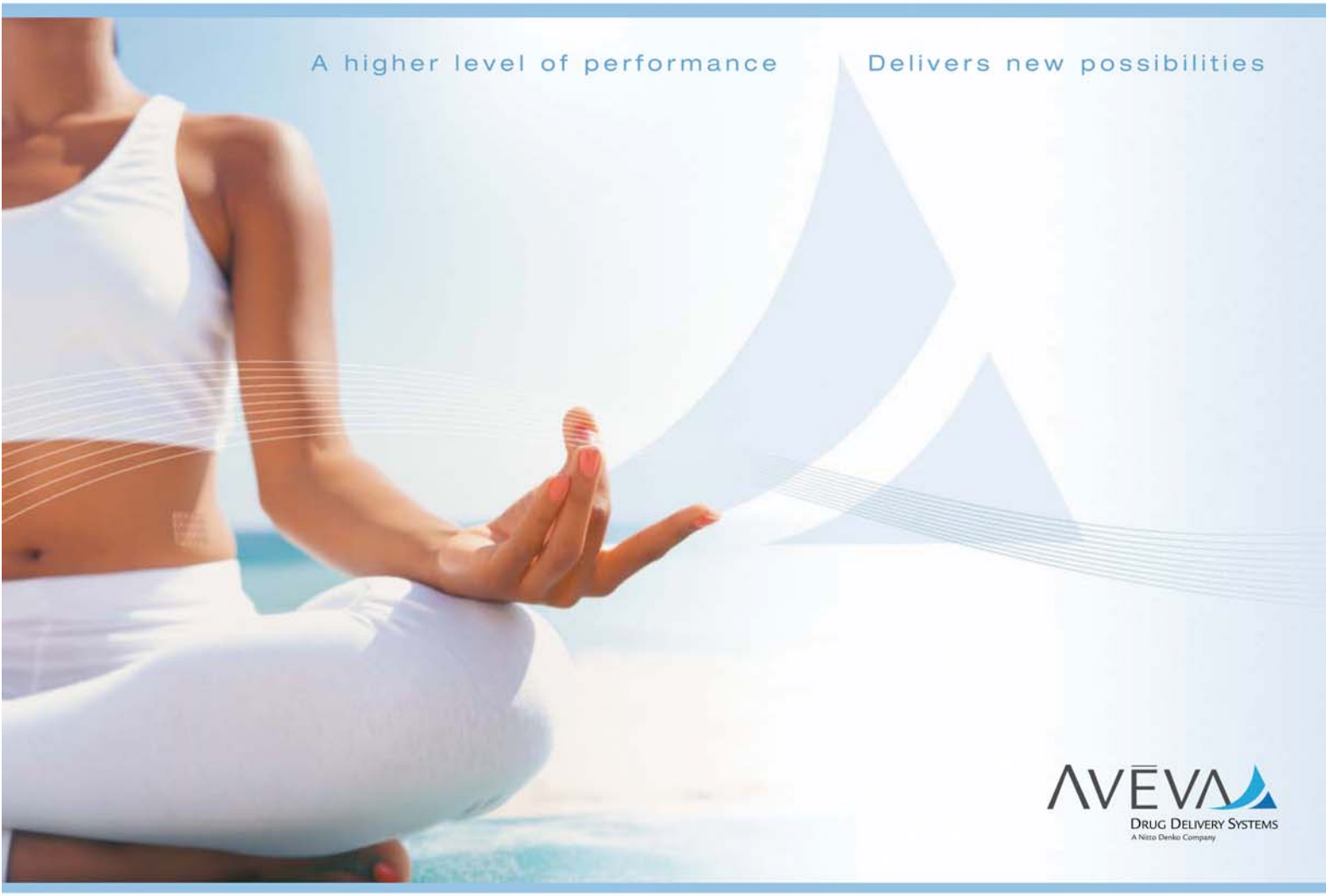
TRANSDERMAL TRANSCENDENCE



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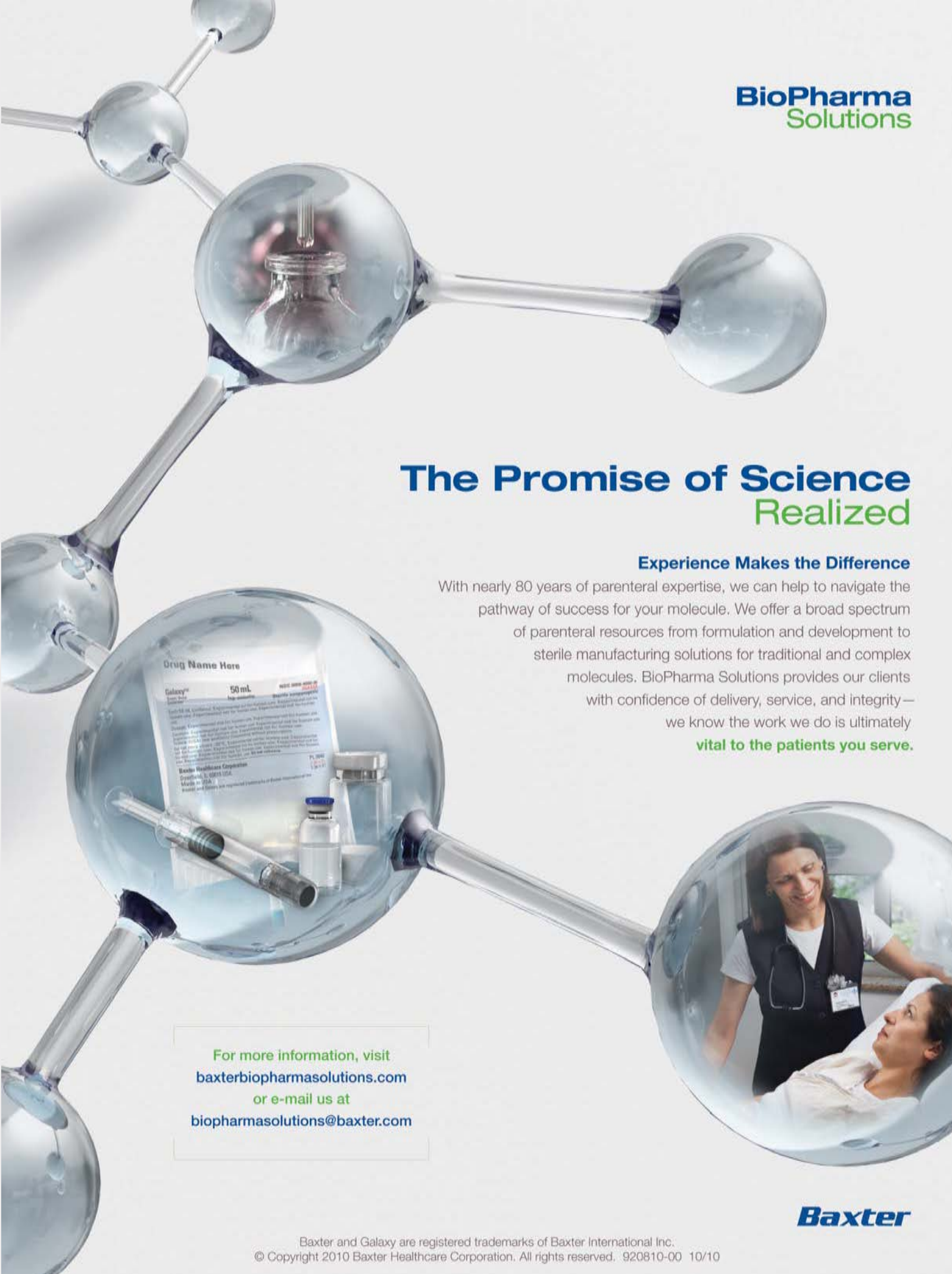

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Market News and Trends

QRxPharma Completes Patient Enrolment of Phase III Comparative Safety Study

QRxPharma Limited recently announced it has completed patient enrolment for Study 022, a Phase III trial comparing the tolerability and safety profile of MoxDuo IR to equi-analgesic doses of either morphine or oxycodone alone. Specifically, the study evaluated the incidence of opioid-related adverse events, including changes in respiratory function, moderate-to-severe nausea, vomiting, and dizziness, in patients with moderate-to-severe postoperative pain following bunionectomy surgery. The trial enrolled 375 patients (n = 125 per treatment group) at 5 US clinical research sites. QRxPharma expects to release top-line data in June.

"This Phase III trial represents a major milestone as it is the first comparison of MoxDuo IR (12 mg/8 mg) to equi-analgesic doses of morphine and oxycodone," said Dr. John Holaday, Managing Director and CEO, QRxPharma. "With patient enrolment complete, we are optimistic that the pending results will confirm the significant tolerability and safety advantages of MoxDuo IR over these two widely prescribed opioids."

A prior comparator study in patients experiencing acute postoperative bunionectomy pain demonstrated the potential side effect and safety benefits of MoxDuo IR (6 mg/4 mg) when compared to equi-analgesic doses of morphine (12 mg) or oxycodone (8 mg). Specifically, the occurrence rate of moderate-to-severe adverse events, including nausea, vomiting, and dizziness was reduced by 50% to 75% in MoxDuo IR-treated subjects compared to patients receiving morphine or oxycodone alone at the same 12-mg MED (morphine equivalent dose).

This Phase III study was similarly designed, but compared MoxDuo IR (12 mg/8 mg - 24 mg MED) with equi-analgesic doses of morphine (24 mg) and oxycodone (16 mg). By design, approximately 40% of the enrolled subjects were age 60 years or older, thus providing ample evaluation of the tolerability of the three treatments in this age group.

Trial results will form part of QRxPharma's European Marketing Authorisation Application (MAA) scheduled for submission in the first quarter of 2012. Study results, when published in medical literature, may, in conjunction with other trial data, be a component of the promotional package following the projected commercial launch of MoxDuo IR in the US in 2012 and in Europe in 2013.

Based on QRxPharma's recent pre-New Drug Application meeting with the US FDA, the company believes it is on track to file an NDA for MoxDuo IR in mid-2011. MoxDuo is a patented 3:2 ratio fixed dose combination of morphine and oxycodone. Immediate-release MoxDuo targets the acute pain market, a $2.5 billion segment of the $7 billion spent annually on prescription opioids in the US.

MicroDose Therapeutx Announces Development Milestone Triggering Payment Under Respiratory Collaboration

MicroDose Therapeutx, Inc. recently announced that a development milestone in its collaboration with Novartis has been achieved, triggering a payment under the multi-product development and licensing agreement for the MicroDose proprietary dry powder inhaler (DPI). This milestone signals the successful incorporation of MicroDose's DPI technology into a Novartis platform pulmonary device.

As previously announced, under the terms of the agreement, Novartis is funding development and commercialization of products that employ MicroDose's DPI technology for the administration of Novartis' proprietary respiratory compounds. In addition to the up-front payment received, MicroDose is eligible for additional milestone payments and royalties on product sales.

"MicroDose is pleased to announce the achievement of this milestone," said David Byron, Vice President of Research and Development, MicroDose. "The collaboration with Novartis has yielded a platform embodiment of MicroDose's DPI technology for Novartis to use in advancing development of a number of their proprietary respiratory pipeline products."

The MicroDose DPI is among a number of key proprietary drug delivery platforms developed by MicroDose. By employing piezo electronics, the MicroDose DPI has the potential to deliver enhanced performance versus other inhalers, for efficient and reproducible delivery independent of patient coordination, inhalation rate, and posture. MicroDose believes that the flexibility of the inhaler makes it a true platform technology, able to support a broad pipeline of products across the spectrum of patient populations and therapeutic categories.

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Sartorius Stedim Biotech & RAUMEDIC Sign Partnership Agreement

Sartorius Stedim Biotech (SSB), an international leading pharma and biotech supplier, and RAUMEDIC, a leading worldwide OEM manufacturer of medical- and pharmaceutical-grade polymer components and systems, recently announced the signing of a global partnership agreement. This covers arrangements concerning the mutual development of innovative fluid systems and marketing of single-use tubing, which RAUMEDIC produces for and will supply to Sartorius Stedim Biotech on a long-term basis.

Sartorius Stedim Biotech will be combining its designing, manufacturing, and validation expertise in single-use systems for biopharmaceutical applications with RAUMEDIC proficiency in the development and manufacture of tubing for medical and biopharmaceutical use. The alliance will provide innovative, high-quality, and reliable fluid handling systems to biopharmaceutical manufacturers. Through this strategic partnership with RAUMEDIC, Sartorius Stedim Biotech will substantially expand its product and service portfolio in the area of liquid transfer technologies.

The companies will strengthen and develop their existing long-term collaboration and merge their expertise for generating new tubing technologies and validation standards. With a new product line, TuFlux, which will soon be launched, Sartorius Stedim Biotech will supply its customers with highly validated polymer and silicone tubing on single-use assemblies as well as stand-alone tubing coils, along with comprehensive validation packages. According to the agreement, Sartorius Stedim Biotech will offer its products backed by RAUMEDIC's support and assistance in order to develop customized solutions and to provide stronger validation and technical support as well as process improvements.

Jean-Marc Cappia, Vice President of Fluid Management Technologies of Sartorius Stedim Biotech, acknowledges the agreement as an important milestone in expanding SSB's product portfolio.

"More than ever, we offer the full capabilities of single-use technologies. For our customers of the biopharmaceutical industry, this partnership will yield a powerful combination of single-use bags, filters, connectors, sensors, and tubing systems and services. Our long-term expertise in characterizing extractables in filters and bags will benefit our tubing technology and hence, we will be offering more comprehensive validation packages for our single-use solutions."

RAUMEDIC is bringing to Sartorius Stedim Biotech more than 60 years of technical expertise and manufacturing excellence in the area of polymer-based systems and components for medical and pharmaceutical applications. The company is renown in material development, compounding of raw materials, and extrusion technologies of all kinds for polymer and elastomer tubing.

"This alliance will provide integrated, single-use systems to the global biopharmaceutical industry, which have been developed and harmonized by two strong partners in this area," added Martin Bayer, CEO of RAUMEDIC.

Novozymes Biopharma Collaborates With University to Tailor the Half-Lives of Proteins

Novozymes Biopharma, part of Novozymes A/S, a world leader in bioinnovation, recently unveiled its enhanced next-generation albumin technology, which was developed in collaboration with the University of Oslo, Norway, one of the world's leading institutions in the research of albumin variants and the neonatal Fc receptor (FcRn).

Built on Novozymes' original Albufuse platform, the proprietary Albufuse Flex technology has been designed to enable users to adapt and control the pharmacokinetics of their target protein or peptide with retained efficacy, ensuring flexibility and optimal use.

"Novozymes Biopharma is thrilled to introduce Albufuse Flex to the industry," said Dave Mead, Business Development Director at Novozymes Biopharma. "Albumin is a natural and benign carrier molecule, and by having the unique ability to decrease or increase its half-life it will help our customers to develop novel drugs with improved pharmacokinetic properties for a wide range of applications."

It has been shown that by manipulating the interaction of albumin and IgGs with FcRn it is possible to tailor their half-lives. The Albufuse Flex technology has been developed to facilitate manipulation based on this FcRn-albumin interaction, enabling a tunable half-life that offers control and flexibility and that, potentially, may improve overall treatment efficacy and patient compliance. In addition to protein- or peptide-based drugs, the enhanced technology also provides a delivery vehicle for small molecules, providing a broad scope of usability.

The enhanced half-life technology has been developed by Novozymes in collaboration with scientists at the University of Oslo. The innovative research developed by the university into the interaction between albumin variants and the neonatal Fc receptor (FcRn) was fundamental in the development of Albufuse Flex.

"The efficacy of peptides, small proteins, and engineered antibody fragments is hampered by short serum half-life," explained Professor Inger Sandlie, Group Leader at the Norwegian Centre of Excellence for Immune Regulation. "Therefore, strategies to tailor their serum persistence and biodistribution are needed. The unique Albufuse Flex technology solves this problem and will result in enhanced treatment efficacy, more favorable dosing regimes, and improved patient compliance."

"The successful development of the Albufuse Flex technology illustrates the importance of industry and academic collaboration in turning scientific excellence into products that address medical needs. Novozymes has been an outstanding partner throughout the development process, and the company truly understands the potential of our academic science," adds Dr Jorund Sollid, Inven2 AS, the University Technology Transfer Office.

Nabi Biopharmaceuticals Completes Final Milestone; $5 Million Payment Received

Nabi Biopharmaceuticals recently announced it has completed the Phase I trial for two of the PentaStaph antigens that began in December 2009. Completion of this trial was the final milestone associated with the sale of the PentaStaph vaccine candidate to GlaxoSmithKline Biologicals S.A. (GSK). As a result of completing this milestone, Nabi has received $5 million under the agreement governing Nabi's sale of PentaStaph (Pentavalent S. aureus Vaccine) and related assets to GSK.

Nabi sold PentaStaph and related technologies to GSK for a total consideration of $46 million, including $26 million associated with accomplishing four milestone tasks. Including this milestone, Nabi has now earned all of the $26 million in PentaStaph milestone payments. In addition to the milestone payments earned, Nabi received a cash payment of $21.5 million when the transaction closed in November 2009 that included $20 million associated with the transaction close, $1 million associated with the sale of a related preclinical program for a vaccine against S. epidermedis and $0.5 million as reimbursement for license fees and clinical materials previously manufactured for use in the Phase I trial.

"I am extremely proud of our accomplishments associated with the sale of the PentaStaph program having achieved all of the PentaStaph milestones in just over a year since closing the sale transaction," said Dr. Raafat Fahim, President and Chief Executive Officer of Nabi Biopharmaceuticals. "We have successfully completed all the milestone tasks under the sale agreement."

Nabi Biopharmaceuticals leverages its experience and knowledge in powering the immune system to develop products that target serious medical conditions in the areas of nicotine addiction and gram-positive bacterial infections. Nabi Biopharmaceuticals is currently developing NicVAX (Nicotine Conjugate Vaccine), an innovative and proprietary investigational vaccine for treatment of nicotine addiction and prevention of smoking relapse.

Avantor Performance Materials to Acquire POCH S.A.

Avantor Performance Materials announced a definitive agreement to acquire POCH S.A. from Kulczyk. Completion of the sale is dependent upon obtaining the necessary clearance from the Polish competition authority, and is subject to customary closing conditions. Terms of the deal were not disclosed.

Avantor Performance Materials, formerly Mallinckrodt Baker, manufactures and markets high-performance chemistries and materials around the world under several well- respected brand names, including the J.T.Baker®, Macron™, Rankem,V and Diagnova™ brands. Avantor products are used in a wide range of industries, including biotechnology and pharmaceutical production; electronics and photovoltaic manufacturing; and in research, academic and quality control laboratories. The company is owned by an affiliate of private equity firm New Mountain Capital.

Based in Poland, POCH S.A. manufactures products designed for use in classic and instrumental analysis, filtration, and microbiology. POCH S.A. also sells laboratory equipment and laboratory glass. Moreover, POCH S.A. also manufactures solvents for liquid and gas chromatography and spectroscopy as well as anhydrous solvents. Its markets include pharmaceuticals; food and feed; chemical and petrochemical; environmental protection and research; and analytical chemistry.

“The transaction is part of Avantor’s strategy to strengthen its presence in the global market by growing both organically and through acquisition, expanding into new markets and geographies,” said Avantor President and Chief Executive Officer Jean-Marc Gilson. “POCH fits this strategy because of its established and expansive manufacturing presence and distribution channel in Poland and Eastern Europe.”

“This acquisition will allow for synergies in market and production know-how and enrichment of the combined product portfolio, significantly increasing the level of expertise dedicated to various industry sectors,” said POCH S.A. Chief Executive Officer Jaroslaw Bieszczad. “It will also enhance the competitive standing of POCH, enabling us to offer the high-quality Avantor product lines to our customers, while also giving us new markets for our products through the global Avantor organization.”

Axcan & Eurand Announce Name Change

Axcan Intermediate Holdings Inc. recently announced it is changing its name to Aptalis Pharma. The rebranding follows the recently completed combination of two specialty pharma companies focused on gastrointestinal diseases: Axcan and Eurand. Aptalis Pharma also has a new corporate logo and website: www.APTALISPharma.com.

"Our new name, Aptalis, is intended to capture the essence of two great companies that have transformed into one combined organization. Aptalis brings together the strengths and capabilities of our employees, our robust portfolio and growing pipeline, our innovative platform technologies, and our exceptional manufacturing capabilities to exceed the expectations of customers and patients," said Frank Verwiel, MD, President and Chief Executive Officer.

Aptalis currently markets several products around the world, including ZENPEP, CANASA, CARAFATE, PYLERA, LACTEOL, DELURSAN, and SALOFALK and has several compounds in various stages of development targeting unmet medical needs. The pipeline includes another recent acquisition, AEROQUIN from Mpex Pharmaceuticals, currently in Phase III clinical trials for the treatment of pulmonary infections in patients with cystic fibrosis.

Above all, Aptalis will continue to put patients and their caregivers at the center of everything it does, striving to improve their quality of care thanks to a broader range of products in cystic fibrosis and gastrointestinal disorders; robust pipeline, technology platform, and manufacturing capabilities; and skilled team of professionals with deep understanding of customers' needs.

Moving forward customers will receive the same great level of service and dedication from Aptalis that they have come to expect from Axcan and Eurand.

"This is an exciting time for Aptalis on our journey to becoming the reference specialty pharmaceutical company providing innovative, effective therapies for unmet medical needs, including cystic fibrosis and gastrointestinal disorders," added Dr. Verwiel.

PolyPid Announces Revolutionary Drug Delivery System

PolyPid, a developer of innovative drug carriers, recently announced the company's flagship platform - PolyPid, an innovative family of drug carriers, based on a fusion between two known drug delivery systems: polymers and lipid-based systems. The new drug carriers enable long-lasting and controlled release of therapeutic drugs. The revolutionary, patented carrier can be tailored to almost any drug - small molecules, peptides, proteins, and nucleic acids-based drugs. The formulations can be pre-planned in order to achieve the desired release rate of the drug/s and the optimal duration, which can last up to several months.

"PolyPid is a groundbreaking drug carrier that will help pharmaceutical and biotech companies enhance their drugs and meet their challenges," said Dr. Noam Emanuel, PolyPid's Chief Technology Officer. "Due to its flexibility, the PolyPid platform can be utilized to address numerous medical indications in various fields, such as orthopedics, urology, periodontal, anti-cancer/anti-fungal treatments and surgical accessories."

PolyPid technology makes it possible to entrap a large variety of one or more biologically active molecules, and to release them at a pre-programmed rate for up to several months, all according to the desired clinical rate. During its long-lasting effect, the drug reservoir is fully protected from both biodegradation and hydration.

The first PolyPid-based solution is BonyPid, biodegradable bone void filler that is micro-coated with a PolyPid biodegradable formulation. The coating gradually releases one or more selected antibiotics into its surroundings. Subsequently, the bone void filler scaffold remains and supports bone recovery. Thus, using BonyPid will not change the current method of treatment that used bone grafting. The physician will simply replace the conventional bone void filler with BonyPid to obtain the benefits of conventional bone void filler combined with an effective local drug delivery system.

Due to its flexibility, the PolyPid platform can be utilized to address numerous medical indications in various fields, such as orthopedics, urology, periodontal, anti-cancer/anti-fungal treatments, and surgical accessories. PolyPid Ltd. is owned by Xenia Venture Capital, private investors, and the founders.

Critical Outcome Technologies Initiates Development of Optimal Oral Oncology Formulation

Critical Outcome Technologies Inc. recently announced it has initiated a project to develop an optimal oral formulation of COTI-2. This lead oncology product has demonstrated efficacy as a single agent and in combination therapy in a number of animal models of human cancers. Development of an oral formulation for use in humans will maximize the amount of an orally administered dose that is absorbed into the body.

Following the completion of a successful private placement in April, COTI announced its intention to launch three studies related to the continued development of COTI-2 based on scientific and business feedback from prospective licensing partners. The first study, a pharmacodynamic animal experiment, is already underway. This recent announcement represents the initiation of the second research study. An agreement between COTI and Xcelience Formulation Development, LLC (Xcelience) of Tampa, FL, was signed on May 2, 2011, and work on the project is now underway.

The third study will be the completion of the 28-day Good Laboratory Practice (GLP) toxicity experiments in two species that forms part of the Investigational New Drug (IND) enabling experiments required by the Federal Drug Administration prior to beginning clinical trials.

"We are committed to achieving all three of these COTI-2 developmental milestones, and we are pleased with the initiation of the oral formulation optimization project," said Dr. Wayne Danter, COTI's CEO and President. "Xcelience is a recognized industry leader with an impressive track-record of success in formulating more than 100 development-stage small molecules for clinical use."

