Drug Development & Delivery

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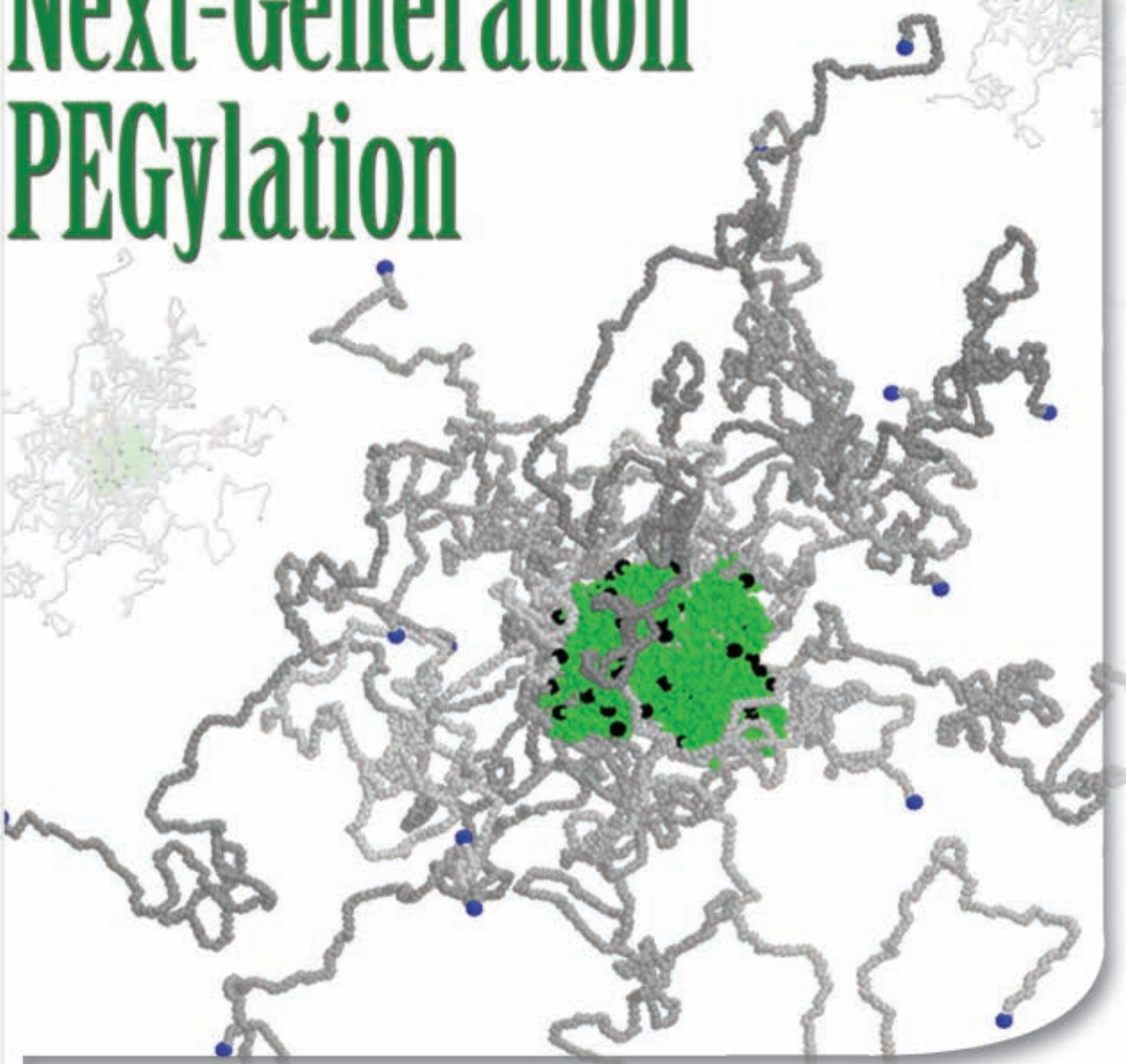
Next-Generation PEGylation



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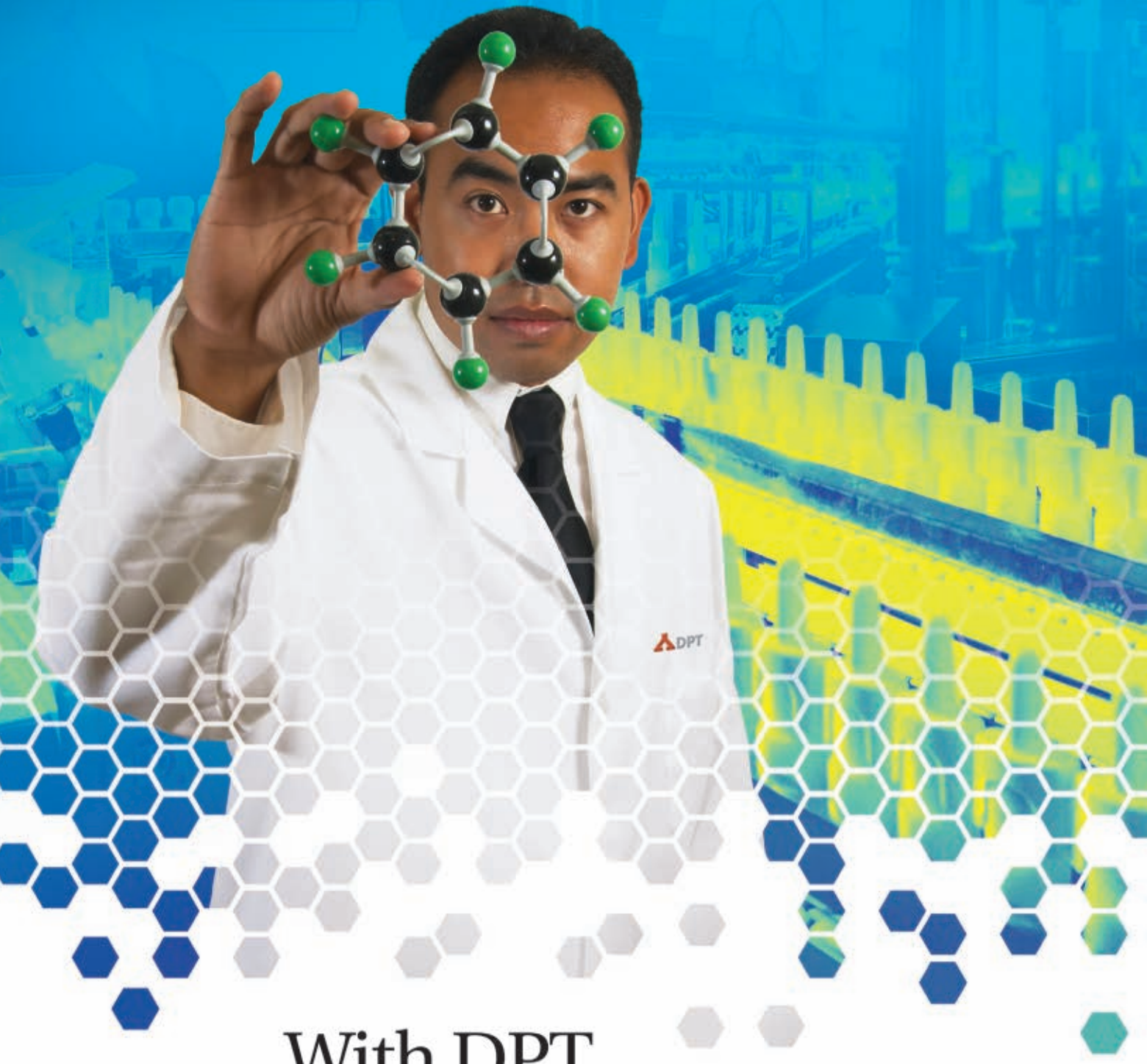

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Corporate/Editorial Office
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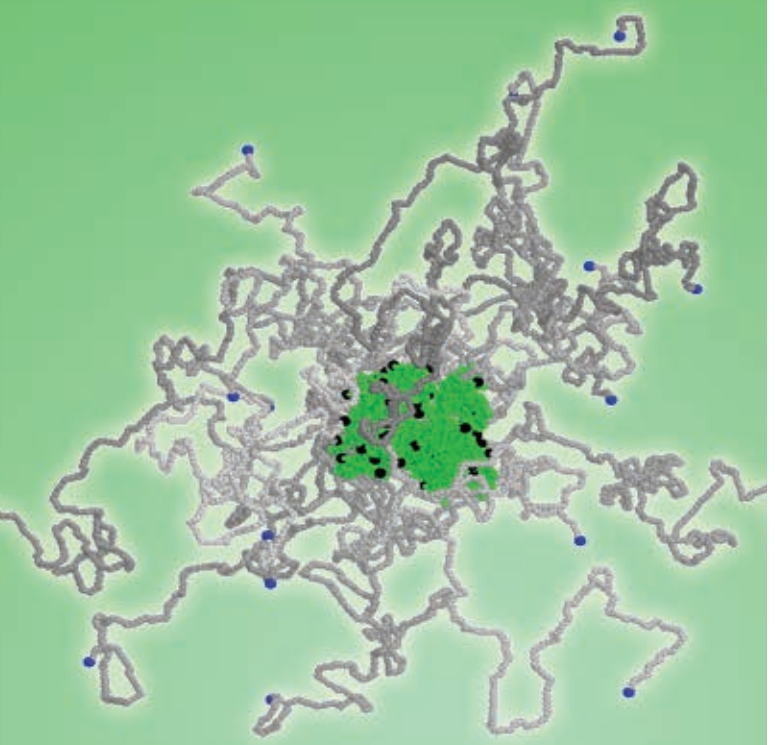
Next-Generation PEGylation



"The ensemble of data presented here and in our previous publications suggests that clinically important decreases in the immunoreactivity of a next generation of PEGylated drugs (PharmaPEG® conjugates), including proteins, liposomes, nucleic acids, viruses, and red blood cells, may be attainable by the use of monofunctionally activated hydroxyPEGs instead of methoxyPEGs in their synthesis."

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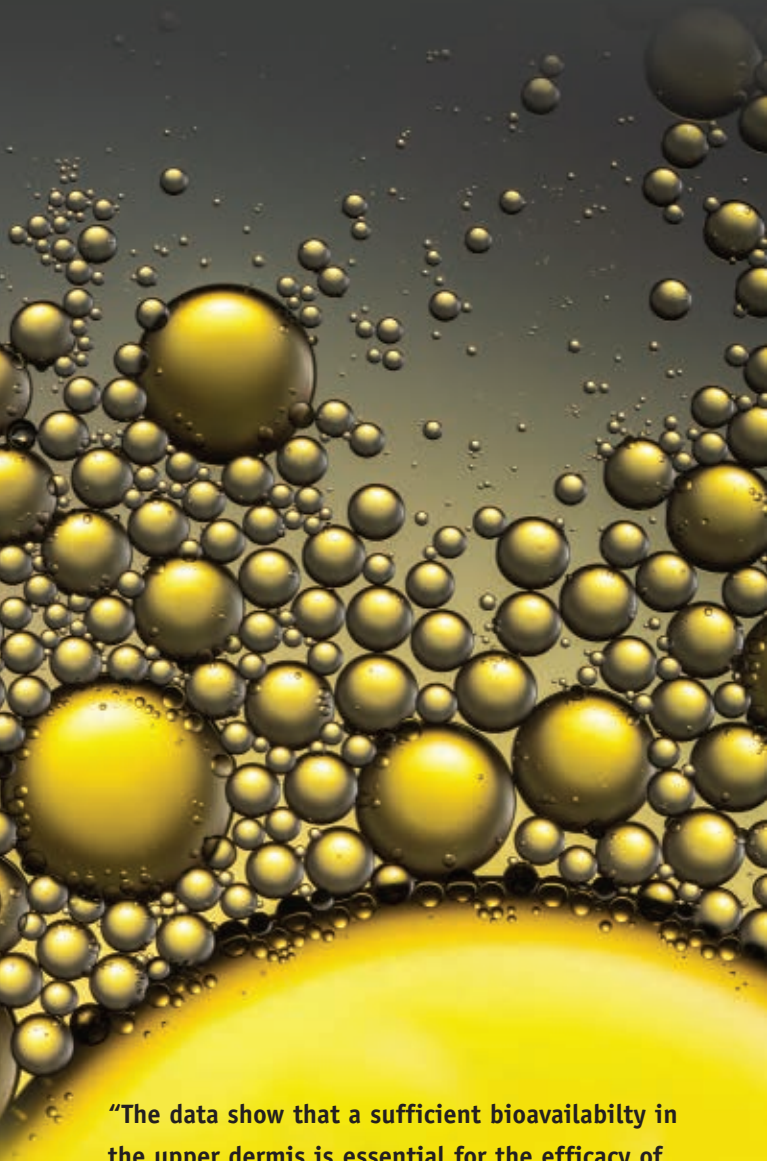

"The data show that a sufficient bioavailabilty in the upper dermis is essential for the efficacy of Tacrolimus. Both the nuclear hyperparakeratosis, which can be detected micromorphologically, as well as acanthosis as part of the pathological condition of the psoriatic epidermis, alter the conditions for diffusion fundamentally. To overcome this galenic problem, a colloidal preparation, a microemulsion, has been developed that meets the specific conditions for penetration of the psoriatic skin, and achieves the required bioavailability of the drug in the underlying tissue, which cannot be achieved by conventional formulations."

