Drug Development & Delivery

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Terahertz Scanning Reflectometry

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

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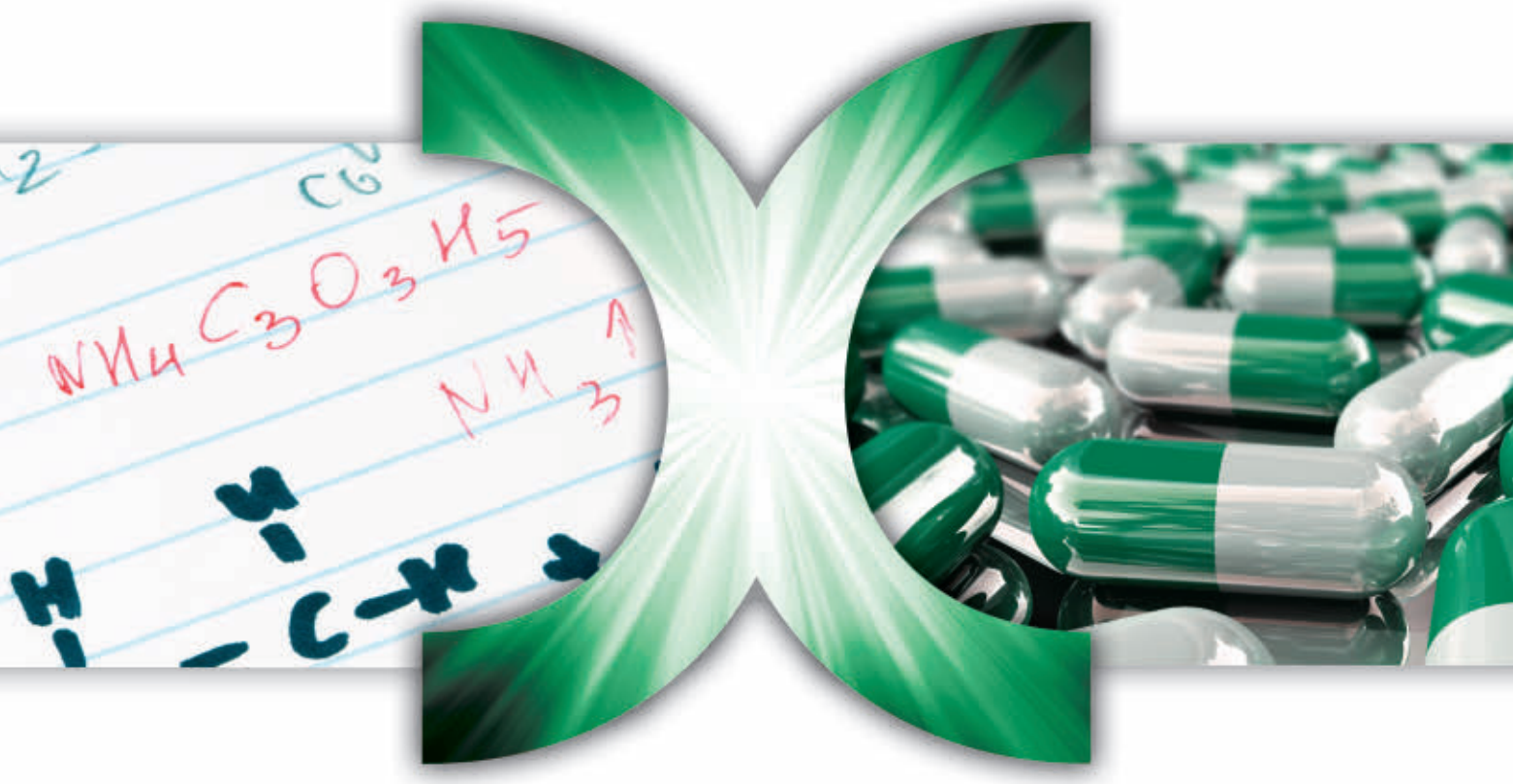

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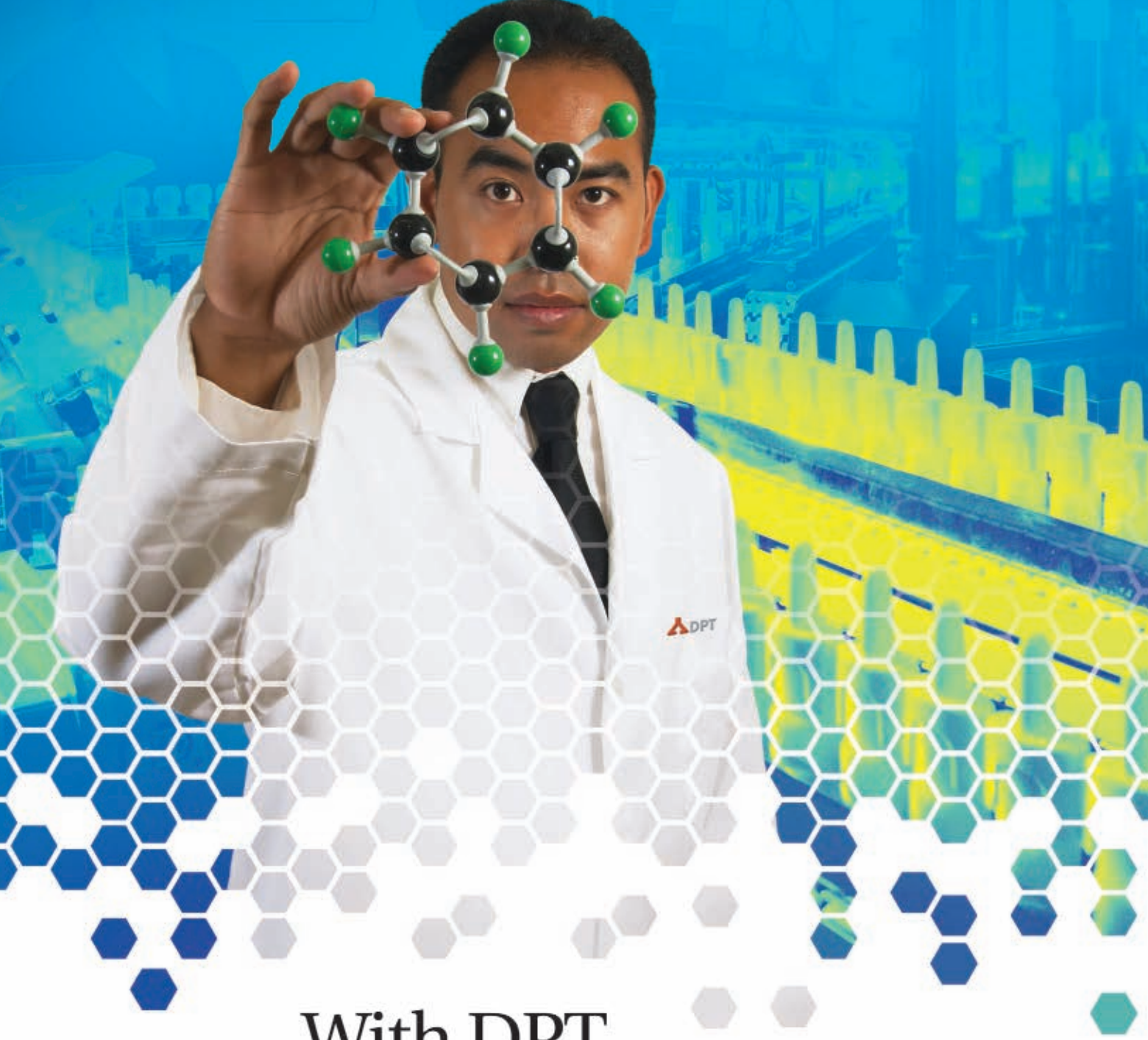

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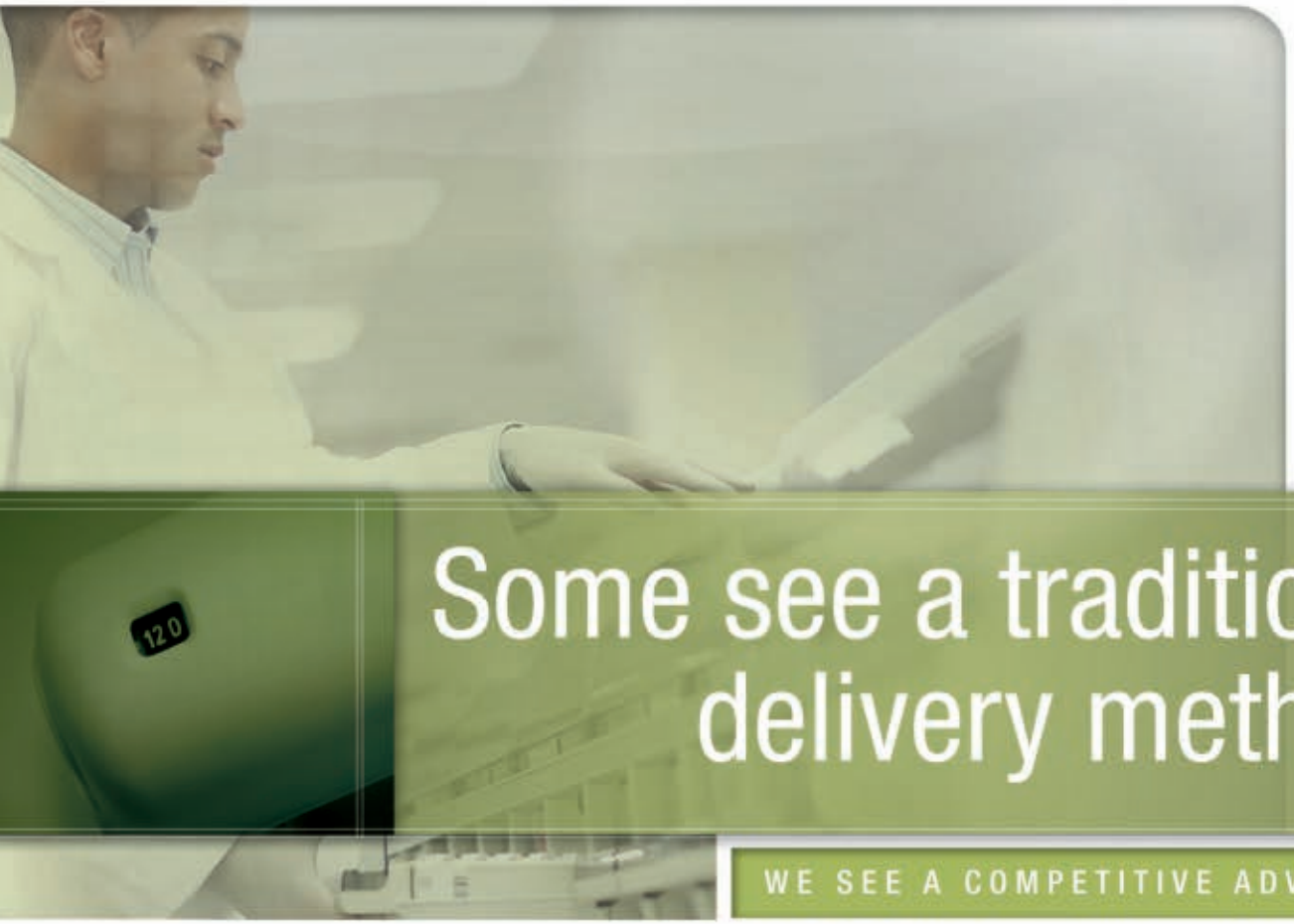

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"A report by London-based business information company Visiongain, Pre-Filled Syringes: World Market Outlook 2011-2021, predicts world prefilled syringe technology revenues will reach $3.9 billion in 2015, up from $2.7 billion in 2010. Expansion of the prefilled syringe market will be dependent upon developments in syringe technologies and materials. Improvements to performance, product stability, convenience of use, and cost-effectiveness will stimulate increasing use of prefilled syringes and related devices this decade."

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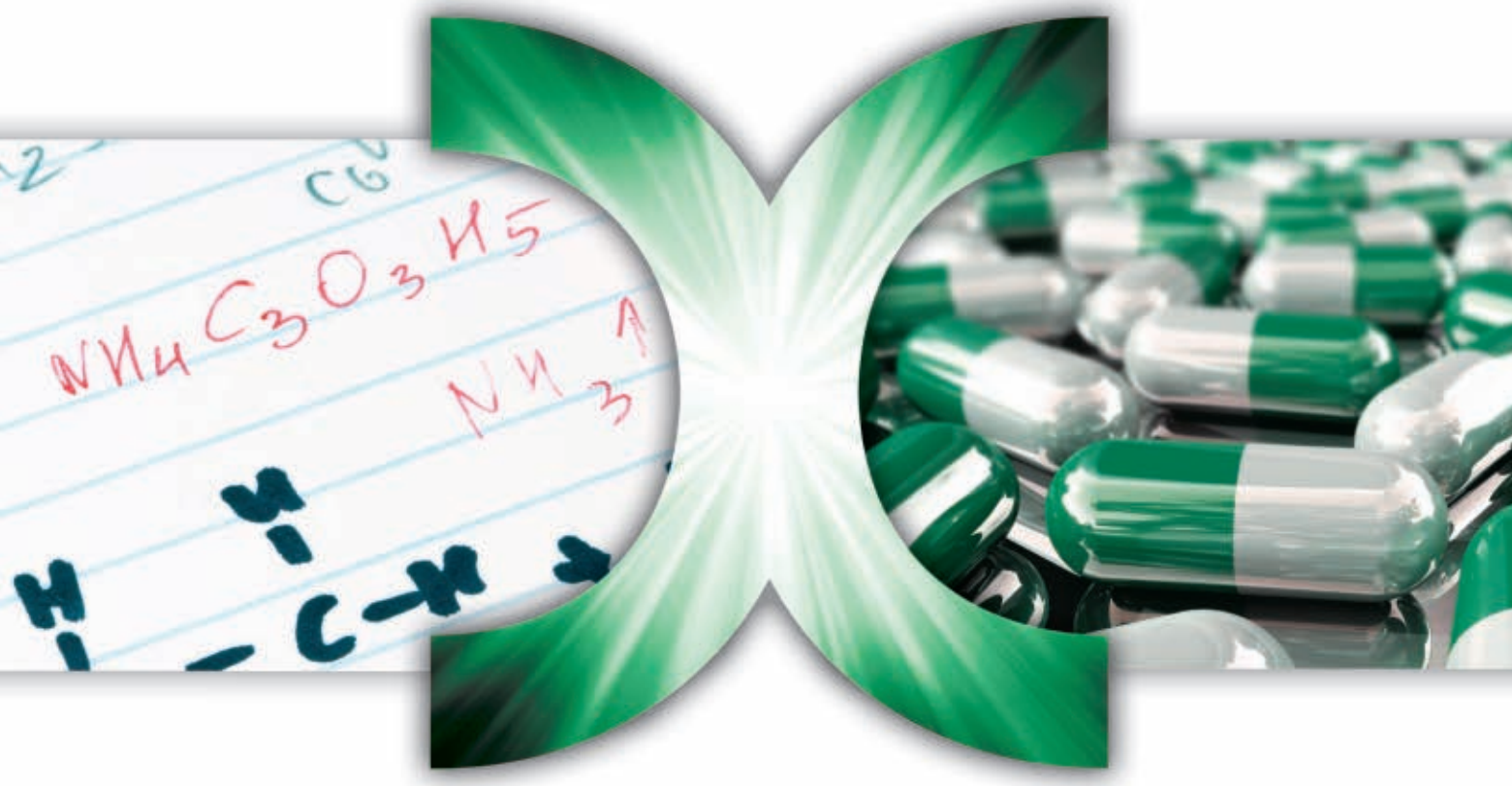

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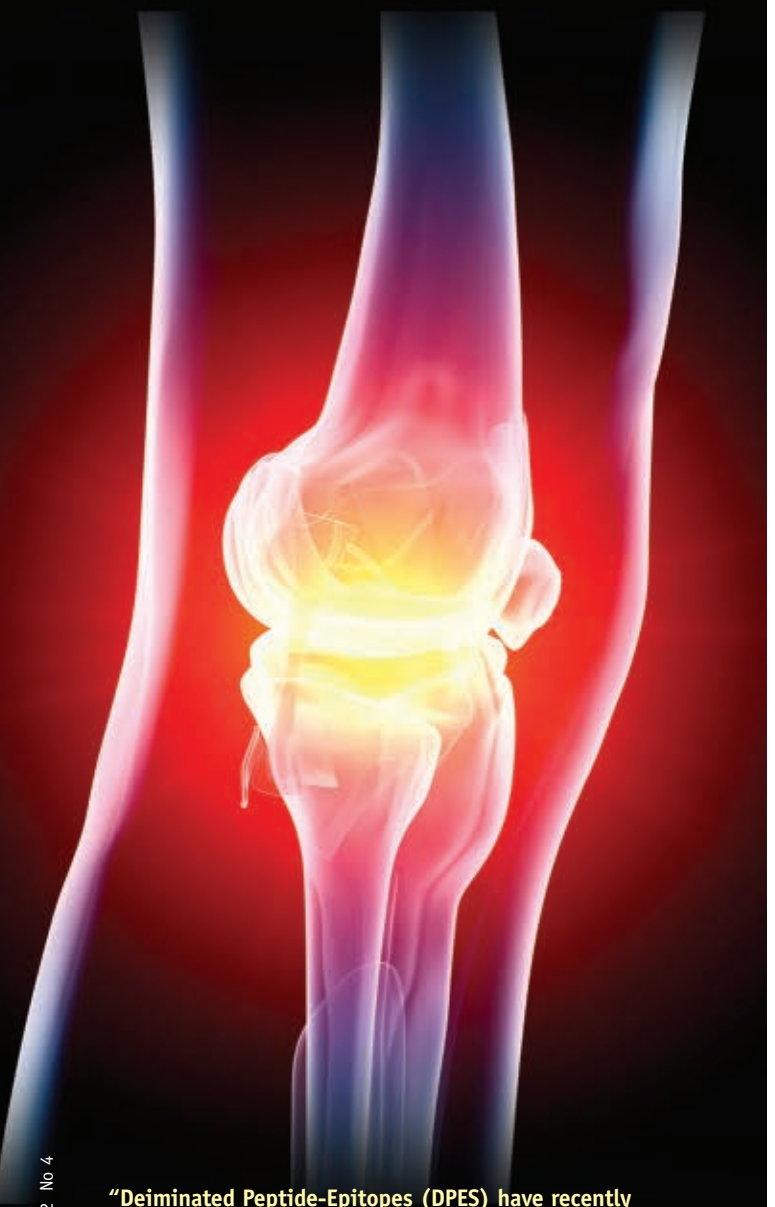

"Deiminated Peptide-Epitopes (DPES) have recently been recognized as a very specific marker for RA. These, as previously explained, contain citrulline residues modified from arginine residues by PAD enzymes released in the progression of RA pathology. ModiQuest of the Netherlands have undertaken a number of studies into specific anti-Citrulline antibodies and have discovered a subset (family) of rCit-hMabs (recombinant human anti-citrullin epitope antibodies), which could provide a valuable therapeutic in the treatment of early onset RA."

p.64

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Market News and Trends

Nascent & Catalent Sign Cancer Antibody Development Deal

Nascent Biologics, Inc. and Catalent Pharma Solutions recently announced the signing of a product development agreement. Under the terms of the agreement, Catalent will engineer a cell line expressing Nascent's proprietary Pritumumab antibody using Catalent's GPEx technology, and will subsequently produce purified monoclonal antibody to support Nascent's Phase I/II human clinical trials with Pritumumab for treatment of an unmet clinical need, treatment of brain cancers, such as astrocytomas and glioblastomas. GPEx technology is used to generate mammalian cells with high yields and stability, which will help speed the drug to clinic.

"We are committed to bring this potential new treatment to patients afflicted with this terrible disease," said Mark Glassy, PhD, CEO of Nascent. "Our first clinical data are very encouraging, and we look forward to working with Catalent to gather the key clinical data that will enable further development to be fast tracked with relevant regulatory agencies on a worldwide basis. Nascent Biologics is in the process of forming a commercial partnership for further clinical development, registration, and marketing of its Pritumumab product."

"We are delighted to be part of a program that will not only validate our GPEx technology as a leading system for the manufacture of biologic products, but will also aid in significantly improving the treatment outcomes for such a serious and untreatable disease," added Kent Payne, Vice President and General Manager of Catalent's Biologics business.

Glioblastoma, a form of brain cancer from which Senator Edward Kennedy recently succumbed, afflicts 10,000 Americans each year, with a 1-year survival rate of 50% and a 5-year survival rate of just 3%. There is currently no effective treatment for this disease. In previous clinical trials with Pritumumab, 5-year survival rates of brain cancer patients were about nine-fold higher, at 27%. Nascent wishes to confirm and validate the earlier clinical trial data and move forward into Phase III and subsequent registration of the product.

From drug and biologic development services to delivery technologies to supply solutions, Catalent Pharma Solutions has the deepest expertise, the broadest offerings, and the most unique technologies in the industry. With over 75 years of experience, Catalent helps customers get more molecules to market faster, enhance product performance, and provide superior, reliable manufacturing, and packaging solutions.

Nascent Biologics is an early stage biopharmaceutical company developing two proprietary platform technologies, MultiPharm and Uberkine, under the clinical premise that the most effective way to treat disease is to modulate (boost or suppress) the human body's natural ability to generate an immune response. Pritumumab is the first in a series of treatments for a variety of cancers and auto-immune diseases.

Alitair Announces Patent Allowance for Platform Delivery Technology

Alitair Pharmaceuticals, Inc., a mid-stage pharmaceutical company with multiple respiratory product candidates in development, recently announced it has received a Notice of Allowance from the United States Patent and Trademark Office (USPTO) for its ion-exchange resin platform drug delivery technology, REA. Alitair has out-licensed two product candidates utilizing its REA platform technology, and additional product candidates are available for out-licensing.

"Our propriety ion exchange resin delivery platform can be utilized across a range of therapeutic classes and with many different molecules," said Alitair President and CEO, William W. Howard, PhD. "The REA platform technology allows us to improve upon currently available therapies and create new oral-solid formulations with less-frequent dosing schedules, both of which have been shown to improve patient adherence."

"Receiving this Notice of Allowance is an important milestone in our product development strategy and the growth of Alitair," continued Mr. Howard. "We will continue to pursue additional patent protection in the US and in key markets around the world. This Notice of Allowance from the PTO and our equally strong International Preliminary Examination Report (IPER) means we will have a truly global patent portfolio in a short time. We are also actively seeking funding and development partners to build on the momentum we've created and advance our product development programs."

Alitair Pharmaceuticals, Inc. discovers, invents, and develops medicines for the treatment of respiratory illnesses. Alitair has out-licensed two prescription cough candidates that use its proprietary ion-exchange resin technology, REA, and other product candidates are available for out-licensing.

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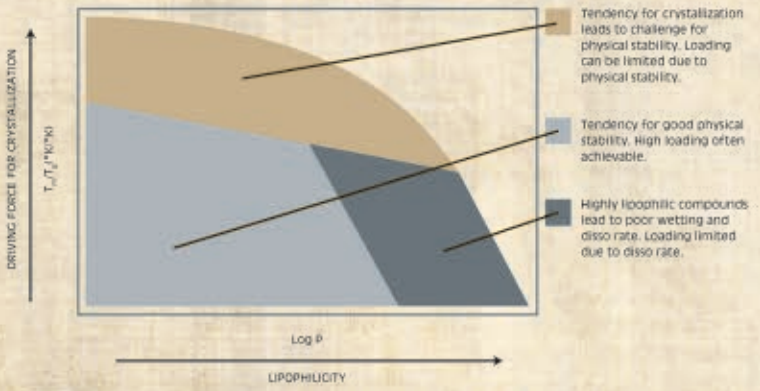

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EMD Millipore Launches Model for In Vitro Transdermal Diffusion Studies

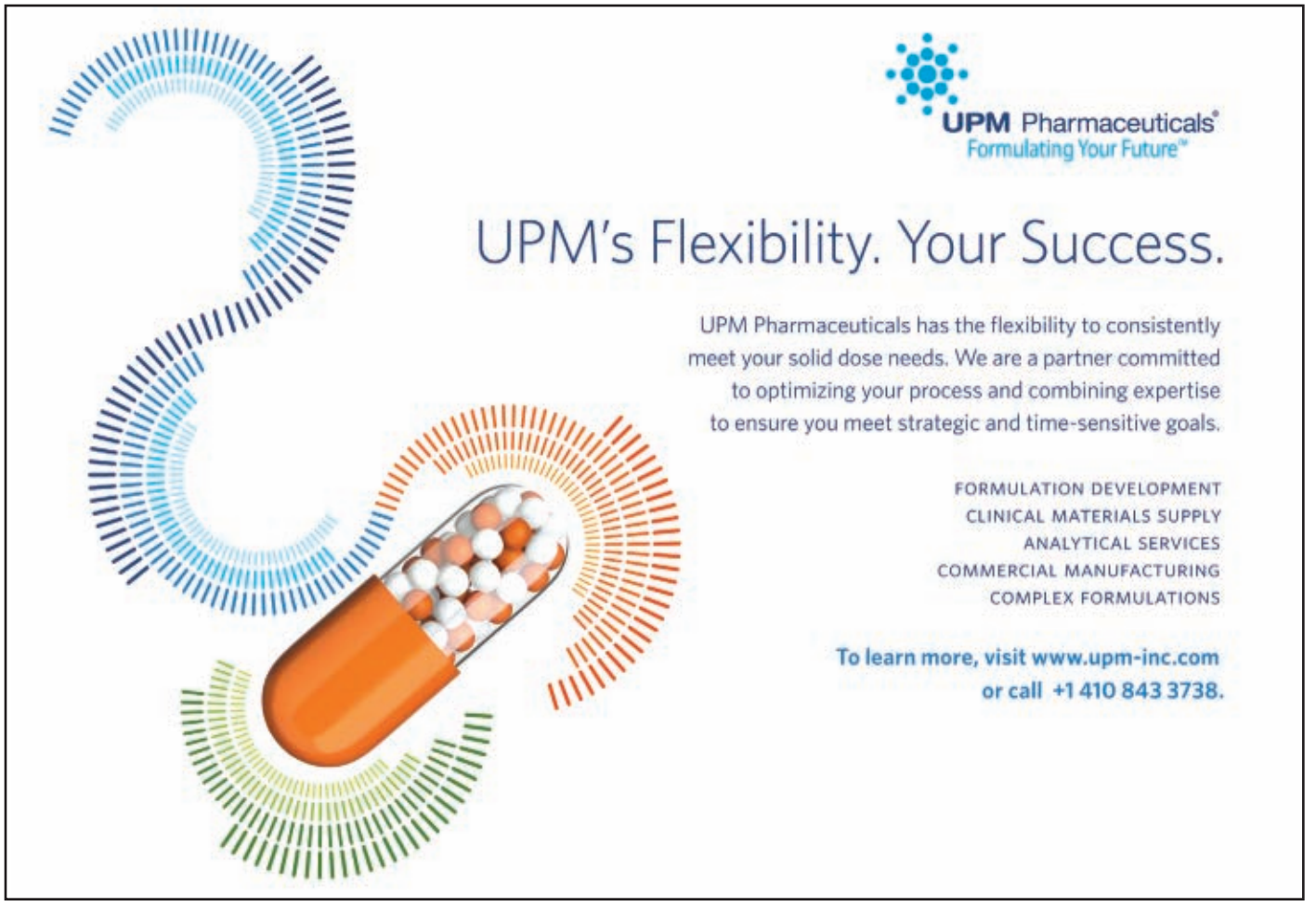
EMD Millipore recently introduced Strat-M membrane for screening compounds and formulations via in vitro diffusion studies. The synthetic membrane can be successfully used in place of human or animal skin to provide meaningful and reproducible information about permeation characteristics of the compound through human skin.