"We are pleased to be recognized for our strength in formulation development expertise and selected for the COTI-2 program," said Derek G. Hennecke, CEO and President of Xcelience. "The partnership that has developed is a great example of the value two companies can create when they work together to achieve program objectives."

COTI-2 has shown itself to be highly effective both as a single agent and in combination therapy in a number of animal models of human cancers. Other cancer treatments involve the killing of healthy growing and dividing cells in the body, resulting in significant toxic side effects, while COTI-2 appears to target and destroy cancer cells only and has demonstrated low toxicity in normal human cells compared to human cancer cells. The combined scientific evidence indicates that COTI-2 is an ideal agent for combination therapy with current standard agents for a number of cancers, including small cell lung, non-small cell lung, colon, brain, ovarian, endometrial, triple negative breast, and pancreatic.

In scientific terms, COTI-2 is a novel small molecule that acts by inhibiting Akt/PKB phosphorylation that leads to caspase-9 activation in cancer cells resulting in tumor cell death. COTI-2 has demonstrated greater selectivity as well as an improved safety profile and pharmacokinetics in comparison to other Akt inhibitors. COTI is currently evaluating partners to share in the development of COTI-2 via a licensing agreement.

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When Deals Work - & When They Don't: Large Pharma Strategies for Off-Loading Shuttered Capacity

Part 3 of a 6-part series on how not to blow the recovery.

By: Derek Hennecke, President & CEO Xcelience LLC

As large pharma struggles with overcapacity, CROs are increasingly becoming part of the answer. But bagging large pharma as a partner can be as risky as it can be rewarding.

Sanofi's strategic deal with Covance was a creative way of handing off excess capacity. Sanofi gives Covance between $1.2 and $2.2 billion in work, in exchange for which Covance buys two facilities in France and the UK for $25 million. Smooth.

When they work, these deals are a boon to contract research organizations (CROs). But CROs beware. Even the largest CROs are only worth $1.5 billion, compared to large pharma's $100 to $150 billion. Large pharma has less incentive to move, and fulfillment of these strategic deals is more important to the CRO than to the pharma company. Such promises may be trivial to the mother ship, but can sink a smaller boat.

Parexel recently got tossed around in big pharma's wake. This company experienced a huge run-up in hiring and expansion costs in anticipation of future large pharma deals - a 0.09 cent per share increase in overhead. Maybe they should never have run up those costs without booking the revenue. When the deals were delayed, Parexel was left with nothing but a handful of bills to show investors. The delays startled investors in May reports, and the stock suffered a precipitous 20% plunge the next day.

CROs chasing these big deals need to be sure to have cancellation fees if large pharma doesn't meet its obligations. No matter how friendly things are when the deal is cut, situations evolve. What's a large pharma to do if some juicy biotech happens by later offering cheaper late-stage assets that offer the potential to bypass the CRO completely? Even cancelation fees don't cover risk of delays, and a CRO can find itself sitting nervously with increasing costs and an empty plant.

Things look exceptionally bright for CROs right now with an industry book-to-bill ratio that's up well over 1.10. That means CROs are signing a lot of contracts. But declared cancellation rates are rising too, and it's safe to assume there are even more cancellations that never actually get declared, because it's easier to just push them indefinitely into the future to avoid having to declare a material event to shareholders.

When companies fail to find the right strategic deal, the consequences can be dire. AstraZeneca made headlines when, after announcing a 3-year plan cutting 10,400 jobs, they also reported they would be demolishing a 2.2 million-sq-ft facility in Wilmington, NC.

It's bad enough they had to let go of those jobs, but why, bloggers and columnists throughout the industry demanded, would they then proceed to raze the building to the ground? Surely this was unnecessarily dramatic? Obviously a built-out facility has more commercial value than a lot of grass and butterflies.

Actually, in the world of financial accounting, such a thing is not obvious at all. As we work through this tepid recovery, difficult (sometimes unpopular) decisions have to be made along the way. The reasoning behind these decisions is often not transparent. AstraZeneca's decision may be a perfect example.

There are a number of reasons why an empty lot can be worth more than a built-out one. Consider depreciation, for one. Generally, when large pharma renovates a lab, the concerned division sets up a very, very long depreciation schedule on the investment. The longer the schedule, the more they can boost short-term profits. But such a schedule has a nasty side-effect of attracting higher state property taxes. There is only one way to get that tax removed, and that is to physical demolish the building. Perverse, but true.

That's only the first point. Consider insurance. Insurance runs almost 50% higher on an unoccupied building. This makes sense - with no one around to spot leaks and fire hazards and monitor security systems, more stuff happens. Insurance companies know this.

The real estate market itself is a factor. I know of at least five pharma or small contract development and manufacturing organizations (CDMOs) that have been on the market for more than 3 years. And those are smaller, more adaptable facilities. AstraZeneca had a purpose-specific 2.2 million-sq-ft 30-year-old facility connected with walkways. Even Home Depot couldn't be expected to make something of that.

As for repurposing, well, there are just too many empty pharma plants in the US to make them all bio-incubators. Adding to this problem is the perception that a bio-incubator has to look state-of-the-art, and therefore must have been built within the past 8 years. I can't say I completely agree with this - on a recent milk run through the Cambridge area last week, I saw several bio-incubators, and the one that stands out in my mind is a well-funded virtual company housed in

an aging building beside the Boston Medical Center. It really looked to me like the investor's money was going to clinical trials, not glass and chrome. But perception plays a large role in investing, and most investors are looking for state-of-the-art facilities.

There are also the less-tangible factors implicit whenever a large company is managing a facility - empty or not. Internal costs are generally higher in a large company. Let me give you an example. In 2001, I worked for a large company that charged $300 per month for every internet connection. How did the manager in charge of the unit react to this cost? He reduced the number of people with access to the internet. Yes, really.

Then there is the simple fact that no one in a large company makes a career for themselves by selling or repurposing an empty facility. It's more glamorous and more visible to be working to develop new business or products than to deal with the waste products of previous businesses.

By far, the better solution in AstraZeneca's case would've been a creative deal to offload their excess capacity, but in this case, it wasn't to be.

It's a risky business, but the trend toward more strategic partnerships between CROs and large pharma is growing, and I fully expect it will continue to grow. I suspect part of the reason is that many CROs fear if they don't make such partnerships, someone else will, and they'll be left out in the cold.

The good news is that these partnerships are driving business toward outsourcing. The bad news is the deals offer large volumes of business in exchange for lower prices and margin. For those companies willing and able to engineer their processes to produce high volume and lower prices per unit, it's all good. Still, others will find opportunity in specialty projects or solutions-driven work. Only for those incapable of carving out either niche is the outlook glum. One thing is for sure: the CRO landscape is about to get a lot more interesting as firms differentiate on what it means to serve different client segments well.

For large pharma, working strategically with a single CRO has numerous advantages. You can bring them into the process earlier, ensure a smoother transition, achieve the efficiencies that come with working with the same partner repeatedly, and lower costs by negotiating volume deals.

Over the long run, these alliances will change the CRO landscape, but they will also drive innovation. Trials are becoming bigger, more complex, and more global. Global CRO players have a better shot at long-term growth and profitability, particularly as production levels normalize.

As economic conditions improve and drug makers begin to unfreeze pipelines - and the CRO book-bill ratios of at least 1.0 during the fourth quarter show that this is happening - we can expect this trend of drug makers outsourcing more and more of their R&D budgets to CROs to continue.

Tough decisions are being made by large pharma in this economic environment, and agile dealmakers in the CRO world stand to benefit. But as always in a relationship in which both partners don't come into it on an equal footing - consider a good pre-nup. ◆

BIOGRAPHY

Derek G. Hennecke
President & CEO
Xcelience

Derek G. Hennecke is a founding member, CEO and President of Xcelience. He has a long history of growing strong businesses around the world. Blending a scientific and business background, he has nearly 2 decades of international experience in the healthcare industry and a track record as a highly successful international turn-around manager in the global drug development community. Xcelience is the first company Mr. Hennecke has managed as an owner, having launched a management buy-out from MDS Pharma Services in 2006. The newly formed company immediately embarked on a robust pattern of strong growth. This growth was recognized in May 2008, when Mr. Hennecke was selected as a finalist for the coveted 2008 Ernst & Young Florida Entrepreneur of the Year award, a nomination based on the demonstration of extraordinary success in the areas of innovation, financial performance, personal commitment to community, and perpetual growth. Mr. Hennecke was also recognized as a finalist for the Ultimate CEO awards by the Tampa Business Journal and Small Business of the Year by the Greater Tampa Bay Chamber of Commerce, in 2008. Before founding Xcelience, Mr. Hennecke spent more than 10 years abroad working for the Dutch-based conglomerate DSM. In Montreal, he was GM of a 250-staff Biologics plant for more than 2 years. In Cairo, Egypt, as GM, he oversaw a radical turn-around in an anti-infectives plant that had been slated for closure. He spent 2 years in Holland developing new Pharma intermediates, and two years in Mexico as Commercial Director covering Central and South America. He also worked for Roche, both in Canada and Germany. Mr. Hennecke has a BSc in Microbiology from the University of Alberta and an MBA from the Erasmus University in The Netherlands.

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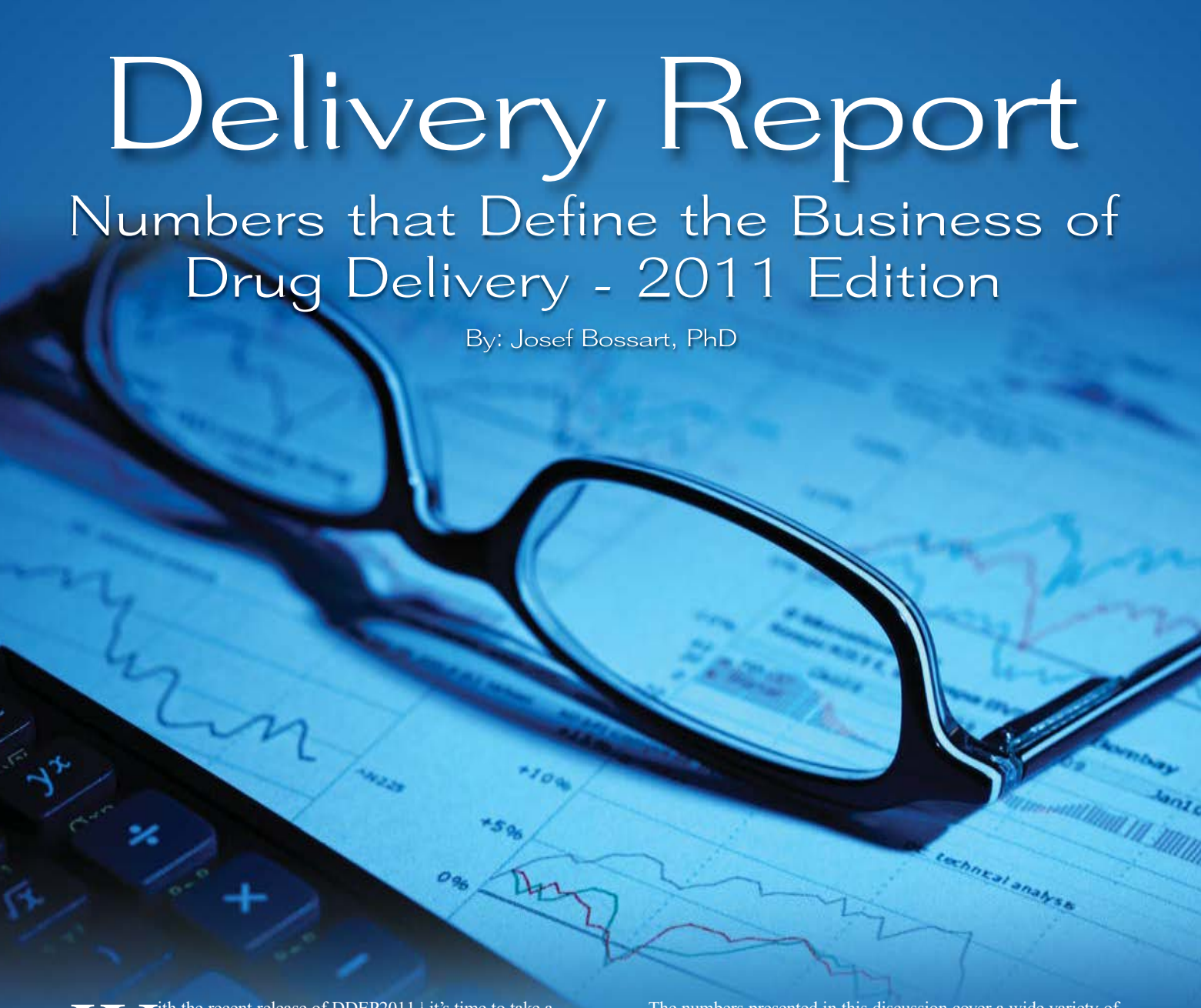
Delivery Report

Numbers that Define the Business of Drug Delivery - 2011 Edition

By: Josef Bossart, PhD



With the recent release of DDEP2011,[1] it's time to take a peek at the numbers that define the business of Drug Delivery. Understanding these numbers provides a foundation to better plans and outcomes in the real world of drug delivery development and commercialization.

WHAT IS A DDEP?

This is a question that's worth reviewing before heading into the numbers. The acronym DDEP stands for drug delivery enabled/enhanced product. A DDEP is a pharmaceutical product that depends on drug delivery technology to enable, enhance, expand, or transform its therapeutic value. This definition excludes products that incorporate simple formulation technologies because all pharmaceutical products in some way or other require formulation technologies. For this discussion, drug delivery technologies are those technologies that are intended to deliberately impact the physical form, absorption, distribution, metabolism and/or excretion of a pharmaceutical active with the intent of improving its therapeutic benefit. There are some exceptions; these exceptions include technologies that have been around for decades and have become part of the standard formulation toolbox, for example simple enteric coating.

The numbers presented in this discussion cover a wide variety of DDEPs, including oral extended-release products for systemic indications, inhalation products targeted to locoregional diseases, and implants for local metered release. Given this very wide variation, it's important to realize that averages are just that - averages. Particular classes of DDEPs may vary from the overall averages, and individual products often show variability within these segments. Even so, the averages can provide meaningful insight into the demands and rewards of DDEP development and commercialization. This review is limited to providing top line results; additional details are provided in the full report, DDEP2011, available at Pharmanumbers.com.

DEVELOPMENT TIMELINES

We estimate the current mean average clinical development and approval time for all DDEPs is 6.7 years. This is the period of time it takes to move a DDEP from a first-in-human trial to FDA approval. The current median average is a somewhat shorter 6 years. This average clinical development and approval time has been creeping up since the mid-1990s. Drug delivery enabled/enhanced products approved in the years 1996-2002 took on average 5.5 years to progress from a first clinical trial to FDA approval.

Optimists can take comfort in knowing that some DDEPs were approved in as little as 2 years. Cynics can point to the fact that some products took as long as 16 years from the start of clinical trials to eventual approval. Looking at the distribution of development and approval times, Figure 1 (1996-2010), one is struck by the fact that only one in 12 DDEPs was approved in less than 3 years, and about half of all approved DDEPs took longer than 5 years. These figures seem to be at odds with many budgets and development plans that forecast development and approval in 4 years or less. It certainly is possible to do so, but it is clearly not the norm.

The majority of time involved in the clinical development and approval process is associated with the clinical development process. For the period of 1996-2010, about half of all approved DDEPs were reviewed and approved by the FDA in 16 months or less. This figure has increased by about 4 months throughout the past decade and a half and suggests clinical development times have increased by about 10 months in this same period.

These averages disguise the variability of clinical development and approval times among different classes of DDEPs that are described in detail in the DDEP2011 report. A notable difference was seen with DDEPs that depended only on bioequivalence trials, which took much less time than the overall average for DDEPs. Unsurprisingly, inhalation products on average took longer than 6.7 years. Differences were also seen between DDEPs that were approved with only convenience enhancement claims as opposed to products that were approved with enhanced efficacy and safety claims. A difference was also seen depending on whether or not the underlying drug delivery technology had been validated by a previously approved product. In many cases, the differences are large enough to warrant consideration when developing or revising a DDEP development plan.

APPROVAL RATES

With an understanding of how long it takes on average to move a DDEP through clinical development and approval, our attention turns to understanding what proportion of DDEPs entering clinical trials actually end up securing FDA approval. These are not easy numbers to uncover. With an average 6-year development and approval time, it's really only possible to measure the approval performance of products that started clinical development more than 6 years ago. Fortunately, a good sense of current figures can be determined by extrapolating recent phase-transition rates.

Pharma products have a projected clinical development and approval success rate of about 16%.[2] This means about one in six products entering the clinic, primarily new molecular entities, can be expected to receive FDA approval.

The numbers for DDEPs are better, but perhaps not as much better as one might have expected given that the majority of these products incorporate a previously approved pharmaceutical active. For the period of 1996-2002, the approval rate for DDEPs entering a first clinical trial was 34%, about one in three products. For the current crop of DDEPs, the figure has dropped to about 25%. One in four DDEPs that now enter the clinic are expected to eventually receive FDA approval.

This overall figure disguises the significant variability in success rates between disparate types of DDEPs. Among different delivery routes, success rates can range from low double digits to well over 50%. Significant differences in success rates are also seen depending on whether a DDEP incorporates a device as opposed to relying solely on formulation enhancements. Understanding the differences can make a big difference in properly balancing a pipeline to improve the odds that at least one product reaches approval. While it's nice to believe that your only development candidate will receive FDA approval if you provide enough resources and expertise, the reality is that there are elements of chance and external influences that conspire to confound even the best plans and execution.

FIGURE 1

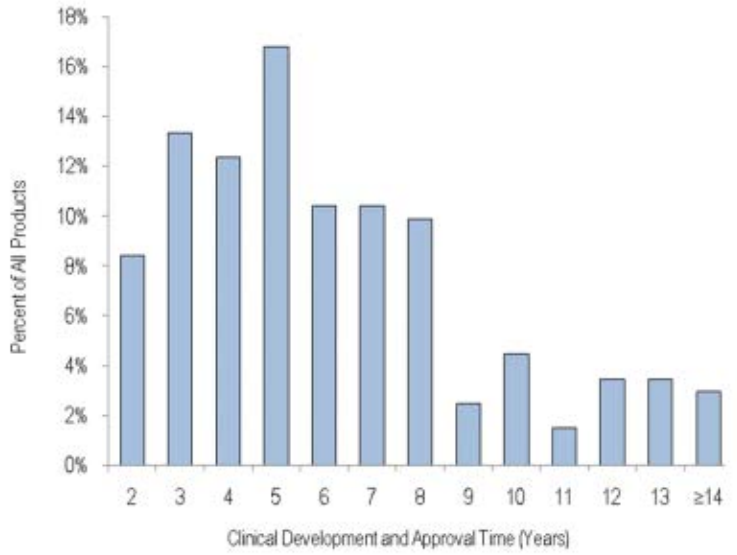


TABLE 1

	Mean Average	Median Average	Range
Clinical Development & Approval Time	6.7 Years	6 Years	2-16 Years
Clinical Development & Approval Success Rate	25%	N/A	10%-60%
Clinical Development & Approval Cost (Direct Costs)	$98 Million	$96 Million	$27-$180 Million

Key DDEP Development Figures[3]

DRUG DELIVERY DEVELOPMENT COSTS

These figures are likely to be controversial as they are at odds with what most companies, particularly start-ups, budget when developing their clinical development and approval plans. The numbers discussed below reflect the actual costs incurred by companies that have taken products through development and have received FDA approval.

The mean and median average clinical development and approval cost for a DDEP is about $95 million in 2011 dollars. This includes direct costs, but excludes expenses incurred prior to the start of clinical development, such as platform development expenses and preclinical safety studies. This $95 million figure does not adjust for development risk or include a financial discount rate as is applied to the published cost of development figures for pharmaceutical products.[3] The $95 million figure is calculated by summing the company disclosed costs by product by year, inflating costs by 4.5% annually to establish 2011 costs, and then averaging the total over the number of DDEPs in the sample.

The $95 million average figure is just that, an average. Actual expenses for approved DDEPs range from a low of about $27 million to over $200 million in 2011 dollars. These figures are for products that have been approved and have received labeling that permits promotion of safety or efficacy claims.

It is entirely possible to develop and gain approval for DDEPs for less than the $95 million average, even the $27 million minimum noted above. Although these figures are not publicly available, there are a number of DDEPs approved under the 505(b)(2) regulatory process using only bioequivalence studies for approval. An example would be an orally dissolving tablet (ODT) formulation of an approved oral tablet product. Although there are no good published figures, it's hard to imagine these products have required more than $5 to $10 million in development costs, about the same as for an ANDA product. These products though are limited to the existing safety and efficacy claims of the reference product they conducted the bioequivalence trials against. Product-specific promotion is limited to claims, such as improved dosing frequency or a simpler dosing format (ie, ODT versus tablet or capsule), with few barriers to competition. Even the 3-year regulatory exclusivity period provided by federal regulations for NDA products based on a previously approved active provides little protection if a competitor with a similar delivery platform decides to conduct bioequivalence only trials using the same reference product.

If we risk-adjust these clinical costs, we come up with a $175 million figure for the clinical development and approval costs of an "average" DDEP. This is the average cost a company would need to budget in 2011 dollars to bring a single DDEP to approval based on average costs and success rates. This would not include additional costs related to platform development and general corporate expenses. These costs can be discouraging, but there is no reason a company can't get its first and only DDEP through clinicals and to approval for $25 million with skill, knowledge, and a big helping of good luck.

REFLECTIONS

Drug Delivery as a business and sector has changed in the past decade and a half in step with technology as a business sector in general. The garage or dormitory start-up has been replaced by well-funded venture-backed entrepreneurs. Drug Delivery has much promise, but it won't be realized without significant investment. The prospect of leveraging $5 million of funding into a commercially attractive approved DDEP is unreasonable. And $10 million is still not enough to get it done. Start-ups and their investors no longer look at raising $5 or $10 million to get a product to approval; this is an amount they hope will support development of their DDEP to a point of validation that secures interest and investment from a larger and better resourced company.

This analysis doesn't mean drug delivery product development success is inaccessible to any but large companies with $90 million or more to invest in a product candidate. Smaller investments can be successful if you know the numbers and play the odds intelligently. With average DDEP product development success rates ranging from the very low double digits to well over 50%, and development timelines ranging from 2 to 16 years, a company needs to pick its product candidates carefully to optimize the prospect of a successful outcome. And showing potential partners and investors that a company really understands what it takes to get a DDEP through development and approval can only improve their odds of funding and approval success. ◆

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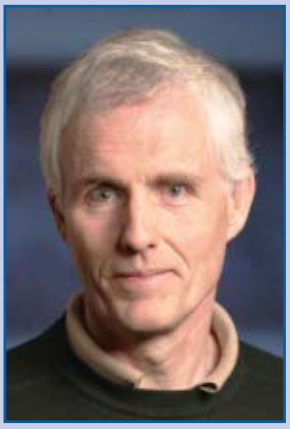
BIOGRAPHY



Dr. Josef Bossart is Managing Director of The Pharmanumbers Group, a boutique research and consulting group providing the biopharmaceutical industry with analysis and insights that improves business outcomes. In addition to issuing industry reports, such as DDEP2011 - Drug Delivery Product Success Rates, Development Times, Costs and Marketing Exclusivity, Pharmanumbers provides strategy consulting and forecasting support for emerging and commercial-stage drug delivery companies. Dr. Bossart has more than 3 decades of experience in the biopharmaceutical sector, including senior sales, marketing, business development, and management positions with Enzon Pharmaceuticals, GeneMedicine, US Ethicals, and Rhône-Poulenc Rorer. Dr. Bossart earned his PhD in Medicinal Chemistry from The Ohio State University, College of Pharmacy.