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The DDS Company Viewpoint on Partnering
3M Drug Delivery Systems • Mannkind • Steadymed

Wall Street Update on Drug Delivery Business Models
Alex Zisson, Partner, Thomas McNerney & Partners

Developing & Commercializing Early Stage Technologies from Academia
Led by Enlight BioSciences & BioPontis with Pfizer and UC Santa Barbara

Strategies for Developing and Commercializing Biobetters & Biosimilars
Momenta Pharmaceuticals • Shire HGT • STC Biologics

How Drug Delivery is Changing the Therapeutic Landscape
Alcyone • US CEEDD, GSK • Alnylam Pharmaceuticals • Medtronic • Shire HGT

DRUG DELIVERY PRESENTATIONS

Track One - *Drug Delivery Formulation Technologies*
Company presentations on formulation technologies that can enhance, enable, or facilitate delivery of a drug.

Track Two - *Drug Delivery Device Technologies*
Company presentations on needle-free delivery devices, auto injectors, pen injectors, powder injection devices, microneedle systems, inhalation devices, nasal delivery devices, non-biodegradable implants or similar, transdermal patches, patch pumps and other wearable drug administration systems, etc.

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Market News and Trends

Piramal Healthcare to Buy US Drug Data Firm for $635 Million

Piramal Healthcare Limited recently announced it has agreed to acquire Decision Resources Group for a consideration of approximately $635 million. Decision Resources Group provides high-quality, web-enabled research, predictive analytics via proprietary databases and consulting services to the global healthcare industry. With 20% CAGR for the last 5 years, it is one of the fastest growing companies in the $5.7-billion global healthcare information industry. DRG projects revenues of $160 million for 2012. Forty-eight of the top 50 global pharmaceutical companies are its customers, and it has an overall customer retention rate of 95%.

DRG is focused on three market segments: (1) the biopharma business unit provides reports, databases, and advisory services on drug utilization trends and forecasting in a variety of therapeutic areas; (2) the market access business provides database and analytical services that healthcare companies use to assess the current and future opportunity of their products' acceptance into a market; and (3) the medical technology business provides actionable insights and data on the medical device markets.

DRG's products include detailed market assessments based on a specialized network of over 125,000 healthcare professionals (primarily physicians), proprietary databases of market information, and detailed analytical reports on specific therapeutic areas. The three market segments that DRG covers are worth approximately $2.5 billion, leaving considerable room for DRG to continue to grow its revenues.

After the sale of its healthcare solutions business to Abbott Laboratories in May 2010 for $3.8 billion, Piramal Healthcare has embarked on a strategy to acquire global growth businesses with sustainable returns.

Following the completion of the DRG acquisition, Piramal will operate DRG as a stand-alone business. DRG will remain headquartered in Burlington, MA. The company will continue to be led by Mr. Hoenigsberg and the existing senior management team. The transaction is expected to close by the June 30, 2012, subject to customary regulatory approvals and closing conditions.

Agilent to Acquire Cancer Diagnostic Company for $2.2 Billion

Agilent Technologies Inc. and EQT, the Sweden-based private equity group, recently announced the execution of a definitive agreement for Agilent to acquire Dako, the Denmark-based cancer diagnostic company. The $2.2-billion acquisition (on a debt-free basis) is the largest in Agilent's history.

"In the rapidly growing diagnostics market, Dako's products and capabilities are a strategic complement to Agilent's existing offerings," said Bill Sullivan, Agilent President and Chief Executive Officer. "Dako is one of the world's leading providers of cancer diagnostics tools, and together we will be able to develop a wider range of products that help in the fight against cancer."

"Agilent's strategy in acquiring Dako is about strengthening the company's presence in life science and about revenue growth," continued Mr. Sullivan. "Dako employs extremely talented people with specialized expertise that we highly value. Their knowledge and experience will be very important as we move forward together."

Dako provides antibodies, reagents, scientific instruments, and software primarily to customers in pathology laboratories to raise the standards for fast and accurate diagnostic answers for cancer patients. Dako also collaborates with a number of major pharmaceutical companies to develop new potential pharmacodiagnostics, also called companion diagnostics, which may be used to identify patients most likely to benefit from a specific targeted therapy. Dako's products are sold in more than 100 countries, and in 2010 its annual revenue was approximately $340 million. The company employs more than 1,000 people, primarily in Denmark, in Carpinteria, CA, and other parts of the world.

Agilent Technologies Inc. is the world's premier measurement company and a technology leader in chemical analysis, life sciences, electronics, and communications. The company's 18,700 employees serve customers in more than 100 countries. Agilent had net revenues of $6.6 billion in fiscal 2011.

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Ra Pharma Closes $8.6-Million Second Tranche of $27 Million Series A

Ra Pharmaceuticals recently announced it is pursuing hereditary angioedema (HAE) as a lead program, leveraging the company's proprietary Cyclomimetic drug discovery and development platform. HAE is a rare, but serious and often fatal disorder of the innate immune system that causes intermittent attacks characterized by swelling and pain of the face, airways, and intestinal tract. Ra Pharma has discovered HAE drug candidates designed to prevent these attacks by inhibiting plasma kallikrein, which controls the release of bradykinin, a mediator of swelling and pain associated with HAE attacks. Cyclomimetics are a new drug class with the diversity and specificity of antibodies, coupled with the beneficial properties of small molecules.

"Ra Pharmaceuticals is developing Cyclomimetics to address diseases with significant unmet medical need, such as HAE," said Doug Treco, PhD, Co-founder, President, and CEO, Ra Pharmaceuticals. "The only FDA-approved treatment for the prevention of HAE attacks is delivered intravenously every 3 to 4 days and produced from human blood. Our synthetic Cyclomimetics are easily produced, and could offer a stable, highly potent option for patients suffering from HAE. In addition, Cyclomimetics have the potential to be orally available, which would significantly increase the quality of life for patients with HAE. "We will continue to build out our pipeline using our high-diversity drug discovery platform capable of generating optimized lead candidates in a matter of weeks, but also hope to secure discovery and development partnerships as we gain momentum with our internal programs. The company is on sturdy ground with the recent second tranche closing of our $27-million series A financing and a strong IP portfolio covering our lead candidates, display technologies, and the ability to generate peptidomimetic libraries with multiple non-natural amino acids."

Cyclomimetics are peptide-like molecules characterized by their cyclic structure and backbone and side-chain modifications that provide unique, beneficial properties not found in natural peptides. The result is a highly specific and stable molecule with improved cell permeability and the potential for greatly increased bioavailability.

Cyclomimetics result from the company's proprietary Extreme Diversity platform. The platform is unique in that it combines in vitro display technology, a completely defined translation system, and a wide variety of non-natural amino acids. Unlike certain other display technologies, in vitro display does not require the use of a bacterial or yeast host, and it can produce libraries of 10 to 100 trillion members. Further, the technology has the potential to address protein-protein interactions and other previously undruggable targets.

Mucosis Announces Positive Data for Mimopath Platform

Mucosis B.V. recently announced Phase I clinical data providing proof-of-concept that Mimopath-based mucosal vaccines are safe and well tolerated as well as able to produce balanced immune responses in both circulating blood and the respiratory tract.

Mucosis, in conjunction with the Centre for Human Drug Research (CHDR; Leiden, the Netherlands), conducted the clinical trial to assess the safety, tolerability, and immunogenicity of nasally administered FluGEM, a Mimopath-based mucosal influenza vaccine containing bacterium-like particles (BLPs) in addition to a standard amount of trivalent split influenza antigen. This Phase I study, which began in March of 2011, was a randomized, blinded, placebo-controlled study and enrolled 60 human subjects 18 to 49 years of age who received either standard amounts of trivalent split influenza antigen or FluGEM vaccine containing increasing doses of BLPs.

Nasal FluGEM was well tolerated with no vaccine-related serious adverse events, and the rate of overall events was comparable to that in the control group. Moreover, FluGEM induced strong hemagglutination inhibition (HAI) antibody responses against the influenza H1N1, H3N2, and B strains. The systemic HAI responses met the seroconversion criteria for licensure as outlined in the EMA guidance document for influenza vaccine licensure, a difficult-to-reach endpoint for mucosal vaccination. Seroconversion rates (ie, percentage of subjects with a 4-fold or higher rise in HAI titer from baseline) ranged from 54% for H3N2, 46% for H1N1, and 50% for B strains. In addition, a potent mucosal immune response was observed in 77% of the subjects, as evidenced by secretion of influenza specific immunoglobulin A molecules in the nasal cavity.

Mucosis's lead vaccine candidate, SynGEM, is designed to prevent infections with Respiratory Syncytial Virus (RSV), which affect over 60 million people worldwide ranging from the very young to the elderly with more than 1 million hospitalizations annually. An RSV vaccine does not yet exist.

Mucosis B.V. is a clinical-stage Dutch biotechnology company with a proprietary platform technology, Mimopath, on which it develops mucosal vaccines with improved efficacy. Mucosis's lead product is SynGEM, a vaccine to prevent RSV viral infection. In addition, the company develops PneuGEM, a vaccine to prevent diseases caused by pneumococcal bacteria and FluGEM, a vaccine to prevent influenza. Mimopath-based vaccines can be administered needle-free in the nose and mouth, evoking a more natural immune response with a broader base of protection.

The Mimopath technology is based on Lactococcus lactis, a safe bacterium commonly used in the food industry. Mucosis has developed a robust technique to formulate the L. lactis bacteria into non-living bacterium-like particles (BLPs) that can be loaded with antigens from viral, bacterial, parasitic, or tumor origin. The antigen-covered BLPs form a vaccine that can be delivered into the nose or mouth, without the need for a needle. These vaccines raise protective immunity by activation of both the innate and the adaptive immune system.

Relay Technology Launches Intelligence & Data Visualization Solution

Relay Technology Management recently announced the official launch of Business Development Live (BD Live!) - a new unified, real-time data visualization, comparative asset analysis and tracking platform for the life sciences industry. Relay TM supports life science business development, and licensing professionals validate opportunities and discover new assets.

"BD Live! provides access to a comprehensive information repository on biopharma assets and other relevant entities and utilizes cutting-edge data visualization technologies to create interactive dashboards that dramatically improve the user experience," said David Greenwald PhD, Relay TM's Co-founder and Managing Director. "We are excited to open the platform more broadly after having successfully tested our innovative approach with a number of leading pharmaceutical and biotech companies. We look forward to working with customers to fulfill their business intelligence needs."

"Identifying and evaluating assets, and finding the most appropriate partners for pharmaceutical companies is time-consuming, resource-intensive, and often based on partial information," shares Peter Collins, Business Intelligence Director at the Nature Publishing Group, which created a collaborative partnership with Relay and made a strategic investment in the company in 2011. "Relay is uniquely positioned to bring much needed objective data aggregation and analysis to speed up the drug development process."

Relay TM complements competitive intelligence by assessing the relative attractiveness of life science assets - drugs, targets, researchers, and institutions, historically and in real time, from one screen.

Cornerstone to Acquire EKR Therapeutics for $150 Million

Cornerstone Therapeutics Inc. and EKR Therapeutics, Inc. recently announced they have entered into a definitive merger agreement whereby Cornerstone Therapeutics will acquire EKR Therapeutics. The acquisition expands Cornerstone's product offerings and commercial infrastructure in the hospital market. The transaction is subject to customary closing conditions, including adoption of the merger agreement by EKR's stockholders and expiration or termination of any waiting period under US anti-trust laws. The transaction is currently expected to close in late June 2012.

As part of the transaction, Cornerstone will acquire product rights to CARDENE I.V. and RETAVASE. CARDENE I.V. is indicated for the short-term treatment of hypertension when oral therapy is not feasible or desirable. RETAVASE is indicated for use in the management of acute myocardial infarction (AMI) in adults, for the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. In 2011, EKR generated $58 million in net revenue, primarily from sales of CARDENE I.V. In 2013, Cornerstone is targeting FDA approval of a new active ingredient supplier and relaunch of RETAVASE, which could increase revenues significantly versus 2012. These products complement Cornerstone's existing hospital products: CUROSURF, which is indicated for the treatment of neonatal respiratory distress syndrome (RDS) in preterm infants, as well as CRTX 080, a product candidate for treatment of hyponatremia.

Under the terms of the agreement, Cornerstone will make an initial cash payment of approximately $125 million, subject to adjustment in accordance with the terms of the merger agreement, and make certain additional payments contingent upon the achievement of certain milestones related to regulatory approval of a new active ingredient supplier for RETAVASE and sales of RETAVASE during approximately the first 3 years following commercial relaunch. Pursuant to the merger agreement, a newly formed, wholly owned subsidiary of Cornerstone will merge with and into EKR, with EKR continuing after the merger as the surviving corporation and a wholly owned subsidiary of Cornerstone. The EKR Board of Directors has approved the merger agreement and recommended its adoption by EKR's stockholders.

Nuevolution Receives Milestone Payment From Boehringer Ingelheim

Nuevolution A/S recently announced that it has received a milestone payment derived from its collaboration with Boehringer Ingelheim. The payment was triggered following identification of potent small molecule compounds that have been shown to disrupt the protein-protein interaction of an undisclosed therapeutic target.