Strat-M membrane is a synthetic membrane constructed of multiple layers of polyethersulfone polymer creating morphology similar to human skin; membrane layers are increasingly more porous and thick through the depth of the membrane. After casting, the membrane undergoes a post treatment to impart lipophilic characteristics similar to human skin.

During development of transdermal drugs and personal care products, assessment of percutaneous adsorption and diffusion of the active ingredients is typically conducted using human cadaver skin or animal skin models (rat, mouse, pig). Unfortunately, a number of drawbacks to these biological models exist - the most significant being high variability. The diffusion rate through human cadaver skin is dependent on the site from which the skin is removed and affected by the age, race, and sex of the donor. Plus, biological models have special storage requirements, may be difficult to procure, and are considered biohazard and need special disposal.

"Results from our internal studies indicate that diffusion through the Strat-M membrane is predictive of diffusion through human skin for a wide range of compounds and formulations," said John Sweeney, Head of Life Science Business Field, EMD Millipore. “In most cases, the correlation between Strat-M membrane and human skin is much better than the commonly used animal skin models for in vitro testing of transdermal formulations. Furthermore, the benefits of a synthetic test model with low variability simplify experimental design and data analysis.”

EMD Millipore is the Life Science division of Merck KGaA of Germany and offers a broad range of innovative, performance products, services, and business relationships that enable customer success in research, development, and production of biotech and pharmaceutical drug therapies. Through dedicated collaboration on new scientific and engineering insights, and as one of the top three R&D investors in the Life Science Tools industry, EMD Millipore serves as a strategic partner to customers and helps advance the promise of life science.



Baxter International's New Plant to Bring 1,500 High-Paying Jobs

Baxter International Inc. recently announced it will build a new state-of-the-art manufacturing facility in Georgia to support growth of its plasma-based treatments. These therapies include treatments for immune disorders, trauma, and other critical conditions.

Baxter expects capital investments at the Covington, GA, site to exceed $1 billion over the next 5 years and to result in the creation of more than 1,500 full-time positions in Georgia and more than 2,000 jobs in total across multiple US locations.

"This investment demonstrates our long-term commitment to patients around the world who rely on our plasma-based therapies," said Robert L. Parkinson, Jr., Baxter's Chairman and CEO.

Construction will begin this year at the new Covington site, which will include operations supporting plasma fractionation, purification, fill-finish, and a testing lab. Commercial production is scheduled to begin in 2018, with the new plasma fractionation facility adding up to 3 million liters of new capacity annually when fully operational. The Covington site will have the flexibility and necessary infrastructure to expand further to support additional global market needs.

"We would like to thank Governor Nathan Deal and the many other officials involved in the site selection process, and we look forward to becoming part of the Georgia community," said Ludwig Hantson, PhD, President of Baxter's BioScience business.

In connection with this investment, the company also expects to create more than 200 new positions in Illinois, including jobs associated with expanded filling and finishing capacity at its existing manufacturing facility in Round Lake, IL. The new jobs at the Round Lake facility will support production of FLEXBUMIN, a preparation of plasma-based albumin treatment in a flexible container.

Baxter is a scientific leader and innovator in plasma-derived therapies, with a focus on providing solutions to unmet patient needs. Its products include GAMMAGARD LIQUID (marketed as KIOVIG outside the US and Canada), an immunoglobulin therapy (IG) for people living with primary immunodeficiency (PI), albumin therapies used to treat burns and maintain adequate fluid volume in critically ill patients, as well as blood protein therapies for people suffering from alpha-1 antitrypsin deficiency. The company continues to investigate its treatments in additional areas of significant patient need, including multifocal motor neuropathy and Alzheimer's disease. These products are produced from plasma that is collected from human donors.

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Ei Increases Capabilities Through New Partnership

Ei, A Pharmaceutical SolutionWorks, recently announced a new partnership with KeraNetics. Ei has begun a $13.2-million expansion within their recently completed 147,000-sq-ft facility in Kannapolis, North Carolina. Ei is providing product formulation and development to commercialize the patented product lines of KeraNetics. The new expansion, in part funded by a North Carolina state grant, will broaden Ei's manufacturing capabilities. Through their relationship with KeraNetics, Ei will manufacture and produce an advanced biomaterial to support the product lines for KeraNetics.

KeraNetics specializes in the creation of therapeutic medical products utilizing keratins, a class of structural proteins with unique physical, chemical, and biological characteristics designed to promote soft and hard tissue repair and regeneration by providing an environment to support the body's natural healing process. KeraNetics controls numerous patents for methods of purifying keratin proteins and applications for regenerative medicine and trauma.

"We are excited to announce our new partnership with KeraNetics," said Michael Kane, CEO, Ei. "We believe KeraNetics recognizes our team as product knowledge experts. A relationship of this magnitude showcases the level of skill and technology-driven innovation that exists in the DNA of Ei. Further, it illustrates the intellectual capital Ei brings to the table and taps into the strong business-to-business relationships we have forged and continue to maintain with our customers. We are not only assisting in the development and manufacturing of exciting new products, but are providing an added value to KeraNetics as a bridge to Ei's like-minded customers."

"The relationship with Ei has developed as a result of KeraNetics' intent to bring these exciting new keratin-based products to market," addedd Kim Westmoreland, Managing Director, KeraNetics. "We were originally looking at building a facility to manufacture these cutting-edge, keratin products that would have involved years of planning and construction. After meeting the leadership team at Ei and touring their state-of-the-art facility, we realized this partnership would allow us to cut those years out of the equation and create access to these products much more quickly. We could not be more pleased."

Ei focuses on Rx pharmaceutical, OTC, therapeutic skin care, and animal health markets. The company provides product development services ranging from formula development, testing, and package development. Ei specializes in regulatory assistance through clinical trial manufacturing, scale-up, and commercial production as well as offering specific development and manufacturing services.

KeraNetics is the global leader in the development and manufacturing of purified keratin medical products. Headquartered in Winston-Salem, NC, KeraNetics is developing first-in-class therapeutic medical products utilizing keratin biomaterials.

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US CMO Market Revives as Pharma Companies Increasingly Outsource

The upturn in the fortunes of pharmaceutical companies after the recession is mirrored by the US CMO market, which is expected to grow at a compound annual growth rate (CAGR) of 8.3% from 2011 to 2016. The sterile segment accounts for the highest share of revenues, with 38.7% in 2011, which is expected to rise to 47.5% by 2016.

New analysis from Frost & Sullivan's (http://www.pharma.frost.com) Analysis of the United States Contract Manufacturing Outsourcing Market research finds that the market earned revenues of $10.73 billion in 2011 and estimates this to reach $15.97 billion in 2016.

"The continued expansion of the US pharmaceuticals industry and the big pharma's increased outsourcing to improve cost structure and focus on core competencies will significantly augment the market's revenue growth," said Frost & Sullivan Consultant Jesse Sullivan. "The pharmaceutical companies that had used their excess capacity during the downturn to retain in-house manufacturing are expected to gradually outsource as the economy improves."

Despite the inclination for pharmaceutical companies to outsource, R&D spending dipped from 2010 to 2011, resulting in fewer drugs being developed and marketed. As the CMO market's revenue inflow is contingent on drug development, the torpid R&D activity has slowed the pace of market development.

The fragmented nature of the CMO services market has necessitated consolidation to improve profitability. Many CMO providers rely on a single client for more than 50% of their revenue. This tilts the balance of power in favor of the manufacturers and reduces prices across the industry.

"To demonstrate value to clients, CMO providers are likely to continue focusing on strategic relationships and promoting more services, such as formulation improvements, alternate dose forms, real-time order tracking, and logistics support," said Ms. Sullivan. "Further, numerous CMO providers are offering preclinical development services, which creates long-term relationships with manufacturers."

Analysis of the United States Contract Manufacturing Outsourcing Market is part of the Life Sciences Growth Partnership Services program, which also includes research in the following markets: European Pharmaceutical and Biotech Contract Manufacturing Markets; Strategic Analysis of Contract Research and Manufacturing Services Market in India; US Contract Research Outsourcing Market: Trends, Challenges and Competition in the New Decade; and Global CRO Market: Quantitative Assessment. All research services included in subscriptions provide detailed market opportunities and industry trends evaluated following extensive interviews with market participants.

NuSil Technology Announces Major Expansion

NuSil Technology LLC, the global leader in silicone materials for the healthcare, aerospace, pharmaceutical, aircraft, and drug delivery industries, recently announced plans for a major facility and capacity expansion in Bakersfield, CA. Construction of a third building is complete, and the site is on track to reach a total of seven buildings on the 15-acre campus.

"This facility expansion will result in increased employment opportunities across many functional areas at NuSil Technology's Bakersfield campus," says Bill Klansek, Vice President of Manufacturing. "MorehouseCowles, a NuSil subsidiary, will be designing and building much of the equipment necessary to support the new manufacturing processes."

The newly completed third building significantly increases the polymer processing capacity while adding additional warehousing space. The fourth building, at approximately 35,000 sq ft, is now under construction and is scheduled for completion in September 2012. This new structure will become the center for Quality Assurance, Human Resources, and Engineering, and will feature an enlarged QA testing laboratory and expanded office facilities. Two additional manufacturing buildings have been designed and are quickly entering the permit stage.

"The goal of this campus expansion is to increase plant capacity by three to four times over the next few years," said Jim Yabsley, Vice President of Engineering.

NuSil is a leading formulator of silicone compounds for healthcare, aerospace, electronics and other applications requiring precise, predictable materials performance. ISO 9001-certified since 1994 and AS 9100-certified since 2008, NuSil operates state-of-the-art laboratories and processing facilities in North America and provides on-site, in-person application engineering support worldwide.

Horizon Partners With EMQN to Minimize Variability in Cancer Diagnostic Testing

Horizon Diagnostics (HDx), a division of Horizon Discovery Limited, a leading provider of research tools to support the development and prescription of personalized medicines, recently announced it has signed a strategic partnership agreement with the European Molecular Genetics Quality Network (EMQN). Under the terms of the agreement, HDx will provide genetically defined human cell line reference standards for distribution to molecular diagnostic laboratories around the world as part of EMQN's annual External Quality Assessment (EQA) schemes to ensure sensitivity and reproducibility of diagnostic assays.

The reference materials provided by Horizon will contain known frequencies of mutations that currently guide the prescription of cancer therapies, and particularly melanoma, colon, and lung cancers. The reference materials will be distributed to participants in EMQN's proficiency testing schemes, which will be assessed for their ability to accurately test the samples and provide a clear and concise test report on the results.

Diagnostic EQA providers face significant difficulties in sourcing reliable reference materials for diagnostics testing, either from patient samples or immortalized cell lines, especially as increasing numbers of rare mutations are being discovered. Horizon's reference standards overcome this by reconstituting mutations of interest in human cell lines using its proprietary genome editing technology, GENESIS, and creating a defined wild type parental-to-mutant ratio in each sample.

"Quality assurance schemes, such as those organized by EMQN are essential to ensure that patients receive the correct treatment regimen based on their tumor mutation status," said Dr. Paul Morrill, Commercial Director, Horizon Discovery. "Horizon's technology offers pathologists and biologists an unprecedented level of control, and a resource for benchmarking the performance of assays against validated empirical reference standards. This is an invaluable component of patient care."

"The availability of Horizon's defined reference standards enables vastly improved proficiency testing across the diagnostics industry," added Dr. Simon Patton, Director of EMQN. "We look forward to working with Horizon on developing standards for the increasing number of clinically relevant mutations that are supported through our EQA schemes."

Spinnovation Biologics Predicts Biomanufacturing Success

With expertise and know-how in high-end analysis for biologics, Spinnovation Biologics recently announced the launch of a breakthrough solution -Spedia-Predict- for Bioprocess performance troubleshooting and performance prediction of bioproduction, at the annual Bioprocess International European meeting.

Spedia-Predict monitors and validates process-critical parameters as a company looks to manage the culture media consistency used in their production environment. Good Manufacturing Practice (GMP) and FDA Quality by Design (QbD) approaches demand close control, but traditional analytical methodology can be costly, time-consuming, and require sample preparation ahead of measurement. They also lack the ability to characterize chemically complex media. As a result, many companies monitor only a handful of components, failing to get the complete picture and missing information on how it will perform in scale-up.

Spedia-Predict rapidly profiles most constituents in a medium; it delivers quantitative data and can be applied equally to chemically fully defined or complex media. Spedia-Predict allows identification of markers that can correlate with performance of a specific bioprocess, and monitor batch-to-batch consistency, for example. As a result, it helps to prevent failure and performance variability in large-scale commercial production, by enabling efficient and cost-effective processes.

"Using Spedia-Predict, we help our clients to understand and monitor the factors that are most influential to their cell culture performance," said Dr. Frederic Girard, CEO. "This is a huge advantage. Importantly, we provide information early in production planning - effectively establishing a QC standard - which can then be used in routine manufacturing to reduce the risk of process failure, and increase the consistency in production performance. Risk factors are reduced and replaced with consistent, reproducible results."

Spinnovation's core expertise in Nuclear Magnetic Resonance Spectroscopy (NMR) and Mass Spectrometry (MS) to study molecules and materials is increasingly being applied in the biopharma production environment. The introduction of Spedia-Predict demonstrates the company's continuous efforts to develop and implement new analytical methods to meet most demanding industry requirements.

Comparitive Analysis

Fiat, Help Remedies, Drug Guarantees, Golf Courses

Part 3 of a 6-part series on lessons learned from other industries.

By: Derek Hennecke, President & CEO Xcelience LLC

Should you, too, be channeling the management spirit of Steve Jobs? If you haven't already considered the possibility, run, don't walk, to the bookstore. You are among the last to pick up or download Walter Isaacson's biography of Steve Jobs. Amazon's number one bestseller in 2011, the book is still number five on the New York Times Bestseller List. Managers everywhere are donning black turtlenecks and saying "one more thing" when introducing a new product.

I'm not going to tell you to simplify, focus, take responsibility from end-to-end, or remind you that, when behind, you should leapfrog. These may all be excellent strategies, but many of you have already read the book, or heard someone with a beer in one hand pontificate on it. I'm here today to remind you there are other companies out there besides Apple. Sometimes we learn from their outstanding successes. Sometimes from their tragic failures.

THE FIAT FLOP

Take Fiat. The Italian car company looked to the American market and saw an entire country infatuated with all things Italian. Italian clothing, Italian pasta, Italian gelato, Italian wine. Americans already adore Ferraris. Surely they would fall equally in love with a car already much-loved throughout Italy and rapidly conquering Europe?

"We thought we were going to show up and just because of the fact people like gelato and pasta, people would buy it," laments CEO Sergio Marchionne after the Turin-based automaker's disappointing launch of the tiny 500 subcompact. "This is nonsense."

Why did this cute little car so beloved on Europe's streets fall flat here? It wasn't like they just threw the car blindly into the world's largest consumer market. Teamed with Chrysler, the car was significantly re-engineered for Americans, including the all-important addition of cup holders. What could go wrong?

But there were other factors, which were apparently too big to overcome. Such as America's enduring love of large vehicles. No other car smaller than the Fiesta has ever succeeded in America before. The Fiat was, in this respect, an idea whose time has not yet come. Or maybe it just missed in establishing that illusive perfect combination of style/product/price. If all else fails, call it bad luck. Steve Jobs had some of that along the way as well.

HELP REMEDIES TO THE RESCUE

If luck comes in a liquid or a pill, then Help Remedies has been overdosing on it. Or maybe it just took a fresh eye from outside the industry to see what seems so obvious in this young company's wake.

Medical branding is full of confusing packaging, incomprehensible jargon, and products containing a myriad of drugs, leading consumers who combine medications to accidentally take too much. Overdoses of acetaminophen, a drug commonly used in combination-drugs, is the number one reason for a call to Poison Control.

Help to the rescue. Launched in 2008, Help Remedies offers single-ingredient, low-dose drugs with symptomatic titles. "Help: I Have a Stuffy Nose" gets you a plain white tablet with phenylephrine. "Help: I Have a Headache" buys you a bottle of acetaminophen. Plain, biodegradable white packages contain pills with no fancy colors or coatings.

Add to this simple recipe a dose of laughter, the best medicine. The back of Help's nausea medication touts the package's flavorless pills, then adds, "We were going to make them deviled-egg flavor, but then we thought it might defeat the purpose."

Google the home page of Help Remedies and you will find a whole list of solutions, from "Help: I've never been kissed" (solution: a screen opens with a particularly unattractive set of lips in slobbery motion and the instructions - place lips on screen), to "Help, I'm worried about the size of my [sex organ]" (I'll let you read that solution yourself).

Not an approach I've seen yet from J&J or Dramamine, but it's working. In 2011, Help rang up $4 million in sales, a respectable 1,000% increase over 2010. The company anticipates sales of $15 million this year.

Co-founder Richard Fine is the son of two medical professors in England. "Medicine's an entirely self-referential world filled with terrible communicators," he says. By cutting through the confusion, Help speaks directly to the reason the consumer is in the pharmacy aisle in the first place. It took an outsider to think of the obvious.

GUARANTEES FOR MEDICATIONS

You probably wouldn't dream of buying a computer without some kind of guarantee. When you buy a new car, you expect warranties. Would you pay for a new air conditioner and then just shrug your shoulders and buy another model if it failed to

cool your house?

Why is the pharma business any different? Every day consumers spend hundreds, or even hundreds of thousands of dollars just to try a medication that fails to work. Then they move on and try the next.

Sam Waksal, the notorious insider-trader whose scandal involving ImClone Systems (briefly) brought down Martha Stewart, put forth in a New York Times op-ed in March that patients and insurance companies should only pay when a drug works.

Mr. Waksal, still a major biotech investor, argues that slashing the high cost of drugs is not the answer to our rising healthcare costs. Instead, we need to pay for performance. Patients shouldn't be paying upward of $100,000 for a cancer drug that only prolongs life by a few months.

By paying only for drugs that work, he says we would incentivize drug companies to better understand what traits lead to a higher success rate, and what traits lead to more failures. The strategy would channel medical research away from the “me too” drugs, which more or less replicate what's already out there, and focus in on drugs tailored toward smaller groups of patients, often with a similar genetic marker.

Mr. Waksal suggests the FDA could assist in developing criteria, which might range from tumor shrinkage or survival in the case of cancer, to “sustained viral response” in the case of Hep C.

Detractors argue that with fewer paying customers, costs for those who do pay will spiral, with no net savings. Then there is the question of those in the gray areas - would those for whom success is less certain be

SIDEBAR

State of the Industry: Eli Lilly's Goes All In

In one of the most nail-biting moves in pharmaceutical history, Eli Lilly just went all in. And not with a pair of Aces, either. Company executives are eagerly awaiting clinical trial results from solanezumab, a late-stage Alzheimer's candidate that has many analysts watching over Lilly's shoulder shaking their heads. Lilly stands at the precipice of a patent expiration cliff. Fourth-quarter profits were down 27% from a year ago, and full-year profits down 14%, largely due to the expiration of the antipsychotic drug Zyprexa and chemo drug Gemzar. The antidepressant Cymbalta, which brought in one-fifth of last quarter's revenue, faces expiration in 2013, as well as Evista, for osteoporosis. These four drugs constitute nearly half of Lilly's total revenue in 2010. Other companies face similar cliffs, but most have a parachute. Lilly is not diversified. With no consumer or medical devices divisions to soften the blow, it feels every peak and valley of the pharma pipeline. Solanzumab is a monoclonal antibody that binds to soluble amyloid beta cells and then sweeps them out of the brain via the bloodstream. In so doing, this should block the formation of amyloid plaque, which is believed to kill brain cells and cause Alzheimer's. There are too many shoulds in this story. Amyloid plaque has not been proven to be the cause of Alzheimer's. Reducing plaque as a method is unproven. And Lilly doesn't hold all the cards: J&J, Pfizer, and Elan are also pursuing FDA approval for a competitor called bapineuzumab. Data for both drugs are expected in the third quarter of this year. As it is, CNS drugs are widely considered to be one of the most challenging fields in drug development. The mean clinical time for CNS drugs was 102 months between 1996 and 2010, some 40% longer than other drugs required. CNS drugs then took 20 months to gain approval, 13% longer than other drugs, according to the Tufts Center for the Study of Drug Development. On the bright side, however, Tufts says that the CNS drug pipeline grew 6% a year over the past 10 years, and is now responsible for 11% of all drug development projects around the world. If Lilly's big bet wins, solanezumab will be first into a market that could be worth as much as $14.3 billion by the end of the decade. If it loses, Lilly says it can weather the storm, having already reorganized, begun to lay off 5,500 workers, and announced no raises for employees in most countries in 2012. It also sites more than a dozen other late-stage drugs, including treatments for diabetes, cancer, and depression, all markets of significant size. Whatever the outcome, Lilly will still be in the game. It just may not be able to play at the high stakes table for quite a while.

denied treatment?

Like it or hate it, I believe it's a discussion worth having. Changing the incentives in drug development could have a profound effect on what research is performed. Whether you prefer this model or another one, we need to study the ways of directing research to where it is of the most benefit.

I see the gaps in our research in my everyday life. A friend of mine struggles with Crohn's. He's on nine different meds right now. There are almost no studies on the interactions between any of them. As his side effects multiply, his poor doctor is left to decide which symptoms are related to the medication and which to the illness. Then, as the doctor doubles this med and triples that one, neither my friend nor the doctor can possibly know with any degree of certainty what the outcome will be. And nobody is logging the results to help forewarn the next poor guy who finds himself in the same chemical soup pot.

Of course, for our industry, this or a similar incentivisation would also be a boon, as drug companies go back to the drawing board to better understand who benefits and who doesn't from existing drugs, and to unravel the web of drug interactions.

HEY BUDDY, WANNA BUY A GOLF COURSE?

If the market for golf courses is any indication, economic conditions are on the upswing. A golf course in 2006 would've cost you a hefty median price of $4.5 million, if you were looking. Today, you could buy that same 18-hole course for a mere $3 million, according to recent data from Marcus & Millichap Real Estate Investment Services. Donald Trump and luxury home builder Toll House are getting into the game.

The market for golf courses probably got a bit overheated during the Tiger boom years, when TV ratings would rise 50% every time Tiger Woods graced the screen at a tournament. Golf courses were popped up like divots on the fairway. Then the recession hit, General Electric's finance arm pulled its green out of golf course deals, and investors in commercial mortgage-backed securities followed suit in the midst of massive real estate losses.

"Lack of financing is really causing a discount to value, and investors are taking advantage," says Steven Ekovich of Marcus & Millichap. "Golf courses may never be as cheap as they are today."

Arguably the same thing is happening in biotech as big pharma sees the discounted rates available for early stage development, with record inflows in the fourth quarter of last year. Our industry may not have Donald Trump buying biotech or Tiger Woods drawing investors, but we can still look forward to basking in the glow of a game well-played, as we sit around the 19th hole when this recession is safely behind us. ◆

BIOGRAPHY

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 growth. 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 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.

Marketing Matters

Applying Social Media to Your Business

A multiple part series on effective messaging and communications in the life science industry.

By: David F. Scelba, Partner, LifeSciencePR

As the second column in our series, I will discuss a four-step social media practice I developed that will help every marketing professional in the Life Science and related industries. Using four easy-to-remember trilogies, your company will effectively and efficiently communicate with multiple audiences, strengthen your brand, and ultimately increase sales.

STEP 1

Step 1 is my 3E goals everyone should embrace regardless of the type of business they are in; however, this trilogy is especially important for emerging industries, especially Life Science. The 3Es stand for Entertain, Educate, and Engage your audience. I've said it before and I'll say it again. People's attention spans are becoming shorter and shorter each and every day, and content must be brought to life in an entertaining and memorable way. When you entertain, you can effectively educate and ultimately engage an audience. Statistically, video has proven to be the most effective tactic to achieve these goals.

STEP 2

Step 2 is my 3R formula that stands for Re-allocate, Re-purpose, and Re-distribute. Without increasing your overall marketing budget, simply Re-allocate a portion to re-purposing press releases, white papers, articles, and even ads into short video presentations. Then Re-distribute the videos to all of your social networks. More than two billion YouTube videos are viewed daily with the average person spending at least 15 minutes each day on the site. And now hundreds of millions of people view videos on their mobile devices, which are also hosted on YouTube and easily and quickly shared throughout the multiple social networks like Facebook and LinkedIn.

STEP 3

Step 3 is my 3I process that stands for Interest, Integrate, and Interact, which needs to be applied to all of your socials, website, and blog touch points. Creating an interest amongst your fans, friends, and followers is of the utmost importance. We all know content is always king, but incentives like seminars or promotions and mobile apps will also help drive traffic back to your website or blog. A seamless integration of all online touch points will ensure the opportunity of establishing key relationships with your targeted audience.

STEP 4

Step 4 is a constant that I refer to as my 3Ms, for Monitor, Measure, and Maintain. Online transparency provides the ability to constantly and consistently monitor not only your own social networks, websites, and blogs, but also your competitors. It is essential to regularly measure the effectiveness of your online communication tactics and adjust the activities and budgets accordingly. But other benefits of consistent monitoring are the ability to proactively enhance your brands integrity while protecting it against any possible online sabotage or harm.