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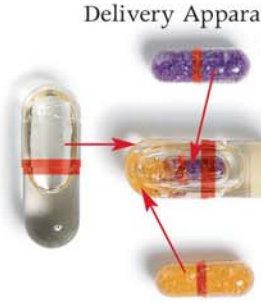
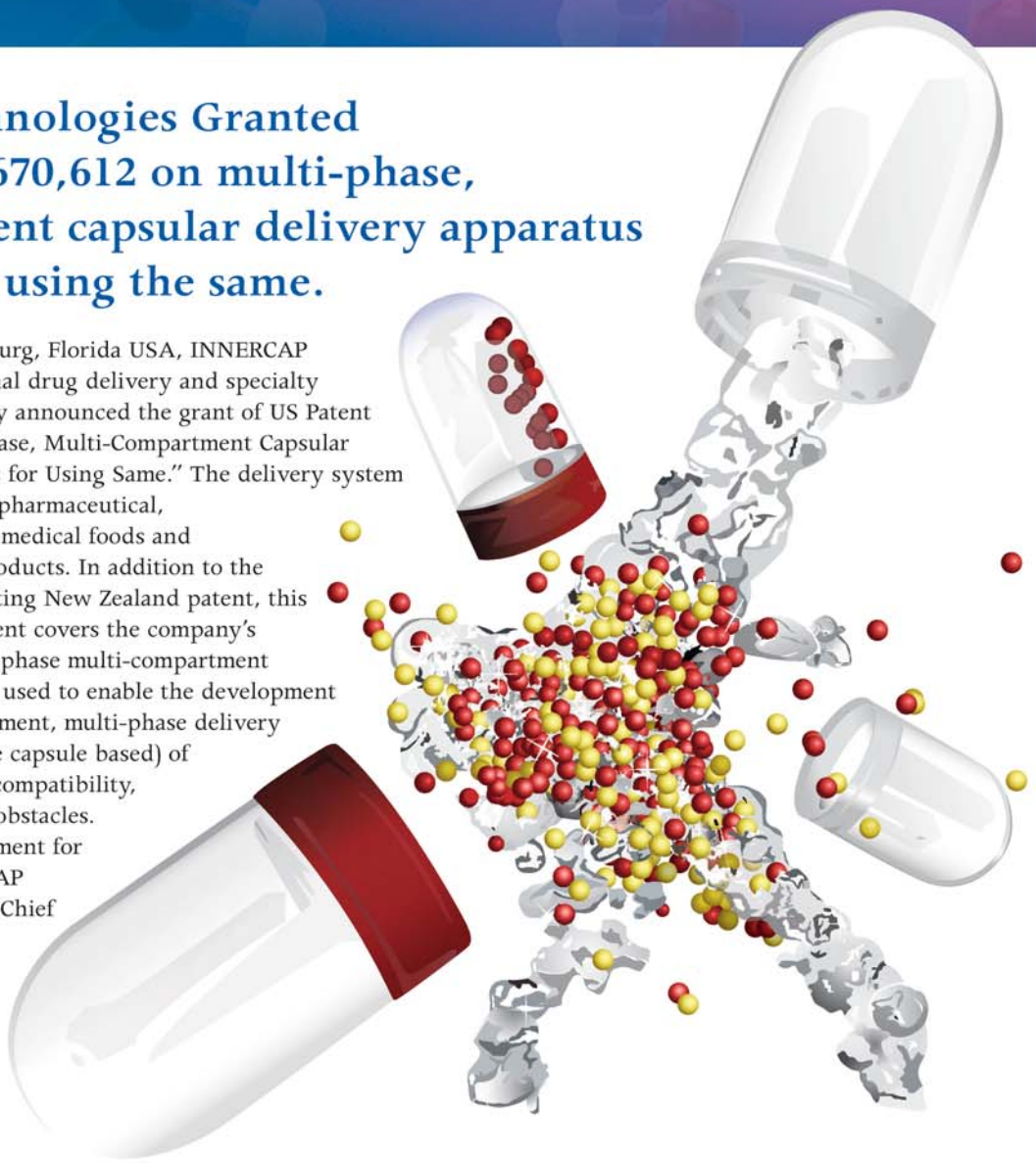
INNERCAP® Technologies Granted US Patent No. 7,670,612 on multi-phase, multi-compartment capsular delivery apparatus and methods for using the same.



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
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ADVANCED DELIVERY DEVICES

Human Factors: The Drug Delivery Challenge & Opportunity

By: Iain Simpson and Kay Sinclair

Pharmaceutical companies face the challenge of adhering to new human factors standards for drug delivery devices, but should seize the opportunity to use enhanced usability as a point of market differentiation

Pharmaceutical companies are increasingly using delivery devices as a primary differentiator in a market becoming extremely competitive. At the same time, regulators adopted new human factors standards introduced throughout the past few years, which means all devices now need to undergo rigorous usability evaluation at every stage of development. This is becoming significantly important as it is more common for devices to be used by a patient population with less experience and training than healthcare professionals.

Recently, several new standards covering human factors engineering have been developed, notably HE74, HE75, and IEC62366. In the past 2 years, the FDA adopted IEC62366, which focuses on the human factors process employed in device development (this standard essentially replaces HE74 and may replace ISO60601-1-6 in the longer term). More recently, the FDA has also adopted HE75, which provides a reference on key human factors topics, such as visual displays, packaging design, and general design principles. The FDA now expects companies developing drug delivery devices to follow these standards or at least demonstrate an equivalent approach.

The uptake of these standards will have a significant effect on the design and engineering process and will hopefully bring benefits in terms of reduction of use errors for a wide range of medical devices. Human factors play an important role in regulatory compliance (which demands safety and risk mitigation) and market differentiation (which relies on effectiveness), as well as several grey areas where factors affecting safety and effectiveness interact and sometimes conflict with one another. The new standards provide sensible guidance to incorporate human factors research throughout the development process and hopefully reduce the number of design iterations required to develop devices that meet patient needs alongside those of other key stakeholders, such as providers and payers.

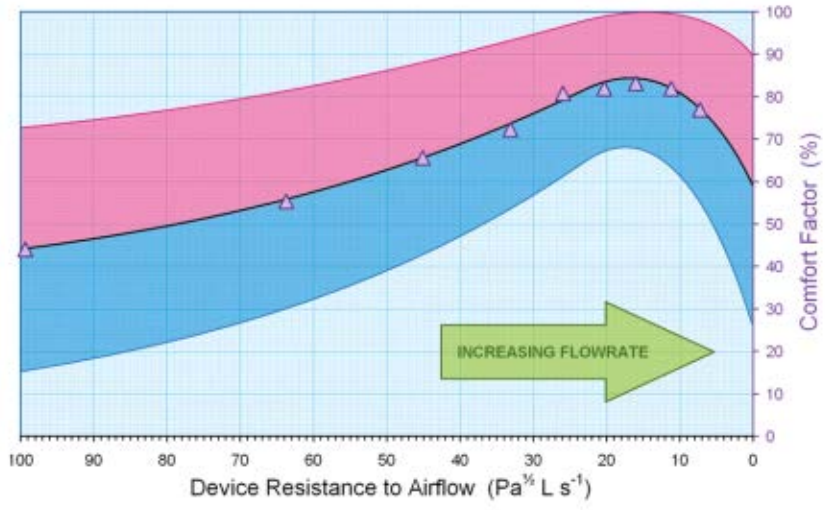
Ensuring the usability of a drug delivery device is important on three levels. First, it should be safe for use and pose no risk to the user. Second, it should be designed so the intended user can and will use it appropriately. And finally, it should be designed in a way that makes the user want to use it. While the first of these is arguably the most crucial, the second and third will have an important impact on patient compliance and, therefore, clinical outcomes. What's more, consideration (or lack thereof) for the second and third can have an undesirable impact on the first.

Ultimately, emphasis put on each stage will depend largely on the stage of maturity of the device in question, including the competitive landscape, reimbursement, regulation, and time in the market. For example, in the diabetic market, insulin pens have been available since the early 80s and evolved through a number of design generations, successfully improving usability and patient appeal. In contrast, single-use auto-injector devices used to treat rheumatoid arthritis are relatively new to the

FIGURE 1

Seven capability categories are helpful to measure a person's capability, or assess the ability level that a device demands in order to use it (source: www.inclusivedesigntoolkit.com).

FIGURE 2



As an inhaler's resistance to airflow decreases, so does the comfort factor for the patient.

market, and the designs less mature, so there is still an opportunity to create differentiation and improve usability. More complex devices emerging today, such as wearable pumps and electronic delivery systems, present more opportunities for usage error, a key driver for the introduction of new regulations.

DON'T HURT ME

By requiring companies to track user feedback and justify proposed use error mitigation approaches, the new standards emphasize the important role usability plays in product safety. Device manufacturers must apply human factors research at all stages of a product's development to prevent risk of injury and minimize the potential for user error. Additionally, they are required to prove how this has been done. This calls for rigorous processes that identify potential hazardous scenarios and use cases, assess the likelihood and severity of these cases, and put mechanisms in place to prevent accidents and/or minimize their impact. This can't be done effectively without a thorough understanding of the target user's traits, characteristics, and behaviors. While this is a challenge, there are well-established tools to help device developers do this.

Context Exploration

Context exploration tools help define and understand target user(s) and their use environments. This will involve task analysis and exploration of use scenarios, potential user errors, and hazards. Exploring capability, including the physical, cognitive, and sensory boundaries of each user profile, should also be a key part of human factors testing.

User Perspective Exploration

User study tools come in a number of different forms, but the aim is to explore potential use errors and hazards, user preference and instinct, physical and cognitive demand, user performance, and capability boundaries, etc. This should include a cross-section of all potential user types, including patients, care givers, and health professionals.

As illustrated in Figure 1, capability is measured on seven different levels: vision, hearing, thinking, communication, locomotion, reach and stretch, and dexterity. While one person's sensory and communications capabilities may be considered high, their physical capabilities may be low. The importance of each capability level will depend on the device that person is expected to use.

Justification & Documentation

All FDA documentation now needs to include an explanation of the company's plan for managing and mitigating possible risks. There are many tools to address this requirement. A single document approach to tag and trace all potential usability issues is perhaps amongst the best. Regardless of format, companies will need to justify their device decisions from the perspective of the user. In the past, the FDA may have accepted a design goal that "80% of users must be able to open the device first time," they now want to know more about the 20% that couldn't - what they did, why they did it, and what is the resulting safety risk. A plan to mitigate or control expected or actual usage error will also be required.

I CAN (AND WILL) USE IT

Product safety is a minimum requirement for any medical device, but even a safe product will be rendered ineffective if intended users can't operate it properly or choose not to use it. If the effective delivery of the drug depends on the proper (not just safe) use of the device, then device developers must adopt inclusive design principles to gain thorough understanding of the usage drivers and barriers. To do this, it's important not to make assumptions about large patient groups. For example, while diabetes does affect a

patient's eyesight, which should be taken into account when designing an insulin pen that requires the user to read a display, it's also important to recognize that diabetes affects a broad range of the population (young and old, active and fragile, etc), subsets of which will display different capabilities and behaviors.

A person's ability to operate a device will depend on his or her cognitive, sensory, and motor skills: if a device intended for use by a patient population known to have poor grip requires a sharp twist to function and deliver the drug, it is unlikely to be effective.

Even if physiological factors don't prevent a patient from using a device, they may affect the performance of that device or the patient's motivation to use it. For example, dry powder inhalers for the treatment of asthma and chronic obstructive pulmonary disease rely on the user's lung capability to disperse and aerosolize the drug and transport it to the lungs. Research has shown that even a healthy person's lung characteristics vary greatly with age and height, meaning an inhaler designed for adults will not be as effective or as comfortable to use for children. If a device is uncomfortable or unnatural to use, it will be difficult to ensure compliance.

Patients' ability to remember to administer their drug is also an important factor to consider when designing a drug delivery device. With this in mind, continuous infusion devices are being developed that reduce the frequency with which patients need to administer their own treatment. In this case, it's crucial to find the right balance between reducing the burden on a patient's daily life and making the treatment so unobtrusive, the patient could forget altogether. Reminder mechanisms can also be built into devices, but can actually have a demotivating effect as they serve to remind the patient about their disease. One solution is to integrate reminders into the user's normal environment. For example, if people are accustomed to receiving reminders for other daily tasks via their smart phones, the addition of a reminder to administer the treatment may mean the user is less likely to feel abnormal. Similarly, technology can be used to monitor a patient's use of a device, assisting with feedback and ensuring compliant use. However, the level of technology integrated into a device should depend on the capabilities and attitudes of the user base; while technology may encourage younger patients to comply, it may actually discourage older generations less comfortable using technology and wary of relying on it. Consideration should be given to how much of the device's operation and feedback mechanisms are dependent on technology versus user input.

FIGURE 3

Disposable insulin pens - a non-medical look to be more discreet, more desirable, and easy to use.

I WANT TO USE IT

Being willing and able to use a drug delivery device effectively is one thing, but wanting to do so is another matter. The powerful combination of good usability and design of a device can have an important impact on consumer motivation and can be a key market differentiator for drugs in mature markets where the drug and formulation patents have expired. Not only can it impart brand loyalty amongst patients and providers, but most importantly, it can have a major impact on user compliance and, therefore, clinical outcomes.

Rather than focusing on brand identity as a means to maintain consumer loyalty, device manufacturers would do well to remove barriers to use by focusing on the target users' lifestyles and preferences. By designing devices that blend in with a person's lifestyle, they are less likely to be embarrassed or reluctant to use it. Market segmentation is therefore crucial: a diabetic who needs to take medication while at a restaurant might want something discreet, fast, and executable with one hand without looking; other users may want a rugged, sporty device or one that is business-like or more style conscious; others

may have no regard for style and prefer a device that is solely easy for them to use. Children are an important market segment too, particularly for conditions such as asthma and diabetes. For this group, motivation to use a device can be encouraged by introducing an element of fun or reward. For example, an inhaler device may be configured to make a fun noise when the child inhales correctly or, distinct from the device itself, the child could be rewarded with an electronic game to play each time a dose is correctly administered at the right time.

Medical device manufacturers can learn a thing or two from the consumer industry in this regard but must also consider the impact that style and discretion could have on practicality. For example, with some auto-injectors, it can be hard for a user to distinguish the needleshield at one end of the device from the actuation button at the other. This has been known to cause some patients to inject into their thumb because they hold the device the wrong way.

Sensible cues are crucial; while there may be a desire to hide the fact there's a needle for aesthetic and social reasons, there are ways of doing so that will maintain the safety of the device: it's important to make sure people are aware of the presence of a needle, so that steps can be taken to ensure safety of the user and those around them.

SEIZING THE OPPORTUNITY

The importance of human factors is evident; not only is consideration at every stage of the product lifecycle now a regulatory requirement, but it is also good design practice. Ensuring a product's usability can be challenging because so many human factors interact and conflict with one another, but it should also be viewed as an opportunity for pharmaceutical companies striving to prove comparative effectiveness.

Emerging technologies will have an important role to play as pharmaceutical and medical device companies seek to improve the usability of their products. Innovating around the improved use of existing drugs carries much lower R&D costs than developing new molecules and also eliminates the commercial and patient risks associated with launching a new drug. Advances in technology are already leading to the development of new delivery approaches and technology-driven improvements of existing drug delivery devices, such as the ability to develop smaller, more discreet products. The technology that more and more of us already have in our pockets is also an opportunity for pharmaceutical companies to seize: for example, smart phone apps can be developed to help patients manage conditions and improve compliance.

While the most important consideration for any pharmaceutical company developing a drug delivery device is "don't hurt me," the new standards also bring a requirement to understand users and user scenarios. Although this is a challenge, it's a huge opportunity to improve user compliance and reduce the total cost of treatment for many chronic conditions through a reduction in wasted drugs and missed opportunities to prevent a patient's condition from deteriorating.

Time will tell if the new standards can really support a drive to improve usability and compliance, but they do offer a positive step in the right direction. They should be embedded in pharma companies' development processes in order to, at the very least, meet mandatory requirements. But ideally, companies will see the benefits in going beyond this basic regulatory need and strive to develop devices that can appeal to the user on all three usability levels outlined in this discussion.

BIOGRAPHIES

Iain Simpson is a Principal Consultant in Drug Delivery at Sagentia, with more than 10 years of experience in drug delivery, including technical due diligence and project management on inhaled and injectable delivery technology development programs. He has a degree and PhD in Physics and an MBA in Technology Management. Outside drug delivery, Mr. Simpson maintains a broad interest in R&D and the uptake of new technologies.

Kay Sinclair is a Human Factors and Usability Expert at Sagentia, with more than 15 years of experience focusing on early stage product and service development. Her expertise ranges from the diversity of customer understanding approaches and inclusive design to large-scale advisory project management. She has a degree in Product Design Engineering from the University of Glasgow & Glasgow School of Art, and a Masters in Design, Manufacture and Management from Cambridge University.

Diabetes Management: Injecting the End-User's Perspective

By: Misty Hughes, Industry Analyst, Pharmaceuticals & Biotechnology, Frost & Sullivan

INTRODUCTION

Around the world, birth rates are rising and people are living longer. At the same time, people are exercising less and eating less healthy foods in greater quantities than ever before. The result: the total number of people in the world with diabetes is spiraling out of control. The number of people suffering from diabetes globally is expected to double throughout the next 20 years, skyrocketing to 366 million by 2030, according to the World Health Organization (WHO). According to the American Diabetes Association, 8% of Americans (23.6 million) have diabetes, and 1.6 million new cases are diagnosed each year. As such, companies in the pharmaceutical industry are hard at work to cash in and capture share in this booming market.

Although the cause of diabetes is not fully understood, it is thought that both genetics and environmental factors, such as obesity and lack of exercise, play a significant role in developing the disease. There are two main types of diabetes, type 1 and type 2. Type 1 diabetics comprise around 10% of the diabetic population. They produce little to no insulin due to the autoimmune destruction of the insulin-producing cells in the pancreas and are dependent on insulin injections in order to survive.

Although type 1 diabetics rely strongly on insulin injections, the type 2 patient population comprises 90% of diagnosed diabetics globally, roughly one-third of which depend on insulin for controlling blood glucose levels. Many type 2 diabetics are obese, which adversely affects insulin's ability to work. While they are able to produce insulin, their cells are unable to respond to it. The use of insulin is increasing among this patient population as oral agents fail to get patients to goal (HbA1c less than 7%) and insulin becomes easier to administer.

In either case, the inability of glucose to move into the cells results in elevated blood glucose levels which, over time, can cause serious complications, such as organ damage involving the nervous system, kidneys, eyes, and cardiovascular system.

CURRENT TREATMENT METHODS

Diabetes is a chronic disease that is difficult to manage, requiring effort from both the patients and their physicians. Medications for diabetes come in various classes, some of which are administered orally while others require injection. Injectable insulin is, and will remain, the cornerstone therapy for diabetes. However, for injectables, the noncompliance rate is particularly high. When compared to oral and inhaled modes of delivery, the injectable route can be complicated, expensive, uncomfortable, and inconvenient.

When insulin therapy was first introduced, only short-acting insulins that had to be injected three to four times a day were available. Subsequently, the introduction of long-acting insulins reduced the number of daily injections required to around one or two. Despite advances in diabetes treatment, effective disease management remains a challenge. In response to the rising demand from patients, physicians, and managed care providers for cost-effective injectable delivery modes that improve self-administration, compliance, and safety, manufacturers are moving away from traditional vial-disposable syringes and toward self-injectable, prefilled syringe pens.

Prefilled syringe pens make injectable medications safer and easier to use. Containing an exact dose of medication and a fixed needle, using a product packaged in a prefilled syringe typically involves nothing more than removing the syringe's packaging and

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injecting. By essentially eliminating the tedious steps that are required before using a drug in a vial, parenteral packaging innovations like these have helped physicians tackle tough compliance barriers they face with patients on injectable drug regimens.

For drugs that require a subcutaneous injection, an injection pen can be a more accurate and convenient delivery system of insulin into a diabetic's bloodstream. There are a variety of insulin injection pens on the market for diabetic patients, including disposable and durable pens. The disposable pens need to be replaced once the insulin cartridge is emptied, and the durable pens use replaceable insulin cartridges.

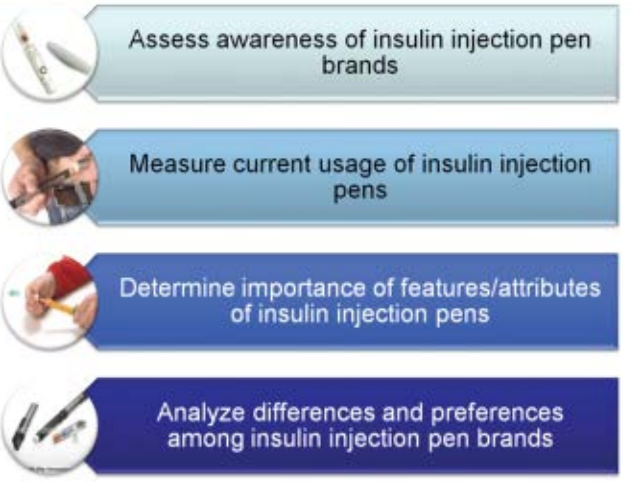
PATIENT FEEDBACK ON INSULIN INJECTION PENS

The market's acceptance of prefilled syringes has grown throughout the past decade, further encouraging pharmaceutical companies to employ them as a means to extend product lifecycles and differentiate existing and new products from the competition. As part of the Frost & Sullivan customer research survey titled 2010 US Type 2 Diabetes Patients' Choice: Awareness, Usage, and Preferences of Insulin Injection Pens, 1,002 adult type 2 diabetes patients who use insulin injection pens to regulate their disease were surveyed to assess their awareness of insulin injection pen brands and measure current usage of insulin injection pens (Figure 1).

Prefilled injection pens are used and preferred by nearly all respondents, with the majority reporting they use prefilled injection pens that are entirely disposable. It appears that prefilled injection pens in general may be preferred as patients no longer need to worry about refilling them. The majority of patients surveyed use injection pens to self-administer insulin once to twice a day, and only a small proportion of respondents reported that their insulin is administered by someone else in the household. For patients with busy lifestyles, a pen prefilled with insulin is simply more convenient to use. And when the insulin cartridge or reservoir is empty, the entire unit is discarded (Figure 2).

FIGURE 1

2010 U.S. Type 2 Diabetes Patients' Choice: Awareness, Usage, and Preferences of Insulin Injection Pens



As part of the survey, participants were also queried to determine the importance of features/attributes of insulin injection pens, and to analyze differences and preferences among insulin injection pen brands.

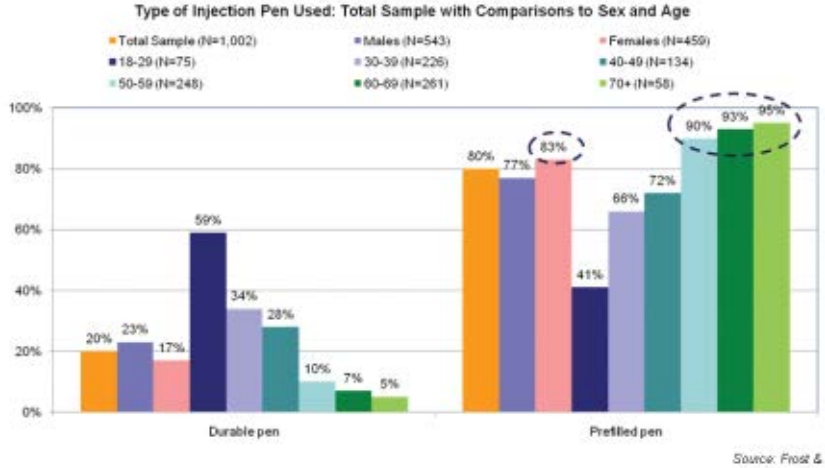
The largest proportion of respondents cited they were most satisfied with the NovoPen Junior (Novo Nordisk) and the Lantus SoloSTAR pens (sanofi-aventis). The NovoPen Junior injection pen brand received the largest proportion of "most satisfied" ratings, owing to the patients' perception that it is easiest to self administer. It isn't surprising this is the most important reason for satisfaction with this brand, as most type 2 diabetic patients reported that they administer the insulin to themselves.

As the brand that most respondents cited they currently use, the Lantus SoloSTAR injection pen received significantly more number-one rankings as its nearest competitor for the "easiest-to-read results" category. The

FIGURE 2

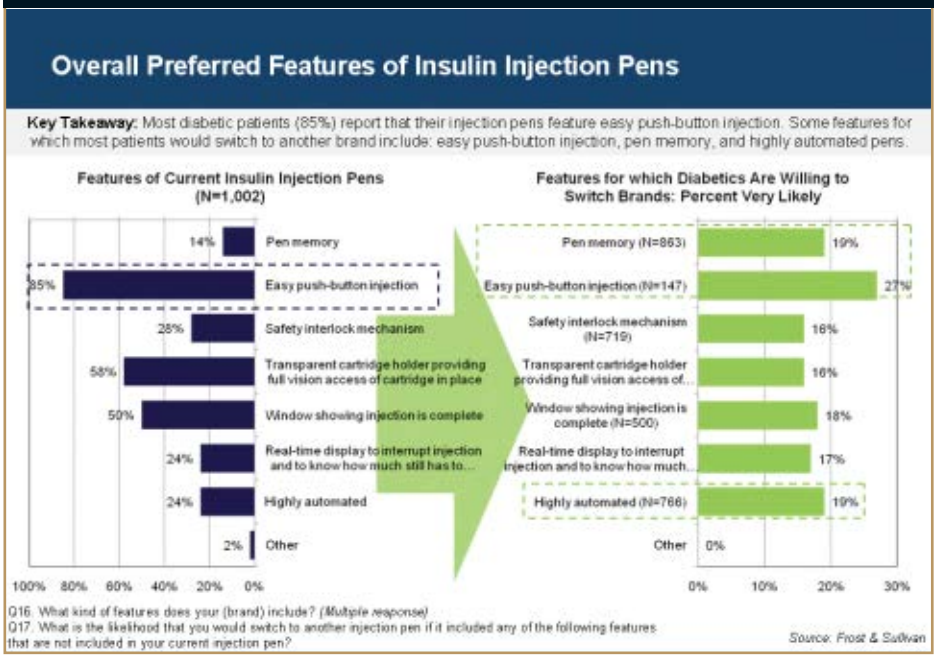
Type of Injection Pen Used

Key Takeaway: The majority of respondents use prefilled injection pens that are entirely disposable. Specifically, female patients and patients over the age of 50 show stronger preference for prefilled injection pens.