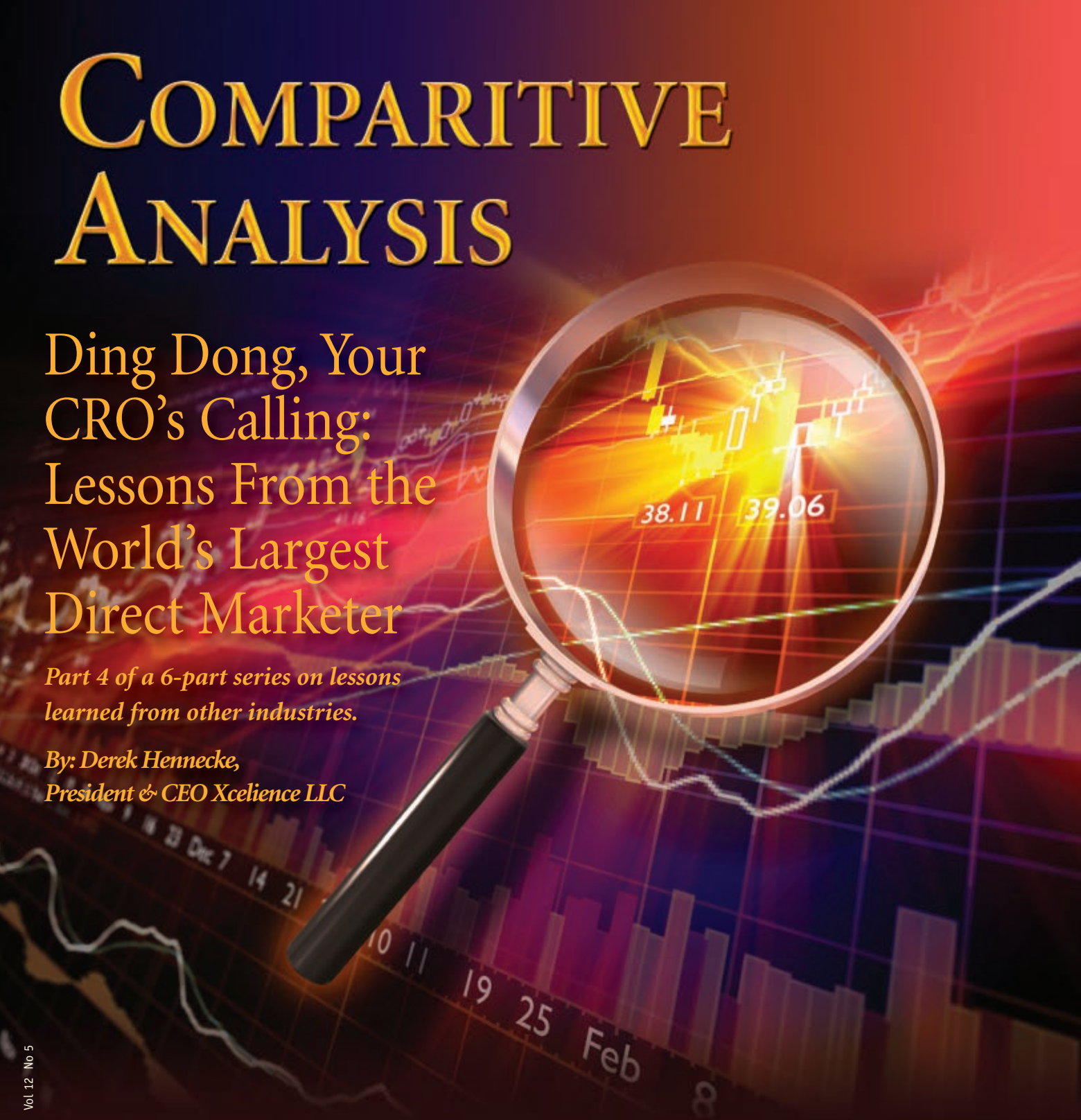
In its collaboration with Boehringer Ingelheim, Nuevolution is applying its proprietary Chemetics technology to identify novel small molecule leads against drug targets of interest to Boehringer Ingelheim. Nuevolution has so far screened about 300 million small molecules against the first of the targets selected under the collaboration.

The Chemetics platform uses innovative DNA labeling to allow fragment-based drug screening at an unprecedented scale forming small molecules and synthetic biologics. In existing collaborations, Nuevolution has successfully identified drug-like small molecules for several challenging target classes, including enzymes and protein-protein interactions.

"We are very pleased about the results that have been obtained thus far in the collaboration with Boehringer Ingelheim. The use of ultra large libraries under the optimized work flow implemented by Nuevolution during the last couple of years, has allowed the rapid identification of interesting compounds for this target," said Alex Gouliaev, CEO of Nuevolution A/S. "The current results provides a promising basis for the further compound optimization."

Boehringer Ingelheim and Nuevolution entered into the collaboration in September 2011. Nuevolution is a leading small molecule lead discovery company founded in 2001 and based in Copenhagen, Denmark. The company has developed Chemetics, a unique, patent-protected hybrid of proven wet chemistry and molecular biology, which represents the ultimate fragment-based drug discovery technology. Chemetics enables rapid synthesis and DNA-tagging of hundreds of millions of chemically diverse drug-like small molecule compounds and the efficient screening of these, facilitating the identification of potent drug leads at unprecedented quantity, quality, and speed compared to existing drug discovery technologies. Nuevolution's library collection currently exceeds 1 billion small molecule compounds and synthetic biologics for screening.

COMPARITIVE ANALYSIS



Ding Dong, Your CRO's Calling: Lessons From the World's Largest Direct Marketer

Part 4 of a 6-part series on lessons learned from other industries.

By: Derek Hennecke, President & CEO Xcelience LLC

When the glamorous 41-year-old Andrea Jung took over Avon in June 2004, the investment world swooned. Clothed in Chanel suits, with an elegantly coordinating resume rich in companies like Neiman Marcus and Bloomingdale's, share prices tripled after she took office. Invited onto the boards of Apple and GE, she rose to become the sixth most powerful businesswoman in the world last year, according to Fortune. Chic and stylish, Ms. Jung was the epitome of everything Avon wanted to be.

And yet, Avon is nothing like Andrea Jung. Avon is not a retail franchise like Neiman Marcus. Avon is a direct-marketing company. Not just any direct-marketing company, Avon is by far the biggest direct-selling enterprise in the world, with 6.4 million active reps promoting its products every day. Avon reps don't wear Chanel suits. Most earn less than $50,000 a year.

They represent Avon for extra pocket money, earning on average below the minimum hourly wage.

Under Jung, the company tried to move down a path toward a more upscale image, and away from direct marketing, competing with the cosmetics counters at the local mall. The 126-year-old company's classic ad campaign, Ding Dong, Avon's Calling, was replaced by The Company for Women, a slogan befitting a business moving beyond direct marketing. Mall kiosks were opened, and JC Penny debuted an Avon line.

Meanwhile, support for direct marketers fell short of the rep needs. In the US, direct marketing is considered a somewhat dated idea, but in Brazil, the sales model enjoys immense popularity. In 2010, Brazil surpassed the US as Avon's largest market. A year later, in response to complaints about lack of technical support in the country, Avon announced a new information management system for Brazil that had been 2 years in development. Two years proved insufficient: the system was a disaster. Late orders were missed, products arrived behind schedule, orders weren't filled, and shipments were delayed. Sales dropped 8% in one quarter. Poor execution.

To make matters worse, the company took a serious blow to its reputation for integrity. The SEC is currently pursuing two investigations into Avon; one looking at whether Avon improperly shared information with analysts, and another into allegations of bribery by employees in China and other countries.

As I write, Avon shares sell for just over $21 per share, or less than half of their value shortly after Jung came on board. In March, a German holding company made a $10-billion unsolicited offer for Avon - something no one could've imagined 10 years ago when the market value of the company was $21 billion. In April, the company announced that Jung would step down as CEO, replaced by J&J veteran Sherilyn McCoy.

A FLAWED EXECUTION OF STRATEGY

Was Jung's strategy flawed? Was it a mistake to try to bring Avon more high-end? Maybe. Maybe not. Presenting a more sophisticated image is a reasonable strategy for a beauty company. And certainly, Avon is acutely aware that direct selling as a method has been falling out of favor in the US. The fifth largest beauty company in the US has reason to worry it could be left behind the competition, at least in the US market. The problem wasn't the strategy, it was the implementation.

First, they chose to concentrate on opening new retail channels, rather than working the strategy through their existing massive direct sales force. Can any direct sales organization in the beauty industry be high-end? I don't know. But if there

was ever a company to test that idea, it's Avon. They chose instead to go retail. Their second questionable execution was in their choice of retail outlets - mostly mall kiosks, Sears and JC Penny - not a very convincing way to pursue an up-scale strategy.

Avon's purchase of Silpada, the direct-market jewelry company was a similar head-scratcher. While there are some superficial convergences in the two businesses - they both sell directly to women - jewelry is a substantially different business model and very susceptible to commodity price fluctuations. Avon's purchase of Silpada would be akin to Xcelience opening up a division devoted to multivitamin research. It's all about pills, right? Wrong. When silver prices spiked, the company was caught unprepared and had to take a $263 million write-down in the fourth quarter of last year.

AVON DOESN'T SELL COSMETIC'S TO WOMEN: IT SELLS INCOME-EARNING OPPORTUNITIES TO REPS

Avon's most glaring mistake was its neglect of its massive direct marketing sales force. Under Jung, the world's largest direct marketing company failed to embrace who it was. For the past century, Avon did not sell cosmetics to women. It sold income-earning opportunities to reps. By frustrating reps with poor technology and undercutting them by selling in retail outlets, Avon alienated the world's largest sales force.

Our industry shares this with Avon. CROs are direct marketers. There is no Neiman Marcus or JC Penny of CROs, nor will there ever be. Our customers are too few; our products too cerebral for any retail strategy. Instead, our industry uses a mixture of paid and unpaid reps. The paid reps are our sales force. The unpaid reps are consultants. The regulatory consultants are by far the most important, and my sales force would be the first to tell you this. Words of praise for Xcelience out of the mouth of a consultant - one with the trust and the ear of one of our potential clients - are worth dozens of sales calls.

As the manager of a direct-marketing company, I understand that only a quarter of our efforts should go into persuading new clients to come to us, and about 75% should be spent on delivering operationally so that the clients' consultants can see that recommending Xcelience will enhance their reputation for providing the highest quality of advice. The last thing I would ever do is attempt a strategy that made the consultants angry with Xcelience.

MEDICAL JOURNALS: ANGERING CONSTITUENTS

And yet, companies alienate their bread and butter all the time. Take medical journals. The publishers of some of these periodicals have been packaging their most sought after titles with other less-desirable journals and selling them exclusively in this higher-cost bundled format.

Again, theirs might have been a good strategy, but for the execution. The customers needed to feel they were getting greater value for their increased outlay, and that the outlay was within reason. Instead, the libraries felt trapped, forced to purchase large bundles at inflated prices to receive a single title. When prices for some bundles topped $40,000 for a single subscription, the reputedly mild-mannered librarians took to the streets, leveraging their most important asset: access to the men and women who write the articles.

An April 17 article in Pharma Blog quotes the Harvard University Faculty Advisory Council urging Harvard faculty to publish only to open-access publications or publications with reasonable subscriptions fees, and to resign from the editorial boards of journals that don't promote open access, among

other tactics.

No strategy can achieve long-term success without keeping it's buyer's interests in mind. While the publisher's strategy is enriching businesses for the moment, if the Harvard library succeeds in driving authors away from these pricey journals, the result could be a groundswell of free, open-access publications. Then the publishers will collect no subscriptions at all.

ONE-STOP-SHOPS: TRYING TO BE EVERYTHING TO EVERYONE

Closer to home, the one-stop shop is an example of a good strategy with flawed execution in our industry. One-stop shops are created when a company that is successful with one approach expands up and down the pipeline buying companies that are essentially unrelated businesses, except for their proximity in the pipeline. Think of the late Azopharma, MDS, and a few others.

The concept is not necessarily a bad one. Farming out a molecule to just one company for all contract needs could have its appeal to some clients. Unfortunately, delivering the highest possible quality across 26 Pharma steps is a logistical nightmare. It has yet to be accomplished. Even if a company is somehow able to take a molecule successfully through 20 steps, when it fails on the 21st, that's it. The customer has just sunk money into 20 steps and there are no rebates. The one-stop shop will never see that customer again, not in any of its divisions. Then word of mouth takes over in our small industry, and it saps the shop's ability to get new clients. And rightly so, I might add. In an industry like ours, quality isn't a subjective trait like it is at Avon. In the beauty industry, quality means a glossier gloss or a longer-lasting lip color. You pay more to get more or better. In Pharma, quality is an entry barrier. The FDA sets the bar on quality, and any step in the clinical trial process that fails to clear that bar doesn't get approved.

The recession forced a lot of companies to take more critical, hands-on control of the handling of their molecules. They are far less likely in today's tight, competitive market to just hand over the keys to a one-stop shop, with all the inherent risks. Trying to be everything to everyone through every step of the drug development is like trying to lead a band and play every instrument in it. Logistically, the band would sure be a breeze to book and transport; but quality of the music would suffer.

A good strategy always begins with knowing who your customer is, and what your customer wants. But a good strategy is worthless without good operational execution. For that, you must formulate your core strengths and competencies to deliver the strategy. Basically, just stick to what you do best and always keep your focus on the ones you sell to. ◆

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.

Meeting the Needs of Nasal Delivery Devices for Powder Formulations

By: Shunji Haruta, PhD, and Tatsuo Tsutsui, P.E.Jp

The increase of overburdened healthcare systems around the world has transformed how healthcare is provided to patients. As a result of this major transformation, greater emphasis on reliable and effective out-patient care has become a necessity. This move toward out-patient care has placed upon patients the responsibility of self-administration outside the comfort of their clinics. Given this new healthcare climate, patients need drugs that are easy, safe, and convenient to administer; patients need to feel confident in their ability to safely and effectively deliver their own medicine. Clearly impractical, intravenous (IV) or intramuscular (IM) formulations that would typically require assistance from a healthcare provider do not fit into the new schema of patient-centric healthcare. Concurrently, the diminishing success rate of the pharmaceutical industry in bringing new chemical entities to market have led pharmaceutical companies to focus efforts on identifying new uses for existing drugs, including the development of alternative routes of administration. The move toward out-patient care and the shift in pharmaceutical strategy have presaged the emergence of nasal drug delivery as an increasingly viable delivery technology.