I hope my four-step practice and simple trilogies help you to better apply social media for your business. As a final note, don't let the techies and so-called online marketing gurus confuse you. Data is data, and any professional marketing or business strategist is more than capable of interpreting the information and adjusting your social communication tactics and budgets to be the most effective and efficient they can be. ◆

BIOGRAPHY

David F. Scelba is the Founder and Chairman of SGW Integrated Marketing & Communications and is a Partner at LifeSciencePR. He is responsible for the development of the company's new interactive products and services and plays a key role as senior strategist for developing clients' integrated marketing communications programs. He is also involved in researching and investigating acquisition opportunities and for initiating negotiations on behalf of the company. As a consultant to the broadcast, computer, and telephony industries Mr. Scelba experienced the technology convergence first hand. This unique background provides him the ability to develop innovative products and services that generate the most cost-effective and efficient marketing strategies available today. His diversified B2B, consumer, and retail experience encompasses industries such as: automotive; biochemical; broadcast; education (K-12-colleges/universities); healthcare; hospitals; life science; microwave; pharmaceutical (research/drug delivery); political; professional video/audio; medical; telecommunications; and more. He is a keynote motivational speaker who's audiences include marketing professionals, college professors, MBA graduate students, and undergraduates seeking careers in the marketing- and communications-related industries. He also mentors business and government leaders on the use of technologically innovative tools for better communication with their targeted audiences. Mr. Scelba earned his BA and MA in education, a CFP Certification, with series 6 qualifications, Health/Life and Real Estate Licenses, which contribute to his common sense marketing philosophy.

ADVANCED DELIVERY DEVICES

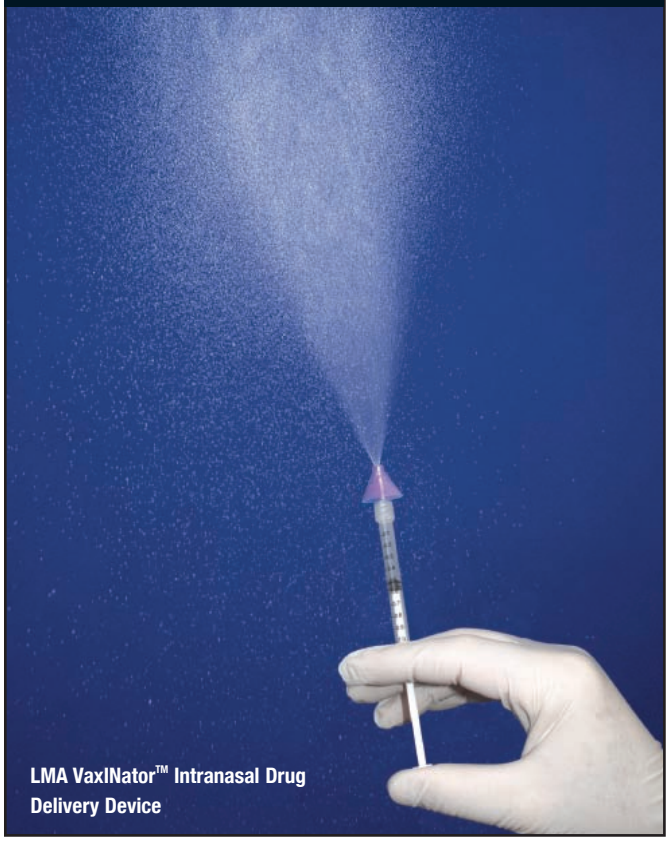
Intranasal Medication Delivery in Clinical Practice - Its Time Has Come

By: Tim Wolfe, MD

Intranasal drug delivery has crossed the threshold from an experimental delivery concept used by researchers to a clinically proven drug delivery modality poised to become a standard alongside traditional medication delivery methods, such as oral, intramuscular, and intravenous drug delivery. Crossing this threshold took a long time given that transmucosal medication delivery has routinely been used by medical personnel (ie, sublingual nitroglycerin) for decades and has been a common illicit drug delivery method (snorting opiates) for a millennium. The reasons for this slow adoption of intranasal medication delivery are likely due to the existence of well-established, effective drug delivery methods, such as intravenous and intramuscular injections combined with few drugs that have obtained regulatory approval for nasal medication delivery. In this author's opinion, the recent worldwide H1N1 influenza epidemic brought intranasal medication delivery to the attention of both medical providers and the broad public, exposing them to the insight that vaccines can be delivered via the nose. The fear of this disease led to a higher percentage of people seeking out immunizations than in previous influenza seasons, and many were treated with the intranasal vaccine. Another possible explanation for the growing acceptance of intranasal medication delivery by the medical community is the rapid increase in research studies showing the efficacy and ease of application of commonly used intravenous medications being successfully delivered intranasally in an actual clinical setting (as opposed to a research lab with volunteers).[1-5]

For many of us who have used intranasal medication therapy in our practices for decades, it is surprising how long it took for this concept to gain a tentative foothold in clinical practice. The advantages of intranasal medications are considerable and easily understood by practicing clinicians. They are easy to deliver, requiring almost no preparation and no need for an IV or exposure of a limb for injection. They are convenient, and in the proper clinical setting can significantly reduce nursing or doctor resource utilization and time by eliminating the need to start an intravenous line. Because their onset of action is rapid and they can be given to patients without an intravenous line, intranasal medications typically result in faster clinical improvement than injections.[4] Because intranasal medications do not involve a needle or an injection, they can be delivered by almost anyone, including the lay public.[3,6] Intranasal medications are also painless, an important feature when caring for children.[5] Finally, intranasal medications put the provider at no risk for needlesticks, making their delivery safer, and there are no issues related to disposing of a blood-contaminated sharp instrument.[7] All these features also make intranasal drug delivery a patient-satisfaction tool, an important issue in clinical medicine.

FIGURE 1



LMA VaxINator™ Intranasal Drug Delivery Device

This does not mean intranasal medications are a panacea. Many medications are not effectively absorbed when delivered via the nasal mucosa and clinical situations, such as epistaxis and rhinorrhea, can reduce absorption. Furthermore, many patients need an intravenous line for other clinical indications. Intranasal drug delivery will never completely supplant injections of medication, it simply offers another tool in the therapeutic armamentarium of the clinician that can be used in the appropriate clinical setting.

VACCINE DELIVERY

The promise of nasal drug delivery in public health is probably best demonstrated in its potential use for vaccinations of large populations. The nasal mucosa is the first line of defense against most microbes, and generating an immune response using nasal

vaccines rather than injected vaccines provides a broad immune protection leading to both mucosal and systemic immune responses, including antibody formation and circulating immune cells.[8] The delivery system is non-invasive, painless, and offers an option of vaccination to the many patients who suffer a strong fear of injections. Because no shot is required, the delivery system also does not need to be sterile, making manufacturing and distribution easier. Furthermore, due to the non-invasive delivery method, it does not require highly trained personnel to administer the vaccine and could theoretically be passed out to large populations for self-administration in an epidemic setting. Due to the lack of any needle and any blood contamination of the delivery device, the risk of provider needlesticks is eliminated, and the disposal of the administration device is much simpler and safer. The LMA VaxINator™ (Figure 1), a high-volume low-cost nasal atomization system developed by LMA Atomization™ offers other unique advantages. It has a unique patent-pending design that essentially eliminates dead space, allowing nearly complete delivery of all vaccine to the patient. It also has an auto-disabling feature (Figure 2) that prevents reuse so no patient cross-contamination can occur. Furthermore, the Vaxinator progenitor, MAD Nasal™ (Figures 3 & 4), has more than a decade of clinical use in millions of patients, validating the clinical efficacy of its nasal drug distribution.

FIGURE 2

VaxINator™ Auto-Disable Syringe Feature

Direct Targeting of the Brain - Proteins & Peptides for CNS Diseases: Another potential use for intranasal drug delivery is direct targeting of the brain with proteins and peptides useful for treating CNS diseases.[9] Many of these molecules do not cross the blood brain barrier and are therefor not amenable to delivery via oral or injection routes. However, the olfactory mucosa offers an option for some of these molecules to enter the brain via direct transport along the olfactory nerves (nose-to-brain pathway). There are still issues to overcome with this delivery method, including adjuvant combinations to improve absorption of these complex molecules, muco-adhesives to enhance absorption times, and devices designed specifically to targeting the olfactory mucosa rather than the respiratory mucosa. The MAD Nasal mucosal atomization devices offer some solutions to this final issue. Data using the MAD products show that both head positioning techniques or directed delivery using the elongated flexible stylet of some MAD designs can improve targeted delivery to the olfactory and other mucosal sites.[10,11]

Pain Control: Acute pain is a common symptom leading patients to seek medical care. Due to the broad diversity of illnesses seen, a variety of treatment options are required to individualize pain control appropriately. Sometimes an oral drug is appropriate, other times, such as situations like an acute fracture, minor burn, renal colic, or breakthrough cancer pain, a fast-acting pain killer is more appropriate. Although rapid pain control is appropriate, many of these patients rarely need an intravenous line for anything more than rapid pain control. Nasal opiates offer a non-invasive, painless method of treating acute pain that is equivalent in efficacy to an IV infusion of morphine sulfate, but due to no need for IV access, can be given to any patient with these symptoms immediately.[4,12] In fact, using nasal opiates results in faster onset of pain control than using injected opiates.[4] This application of nasal medications offers a huge opportunity for the pharmaceutical industry. In the US alone, there are more than 120 million emergency room visits per year, many for acutely painful conditions. A rapidly effective, titratable method of treating pain whereby the patient could obtain rapid pain control without the resource consumption, delays, and pain associated with intravenous therapy would be very useful in overburdened emergency rooms, ambulances, and hospice settings as well as in many clinics caring for patients with minor injuries and painful conditions.

Interestingly, time to delivery of pain medications is a new CMS reportable core measure for all emergency rooms in the US (Centers for Medicare and Medicaid Services - Outpatient prospective payment system: OP-21). In other words, reimbursement bonuses (or penalties) for care of these patients will be implemented requiring rapid and effective pain control. This new quality measurement offers a compelling reason for emergency departments to adopt intranasal delivery of pain medications because it has been clearly shown to reduce time to drug delivery and pain control.

Seizure Therapy: Seizures occur in about 3% of the population at some time in their life. Most seizures are brief and resolve rapidly. However, if they persist for more than 5 minutes, early termination with benzodiazepines is recommended because this leads to better patient outcomes.[6] Because

FIGURE 3

MAD Nasal™ Delivery Device

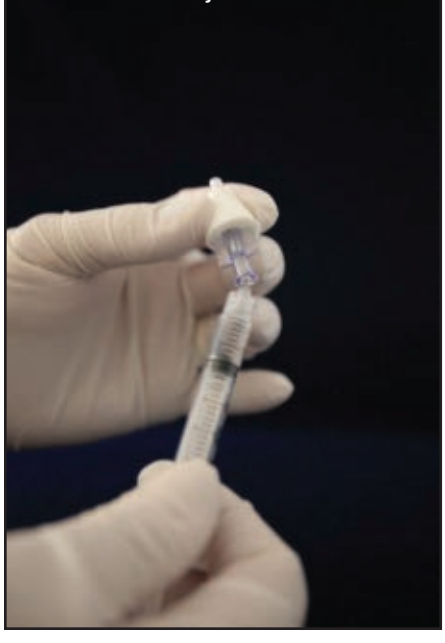
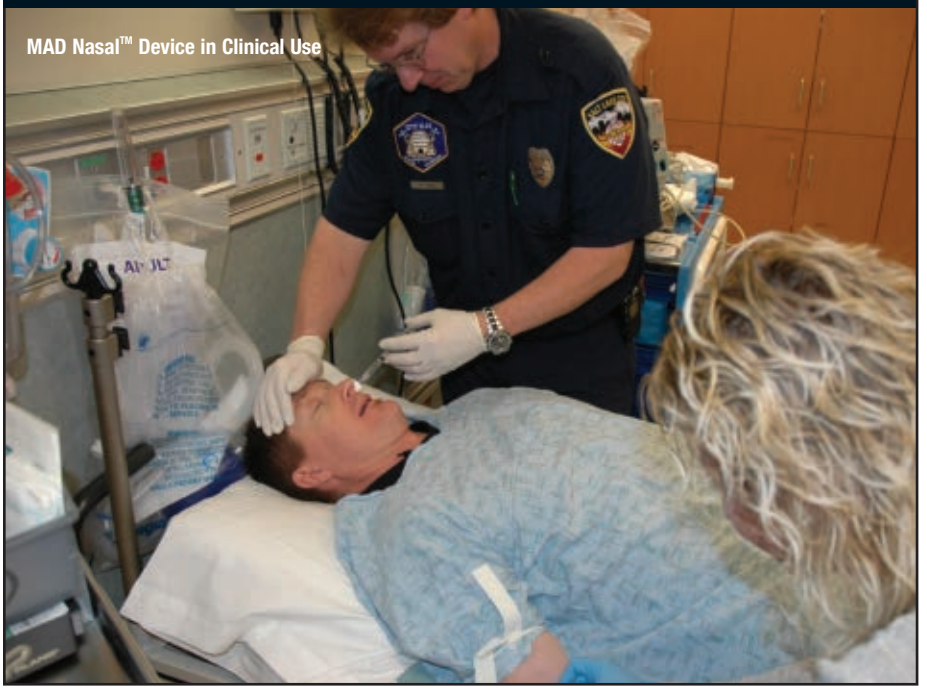


FIGURE 4



MAD Nasal™ Device in Clinical Use

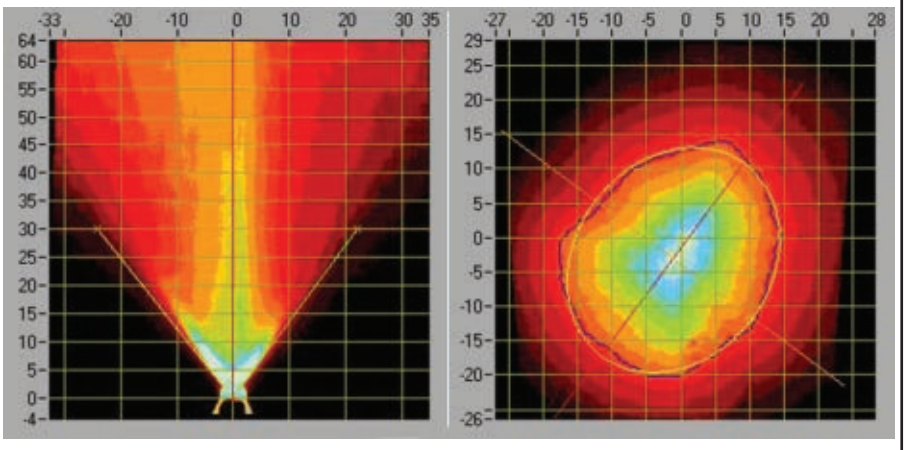
most prolonged seizures occur outside the hospital, it would be ideal to have the antiepileptic medication delivered by a family member, a caretaker, or by the first responder ambulance personnel. To accomplish this reliably (many lay people will not or should not give a shot), the drug must be available in a non-injectable formulation. Currently, transmucosal rectal diazepam is the first line outpatient therapeutic approach. Unfortunately, this treatment modality suffers from the downsides of relatively poor efficacy (compared to injections), variable bioavailability depending on how much of the drug is absorbed into the portal circulation, slower onset of action, and social non-acceptance that limits compliance with delivery.[13] Intranasal benzodiazepines offer an attractive and effective alternate option that is supported by extensive clinical research from around the world in settings including the home, third-world clinics, care centers, ambulance vehicles, and emergency rooms.[2,6,13] Many of these studies used the MAD Nasal as the delivery device due to the enhanced mucosal coverage it provides compared to simple syringe dropper methods. As more optimal concentrations of these medications are developed for nasal drug delivery, it is likely (if supported by additional research) that this route will displace most other methods for initial early treatment of status epilepticus.

SEDATION: Mild-to-moderate sedation can also be easily achieved with intranasal medications, such as benzodiazepines, dexmedetomidine, ketamine, and synthetic opiates. This non-invasive rapidly effective form of sedation is now used in a broad array of clinical settings ranging from preoperative, dental, emergency rooms, radiology, and ambulance settings.[5,14] While the level of sedation typically is not deep, the safety and limited need for intense monitoring makes this an attractive option in the appropriate clinical setting.

OPIATE OVERDOSE REVERSAL: According to the Center for Disease Control and others, opiate overdose deaths fueled by an increase in powerful prescription medications have surpassed motor vehicle deaths in the US.[3,15] This is an epidemic requiring an aggressive response both in terms of reassessing prescribing of pain medications and in providing methods to prevent death in many of these patients. One partially effective solution to this epidemic is layperson administered naloxone. Naloxone is an effective reversal agent for opiates with a high therapeutic threshold of safety. Naloxone is rapidly absorbed across the nasal mucosa and delivery via the intranasal route can be easily taught to the lay public. Numerous programs exist now that pass out concentrated naloxone along with a MAD Nasal to family members of patients deemed high risk for accidental opiate overdose.[3,15] In an effort to stem this flood of deaths in young adults, the FDA is staging a public hearing in the spring of 2012 to discuss making naloxone an OTC medication option.

OTHER OPTIONS: Numerous other medications are bioavailable when delivered via the nasal mucosa, but extensive clinical research is lacking on their overall efficacy. Interesting potential options include nasal glucagon for home use in diabetics, nasal hydroxocobalamin for cyanide toxicity occurring during a mass casualty, nasal antipsychotic medications to calm agitated patients, and nasal antiemetics for patients suffering from nausea and vomiting. Time will tell which of these therapies progress from the research arena to clinical practice.

FIGURE 5



VaxINator™ Plume Geometry & Spray Pattern

MUCOSAL ATOMIZATION DEVICES

Many of the clinical research studies discussed in this review used the mucosal atomization device (MAD) as the delivery system for their medication, validating the effectiveness and ease of use of this simple device.[5-7,10,11,14] Pharmaceutical companies looking for a validated nasal delivery system for new medications should consider this already proven technology in development strategies for single-dose nasal medication delivery. The advantages of the MAD and VaxINator™ technology for these applications are evident. The devices are simple and extremely reliable. There is no capital outlay for a complex drug delivery system, and there is very little probability of any malfunction. Due to the simplicity and reliability of MAD, they can be manufactured in high volumes at competitive pricing. The device has been used extensively in clinical practice in millions of patients across the world and is the delivery system used by a large number of clinical investigators due to its proven efficacy and dependability. Its current plume geometry is designed to deliver drugs to both the nasal mucosa as well as to the olfactory mucosa (especially if the head is properly positioned) allowing both system absorption and some direct nose-to-brain delivery. Plume geometry and spray pattern (Figure 5) adjustments are possible if desired.

SUMMARY

Intranasal medication delivery is no longer a concept limited to research. It has entered the consciousness of mainstream medical providers and will grow rapidly as they understand and recognize the benefits of this "new" medication delivery modality. Simple, effective, and proven delivery systems, such as the VaxINator and the MAD Nasal will assist in adoption of this new concept and may enhance the ability to distribute and sell newly developed nasal pharmaceuticals. ◆

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BIOGRAPHY

Dr. Tim Wolfe is an Adjunct Associate Professor of Surgery and Emergency Medicine at the University of Utah Health Sciences Center. He earned his MD from the University of Utah, Salt Lake City, Utah, in 1988. He practices emergency medicine in Salt Lake City, and he is the Medical Adviser for LMA atomization.

EXCIPIENT UPDATE

EXCiPACT™: A New International GMP & GDP Certification for Pharmaceutical Excipients

By: Frithjof Holtz and Najib Sehat, PhD

About a thousand different excipients are used in formulating medicines, making up, on average, 80% of each product. The excipients category includes a broad range of substances, such as antiadherents, binders, coatings, disintegrants, diluents, flavors, colorings, preservatives, and sweeteners, just to list a few.

Pharmaceutical excipients are substances that are included in a pharmaceutical dosage form to aid the manufacturing process; to protect, support, or enhance stability; or for bioavailability or patient acceptability. They may also assist in product identification and enhance the overall safety or function of the product during storage or use. Excipients represent a market value of approximately $4 billion, accounting for 0.5% of the total pharmaceutical market, according to industry experts.[1]

No longer characterized as inert additives to an active pharmaceutical ingredient (API), recognition of the need for stringent quality management of excipients is growing rapidly. Adding to this challenge is the fact that only a small percentage of excipients are manufactured solely for pharmaceutical use.

Pharmaceutical excipients clearly require stringent quality management and yet there is a lack of dedicated, binding regulation despite being major components of dosage forms and the possible hazard to patients.

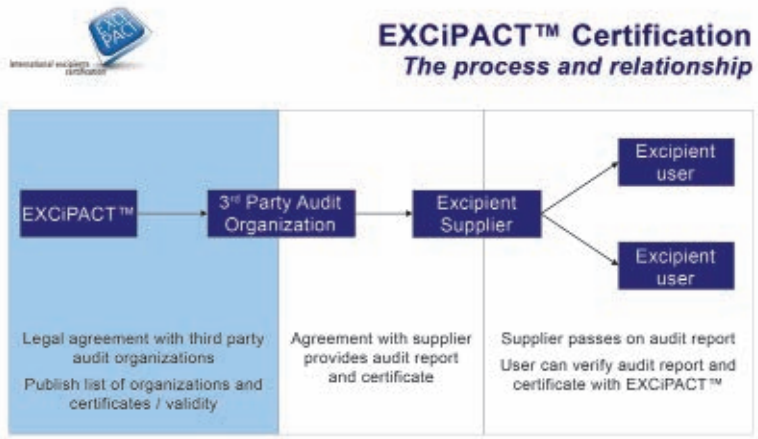
In 2006, at least 100 deaths were attributed to the presence of diethylene glycol in bottles of cold medicine prepared by the Panamanian government. What was believed to be 99.5% pure glycerin was not and had passed through multiple trading companies on three continents. An investigation by the New York Times revealed that in the course of the supply chain, a certificate attesting to the purity of the "glycerin" was altered, eliminating the name of the manufacturer and previous owner.[2] Information relating to the material's origin was erased. It was later found that the manufacturer was not certified to produce pharmaceutical-grade ingredients.

In 2010 alone, five drug recalls in the US that were due to dissolution failure were ascribed to excipients.[3] In one case, the FDA issued an advisory to drug and dietary supplement manufacturers warning of high levels of peroxide in the excipient crospovidone manufactured in China and issued an import alert.[4]

A number of industry standards with the aim to improve the overall quality of pharmaceutical raw materials have been developed in recent years. In the US, the recently introduced Drug Safety Enhancement Act includes the following parameters:[5]

- Establishment of registration for excipient manufacturers
- Failure to have an effective quality system would deem the drug "adulterated"
- Quality systems would encompass management responsibility and an internal and independent quality unit
- Risk management and supply chain management

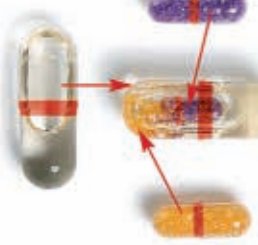
FIGURE 1



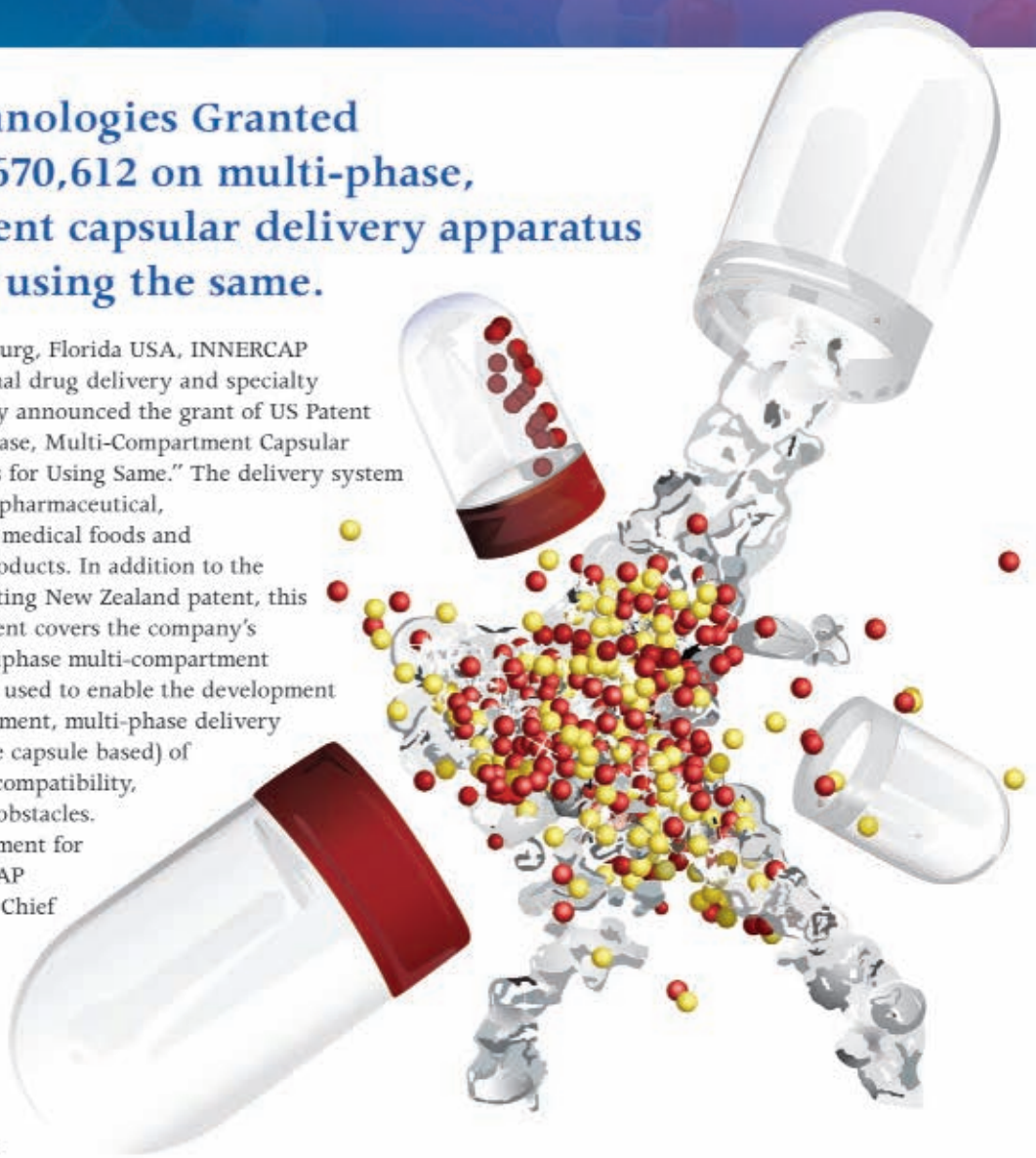
The EXCiPACT™ Certification Process

THE ADVANTAGES
OF MULTI-PHASE, MULTI-COMPARTMENT CAPSULES ARE CLEAR

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



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



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

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

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

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

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

INNERCAP® TECHNOLOGIES, INC

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

9216 Palm River Road, Suite 203 • Tampa, FL 33619 USA • (813) 837-0796 • www.innercap.com • busdevelopment@innercap.com

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Inspections for drug product and API would occur once every 2 or 4 years, and inspections of excipient manufacturers "may occur." Inspection of foreign sites would be on par with inspection of US manufacturing sites.[5]

The EU has included pharmaceutical excipients in the recent amendment of Directive 2001/83/EC. Despite these efforts, there are no binding regulations for excipients. Further complicating matters is the fact that excipient safety requirements may differ from country to country.