Source: Frost & Sullivan

FIGURE 3



Lantus SoloSTAR is also perceived by the largest number of respondents as being the easiest-to-assemble and easiest-to-hold injection pen. Lantus has become the basal insulin of choice for type 1 diabetics and the dominant add-on therapy for type 2 patients that have failed on oral anti-diabetic agents. Lantus is the leading branded insulin in the US, partly due to the SoloSTAR pen. A major growth driver for the Lantus franchise, SoloSTAR is a prefilled disposable pen that allows patients to administer doses ranging from one up to 80 units in a single injection.

Easy push-button, pen memory, and safety interlock mechanism are the top features most commonly recalled among current insulin injection pens users surveyed. Aside from being the highest rated feature, easy push-button injection is also the highest rated reason for patients to switch to another injection pen brand if their current brand does not include this feature. Given that both easy push-buttons and pen memory are among the top reasons for patients to switch to another brand, brands looking to compete must have at least these two features in their product (Figure 3).

INJECTABLE INSULIN PENS: GROWING, VALUE-ADDED MARKET

Prefilled injectable insulin pens represent a growing, value-added market. However, commercial advantages are key to a product's success. Medicines within therapeutic categories are increasingly hard to differentiate, making market conditions difficult for industry participants. Feedback from patients and physicians on factors such as perception, desired attributes, compliance, and drivers of adoption/non-adoption for different insulin injection pens is valuable to companies developing or seeking to increase patient awareness and utilization of their product. This could yield an education opportunity to developers if product benefits can be translated to the patient.

For more information on this and other relevant topics, please visit Frost & Sullivan at www.frost.com.

BIOGRAPHY

Misty Hughes is an Industry Analyst for Frost & Sullivan's North American Pharmaceutical & Biotechnology practice. She focuses on monitoring and analyzing emerging trends, technologies, and market dynamics in the pharmaceutical and biotechnology industry in North America. Since joining Frost & Sullivan in April 2007, Mrs. Hughes has completed several research studies and consulting projects in oncology (breast cancer), vaccines, ophthalmic diseases/drug delivery, hyperlipidemia, and Alzheimer's disease. Prior to joining Frost & Sullivan, Mrs. Hughes worked as a pharmaceutical sales representative for Schering-Plough, Synthon Pharmaceuticals, and JDS Pharmaceuticals, where she covered the cardiovascular, allergy, and central nervous system markets. She earned her BA in Biology from Southwestern University in Georgetown, Texas.

EPICUTANEOUS DELIVERY

Viaskin®: Epicutaneous Immunotherapy for Treating Food Allergies

By: Lucie Mondoulet, PhD; Nathalie Donne, MSc; Pierre-Henri Benhamou, MD

INTRODUCTION

The worldwide incidence of allergy is growing, and food allergies represent the segment in which life can be directly threatened - but no therapeutic treatment is available. Food allergy affects as many as 5% of children and up to 4% of the adult population in North America.[1] Studies in the United Kingdom and North America focusing on peanut allergies indicate that prevalence rates in children have increased, essentially doubling, and exceed 1% in school-age children. A 2008 Centers for Disease Control and Prevention report indicated an 18% increase in childhood food allergy from 1997 to 2007, with an estimated 3.9% of children currently affected. Peanut allergy is one of the leading causes of fatal and life-threatening reactions to food, making peanut allergy a major health concern worldwide, especially in developed countries with rising prevalence throughout the past decade.

Until now, avoidance of the culprit food has been the primary acceptable solution. Immunotherapy (IT) is recognized by the World Health Organization as the gold standard treatment for IgE-mediated allergy, yet it has rarely been used in food allergy throughout the past decades, owing to safety concerns, mainly regarding the risk of systemic reactions.

Despite the promising results reported with subcutaneous and oral IT, safety and liability concerns prohibit the use of these methods in daily practice. A novel technology combining safety and efficacy is desperately needed by food allergists and patients.

DBV Technologies is a leader in food allergy diagnosis and treatment solutions. Its product portfolio boasts groundbreaking products like the non-invasive VIASKIN® patented delivery system. The genius of VIASKIN lies in its ingenious method of antigen delivery. The original method developed and patented by DBV Technologies consists of the administration of allergens onto intact skin using its VIASKIN epicutaneous delivery system.

VIASKIN TECHNOLOGY

Epicutaneous immunotherapy (EPIT) has the significant advantage of being completely non-invasive, with allergens remaining on the epidermal side of the basement membrane that separates the epidermis from the dermis. As a result, free allergens cannot reach the bloodstream, avoiding the risk of triggering anaphylactic reaction. The VIASKIN epicutaneous delivery system includes a condensation chamber as a key component to deliver proteins to the epidermis. This condensation chamber achieves both solubilization of the proteins to be released for a direct contact to and hydration of the skin in order to facilitate the delivery through the stratum corneum to the epidermis.

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FIGURE 1

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electrospray deposit technology, a process that turns liquid formulas into dry precision deposits. Nanometric droplets of allergens are deposed through an electric field on an electrically conductive backing made by a gold- or titanium-coated PET membrane.

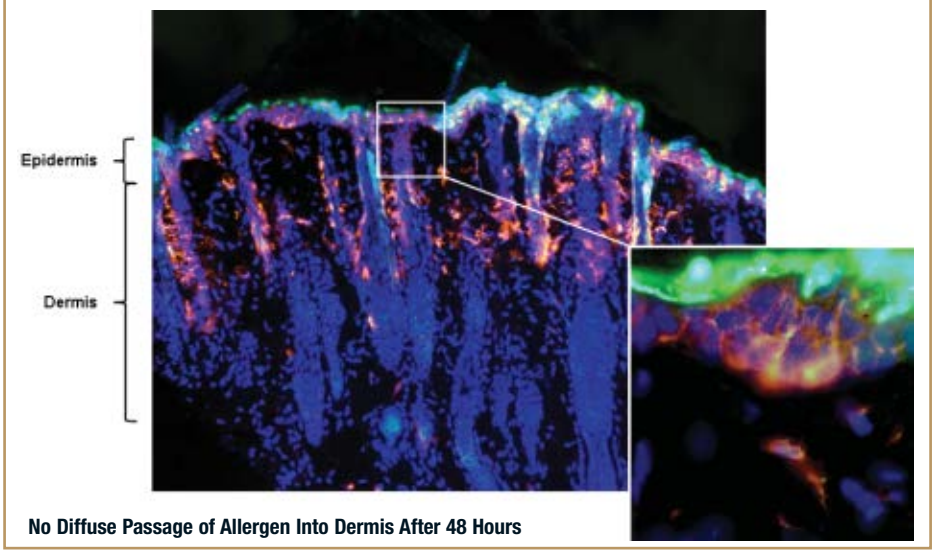
VIASKIN thus is capable of delivering a perfectly controlled amount of allergens on the surface of the skin. When it is applied on the skin, VIASKIN enhances an intensive perspiration, thus provoking a dilution of the allergen and favoring the diffusion of the proteins in the superficial layers of the stratum corneum, thanks to the hyper-hydration of the superficial layers of the stratum corneum that came into contact with Langerhans cells.

MECHANISM OF ACTION

The originality of epicutaneous immunotherapy using VIASKIN is the mechanism of allergen delivery through intact skin. The main function of the skin is to form a barrier between the external hostile environment and the internal milieu of the host, underlying the importance of maintaining the integrity of the different layers of the skin. When applied onto intact skin, VIASKIN preserves its architecture, including the more superficial layers. Experiments with labeled antigens (Ags) in transdermal in vitro models have shown that it allows native proteins to concentrate inside the stratum corneum within the vicinity of immunological cells, without passage through the skin.[2]

Recent studies published by DBV's research team have clearly demonstrated that allergen is captured by a highly specialized population of cells: dendritic cells and Langherans cells.[3] After capture of allergen in the epidermis, these cells migrated through the dermis toward afferent lymph nodes, where they induce the activation and modulation of adaptive immune responses. Furthermore, repeated applications down-modulate the local eosinophil recruitment after OVA exposition and decrease systemic allergen-specific immune responses while increasing regulatory T cells (Tregs). The abundance of these immune cells makes the skin ideal for immunotherapeutic approaches. The epicutaneous exposure is non-invasive,

FIGURE 2



No Diffuse Passage of Allergen Into Dermis After 48 Hours

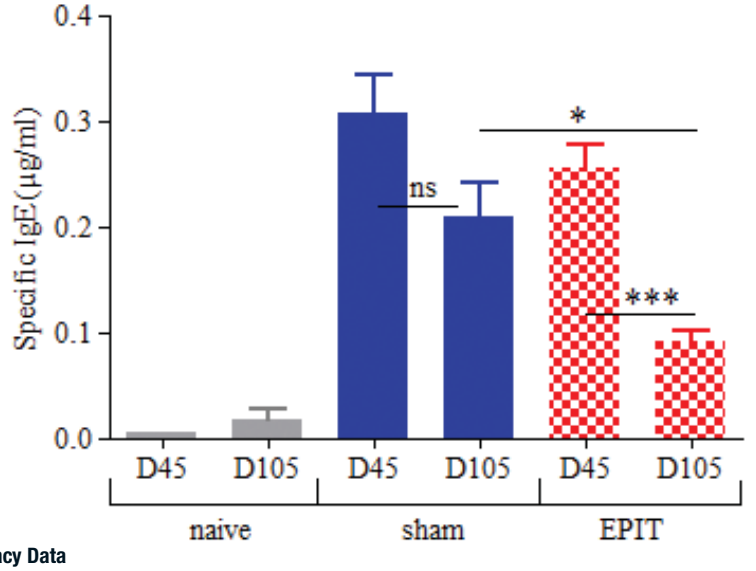
and the allergen does not enter the bloodstream, thereby significantly reducing the risk of inducing anaphylaxis.

SAFETY & EFFICACY

Preclinical Data on Safety

The safety of epicutaneous immunotherapy is a major concern in the field of food allergy. This issue was addressed in a model of guinea pigs sensitized to peanut proteins. Guinea pigs are very sensitive to challenge and develop clinical symptoms to those observed in humans. Sensitized guinea pigs, treated epicutaneously with a lethal dose (defined by iv administration) of peanut proteins, did not exhibit any systemic reactions during the 3 months of epicutaneous treatment. No local or systemic clinical signs other than the local cutaneous reactions were reported throughout the course of treatment, suggesting the safety of the epicutaneous repeated applications of potentially lethal doses of peanut proteins using the VIASKIN.

FIGURE 3



Efficacy Data

Measurement of specific IgE expressed in micrograms/ml. D45 = values obtained at the end of sensitization phase (before immunotherapy); D105 = values obtained at the end of the immunotherapy.The groups were EPIT (epicutaneously treated mice), sham (sham-treated mice), and naive (naive mice). Data are presented as means ± SEM for each group of 20 mice. Ns non-significant, * $p < 0.05$ and *** $p < 0.001$.

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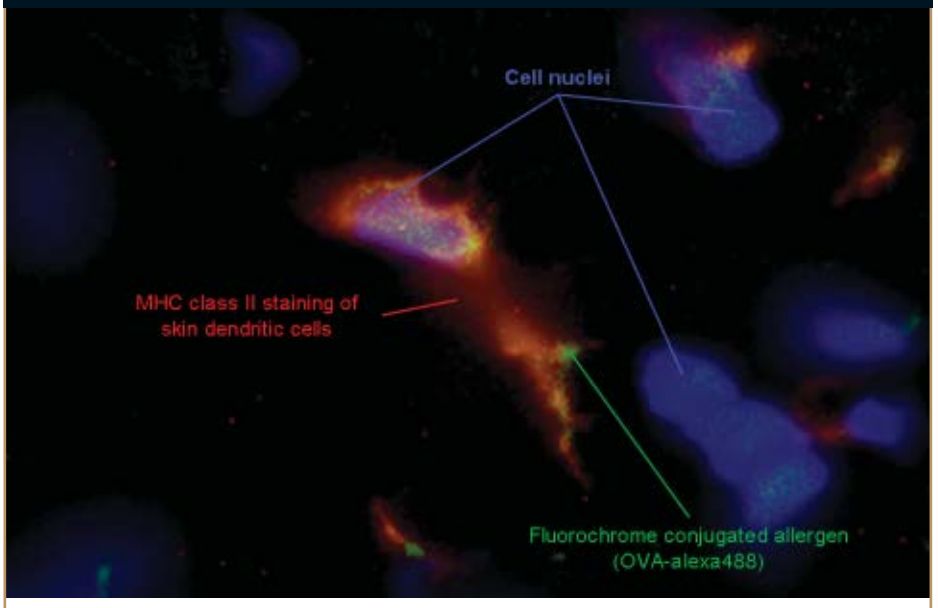
FIGURE 4



Dendritic Cell That Captured Allergen & Migrated Through the Dermis
Cell nuclei are stained with DAPI (blue) and dendritic cells with MHC class II specific antibodies (red). In the dermis, fluorochrome conjugated allergen (green) is only observed inside dendritic cell.

Preclinical Data on Efficacy

The efficacy of epicutaneous immunotherapy was evaluated in validated models of mice sensitized to various allergens (ovalbumin, pollen, house dust mites, and peanut).[4,5] The epicutaneous treatment was compared to the subcutaneous one, the gold standard for the specific immunotherapy in allergy. At the end of the treatment, a shift in the serological profile of mice was induced from a Th2 profile to a more balanced Th1/Th2 profile with a significant decrease of specific IgE and a significant increase of specific IgG2a. A noted improvement of the bronchial hyperreactivity was also observed for treated mice as measured by a non-invasive method (the whole-body plethysmography) and an invasive one (the resistance-compliance). The switch from a Th2 to a Th1 response was also observed in the serological analyses of specific IgE and IgG2a. As a consequence, EPIT induces regulatory T cells that can down-regulate the allergic responses. In the study of the efficacy of EPIT in a model of mice sensitized to peanuts, we have also shown that the epicutaneous treatment induced a decrease of anaphylactic reactions by measuring the decrease of histamine release after an oral challenge for sensitized mice treated with VIASKIN.[5] All the data in murine models suggest that EPIT may represent an alternative to the subcutaneous route of administration for the treatment of allergies.

Clinical Proof-of-Concept

A pilot study conducted in two French pediatric units (CHU Nantes, Hôpital Saint Vincent de Paul, Paris) evaluated the safety and acceptability of the epicutaneous immunotherapy using VIASKIN in cow's milk allergic children.[6]

This double-blind, placebo-controlled study enrolled children from 3 months to 15 years of age with a history of systemic symptoms related to milk ingestion and unable to tolerate more than 10 ml of milk. Treatment was well accepted by the patients. No child interrupted treatment because of an AE, and none received epinephrine or was admitted to the emergency room or hospital.

EPIT treatment tended to increase the amount of milk the children were able to tolerate. Thus, the amount of milk they were able to drink without showing clinical symptoms was significantly increased during treatment from baseline 1.77 ± 2.98 mL and increased further after 3 months of active treatment to 23.61 ± 28.61 mL at D90 ($p = 0.18$). In the placebo group, patients were not improved (from 4.36 ± 5.87 mL at D0 to 5.44 ± 5.88 mL at D90). The mean value of the increase of tolerated milk after 3 months of treatment was 12-fold the initial value in the active group versus 8% in the placebo group ($p = 0.13$).

VIASKIN PEANUT

DBV Technologies is currently aiming to develop a market-first, peanut desensitization treatment. Clinical trials of VIASKIN Peanut Epicutaneous Immunotherapy technology have already begun. As more than 3 million people suffer from peanut allergy, VIASKIN Peanut is expected to fill a significant unmet medical need and be enthusiastically supported by allergists in Europe and the US. DBV is currently involved in several clinical studies in the US and Europe with the peanut-specific immunotherapy. A Phase Ib clinical study of VIASKIN Peanut sponsored by DBV Technologies is underway at five centers in the US: Duke University Medical Center, National Jewish Medical Research Center, Arkansas Hospital, CRI Worldwide, and Aspen Clinical Research. A large study of efficacy is planned in Europe and the US after the Phase Ib completion. VIASKIN Peanut's development is also supported by the Consortium of Food Allergy Research (CoFAR), and a study is expected to start in late 2011. This Phase II study in peanut allergy desensitization will be funded by a renewed 5-year grant from the US National Institutes of Health (NIH).

SUMMARY

Treatment of food allergies is an unmet medical need. VIASKIN is an epicutaneous patch that can desensitize against peanuts, milk, and other major food allergies with significant reduction in anaphylaxis risk. DBV Technologies' latest project is the development of a market-first peanut desensitization treatment. DBV's VIASKIN Peanut is the first pharmaceutically conceived therapeutic product intended to desensitize patients suffering from peanut allergy, the most deadly food allergy with a high social burden for the patients and families involved. The VIASKIN patch, the "Allergy Patch," is designed to be easily and painlessly applied

by healthcare professionals and also by patients or their parents at home, which facilitates compliance with the treatment. A successful outcome for the system in clinical trials could bring relief to millions.

DBV Technologies is very proud that this VIASKIN technology has been recognized with an historic importance on the cover of the Journal of Allergy and Clinical Immunology January 2011 issue by including the VIASKIN patch in its timeline Commemorating 100 years of Allergen Immunotherapy.

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BIOGRAPHIES

Dr. Lucie Mondoulet earned her MSc in Biochemistry from the National Institute of Applied Science, Toulouse, France in 2002. In 2005, she earned her PhD in the field of Allergy at INRA under the supervision of Dr. Jean Michel Wal. She studied the biochemical composition of peanuts and the effect of thermal and enzymatic treatments on the allergenicity of the peanut allergens. In 2006, she assumed a post-doctoral position at CNRS, Paris, France, in the Department of Allergy and Environment, where she was in charge of the purification of allergens from pollen and the study of the repertoire of immunological response of allergic patients. She joined DBV Technologies for a permanent position in the Research Department. Currently, she developed the pharmacology studies in the field of food allergy, particularly peanut allergy. Scientific results were communicated through international and national publications, oral communications, congress, and patents.

Nathalie Donne graduated with a degree in Biology from the University Paris VI France and a Master's degree in Biotechnology Innovation from the National Institute of Agronomy in Paris and Reims Management School. She joined DBV Technologies for a permanent position in 2003 as Product Manager, where she first worked on Diallertest® Milk and then later on projects on the Diallertest product range. She is now in charge of new development around DBV's Technology: VIASKIN and new applications.

Dr. Pierre-Henri Benhamou is a Co-Founder and the Chief Executive Officer of DBV Technologies. After studying medicine in Paris, Dr. Benhamou graduated with a medical degree in Pediatrics from Amiens University and went on to specialize in Pediatric Gastroenterology. Dr. Benhamou has held a number of senior clinical positions, including Senior Consultant at St. Vincent de Paul Hospital in Paris. Since 1989, Dr. Benhamou took up a position at the Centre for Digestive Exploration of Infants at the Surgical Clinic of Boulogne-Billancourt, where he specialized in Pediatric Gastroenterology and Nutrition. Dr. Benhamou was the winner of the Altran Foundation Prize for Innovation in 2003 for his work on the development of patch tests for the diagnosis of cow's milk allergy.

SPECIAL FEATURE

Outsourcing Formulation Development: A Continuum on the Road to Drug Development

By: Cindy H. Dubin, Contributor

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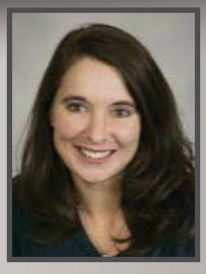
Formulations
Development
AAIPharma
Services Corp.

Paul F. Skultety, PhD
Director, Pharmaceutical
Development Services
Xcelience, LLC



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With the cost of discovering and developing a new drug predicted to tip at approximately $900 million, the pressure to reduce time and costs to market while ensuring soluble, stable, and profitable products is higher than ever. To tackle this issue, many pharmaceutical companies are now, more than ever, streamlining their formulation strategies to mitigate risk and ensure investment in successful candidates.

This is where contract providers enter the picture. Their breadth and scope of critical formulation development issues, such as solubility, bioavailability, protein and peptide formulation, and analytical development, can accelerate a molecule through development to market. Enticed by these capabilities, pharmaceutical companies have made outsourcing formulation development an integral part of their drug development program. And the proof is in the numbers: Global pharma outsourcing is expected to grow to an estimated $83 billion this year and $108 billion by 2014, according to CPhI WorldWide and ICSE.

In this annual *Drug Development & Delivery* exclusive roundtable discussion, third-party formulation developers reveal how their individual services are suited for today's pharmaceutical development challenges. Participants include: Jim Murtagh, PhD, Senior Director, Formulations Development, AAIPharma Services Corp.; Paul F. Skultety, PhD, Director, Pharmaceutical Development Services, Xcelience, LLC; Dr. Lisa J. Graham, Vice President and COO, Bend Research Inc.; William E. Weiser, PhD, RAC, Group Director, PDS – RTP, Patheon Pharmaceuticals Inc.; and Oliver W. Mueller, Executive Vice President, Business Development, Glatt Pharmaceutical Services Division, Glatt Air Techniques, Inc.

Q: How do you tackle issues of solubility and bioavailability in formulation development?

Dr. Weiser: Given that 90% of the New Chemical Entities currently in development are in BCS Class II or IV, overcoming low solubility is vital for effective formulation development. Patheon develops effective formulation for low-solubility molecules by understanding the biological target, using pharmacokinetics information, and balancing those needs with unique physical/chemical properties of the active ingredient.

Many effective strategies have been developed to improve bioavailability of poorly soluble compounds; however, these approaches are typically executed serially based on the experience of formulation scientists. In many cases, a series of niche technologies are often used in a shotgun approach from several vendors with the hope that one will be successful. Unfortunately, if a vendor has only one technology, usually proprietary, and that technology doesn't work, the customer is left out in the cold. The only recourse is to identify the next formulation approach and essentially start the development process over again. Patheon approaches this challenge with a multidisciplinary team to efficiently attack this problem with parallel evaluation of a range of formulation development strategies. Specifically, our SoluPath® approach to rapid development of low-solubility formulations is based on multiple screening in parallel with particle size reduction, solubilization, and solid dispersion. Multiple formulations are prepared and tested simultaneously for all approaches, and the promising formulations are selected, optimized, and quickly screened in animal PK models. We can complete the *in vitro* formulation development in 4 months and complete the animal PK work in 1 to 2 additional months.

Mr. Mueller: The knowledge of the physical and chemical properties of an API is important to formulation development. Preformulation work, such as establishing a pH solubility profile and a pH stability profile of the API, form an important foundation of information to guide formulation. The BCS, which classifies an API based on its solubility and permeability, and any guidance available from FDA, are good places to start for any API under investigation. The dose range of the API, target finished product characteristics (ie, release profile), and pharmacokinetic parameters of the API will also help in forming formulation concepts for the intended API(s) and application(s).

Dr. Murtagh: Drug substance solubility can and should be evaluated using physico-chemical methods. We frequently see that the chemists involved in synthesis work have evaluated solubility as a function of pH and in organic solvents, but don't consider excipients used in oral formulations, which can achieve significant solubility improvements. Evaluation of solubility enhancement using these types of excipients (self-emulsifying systems, surfactants, vegetable oils, lipids and their derivatives, and water soluble polymers) is a straightforward evaluation that will not consume a lot of time, material, or cost. At AAIPharma Services, we restrict the excipients to those established to be in commercial use in approved products in the United States. We have established a collaborative agreement with Crititech to

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exploit technology for solubility enhancement.

One would like to believe that achieving solubility for a drug substance candidate will provide good bioavailability; unfortunately, that is not necessarily the case. This is an assessment that, in our view, requires animal model evaluation or cell-based absorption system models. In both cases, the reliability of the model to predict bioavailability in humans is a concern. Bioavailability enhancement, then, is an iterative process based on experienced guesswork followed by evaluation in model systems and, ultimately, in clinical studies. We collaborate with Emisphere for access to its Eligen® technology to evaluate candidate molecules.