Nasal delivery of therapeutics and vaccines has a number of compelling advantages over other routes of administration, namely: its non-invasiveness, rapid attainment of therapeutically relevant concentrations to the bloodstream, no first-pass metabolism, and ease of administration. In addition to liquid formulations used in most existing nasal products, powder formulations are also receiving attention as a possible solution. Nasal powder formulations generally are associated with higher stability compared to their liquid counterparts, which may provide an advantage to a nasal product, which is usually designed to be portable. Also, powder formulations are less susceptible to running out of the nasal cavity than liquid formulations. Furthermore, powder formulations provide a better opportunity for a drug compound to absorb through the nasal cavity. Conversely, only a handful of devices are

FIGURE 1

Company (Product Name)	Device Features
Optinose US Inc.	• Capsule-loading multiple-use (Steel pins pierce the capsule.) • Single nozzle • Breath-powered
Teijin Pharma Limited. (Rinocort® powder spray)	• Pre-filled multiple-use • Single nozzle • Hand actuated
Nippon Shinyaku Co., Ltd. (Twin-lizer®)	• Capsule-loading multiple-use (Steel pin pierces the capsule.) • Dual-nozzle • Hand actuated
Aptar Group Inc. (Prohaler®)	• Pre-filled unit- and bi-doses • Single nozzle • Hand actuated
Direct Haler A/S (DirectHaler™)	• Pre-filled unit-dose • Single nozzle • Breath-powered
Becton, Dickinson and Company (SoloVent™)	• Pre-filled unit-dose • Single nozzle • Hand actuated
SNBL (Fit-lizer™)	• Capsule-loading multiple-use (Pre-filled Single-use version also available) • Single nozzle • Hand actuated

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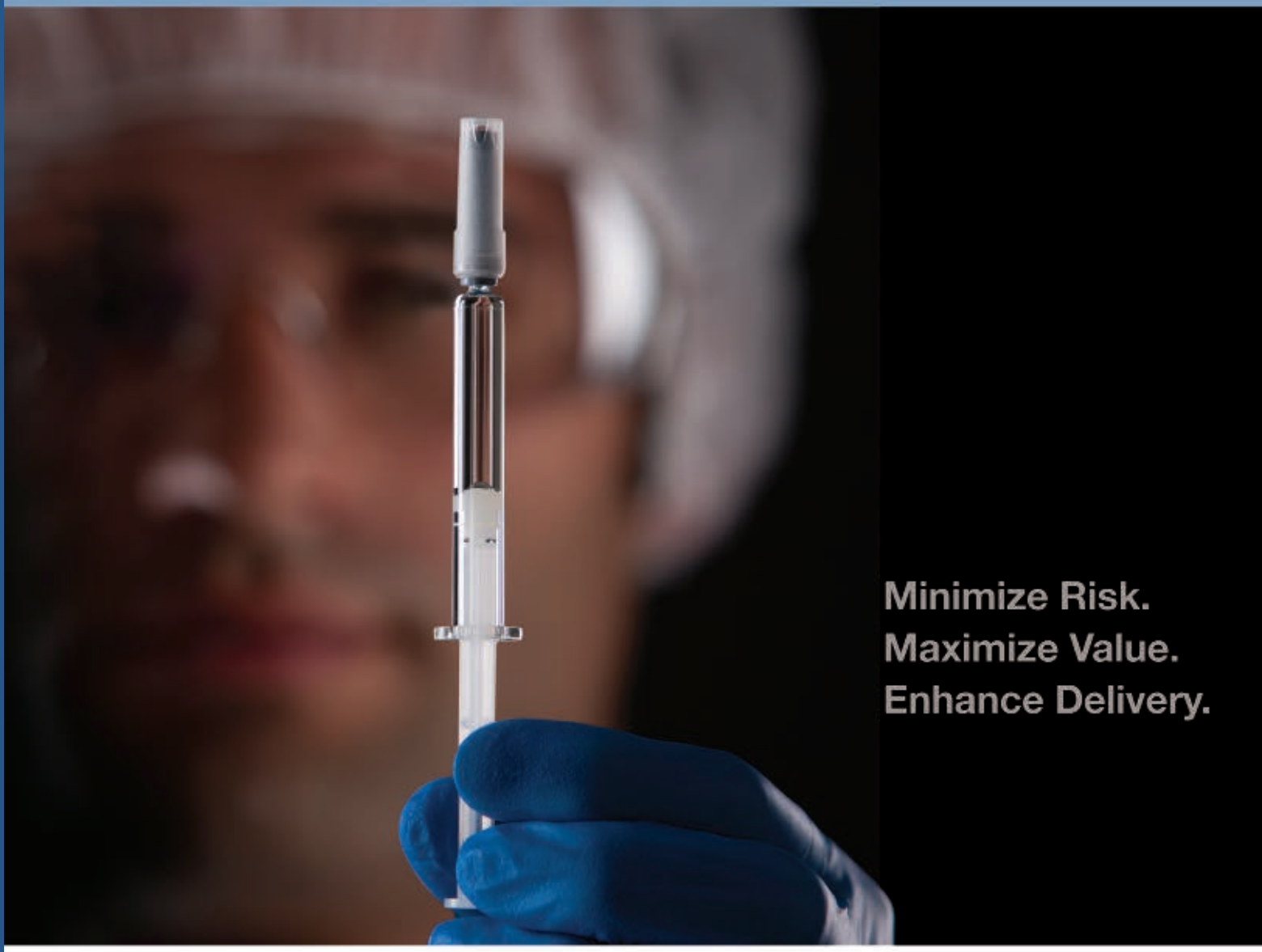

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FIGURE 2

optimized to effectively deliver powder formulations (Figure 1). The brevity of this list illustrates that the drug device development community continues to face many hurdles in optimizing existing, or designing, new technologies. These hurdles range from challenges in absorption and stability, avoiding unwanted deposition to the stomach and lungs, to devices requiring consistent delivery and ease of use that ensure effective treatment along with preventing microbial contamination of multi-use devices.

FIT-LIZER™ PRODUCT CONCEPT

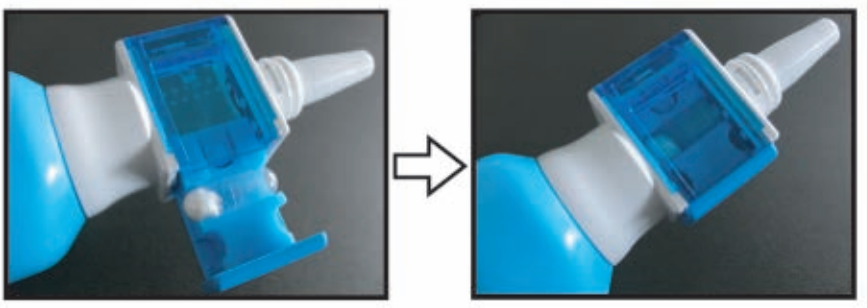
SNBL's µco™ System is a product of more than 10 years of R&D and represents a major advance in nasal drug delivery. Understanding the pitfalls of liquids in nasal delivery, the concept aim was to design a technology in which liquids were unnecessary. The attainment of such a goal was realized with µco System's two primary breakthroughs: a powder formulation mucoadhesive carrier technology and an accompanying easy-to-use device (Fit-lizer) to deliver its powder drugs into the nasal cavity in a highly reproducible fashion.

Development of µco System ran in parallel with Fit-lizer, and from the outset, the creators defined the following set of key design objectives in order to achieve a best-in-class device:

- easy for patient to use
- multiple-use device
- loading of drug via a convenient capsule
- complete and highly reproducible delivery of a fixed dose of drug independent of environmental factors, including hand-actuation pressure
- allows patients to confirm correct capsule is loaded prior to delivery
- allows patients to confirm that the drug was delivered completely
- safe to use without the use of any sharp pins or needles required to release and deliver drug from capsule
- capable of delivering multiple drug types, including small molecules, peptides, and vaccines (including low-flow powder formulations) for either local nasal or systemic administration
- small, preferably pocket-sized

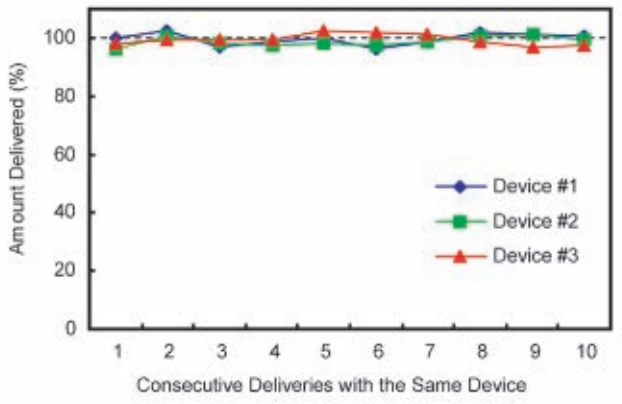
The development team also saw the value and room in the market for a single use device; specifically for applications in which multi-dosing is either not necessary or could be easily abused for potentially addictive drugs (eg, potent analgesics). A similar, single-use device meeting the same aforementioned needs was developed in complement with the multi-use device. The following describes the engineering and design features of Fit-lizer and its successful application in a clinical trial setting.

FIGURE 3



Simple Device Operation

FIGURE 4



Complete & Consistent Delivery

ENGINEERING & DESIGN FEATURES OF FIT-LIZER

Complete & Consistent Delivery

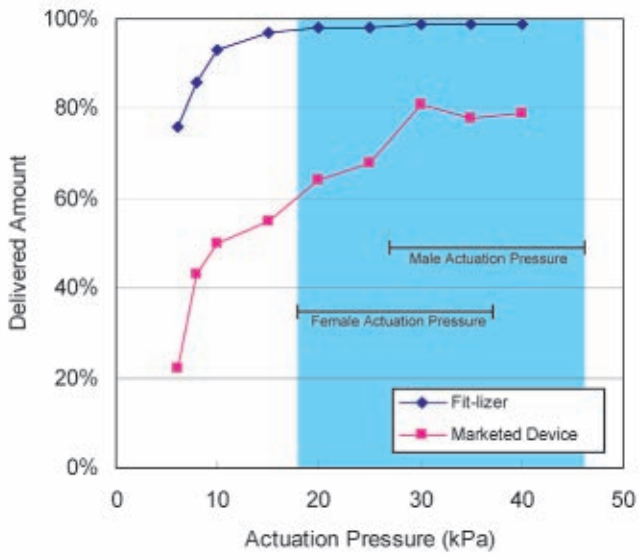
Numerous functions have been built into Fit-lizer to provide complete delivery of powder formulations into the nasal cavity. First, creation of the airflow pathway is completed upon the loading of the powder formulation-containing capsule. Capsule ends are severed as the chamber is closed, which then creates a smooth airflow pathway.

Through this method, the device circumvents the creation of a lip in the airflow pathway; this is significant because a lip in the airflow typically hinders the complete clearance of the drug at the puncture point in the airflow pathway, which necessitates the need for an additional function, such as the inclusion of vibration. Second, the device is designed so that when the capsule is loaded, it simultaneously compresses the capsule longitudinally, nestling the capsule to become apart of the airflow pathway. This air-tight seal between the capsule and device prevents any leakage of drug formulation as the manually compressed air passes through the capsule during actuation. Third, and importantly, there is a one-way valve function below the powder formulation-containing capsule. This one-way valve ensures the powder remains in the capsule prior to actuation; during actuation, the same valve directs the airflow to activate the powder formulation along the intern wall of the capsule, which otherwise would remain. These design functions allow delivery of the entire capsule content with minimal residue left in the device (Figure 2).

Patient Compliance

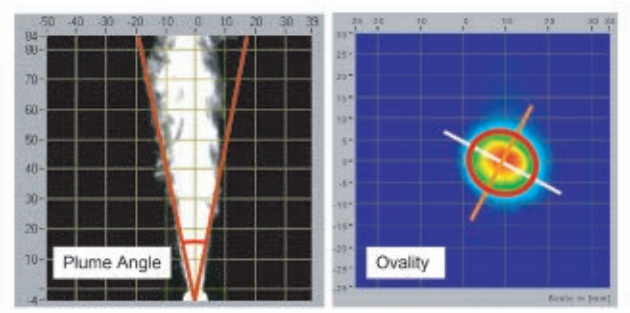
Patient compliance must always be the end goal, otherwise both drug and device have not met the patients' needs. Having created Fit-lizer with this understanding, the device provides an end-user experience resulting in ease-of-use with minimal room for patient error. An airflow regulator to normalize airflow rate is utilized in the design, which ensures consistent and adequate airflow no matter how hard or soft the patient actuation. In addition, the capsule-loading chamber is made of transparent material, so the patient can see the capsule in its loaded position. Before use, this allows the patient to confirm the correct capsule has been properly loaded, which can be useful for therapies that require the patient to choose from multiple drug doses. Following use, the patient is able to confirm the entire drug formulation has been delivered from the capsule through the transparent window. Lastly, Fit-lizer's blades, which cut the capsule ends, are inaccessible from the outside, providing an added level of safety. These functions paired with a simple device operation mean Fit-lizer is able to maintain reliable performance (Figure 3).

FIGURE 5



Actuation Force Versus Delivered Amount

FIGURE 6



Delivery Geometry

FIT-LIZER DELIVERY PERFORMANCE CHARACTERISTICS

Complete & Consistent Delivery

Fit-lizer displays consistent dose delivery over multiple uses. As illustrated in Figure 4, three individual devices were tested with consecutive delivery of 10 capsules each. Results yielded 99.6 ± 2.0%, 98.8 ± 1.6%, and 99.4 ± 1.9%, almost complete delivery repeated for each of the three devices, with negligible residue build-up over the multiple uses. In another study, the device yielded consistent delivery for 100 capsules without maintenance and with negligible build-up residue of the drug formulation.