Excipient suppliers shall be able to demonstrate their process for manufacturing and handling of pharmacopeia-grade materials is appropriately and consistently controlled. Adding to this requirement is the need to have complete control over supply chains that are becoming longer and more complex.

TABLE 1

Guiding Principles	Products
International A pharmaceutical excipient manufacturer's certification should have the same acceptance and value anywhere in the world **Inclusivity** The scheme will provide quality standards and be applicable to all pharmaceutical excipients **Accessibility** The scheme should be accessible from as many 3rd party auditing organizations as possible **Evolution not Revolution** Builds upon existing best practices, guides and standards **Simplicity** The overall scheme should be as simple as possible	• Approval and qualification of third party audit companies using the EXCiPACT™ certificate • Excipients GMP annex to ISO 9001® • Excipients GDP annex to ISO 9001® • Requirements for auditor competency and third party organizations providing certification **Services** • Oversight of pharmaceutical excipient manufacturer and distributor certification • Auditor competency development and qualification • Comprehensive website with certification status, including data on compliance

Summary of EXCiPACT™ Guiding Principles, Products & Services

THE LAUNCH OF EXCIPACT™

With proposed legislation requiring current good manufacturing (cGMP) and current good distribution practice (cGDP) for excipients in Europe and the US, excipient suppliers will be faced with new requirements for quality audits and related requests to ensure their facilities and products are in compliance.

In response to more stringent regulation, excipient suppliers, distributors, and the pharmaceutical industry recently came together to renew and formalize their commitment to control the use of high-quality excipients throughout the supply chain and ensure this through self-regulation.

Industry experts from the European Fine Chemicals Group (EFCG), the International Pharmaceuticals Excipients Council (IPEC) Europe, IPEC Americas, the European Association of Chemicals Distributors (FECC), and the Pharmaceutical Quality Group (PQG), have created EXCiPACT™, a voluntary, international certification scheme to provide for independent, third-party certification of manufacturers, suppliers, and distributors of pharmaceutical excipients as a means of ensuring patient safety while minimizing the overall supply chain costs. These parties are in agreement that an international pharmaceutical cGMP and cGDP certification scheme is one of the tools that help ensure the quality and reliability of these key ingredients for medicinal products throughout the supply chain (Figure 1).

EXCiPACT was launched early in 2012 initially targeting the European and North American markets with other interested countries following as soon as possible afterward. In short, the mission is that EXCiPACT becomes the preferred global standard for pharmaceutical excipient manufacturers, suppliers, distributers, and regulators. The organization's guiding principles, products, and services are summarized in Table 1. The EXCiPACT certification scheme is the industry response to help mitigate the risks by addressing the auditing challenge. EXCiPACT will ensure cGMP and cGDP requirements are applied to pharmaceutical excipients through a recognized auditing and certification process, thereby increasing safety and reliability as well as transparency of the pharmaceutical supply chain.

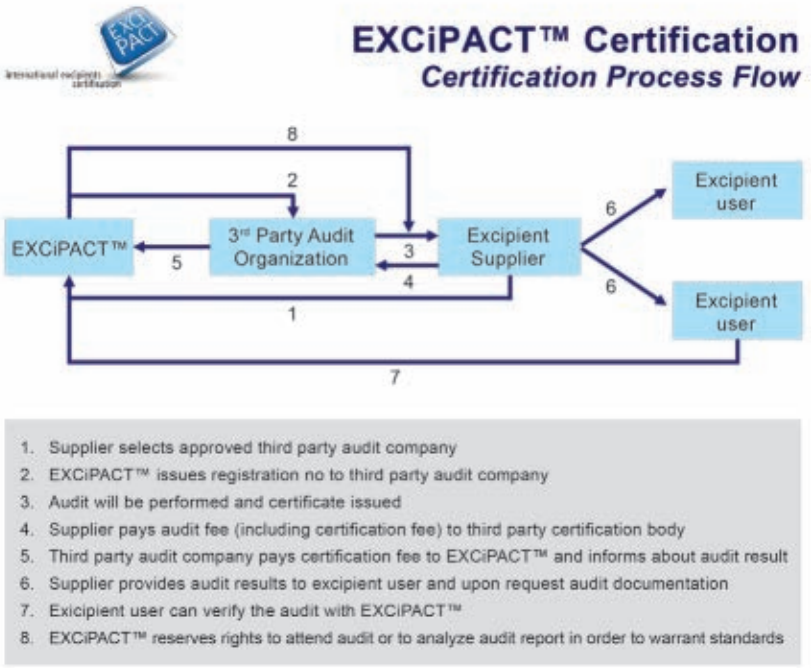
As an independent organization, the EXCiPACT Association, based in Brussels, will be able to objectively set cGMP and cGDP standards today and in the future. The organization will also define third-party auditor competency and training requirements. Establishment of certification scheme rules for third-party audit organizations results in an EXCiPACT certificate for pharmaceutical excipient manufacturers (cGMP) and distributors (cGDP) (Figure 2). This certification will provide a cost-efficient method of ensuring cGMP and cGDP are applied throughout the pharmaceutical supply chain. Certifying bodies, certified auditors, and qualified organizations will be listed on the EXCiPACT website (www.excipact.org).

EXCiPACT standards will act as annexes to ISO standards 9001, 19011, and 17021, and organizations already ISO certified will find it very effective to extend their ISO certifications to these cGMP and cGDP standards. Alternatively, suppliers who do not hold ISO 9001 certification will be able to obtain an equivalent certificate through the forthcoming US national standard (ANSI-NSF 363), which also is based on the IPEC-PQG Excipient GMP standards. All suppliers will therefore have the choice of which certification route to follow. In either case, the requirements will be the same.

EXCIPACT™ BENEFITS

The EXCiPACT certification scheme permits the excipient supplier to proactively demonstrate a commitment to GMP and GDP in the manufacture and supply of their

FIGURE 2



The EXCiPACT™ Certification Flow

product. The certification audit can be proactively planned and scheduled by the supplier, and the certificate and audit reports can be shared with the user at an early stage of a business relationship.

Figure 3 summarizes the expected cost savings for excipient suppliers and users. The overall ISO 9001 and EXCiPACT or ANSI audit will typically require from two to six full-time employee days. The cost for the audit will be at the third-party certifying body rate (typically $2,000 per day, per person); approximately $13,500 per plant. The EXCiPACT association charges a certification fee of $7,500 with the certificate being renewed every 3 years. Annual surveillance audits will require 2 to 3 days and cost approximately $6,500 per year. The total cost is expected to be $40,000 over a period of 3 years.

The middle column of Figure 3 summarizes the expected savings to excipient suppliers. If EXCiPACT certification saves at least one 2-day audit per month (plus 1 day for preparation/corrective and preventative action - CAPA; a conservative assumption), the cost-savings results would be:

- 36 work days ($950/d) a year (about 15% of working year), which could equate to $33,500 total personnel cost
- $6,500 travel expenses (potentially) if the representative has to travel to other company locations to host the audit
- The total savings to the excipient supplier over the course of 3 years would be $80,000.

The right hand column of Figure 3 summarizes the benefits to the excipient user. If EXCiPACT certification saves at least one 2-day audit per month, (plus 3 days for travel and preparation of the report; again, a conservative assumption), the cost-savings results would be:

- 60 work days ($950/d) a year (about 30% of working year), which could equate to $56,000 total personnel cost
- $24,000 in travel expenses
- The total savings to the excipient user over the course of 3 years would be $320,000.

EXCiPACT is a joint initiative of the excipient supplier industry and excipient user. It addresses three of the currently most critical challenges for these industries: quality of medicines, risks in the supply chain, and the cost ensuring all this, particularly with regard to the burden of audits. For Merck Millipore, as a supplier of pharmaceutical excipients, joining EXCiPACT has been a logical step. For a long time, we have been addressing the risks in the pharmaceutical supply chain but feel the lack of mandatory application of cGMP for pharmaceutical excipients limits our efforts to improve patient safety. EXCiPACT is filling this gap and helps level the playing field. EXCiPACT is setting clear standards that will improve quality of medicines that can be reached with appropriate efforts. Therefore, we strongly support EXCiPACT as we are sure to be on the right path with this initiative.

Third-party auditor training began in January 2012, and the contracts with third-party auditing organizations are under negotiation. A pilot study will follow in the second quarter of 2012 to complement the overall launch process.

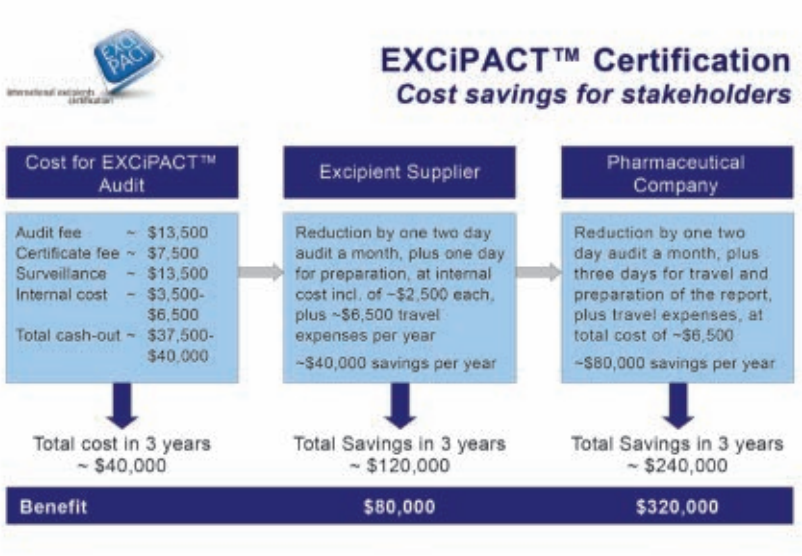
SUMMARY

The risks associated with pharmaceutical excipients have been underestimated in the past. Making up perhaps 80% of a final dosage form, the quality of excipients should match the quality expected for APIs. Once manufacturers of excipients, manufacturers of final drugs and regulatory authorities align with a common standard as the basis for manufacturing and handling of excipients, drug quality and patient safety will improve.

EXCiPACT reflects the commitment of pharmaceutical excipient designers, manufacturers, suppliers, distributors, and users to achieve this much-needed vision. EXCiPACT incorporates the following features to deliver higher quality excipients:

- International: Enables a pharmaceutical excipient manufacturer and distributors certification to have the same acceptance and value anywhere in the world
- Ease of Access: Certification from many third-party audit organizations
- Evolutionary: Builds on existing ISO 9001 certification and uses well-

FIGURE 3



Estimated Cost-Savings Offered by EXCiPACT™ for Excipient Suppliers & Users

known IPEC-PQG GMP and IPEC GDP guides

- Simple: Easy to understand and apply for all stakeholders
- Inclusive: Applicable to all pharmaceutical excipients manufacturers and distributors
- Supplier Commitment: Permits the supplier to proactively demonstrate commitment to cGMP and cGDP in the manufacture and supply of their pharmaceutical excipients

As industry organizations and regulatory authorities evolve toward more stringent regulations, the international EXCiPACT approach to pharmaceutical excipient cGMP and cGDP certification will help ensure the quality and reliability of these key ingredients for medicinal products throughout a supply chain that can stretch around the world.

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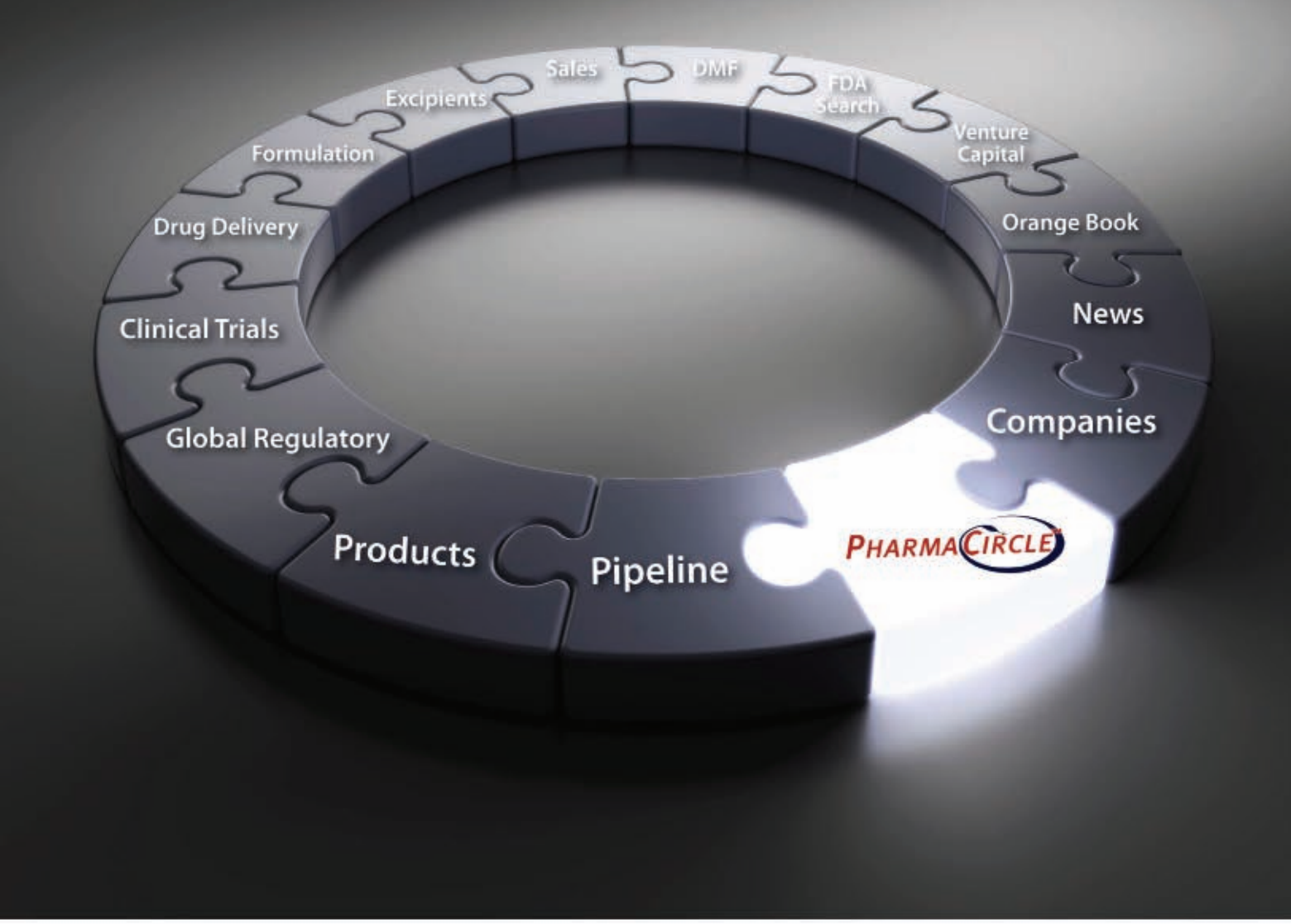
BIOGRAPHIES

Frithjof Holtz is a biologist and has been working for more than 20 years with Merck, having a long year experience in quality assurance and regulatory affairs. As Director of Advocacy, he is responsible for the advocacy activities of the pharmaceutical raw materials business of the Merck KGaA Division, Merck Millipore. Mr. Holtz is an active member of several international industry associations and industry initiative as IPEC (Vice-Chair IPEC Europe), EFCG, APIC, Rx-360, and EXCiPACT.

Dr. Najib Sehat is Director for Regulatory & Technical Services at Merck Millipore. He has been with Merck Millipore for over 13 years and has held various leading positions of increasing Regulatory responsibility in various Merck Chemical Divisions. Prior to joining Merck, Dr. Sehat gained experience at Hamburg University where he focused on research. He then held positions at the German Health authority (Hygiene Institute in Hamburg) and the US Food and Drug Administration (Washington DC). He earned his PhD in Food Chemistry and has published in his academic career 22 peer-reviewed journal articles, 19 abstracts, and 3 textbook chapters on various topics (ie, Food Chemistry Encyclopedia, New Techniques and Applications for Lipid Analysis) as well as several interview publications (CHEManager Europe, Pharmaceutical Technology). He is a member of various professional organizations, such as IPEC Europe, IFT (USA), German Chemical Association, Board of Director for the Rx-360 Consortium, and Global Steering Committe of EXCiPACT.



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SPECIAL FEATURE

Prefilled Syringes – A Container of Choice for Pharma

By: Cindy H. Dubin, Contributor

The total syringe market (disposable and reusable) could reach $11.8 billion by 2017, with much of that being stimulated by the prefilled syringe sector (a group that includes prefilled pen injectors, auto-injectors, and needle-free injection devices). According to Global Industry Analysts Inc., prefilled syringes are finding increased use due to their ability to eliminate risk of cross-contamination, and other risks, such as that of drug counterfeiting and dosing error, that may occur with ampoules or vials.

A report by London-based business information company Visiongain, Pre-Filled Syringes: World Market Outlook 2011-2021, predicts world prefilled syringe technology revenues will reach $3.9 billion in 2015, up from $2.7 billion in 2010. Expansion of the prefilled syringe market will be dependent upon developments in syringe technologies and materials. Improvements to performance, product stability, convenience of use, and cost-effectiveness will stimulate increasing use of prefilled syringes and related devices this decade. Increased volume and viscosity-handling capabilities and launches of devices that are easier to use are already benefiting sales of the devices and filled products.

According to the report, "The advantages are great with prefilled syringes taking over from traditional formats. Prefillable syringes constitute one of the fastest growing markets in the drug delivery and pharmaceutical packaging industries."

Drug Development & Delivery recently interviewed leading players in the prefilled syringe market to find out about their product or service offerings and how they are addressing pharma's needs for safety, ease of use, cost, and product differentiation.

ALTHEA TECHNOLOGIES–CRYSTALLIZED PROTEINS CREATE PATIENT-FRIENDLY DOSAGE & DELIVERY

Althea is a contract development and manufacturing organization that specializes in cGMP manufacturing, analytical development, aseptic filling into vials and syringes, and protein delivery technology for recombinant protein and parenteral products. Althea's Crystalomics® technology produces highly concentrated crystallized therapeutic proteins in suspension, creating a product with a more patient-friendly dosage and delivery format. Crystalomics' improved product profile comes without creating a new biological entity.

Crystallized proteins are a new state of the same molecule, albeit with improved stability and increased half-life. Once dissolved in the subcutaneous space, the therapeutic protein is identical to the protein in solution. Crystallization does not change the biochemical, structural, or

FIGURE 1

Syringes that can be filled on Althea's large-scale high throughput syringe line for clinical to commercial development.

in vitro characteristics and behavior of the protein. Therapeutic proteins in solution and in crystals are considered different formulations of the same biological entity. This makes crystallization technology an ideal platform for producing BioSuperior therapeutic properties. Superior second-generation biotherapies can be produced using the same biological entity, the same biological target, and the same disease indications. First-generation biotherapies can be reformulated to give demonstrable patient benefits covered under new intellectual property.

Crystallized proteins can be formulated up to 350 mgs/ml, allowing the conversion of low-concentration IV infusions, typically administered in a hospital or doctor's office, to subcutaneous injections that can potentially be administered by the physician or patient at home. The crystal formulations have low viscosity, allowing use of 29-guage or narrower needles, limiting patient discomfort. Additional technology allows for increased serum half-life of short-lived proteins, decreasing the dosing frequency from daily to weekly injections, and increasing patient convenience and compliance.

According to Althea President Rick Hancock, Althea spent the past year addressing the industry's rapid movement to prefilled syringes. For instance, as the industry trend is to move into a prefilled syringe earlier in the drug development cycle, Althea offers small-scale prefilled syringe filling for stability studies and small clinical trials through large-scale high throughput for commercial supply.

There are also industry concerns about glass delamination, breakage in secondary devices, and biologic product compatibility, which have sparked an interest in polymer syringes. To meet this need, Althea is filling polymer syringes on its small-scale, semi-automated line and is developing a strategy for filling polymer syringes on a large-scale automated filling line, explains Mr. Hancock.

FIGURE 2

Syringe filling at Baxter's BioPharma Solutions' facility.

"It appears to us that more products are moving from vials to prefilled syringes, especially in the generic biologics arena," says Mr. Hancock. "This can be a fairly easy differentiator if the innovator product is a vial fill."

BAXTER'S BIOPHARMA SOLUTIONS–ADDRESSING DIFFERENTIATION & ENHANCING COMPLIANCE

As the prefilled syringe market matures into an established approach for enhancing patient compliance in alternate settings, and acts as a delivery differentiator, Baxter's BioPharma Solutions business has responded with a variety of packaging options, including prefilled syringes, cartridges, and flexible containers for IV infusion. All these configurations are designed for ease of use, reduction in medication errors, and improved compliance.

"The need to move from hospital to alternate care settings (such as home use) has driven the industry toward user-friendly devices, such as prefilled syringes and cartridges," says Mahesh V. Chaubal, Senior Director, Drug Development, Baxter's BioPharma Solutions. The company has the automated assembly to configure the syringes with safety devices, such as BD Preventis™, which is an automatic needle-shielding system designed to prevent needlestick injuries.

In addition to improving syringes for patients, pharma companies see prefilled syringes as a way to set themselves apart.

"The pharmaceutical industry continues to move toward developing differentiated products, and often this differentiation is achieved via delivery devices," says Mr. Chaubal. "Prefilled syringes are becoming a conventional approach of enhancing user friendliness of a therapy, allowing for use in alternate settings (such as home). Differentiation is also expected to be a driving factor for biosimilars given that the recent FDA guidance for biosimilars appears to be cognizant of the need for such devices. We work with pharmaceutical and biotech companies to address their specific needs."

Speaking of the FDA, Baxter has seen increased scrutiny from the regulatory

agency with respect to the functionality and functional testing of prefilled syringes. In response, Baxter has developed expertise for functional testing of syringes. Responsiveness to customer needs also drives enhancements at Baxter.

"One example is that we have developed capabilities to fill syringes online with completely disposable equipment to help alleviate the concerns for cross-contamination, and we have developed and validated rigorous cleaning procedures, which may be challenging for certain drug families," explains Mr. Chaubal.

Baxter's BioPharma Solutions fill/finish facility in Bloomington, IN, is amenable to multiple compendia products and has successfully passed inspections from health/regulatory agencies all over the world.

"Recognizing the need for stringent in-process controls, we have developed 100% automatic inspection capabilities on our prefilled syringe lines," he says. "We have high-speed lines that can process several hundred syringes per minute. We have also developed cold chain processing on some lines to accommodate drug molecules that are labile and need such protection during processing."

CATALENT PHARMA SOLUTIONS–BIOLOGIC DEVELOPMENT & FORMULATION

Catalent offers a diverse range of prefilled syringe products, specialized manufacturing capabilities, and innovative self-injection solutions such as auto-injectors. Its syringe-filling capacity is more than 175 million units, and their facilities are designed for the growing biopharmaceutical market demand.

Mike Riley, Vice President, Strategy for Medication Delivery Solutions, Catalent Pharma Solutions, says that he sees two drivers in the prefilled syringe market. First, he believes prefilled syringes will continue to be a key delivery form for injectable products, driven by the strong drive toward patient self-administration, improved safety and compliance, and dosing precision, particularly for higher value products like biologics.

"We see prefilled syringes as a key piece of a growing suite of Catalent technologies that will allow us to bring better treatments to market faster for our clients," he says.

Second, due to the growing pipeline of biologic therapies, Mr. Riley sees an increased demand for more sophisticated formulation and process development capabilities, as well as specific handling and storage (including cold chain management).

"At Catalent, we are building on our capabilities for biologic development and formulation, combined with our globally approved prefilled syringe capacity, and are continuing to invest in specific handling capabilities for these complex injectable products in order to provide a differentiated solution to our customers."

MEDPRO SAFETY PRODUCTS, INC.–TURNING PREFILLED UPSIDE DOWN

MedPro has been focused on protecting healthcare professionals through innovative product design. The company introduced a platform of blood collection devices that offer the highest level of needlestick protection for the healthcare worker, with safety shield activation that occurs automatically to prevent the worker from being stuck with a contaminated needle. More recently, MedPro launched a drug delivery platform that has improved needlestick protection features.

MedPro's Prefilled Cartridge can be used with its Safety Injection Syringe to automatically protect the healthcare worker and increase patient safety over a typical vial delivery procedure, as well as decrease

FIGURE 3

Diverse range of prefilled syringe offerings by Catalent Pharma Solutions.

the chance of contamination due to the reduced number of steps required for administration.

"All of these devices lead to time-savings for the nurse, which is also important," says Garyen Denning, Executive Vice President, MedPro Safety Products, Inc. For IV delivery, the same prefilled cartridge is used, made of Type 1 glass or plastic, while the luer connection remains plastic. "This helps to alleviate common concerns we see with glass luer tips breaking or having compatibility issues in the marketplace."

The need for better needlestick protection devices and plastic IV delivery are two issues MedPro has chosen to focus upon with regard to syringes.

"With EU needlestick protection regulations taking effect in May 2013, both the US and EU are now on the forefront of needlestick protection and providing easy-to-use solutions to the healthcare worker," says Mr. Denning. "We also see higher demand for non-glass luer connections for IV delivery, and the vast majority of prefilled syringes today are still glass, which creates opportunity for products

such as our IV Shuttle."