Dr. Graham: Developing formulations with enhanced solubility and bioavailability is a primary area of focus at Bend Research Inc. We use internally developed and commercial modeling programs, as well as a process-development flowchart methodology, to quickly and efficiently determine the best formulation approach for a given compound based on the physical and chemical properties, the required absorption/pharmacokinetic profile, and the dosage-form requirements.

We offer a suite of drug delivery platform technologies for improving the solubility and bioavailability of low-solubility drugs. Our technologies include amorphous spray-dried dispersions (SDDs), amorphous drug/polymer melt extrusions, crystallized SDDs, nanoadsorbates, submicron crystals, and amorphous drug/polymer nanoparticles suitable for delivery using a variety of dosage forms and delivery routes, such as oral, inhalation, and ocular.

The SDD technology, for example, has been applied to more than 400 compounds and successfully tested in preclinical *in vivo* studies. In addition, more than 40 drugs have been tested in human clinical trials (Phases I through III) as SDD suspensions, tablets, and capsules. SDD formulations typically enhance absorption from around two-fold to more than fifty-fold of that seen with crystalline drug, and can reduce or eliminate fed/fasted absorption differences.

Dr. Skultety: Today's formulators face unprecedented challenges with drugs of poor solubility and challenges associated with poor bioavailability. Xcelience employs both conventional and alternative strategies to overcome challenges associated with poor compound solubility. Conventional strategies include use of water-soluble excipients, API micronization, pH modifiers, or solubilizing or wetting agents. Alternate processing approaches may include the addition of an aqueous granulating solution that contains a wetting or solubilizing agent, using high-shear homogenization to reduce the API to nanoparticles, potentially altering the API characteristics.

Xcelience liquid-in-capsule services enable small-molecule developers to exploit the potential of lipid-based formulations to overcome poor aqueous solubility and improve compound bioavailability. Liquid fill is an important option for companies facing challenges with the physical or chemical properties of their API or with dosing requirements. Challenging properties may include poor bioavailability, low melting point, poor stability, or a compound that naturally exists in a liquid form. Dosing requirement obstacles for liquid fill may include low or high dosage strengths. For the former, Xcelience would apply liquid-fill technology in order to ensure content uniformity. For the latter, Xcelience would evaluate and select an appropriate lipid material in order to achieve solubility necessary for the higher dosage strength.

The developed liquid formulation is filled into appropriately sized gelatin or HPMC capsules to provide a stable prototype formulation that accelerates development timelines to Phase I studies.

In addition, delivering the API as a solution usually helps to increase bioavailability. For manufacturing liquid-filled formulations for clinical supplies, Xcelience uses Capsugel's CFS 1200™ with LEMS™ sealing technology. Hot-melt technology may be used as an alternative to liquid fill to improve stability, bioavailability, and provide controlled release.

Q: Describe your services for formulation development of proteins and peptides.

Dr. Murtagh: Formulation of peptides and proteins is typically focused on formulation of an injectable product. We have experience with oral formulations in this area also, but this is a rare and special case. Most formulations are well below the solubility limit of the active species and focus is on aggregation, chemical stability, and absorptive losses or loss of activity during sterilization, fill, and finish. Clients frequently insist on a lyophilized formulation, which is more time-consuming to develop and manufacture, in the hope of minimizing stability concerns found with liquid formulations. Other clients are willing to consider a frozen liquid formulation. From our perspective, a refrigerated liquid formulation may be a better alternative for early clinical trials. It is frequently a challenge with these types of

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molecules to have enough confidence early in development that the analytical methods are robust enough to provide meaningful data to guide formulation development.

Dr. Graham: With a focus on cost, yield, and performance, we know the development of protein and peptide formulations benefits from the modeling- and fundamentals-based approach that we have optimized for other types of compounds. Our formulation approach is to use excipients in a functional manner, for example, adding glassy stabilizers to inhibit unfolding, and glassy components with high glass-transition temperatures to reduce particle agglomeration and inhibit mobility in the solid to reduce protein agglomeration.

Frequently, our approach involves combining established methodologies to provide new quantitative measurements that can be used as inputs to predictive models. Working knowledge of the molecular and cellular networks that drive disease states facilitates our development of drug formulations. The pathobiology inherent to a disease plays a critical role in guiding the development of our advanced drug formulations. Cellular heterogeneity, receptor type, and cell density, as well as the physical space around drug targets, are factors we consider when developing our platforms. We use molecular and cellular biology techniques to translate our analytical results into truly quantitative measurements of performance. In addition, we offer extensive capabilities in particle engineering, producing spray-dried formulations as an alternative to lyophilization or as the basis of inhaled formulations.

Dr. Weiser: The formulation of proteins and peptides requires a range of integrated capabilities based on the stage of development, the availability of API, and the specific formulation requirements of the protein or peptide. Patheon has developed more than 100 biopharmaceutical products from early development to product commercialization. Our development capacity spans small-scale hand-filling in isolators through large-scale commercial lines, in most cases using disposable processing to eliminate cleaning and contamination concerns. This small-scale capability allows us to rapidly provide supplies for toxicology and clinical studies with the typically very limited supplies of API in early development. These production processes, including lyophilization, are supported by our in-house biopharmaceutical and cellular-based assay capabilities.

Q: As combination products (ie, a drug product combined with a medical device) and fixed-dose combination products seem to be gaining interest among the pharma community, what formulation development challenges do you face?

Dr. Graham: Bend Research has extensive experience working with device manufacturers and in the development of fixed-dose combination products. In past projects, we have contributed to innovations and improvements to medical devices and have been instrumental in developing fixed-combination products. For instance, we have experience in spray-drying engineered particles for inhalation with dry-powder inhalers and have found that the tunability of the process makes it easier to precisely match the powder properties needed to meet device specifications. In addition, spray-drying is ideal for reducing content-uniformity issues because the process begins with a homogenous solution or suspension. Our amorphous SDD technology can also enable fixed-dose combinations of highly lipophilic compounds (traditionally formulated as hard- or soft-gel dosage forms) with more traditional "rule-of-five" active compounds in tablet dosage forms. We have advanced fixed-dose combination products through large-scale Phase III testing.

Dr. Weiser: Our experience is mainly on fixed-dose combination products for which we have developed an extensive array of formulations. One of the key challenges with combination products is the simultaneous optimization of the product delivery profile and pharmacokinetics of each drug. If the two drugs have different physico-chemical properties, stabilities, solubilities, pharmacokinetics, and dosing requirements (which is usually the case), then combining the two in a single formulation blend is difficult. We use multi-layer tablet technology (bilayer and trilayer) to produce solid oral dosage forms with physical separation of the two components to deliver the drugs at different rates. If the two component formulations are incompatible, then a trilayer approach can physically separate the two formulations. Furthermore, combinations of coated beads can be filled in a capsule or compressed as a tablet. The bottom line is that formulation development solutions for combination products must simultaneously achieve the target bioavailability and the rate of absorption of each component, and the formulation must be robust in terms of stability and manufacturability.

Dr. Skultety: One thing that comes to mind in working with medical devices is making sure the API has the necessary

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properties to ensure the device operates appropriately for its intended use. For example, making sure the API has the right particle size for inhalers. For combination products, it is necessary to make sure the dose is right for both compounds. In many cases, the APIs will differ greatly in their quantities, which will make it more difficult to obtain good content uniformity. In addition, the combination product will need to account for processing and stability concerns for both compounds, such as light sensitivity, possible hydrolysis, poor compressibility, etc. The formulation has to overcome problems associated with both APIs.

Dr. Murtagh: Frequently, prototyping the combined product is difficult, if not impossible, due to the nature of the device and its manufacture. The inability to evaluate prototypes results in long lead times and a lack of understanding of the potential issues in manufacturing until very late in the development cycle. We have seen the most success in this area where the drug product can be packaged by conventional, established processes and then combined with the device at the clinical site or a pharmacy. We have successfully developed fixed-dose combination products through analytical development and validation, manufacturing support, and process validation.

Q: How do you incorporate Predictive Tools and Design of Experiments (DOE) into your formulation development, and why is this beneficial to your customers?

Mr. Mueller: The concept of QbD (Quality by Design) is a "hot topic" for the FDA and the pharmaceutical industry. It is not sufficient to simply identify the formulation of a product that achieves the desired results. You must justify why and how the formulation was chosen through actual experimentation. Regarding excipient selection, it is necessary to identify the "critical" excipients and justify the level (concentration) of each excipient in the formulation. A DOE is an effective way to challenge excipient levels. For example, in the formulation screening phase, a DOE can be performed by varying the concentration of the API and one or two critical excipients in the formulation (three factors, two levels). The response measured can be the time to reach a target total drug dissolution specification (ie, total % drug released at a specific time point).

Once the formulation has been established and challenged through DOE, the focus shifts to the "robustness" of the process established with the formulation. A DOE may be performed to demonstrate the effect of parameter changes on desired product performance and justify the ranges selected for each parameter.

The practical outcome of a development program employing such a DOE approach is to establish and ensure future manufacturing robustness, reproducibility, and product quality.

Dr. Weiser: Our DOE approach has been effectively used to develop and optimize formulations, manufacturing processes, and analytical methods consistent with the Risk Management strategies presented in ICH Q8 and Q9. For example, in a typical process development, our approach convenes a multidisciplinary team (formulation scientists, process engineers, analytical scientists) to create the experimental strategy, execute the designed experiments, analyze the data, conduct additional optimization experiments as needed, and summarize the findings to define the critical process operating ranges. During the experimental design stage, we focus on identifying the critical product quality attributes and parameters and then set up the statistical design to understand the influence and interaction of the critical parameters (factors) on the responses (eg, the product attributes).

The DOE exercise often provides an understanding of the failure mode for the product. Our DOE also includes statistically defined sampling and experiment plans to acquire the data as well as a plan of data analysis. Typically, our experiments involve established statistical methods, such as factorial (full or partial) design and response surface analysis. The data analysis includes graphical presentation, pair comparisons, ANOVA, attribute interaction maps, and process control charting to help establish the design space. Once we have critically evaluated the information, we are then in a position to define the design space, specifications, and process control strategies to maintain parameter limits. This approach has been successfully applied to products in pharmaceutical development services and commercial production.

Dr. Murtagh: Formulation Development is frequently asked to incorporate QbD principles into projects. Scouting studies and feasibility evaluations should be executed prior to initiating any designed study plans, as these techniques are more effective and useful once there is some idea of the key variables to evaluate. We have found DOE tools to be particularly effective when analyzing unit operations for critical process parameters.

Dr. Graham: DOE is part of our fundamentals-based approach to problem-solving. Our focus on fundamental material

science and engineering principles helps us determine the best production processes for our clients' compounds and to develop those processes with speed and efficiency. We use predictive tools to identify and understand the critical process physics that affect product properties, throughput, and yield, reducing the number of variables that must be investigated. Depending on the unit process, critical process parameters are evaluated through first-principle model interrelationships (eg, thermodynamics, atomization, computational fluid dynamics [CFD]). These models are also used to establish parameters, ranges, and study designs for DOE.

We use DOE to confirm robustness ranges rather than empirically establishing parameter interrelationships. Core services include process development using a custom flowchart development scheme; predictive tools to minimize the number of complete experimental trials; formulation, processing, and testing capabilities at a range of equipment scales; and in-depth process modeling to refine process and equipment parameters.

Dr. Skultety: A good DOE defines the processing parameters that have a significant effect on the product and will define the work space that will ensure the finished product has the desired characteristics. DOE requires a lot of time, resources, and a large quantity of API. It is best to run the DOE on a scale sufficiently large enough to be representative of the commercial process. This ensures the product will have the same safety and efficacy profile from lot-to-lot.

Q: What should readers understand about the benefit of outsourcing formulation development?

Dr. Graham: Outsourcing offers breadth of expertise, multidisciplinary scientific staff and project teams, proximity of subject-matter experts, and close integration of development and cGMP manufacturing operations. For areas in which we do not have expertise, we have developed a global network of affiliated companies that share our values, high standards, and commitment to our partners' success.

By picking the right partner, outsourcing does not need to be a scary proposition. Successful collaborations are based on technical expertise in the areas in which help is needed, a sound basis in fundamentals, lack of attachment to a given (usually proprietary) technology "solution," and a clear focus on client needs.

Mr. Mueller: In selecting an organization to perform the formulation development of a product, it is critical to consider the skill sets and facility assets required to achieve the target product specifications and to ensure the future partner possesses a depth of those skills and assets. Of equal importance is the development philosophy and culture.

Dr. Murtagh: The most important element for successful formulation development is experience in solving similar formulation challenges and problems. Working with a contract services provider that has been involved in many formulation projects allows pharma companies to reap the benefits of that experience, which can make an important difference in any formulation development project.

Dr. Skultety: Partnering with an early drug development specialist can reduce product risk and accelerate development timelines. Outsource providers help expedite drug development and reduce compound risk as well as help overcome challenging physical and chemical properties in a manner that results in improved solubility and compound bioavailability.

Dr. Weiser: Outsourcing formulation development and manufacturing is a fundamental strategy to achieve rapid and reliable availability of drug product for clinical trials and robust processes for registration and commercial production. The breadth and scope of outsourced formulation development and manufacturing experience is frequently greater than that at large pharma companies.

Outsourcing formulation development is not an isolated activity, but rather a part of the continuum of drug development starting from discovery and culminating in commercially manufactured product. Many vendors can provide specific elements of this process; however, the value of outsourcing is only realized when these elements collectively achieve the project goals.

The best outcomes are achieved when clients focus their energy on their core strengths and allow the outsourced drug development companies to execute on their core formulation development and manufacturing strengths. ◆

SUSTAINED RELEASE TECHNOLOGY

Sustained Delivery to the Oral Tissues

By: Jerry Gin, PhD, MBA

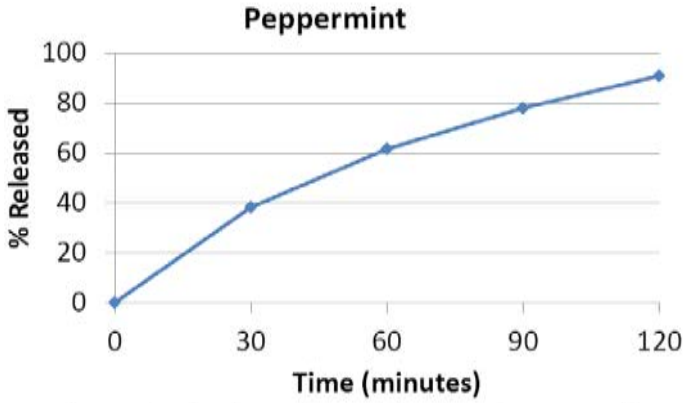
ABSTRACT

For ingredients to be effective for treatment of conditions in the mouth, they must be in contact with the tissues for a sufficient length of time. A matrix delivery technology (SuRe™), in the form of a long-lasting lozenge, has been developed to accomplish this task. The technology is versatile in that virtually any ingredient or mixtures of ingredients may be delivered for variable lengths of time from 15 minutes to 3 hours. The technology has been applied to the area of oral health, including dry mouth (xerostomia) and reduction of bacteria in the mouth, which would impact gum disease and decay, halitosis, and teeth whitening. As a result of the sustained delivery of ingredients to the mouth, the technology offers a significant potential for systemic delivery via the transmucsal/transbuccal route.

THE PROBLEM

It is often desirable to deliver ingredients to the oral mucosa or the buccal region of the mouth, either for the benefit of the oral tissues (gums) or as a means for systemic delivery. This subject is well reviewed in the scientific literature.[1] For the oral tissues, the benefits are typically for the oral problems of the gums and teeth (periodontal diseases, infections, inflammation, decay, xerostomia). In the case of colds or sore throats, the benefit would be in reducing the duration of the cold and treating the sore throat. For systemic delivery, if ingredients are not well absorbed or are not stable by the gastrointestinal route, then delivery via the oral mucosa or buccal route would become preferred based on the thinness of the membranes in the mouth and the nature of the molecules being absorbed. The main challenge for both treatment of oral tissues and absorption for systemic applications via delivery in the oral cavity is duration - the ingredient must be in contact with the oral tissues for a sufficient length of time to be absorbed into those tissues. Conventional delivery systems (paste, rinse, lozenges, fast-release films, etc) deliver active ingredients for a short period of time, ranging from 30 seconds for rinse products or films to approximately 2 minutes for paste or 5 to 10 minutes for lozenges. These systems typically result in times that are too short for therapeutic effects via the oral route. There are various mucoadhesive technologies that can result in longer residence times in the mouth, but also provide the potential problem of local irritation.[1]

FIGURE 1



Curve shows the *in vitro* release kinetics of peppermint

Peppermint Release Kinetics

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THE SURE TECHNOLOGY SOLUTION

A versatile proprietary Sustained Release technology (SuRe) was developed to enable delivery of ingredients into the oral tissues. One form of the technology is a long-lasting lozenge. The lozenge can last anytime from 30 minutes to more than 2 hours, and acts upon the oral cavity with substantially lower therapeutic doses of active ingredients for a significantly longer duration. The technology allows for the sustained and gradual delivery of active ingredients in the oral cavity. Specifically, this technology is a matrix constructed of a cellulose polymer and essential oils. All base ingredients are registered food products and are Generally Recognized As Safe (GRAS).

The resulting product may take the form of a small, soft, pliable lozenge that holds the active ingredients uniformly distributed throughout. The delivery mechanism, which works via a process of slow erosion, delivers an even and continuous stream of active ingredients for the life of lozenge. Thus, a lozenge formulated to last for an hour will continuously and gradually release active ingredients for an hour while maintaining a pleasant flavor. As ingredients are washed away by saliva, new ones are released from the lozenge.

As a result, the SuRe technology achieves unprecedented prolonged activity and efficacy for ingredients delivered in the oral cavity. The SuRe technology is well suited for the release of a variety of ingredients, including dental care, cough/cold, nicotine for smoking addiction, etc.

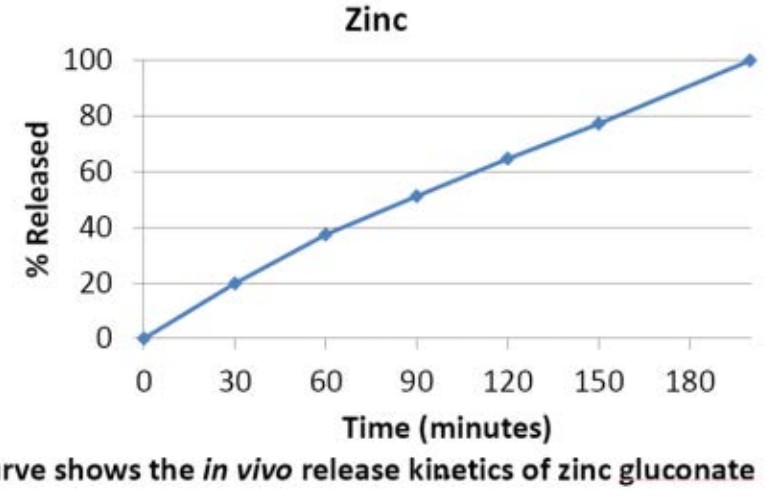
BENEFITS/CHARACTERISTICS

SuRe technology delivers active ingredients for a prolonged period of time. Conventional delivery technologies tend to over-deliver active ingredients for a short period of time, ranging from seconds (rinse) to a few minutes (paste, lozenge, chewing gum). In contrast, SuRe products are formulated to deliver a consistent stream of active ingredients for an extended period of time, ranging from 30 minutes to 2 hours or more.

FIGURE 2

Effect of Salese Lozenge on pH of Patients With Xerostomia

FIGURE 3



Zinc Release Kinetics

FIGURE 4

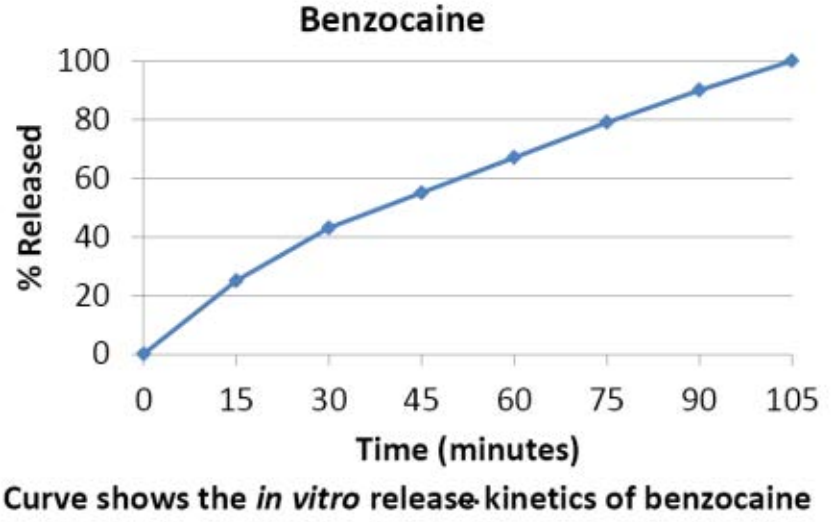


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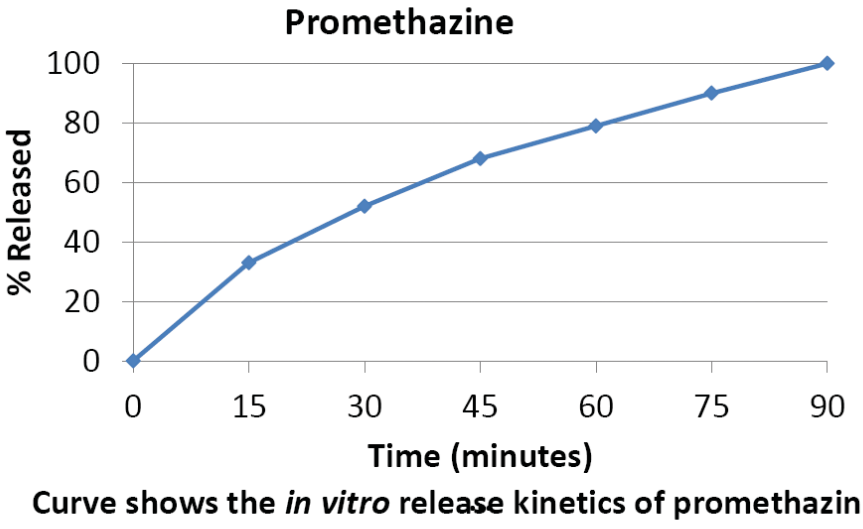
FIGURE 5



Curve shows the *in vitro* release kinetics of promethazine

Promethazine Release Kinetics

Equal or better product efficacy, with an improved safety profile, is achieved with a lower dosage of active ingredients. It is widely accepted that lower ingredient dosage results in improved efficacy provided that the ingredient remains in contact for a prolonged time. Additionally, lower ingredient dosage is desirable from a consumer (marketing) as well as a COGS (financial) perspective, provided that product efficacy remains unchanged.

SuRe technology delivers a gradual, uniform stream of active ingredients, which are evenly embedded in the polymer/essential oil matrix and are released with the gradual, uniform erosion of the finished product. As a result, the release of the active ingredients remains constant throughout the use of the product.

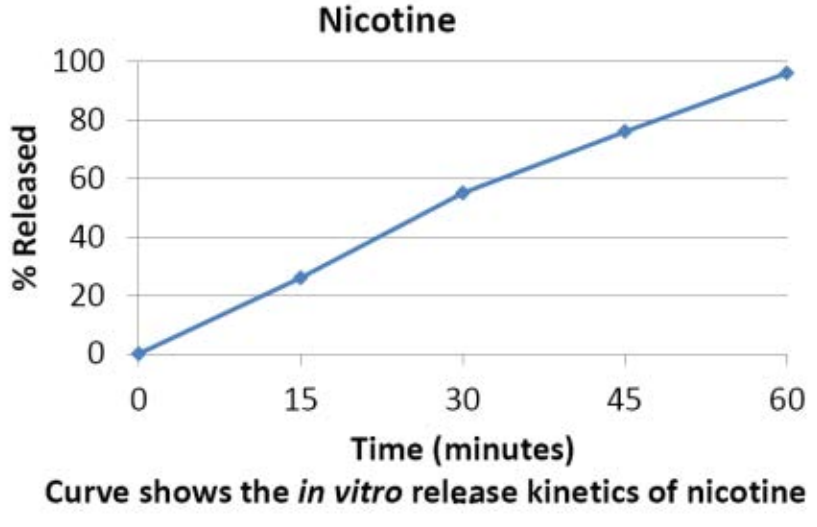
The desired flavor for the commercial product is highly flexible. The flavor may be any of the essential oils (peppermint, spearmint, wintergreen, etc) combined with traditional flavoring agents to enhance or mask the inherent flavor of essential oils. Therefore, a wide variety of desirable flavors may be achieved. Due to SuRe's matrix characteristics, the finished product will not experience flavor degradation throughout the use of the product.