Actuation Force Versus Delivered Amount

Delivered amount was tested at various actuation forces with Fit-lizer and a marketed powder nasal delivery device (Figure 5). The range of actuation force used in the study was chosen to include the genuine actuation forces measured from 10 male and 10 female subjects. Often, marketed nasal powders with device have shown variability with incomplete delivery. It is notable that a studied marketed device produces delivery amounts ranging from 64% to 81% by typical human actuation forces; Fit-lizer produces 98% to 99% delivery within the same range. This has shown the ability of Fit-lizer to be used successfully by a wide variety of patients exerting varying actuation forces.

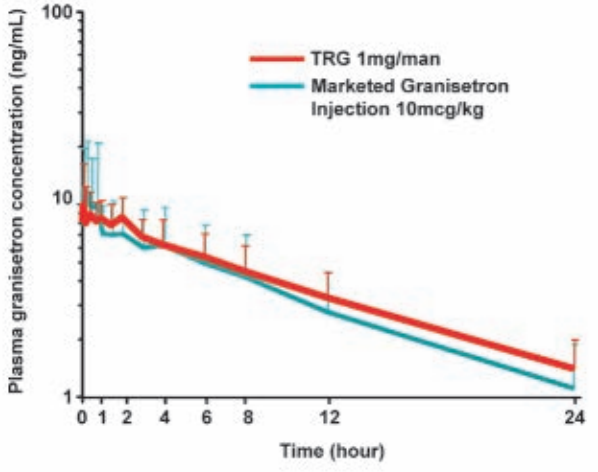
Consistency of Delivery Geometry

Geometry of the delivered formulation is used to characterize nasal and pulmonary delivered drug products. The Fit-lizer device demonstrates high reproducibility in the geometry of the delivered formulation (Figure 6). In a study using laser-sheet high-speed photography technology, the delivery geometry of the device was measured by plume angle and ovality (Dmax/Dmin) at 30 mm from the device tip. The results showed very little variability, with plume angle at 23.2 ± 2.3 deg and ovality at 1.48 ± 0.22 (n = 20), signifying the device is able to deliver a consistent shape, which enables the powder drug formulation to be delivered in the same way for reproducible distribution in the nasal cavity.

FIT-LIZER PERFORMANCE IN CLINICAL STUDIES

In clinical trials conducted to date, Fit-lizer has demonstrated robust performance in both healthy human subjects as well as patients. The first drug compound to be clinically tested with Fit-lizer was granisetron, which is marketed as an oral tablet and an IV injection formulation, indicated for the prevention of chemotherapy-induced nausea and vomiting (CINV) for cancer patients. Figure 7 shows the pharmacokinetic properties generated by TRG (Fit-lizer delivering granisetron that is formulated with SNBL's proprietary mucoadhesive carrier). TRG exhibited a PK profile that is highly similar to that of the IV formulation. Specifically, TRG showed complete absorption (100% relative to IV granisetron), achieving maximum plasma

FIGURE 7



Pharmacokinetic Profile of TRG Versus IV Granisetron

FIGURE 8

concentration (Cmax) by 20 minutes post-administration, consistent with the notion that almost all of TRG is delivered out of the device into the nasal cavity. Furthermore, 70% of the delivered dose was reached within 5 minutes of dosing. In a subsequent Phase II study, TRG demonstrated dose-dependent efficacy comparable to that of IV granisetron in preventing vomiting, moderate-and- severe nausea, and precluding the use of rescue medication in cancer patients being treated with highly emetic chemotherapy. TRG has been evaluated in 94 human subjects to date and has shown a safety profile comparable to that of IV granisetron without any observed local nasal irritation or other route-specific adverse events. In both clinical studies, Fit-lizer was well accepted in terms of its usability.

SINGLE-USE DEVICE

SNBL has taken the same strategy and spirit in the design and development of the Fit-lizer single-use device (Figure 8). As previously mentioned, the need for a single-use device was noted when taking into account non-chronic therapies, such as pain relief, sedative administration, seizures rescue, vaccinations, etc. The single-use device has demonstrated the same dependable and consistent delivery as its multi-use line-sibling. Prefilled and ready to use, the single-use device is convenient and reliable, and can be disposed of after use.

SUMMARY

In summary, in preclinical and clinical studies to date, Fit-lizer has fulfilled the performance objectives defined during its design conception and therefore represents a significant advance in nasal drug delivery, addressing many patient compliance issues; delivering consistent, complete drug doses over multiple uses across variable individual patient types.

The changing landscape in the pharma and healthcare fields will likely continue to demand advanced delivery devices to surpass the current delivery standards seen in the market today. Out-patient care, with the convenience and comfort of the home, continues to grow; answers to the challenges of self-administration need to meet this growth. Patient-centric products and delivery are highlighted as the future of healthcare, and nasal drug delivery offers a compelling road to get there. ◆

BIOGRAPHIES

Dr. Shunji Haruta is an Executive Officer at SNBL, Ltd. and the General Manager of NDS Division, with focus on the R&D of µcoTM System. Dr. Haruta has been with µco System since its inception over 10 years ago and continues to oversee the R&D and business operations relating to µco System. Dr. Haruta earned his PhD in Pharmaceutical Sciences from Okayama University, Japan. His scientific background includes pharmaceutics, specializing in drug mucosal absorption, formulation technology with muco-adhesive and controlled release, and the effect of gastrointestinal transition on drug absorption and pharmacokinetics. He formerly worked as a clinical pharmacist and researched drug absorption at Miyazaki Medical College Hospital, Japan.

Tatsuo Tsutsui, PEJp (Professional Engineer, National Certification, Japan) is Chief Engineer at SNBL, Ltd. He was Co-Founder of Bioactis, Ltd., which is now apart of the Nasal Delivery Systems business of SNBL Group. Mr. Tsutsui designed and developed Fit-lizerTM, in addition to having designed a series of other nasal and pulmonary drug delivery devices. Previous to founding Bioactis, Ltd. and joining the SNBL Group, Mr. Tsutsui worked at Hitachi Automotive, where he gained extensive knowledge in airflow management through designing EGR valves, airflow meters, and throttle chambers of automobiles. Mr. Tsutsui studied Mechanical Engineering and graduated from the University of Chiba, School of Engineering, Japan.

PROTEIN-BASED THERAPEUTICS

Tunable Half-Life Extension Based on Recombinant Albumin - Tailoring Pharmaceuticals to Specific Medical Needs

By: Mark Perkins, PhD

INTRODUCTION

Protein-based therapeutics often exhibit notoriously short plasma half-lives, meaning the human body eliminates them very quickly. This can lead to reduced bioavailability of the drug, creating a need for larger and more frequent dosage regimes. This can pose a significant health risk to patients, with increased incidence of side effects. In addition, there is greater potential for lack of patient compliance, which subsequently increases healthcare costs. As a result, a short plasma half-life is generally recognized as a key factor limiting the safety and efficacy of protein-based therapeutics.

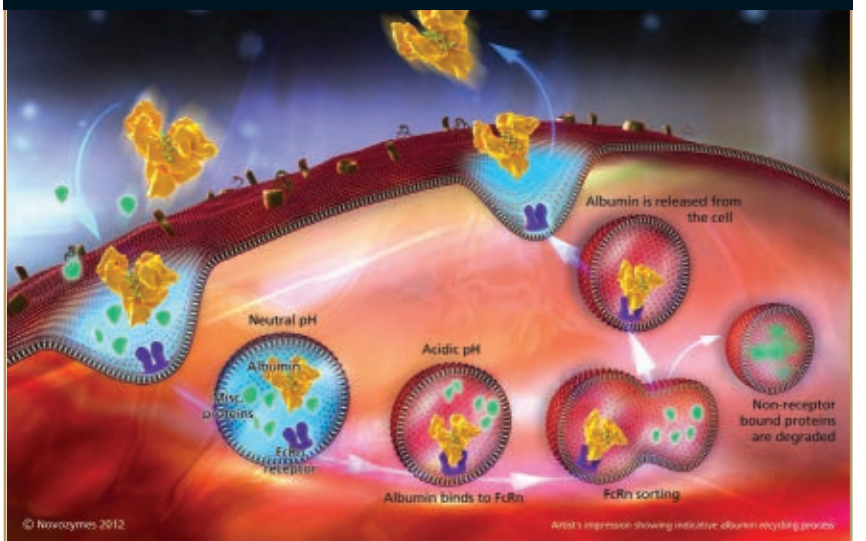
For many years, there has been an orchestrated effort within the pharmaceutical industry to develop technologies capable of extending plasma half-lives of protein-based therapeutics. Currently, the most popular techniques are those that increase the hydrodynamic volume (PEGylation) and those that use FcRn-mediated recycling (albumin fusions). However, while these techniques have proven particularly successful in extending plasma half-lives, they lack the ability to tune protein half-lives to deliver specific pharmacokinetics.

In response, Novozymes has developed a tunable half-life extension technology (Flex) to serve as a flexible drug delivery platform designed to enable manufacturers to tune protein or peptide half-lives to specific medical needs. Through subtle modification of the albumin molecule, the new technology provides drug development scientists with the flexibility to adapt and manage the pharmacokinetics of the target protein while retaining drug safety and efficacy.

THE UNIQUE PROPERTIES OF ALBUMIN

Albumin is the most abundant plasma protein in blood, constituting approximately 60% of total protein, and has a pivotal role as a transporter of fatty acids and drugs. It also has a long serum half-life of approximately 19 days, in contrast to protein-based therapeutics that are generally cleared from the human body within a range of minutes to hours. Albumin's extended half-life is due in part to its large hydrodynamic radius, which protects the 67 kDa molecule from renal

FIGURE 1



Hypothetical model based on knowledge of IgG recycling. The neonatal Fc receptor (FcRn) functions to protect albumin from degradation resulting in prolonged half-life.

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clearance, and also due to its relationship with and affinity for the neonatal Fc receptor (FcRn).

FcRn is a dual-binding receptor that binds both Immunoglobulin G (IgG) and albumin, at distinct sites, and protects them from intracellular degradation. Like IgGs, albumin is taken up by cells through non-specific pinocytosis and is protected from intracellular degradation through pH-dependant binding to the FcRn in acidic endosomes. This interaction with the FcRn allows albumin to then be recycled back to the cell surface, where it is released into circulation due to the physiological pH of the blood (Figure 1).

NOVEL ALBUMIN FUSION TECHNOLOGY

By exploiting the pH-dependant interaction between albumin and FcRn, it becomes possible to tune albumin's half-life. Previous studies have demonstrated that altering the interaction of IgG with FcRn can change the pharmacokinetics of the IgG. One such example is Avastin®, an anti-vascular endothelial growth factor (VEGF). When this was engineered to have increased binding affinity for FcRn, a significant increase in half-life was observed, notably 24 days instead of 11 days in macaques.

Similarly, Novozymes Biopharma's tunable half-life extension technology functions to modulate half-life extension through constructing albumin variants with altered binding affinity to FcRn, making it possible to offer drug developers control and flexibility in their drug design. Through subtle modification of the albumin molecule, this innovative technology aims to improve the circulatory half-life of the albumin molecule itself, and as a consequence to confer these advantageous properties to any fused or conjugated drug.

In collaboration with scientists at the University of Oslo, Norway, Novozymes Biopharma's analysis of natural polymorphisms, cross-species binding studies, and sequence alignments have identified potential amino acids involved in the binding of albumin to FcRn. Subsequently, numerous albumin variants have been generated with single amino acid substitutions. Binding affinity studies of each albumin variant to FcRn at acidic pH have identified single amino acid positions capable of generating a range of affinity variants with distinct binding differences. Variants have been measured with both increased and decreased receptor binding affinities potentially translating to modulation of albumin half-life.

The key benefit associated with the use of Novozymes Biopharma's Flex technology is the flexibility to allow drug manufacturers to develop novel drugs tailored to specific disease states, by tuning the degree of half-life extension in proteins. The fusion of numerous therapeutically relevant proteins and peptides to albumin using the new technique can extend the drug's half-life significantly. As a result, the drug's pharmacokinetic properties are considerably improved, while the frequency and level of dosing are reduced, minimizing side effects. Overall, patient quality of life can be significantly enhanced, patient compliance improved, and healthcare costs reduced.

TABLE 1

Genetic Fusion	Conjugation
Contiguous cDNA encoding target drug plus albumin produces a single protein	Chemically modify drug to allow covalent attachment to albumin molecule
Flexible options -N- and/or C-terminal fusion -Combinations, linker molecules	**Lysine, tyrosine, free thiol (SH)** -Free thiolin albumin is the most widely used conjugate route -Specifically reactive with maleimide groups
Applicable to amino acid-based products -Peptides, proteins, antibody fragments	Applicable to complete drug pipeline -Small molecules, large molecules, nucleic acids
Compatible with yeast and mammalian host expression systems	No expression system required
Fusion manufactured at one time and in one host	Manufacture each component separately
Homogenous final product	Heterogeneous product or site-specific conjugation to produce homogeneous product
No additional post-manufacturing costs	Re-purification, additional post-manufacturing costs.

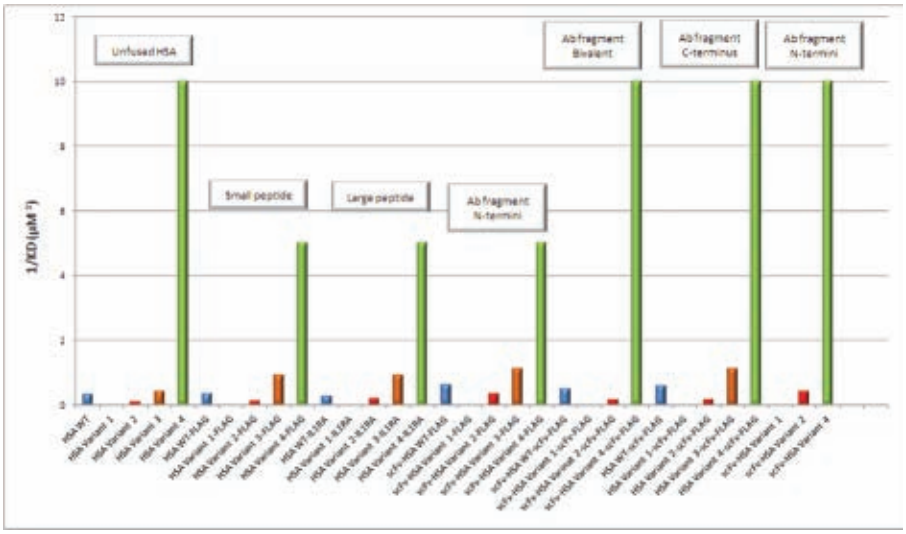
Comparison of albumin fusion strategies. Conjugations versus genetic fusion.