Glass as the primary container is critical to most drugs today, due to the cost of the copolymer or lack of stability history, thus Mr. Denning believes that MedPro's IV Shuttle meets the needs of glass as the primary container, while maintaining a plastic luer tip for connection purposes.

"At MedPro, we have taken the prefilled syringe and turned it upside down. We believe in the cartridge as the primary container. This eliminates concerns of tungsten you may find with staked needles and is a proven primary container. Our technology allows for the cartridge to be used with needlestick safety or IV delivery just as prefilled syringe would," he says.

MedPro has also announced a ready-to-fill cartridge solution, which allows pharmaceutical companies with prefilled syringe lines to adopt the technology, as well as those who have cartridge-filling capabilities.

Mr. Denning says, "By turning the prefilled syringe upside down, we offer the cartridge as a stable primary container that does not introduce new variables to the pharmaceutical product. When paired with our safety skin-injection device, the product offers the highest level of safety on the market. Our safety shield activates automatically, without user intervention, during the injection. Safety devices available today require the full dose to be administered and often times require the user to use additional force to activate some type of safety mechanism. Our technology protects the user automatically during the injection, not after."

Broadening its focus a bit this year, MedPro turned to the growing field of biologics and is working on ways to deliver highly viscous drugs safely and efficiently.

"Our cartridge is a stable primary container for these types of drugs, and because nearly all of them are delivered via skin injection, it is a compelling story for our drug delivery platform."

With respect to syringes in general, Mr. Denning believes pharmaceutical companies are looking to the prefilled syringe as a delivery solution now more than ever because of the benefits that are well known: time savings and medication error reduction. At the same time, the fill-finish capabilities, compatibility concerns, and costs continue to be driving factors in life cycle management.

"Our technology addresses those three concerns by offering a ready-to-fill solution or cartridge filling, using a standard cartridge, and having an attractive economic value proposition against the competition," says Mr. Denning. "Separating the primary container from the safety syringe allows us to do just that."

UNILIFE–A PORTFOLIO OF DEVICES FOCUSED ON SAFETY & USABILITY

Industry reports cite market demand for prefilled syringes growing by more than 1 billion units throughout the next few years. Much of this demand is being driven by the launch of new prefilled drugs that will be launched in competitive therapeutic classes. The use of standard commodity-type prefilled syringes is no longer considered enough to generate brand differentiation. There is an increasing market focus on the selection of prefilled syringes and associated devices such as auto-injectors with unique market-leading features that can set a drug apart and improve therapy compliance.

Marking its place in this market, Unilife has announced the rapid diversification of its proprietary portfolio of device technologies this year. At the leading edge of this portfolio is Unifill, a prefilled syringe with USP-compliant materials within the primary container and fully integrated safety features. The company has also developed drug reconstitution delivery systems, such as the EZMix that are highly intuitive, and can minimize steps of use. The AutoInfusor platform has been developed to serve as a wearable disposable delivery system for large-volume doses between 3 mL and 15 mL. The development of a range of highly compact auto-injectors with true end-of-dose indicators was also announced this year. Rounding off the portfolio of devices is a series of specialized technologies for the delivery of novel drugs. Any of these devices can be tailored to address specific customer, formulation, or patient needs, explains Stephen Allan, Vice President, Marketing & Communications, Unilife.

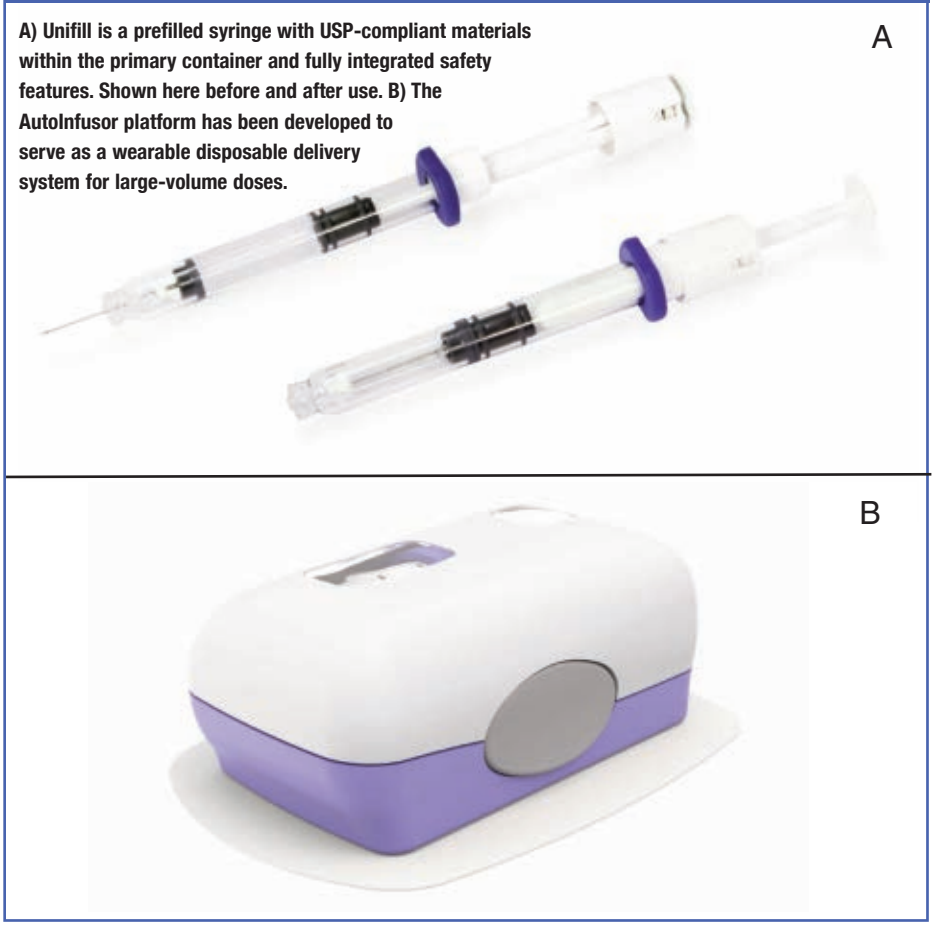
"It's not just our products that are differentiated from others in the market. It's the long-term integrated way in which we go about creating market-leading drug-device combination products with our pharmaceutical partners," he says. "Our mission is to develop innovative, differentiated device technologies that can enable and enhance the commercial success of our customers' injectable

FIGURE 4

By using a standard cartridge as the primary container, MedPro can offer needlestick protection for the healthcare worker, increased patient safety, and easier adoption by pharmaceutical companies.

FIGURE 5 A&B

A) Unifill is a prefilled syringe with USP-compliant materials within the primary container and fully integrated safety features. Shown here before and after use. B) The AutoInfusor platform has been developed to serve as a wearable disposable delivery system for large-volume doses.



therapies. We have the operational capabilities, expertise, and diversified portfolio to serve these customers across relationships that can begin during the early clinical development of their drugs and span the entire commercial lifecycle."

There are a series of converging market trends for injectable drug delivery. The complexity of biological molecules is driving demand for better quality, reliability, and flexibility within the primary container. Many biologics must also either by lyophilized or supplied in a liquid stable format in dose volumes larger than 1 mL. This is driving rapid demand in particular for intuitive drug reconstitution delivery systems and a new generation of wearable pump delivery systems.

"Combine these specific formulation needs with market trends for patient self-administration and needlestick safety, and you have a situation in which rigid commodity devices are becoming increasingly unable to address emerging customer needs. Our portfolio of device technologies is positioned to serve pharmaceutical and biotechnology customers with specific delivery requirements for their injectable molecules," says Mr. Allan.

When it comes to material selection for primary drug containers, Unilife customers desire flexibility in the supply chain. Unilife uses an open architecture model where we can source component materials from a range of established suppliers.

"For needlestick safety, we have identified a growing dissatisfaction among healthcare workers and their patients in the use of prefilled drugs that put the onus for protection on them. We are responding to their needs with highly intuitive devices with fully integrated, automatic safety features that can virtually eliminate the risk of needlestick injuries," says Mr. Allan.

No matter the drug or the device, the goal is to develop the right device to deliver the right drug at the right dose to the right patient. As the primary interface between the drug and the target patient, the safety and simplicity of a device has a direct impact on optimizing therapy compliance and reducing healthcare costs.

Mr. Allan says, "When a pharmaceutical company has access to innovative, highly differentiated devices, they are in a strong position to leverage these advantages for the combination product and build market share against their competitors. This is the core value proposition that Unilife can provide to pharmaceutical customers seeking innovative device solutions that can help generate powerful brand differentiation for their injectable drugs and vaccines."

VETTER FILLING PRE-STERILIZED SYRINGES

As a contract development and manufacturing organization (CDMO), Vetter responds to the needs of its customers from the early development stage of drugs to long-term commercial production. For example, the company created a facility for secondary packaging to meet the growing demand for administration devices, like auto-injectors, pens, and other safety devices.

"Vetter understands prefilled syringes are complex products–technically challenging and expensive to develop," says Peter Soelkner, Managing Director of Vetter. "Thus, the company's state-of-the-art filling lines as well as manual and fully automatic visual inspection enable high safety of the products."

Prefilled syringes are gaining greater significance on the vaccine market. The global vaccine sector is experiencing an upswing due to progress in scientific research. And because of more comprehensive biotechnological research and development, many new substances are

being developed. The prefilled syringe is a way to meet multiple targets, such as superior dosing accuracy, reduced substance loss, and greater user convenience.

"Vetter has anticipated this dynamic market trend and therefore, decided to build a high-performance line for filling pre-sterilized syringes," explains Mr. Soelkner. "The line is especially designed for vaccines, and will allow for a large output. Because the vaccine market requires that a large number of doses be made available quickly, speed is essential."

In the past year, Vetter and its preferred partner, West Pharmaceutical Services, have collaborated to provide customers with the ability to source 1 mL-long Daikyo Crystal Zenith® insert needle syringes. Investments in filling capabilities have been made at one of Vetter's facilities in Germany and at a new Chicago facility. Capabilities will initially exist for early phase clinical filling in Germany. Options for commercial-scale filling will be available.

"Vetter will be the first CDMO to offer filling of 1 mL-long Daikyo Crystal Zenith insert needle syringes in its portfolio," says Mr. Soelkner. "These syringes have been developed by Daikyo Seiko specifically to meet the needs of sensitive biologic products, and eliminate materials such as silicone oil, tungsten, and adhesive, which often are sources of potential interaction with certain drug substances. The CZ syringe has been designed to be compatible with existing devices such as auto-injectors."

Critical to Vetter and its customers is a comprehensive supply chain management that provides efficiency throughout the whole production process. Vetter is focusing its supply chain management toward the needs of its customers and the capacities of the supplier.

"This is how we manage to implement smooth processes from delivery of components, like glass barrels and closures, to filling and delivery of the prefilled syringes," says Mr. Soelkner. "And we also implement a forceful quality management system that covers everything from supplier audits to high filling standards. Finally, to optimize processes methods like Six Sigma, lean management, and a continuous improvement process system have been put into place."

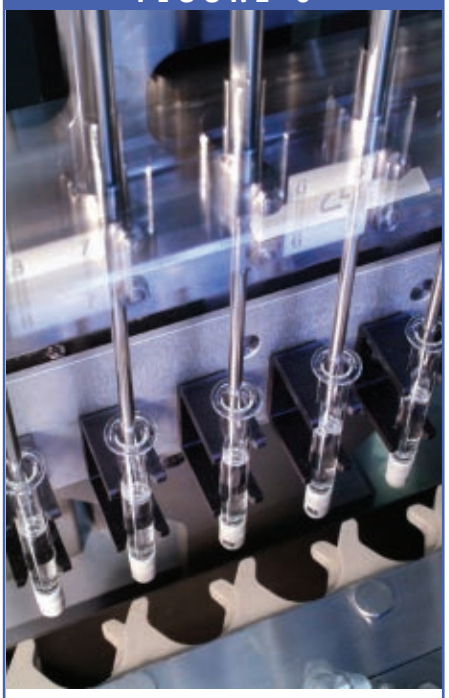
WEST–INTRODUCING NEW MATERIALS FOR IMPROVED DEVICES

Drug delivery devices and systems are becoming increasingly essential due to growth in injectable therapies driven by increased incidence of long-term diseases, such as diabetes and auto-immune diseases. Many of these treatments require regular injections, often performed by the patient or caregiver in the home setting. Understanding the needs of these patients or caregivers is essential when considering designs for drug delivery systems.

There can be a cost benefit when transitioning healthcare delivery from the hospital environment to the home environment or other healthcare facilities. Effective drug delivery devices and systems that enable a patient to self-inject can aid this transition. For example, it is now possible to transition from hospital IV to home-administered subcutaneous injection through the use of an electronic patch injector or auto-injector.

Pharmaceutical and biotech companies are working closely with drug delivery device manufacturers at an early stage to ensure there is efficient development of an overall system to enable cost-effective drug delivery. Cost factors may include the ability to move the product to market as quickly and effectively as possible; reducing in-process rejects due to breakage or lack of function; and the overall cost of quality, which has to be built into a system from the start. Prefillable syringes can aid in patient compliance, but most are still based around conventional glass syringes, which may cause safety issues such as breakage and delamination. Newer drugs, including those with high viscosity or that need to be administered in high volume, can present additional administration challenges.

FIGURE 6



Vetter is an international CDMO supporting pharmaceutical and biotech clients from preclinical development through regulatory approval and global market supply.

Delivery systems companies, such as West, are introducing new materials for prefillable syringes, including break-resistant cyclic olefin polymers, such as Daikyo Crystal Zenith (mentioned earlier), and designs that allow for easier and safer injection. These systems are not only manufactured from a novel polymer material that reduces the risks of breakage, but the dimensional tolerances, quality standards, and freedom from materials, such as silicone oil, tungsten, or adhesives ensure the systems provide the combined benefits of a plastic with the features necessary to contain a sensitive biopharmaceutical, explains Graham Reynolds, Vice President, Marketing and

FIGURE 7

A Daikyo Crystal Zenith polymer syringe system includes a break-resistant barrel and either a rigid or standard needle shield or a tip cap. Photo courtesy of West Pharmaceutical Services, Inc.

Innovation Pharmaceutical Delivery Systems, West.

According to Mr. Reynolds, prefilled syringes remain a container of choice for many biologics. In many cases, the pharmaceutical company may look to several formats for the delivery system that are all based on the same primary container. As an example, for home administration, they may look toward auto-injectors, which can provide fully automated needle insertion, dose delivery, and needle retraction. Alternatively, many patients prefer the ability to inject the drug manually, and accessories to aid in this process (such as extended finger flanges, needle shield removal systems, or ergonomic plunger rods) can be valuable in addressing patient needs. For hospital-based administration, needlestick prevention systems can be essential to meet legislation and protect healthcare workers.

Understanding the interactions between all elements of the drug delivery system (including the drug, container, delivery device, and the patient) is a key factor in ensuring success.

"If any one of these factors is not adequately considered, the success of the overall treatment may be compromised," says Mr. Reynolds.

West offers several delivery systems, such as the ConfiDose® auto-injector system technology platform, which can be used with a Daikyo Crystal Zenith 1-mL insert needle syringe or traditional prefillable syringe, and the SmartDose® electronic patch injector technology platform. These platforms offer a range of options for dose volume, injection time, and electronic control/feedback.

After several years of development West, along with its partner Daikyo Seiko in Japan, has commercialized the 1-mL long Daikyo Crystal Zenith syringe system. This is a polymer syringe system, incorporating an insert-molded needle, and containing no glue or tungsten. The fully validated syringe system is provided in a sterile tub and nest format, and has been designed to be compatible with existing filling equipment. West has also collaborated with Vetter Pharma, a leader in biologics filling, to provide customers with a fully integrated system for obtaining a filled syringe, ready for stability studies.

"Several customers are at various stages within their approval processes, and we expect this system will become a syringe of choice for many new or existing biologics in which problems of quality, breakage, extractables, and drug interaction could be a challenge with traditional glass syringes," says Mr. Reynolds.

To add to its current self-injection technologies, West has completed the acquisition of the SmartDose electronic patch injector technology platform, the result of a 2-year co-development program. The system enables higher volumes of drug to be injected slowly, and can offer patient benefits in terms of reduced frequency of injection. West is now ready to support customers' early phase evaluation of this system through active scale-up and validation programs.

Mr. Reynolds predicts prefilled syringes will continue to be a container of choice for many injectable products; however, requirements for improved quality, reduced material interaction, and safety and effectiveness within devices will continue to be key considerations.

Trends in modern biologics will require systems to contain and deliver higher dose volumes and higher viscosities, and need to be designed with the patient in mind. Advantages of certain polymers will continue to be a key driving force, and will lead to more novel syringe/container designs, in turn, leading to more flexibility in device design. ◆

TERAHERTZ SCANNING REFLECTOMETRY

Diffusion Kinetics & Permeation Concentration of Human Stratum Corneum Characterization by Terahertz Scanning Reflectometry

By: Anis Rahman, PhD; Scott Frenchek; Brian Kilfoyle; Leena Patterkine, PhD; Aunik Rahman; and Bozena Michniak-Kohn, PhD

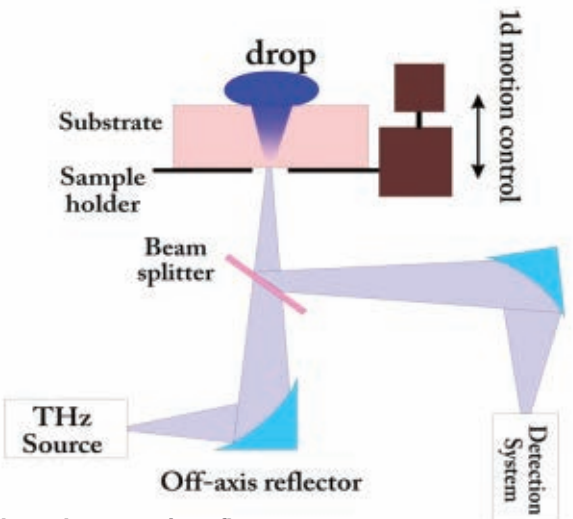
ABSTRACT

Terahertz reflectometry and spectrometry was used to investigate the permeation kinetics and concentration profile of active ingredients into the stratum corneum (SC). To our knowledge, this is the first effort of direct, non-invasive, and real-time measurement of kinetics and concentration gradient of analytes into the SC. Moreover, this is a general method that is applicable to any substrate and analyte combinations. It was found that the analyte concentration in the SC of 1% hydrocortisone solution in propylene glycol is significantly higher than 1% caffeine in deionized water. These findings are important for quantifying transdermal drug delivery formulation with these solvents and can be extended to other analytes and solvents. Terahertz spectra of untreated SC versus those treated with a 10-mM N-0915 solution were distinctively different. Additionally, the N-0915-treated specimen exhibits prominent absorption peaks in the 7.27 THz, 11.88 THz, and 18.42 THz region, while the spectrum of blank specimen exhibits a monotonous increase of absorbance with frequency. This indicates the importance of broadband terahertz spectroscopy of a range of 20 THz or more to be able to probe molecular events.

INTRODUCTION

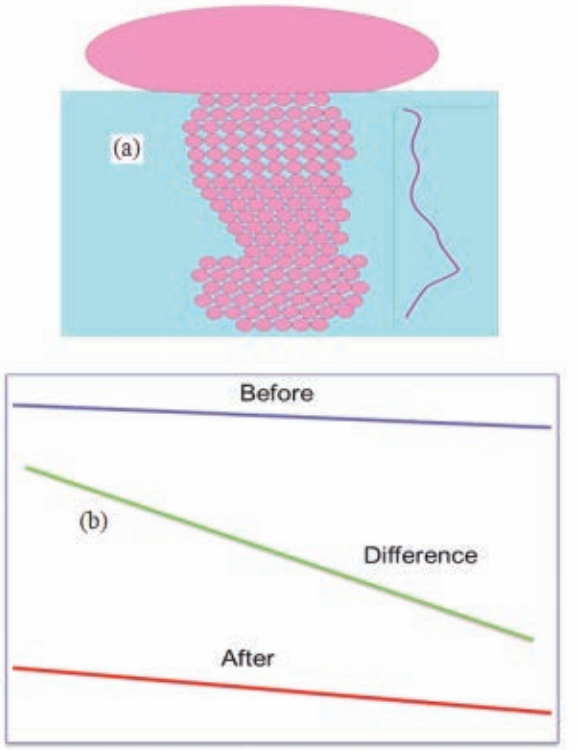
Terahertz spectrometry is an emerging novel technique that has great potential in diagnosis of certain disease conditions as well as in the analysis of actives in certain biological tissues. Broadband terahertz technology utilizes frequencies from ~100 GHz to over 30 THz that can be used to obtain tomographic information on the

FIGURE 1



Set-up of the terahertz scanning reflectometer.

FIGURE 2



(a) Cartoon of molecules permeating in to substrate, (b) computation of analyte concentration from scan of blank (before) and saturated substrate (after).

tissue surface and its interior, as well as interaction of the actives with tissue.[1-5]

The present study aims at investigating the field of transdermals/topicals and cosmetic formulations via terahertz spectroscopy and terahertz scanning reflectometry. Transdermals and topicals often involve use of compounds that enhance or retard the permeation of the active ingredients across the skin. The agents that enhance the permeation of the actives across the skin are termed permeation enhancers, and the agents that slow down the penetration of the active are known as retardants.[6,7] Permeation enhancers play a great role in increasing the bioavailability and efficacy of therapeutic agents by compromising the barrier properties of the skin and lead to enhancement in the delivery of the active across the skin. The retardants help in limiting the skin absorption of agents such as agrochemicals (pesticides), chemical warfare agents, mosquito repellants, sunscreens, and household chemicals that have the attributes of easily permeating through the barrier of the skin.

Many formulations used in transdermal and topical drug delivery use water and/or propylene glycol as solvents or penetration enhancers. For the present study, we examine permeation of two compounds in the SC: (1) hydrocortisone dissolved in propylene glycol (PG), and (2) caffeine dissolved in water.

Propylene glycol (1,2-propanediol) is a diol with chemical formula $C_3H_8O_2$. It is a colorless, nearly odorless, clear, viscous liquid used as a solvent in many pharmaceuticals, moisturizers, hand sanitizers, and antibacterial lotions. Propylene glycol is used as a vehicle for penetration enhancers but is also considered a penetration enhancer in its own right. It permeates through the SC that alters the thermodynamic activity and partitioning of associated drug. Water is a common solvent; the water content of human SC is typically around 20% of the tissue dry weight but by soaking or occluding the skin, the SC water content can reach up to 400% of the tissue dry weight. Increased hydration can lead to increased permeation of associated drug as free water within the tissue alters the solubility of drug and therefore partitioning into the skin.

Additionally, terahertz spectroscopy was conducted on SC specimens treated with an active ingredient (N-0915). The spectra of blank SC and those saturated with N-0915 are also reported.

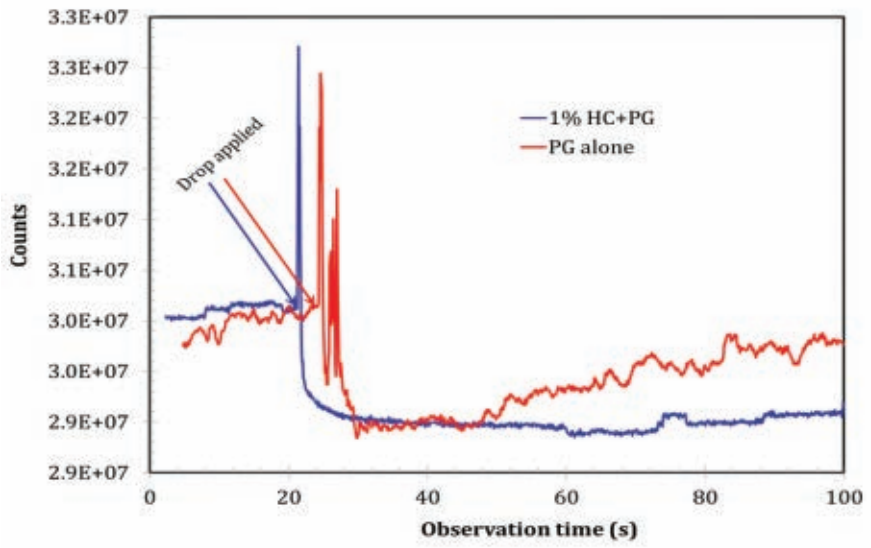
EXPERIMENTAL METHOD

The measurements were carried out on a terahertz scanning reflectometer.[8] The experimental setup is shown in Figure 1. A CW terahertz source was

FIGURE 3

Human SC mounted on the sample holder on which a drop is applied.

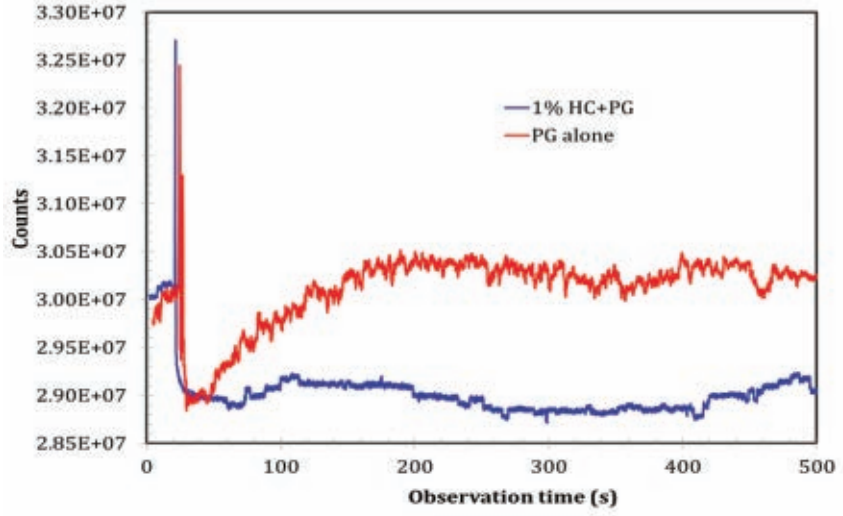
FIGURE 4



Kinetics of permeation of two solutions into SC (close-up view).

used that generates the terahertz radiation from an electro-optic dendrimer via a difference frequency method.[9] The terahertz beam was focused on to the specimen at a 90 degree angle via an off-axis parabolic reflector (normal incidence). The beam reflected by the substrate was directed to the detection system via a beam splitter. The specimen cell was composed of a platform controlled by a 1-d motion controller. The main purpose of this arrangement is as follows. The off-axis parabolic reflector was adjusted such that initially the terahertz beam remained focused on the substrate surface. At this position, the motion control can be engaged to move the focal point inside the substrate to interrogate the reflectance across the thickness; this gave the partial $\frac{\partial C}{\partial x}$ (Equation 1) when the blank substrate reflectance was subtracted from the reflectance of the same substrate treated with a desired ingredient (Figure 2).