The technology offers highly variable product shape and consistency. Throughout the production process, a paste of variable hardness is formed that may be shaped into any desirable form. The consistency of the finished product is soft and pliable and may take the form of a soft to "hard" lozenge, gel-like sunbstance, or chewing gum.

The consistency will impact the release properties of the final product. In general, the softer the finished product, the faster it will release the active ingredients. Conversely, the harder the final product the slower the active ingredients will be released.

Another benefit is low cost of goods sold (COGS), which is closely related to production volume and correspond to the COGS of chewing gum.

FIGURE 6



Curve shows the *in vitro* release kinetics of nicotine

Nicotine Release Kinetics

APPLICATIONS

Oral Health

Using the SuRe Technology, Nuvora, a company that concentrates on oral health, has three products in this category. Salese is a product for oral hygiene for dry mouth, Dentiva is for oral hygiene, and NuvoraBreath focuses on reduction of compounds causing bad breath. All three products release essential oils to kill bacteria, xylitol to inhibit bacterial growth, ingredients to raise the pH to neutral to prevent demineralization of the teeth, and ingredients to capture sulfur compounds that cause bad breath.[2-4] In addition, Salese releases a polymer that has a wet film property that helps people with dry mouth. Both Salese and Dentiva also have calcium and phosphate to help remineralize teeth. NuvoraBreath has extra amounts of the ingredient to capture volatile sulfur compounds that causes bad breath. Figure 1 shows the in vitro release curve for peppermint oil for these lozenges. Also presented is the curve showing the effect on pH in saliva for Salese (Figure 2). People with dry mouth are at high risk for decay and gum disease; the ingredients used in Salese (and Dentiva) reduces the risk.

Acidic pH (below 6.8) is known to demineralize tooth enamel or cause dental decay. In an in vivo clinical pH study, the SuRe lozenge (Salese) started to raise oral pH from acidic to neutral within minutes of product use.[5] In addition, when the neutral pH level was achieved, it was maintained for a prolonged period of time, even after the SuRe lozenge had dissolved. Decay is a significant problem in patients with xerostomia.

Colds

Recent evidence now states that zinc has a beneficial effect on duration of colds.[6,7] A long-lasting lozenge has the added benefit of being able to have zinc be in contact with the oral tissues for a prolonged time. For current zinc tablets, up to 10 tablets per day are recommended, leading to the potential of zinc toxicity. Much lower zinc doses may be used with the SuRe technology lozenges. In addition, the stringent taste of zinc is eliminated because of the masking effect of the lozenges with the essential oils. Figure 3 shows in vivo release curves for a zinc lozenge.

Sore Throat

Benzocaine is well recognized as an effective treatment of sore throat pain. Figure 4 shows the in vitro release characteristics for benzocaine.

Systemic Delivery

To demonstrate the potential for systemic drug delivery, lozenges were prepared, and in vitro release curves were run to obtain sustained delivery of a variety of drugs.

Once onset of nausea and vomiting occurs, the gastrointestinal route has limited efficacy due to lack of absorption. Thus, the intravenous route or use of suppositories is used; however, the oral route for these drugs is most preferential. Figure 5 shows the in vitro release characteristic of one such drug, promethazine.

Although there are a variety of nicotine lozenges to treat addiction on the market today, there are distinct advantages of a long-lasting nicotine lozenge. Figure 6 shows the in vitro release characteristic for nicotine release.

CONCLUSION

The SuRe technology can be applied to a wide variety of ingredients to create long-lasting lozenges for sustained release of the ingredients in the oral cavity. The application of the technology has been demonstrated for use in treating and preventing disorders of the oral tissues. Because of the versatility of the technology, the SuRe technology can potentially be used for systemic drug delivery through the oral mucosa/buccal areas .

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BIOGRAPHIES

Dr. Jerry B. Gin has spent more than 40 years in the healthcare and pharmaceutical/ biotechnology areas. He is currently President/CEO and Founder of Bennes/Nuvora, specializing in sustained-release technology for delivery of ingredients to the oral cavity. Nuvora currently has products on the market for dry mouth, oral hygiene, and teeth whitening. Dr. Gin was also Co-Founder, President, and CEO of Oculex Pharmaceuticals. Oculex developed the controlled-release technology for delivery of drugs to the interior of the eye to solve the problem of macular edema (purchased by Allergan). Prior to Oculex, he was Co-Founder of ChemTrak, developers of the home cholesterol test commonly sold in drug stores today. Prior to ChemTrak, he was at Syntex and Dow Chemical. He earned his PhD in Biochemistry from University of California, Berkeley, his BS in Chemistry from the Univeristy of Arizona, Tucson, and his MBA from Loyola College, Baltimore.

DRUG DEVELOPMENT Executive

APTALIS Pharmaceutical Technologies

APTALIS: MAXIMIZING DRUG DELIVERY TECHNOLOGIES IN TODAY'S PHARMACEUTICAL ENVIRONMENT

Mr. John Fraher
President
Aptalis Pharma

"Through collaboration agreements, Aptalis Pharmaceutical Technologies has successfully applied technologies to drug products in a diverse range of therapeutic areas, resulting in a broad portfolio of products for out-licensing. The partnership process provides our partners with an experienced management team across all functions and stages of the product development cycle. In addition, our global business development and licensing teams strive to offer flexible deal structures to maximize our partners' interests."

In February 2011, Axcan Intermediate Holdings Inc. completed its acquisition of Eurand N.V., and on May 4, the two companies announced their combined name as Aptalis. Aptalis is a specialty pharmaceutical company that provides innovative, effective therapies for unmet medical needs, including cystic fibrosis and gastrointestinal disorders. Aptalis currently markets pharmaceutical products around the world, including ZENPEP®, CANASA®, CARAFATE®, PYLERA®, LACTEOL®, DELURSAN®, and SALOFALK®, and has several compounds in various stages of development, including AEROQUIN® in Phase III clinical trials for the treatment of pulmonary infections in patients with cystic fibrosis. Aptalis Pharmaceutical Technologies, formerly known as Eurand Pharmaceutical Technologies, will continue to develop and manufacture products for its partners, as well as support the drug development process for the Aptalis Pharma pipeline and portfolio of products. Aptalis Pharmaceutical Technologies offers a broad portfolio of oral drug delivery technology platforms: Customized Drug Release, Bioavailability Enhancement, and Taste-Masking for ODTs (orally disintegrating tablets) and other dosage forms. Together, these technology platforms combined with licensing, manufacturing, and R&D capabilities enable Aptalis Pharmaceutical Technologies to produce customized drug formulation solutions for partners across a range of dosage forms and therapies with high patient acceptability. Mr. John Fraher, President of Aptalis Pharma, who serves a key role in setting strategic direction for Aptalis, with specific oversight of the company's Pharmaceutical Technologies and Global Supply Chain business unit, discusses the increasingly important role of drug delivery technologies for today's pharmaceutical marketplace.

Q: What are some of the macro factors impacting the pharmaceutical industry today?

A: Difficult-to-formulate molecules and a decline of New Chemical Entities (NCEs) for new therapies have resulted in pipeline gaps, weakened product portfolios, and a challenging R&D environment. Influencing factors include lengthened discovery timelines requiring large investment coupled with high/risk reward ratios associated with the drug development process. Additionally, requirements are more stringent to gain regulatory exclusivity on existing molecules and hinge on demonstrating improved clinical

outcomes, such as increased efficacy or reduced side effects. As such, pharmaceutical companies are seeking solutions from drug delivery that enable them to improve existing drugs for established and emerging markets, and also to create new products to address unmet medical needs in specialty therapeutic segments. These drug delivery solutions can extend patent lifecycles, and protect brands from the rapid entry of generic competition.

Pharmaceutical companies are now looking beyond the leading industrial nations to the increasing growth potential of emerging markets. For example, the seven major emerging countries, which include Brazil, China, India, Indonesia, Mexico, Russia, and Turkey, by 2020 could account for almost 14% of a projected pharmaceutical market of $800 million.

In a landscape that has been plagued by fewer new drug launches, pressure to cut drug prices is also a factor. Patient convenience and compliance was sufficient to drive reimbursement pricing in the past. Today, exacting pharmaco-economic data is the primary reimbursement driver at a time when safety is more heavily scrutinized than ever before. Efforts to cut industry costs can be seen in languishing start-ups, while Big Pharma M&A consolidation activities are on the upsurge.

Q: What is the role of drug delivery technologies in today's current pharmaceutical environment?

A: As the nation's leaders continue their endeavors to reshape healthcare via new models of efficiency, the pharmaceutical industry must ask the question: "How is our industry going to evolve over the years to come, and what can we do to reshape healthcare?" The answer lies in the application of drug solutions that improve the clinical benefits of drugs.

It is well known that patient compliance is fundamental to the successful medical management of the vast majority of diagnosed disorders. It is estimated that 40% of patients are considered non-compliant to a drug regimen, due in part, to poor taste, difficulty in administration or swallowing, and the inconvenience of multiple doses per day. Drug technology solutions can be applied to improve the clinical benefits of a drug by increasing patient acceptance and adherence via improved side-effect profiles, taste-masking of bitter ingredients, or dosing convenience through ease of administration. Technology advances and increasing regulatory demand for safer and more efficacious drugs have enhanced their applications, and now drug delivery technologies are used throughout the drug development process. Traditionally, patent expirations have led pharmaceutical companies to seek adoption of new drug delivery systems for marketed products, potentially adding years of additional patent protection and enhanced market longevity. Today, however, drug delivery technologies are significant in many stages of the product life cycle. For example, pharmaceutical companies use drug delivery technologies to optimize returns on R&D investment by reformulating existing products and/or creating effective formulation for promising but difficult-to-deliver molecules that may have been halted in clinical development.

Early application of drug technologies can strengthen market adoption by creating a more differentiated, attractive product upon market entry. This type of approach adds further market protection to the brand by establishing a broader IP estate to challenge generic entry through the addition of new

patentable material and extended patent expiry dating.

By moving away from the traditional business model that has shaped the pharmaceutical industry in the past, pharmaceutical companies can look to drug delivery companies as full strategic partners. These partnerships will enable increased R&D productivity, improved drugs, extension of product life cycles, and strengthened offerings resulting in clinical relevance that reshapes healthcare.

Q: What is the value of the Aptalis Pharmaceutical Technology portfolio to product development?

A: Aptalis Pharmaceutical Technologies has built one of the broadest drug delivery technology portfolios in the industry. In total, we have three technology platforms with eight distinct technologies that we apply to meet a range of challenging drug development objectives. These technologies are employed in more than 40 marketed prescription and OTC pharmaceutical products across a wide range of therapeutic indications, including cardiovascular, gastrointestinal, pain, nutrition, and respiratory. Our partners include such notable healthcare companies as Johnson & Johnson, GlaxoSmithKline, Bayer, Merck Serono, Pfizer, Bristol-Myers Squibb, and Cephalon. Several other drug delivery reformulations are in various stages of development.

Our multiple platforms (and range of technologies within each platform) allow for product feature differentiation while meeting patient needs. Our Customized Drug Release technology platform increases patient acceptability and adherence through less-frequent dosing. Patients also benefit from our Taste-Masking technology platform, which offers them pleasant taste and excellent mouth feel, thereby enhancing patience adherence and appeal. Our Bioavailability Enhancement technology increases drug solubility, which effectively aids bloodstream absorption of the therapeutic.

Q: How does your technology portfolio address significant industry challenges, such as poorly soluble drug candidates?

A: Our BIORISE® Technology enhances bioavailability of poorly water-soluble and readily permeable drug molecules by breaking down crystalline forms into nanocrystals and/or amorhpous (noncrystalline) drug. The drug is then stabilized in a carrier system that increases intrinsic solubility and dissolution rate of the drug to enhance rate and extent of absorption for a faster onset of action, equivalent therapy at lower doses, and/or oral dosing of poorly soluble drugs. BIORISE has two distinct proprietary activation systems (top-down and bottom-up approaches), and the development process can be customized to optimize the risk-to-spend ratio often associated with NCEs or challenging compounds. BIORISE offers partners a shorter processing time cycle and cost-convenient manufacturing processes.

In the feasibility stage, the application of novel drug delivery technology can rescue promising but difficult-to-formulate R&D pipeline candidates, addressing the pressing issue of R&D productivity.

Q: What are the advantages of other Aptalis Pharmaceutical Technologies?

A: Our technology platforms enable the flexibility to be utilized separately or in combination during product development for customized solutions to our partners' needs. For example, patients often desire a convenient dosage form, such as an ODT, but will not remain compliant

if taste is compromised during administration. At Aptalis Pharmaceutical Technologies, we combine our proprietary AdvaTab® ODT technology with our patented MICROCAPS® taste-masking technology to deliver patients a pleasant taste experience with a smooth and creamy mouth feel in an easy-to-swallow dosage form. AdvaTab ODTs dissolve in 15 to 30 seconds and are designed to meet FDA guidelines. Additionally, the ODTs are capable of high drug loading during formulation. The robust tablets are compatible with standard and blister packaging, which allows flexibility for our partners. Some commercial examples of the AdvaTab technology include Lamictal® ODT™ (Lamotrigine) Orally Disintegrating Tablets, which is a prescription medication for certain types of epilepsy, and Unisom® Sleep Melts™, a non-prescription sleep aide.

Our MICROCAPS Technology is a market-proven microencapsulation technology that uses a proprietary coacervation process to create a complete and uniform physical barrier around individual drug particles for outstanding taste- and odor-masking for high patient acceptability. The technology is capable of encapsulating an assortment of drug particle shapes and sizes, and is also used for encapsulating liquids for delivery in a solid oral dosage form.

Our Customized Release Platform consists of a range of technologies that provide a wide variety of customized release profiles. The DIFFUCAPS® Technology enables novel drug combination therapies incorporating multiple release profiles all in one dosage form (eg, two different drugs and two release profiles) overcoming potential compatibility issues. The technology can also be used with molecules that exhibit extreme pH-dependent solubility profiles. When used in combination with AdvaTab ODT technology, DIFFUCAPS technology allows for the novel delivery of a controlled release orally disintegrating tablet.

Q: How would you summarize the continuum of services offered by Aptalis Pharmaceutical Technologies?

A: Through collaboration agreements, Aptalis Pharmaceutical Technologies has successfully applied technologies to drug products in a diverse range of therapeutic areas, resulting in a broad portfolio of products for out-licensing. The partnership process provides our partners with an experienced management team across all functions and stages of the product development cycle. In addition, our global business development and licensing teams strive to offer flexible deal structures to maximize our partners' interests. To meet our partners' business needs, we offer resources for the development of new product formulations, or licensing availability of existing product formulations.

Our R&D and manufacturing processes are physically integrated within our facilities to enhance the flow of product development from formulation through scale-up and commercial manufacturing, preparing a customer's drug candidate for a smooth pathway toward commercialization. We manufacture all of the products that we develop for our licensees with facilities owned and operated by Aptalis. These high-quality cGMP facilities in the United States and Europe are also approved to handle controlled substances. Our positive history of cooperative collaboration with the US FDA and other multiple regulatory agencies and licensees in Europe, Asia, and the Middle East have resulted in successful quality inspection rates and international audits with multiple audits conducted yearly.

Best-practice alliance and project management teams enable pharmaceutical companies to work with us in collaborative partnerships with common expectations and goals. This model promotes quality partnerships and enables shared expertise, information, and workflow optimization across all functions and stages of the product development cycle.

Q: How do you see Aptalis Pharmaceutical Technologies growing and evolving?

A: Our strategy is to continue to be a leader in oral drug delivery and develop enhanced pharmaceutical and biopharmaceutical products based upon our drug formulation technologies. To support that strategy, we will continue to improve our drug delivery technologies, thereby contributing to the development of products for out-licensing that offer therapeutic, market, and patient benefits.

This integrated pharmaceutical route will enable us to continue our collaborative partnerships while continuing streams of revenue from the development and manufacture of products for our partners, as well as support for the drug development process for the Aptalis Pharma pipeline and portfolio of products. We will also look to expand our growing potential in emerging markets. Disease profiles in emerging markets are evolving to more closely resemble those of developed countries, shifting from infectious disease control to management of more chronic conditions, such as cancer, diabetes, and respiratory and cardiovascular disease. For example, according to the World Health Organization (WHO), in the US, only 12% of deaths from cardiovascular disease occur in working-age people, compared with 28% in Brazil, 35% in India, and 41% in South Africa. There is a growing market for products that address unmet medical needs in these countries; and for products that also enhance therapeutic benefits, such as dosing regimens and targeted dosage forms (such as via drug delivery technologies), that greatly increase the potential for success.

A case in point, Aptalis Pharmaceutical Technologies created a once-daily formulation of cyclobenzaprine, a muscle relaxant that had been on the market for several years, to reduce the need for frequent daily dosing. The result was AMRIX® (Cyclobenzaprine Hydrochloride Extended-Release Capsules), an FDA-approved product that is marketed in the US by Cephalon, designed to provide optimal drug-release profiles with the convenience of once-daily administration. The new extended release (ER) drug formulation not only reduces the need for patients to take multiple daily doses of cyclobenzaprine, but also improves the safety profile and tolerability of the drug by reducing the levels of somnolence associated with the standard immediate-release (IR) drug formulation. This created a successful product with rapid sales uptake in a generic market, with IMS recording sales of $119 million for calendar year 2009. Today, the product is licensed in more than 20 countries around the world, including South Korea, China, Turkey, Israel, South Africa, Russia, Pakistan, and South America.

With more than 40 products commercialized by partners around the world, Aptalis Pharmaceutical Technologies has demonstrated success and experience throughout the past decade in providing technologically advanced products to partners addressing unmet medical needs in these markets. ◆

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Technology & Services Showcase

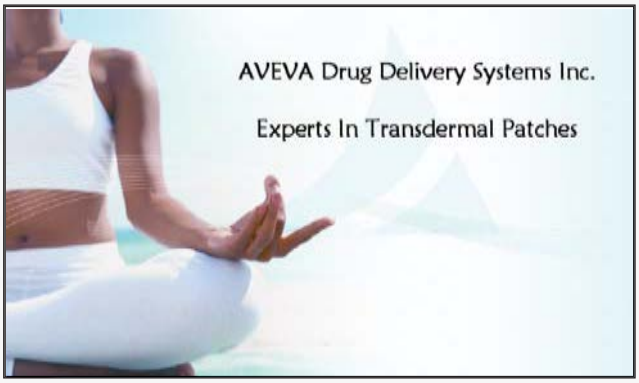
Inhalation Technology

3M Drug Delivery Systems is a leader in inhalation technology. For over 50 years, companies worldwide have looked to 3M for ingenious inhalation systems and components to enable success. Beyond systems and components, 3M delivers the expertise, efficiency, and flexibility you need to accelerate development for a competitive advantage. At RDD, 3M will offer a DPI: Design for Manufacturability & Scale-Up workshop as well as several poster presentations. In addition to our innovative new DPI technology, 3M will showcase our nasal MDI, a variety of MDI drug delivery devices, along with our inhalation components and manufacturing solutions, proving why 3M technology is relied upon by more than 50% of all MDI systems. Set up a meeting and learn more at **www.3M.com/ddsconferences**.

Specialty Pharma

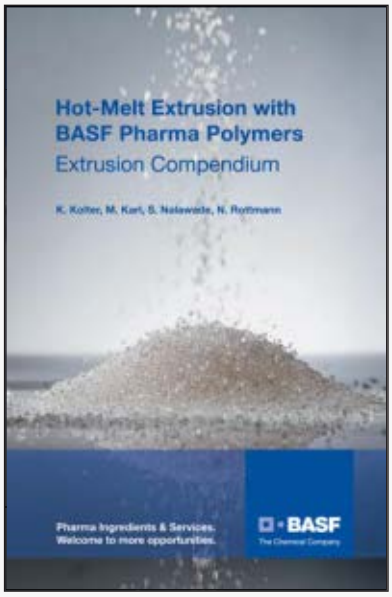
Aptalis Pharma Inc. is a privately held, leading specialty pharmaceutical company providing innovative, effective therapies for unmet medical needs, including cystic fibrosis and gastrointestinal disorders. Aptalis has manufacturing and commercial operations in the US, the European Union, and Canada, and its products include ZENPEP®, CANASA®, CARAFATE®, PYLERA®, LACTEOL®, DELURSAN®, and SALOFALK®. Aptalis also formulates and clinically develops enhanced pharmaceutical and biopharmaceutical products for itself and others using its proprietary technology platforms, including bioavailability enhancement of poorly soluble drugs, custom-release profiles, and taste-masking/orally disintegrating tablet (ODT) formulations. For more information, visit Aptalis at **www.AptalisPharmaceuticalTechnologies.com.**

Licensing & Capabilities



Aveva has a number of products for license from its development pipeline along with a full complement of R&D capabilities to produce transdermal drug delivery systems that fortify 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 with a rich history 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**.

Hot-Melt Extrusion



The first edition of the Hot-Melt Extrusion (HME) Compendium is now available. In this compendium, scientists at BASF present a range of polymers with both low and high glass transition temperatures for pharmaceutical technology. HME is currently generating a significant interest in the pharmaceutical industry as the percentage of poorly soluble compounds continues to increase. HME thus enables such molecules to increase their solubility and bioavailability. The compendium covers the chemistry and applications of polymers in melt-extrusion to achieve the robust processing conditions and desired release profiles of poorly soluble drugs. Download and comment on the Compendium at **www.innovate-excipients.basf.com**

Technology & Services Showcase

Biopharma Solutions

BioPharma Solutions, a business unit of Baxter, partners with pharmaceutical companies to support their 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. 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. BioPharma Solutions offers resources to help solve the high-stakes challenges you face in today's complex parenteral marketplace. For more information, contact Baxter BioPharma Solutions at (800) 4-BAXTER or visit **www.baxterbiopharmasolutions.com**.

New Technologies

Bend Research has decades of experience and a proven track record of success in advancing pharmaceutical compounds. The scope of our work is comprehensive. We develop drug delivery solutions from a base of fundamental understanding, provide formulation and dosage-form assistance, and advance promising drug candidates all the way to commercialization. Our engineering group has a wide range of tools and the expertise to assist customers in process development and optimization, science of scale, and scale-up and technology transfer. We also operate a current Good Manufacturing Practice (cGMP) facility to produce supplies for regulatory, clinical, and commercial use. For more information, contact Bend Research at (800) 706-8655 or e-mailing info@bendresearch.com or visit **www.bendresearch.com**.

Pharmaceutical Solutions

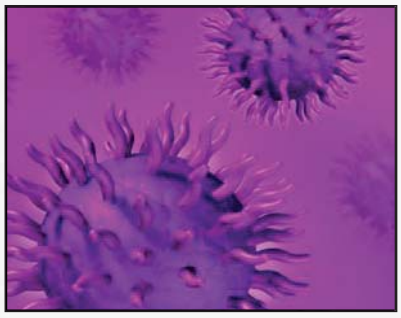
Catalent Pharma Solutions is a world leader in patented drug delivery technologies. For more than 70 years, we have developed and manufactured advanced drug delivery systems and partnered with nearly every major global pharmaceutical company. We continually work to advance the science of drug delivery and enhance the therapeutic and market performance of our customers' drugs. Our advanced drug delivery technologies bring new options to resolve the technical challenges development scientists face every day. These patented technologies can improve the odds of successful formulation by enhancing bioavailability, optimizing the rate of release, and targeting the site of absorption. Our technologies include softgel and Vegicaps® Soft capsules; Zydis® fast-dissolve dosage form; modified-release technologies; and a range of inhaled technologies, including MDIs, DPIs, nasal sprays, and solutions/suspensions for inhalation, nebulizers, and liquid inhalers. For more information, contact Catalent Pharma Solutions at (866) 720-3148 or visit **www.catalent.com**.