APPLICATION AREAS

The tunable half-life extension technology can be used to create genetic fusions or chemical conjugates of drugs of interest. Proteins and peptides can be genetically fused to the N or C terminus, or even to both ends of the albumin variant, generating fusion molecules with monovalent, bivalent, or bispecific affinity. Using a contiguous cDNA of the target protein or peptide with DNA encoding, the albumin variant of choice allows the generation of protein fusions exhibiting the required binding characteristics. Fusions are manufactured at one time and in one host, and the technique ensures a homogeneous final product. Genetic fusion using the Flex technology is applicable to peptides, proteins, antibody fragments, and amino acid based products, while being compatible with yeast and mammalian host expression systems.

If genetic fusion is the strategy of choice, then Novozymes' proprietary yeast expression system provides a high-quality, consistent, and reliable supply of the protein of interest. Based

FIGURE 2



Albumin variants selected for their different FcRn receptor affinities were genetically fused to a variety of proteins and peptides. Each fusion tested was found to maintain similar affinity for FcRn receptor when compared to the unfused variant.

upon strains of *Saccharomyces cerevisiae*, originally developed for the production of a recombinant human albumin (Recombumin®), this expression system delivers high levels of secreted product into the supernatant of shake flask and high cell density fed-batch fermentations.

In addition to protein- or peptide-based drugs, the enhanced technology also provides a delivery vehicle for small molecule NCEs, large molecules, and nucleic acids via chemical conjugation, offering a broad scope of usability. Lysine, tyrosine, and the free thiol residues of the albumin molecule can be used for chemical conjugation to the drug product, with the free thiol residue at position 34 of albumin being the most widely used conjugation route. This approach is particularly useful for peptides containing maleimide groups, which specifically react with the free thiol residue, allowing for the formation of a stable thioether bond between albumin and the peptide.

Table 1, although not exhaustive, outlines the main characteristics of both genetic fusion and chemical conjugation technologies, as these are facilitated using Novozymes Biopharma's Albufuse® Flex platform.

EXPERIMENTAL DATA

To test that the albumin variants would maintain their modified FcRn binding affinity when fused to a protein or peptide, a range of albumin protein fusions have been generated. The variants chosen displayed a range of binding affinities from low affinity albumins (HSA K500A) to albumins with 15-fold increase in receptor binding (HSA K573P). Antibody fragments fused at the C-terminus, N-terminus, or bivalent forms, as well as fusions to small or large peptides were compared to unfused albumin variants for FcRn affinity by SPR using Biocore® technology (Figure 2). All albumin fusions tested showed distinct differences in receptor affinity correlating to their unfused variant. Each fusion demonstrated the same changes in ScRn binding as the control rHSA variant.

CONCLUSION

A natural alternative to PEGylation, Novozymes Biopharma's tunable half-life extension technology enables the molecular fusion of albumin to protein drug candidates for improved half-life and bioavailability. The technology provides the ability to tune, adapt, and control the half-life and pharmacokinetics of the target protein or peptide to suit particular medical needs, while retaining drug safety and efficacy. As a result, the Flex technology can reduce dose frequency requirements and subsequent side effects for patients with chronic or acute conditions. For the pharmaceutical industry, this technology provides a unique opportunity to deliver new therapeutics that were previously not possible.

The Flex technology can be used to develop genetic fusions or chemical conjugates of drugs of interest, depending on the specific application requirements. The technique offers superior flexibility as it is applicable to proteins, peptides, small molecules, and large molecules. Since it was first introduced to the market in May 2011, the technology has received significant attention from small and large pharmaceutical companies developing therapeutics in the fields of diabetes, obesity, fertility, and haemostasis, where frequent dosage and drug toxicity are constant challenges. ◆

BIOGRAPHY

Dr. Mark Perkins is a Formulation Chemist with a PhD in Pharmaceutical Sciences from the University of Nottingham. He joined Novozymes Biopharma in 2010 as a Customer Solution Specialist. Within this role, he works with partners who are evaluating Novozymes Biopharma's recombinant albumin products and associated technologies in the areas of biopharmaceutical formulation and half-life extension. Prior to this position, Dr. Perkins worked as a Materials Specialist at an inhaled drug development company and as a Project Manager within an analytical consultancy. He can be reached at mrpk@novozymes.com.

Combinations for Success: Integrated Delivery Systems That Can Meet Evolving Expectations

By: Graham Reynolds

INTRODUCTION

The number of biologic drug products marketed with an injection device has approximately quadrupled throughout the past decade. The growth in these drug therapies has been driven by several factors, including new, self-administered therapies for chronic conditions such as rheumatoid arthritis and autoimmune diseases. In addition, injectable therapy is now being considered as a treatment for more conditions, including asthma and cholesterol problems.

As convenience and ease-of-use for home administration become desired attributes, the use of prefilled syringes and advanced delivery systems continues to grow. Drug therapy and treatment no longer relies on simply having an effective molecule, but rather the combination of a safe drug within a suitable container and/or delivery system, as well as an understanding of patient needs as they relate to adherence. By working closely with a packaging system manufacturer that has generated partnerships with companies like assembly equipment manufacturers, filling companies, human factors experts, and design companies, pharmaceutical manufacturers can select, design, and/or develop an appropriate system that maximizes the chances of moving a product to market quickly with an optimal drug and packaging combination that can be used by the patient or a caregiver as effectively as by a healthcare professional.

THE EVOLUTION OF DRUG DELIVERY SYSTEMS

Glass vials have traditionally been used to contain injectable drug products due to ease of use for healthcare professionals and the perceived safety of glass container closure systems. While glass has historically been the material of choice for many products, it may not be the optimum choice for today's biologics. Additionally, vial systems require that the drug product's administrator not only store the product correctly, but also measure dosages and administer the drug using a standard syringe. Such a system places patients and caregivers at risk for improper administration and needle-stick injuries. To suit the needs of patients suffering from chronic conditions, self-administration methods had to evolve.

The first injection systems included auto-injectors used in the military, pen injectors, and multi-dose cartridges. However, these systems were limited to specific therapies, such as diabetes and growth hormones, which often required variable dosage. Pen injectors were not ideal for chronic users of fixed-dose medications.

Auto-injectors offer more convenience and ease of use for those who require a frequent method for delivering fixed-dose products. Many modern biologic drug products require high dosage volumes, driven by increasing molecular weight and higher concentrations. These molecules have created a new set of challenges for injection systems, specifically higher viscosities or the need for a higher dose volume. As such, there has been an increasing focus on new technology that can deliver higher volumes of drugs subcutaneously. Innovations in this area include novel devices and containment systems, such as patch injection systems, that are capable of delivering higher volumes of drug product over a longer period of time. Such systems are an excellent example of the evolution of drug delivery from vial/syringe to

integrated combination products that meet the needs of both the drug product and the patient, while providing a competitive advantage for the drug company.

DRIVING TOWARD DIFFERENTIATION

Several market trends, including the move toward self-administration and significant new requirements from global regulatory agencies, have emerged to drive the industry toward combination products. Biotech companies in particular are facing increased scrutiny from regulatory authorities. Because the drug delivery method can have an impact on the effectiveness of a drug product, companies must also ensure that delivery devices and systems function effectively. In addition, new molecules tend to be more sensitive to certain materials than other drug products may have been in the past. Materials such as silicone oil, metal ions, extractables, and leachables from the container closure system are therefore more of an issue and need to be a key consideration when selecting primary containment materials.

As the new drug pipeline slows and market competition increases, companies are seeking ways to maximize the value of existing drug products. Many may choose to do so through the development of new therapies for existing drugs, which may require new methods of delivery. As blockbuster drugs go off patent and competition rises from the generic manufacturers, delivery systems can be a means of market differentiation. Generic manufacturers must enter the market quickly in order to achieve success, and must do so with a product that is not only safe and effective, but also delivered in a way that will help induce patient loyalty away from competitors.

Pharmaceutical and biotech companies facing these challenges are taking a much closer look at drug products not just from a molecular standpoint, but also from the perspective of overall effectiveness and delivery to the patient, which requires a new way of thinking about packaging and delivery. To aid in developing proper packaging solutions, pharmaceutical manufacturers should seek out partnerships with drug packaging manufacturers early in the development process.

THE RISE OF INTEGRATED DELIVERY SYSTEMS

Historically, pharmaceutical manufacturers have focused - and rightly so - on the efficacy and safety of the drug product. However, if the drug is to achieve its therapeutic objective, then its primary container and delivery system must be both compatible with the drug and stable over time, as well as foster adherence from the patient. A drug can only truly have the desired patient benefit if it is taken as prescribed, delivered effectively (often by a patient or caregiver), and maintains performance over time. By partnering with an experienced drug packaging manufacturer with a range of technology solutions and recognized expertise in primary container systems, pharmaceutical companies can ensure an optimized container and delivery solution. As patients take an even greater role in decisions regarding their treatment, easy to use, safe, and effective delivery systems will be essential.

To be successful, an integrated system must combine the needs of the patient or caregiver with the drug, its primary containment system, and its delivery system. To create a truly effective system, there are a variety of considerations that must be acknowledged during the development process. In addition to a drug's clinical benefit, a combination product should provide ease of use, optimum delivery rate and frequency, and aid the patient's ability to adhere to a treatment schedule. Also, the drug must be held in a primary container that maintains the drug's effectiveness, safety, and quality over a period of time. That primary containment system should also be compatible with the delivery system, which must be designed to enhance the drug delivery experience for the patient or caregiver.

So how does a pharmaceutical manufacturer deliver a unique system that meets compliance requirements and the needs of both the drug and the patient? First, a pharmaceutical company should consider the interface between the drug and the container itself. Is the elastomeric material compatible with the drug? What are the levels of extractables and leachables? Will a barrier film or coating be required for the elastomer?

The container format itself also should be considered. Vials may be necessary for initial use, but a syringe or cartridge system may provide the best solution for the patient when the system reaches the market. Custom systems may also help to differentiate the product, and should be considered early in the development process. Novel materials, such as moldable cyclic olefin polymers, can help pharmaceutical companies manage a drug throughout its lifecycle because the material can be used for bulk storage during development and primary containment when ready to move to market.

When the primary container has been selected, efforts must be made to ensure that it works with the delivery system. Dimensional tolerances and functionality should be tested to ensure proper activation and gliding forces.

Perhaps the most essential consideration is the delivery system to patient interface. Even

the most innovative drug can provide the appropriate therapeutic benefit to the patient only if it can be delivered effectively and the patient adheres to the necessary treatment regimen. Human factors testing allows manufacturers to support delivery system development from a range of critical perspectives. From a regulatory standpoint, such testing accounts for important human factors inputs that regulatory agencies expect to see as part of the development process for any delivery system. These same inputs also ensure that risks from user-based errors are identified early in the development process and provide critical user information to the development team for risk mitigation measures. The full development process should consider the effectiveness of the integrated delivery system constantly, and risks should be mitigated.

The process by which a testing team engages users should also yield valuable information regarding a user's physical and emotional needs, desires, and the lifestyle challenges faced in managing the disease. Understanding how to analyze and effectively utilize this information serves as a strong foundation for guiding the design process to develop delivery systems that are not only intuitive and easy to use, but also encourage experiences that enable positive emotional connections between the user and delivery system.

UNDERSTAND MATERIAL INTERFACE

While glass has long been the pharmaceutical container of choice, more and more pharmaceutical companies are considering plastic containment. In fact, the transition is already well established in Japan, and continues in Europe and the US. According to Rx-360, nearly 30% of pharmaceutical manufacturers are considering plastic as a viable option for primary drug containment. An example of such a material, Daikyo Crystal Zenith® cyclic olefin polymer, has been developed specifically for the unique needs of drug containment by West's Japanese partner, Daikyo Seiko, Ltd., and has been approved for marketed drugs in all major global markets.

Experience has shown that if the interface between the primary container and the delivery system is not effectively understood, the performance of the combined system may suffer. For example, when considering the use of a glass prefillable syringe in an auto-injector, manufacturers must ensure that the stress placed on the glass does not cause breakage or that the force in the auto-injector is enough to overcome variability in dimensions, functional performance, and siliconization effectiveness to ensure complete dosing.

Such issues have already caused problems for pharmaceutical manufacturers. In 2006, commercial lots of a drug product delivered by an auto-injector that contained a glass prefilled syringe were recalled in several European countries because of problems with slow or incomplete delivery of the drug.1 There was a similar occurrence in 2009 in the US when an auto-injector batch was recalled because of high force-to-fire values.[2]

An early understanding of the interface can help to enhance performance and reduce issues associated with glass. Innovative syringe systems made from novel materials such as cyclic olefin polymers highlight the opportunity to offer an optimized syringe system that overcomes the limitations of glass and forms part of an integrated system. These high-performance materials possess the valuable properties necessary to manufacture, store, protect, and deliver novel drugs and biologics. When used in combination with a delivery system, such as an auto-injector or electronic patch injector, cyclic olefin polymer systems can be an effective primary container that can be successfully integrated with a delivery system to form a combination product that meets the challenges of high molecular weight biologic applications.