FIGURE 5



Kinetics of permeation of two solutions into SC over longer time.

Equation 1.

$$\left|\frac{\partial C}{\partial x}\right|_{Analyte} = \left|\frac{\partial C}{\partial x}\right|_{Before} - \left|\frac{\partial C}{\partial x}\right|_{After}$$

However, when the beam remains focused at the surface, and the motion control is locked at that position, then the ingredient may be applied on the substrate to let it permeate across the thickness while the reflectance is measured in real time. In this case, the reflectance is directly proportional to the rate of permeation of the ingredient across the substrate partial $\frac{\partial C}{\partial t}$.

RESULTS & DISCUSSION

Analysis was carried out on two batches of dermatomed human skin samples supplied from the Human Skin Bank in New York City, NY. The SC was separated using the heat separation techniques described previously in the literature by Kligman and Christophers and others.[10-12] Two model compounds were selected for this study namely, hydrocortisone and caffeine. The former represented a lipophilic compound, and the latter a hydrophilic one. Solutions for

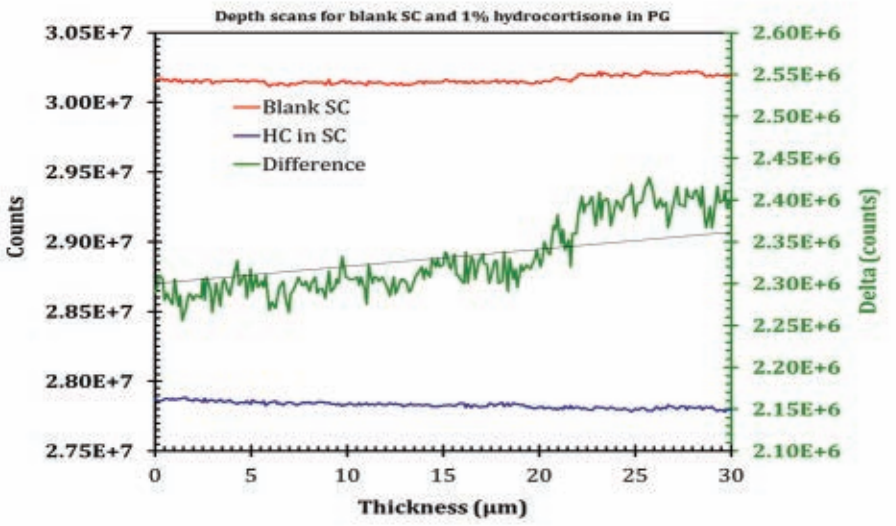
analysis (DI H_2O, propylene glycol [PG], 1% hydrocortisone in PG, and 1% caffeine in DI H_2O) were supplied by Rutgers University. Measurements were taken using a TeraScanR unit from Applied Research and Photonics, Inc. (Harrisburg, PA). An SC specimen mounted on the cell is shown in Figure 2. After all measurements were recorded, the results were imported to Microsoft Excel for visualization and analysis. Primary goals included: measuring the rate at which a given analyte diffused through the SC; and measuring the depth permeated by the analyte after stabilization (saturation).

Samples of SC were cut into squares large enough to cover a 5.31 cm^2 circle cut into a 5x5-cm^2 Plexiglass slide and fixed by the SC's inherent adhesiveness (Figure 3). All SC samples were oriented with the externa facing upward; they were fixed on the cell by a Teflon ring. The cell was then mounted in the TeraScanR reflectometer.

All SC samples that were to receive an analyte solution were vertically scanned to assess their reflectance at increasing depths; this was performed on all samples as a control before application of the analyte. Permeation kinetics, ie, the rate at which a solution penetrated the SC, were recorded after dropping 200 microliters of solution from an adjustable micro-pipette with the drop centered directly over the focal point.

Permeation was considered complete after the kinetics reached a steady state.

FIGURE 6

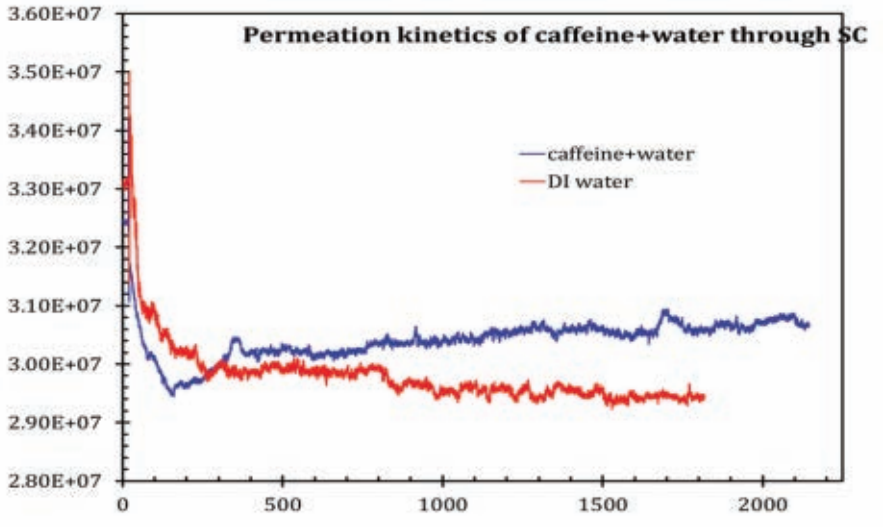


Depth scan of SC. Top (red) scan of blank SC, and bottom (blue) is the scan after the SC is saturated by 1% hydrocortisone solution in propylene glycol. The middle curve (green, right y-axis) is the difference of the top and the bottom curves, indicating the distribution of the hydrocortisone solution across the SC.

The solution was then pipetted off, and the remainder (on top) was carefully absorbed with a cotton swab. A second set of scans were performed to assess the concentration gradient of the analyte across the depth of the substrate. In all cases, at least three runs were taken, average of which is utilized for subsequent analysis.

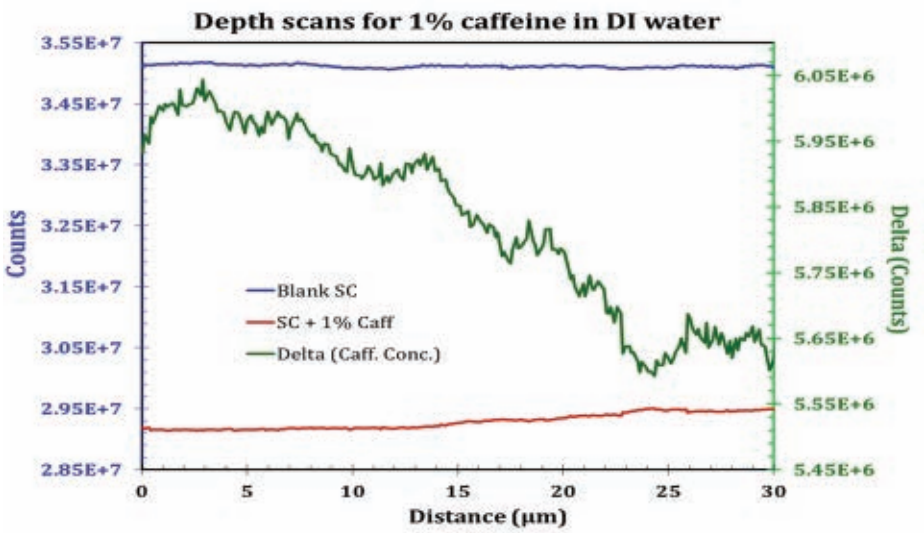
A pure sample of PG was tested as a blank for its permeation kinetics through the SC (Figure 4). This (kinetics) was later compared with that obtained for the hydrocortisone solution in PG. Upon the completion of kinetic measurement (when the kinetics reached saturation), its

FIGURE 7



Permeation kinetics of DI water and 1% caffeine in DI water in the SC.

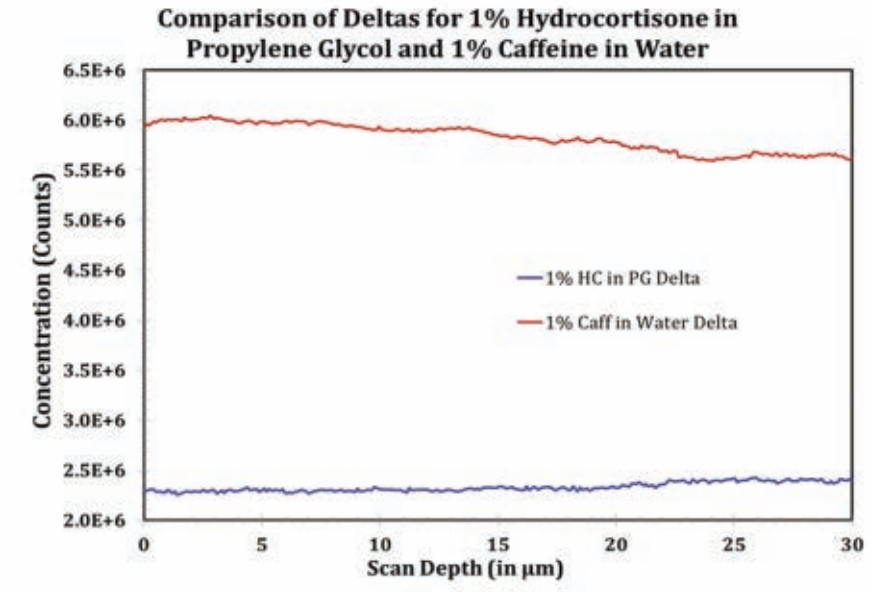
FIGURE 8



Concentration of caffeine solution (right y-axis) in SC.

depth scan was run, and the data stored in a file. Then a fresh specimen of SC was mounted. Three depth scans were performed on the blank SC. The average of these three runs is shown in Figure 6 (marked Blank SC). Kinetics measurement was then carried out with a solution of 1% hydrocortisone in PG (Figure 4). Figure 5 shows a close-up view of the data shown in Figure 4. After removal of analyte from the SC upper surface, three more depth scans were performed to assess the analyte's depth of permeation (Figure 6, marked HC in SC).

FIGURE 9



Comparison of the concentration profile of hydrocortisone and caffeine solution in the SC.

Measurements of kinetics and depth scan for blank SC, DI water, and 1% caffeine in DI water were carried out in sequence in a similar fashion as described earlier. Kinetics of DI water and 1% caffeine in DI water are shown in Figure 7, while Figure 8 exhibits the concentration profile of caffeine in the SC.

Figure 9 compares the concentration profile of both hydrocortisone and caffeine solution in the SC. It can be seen there are significantly more hydrocortisone in PG permeated through the SC than caffeine. This is expected and consistent with many observations from front-cell analysis experiments via HPLC.[13] As seen from Figure 9 (and also from Figure 6), the hydrocortisone profile shows that as we go deeper in the SC, the concentration of hydrocortisone is slightly increased, while the caffeine concentration profile (Figure 8) shows that less caffeine has penetrated deeper in the SC. This observation will be examined further by repeating the measurements and/or by utilizing other solvents.

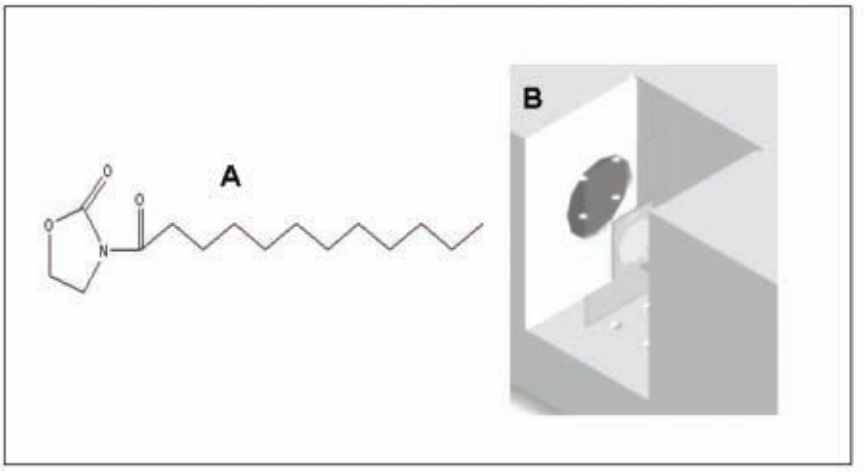
Figure 10 shows an experimental arrangement in which the SC was mounted in a terahertz spectrometer (TeraSpectra, Applied Research & Photonics, Harrisburg, PA). A blank specimen was measured first, and then another specimen was measured that was saturated with a 10-mM N-0915 solution. Here, the objective was to identify the

signals obtained in the spectrum to determine whether they attribute to the treatment with specific penetration modifier (N-0915) or to the components of the SC. Figure 11 shows the Fourier transform frequency-domain spectra of both blank- and N-0915-treated specimens. The spectra are distinctly different in that the SC treated with N-0915 showed prominent peaks in the 7.27 THz, 11.88 THz, and 18.42 THz regions whereas the control (untreated SC) showed a monotonous increase in absorbance as a function of frequency. While the significance of the peaks in the N-0915-treated specimen need to be explained, it is clear that if the spectra did not cover an extended window (up to 20 THz), then the peaks would not have been visible.

SUMMARY

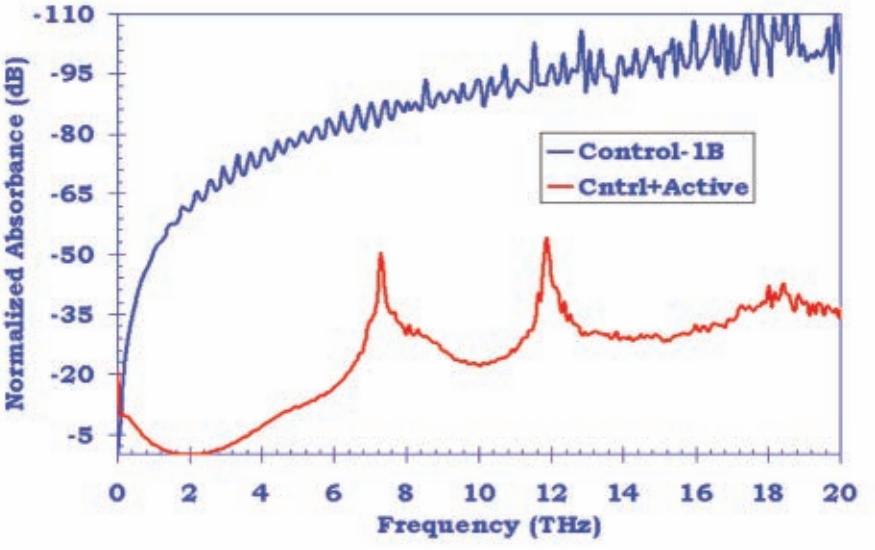
We conclude that terahertz scanning reflectometry is an effective tool for quantitative measurement of permeation kinetics and concentration profile of analytes in skin. To our knowledge, this is the only method for non-invasive quantitation of analytes in skin. These findings are important for quantifying transdermal drug delivery formulations with these solvents and can be extended to other tissues or substrates as well as to a variety of analytes. Unlike other methods, this is a simpler technique allowing direct quantification in a non-invasive fashion. Additionally, a wide broadband terahertz spectrometry allows spectroscopic inspection of differences between blank skin (substrate) and those treated with active ingredients. The N-0915-treated specimen exhibits prominent absorption peaks in the 7.27 THz, 11.88 THz, and 18.42 THz regions, while the spectrum of blank specimen exhibits a monotonous increase of absorbance with frequency. This indicates the importance of broadband terahertz spectroscopy over a wide range (20 THz or more) to be able to probe molecular events. ◆

FIGURE 10



(a) Molecular structure of the N-0915 and (b) the specimen (SC) mounted on the spectrometer.

FIGURE 11



Spectral signature of SC (control, blue line) and the SC treated with N-0915 (red). Terahertz can clearly detect the presence of an active as evidenced from the spectra.

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BIOGRAPHIES

Dr. Anis Rahman is the founder and CTO of Applied Research & Photonics (Harrisburg, PA). He is the originator of dendrimer-based photonics and terahertz science and technology. Here, electro-optic dendrimer is used to generate high-power CW terahertz radiation without requiring femto-second pulsed laser. Dendrimer is the "silicon for photonics," allowing fabrication of a number of important devices for sensing and communication.

Scott Frenchek is an Intern at Applied Research & Photonics. He is majoring in biotechnology at Harrisburg University of Science of Technology.

Brian Kilfoyle is a graduate student at Rutgers University, pursuing a doctoral degree in transdermal drug delivery mechanisms.

Dr. Leena Patterkine is an Associate Professor of Biotechnology at the Harrisburg University of Science of Technology.

Aunik Rahman is a Senior Engineer at Applied Research & Photonics. He is an inventor and a designer of the company's terahertz spectrometer, TeraSpectra.

Dr. Bozena B. Michniak-Kohn is a Professor in Pharmaceutics at the Ernest Mario School of Pharmacy, and Founder/Director of the Center for Dermal Research at Rutgers-The State University of New Jersey, Piscataway, NJ. She is an expert in the area of transdermal, topical, and buccal drug delivery and is a Fellow of the American Association of Pharmaceutical Scientists.

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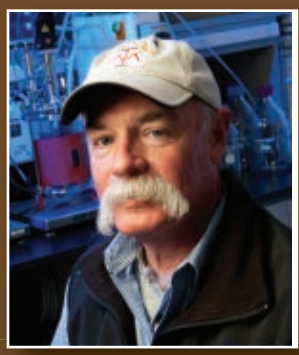

Rod Ray, PhD
CEO & Chairman

Bend Research

"We believe we are differentiated from the rest of the pharma CRO industry in a number of ways. A key example is our continuous drive to develop new technology both with our clients and internally. This is in response to remaining identified technology gaps in the extensive pipeline our clients have entrusted to us."

Bend Research is a leading drug formulation development and manufacturing company whose mission is to improve health through the advancement of its clients' best new medicines. To rapidly progress promising compounds to the clinic, the company strives to solve its clients' most difficult scientific and technical problems using an approach grounded in science and engineering fundamentals. Oral bioavailability represents a significant challenge to the pharmaceutical industry as more than half of the compounds in early development are poorly soluble. Bend Research's spray-dried dispersion (SDD) technology is recognized as a reliable solution to this challenge because of SDDs' proven performance, long-term stability, and excellent manufacturability. While Bend Research is best known for the demonstrated success and broad applicability of its SDD technology, the company is also a leader in novel formulations, encompassing hot-melt extrusion, controlled-release, biotherapeutic, and inhalation technologies; process engineering; and cGMP manufacturing. Drug Development & Delivery recently interviewed Dr. Rod Ray, CEO and Chairman at Bend Research, to discuss his company's approach to difficult drug delivery challenges and the core technologies offered by his company.

Q: Can you provide our readers with a brief background and history of Bend Research?

A: Bend Research was founded 37 years ago as a research and technology development company serving a variety of industries, such as energy production and storage, consumer products, and space exploration. Today, Bend Research works primarily within the pharmaceutical industry helping clients to solve their most difficult drug delivery problems. Our mission is to improve health through the advancement of our clients' best new medicines and technologies.

Our pharma roots stem from a 26-year relationship with Pfizer, which included a 10-year period of exclusivity that ended in 2008. That relationship has given us considerable capability in the pharmaceutical formulation and process space. Our capabilities are now being leveraged by some 75 clients, ranging from a majority of the top 15 pharma firms to numerous mid-tier innovators,

biotechs, and academics. Our client work includes technology development programs and drug discovery support through Phase III clinical programs.

While our primary focus is formulation and process development in the pharmaceutical space, we have recently expanded our offerings outside of the pharmaceutical industry to serve the needs of the nutrition, wellness, chemical, and process industries.

Q: How has the recent economy impacted your company?

A: Bend Research has been quite fortunate during the "restart" period that followed our decade-long exclusive relationship with Pfizer, averaging double-digit growth between 2009 and 2011. We attribute this good fortune to our science-based approach to problem-solving, our world-class staff, our state-of-the-art facilities and equipment, and the intellectual property developed throughout the Pfizer relationship.

Q: What differentiates Bend Research from the rest of the pharma CRO industry?

A: We believe we are differentiated from the rest of the pharma CRO industry in a number of ways. A key example is our continuous drive to develop new technology both with our clients and internally. This is in response to remaining identified technology gaps in the extensive pipeline our clients have entrusted to us. Our pipeline and "gap analysis" allow us to provide novel approaches and innovative offerings in new chemistry and delivery spaces. Examples of these offerings include novel solutions for solubilizing parenterally administered compounds and improved retention of intra-articular delivery of compounds for arthritis.

A second example of how Bend Research is unique is the world-class staff working at our company. Many of our employees have advanced degrees in a broad range of disciplines, giving us a unique outlook on the challenges seen by the pharmaceutical industry. Our multidisciplinary teams work closely with our partners and apply their diverse knowledge to their problem statements. We ensure our staff continues to bring this rare perspective to the industry by repeatedly sharpening their scientific and engineering skill sets on non-pharma problems.

We are also differentiated by the fact that all of the compounds that enter Bend Research are "challenged" in some way, whether due to low solubility, a need for modified release, or a need for an alternate delivery modality. This means our clients can come to us and leverage not only the solutions that have been developed for their portfolio, but also those that have been created with a broad industry view. We approach these drug delivery challenges through the application of science and engineering fundamentals, tools, and protocols to rapidly formulate with minimal use of API. This typically results in lower overall cost for a proof-of-concept (POC) formulation on a shorter timeline. Finally, you might have noticed our brand. To our knowledge, we are the only contract research organization in the pharma space with a western theme. While everyone at the company doesn't necessarily ride a horse to work, our staff does exude the cowboy ethics of discipline, integrity, and hard work. This benefits our clients through open and honest relationships that drive projects to successful and timely endpoints.

Q: How do you work with your clients?

A: Our client relationships are another distinguishing feature of Bend Research. While we do have a few straight fee-for-service clients, we work best in ongoing alliance relationships in which we have established direct scientist-to-scientist or engineer-to-engineer contact. This type of working relationship typically leads to very well-defined problem statements that have been brainstormed together by both companies, as well as excellent communication as projects go forward. Our alliance relationships allow our staff and our partners to maximize the scientific output for programs and to have the flexibility of modifying work plans along the way. Of course, the ultimate goal is to successfully achieve project goals as rapidly and inexpensively as possible.

Another key piece of the Bend Research culture is our loyalty to our customer. Because our goal is to be the preferred partner in solving tough problems, we strive to learn our client's way of doing business and respond with flexibility, so that our business

relationships fit each client's needs, business models, and product profiles. We also constantly strive to improve the "customer experience," for example, through the incorporation of our clients' best practices when appropriate. In the future, this will include significant investments to serve our customers better and faster, with less overall expense.

Q: What is an example of a core technology offered by Bend Research?

A: Bend Research is involved in a number of technology areas as well as formulations for drug delivery by a number of routes. We consider our technologies to be key components in our problem-solving tool chest. Our formulation and drug delivery technologies include oral controlled-release technology, inhalation delivery both to the nose and the lung, controlled release of drugs in the knee joint, as well as other specialty delivery technologies that are in development.

The technology area we are probably best known for, however, is oral solubilization technologies. Solubility enhancement is a critical area of research and development because upwards of 50% of the compounds in pharmaceutical pipelines are considered poorly soluble. This can lead to poor bioavailability and pharmacokinetic variability of the compound.

While we are best known for utilizing spray-dried dispersions (SDDs) to improve the solubility of compounds, we do not use the technology blindly. We use a rational methodology grounded in fundamental science and engineering to choose the best technology and solution for the given problem, whether it be our technology, technology offered by a third party, or an open-source technology. We will do whatever the customer desires, and whatever the science says is the best solution.

Q: What elements are critical to the success of spray-dried dispersion (SDD) technology?

A: There are a number of elements that are critical to effective deployment of the SDD technology. First, it is critical the science of dispersions is sufficiently well understood, so that SDD formulations can be developed at the discovery interface in such a way that minimizes the time and API required. Through modeling and the experience of having formulated more than 500 compounds, we can deliver the appropriate, enabling formulation with as little as 100 mg of API in less than a few weeks time.

Second, the ability to scale the spray-drying process from the initial bulk-sparing phase to clinically and commercially viable scales is critical. We can scale spray-drying material processed from the gram scale to the multi-ton scale with our in-house equipment and computational fluid dynamic (CFD) and mass-transfer models. When you consider our recently announced relationship with Hovione, we now can offer our clients a well-defined "discovery-to-commercial" pathway. The idea of identifying commercializable formulations and processes is core to our company culture and is reflected in the products we have brought to market, in the pharmaceutical realm as well as in non-pharma industries.

Third, incorporation of the spray-dried intermediate SDD into a solid dosage form cannot be ignored, in the same way that performance of the spray-dried intermediate SDD is critical to in vivo performance. This is an area in which we have recently expanded our capabilities with additional equipment and staff - two Korsch XM-12 tablet presses and additional employees with pharmaceutical solid dosage form training.

Finally, it is critical to note that the excipients used in solid amorphous dispersions are considered "functional excipients." That means composition AND function are critical to the performance of the formulation. To this end, we are partnering with world-leading providers of dispersion excipients to ensure the materials science and characterization of the functional excipients meet key performance criteria. We will address this in more detail in an upcoming article.

Q: What does the future hold for Bend Research?