Topical Product Services

Dow Pharmaceutical Sciences currently serves clients worldwide with projects in various stages of development targeted for dermatology, ophthalmology, wound care, topical pain, women's health, and other therapeutic areas. Dow's full range of services include formulation development, state-of-the-art in vitro permeation models to optimize formulations, full analytical support, regulatory consulting, cGMP clinical manufacturing, and clinical labeling. By focusing exclusively on topical formulations for 33 years, Dow has developed more prescription topical formulations than any company in the world. We understand the problems and how to correct or prevent them. Dow successfully developed topical formulations for hundreds of companies of all sizes. Of the 30 prescription topical dermatological product NDAs approved by the FDA in 2005-10, Dow developed the formulations for 11. For more information, visit Dow Pharmaceutical Sciences at **www.dowpharmsci.com.**

Technology & Services Showcase

Bioavailability Enhancement



Elan Drug technologies' NanoCrystal® technology is a drug enablement and optimization platform applicable to poorly water-soluble compounds. Improved bioavailability provided by NanoCrystal® technology can result in the following benefits: increased rate of absorption, reduction in fed fasted variability, improved dose proportionality, rapid formulation development, and reduction in required dose with smaller and more convenient dosage forms. Five products incorporating this technology are now launched in over 100 markets worldwide with over $1.9 billion in market sales achieved in 2009. With over 1,300 patents/patent applications, NanoCrystal® technology has been optimized and simplified from 20 years in development. Applicable to all dosage forms, products incorporating this technology have been manufactured at commercial scale since 2001. For more information on our platform of technology solutions, contact Elan Drug Technologies at edtbusdev@elan.com or visit **www.elandrugtechnologies.com**.

Delivery Platforms

Flamel Technologies

Flamel Technologies SA is a leading drug delivery company focused on developing safer, more efficacious formulations of drugs to tackle unmet medical needs. Our product development pipeline includes biological and chemical drugs formulated with our proprietary platforms, Medusa® and Micropump®. Several Medusa-based products are at various clinical stages of development; Medusa's lead internal product candidate IFN-α XL (long-acting interferon alpha-2b) is currently the subject of a Phase II trial in HCV patients. The company has FDA- and EMA-approved drugs (Coreg CR® and Micropump aspirin, respectively) and manufactures Micropump-based products. Flamel Technologies has collaborations with a number of leading pharmaceutical and biotechnology companies, including Baxter, GSK, Merck Serono, and Pfizer. The versatile platforms may be used to address threshold formulation problems, such as poor solubility, aggregation, and instability for chemical and biological drugs. For more information, visit Flamel Technologies SA at **www.flamel.com**.

Analytical Testing Services

Gateway ANALYTICAL

Gateway Analytical provides quality analytical testing and consulting services to the pharmaceutical, forensics, and material science industries. Our company takes a forensic approach to scientific problem-solving, blending forensic examination practices with standard and innovative analytical methods to get to the root of pharmaceutical issues. With more than 15 years of experience, you can rely on our expertise in 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 information, contact Gateway Analytical at (724) 443-1900 or visit **www.gatewayanalytical.com**.

Innovative Syringe Systems

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Technology & Services Showcase

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Technology & Services Showcase

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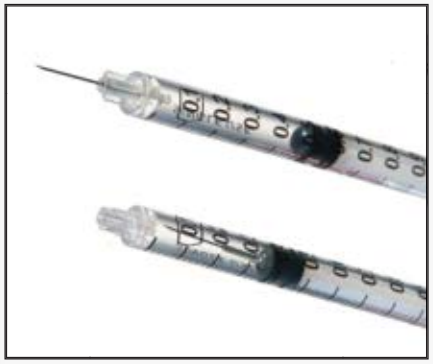
Pharmaceutical excipients produced by Stepan Company feature outstanding performance characteristics for use in the development of medical delivery systems including topical formulations. NEOBEE® Medium Chain Triglycerides are odorless, colorless, and naturally derived. Their low viscosity and polar nature facilitates handling under low-temperature processing conditions and promotes improved dispersibility, spreading, and dissolution of actives. ONAMER® M (Polyquaternium-1) exhibits unique antimicrobial activity, is extremely mild, and exhibits very low toxicity to host cells, allowing ONAMER® M to function in a wide range of medical device applications, including surgical scrubs, surgical preps, and other topical formulations requiring a broad spectrum of antimicrobial efficacy. For more information, contact Stepan at (201) 712-7642 or visit **www.stepan.com**.

Prefilled/Clinical Safety Syringes



Unilife Medical Solutions has a range of prefilled and clinical safety syringes suitable for pharmaceutical companies, healthcare facilities, and patients who self-administer prescription medication. Our products incorporate passive and fully integrated safety features that can help customers comply with needlestick prevention laws and encourage single-use and safe disposal practices outside of healthcare settings. The products feature a passive (automated) needle retraction mechanism allowing operators to control the speed of needle retraction directly from the body into the barrel of the syringe. The Unilife Ready-to-Fill Syringe features a glass barrel and is compatible with the manufacturing procedures used to fill standard prefilled syringes. The Unitract 1-mL Insulin Syringe is FDA certified and now being manufactured in the PA facility. For more information, contact Unilife at (717) 938-9323 or visit **www.unilife.com**.

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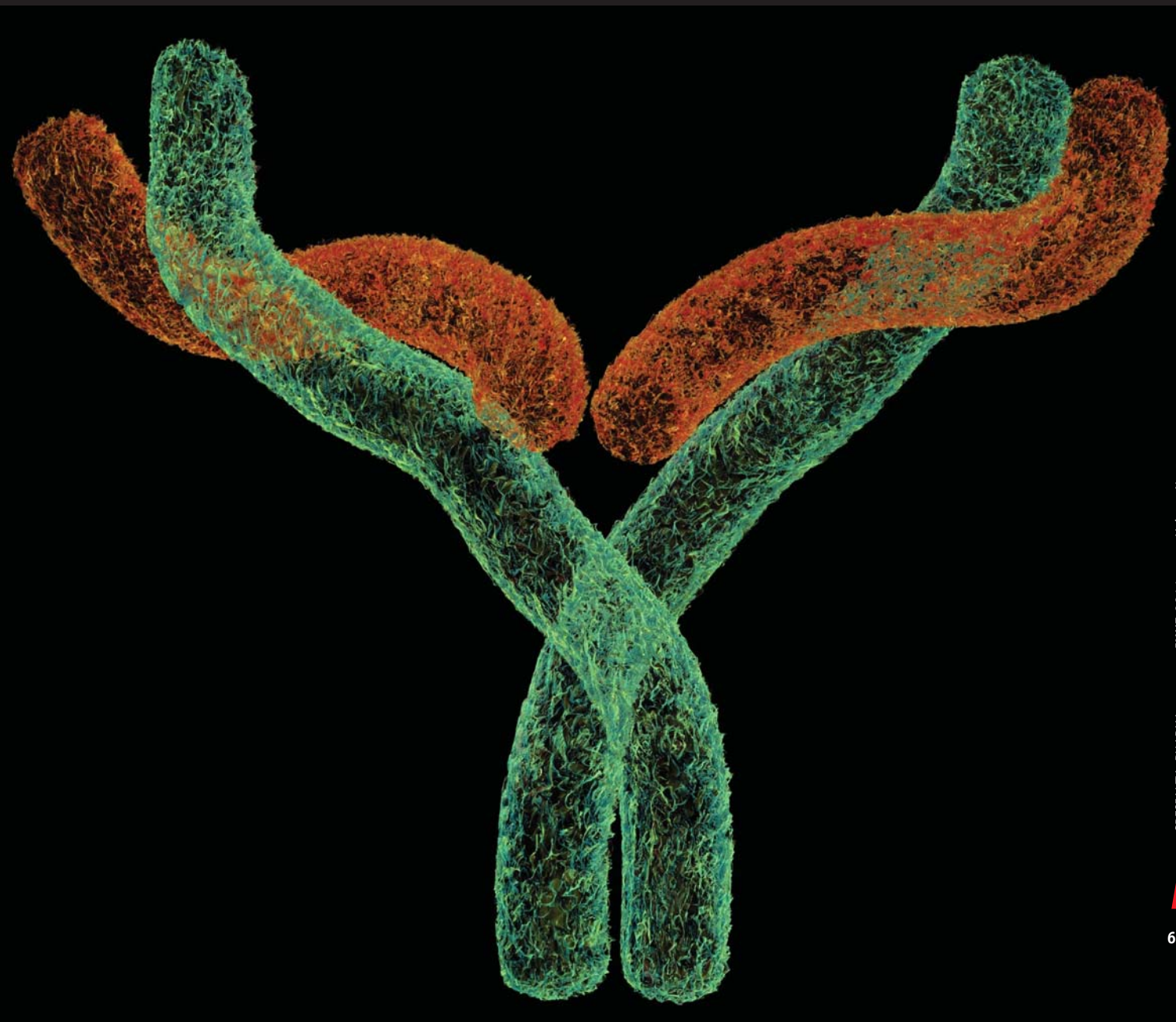
SPECIALTY PHARMA
Strategies For Business Development

Therapeutic Focus

Beyond Monoclonals for Severe Autoimmune Diseases

Guy-Charles Fanneau de la Horie, CEO, and Pierre Vandepapeliere, CMO, Neovacs SA



Chronic inflammatory and autoimmune diseases, such as rheumatoid arthritis (RA), Crohn's disease (CD), psoriasis, and Systemic Lupus Erythematosus (lupus), are major causes of morbidity and mortality, affecting substantial numbers of people across all ages and genders. More than 3% of the population suffers from a severe chronic inflammatory or autoimmune disorder, with an impact on health and well-being that ranges from the very distressing to disabling to life-threatening. In addition to the personal impact, these diseases represent a significant public health and societal burden; as one example, an individual with CD has an 80% lifetime risk of requiring surgery.

Treatment for these diseases has historically focused on symptomatic therapy, such as anti-inflammatory drugs, and second, on disease-modifying drugs, typically broad-spectrum immunosuppressants, including corticosteroids and folate inhibitors. This classical approach has two major shortcomings: first, while treating symptoms, the disease still progresses leading to, for example, irreversible joint damage in RA. Second, the disease-modifying therapies have very significant off-target side effects. For example, it is estimated that up to half of the pathological effects of lupus are attributable to the therapies versus directly to the disease itself.

Throughout the past 12 years, the advent of targeted biologics, especially inhibitors of TNFα, a pro-inflammatory cytokine, has transformed the treatment of many of these diseases. In RA, this class of drugs has shown the ability to arrest and even, in some cases, reverse disease progression, and in CD, they have demonstrated both steroid-free remission and the ability to induce mucosal healing. For such powerful drugs, they are also relatively safe, with the most significant concern being increased vulnerability to certain bacterial diseases and the potential reactivation of latent granulomatous infections, such as tuberculosis. Five TNFα inhibitors are currently marketed, with similar efficacy in RA, although not all appear efficacious in CD. The first of this class was introduced in 1998. Today, this is the most successful category of biologic drugs, with sales in 2010 of over $20 billion, a double-digit percentage increase on 2009.

More recently, the therapeutic arsenal of biological drugs for autoimmune and inflammatory disorders has expanded to other mechanisms of action, to include antibodies targeting CD20 on B cells, the IL-6 receptor, and IL-12/23, as well as a selective T cell co-stimulation modulator. In lupus, historically a very challenging target for drug developers because of the polymorphic and fluctuating nature of the disease, a monoclonal antibody targeting the BLyS/BAFF protein was recently licensed by the U.S. Food and Drug Administration (FDA) for marketing in the United States and is under regulatory review in Europe. This success has unleashed new interest in the field, previously a graveyard of failed clinical trials. For example, a number of companies are pursuing approaches targeting the cytokine interferon alpha, which has been strongly implicated in the pathogenesis of lupus.

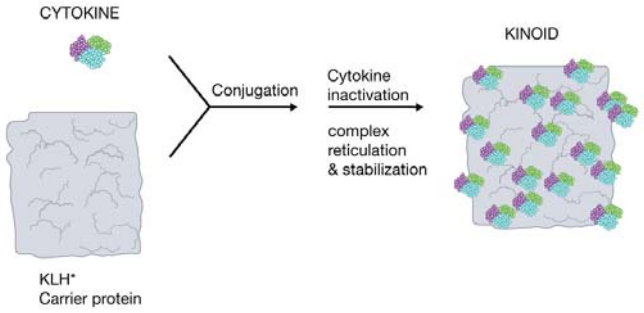


Figure 1. A Kinoid is an Immunogenic But Inactivated Derivative of a Whole Recombinant Cytokine. (Source: Neovacs) Neovacs' Kinoid technology is being developed to treat severe chronic inflammatory and autoimmune diseases, such as rheumatoid arthritis, Crohn's disease, and lupus. Kinoids are active immunotherapies that, when delivered by intramuscular injection 3 to 4 times a year, stimulate the patient's own immune system to address the underlying cause of the disease.

Autoimmune Disease: Unmet Medical Needs

For all this progress, current biologic drugs also have significant drawbacks and as a consequence, there remain significant unmet medical needs. The major shortcomings include the following:

- Many patients do not respond, or do not respond well, to a given drug. It is estimated that up to 40% of patients do not respond adequately to a first TNF inhibitor, although many of these non-responders do respond to a second drug in the same class. Only 50% of RA patients achieve disease remission with a TNFα inhibitor plus methotrexate. Why this should be the case is unknown, although one factor is likely to be that drugs targeting a single epitope on a protein, such as monoclonal antibodies, are vulnerable to losing efficacy if this particular epitope is absent, masked, or lacking therapeutic relevance in some patients. This lack of therapeutic breadth is important in more complex targets, such as interferon alpha for lupus. This cytokine has 13 naturally occurring subtypes, whose individual role in disease is not known: it is unlikely that a monoclonal antibody can successfully target all 13 subtypes.

- In many patients, current drugs lose efficacy over time, often because the patient's immune system generates anti-drug antibodies. In a recent large Danish study, drug adherence at year 2 in RA patients ranged from 40% to 60%.[1] The analysts Datamonitor estimate that up to 90% of CD patients have failed a TNFα inhibitor (infliximab) after 3 years.[2] Such figures clearly represent a major medical challenge in the treatment of chronic diseases typically diagnosed in young or middle-aged adults and for whom lifelong therapy is usually needed.

	Kinoids: Active Immunotherapy	Monoclonal Antibodies: Passive Immunotherapy
Active principle	Induced polyclonal response	Injected monoclonal preparation
Neutralizing antibody titers at peak	Medium	High
Mode/target of Action	Multiple epitopes	Single epitope
Frequency of administration	3-4 times per year	Typically twice per month
Time to onset of immunity	3-4 weeks	Immediate
Compliance	+++	+
Anti-drug antibodies	No	Frequently
Cost of Goods	Lower	Higher

Table 1. Comparison of Neovacs' Active Immunotherapy to Passive Immunotherapies (mAbs). (Source: Neovacs)

- Most current biologics typically require frequent injections, once per week or every other week. Some are delivered by IV infusion. This represents both a compliance challenge and is potentially a burden on caregivers or the healthcare system.

- These drugs are expensive, typically $15,000 to $20,000 per patient/year.

As a consequence of these and other concerns, biologics are typically held in reserve for the most severely ill patients (for example, in Europe and the US, less than 20% of CD patients with moderate-to-severe disease receive a TNFα inhibitor), notwithstanding a growing body of evidence that shows, in both RA and CD, that early use can alter the course of disease long-term.3

Autoimmune Disease Treatment Options in Development

The fact there remains a significant unmet medical need, together with the commercial success of existing therapies, means these diseases are of great interest to the biopharmaceutical industry. There are significant efforts in hand to expand the options open to patients and their physicians, which can be divided into the following three categories:

- Small molecule immune-modulating drugs
- Passive immunotherapy biologics to non-TNF targets
- Active immunotherapies

With regard to small molecule product candidates, a number of companies have compounds in clinical development, in particular tyrosine kinase inhibitors, a drug class with products already marketed in cancer indications. Small molecule drugs have advantages, including low costs of manufacture and the convenience of oral administration. However, they lack the specificity of biologics, increasing the risk of off-target adverse effects, especially in chronic use. Further, a daily or twice-daily pill may represent a compliance challenge, notably in younger patients and those not experiencing any current disease activity.

There are a number of biologic passive immunotherapies to non-TNFα targets, either approved or in development, including ones targeting cytokines, such as IL-6, and others inhibiting B or T cell activity. Most often, these drugs are used in patients who have failed, or are intolerant of, TNFα inhibitors. While providing valuable options to this population, these drugs typically have many of the disadvantages of the TNFα inhibitors, notably the risk of drug resistance, frequency of administration, and cost. In addition, there is not the safety experience with these newer agents, and some of them have relatively significant, if rare, safety concerns.

Active Immunotherapy for Autoimmune Diseases

The third category, active immunotherapy, holds out the promise of addressing the shortcomings of passive immunotherapies, without requiring a new therapeutic pathway. Neovacs' approach, called Kinoids, involves the administration of the target cytokine by intramuscular injection, formulated in such a way as to stimulate the patient's own immune system to generate antibodies directed against the target cytokine (Figure 1). For example, the TNF inhibitors have established that antibody to TNF is efficacious in treating multiple autoimmune diseases; under this modality, instead of administering synthetically produced antibody, TNFα Kinoid administration will foster induction of endogenous polyclonal anti-TNFα antibodies.

The advantages of this therapeutic approach are many (Table 1). Being the antibodies produced are polyclonal, recognizing multiple

epitopes on the target cytokine (unlike passive immunotherapy approaches), they might be expected to have both broader and longer efficacy than passive immunotherapies. In addition, because they are generated by the patient's own immune system, they will not stimulate the generation of resistance through the creation of anti-drug antibodies. Also, while the immune response to the active immunotherapies is transient, testing to date indicates that re-treatment will only be required every 3 to 4 months, a significant reduction in the compliance and patient/caregiver burden. Finally, passive immunotherapies rely completely on the drug administered for their therapeutic effect, requiring gram quantities per patient per year. By contrast with active immunotherapy, it is the patient generating the antibody and hence only milligram quantities per patient per year are required, with obvious implications for cost of goods.

Neovacs' Kinoids: Clinical Development

In principle, this technology can be applied to any cytokine target of therapeutic interest. Neovacs currently has two Kinoids in clinical development: A first-in-man clinical trial in patients with CD of the lead product, TNFα Kinoid, has reported results. Data presented at Digestive Disease World 2011 showed a very good safety profile, immunogenicity at the higher doses tested, and encouraging indications of clinical efficacy. The TNFα Kinoid is now in two Phase II studies: one in RA patients who have failed a TNF inhibitor, and a second in Crohn's patients, also having failed a TNF inhibitor. A second Kinoid, IFNα, is currently in a Phase I/II study in lupus patients in Europe, with initial results presented at the European lupus meeting in April 2011.

Future Developments & Milestones

Looking ahead, Neovacs plans to have full data from the Phase I/II with IFNα Kinoid in July 2011, and first results from the TNF-Kinoid Phase II program in late summer 2011.

Biotechnology has transformed the treatment of severe autoimmune diseases, and continued innovation holds great promise for patients afflicted with these serious and debilitating conditions. Approaches based on active immunotherapy offer significant advantages, and recent breakthroughs in other fields, notably oncology, are also highly encouraging. An approach using active immunotherapy principles will likely play a key role in the future in treating autoimmunity and inflammation, with clinical trials already in hand in CD, RA, type 1 diabetes, and lupus.

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Guy-Charles Fanneau de La Horie, DVM, MBA

Chief Executive Officer
Neovacs SA

joined Neovacs as its CEO in May 2006, bringing over 15 years of experience in biotechnology. Prior to joining Neovacs, he was Vice-President, member of the Executive Committee and General Manager, Europe for IDM. He led the European operations, a fully integrated unit from Basic Research to Business Development with 70 employees. Before that, he spent 8 years with Biogen, where he founded the French and Benelux commercial operations, moved to the US to become National Director of Sales and where his last position was, Vice-President of Strategic Commercial Operations, responsible for the Regulatory, Medical, and Marketing Operations for the International Unit. From 1990 to 1995, he worked at Schering-Plough in various positions, including International Product Manager for Intron A (a recombinant interferon a) and Cytokine Business Unit Manager in France. In 1989, he gained sales experience at Baxter after having started his career in the industry at Boehringer Ingelheim within the Animal Health Department. Dr. Fanneau de La Horie holds a Doctorate in Veterinary Medicine from the Ecole Nationale Vétérinaire de Lyon (France) and an MBA from INSEAD (Fontainebleau, France).

Pierre Vandepapeliere, MD, PhD

Chief Medical Officer
Neovacs SA

joined Neovacs in September 2008 and is responsible for clinical development and regulatory affairs. He brings more than 20 years of experience in clinical development, including 18 in the field of immunotherapy and prophylactic vaccines. Prior to Neovacs, he was Director of Clinical Research and Early Development at GlaxoSmithKline Biologicals, in charge of the clinical evaluation of early phase projects, new formulations, and adjuvants. He has been involved in the development of many major vaccines, including pediatric combinations, hepatitis A and B, herpes simplex, HIV, tuberculosis, Chlamydia trachomatis, and adult Streptococcus pneumoniae vaccines. In addition, he has extensive experience with immunotherapies, including those targeting hepatitis B and C, HPV, HSV, and HIV. Prior to GSK Biologicals, he was at ICI Pharmaceuticals from 1987 to 1990, working on cardiovascular products. Dr. Vandepapeliere holds a Medical Doctorate from the Universities of Namur and Louvain-Brussels, a Postgraduate Diploma in Tropical Medicine from the Institute of Tropical Medicine of Antwerp, and a PhD in Biomedical Medicine from the University of Ghent.

R&D Discussion Series

What Are the Transformational Changes Required in the Big "R"?

Part 2 of a 6-part series

By: Rosemarie Truman, Executive Vice President, Advanced Clinical

Introduction

The previous article (January 2011) in this series positioned R&D as the innovation steward at the center of sustainable growth in an organization. This article will address the transformational changes required, first and foremost, in Research, and how this function can better contribute to driving long-term innovation.While revenue growth for the industry is projected to be about $225 billion from 2010-2014 with global sales reaching $1.1 trillion by 2014[1], greater than $142 billion in sales of drugs will have patent expirations for the same period. However, patent expirations are only part of the problem. New and improved drug approvals, which are needed to get a product to market, also are on a decline.[2] This suggests a great need for more effective and efficient processes to identify the right products that will obtain approval, reimbursement and market adoption. Currently, the time involved in discovering a potential new drug all the way to FDA approval is about 10 to 15 years with capitalized costs of more than $1.8 billion per drug. The discovery or "Research" portion of this development is approximately 5.5 years and with capitalized costs of more than $800 million per drug.[3/4] To put this in perspective, consider the number of products a large pharma has in the market. When it comes down to it - not many. By the time products sift through selection, development, and commercialization, there are far fewer that make it through to market. One out of 24 targets in discovery are launched. Only 9 of these make it out of pre-clinical.[3]A paradigm shift is required in the Research phase to avoid the immense direct cost as well as the opportunity cost of not selecting the right products. This article will explore a new framework for thinking about Research that will improve this function's ability to select the right products. In addition, the article will outline lessons learned in Research from outside of the life sciences industry that can be employed.

The New Imperatives for "R"

Research includes activities ranging from target to hit, hit to lead, lead optimization, and preclinical. The Research function has made major strides in improving success rates by using new techniques. One area that Research has been optimizing is physico-chemical properties, such as solubility, chemical stability, hydrophobicity/hydrogen bonding potential, charge, size, salt form, and

Figure 1. *Growth Framework Illustration*

polymorphism. In addition, there has been much progress in biological analysis, such as intestinal mucosal cell permeation, liver and kidney, clearance, metabolism, transporters, protein binding, blood-brain barrier permeation, target cell permeation, QT interval prolongation (eg, hERG), and toxicity. In spite of the progress, the selection process for the right product to take to market is still lacking. As mentioned earlier, only 10% of products that leave preclinical make it to market. With 46% of the cost and 41% of the time invested in the "R," there is a need to focus more carefully to ensure successful selection of the right product to bring to market.