PARTNERSHIPS PROVIDE UNIQUE SOLUTIONS

When manufacturers are able to combine an effective drug product with expertise in container closure systems and design technology, including a thorough understanding of the pharmaceutical manufacturer's filling requirements, and high-quality manufacture at all stages, they will better meet the needs of the end-users while improving overall value and reducing time to market. However, delivery options with difficult drugs are slim. Users are currently required to either receive multiple injections or an injection at a higher dose, which might mean using intravenous delivery.

New designs are evolving around the needs of the growing biopharmaceutical market. Higher molecular weight biologics require delivery systems that can accommodate higher dose volume and reduced dosing frequency. Because cyclic olefin polymers can be molded into a variety of shapes and designs, unique systems with larger fill volumes and tighter dimensional tolerance can be designed while still remaining compatible with established filling technologies.

Through early partnerships, pharmaceutical and packaging manufacturers can develop proprietary technologies, such as West's SmartDose® electronic patch injector technology (for investigational use only by our pharmaceutical or biotechnology development

partners), which is designed for self-administration. The SmartDose technology platform is customized to a specific drug and features a programmable electronic injection system and a Daikyo Crystal Zenith polymer cartridge designed specifically to hold high-volume doses of sensitive biologics. Designed for subcutaneous delivery, the system adheres to the skin and can deliver the drug over a predetermined time. The technology incorporates user interfaces, such as electronic indicators and alarms, which have been optimized through human factors studies.

Patch injection systems that are tailored to the needs of the end user provide an excellent example of the balance between an effective drug containment system and a user-friendly delivery system. In spite of internal system complexity, patch injector systems can be designed for simplicity and patient comfort, while facilitating the delivery of innovative drug products.

Other options include designs that center on more traditional containers, such as vials or prefillable syringes. Auto-injectors have long been recognized as a convenient method for delivering drug products, especially for patients who may have dexterity or needle phobia issues. Auto-injector systems can be combined with prefillable syringe systems made from cyclic olefin polymers to help prevent breakage.

Whether seeking to create a custom integrated delivery solution or to package a drug product in an existing delivery option, such as an auto-injector, pharmaceutical and biotech companies should seek out a partner with expertise and experience in providing packaging solutions. Packaging manufacturers who are focused on providing quality solutions will have the knowledge and partnerships in place to ensure that all four key elements of an integrated design are met. New and innovative drug delivery systems can optimize the quality of life for patients by effectively managing the interrelationship of the four primary components: the drug, the end user, the primary container, and the delivery system. Partnership with West offers a unique opportunity to partner with the leader in drug containment technology, and an experienced player in the device world, with a range of innovative solutions to meet the needs of todays' drugs. Together, packaging and pharmaceutical manufacturers can work seamlessly as partners to provide innovative solutions that help mitigate risk, encourage patient adherence, and enhance value through unique integrated delivery combinations. ◆

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BIOGRAPHY

Graham Reynolds joined West in 1980 as a Polymer Technologist, and throughout his 31-year career with the company, has held a range of positions with increasing responsibility. In his current role as Vice President, Marketing and Innovation, Mr. Reynolds works within the Delivery Systems business segment, where he leads initiatives and develops strategies for future growth, including the acquisition and development of new technologies that enhance the West portfolio. His activities include work on key strategic areas involving injection devices, safety and administration systems, auto-injectors, and prefillable syringes. In 2005, Mr. Reynolds relocated to the US from Europe, where he was responsible for European Marketing and led the integration of the acquired technologies from West subsidiary, MediMop. His experience within the core West business has been complemented by several years of work in the field of devices and delivery systems. Mr. Reynolds holds a degree in Polymer Technology from Trowbridge College, UK.

Next-Generation PEGylation Enables Reduced Immunoreactivity of PEG-Protein Conjugates

By: Merry R. Sherman, PhD; Mark G.P. Saifer, PhD; L. David Williams, PhD; Shawnya J. Michaels, MS; and Monika A. Sobczyk, MS

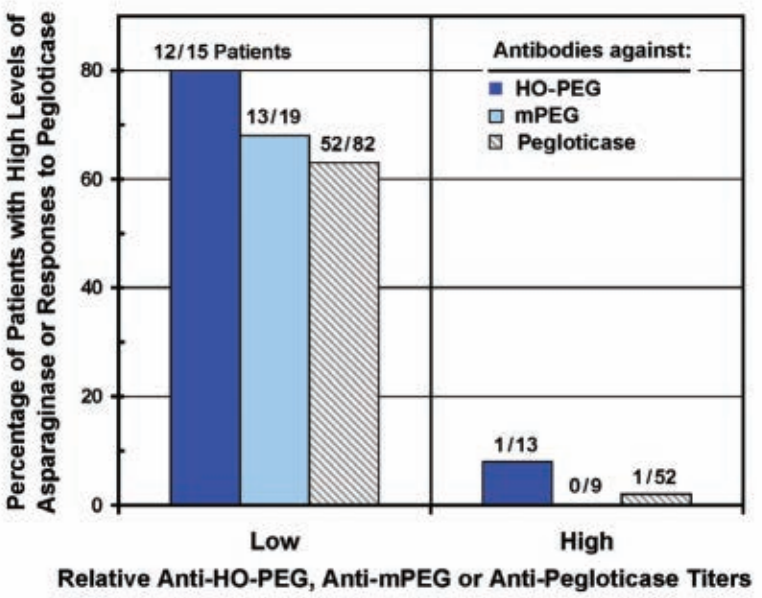
INTRODUCTION

The covalent attachment of therapeutic proteins to poly(ethylene glycol) (PEGylation) is intended to decrease their immunoreactivity, improve their solubility and stability, prolong their duration of action, decrease the frequency of dosing, and enhance their safety. Observations that repeated injections of animals with methoxyPEG (mPEG) conjugates of various proteins provoke the formation of antibodies directed against mPEG, however, are important because all currently approved PEGylated therapeutic products contain mPEG.[1-4] In the case of the mPEG-uricase (pegloticase) that was recently approved for treatment of refractory chronic gout (RCG), most of the anti-pegloticase antibodies detected by enzyme-linked immunosorbent assays (ELISAs) of sera from patients in the Phase I clinical studies, who had received only one subcutaneous or intravenous dose of the drug, were shown to be directed against the mPEG.[5-7]

The potential impact of anti-PEG antibodies on the safety, pharmacokinetics, and pharmacodynamics of many PEGylated therapeutic proteins and other PEGylated therapeutic agents is supported by these observations: 1) high levels of anti-PEG antibodies in the sera of patients with acute lymphoblastic leukemia (ALL) treated with mPEG-asparaginase (Oncaspar®) are associated with an accelerated loss of circulating enzyme; 2) high titers of anti-PEG antibodies in the sera of RCG patients treated with mPEG-uricase are associated with a loss of responsiveness to the drug; 3) clearance of mPEG-modified red blood cells is accelerated after repeated administration; 4) clearance of mPEG-modified liposomes is accelerated after repeated administration; and 5) monoclonal anti-PEG antibodies can be used to accelerate the clearance of several PEGylated proteins.[6-15] Detailed analyses of the anti-PEG antibodies detected in our research have led to the recognition that much of the immunogenicity and antigenicity of the polymers in mPEG-protein conjugates is attributable to the methoxy group at the terminus of the polymer that is remote from the protein.[2,16]

In this report, we illustrate the close parallels between the results of Armstrong et al with respect to anti-PEG antibodies

FIGURE 1



The percentages of acute lymphoblastic leukemia patients with high serum asparaginase after treatment with mPEG-asparaginase (Oncaspar®) correlate inversely with the titers of anti-PEG antibodies measured with a hydroxyPEG ligand (TentaGel® OH) (■) or with mPEG-modified erythrocytes (■).[8,10,11] The percentage of refractory chronic gout patients whose plasma uric acid responds to biweekly infusions of pegloticase (mPEG-uricase; KRYSTEXXA®) correlates inversely with the titers of anti-pegloticase antibodies (hatched bars), which are directed primarily against mPEG.[5-7]

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detected in sera of ALL patients treated with mPEG-asparaginase and the results reported by Sundy et al based on the Phase III clinical trials of mPEG-uricase in patients with RCG.[5,8] We compare the immunogenicity in rabbits and the antigenicity measured in rabbit sera of multi-PEGylated conjugates of human serum albumin (HSA) synthesized using similarly activated mPEG or hydroxyPEG (HO-PEG). The HSA conjugates used in these studies had a similar mass ratio of PEG-to-protein (3-to-1) to that of pegloticase.[1,5] The results of these comparisons suggest there may be advantages to using HO-PEG instead of mPEG in the development of next-generation PEGylated therapeutic agents, including proteins, liposomes, nucleic acids, viruses, and red blood cells.

ANTI-PEG ANTIBODIES & SERUM ASPARAGINASE

Armstrong et al reported that the concentrations of asparaginase in previously frozen sera from ALL patients who were treated with mPEG-asparaginase (Oncaspar) were correlated inversely with the relative titers of anti-PEG antibodies in the same sera assayed by two methods.[8] Some of their data are summarized in Figure 1. When the relative antibody titers (Low versus High, based on a cut-off selected by Armstrong et al) are measured by binding to TentaGel® OH, they reflect antibodies against the PEG backbone and possibly the terminal hydroxy group.[8] They are referred to in this report as "anti-HO-PEG titers," and the dark blue bars in Figure 1 indicate the corresponding data. When the relative antibody titers are measured by the binding to mPEG-modified erythrocytes, they reflect binding to the methoxy group of mPEG, as well as to the PEG backbone. They are referred to in this report as "anti-mPEG titers," and the corresponding data are indicated by the light blue bar(s) in Figure 1.

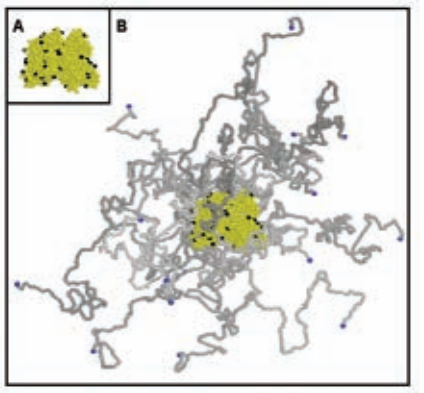
The results represented by the blue bars in Figure 1 demonstrate a clear inverse correlation between the serum asparaginase concentrations and anti-PEG antibody titers, regardless of the method of antibody measurement. Among 28 serum samples analyzed by Armstrong et al, high asparaginase was detected in 80% of those with low titers of anti-HO-PEG antibodies and only 8% of those with high titers.[8] Among the same 28 samples, high asparaginase was detected in 68% of those with low titers of anti-mPEG antibodies, and none of those with high titers. Analyses of a larger number of samples by a common method of measurement of both anti-mPEG and anti-HO-PEG antibodies would be needed to determine whether high anti-mPEG or anti-HO-PEG titers are more closely correlated with low serum asparaginase levels in such patients.

ANTI-PEGLOTICASE ANTIBODIES REDUCE RESPONDERS

Sundy et al summarized the results of two Phase III clinical trials of an mPEG-uricase (pegloticase, KRYSTEXXA®) for the treatment of refractory chronic gout (RCG).[5] Their report includes correlations of the primary endpoint of the trials - the persistent lowering of plasma uric acid below a specified level - with the relative titers of antibodies detected against the PEGylated enzyme as a whole. From the Phase I clinical studies of patients who received a single subcutaneous or intravenous dose of this drug, however, the results of ELISAs of sera from most of the patients with measurable anti-pegloticase antibodies suggested the antibodies were specific for the polymer (mPEG), rather than the enzyme (uricase).[6,7]

Some of the data from the Phase III trials of pegloticase, for patients who received biweekly intravenous infusions of the drug, are summarized in Figure 1 (hatched bars). The inverse correlation of the percentage of gout patients who responded to pegloticase with the relative titers of anti-pegloticase antibodies (Low versus High, based on a cut-off selected by Sundy et al) resembles the inverse correlations of the percentages of leukemia patients who had high serum asparaginase with the relative titers of either anti-HO-PEG or anti-mPEG antibodies after treatment with Oncaspar (blue bars in Figure 1).[5,8] This similarity is consistent with the hypothesis that the anti-pegloticase antibodies detected by Sundy et al in sera from the gout patients in the Phase III clinical trials of pegloticase are directed primarily against the many mPEG moieties in that drug, as reported for the Phase 1 studies.[1,5-7]