A: The future is bright for Bend Research. We look to continue to grow our business with increased development and cGMP spray-drying capacity, added solid dosage form manufacturing capability, the initiation of new technology development programs to solve problems both inside and out of the pharma business, and continued support from our key alliance partners. Most importantly, we hope to continue partnerships that advance our clients' best new medicines.◆

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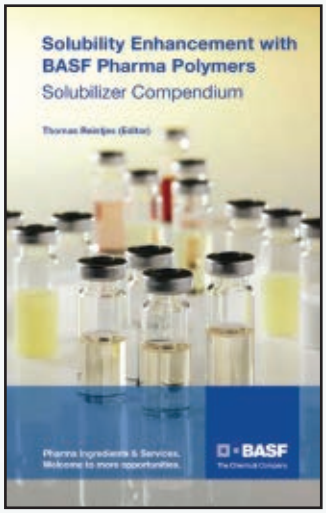

BASF's new solubilizer compendium is a must-read for anyone working with APIs that exhibit poor solubility and bioavailability. It leverages BASF's vast expertise in solubilization and bioavailabilty enhancement, and is the result of many years of research. The publication provides a valuable overview of all relevant BASF excipients (Kolliphor™ grades, Soluplus®, and selected Kollidon® grades), and offers helpful advice on creating solid solutions and dispersions. What's more, it includes a chapter dedicated to high-throughput screening as a means of selecting the right excipient or combination of excipients for a poorly soluble drug. Visit www.innovate-excipients.basf.com to download the compendium as a PDF, or to request a free hard copy. BASF's solubility enhancement experts are happy to answer all your questions. Just send an e-mail to **pharma-ingredients@basf.com**.

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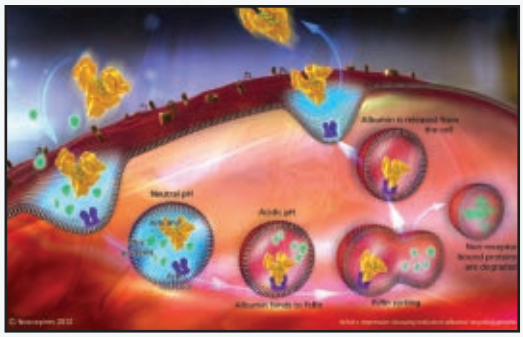

Novozymes' tunable half-life technology has been developed to flexibly tune the pharmacokinetic profile of target proteins and peptides. The half-life of albumin can be tuned up or down to meet the half-life needs of the customers' drugs and applications. The technology is based on the interaction between albumin and the neonatal Fc receptor (FcRn) to extend circulatory half-life. Building on Novozymes' knowledge of albumin and its native receptor, albumin can be modified to increase receptor binding and, consequently, deliver an increase in the pharmacokinetics of fused or conjugated therapeutics. The Flex technology offers the potential to increase half-life according to specific medical needs. This allows delivery of drugs with extended circulatory time, therefore reducing dosing regimes and increasing patient compliance. For further information on Novozymes' Flex technology, please visit **www.biopharma.novozymes.com**.

Technology & Services Showcase

Manufacturing & Development

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

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PharmaCircle is an innovative knowledge management company specializing in the drug delivery, pharmaceutical, and biotechnology fields, with a current client base ranging from start-up life science companies to world leaders in Big Pharma. Clients choose PharmaCircle's services and content for its comprehensive technical (pipeline, products, molecule, and technology) and business (deals, acquisitions, royalty, licensing, drug revenues, market information, etc) related information and analysis, which are ideal for all segments of small and large companies. PharmaCircle helps facilitate product life cycle management (LCM), partnering, licensing, and competitive intelligence efforts as well as supplements internal efforts and costs at a fraction of the cost if performed internally. For more information, contact PharmaCircle at (920) 850-3056 or visit **www.pharmacircle.com**.

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Passive Safety Device

Rexam Healthcare has received 510(k) approval from the FDA for Safe'n'Sound™, its passive safety device for staked prefilled syringes. The approval is the crowning achievement of significant investment and design efforts by the Rexam teams. The aim of the project was to design a safety device that meets the current regulations in North America and Europe. These regulations are aimed at protecting workers in the health sector from needle injuries and contamination from blood-borne pathogens. The fully passive Safe'n'Sound device provides effective protection against the risks of being pricked by a soiled needle due to the protective sheath that activates automatically once the medicine has been administered. This 510(k) approval shows Rexam's commitment to innovation, safety, and quality and allows the product to be marketed in the US. For more information, contact Rexam Healthcare at (800) 537-0178 or visit **www.rexam.com/healthcare**.

Technology & Services Showcase

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UPM Pharmaceuticals® is an independent provider of contract formulation development, analytical services, and cGMP manufacturing. We continue a legacy of intellectual distinction and uncompromising performance with every new project. The talent and experience of our team, our dedication to science-based formulation design, and our commitment to communication and timeliness enables us to offer the highest level of customized drug development services. Our 30,000-sq-ft main facility in Baltimore features cGMP pharmaceutical manufacturing and packaging suites as well as analytical and R&D laboratories staffed by industry veterans. Whatever form your product takes, we ensure rigorous and technically sound product characterization, methods development, and QC release. Our clients enjoy service that is highly responsive and fast with total quality management characteristic of a customer-focused business. For more information, contact UPM Pharmaceuticals at 410-843-3738 or visit **www.upm-inc.com**.

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

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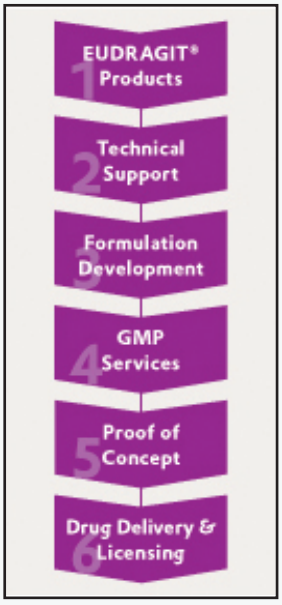
Pharma Polymers



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

DRUG DEVELOPMENT Executive

EVONIK INDUSTRIES

EVONIK: SUPPORTING DEVELOPMENT & COMMERCIAL CYCLES OF INJECTABLES

Jean-Luc Herbeaux, PhD
Head, Health Care Business Line

Evonik

"We are now able to support pharmaceutical and biotech companies alike through all developmental and commercial cycles. Birmingham Laboratories brings decades of expertise in the area of injectable depot formulations and provides services ranging from new polymer design and manufacturing, development, and scale-up of injectable formulations with controlled-release functionality (based on implants and microsphere technology) and manufacturing at clinical and commercial scale."

On November 17, 2011, Evonik Degussa Corporation, an affiliate of Evonik Industries AG, successfully completed its acquisition of the assets of SurModics Pharmaceuticals, Inc. The Birmingham, Alabama-based business, originally founded as Brookwood Pharmaceuticals in 2005, has been integrated into the Health Care Business Line of Evonik, and will continue to operate from the Birmingham site, recently renamed Birmingham Laboratories. Several months have passed since the acquisition and Drug Development & Delivery decided to interview Dr. Jean-Luc Herbeaux, the Head of the Health Care Business Line of Evonik, on the rationale and success of this acquisition.

Q: What are strengths of Evonik with relevance for the new business?

A: Evonik's strengths as one of the world leaders in specialty chemicals and provider of enabling solutions to the healthcare industry are all very relevant for our Birmingham team. Evonik is a global specialty chemical company with activities in over 100 countries around the world. In North America, Evonik employs more than 4000 employees and operates more than 35 manufacturing facilities, the largest of which is in Mobile, Alabama. Our newly acquired facility in Birmingham is three hours away by car from the Mobile site. Our team in Mobile has aided the Birmingham site in a number of areas such as HR, IT, procurement and engineering.

The healthcare market, one of Evonik's expressed areas of focus alongside other megatrends, such as nutrition, resource efficiency, and globalization, is the focus of Evonik's Health Care business. With its strong portfolio of products (APIs, amino acids, and pharma polymers) and associated services (custom synthesis and formulation development services), Evonik Health Care is the perfect home for the Birmingham-based business. We are able to leverage our Tippecanoe, Indiana site, which manufactures active pharmaceutical ingredients (APIs), to support the Birmingham business on topics such as Regulatory and Quality Management. We also connected the Birmingham Laboratories with our regional sales and service teams, thereby increasing

market coverage and capacity to identify new customers and opportunities.

This organizational strength facilitated a smooth and seamless integration of the facilities and of our new colleagues and will undoubtedly help the newly acquired business to thrive on a global scale.

Birmingham Laboratories is now integrated in the Pharma Polymers product line, a leading developer and producer of functional pharmaceutical excipients and provider of formulation development services. Known for its well-established EUDRAGIT® product portfolio used in coatings and matrix systems, which provide controlled release of APIs in tablets and other oral dosage forms, the product line complemented its offering with the addition of the RESOMER® bioresorbable polymer product range in March 2011. RESOMER products are widely used for controlled-release injectables and implants as well as in medical devices. This addition allowed Evonik to expand its application space from oral to parenteral administration.

Q: What does this transaction mean for Evonik?

A: First and foremost, the transaction underscores Evonik's commitment to grow in the healthcare market and to strengthen its position as one of the world's leading solution providers to companies in the healthcare industry.

FIGURE 1

Birmingham Laboratories: Full development and commercial manufacturing capabilities for injectable formulations.

The acquisition of the RESOMER product family in March 2011 got things rolling. The RESOMER business provided Evonik with a strong material portfolio for controlled-release injectables and bioresorbable medical devices. However, it was designed to be a pure product business, and we were convinced that our customers expected more support in formulation development and scale up services. The next step was clear - we needed to ramp up our formulation and scale-up expertise swiftly in order to mirror the high level of technical support our customers receive in the oral drug space. As we know, home growing these competencies can take many years, and we were looking for a meaningful acquisition to boost our competencies overnight.

We were lucky SurModics Pharmaceuticals happened to be for sale at the right time. We had been following SurModics for a while as we believed early on the SurModics Pharmaceuticals business would bring the right set of complementary competencies and expertise, providing a perfect fit to our RESOMER product business.

We were not wrong. The competencies and strengths of Birmingham Laboratories and our existing RESOMER portfolio are a perfect match, which created a unique value proposition to our customers. We are now able to support pharmaceutical and biotech companies alike through all developmental and commercial cycles. Birmingham Laboratories brings decades of expertise in the area of injectable depot formulations and provides services ranging from new polymer design and manufacturing, development, and scale-up of injectable formulations with controlled-release functionality (based on implants and microsphere technology) and manufacturing at clinical and commercial scale. This latest transaction has clearly

FIGURE 2

Leading drug delivery technologies by Evonik: FormeEZE microparticles in a 27-G needle for improved injectability.

positioned Evonik as a partner to the pharmaceutical industry for parenteral dosage forms with controlled-release functionality - from development to commercial supply.

Q: What does the acquisition mean for the customers, which additional value will they get out of the new situation, and how will Evonik respond to current and future customer challenges?

A: Starting with the most obvious benefit - customers can now enjoy the benefit of a very strong PLGA portfolio stemming from the combination of Lakeshore Biomaterials™ and RESOMER, supported by our excellent technical and regulatory teams from early stage to production. This superior portfolio of products also comes with dual supply points (from our German and Alabama cGMP production facilities) for enhanced supply security, a high-value element for many of our customers who rely on our materials to launch and commercialize their drugs. Customers can also look forward to our inherent strength in custom polymer synthesis to match their individual requirements as well as excellent support at their doorstep thanks to our far-reaching global sales and service team.

In addition to excipients, customers can also look forward to full development and commercial manufacturing capabilities for parenteral depot formulations, backed up by excellent facilities, equipment, and technical expertise in Birmingham. We can go beyond proof-of-concept or feasibility studies and accompany the drug development through the various clinical trial phases all the way through commercial launch by providing a unique combination of know-how and cGMP manufacturing resources and facilities. This includes the ability to handle high-potency compounds and manufacture the finished dosage form or parts thereof, should this be a need of our customers. In a nutshell, thanks to our very skilled team of experts with decades of experience in this field, we bring all elements needed for development and commercial launch of parenteral controlled-release drug formulations under one roof. In addition to the excipients, we can also supply the API should this be needed. This means that our customers have the choice to select the services and products they need from us, with an offering ranging from simple product supply to full formulation and manufacturing support.

Q: Which measures does Evonik plan in mid-term related to PLG polymers and associated services?

A: Evonik understands that input from customers is most valuable if our aim is to provide enabling solutions. The constant market input translates into projects and actions to strengthen our portfolio of offerings supported by the many years of experience of our combined teams. R&D activities are already ongoing to develop new products and services in the parenteral space. Our goal is to provide differentiated solutions to our customers and partners in order to allow them to create high-value products in existing or new therapeutic fields. Simply stated, we want to strengthen our position as a strategic resource to the pharmaceutical industry for drug and medical device functionality.

Q: Are there plans for any additional acquisitions in this area?

A: That is the million-dollar-question. Of course, Evonik continues to evaluate potential opportunities to better its market position in key markets, particularly as they relate to the megatrends outlined earlier. In the healthcare market, we are constantly scanning for opportunities while working to ensure a successful integration of our new businesses and team members. Our aim is to constantly seek new opportunities to complement our portfolio of products and services in order to serve our customers better and add value to their business.

Q: Can you tell our readers more about Birmingham Labs? How many employees? Size? Key competencies?

A: As the name indicates, Birmingham Laboratories is located in Birmingham, AL, a city well acquainted with biomedical research and development. Birmingham Labs employs approximately 85 experts working in polymer research and production, quality and regulatory, and development and manufacturing of both drug delivery systems such as implants and microspheres but also finished drug products. Please note that drug product manufacturing is offered to our clients as a service. Evonik is and intends to remain a specialty chemical company serving the pharmaceutical industry.

Q: Who will run the site? Is Evonik installing a new management team?

A: Our intention was to retain as many employees as possible. We recognize that business success hinges on the know-how and goodwill of our team members. We are grateful that all employees of SurModics Pharmaceuticals became members of the Evonik team. The incumbent management team headed by Arthur Tipton and supported by the global integration team, was immediately and unequivocally empowered to grow the business and reduce any risk of business disruption. There is no plan to change the management team - far from it. Evonik recognizes and respects the strengths of the staff and will continue to provide the necessary platform to successfully run the business.

Q: What experience does Evonik have of running pharmaceutical and medical device operations?

A: Honestly, I understand the capabilities of the Birmingham Labs may be seen by some as a departure from the product businesses Evonik is most known for. However, Evonik is able to adapt to market trends and stand out as an excellent provider of enabling solutions to the industry. In the world of parenteral drug delivery systems, this means we have to be able to not only reliably design and supply pharma polymers but also provide our customers and partners with excellent services at each and every stage of the drug life cycle. We make it our guiding principle to provide services that customers need most and to constantly expand our capabilities and expertise beyond the historical core competences of our businesses in order to achieve this goal. Trust us to use all of our determination and skills to be and remain a strategic resource and provider of enabling solutions to the healthcare industry. ◆

Therapeutic Focus

Rheumatoid Arthritis Meets Its Match

By: Jos Raats, PhD, President & CEO, ModiQuest Research B.V.

Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory disease, which is restricting and distressing, affecting around 1% to 3% of the world's population. Although most commonly manifested as swelling, stiffness, and inflammation of the synovial joints (synovitis) of the fingers, toes, knees, and vertebrae, it also involves inflammation of the synovial membrane. The disease may also be displayed more widely in the body as diffuse inflammation in the lungs, pericardium, pleura, and sclera, and nodular lesions in subcutaneous tissue. While the exact etiology of the disease is unknown, RA is a debilitating and degenerative condition for which auto-immunity plays a significant role in the progression and severity. Later stages of RA involve a significant breakdown of articular cartilage and bone in the joint accompanied by severe pain and swelling and sometimes joint ankylosis (immobility and consolidation) (Figure 1).

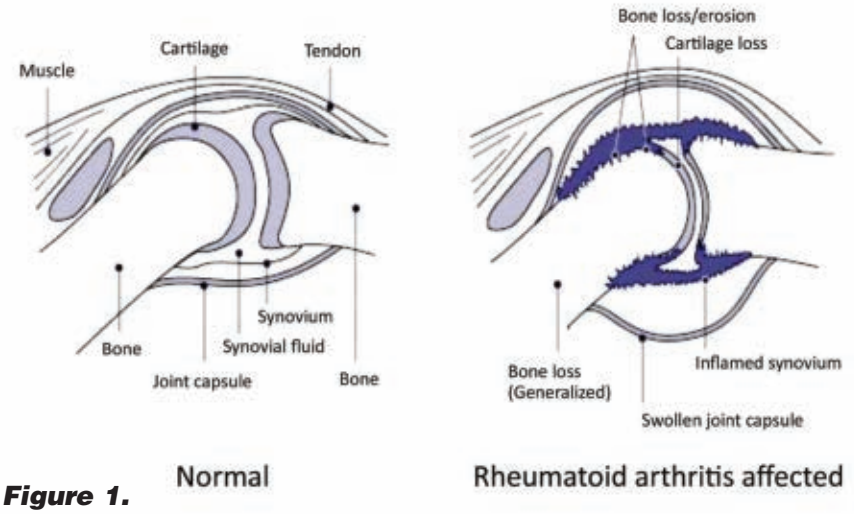


Figure 1.
The inflammation produced by rheumatoid arthritis causes severe loss of bone and cartilage in synovial joints.

Diagnosis

Diagnosis of RA is made in several ways, but the major methods include diagnostic imaging (x-rays) and immunological/serological tests. X-rays can monitor the progression of the disease particularly in multiple joints (polyarthritis) and alert the physician to major degenerative changes. Blood tests and immunological monitoring is the method of choice for differential diagnosis and determination of underlying autoimmune pathology. Very specific serological tests (95%) have been developed based on the presence of anti-citrullinated protein antibodies (ACPAs) or anti-CCP (cyclic citrullinated peptides) - auto antibodies against citrullinated proteins. ACPA tests are also imbued with the advantage that they indicate a predilection for RA up to 10 years prior to the appearance of overt clinical signs allowing early intervention.

Citrullination

(ACPA) or anti-cyclic citrullinated protein antibodies (anti-CCP) are auto-antibodies, directed against the individual's own proteins and are frequently detected in the blood of RA patients. During the inflammatory process, arginine residues in proteins are deiminated to citrulline (citrullination) by peptidyl-arginine deiminase (PAD) enzymes released from dying cells in inflamed joint tissue. If the conformations of these proteins are significantly altered, they may be regarded as antigens by the immune system and subsequently produce RA pathology. An increasing number of studies have indicated that these arginine modifications are key for the initial triggering of autoimmunity and the breaking of tolerance.

Current Treatment

The treatment of RA has generally involved the use of analgesics and anti-inflammatory drugs, such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and glucocorticoids to alleviate disease symptoms. These have varying degrees of success with such a refractory condition and has led to more intuitive treatment regimens. Consequently, in more recent times, a number of biologics have been developed under the banner of Disease-Modifying Anti-Rheumatic Drugs (DMARDs), which not only treat symptoms but also address underlying causes and reduce the rate of damage to bone and cartilage.

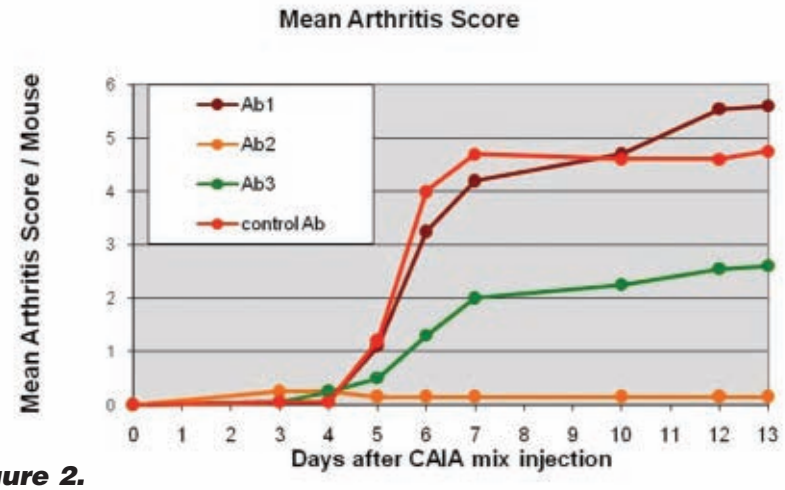


Figure 2.
Mean Arthritis score Antibody Efficacy test in CAIA model. A 99% reduction in inflammatory response was obtained with Ab2.

Example regimens include methotrexate - hydroxychloroquine, methotrexate - sulfasalazine, sulfasalazine - hydroxychloroquine, and methotrexate - hydroxychloroquine - sulfasalazine. The DMARDs are not without problems, however. Because they target the immune system, patients are immuno-compromised and are easily prone to other illnesses as a result. In addition, liver toxicity is a common side effect.

Early Treatment

It is usual to begin DMARD therapy as early as possible because in the early stages of RA, the joints are infiltrated by cells of the immune system, which can signal to one another to produce a positive feedback response and escalate disease progression rapidly. If this process can be interrupted early, then RA can be stopped in its tracks, and long-term outcomes are much improved. There is considerable benefit in establishing effective therapy very early, when there is most response to the appropriate therapy and most to gain - when RA has not destroyed tissue.

New Magic Bullet

Deiminated Peptide-Epitopes (DPEs) have recently been recognized as a very specific marker for RA. These, as previously explained, contain citrulline residues modified from arginine residues by PAD enzymes released in the progression of RA pathology. ModiQuest of the Netherlands have undertaken a number of studies into specific anti-Citrulline antibodies and have discovered a subset (family) of rCit-hMabs (recombinant human anti-citrullin epitope antibodies), which could provide a valuable therapeutic in the treatment of early onset RA. Although as yet only in preclinical development, these novel rCit-hMabs have proved their

Dose (mg/mouse)	Reduction in Inflammation
0.125	14%
0.25	21%
0.5	~100%

Table 1.
Dose Response in CAIA Model

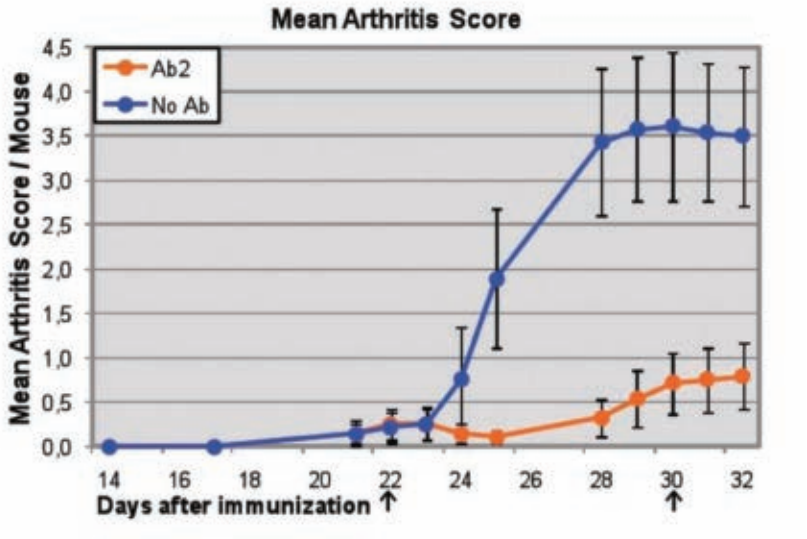


Figure 3.
Mean Arthritis score (Ab2) Antibody Efficacy test in CIA model. A 96% decrease in inflammation on day 25.

effectiveness in preventing the onset of inflammation in both the classical Collagen Induced Arthritis mouse model (CIA) and the Collagen antibody induced arthritis (CAIA) mouse mode - CAIA was a model developed in-house.

The ModiQuest rCit-hMabs antibodies are already in preclinical trials. Histology studies in mouse models treated with rCit-hMabs have shown that bone destruction is prevented and the inflammatory response significantly reduced. The utility of this new range of rCit-hMabs as inhibitors of inflammation has prompted the thought that they are likely to be valuable in the treatment of related auto-immunity mediated citrulline related inflammatory conditions (systemic lupus erythematosus, sarcoidosis, Grave's disease, osteoarthritis, etc). The mechanism of action (MoA) for these rCit-hMabs is believed to be based on their ability to shield citrullinated epitopes from the immune system. Because their MoA does not reduce the immune response, it is hoped that these new treatments will have strongly decreased side effects compared to the current DMARDs.

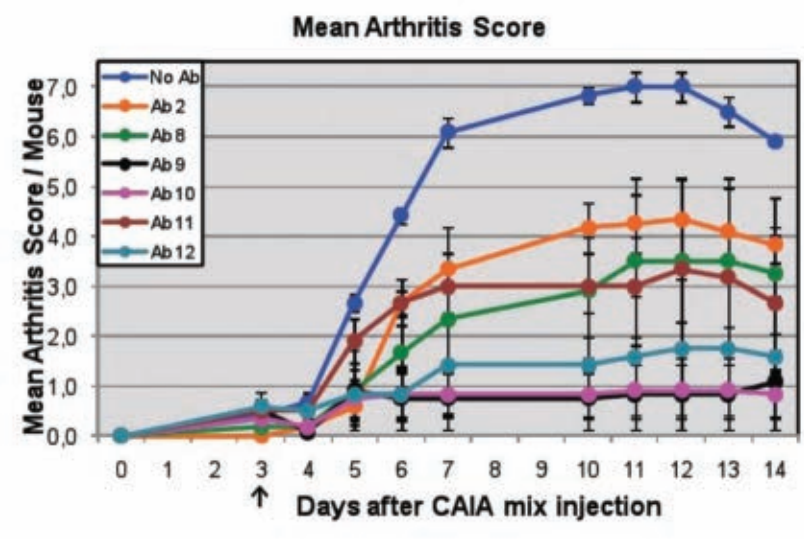


Figure 4.
Mean Arthritis score Antibody test in CAIA model comparing Ab2 and second-generation antibodies.

Experimental

Development of this new family of human therapeutic antibodies arose from an extended study by ModiQuest into the biology of citrullination in inflamed joints. In an immunology study of new DPEs involved in RA, a new generation of rCit-hMabs were recognized, and their therapeutic target DPE characterized using immunoprecipitation (IP), followed by mass spectrometry (MS) on post-lytically huPAD4 deiminated human 293F cells. Having identified and analyzed the target DPE, it was used to generate novel therapeutic rCit-hMabs, which proved in the CIA and CAIA mouse models to be highly effective in preventing the onset of inflammation. In the presence of mild inflammation, administering the rCit-hMabs resulted in stabilization of the inflammation and prevented any further increase of the inflammatory response. Histological analysis of the inflamed joints revealed that bone damage was strongly prevented when directly compared to control animals.

Mouse Studies

More than 10 animal studies were performed using the collagen antibody induced arthritis (CAIA) mouse model, as well as the classical collagen-induced arthritis mouse model (CIA). One of the first studies used the CAIA mouse model in which a total of 20 mice were divided into four groups to receive negative control antibody, Ab1, Ab2, and Ab3 at doses of 1 mg/mouse administered i.p. The arthritis response was based upon a figurative visual evaluation of mouse extremities to allocate an inflammation severity score. In this study, the results obtained by administering Ab2 indicated reduction of the inflammatory response by more than 99% compared to negative control (Figure 2).