Company	Situation	Problem	Results
Kodak	**Maintaining an irrelevant strategy:** •Eastman Kodak turned photography into a national hobby in the late 1800s, defining an industry that would endure nearly a century of innovation and growth. •Kodak developed thousands of innovations throughout the 20th century, including the color instamatic camera. •In 1975 Kodak successfully tested its first digital camera. This was 6 years before Sony introduced its version. •Demand for Kodak products peaked in 1995. This was reflected in an all-time high share price of $95.	**Disruptive technology:** •Staying true to their strategy, Kodak ignored its own technological breakthroughs and focused on the traditional photography segment. •When revenue started to fall, Kodak scrambled to expand its strategic options beyond a single thread. •Kodak's efforts were hampered by its need to finance and restructure around the disruptive technology.	**Downward spiral:** •Shares declined drastically, forcing nearly 100,000 layoffs. •Kodak was a US market leader in digital cameras but, saddled with billions in debt, could not turn a profit.
Corning	**Chasing fast money:** •During the late 90s, Internet and telecommunications companies heat up Wall Street with 60x earnings valuations. •The market forecasted 200% year over year demand growth for internet bandwidth (2000-2006). •Corning abandoned its traditional model of developing components and products for a range of industrial clients and consumer segments, in favor of the promise for quick profits on optical fiber. •In 1999 Corning acquired 12 optical technology companies for $9B, $6B of which is good will. •Company transitions from a balanced product portfolio driven by R&D innovation to an optical fiber company.	**Lack of diversification:** •Corning disregarded the strategy that made it successful – "patient money" and a long-term commitment to technology. •When the market crashed, Corning found itself fully exposed to the technology bubble, having invested heavily in optical fiber related technologies. •This focus left Corning with its other revenue streams greatly diminished, having sold off its cookware and non-telecommunications optical fiber businesses.	**Near death experience:** •Profits spike in 2000 to $3.15B driven by market speculation and drop to $602M by end of 2002. •During the same period, the stock price soars past $100 and crashes to single digits.
Xerox	**Moving from the copier company to the document company:** •In the late 90s, Xerox attempted to move from providing copiers in a manufacturing economy to document solutions and services. •This strategic move was predicted to enable Xerox to reshape its business model from a production economy model to a networked digital economy model.	**Underestimation of the investment required and management trouble:** • Xerox's core capabilities were designed for the old world, and the company was not ready to tackle such a bold transformation. The company grossly underestimated the investment required to execute the change and did not have the necessary resources to do so. •Management fiasco between CEO and CEO successor undermined the company's plan to reinvent itself to succeed in the Digital Age.	**Free fall:** •By 1998, Xerox entered a three-year period of "free fall," in which its share price sank from around $60 to $4, and yearly revenues continued to fall for the next several years. •Later on, the company unveiled new digital printers and office systems and taken market share from competitors, but is still struggling to boost revenue growth in a slow sales market, where pricing pressures have cut into profit margins.

Table 1.

All this, and Research is currently faced with unprecedented dynamics. It used to be that 1 in every 5,000 to 10,000 compounds needed to be sifted through. Now there are many more targets generated; in fact, this number has doubled (and sometimes tripled) given new target generation techniques. Thus, picking the right targets is even more challenging.

The root cause: the "R" is rarely, if ever, connected to the reality of what it takes to get a product through the "D." From a Development standpoint, there is an increased focus on "developability" at maximum efficiency, as the cost of development has skyrocketed. Also, both the "R" and the "D" need to be connected to what will ensure successful "C" (Commercialization). From a Commercialization standpoint, there is more scrutiny by the FDA given CER requirements and, also, reimbursement has become more challenging with health care reform. The variables that present themselves in "D" and "C" need to be examined in the discovery phase to have the highest probability of success.

Research and Development should have a harmonious, productive, and operational partnership, ultimately bringing successful product Commercialization. In the end, the FDA should approve, payers should want to pay, and the product should gain market adoption. Finally and most importantly, life sciences companies should be able to command a premium. So, it's not just about having a seemingly wonderful compound. The product has to be first-in-class, best-in-class, differentiated, address an unmet medical need, and have a market that will reap profits.

Simply put: Research needs to be able to strategically select the right products that can be successfully developed and commercialized. The key paradigm shift: Use comprehensive and systematic rigor in identifying the right focus areas by developing a Research Strategy. From a big picture perspective, what does this mean for Research?

1. First, identify the right focus areas that will yield an opportunity for a breakthrough using RIGOROUS analusis. Start with the end in mind. Strategically select product areas; avoid thinking only of the medical/scientific aspect, but rather, infuse opportunities with variables that need to be

considered further down the road in Development and Commercialization. Will sales meet expectations? Will it serve a large enough patient population? Will insurance companies provide reimbursement? These questions represent just a few of the key questions that must be asked/answered.

2. Once the focus opportunity areas are selected, perform the right due diligence. For each focus area, this means going from 100 potential products/opportunities to 2 to 3. Given the growth breakthrough nature of successful life sciences companies, an intense rigorous analysis is needed to ensure you're selecting a viable, sustainable growth opportunity. Rigor includes assessing market attraction, doability of development, and 15 other dimensions. Due diligence rigor now must be a new capability for the Research function.

Why is Rigor Important?

The Horizon 1-2-3 growth model (Figure 1) provides an excellent framework to evaluate the health of a product pipeline as well as the directional plans of an organization. Horizon 1 growth is focused on short-term tactical growth. Horizon 2 models focus on adjacency growth based on a current market or product. Horizon 3 growth is focused on growth in a "net new" market. Life sciences companies are, by design, forced to focus on Horizon 3 to reach a successful outcome. The right new product therefore must be selected by way of a systematic, rigororous process in the Research phase or it runs the risk of not receiving approval, reimbursement and adoption. Which growth model is representative of your company's current strategy?

Horizon 1 Growth (H1):): Protects the present. Tactics extend the base business in the current market using the same business design, same customers, and same services. H1 has a profit focus that aims for incremental and optimized growth by focusing on improvement levers such as sales force excellence, market effectiveness, price optimization, client account management, and Lean Sigma. For example, to protect current investments, many of the large pharma are shifting sales personnel to Asia in an effort to capture the 20-30% growth rate in demand for drugs from China. New sales tactics are being employed to protect near-term revenue growth and cover the massive territory of China and the fragmented market. In many cases, sales processes and organizational incentives have been bolstered; additional tools and automation has been deployed and several other areas have been improved to help the sales function become more effective and efficient.

Horizon 2 Growth (H2): Drives profit or revenue. Grows business by innovating the base through core capabilities, customer access, products/services, business, or operational models to drive scale across the enterprise. H2 has an incremental profit and revenue focus in current and adjacent markets. For example, same product, new market: diabetes drug Metformin was discovered to potentially prevent the hepatitis C virus from replicating in the body.

Horizon 3 Growth (H3): Drives profit, revenue, and shareholder value. Achieves growth breakthroughs with net newness, "first drug of its class." H3 creates significant market impact by coming a series of new growth elements to create "newness" across a series of dimensions. Key areas of "newness" include, but are not limited to:

- New/improved products/services, for example, Benlysta, a drug from Human Genome Sciences, is the first in a new class of drugs called BLyS-specific inhibitors
- Business model expansion, for example, pay for drug performance offered by companies like Merck, Sanofi and Novartis
- Geographic expansion, for example, expansion into new territories
- Value Chain expansion, for example, the integration of the HIV division of Pfizer and Glaxo to create a new company ViiV Healthcare and develop a joint pipeline and broader value chain for HIV

For example, new product, new market: Benlysta, a drug from Human Genome Sciences, is the first in a new class of drugs called BLyS-specific inhibitors to help treat lupus.

One of the best recent H3 examples in creating a new market can be found in Apple's iPad. Released just over a year ago, the device sold almost 15 million units in 2010, 3 million of those within its first 3 months on the market. Not bad for a product that was unimaginable just a couple years ago.[4] iPads now make us think twice about purchasing personal

computers, a staple in consumer technology.[5]

While most companies are adept at ensuring strong Horizon 1 growth, and many can drive Horizon 2 growth, far fewer achieve Horizon 3 growth. This is the constant challenge of life sciences companies. As stated previously, life sciences companies have no choice but to focus growth on H3.

What Can Be Learned From Other Industries?

The life sciences industry can learn much by examining other industries (Table 1) that have learned how to ensure success in identifying and driving H3 growth breakthroughs. So, what are lessons learned from these companies?

Kodak: Consistently and rigorously examine your strategy; identify internal strategic assets, and rigorously assess them through a systematic process and framework.

Corning: Balance your investment in potentially disruptive innovation (H3s) with core competencies and products; perform rigorous and systematic due diligence on markets before jumping in.

Xerox: Incorporate into your due diligence process, not just market attractiveness but also ability to execute; construct appropriate management structure to incubate disruptive opportunities.

These broad industry examples all have one common theme: the requirement for a systematic approach to strategic planning and performing due diligence. While these industries may not seem to have scientific uncertainty, they definitely have market, operational, and regulatory risk. Imagine, then, if these companies also had the kind of medical/scientific uncertainty that is distinctive of the life sciences industry.

Life sciences companies can learn from these companies. How? Create a strong Research strategy using a systematic approach that uses rigor to identify the RIGHT product area focus. Within each product area, you might have 1,000 to 30,000 opportunities. Now perform due diligence to select the right products that should go into preclinical. Start-to-finish Research will reveal potential challenges before time and dollars have been spent in Development. Given the dynamics of this industry, compared to others, life sciences companies in particular need to drive a different level of rigor in the selection process to help identify growth breakthroughs in early stage Research. A Research planning strategy is critical and must be applied throughout the discovery process to systematically select growth breakthroughs.

Key Questions to Ask to Establish a Research Strategy Plan

A major component of the growth breakthrough selection process means asking the right questions from the start. The framework to select the right breakthrough product needs to rigorously assess these questions, beginning at the discovery stage throughout the Research process, which involves thinking ahead to the Development and Commercialization process. The following are a few of the key questions to think about in the Research phase once you've selected your focus areas.

Development: Can the product be developed? Is it "developable"? For example, will recruiting be successful? What are the risks involved? Can they be mitigated?

Revenue: Will the product command a premium in terms of price point? What will the price point be? What will the business model be (e.g., pay for performance)? Will patients be able to afford it? Will payers/insurance companies or government entities pay for it?

Market Adoption/Patient Care: Where are the patients who are accessible? How many are there? Will patients want it? Does it have a higher standard of care versus alternatives (e.g., fewer side effects, easier to use, faster, etc.)? Will doctors prescribe it?

Approval: Will the FDA approve the product? Is it differentiated? What are the concerns?

Investment Is the upfront investment that is required feasible?

Profit/Pay Back: Will investors invest? When and how much will it pay off? Does it serve a large enough patient population, incidence, and prevalence? Will the life sciences company be able to profit?

Medical/Scientific: Is the product sufficiently differentiated? What will the target product profile look like? What are the endpoints? Are they approved in the countries where the patients are?

In addition to assessing market attractiveness and ability to execute, a successful Research Strategy includes developing a comprehensive investment roadmap. Additionally, processes and analysis frameworks are needed to define strategic focus areas. A systematic approach will create a Research environment focused on results and progress, which properly sets

up a company to achieve sustainable growth.

What Does this Mean for "R"?

As it happens, a growth breakthrough is only as good as the sustainable profit it drives for life sciences Companies. Therefore, the role of Research is clear - Research must identify products that can be developed and commercialized successfully. Fortunately, there is a formula for Research to flourish.

Knowing what is required of Research to identify a growth breakthrough will help you develop a rigorous, calculated plan to deliver on these imperatives. Now ask: What methodology can I use to select the right growth breakthrough product? How do I ensure proper insight when selecting a growth breakthrough? How do I properly ensure market adoption? The next installment in this series will detail how to create a Research Strategy!

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Rosemarie Truman, PhD

Executive Vice President
Advanced Clinical

Rosemarie Truman is the President and CEO of RHT Consulting. She has 19 years of global strategy and transformation experience working with C-suites and Board of Directors as well as senior leadership teams of leading companies in nearly every industry segment, having worked with ~5% of the Fortune 500 and 10% of the Fortune 50. Rosemarie uses her solutions and 'breakthrough innovation' experience to conceptualize and implement a new game-changing framework for life sciences companies called Industry Leading R&D Performance (ILRDP). She is working with a range of biopharmas, biotechnology and medical device companies as well as leading technology transfer government organizations. Key focus areas include: picking the growth opportunities, creating breakthrough productivity in development and redefining technology transfer paradigms. Rosemarie also has a few patents pending on the growth methods she employs. Rosemarie's engagements have estimated results of: ~$20B in Operating Income, having run over 25 transformations in ~10 countries. Fifty percent of Ms. Truman's work has been outside of the US in Europe and Asia.

Ms. Truman completed PhD work in Software Engineering from Oxford University. She also earned an Executive "Mini-MBA" Program, sponsored by Booz Allen & Hamilton, with instructors from Harvard Business School and INSEAD, and graduated Magna Cum Laude from Smith College and Princeton University while earning undergraduate degrees in Mathematics, Economics, and Industrial Engineering and Operations Research.

Executive Summary

Robert T. McNally, PhD
President & CEO
GeoVax Labs, Inc.

GeoVax Labs: Developing Preventative & Therapeutic HIV/AIDS Vaccines

In November 2010, the Joint United Nations Programme on HIV/AIDS (UNAIDS) reported that there were an estimated 33.3 million people living with HIV/AIDS around the globe. As the global community continues to search for innovative and effective ways to wage its war against AIDS, numbers of those infected continue to rise. In 2009 alone, there were 2.7 million new cases of HIV/AIDS reported, demonstrating there is a critical need for a vaccine. A vaccine would not only serve to prevent new cases, but also help those who are already HIV-positive to keep the long-term health challenges and costs of the condition at bay. This is the mission of GeoVax Labs, Inc., an Atlanta-based biopharmaceutical company developing vaccines that are designed to prevent and fight HIV infections. Dr. Robert T. McNally, President and CEO of GeoVax, tells Specialty Pharma about the advances his company is making in its clinical development of a preventative and a therapeutic HIV/AIDS vaccine, and why this work has the potential to play a significant role in combating one of the most devastating global epidemics of our time.

Q: ***Can you tell us a little bit about the background of your vaccine technology?***

A: GeoVax's vaccine candidates were initially developed at Emory University by Harriet L. Robinson, PhD, who currently serves as GeoVax's Chief Scientific Officer, in collaboration with researchers at the National Institute of Health (NIH) and the US Centers for Disease Control and Prevention (CDC). The vaccines are recombinant DNA and Modified Vaccinia Ankara (MVA) vaccines, which work when the DNA vaccine primes the immune system and the MVA vaccine boosts the immune system's response. Our vaccines are designed to elicit antibodies that recognize and block the human immunodeficiency virus from infecting cells and T cells that can then recognize and kill the infected cells.

Q: ***What are the most promising aspects of GeoVax's own vaccine candidates?***

A: GeoVax is harnessing the power of the immune system to fight HIV. Dr. Robinson's early work with HIV vaccines demonstrated that DNA alone would not be sufficient to raise protective immunity for HIV. Consequently, as I mentioned earlier, GeoVax is developing two vaccine components: a recombinant DNA-vectored vaccine and a recombinant MVA-vectored vaccine. Both

of these produce non-infectious, virus-like particles in the body of a vaccine recipient. These non-infectious particles are designed to "train" the immune system of the vaccinated person to recognize HIV in the event that the vaccinated person is exposed to the actual virus by inducing humoral (antibody) and cellular (cytotoxic T cell) responses. Antibodies have the potential to block the virus before it infects cells, and the cytotoxic T cells have the potential to recognize and kill virus-infected cells.

Q: ***What is the aim of the therapeutic vaccine, and where do you stand in its development?***

A: The therapeutic vaccine is designed to treat individuals who are already infected with the HIV virus and is intended to prevent these cases of HIV from progressing to AIDS. The therapeutic vaccine was conceived with the intent of being able to wean these patients off their oral medication and allow their own immune system to fight the HIV virus. Currently, we are in a Phase I clinical trial for our therapeutic vaccine, which is being conducted by the AIDS Research Consortium of Atlanta and the University of Alabama at Birmingham.. This is a non-blinded study in infected individuals who started drug treatment during their first year of infection.

Q: ***And what is the aim of your preventative vaccine?***

A: GeoVax's preventative vaccine is for the vaccination of uninfected people in order to prevent infection by the HIV virus. Its use would thereby also reduce the transmission of HIV, protecting the population at large. To give you an idea of its potential impact, a 50% effective vaccine given to just 30% of the population could cut the number of new HIV infections in the developing world by more than half over 15 years. Currently, our preventative vaccine is in Phase 2a human trials, for which we recently increased enrollment from 225 to 300 individuals. This recent expansion will test the MVA vaccine on its own. Additionally, our early results from part A of an ongoing Phase 2a clinical trial indicated an excellent safety profile and highly reproducible immunogenicity.

Q: ***Why is vaccine development vital for managing the HIV epidemic?***

A: The HIV/AIDS epidemic is a global crisis. To realize the goal of an AIDS-free world, an effective vaccine is crucial because we need to prevent the spread of this disease while helping those already afflicted to maintain a normal life. Additionally, those infected with HIV have a long health-related and financial battle ahead of them. Oral medications for the disease can cost upward of $1,500 per month and $18,000 per year, and this expenditure is a billion-dollar-a-year drain on the global economy. Not only do these medications have an astronomical cost, but they also trigger substantial side effects that can significantly decrease the quality of life for individuals with the disease.

Q: ***Have there been any notable developments in the research community that support the promise of GeoVax's vaccine?***

A: One notable advance was publicized in September 2009 by the US Military HIV Research Program (MHRP), which is focused on developing an effective HIV vaccine for use in Southeast Asia. In a 6-year-long, community-based, Phase III

clinical trial known as RV144, researchers demonstrated that a combination of two vaccines - based on HIV strains that commonly circulate in Thailand - was safe and modestly effective in preventing HIV infection. Additionally, the strategy for our therapeutic vaccine was supported when Bionor Immuno of Oslo, Norway, recently reported success in the reduction of an HIV virus in the bloodstream after the administration of a vaccine. The Bionor vaccine reduced HIV replication by approximately five-fold in the population of treated individuals. Both of these developments give encouragement to all participants in the HIV/AIDS vaccine effort and show that ultimately, success for an effective vaccine will be achieved.

Q: ***What organizations have you partnered with and received support from to help move your vaccines ahead in the pipeline?***

A: GeoVax has been fortunate to have enjoyed substantial academic and government support both financially and in the clinic. Both preventative and therapeutic preclinical vaccine trials are conducted at the Yerkes National Primate Research Center at Emory University. To date, trials for the preventative application have been conducted by the HIV Vaccine Trials Network (HVTN), a network of vaccine trial sites supported by the National Institutes of Health, at no cost to GeoVax. In 2007, the National Institute of Health awarded GeoVax a 5-year, $18-million grant to support our vaccine development efforts. More recently, we were awarded a grant of $244,500 for our HIV/AIDS vaccine development activities under the Qualifying Therapeutic Discovery Project (QTDP) program. GeoVax received the maximum level allowable under the program based on the high number of applicants. The grant was awarded following our submission for consideration of our HIV/AIDS vaccine research and development projects to the US Secretary of Health and Human Services. These types of support are integral to our mission and to achieving our ultimate goal of bringing a vaccine to market.

Q: ***What is your eventual goal for your vaccine technology?***

A: Currently, GeoVax is developing vaccines for Clade B, which includes North America and parts of South America, Western Europe, and Australia. The eventual goal is to facilitate global access to the HIV vaccine and the additional clades - a step that will most likely be financed through world health type organizations and eventually will be undertaken by a large pharmaceutical firm that will license or acquire the rights to the vaccine from GeoVax.

Q: ***What would you say to our readers who have HIV/AIDS or know someone who does?***

A: Those who are affected by HIV or AIDS, either personally or through someone they know, should be aware of the committed researchers working tirelessly to find a vaccine for this disease. Although it is still too early to provide a timeframe for - or quantify the probability of - ultimate success, there is a strong belief that a vaccine is a realizable goal; one that if achieved could mean a better life for millions worldwide. As Seth Berkley and Alan Bernstein - who are, respectively, President and CEO of the International AIDS Vaccine Initiative and Executive Director of the Global HIV Vaccine Enterprise - wrote in The New York Times this past summer, "Ending HIV/AIDS urgently requires a vaccine. The evidence that a safe and effective HIV vaccine can be developed is stronger than ever." ■

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EXTERNAL DELIVERY

The Rest of the Story

By: John A. Bermingham

Great new ideas hopefully become great new companies that begin with a technology, product, or service idea. Then comes the hard part - raising the money that will get the company moving forward. What I have experienced throughout the years is that great ideas attract investor interest, but the start-up company never gets funded because the entrepreneurs neglect to tell the "rest of the story" properly. What I mean by this is that while the great new idea is indeed a great new idea, it is not presented to the investors with the proper documents in the proper format. The following will discuss the three documents that become the rest of the story.

Business Plan

You have to keep in mind that investors receive substantial amounts of business plans every day. Most are not that well written and only receive a perfunctory scan; many are much too long and do not contain the requisite information that will create interest with the investors; several will be paper clipped together rather than professionally bound; and some will even contain significant typos and grammatical errors.

A good business plan should be about 20 pages giving the requisite detail on the new idea and then include appendices at the back that contain management bios, a very detailed income statement, balance sheet, statement of cash flows, and other pertinent information the investors can examine if interested after reviewing the business plan. The main body of the business plan should also contain an abbreviated income statement.

Executive Summary

This is your escalator pitch (see May's column). This two- or three-page document, based on the business plan, is often sent as the initial mailing to investors to create interest and to be followed by a call to the investors by you referencing the executive summary you sent. You then suggest that you will send your business plan to the investors via overnight mail, FedEx, or UPS.

Power Point Presentation

If you get to the point where you are going to make a Power Point Management Presentation personally to an investor, you are close to the goal line. But this is an event where you can quickly fumble the ball. This is a presentation that should take 30 to 45 minutes and consist of no more than 15 slides. That is because the investor(s) have already read the business plan, and maybe even the executive summary as well, and are at this meeting really to get to know you and your people and ask questions. A 35-slide Power Point presentation is killer stuff. Investors often have several presentations or meetings scheduled every day, and their time is valuable and limited. So please keep in mind that a great idea is only the beginning of the story. The rest of the story is how you present it. ◆

BIOGRAPHY

John A. Bermingham is currently the Co-President and COO of AgraTech, a biotech enterprise focused on chitosan, a biomaterial processed from crustacean shells (shrimp, crawfish, crab, etc). He was 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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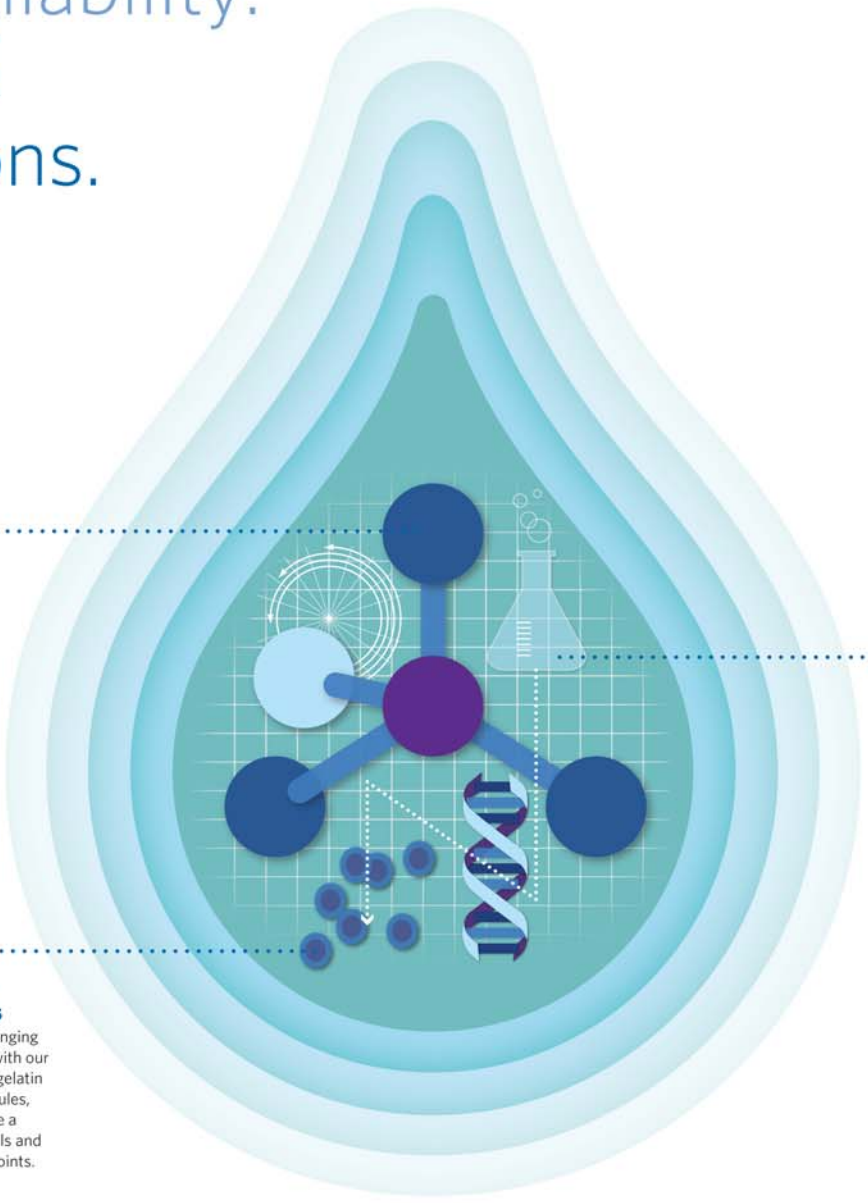

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