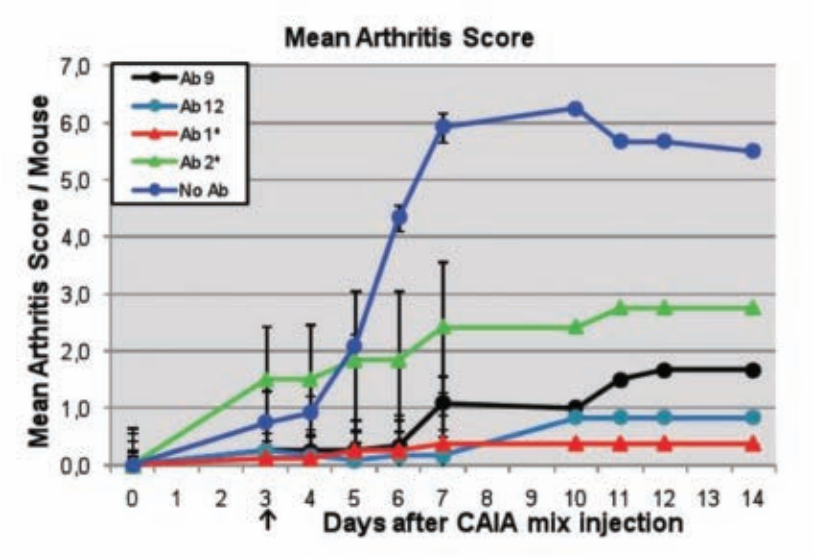


Figure 5.
Mean Arthritis score Antibody test in CAIA model comparing second-generation antibodies.

Dose Response & Safety

Following the notable efficacy results for Ab2 in the CAIA model, a dose response study for Ab2 was performed in the same model. Treatment per group (n=5) included negative control Ab, Ab2 at 0,125 mg/mouse, Ab2 at 0.25 mg/mouse, and Ab2 at 0.5 mg /mouse administered i.p. A marked reduction in inflammation varied from 14% (0.125 mg/mouse) to 21% (0.25 mg/mouse) to almost 100% (0.5 mg/mouse) when compared to the negative control underlining the therapeutic potential of the Ab2 antibody (Table 1). In a similar study to determine the effective dose and effects of overdose, no signs of toxicity were observed at levels of up to 20 mg Ab2 per mouse.

Therapeutic Concept

In a further validation of the therapeutic concept, Ab2 was tested in the classical CIA mouse model. A total of 14 mice were divided into two groups to receive either negative control (diluent) or Ab2 i.p. at (6 mg/mouse) on day 22 and day 30. While the negative control group developed maximum inflammation in the joints of their paws, Ab2 was able to decrease inflammation by 96% on day 25 compared to the control group. Reinjection of Ab2 on day 30 completely stabilized the inflammatory response (Figure 3). It is hoped that treatment using these new antibodies would only be necessary at the onset of disease and subsequent flare-ups, unlike current treatments, which require chronic treatment regimens.

Histology Studies of Mouse Tissue

To validate the fact that administration of Ab2 seems to prevent further increase of the inflammatory response, histology was performed on CAIA mice that were treated with Ab2. All known parameters for joint erosion were decreased compared to control mice with the same level of arthritis score. When scoring inflammatory cell influx, cartilage erosion, cartilage PG depletion, chondrocyte death, and bone erosion, a significant decrease was observed in the experimental group that had been treated on day 7 with Ab2, indicating that Ab2 had a strong therapeutic potential in regard to preventing joint damage during inflammation.

Development of New Therapeutic Antibodies

To increase and improve the library of therapeutic antibodies, the next step was the selection of novel therapeutic antibodies using the identified therapeutic DPE. Various new antibodies were compared to the initial identified Ab2 using the CAIA model. In the study, a total of 21 animals (three per group) received 3 days after administration of the CAIA mix, LPS only (negative control), or LPS and Ab2, Ab8, Ab9, Ab10, Ab11, or Ab12 all at 1mg/mouse i.p. As shown in Figure 4, all new antibodies demonstrated an increased inflammation inhibitor effect compared to Ab2, with a maximum of 89% inhibition. Ab9, Ab10, and Ab12 performed best and showed an inflammation inhibition of 89%, 87%, and 74%, respectively, when compared to the negative control group on day 12.

Further Refinement of the Antibody Family

Further expansion of the antibody library with mouse monoclonal antibodies was generated by immunizing mice with the original citrullinated target antigen, and subsequent hybridoma generation. These novel mouse antibodies coded Ab1* and Ab2*, were compared with Ab9 and Ab12 using the CAIA model. A total of 15 mice were divided into 5 groups. Treatment per group included negative control, Ab1*, Ab2*, Ab9, or Ab12 all at 1 mg/mouse i.p. for 3 days following the administration of the CAIA mix. Mouse Ab1* demonstrated an inflammation reduction of 94%, compared to the control group on day 10 and showed a slightly stronger inhibitor effect than Ab9 and Ab12 (Figure 5).

Summary

ModiQuest is using its proprietary technology and experience to develop a large family of novel rCit-hMabs, which has strong therapeutic potential in autoimmune disorders, such as RA, in regard to preventing the onset of the inflammation, joint damage during inflammation, further increase of inflammation and swelling, and inflammation relapse and tissue/joint damage.

Added potential benefits include a lack of side effects that are normally associated with drugs that compromise the immune system, and reduced liver toxicity compared to current treatments.

The availability of the ACPA diagnostic test for RA (as mentioned earlier) is capable of detecting RA up to 10 years before onset of the disease, significantly increases the potential of this novel therapeutic approach. The best clinical outcomes in RA result from early treatment and the new family of rCit-hMabs are of particular value in treatment of early stage RA. However, even in more progressive RA, an effective combination therapy might be possible using existing biologicals that have different mechanisms of action in conjunction with the new antibodies. ■

Jos Raats, PhD,

President & CEO
ModiQuest Research

Dr. Jos Raats established ModiQuest Research and its sister company, ModiQuest B.V, to focus on the development of novel therapeutics for autoimmune diseases in 2004. He has been involved in scientific research for more than 15 years, with over 45 publications from work at the University of Nijmegen, the Wellcome/CRC Institute in Cambridge (UK), and at the University of Minnesota, in Minneapolis. Currently, he also holds a guest appointment as Assistant Professor of Biomolecular Chemistry at the University of Nijmegen (The Netherlands). He has initiated and managed various combined projects of university research groups and commercial enterprises, including a new diagnostic target for rheumatoid arthritis (CCP), which has been developed into a highly sensitive early diagnostic test for RA (anti-CCP test).

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Executive Summary

Scott Siegel, PhD
Vice President, Business Development
Ezose Sciences Inc.

Ezose Sciences: High-Throughput Glycomics for Biomarker Discovery - Bringing Glycan Analysis Into Everyday Research

Ezose Sciences Inc. is moving to the forefront of glycomics to advance wide-ranging biomedical research initiatives, both on its own behalf and with a growing list of corporate partners. Glycomics is the study of complex sugars, or glycans. Central to this study are the glycans that attach to proteins during post-translational modification, which can crucially affect the role of the resulting glycoproteins in health and disease. Ezose's Glycan*Map*® technology platform, based on research originating from Japan, is enabling glycan analysis where the technical challenges once deterred such investigation. Indeed, by innovating high-throughput methods, Ezose is helping to expand glycomics research to a scale comparable to that of genomics and proteomics. Ezose operates as a US biotechnology company in the heart of New Jersey's "pharm-country," from where Ezose partners with the pharmaceutical industry. At the same time, Ezose maintains a Japanese heritage as an affiliate of the Diagnostics Division of Shionogi & Co., Ltd. Thus, Ezose is seeking to identify novel glycan biomarkers that can enable more efficient drug development for its partners and serve as the basis for novel diagnostics, including companion diagnostics. Through collaborations, Ezose is also exploring uses of glycan analysis in improving the development and manufacture of glycosylated biologic and biosimilar drugs. Specialty Pharma recently interviewed Scott Siegel, PhD, Vice President of Business Development at Ezose, to learn more about how this unique company is catalyzing progress across an emerging research front.

Q: ***How do you see glycomics research evolving?***

A: It has been thought for some time that glycomics research would contribute importantly to medical research if only more of the technical hurdles could be crossed. Well, now we're crossing them, and we believe glycan analysis will find applications across a very wide spectrum of biomedical research endeavors.

Identifying novel glycan patterns brings an entirely new dimension to the discovery of biomarkers, a critically important area that holds promise for more efficient and focused drug development. That's the application of chief interest to a number of our collaborators. New biomarkers can also lead to new diagnostic products, including companion diagnostics, and it goes without saying that's one of our own corporate interests.

But there's more. Glycan analysis may also prove useful in elucidating underlying biological mechanisms and disease pathways. It could offer up new drug targets, either via the glycans themselves or through the parent glycoproteins. There is also the practical application of new glycomics technology to the development and manufacture of glycosylated biologics - an area that has traditionally suffered from a lack of analytic capability. Expansion of this capability could be critically important for the next generation of development and regulatory approaches to glycosylated biologics, biosimilars, and biobetters. So the field is wide open. The human glycome remains largely

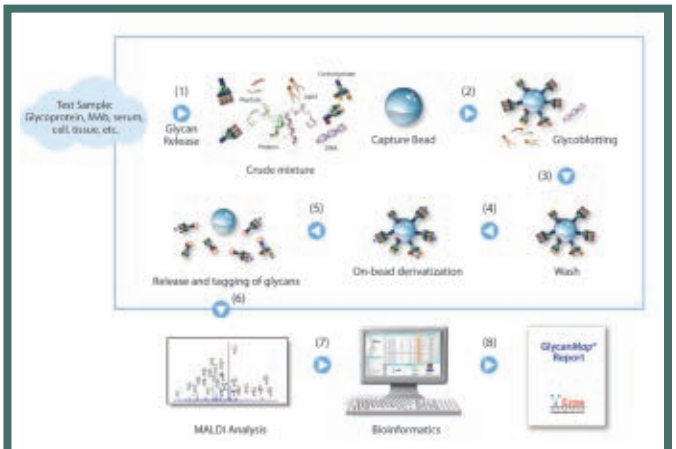
unexplored. The critical point is that we've now assembled advances in laboratory methods into a proprietary platform that makes high-throughput glycan analysis feasible. With each new study, we have the potential to uncover novel and patentable findings.

Q: ***What has Ezose been doing to realize this promise?***

A: Basically, we're making the research simpler and faster. Glycomics has been an especially tough field for the everyday lab. The reason lies in the complicated structure of glycans, their chemistry, and the difficulty in establishing broadly applicable high-throughput analytic methods.

Our solution to this problem is the GlycanMap platform. It's our proprietary, core technology. In short, its defining features are a bead-based chemoselective process that enriches oligosaccharides from crude mixtures, coupled with an automated glycan-sample-processing robotics system, MALDI-TOF mass spectrometry, and custom bioinformatics. The platform itself is the result of years of painstaking research by an interdisciplinary collaboration between leading academic and industry scientists in Japan, evidenced by the more than 20 peer-reviewed papers emanating from this research. Ezose was founded here in the US with the goal of further refining the technology and building partnerships in biomarker discovery. Our platform can accommodate up to 96 samples per robot in a single run and generate data in less than 24 hours - far faster throughput than what can be achieved through traditional methods. And it's entirely scalable. Right now, we have two robot systems but can anticipate adding more over time. We can capture and quantitate either N-linked or O-linked glycans from diverse biological samples, including serum, plasma, cerebrospinal fluid, and cell and tissue lysates. A small sample suffices for a full analysis.

Now that we have the GlycanMap platform up and running, we can start to identify the characteristics of glycans in clinical-trial serum and tissue samples. Think of all of the freezers all over the world that are holding serum and tissue samples from so many previous clinical studies. The intent in creating these banks was to store such samples until new and exciting methods of analysis came along. We intend to be one of those new methods, looking for glycan markers that correlate with disease state or response to therapy. We need only a small amount of sample for our initial analysis, preserving the bulk of the sample for other approaches yet to come. And, with our ancillary glycomics technologies, we can also begin to identify the parent glycoproteins containing glycans of interest. We believe this work may also lead to new drug targets and therapies, possibly including therapeutic vaccines as well as biologicals and small molecules. As I said, the field is wide open, and we and our partners are exploring it.



The Glycan*Map*® platform is an automated high-throughput method of identifying and quantitating glycans, the complex sugars that are attached post-translationally to proteins, affecting protein function and stability. Because the Glycan*Map*® method uses 96-well plates, many biological samples can be tested simultaneously, such as multiple patient samples (serum/plasma, CSF, cell or tissue lysates) or multiple batches of a biologic. Glycans are first released from their parent proteins (1) and attach to a bead through a selective reaction called glycoblotting (2). Following a wash (3) to remove other materials (proteins, salts, lipids, etc.), the glycans are derivatized to stabilize the labile sialic acid residues (4). Glycans are then simultaneously tagged and released (5) prior to analysis by MALDI-TOF mass spectrometry (6). Proprietary bioinformatics identify the composition and concentration of each glycan in a sample (7) and generate a Glycan*Map*® report (8), which, for biomarker studies, also includes statistical analysis and interpretation of glycan changes with respect to disease/treatment. Steps 1-5 (enclosed in the blue box) are fully automated.

Q: ***Are there yet any clinical data that show the relevance of glycosylation to health and disease?***

A: In fact, there are several good examples. First, two well-known glycan biomarkers are already in widespread clinical use today. CA 19-9 is a sialylated Lewis antigen of the MUC1 protein, and is used to evaluate patients with suspected pancreatic cancer and to monitor therapy. A test is also now available to determine a variance in glycosylation of the tumor marker alpha-fetoprotein (AFP). Measuring the variant form, AFP-L3, as a fraction of total AFP levels helps to provide an early assessment of liver cancer. While these examples validate the utility of glycan biomarkers in medical practice, we believe further study will uncover many more exciting biomarker candidates.

Second, in the case of biologic and biosimilar drugs, the evidence that glycans and glycosylation are critical factors is also strong. Not only is it well understood that the pharmacokinetics and immunogenicity of certain glycoprotein drugs can be significantly

affected by glycosylation patterns, but they are also known to impact the functionality of the molecule - and its concomitant clinical efficacy. A good example of this latter effect is with monoclonal-antibody therapeutics, a major and growing class of drugs. In this case, the presence or absence of a single glycan moiety, fucose, can significantly alter the functionality of the antibody in key immunologic or "effector" function, which can directly impact its clinical efficacy. So the evidence is clear, glycans can be a hugely important factor in determining the biological activity and function of proteins in a variety of ways.

But the need has remained for a high-throughput method to enable more of these medical advances faster. In a collaborative study with Genentech, we compared the GlycanMap method and a traditional fluorescent HPLC method for recombinant glycoprotein characterization. The comparison shows good agreement between the two methods, but only the GlycanMap method yields absolute quantitation and enables high-throughput capability.

So the technology is sound. Now we and our partners are bringing it to bear on biomedical questions.

Q: ***How does Ezose fit into the bigger picture at Shionogi?***

A: Since Ezose was founded in 2009, it has operated as a US biotechnology company, based in New Jersey. That's the way Shionogi set it up, with Japanese and American scientists working together in the US. So we are structured to move with the speed and agility that you would associate with an entrepreneurial small biotech. Yet we have the resources of an international pharmaceutical company behind us.

Within Shionogi, we are affiliated with Shionogi's Diagnostics Division. This alignment makes perfect sense as it marries the front-end biomarker discovery at Ezose with the back-end diagnostics development and commercialization capabilities of Shionogi. For our corporate parent, we can turn our discoveries into diagnostic products and bring them to market.

For our partners, on the other hand, we bring an entirely new dimension to the discovery and development of the biomarkers they need to enable more efficient drug development and facilitate advances in the growing field of personalized medicine. We are always looking to enter more collaborations, with a focus on biomarker research.

Given the potential scope of glycomics research, and our experience to date, we believe our work with other companies will encompass a wide range of scientific inquiry and product development.

Q: ***What has been your partnering experience to date?***

A: We're busy. Since starting operations just over 2 years ago, we've completed over a dozen projects with 8 different partners. Others are still ongoing, and new ones are being explored all the time. Everybody has known that glycosylation of proteins can be critical to many cellular activities - cell signaling, immune modulation, receptor binding. But glycan analysis was just too difficult, too tedious. It didn't become part of the usual ensemble of investigative techniques.

Now that's changing. When potential partners see what we can do, they may be surprised, but they're usually interested. They know they can access glycomics capability through us. Glycomics is our sole focus. Our partners don't have to incur the expense of creating a full capability in-house.

We tailor every agreement to our partner's need. We're now doing more research collaborations, but we also do turnkey analytics on a project basis. We will sometimes work under service agreements, too, especially in biologics projects. It depends upon the situation. We work out the respective intellectual property rights in a way that serves both parties' needs, especially when new biomarkers may be discovered. We maintain a firewall with regard to Shionogi to protect any proprietary information relating to our partners. Looking forward, you can imagine that we will be forming some long-standing relationships with our partners, as a number of them are primarily interested in biomarkers to accelerate drug development, and our internal emphasis is on diagnostics. So as glycan markers lead to a new pharmaceutical, we can be working on the companion diagnostic.

Typically, our partners want to do a feasibility study before committing to a significant relationship. It was earlier studies with Merck, for example, that led to our recently announced collaboration with Merck, where we're using our GlycanMap platform to help discover glycan biomarkers relevant to diabetes.

At scientific congresses, we've reported studies in cooperation with some of our partners. We've done that with Genentech, with the National University of Ireland, Galway, and with Hokkaido University. We hope to do further joint presentations and publications.

Word is getting out. Glycomics is doable. ■

May 2012
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The Dominator

By: John A. Bermingham

Every company has a Dominator, or two or three, on staff, and they have a bad habit of prolonging a meeting and, in most cases, monopolizing it. Just when the meeting participants are ready to set action plans and next steps or to end the meeting, The Dominator continues on. This results in a mob reaction of negative body language, rolling eyes, and stares at each other across the conference table. If you are chairing the meeting or the committee, then you have to deal with this person, and that means finding out why the person has taken on the persona of The Dominator.

One reason could be that this person wants more detailed information because he or she wants to be a good participant and contribute to the meeting in a responsible manner. If this is the case, I believe the best solution is to meet with The Dominator prior to the meeting to answer questions he or she may have or to supply the additional information being sought. They should understand their participation is important but the meeting can only be allocated so much time.

It could be that The Dominator wants everyone to know how well prepared they are for the meeting and is proving it by acting in this manner. In this case, I would meet with The Dominator privately and say that you and others are wondering why and where all the questions and concerns are coming from that he or she is bringing up at the meetings. You could then suggest that the two of you meet before the meeting to address the questions and concerns ahead of time so the meeting does not run long, negatively impacting everyone's schedule.

Another reason, and the one I have seen most often and is the most dangerous, is that The Dominator has a hidden agenda. The unending questions, confrontation, challenges, push back, and negative opinions are all for a specific reason. Is the big D trying to impress someone in the meeting? Say your boss? His or her boss? Is this person trying to take over your meeting or committee leadership for their own career benefit?

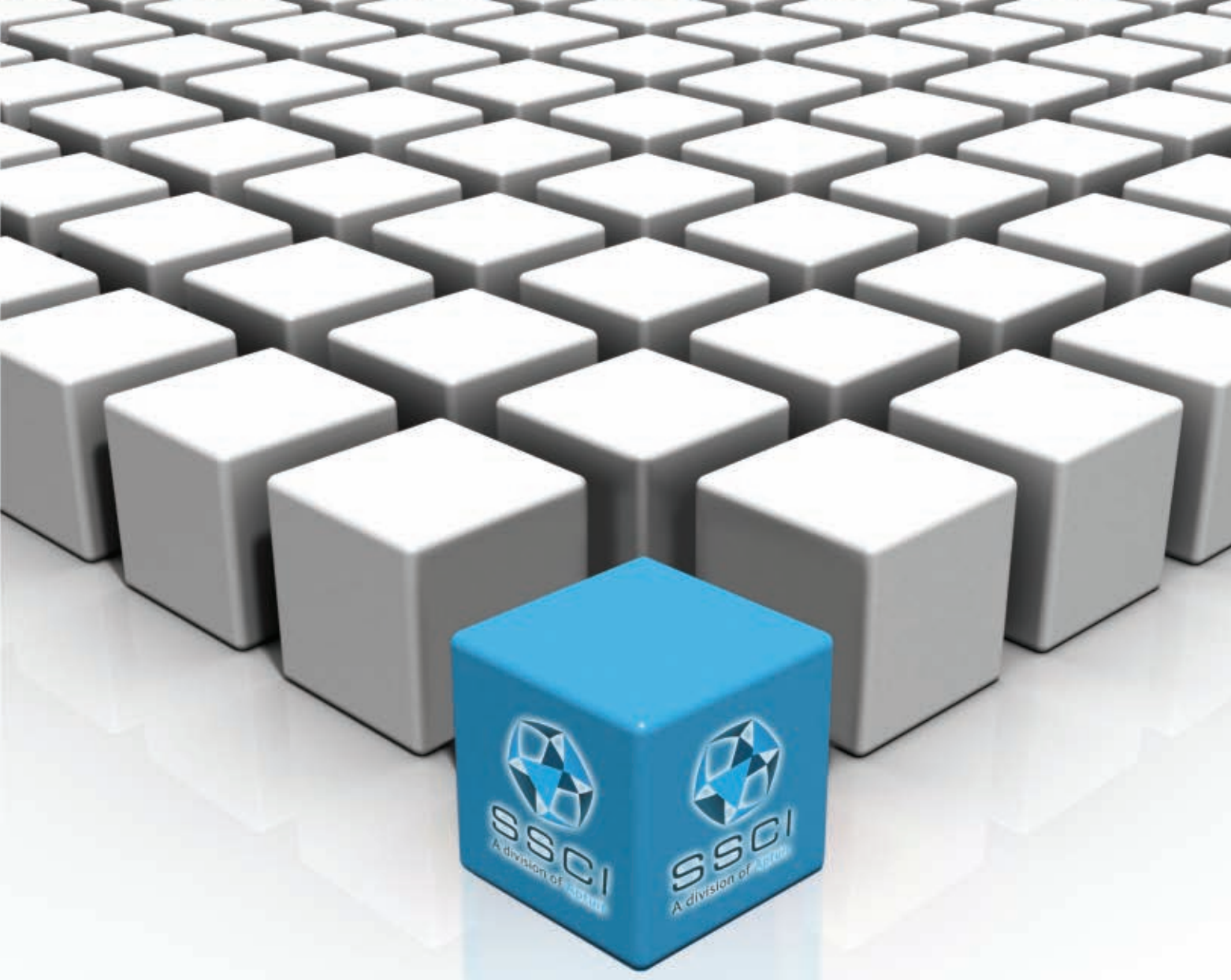
Regardless, you have to deal with this situation and person. You cannot let it go as you will lose in one way or another.

I would take The Dominator aside and discuss the issue with them in a direct manner and let your feelings be known without sounding like you are whining or threatening. Let them know you value their opinion but not one offered in a negative or abusive manner. Work on the company culture with them as to how people work together for the benefit of the company. Unfortunately, sometimes this does not work with certain people.

In that case, I have often enlisted the aid of Human Resources to help with this situation to include a self-assessment by The Dominator with a feedback analysis by HR, the inclusion of an Executive Coach, a 360 Degree Feedback meeting, or just finding a way to get them off of the committee or off the meeting attendee list. But whatever you do, you must deal with The Dominator quickly! ◆

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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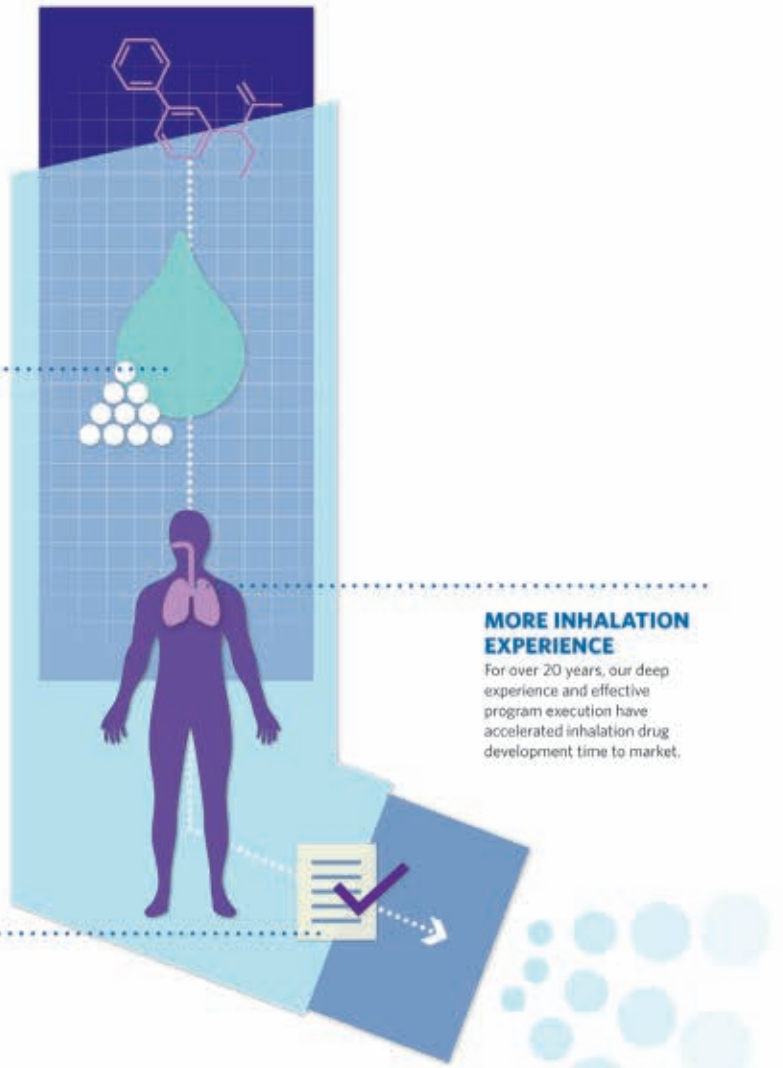

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