FIGURE 2



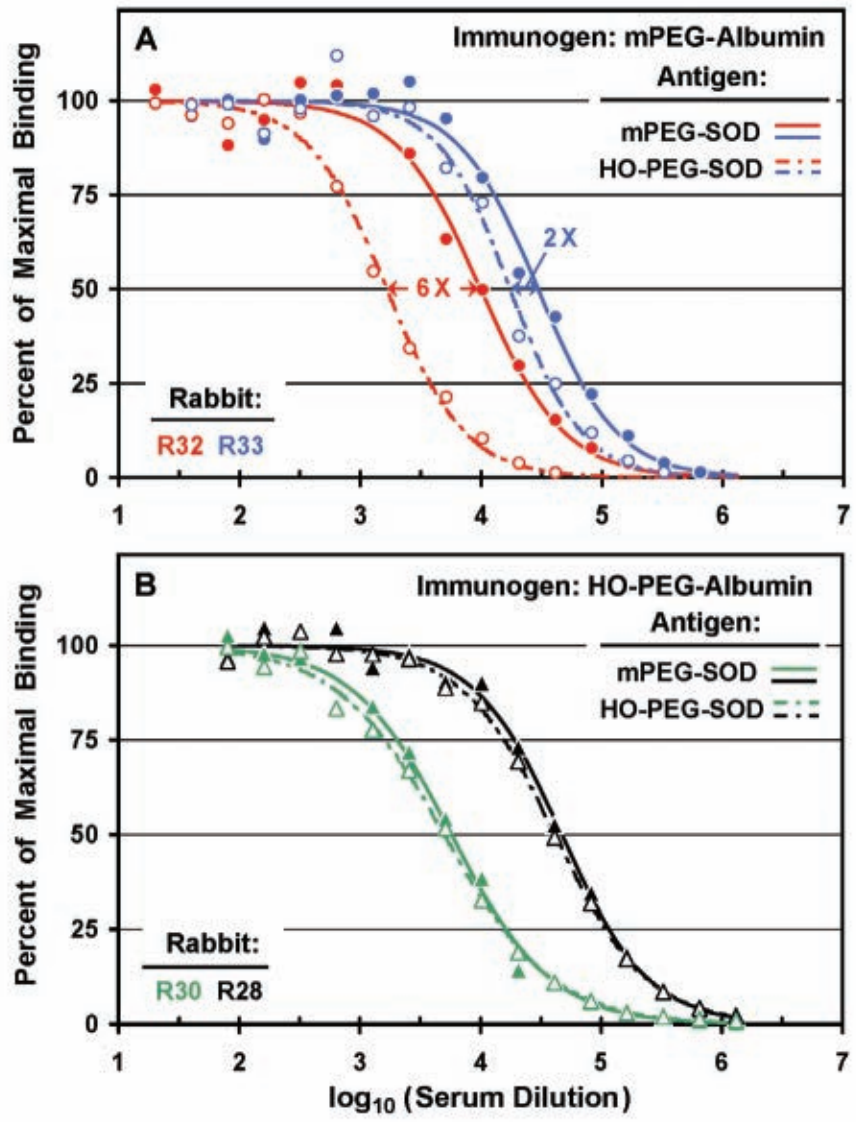
Space-filling molecular models of human serum albumin (A) and a conjugate of albumin with 17 molecules of 10 kDa PEG (B) were generated as described previously for uricase and PEG-uricase.[1] In both models, albumin is shown in yellow, with the nitrogen atoms of the epsilon amino groups of lysine residues in black. In B, the PEG molecules are shown in shades of gray, with the terminal oxygen atom of each PEG enlarged slightly and shown in blue. This is the site of the methoxy group at the remote terminus of each polymer molecule in mPEG.

MODELS FOR MULTI-PEGYLATED THERAPEUTIC PROTEINS

The PEGylated therapeutic proteins currently approved for sale in the US and/or Europe are reported to contain between one and an average of 40 molecules of mPEG.[3,4] This report is based on data from rabbits immunized with HSA coupled to between 17 and 20 molecules of either 10-kDa mPEG (n=7) or HO-PEG (n=7) or recombinant human interferon-alpha coupled to one or two molecules of 20-kDa mPEG (n=5) or HO-PEG (n=6). Some of the data for 17 of these rabbits were published previously.[2] Data from eight additional rabbits, four each immunized with mPEG-HSA or HO-PEG-HSA, are included in this report.

Space-filling molecular models of unPEGylated HSA and HSA conjugated to 17

FIGURE 3



Anti-mPEG and anti-HO-PEG antibodies were assayed in sera from four rabbits that had been immunized with human serum albumin conjugates of either mPEG (A) or HO-PEG (B). Direct ELISAs were performed on assay plates coated with porcine Cu-Zn superoxide dismutase (SOD) conjugated to either mPEG (filled symbols, solid curves) or HO-PEG (open symbols, dashed curves). Data for rabbits R28, R30, R32, and R33 are shown in black, green, red, and blue, respectively.

molecules of 10-kDa PEG are shown in Figures 2A and 2B, respectively. These models were developed using the methods and computer programs described previously for analogous models of uricase and PEG-uricase.[1] A comparison of the models of "naked" albumin and multi-PEGylated albumin reveals a marked difference in size, even though PEG is not coupled to all of the solvent-accessible lysine residues, which are identified in Figure 2 by the black-colored nitrogen atoms of their epsilon amino groups. This difference in size between albumin and multi-PEGylated albumin has been demonstrated in size-exclusion chromatographic analyses of the naked and PEGylated protein (see supporting information of Sherman et al).[2] In the model of PEG_{17}-albumin in Figure 2B, the terminal oxygen atom of each strand of PEG is enlarged and colored blue. This is intended to emphasize that the terminal methoxy groups of conjugates synthesized with mPEG are predicted to be accessible in vitro to anti-mPEG antibodies in the sera of laboratory animals or patients previously immunized with mPEG-protein conjugates and to the immune system in vivo.

HO-PEG LESS IMMUNOGENIC THAN MPEG

In the direct ELISAs shown in Figure 3, the wells of the assay plates were coated with mPEG or HO-PEG conjugates of porcine superoxide dismutase (SOD) that were PEGylated to the same extent. Serial dilutions of sera from rabbits immunized with either mPEG-HSA or HO-PEG-HSA were added to the wells, followed by the addition of an enzyme-linked secondary antibody, as described previously.[2] Goat anti-rabbit IgG (H and L chain specific) conjugated to horseradish peroxidase was used to enable colorimetric quantification of the binding of the rabbit primary antibodies to PEG-SOD in the wells. No Tween® or other PEG-containing detergent was used in washing the assay plates.[2]

The assays of sera from two rabbits in Figure 3A illustrate that 1) the absolute titers of anti-PEG antibodies (reflected by the serum dilution at which 50% of maximal binding is attained) varied between the rabbits, and 2) the ratio of the titer detected with mPEG-SOD to the titer detected with HO-PEG-SOD (the "relative titer") also varied between the rabbits, from 2X to 6X in these examples. The consistent observation was that when rabbits were immunized with mPEG conjugates of HSA or two other proteins, the titers detected with mPEG-SOD exceeded the titers detected with HO-PEG-SOD, with only one exception among 15 rabbits tested to date.[2] In contrast, as illustrated in Figure 3B, when rabbits were immunized with HO-PEG conjugates of HSA or other proteins, the titers detected with mPEG-SOD and with HO-PEG-SOD did not differ appreciably in sera from any of 16 rabbits tested to date. From these results and related data published elsewhere, we infer that the methoxy groups of mPEG-proteins are important contributors to the immunogenicity of the conjugates.[2,16] In contrast, our assays have revealed no contribution of the hydroxy groups of the HO-PEG moieties to the immunogenicity of HO-PEG-protein conjugates.

ANTI-MPEG VERSUS ANTI-HO-PEG AFFINITY DIFFERENCES

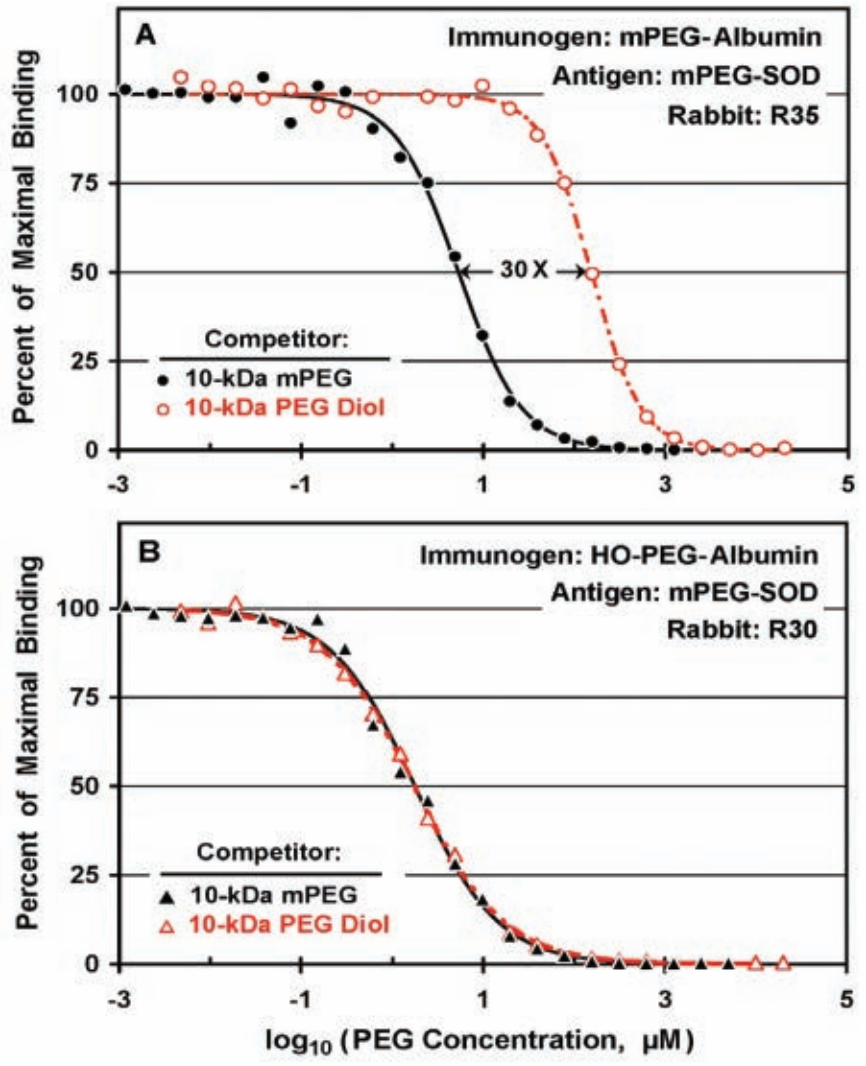
In the competitive ELISAs shown in Figures 4 and 5, the independent variable is the PEG concentration in the competitor, rather than the dilution of serum (as in the direct ELISAs shown in Figure 3). Figure 4A demonstrates that in serum from the particular rabbit tested (rabbit R35), the anti-PEG antibodies have 30 times higher affinity for 10-kDa mPEG than for 10-kDa PEG diol (HO-PEG-OH). The ratio of the affinity of this rabbit's antibodies for mPEG to that of PEG diol is much higher than the relative titers determined by direct ELISAs (30 fold versus 3 fold; data not shown for the direct ELISAs of rabbit R35). The high relative affinities suggest that if an animal or a patient were previously immunized with an mPEG-protein conjugate, subsequent treatment with a HO-PEG conjugate of the same protein would be less susceptible to accelerated clearance because of its much lower affinity for the circulating antibodies.

In contrast with the results in Figure 4A, the data in Figure 4B show that the affinities of antibodies elicited by HO-PEG-albumin for mPEG and PEG diol are indistinguishable. This has been a consistent observation for sera from all rabbits immunized with HO-PEG conjugates of each of three proteins: human serum albumin (n=7), recombinant human interferon-alpha (n=6) and porcine uricase (n=3).[2] These results imply that the anti-PEG antibodies formed against HO-PEG-protein conjugates are directed primarily against the polymer backbone and that competition for their binding to a PEG-protein antigen (such as PEG-SOD) is neither enhanced nor inhibited by the presence of a methoxy group in a competitor.

MULTI-PEGYLATION AMPLIFIES AFFINITY DIFFERENCES

The differences between the affinities for mPEG and HO-PEG of antibodies elicited by mPEG-protein conjugates were amplified when competitive ELISAs were performed with multi-PEGylated competitors, such as HSA conjugates containing an average of 19 molecules of 10-kDa PEG (PEG_{19}-albumin), as shown in Figure 5. The illustrated data were obtained with serum from a rabbit immunized with a conjugate of recombinant human interferon-alpha containing two molecules of 20-kDa mPEG ($mPEG_2$-IFN-alpha), synthesized as described previously.[2] In this serum, the ratio of the affinity for mPEG-HSA to that for HO-PEG-HSA was so high (more than three orders of magnitude) that the highest available concentration of HO-PEG-HSA was able to inhibit only half of the binding of the antibodies to mPEG-SOD in the wells of the assay plate. In analogous experiments with sera from rabbits immunized with mPEG conjugates of porcine uricase (n=3), recombinant human interferon-alpha (n=5) or HSA (n=7), the ratios of affinities for mPEG-HSA versus HO-PEG-HSA, each containing 17 to 22 molecules of 10-kDa PEG per molecule of HSA, exceeded 1,000 in all except one of the sera tested.[2]

FIGURE 4

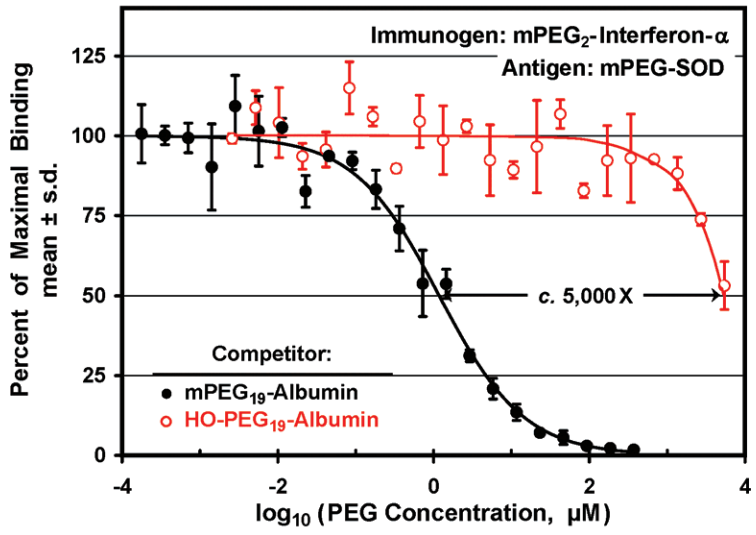


Competitive ELISAs show that antibodies elicited by mPEG-albumin bind 10-kDa mPEG with 30-fold higher affinity than 10-kDa PEG diol (A). In contrast, antibodies raised against HO-PEG-albumin have the same affinities for mPEG and PEG diol (B).

CONCLUSIONS

Despite the underlying assumption of countless scientific reports on the use of PEGylation to enhance the solubility and stability, prolong the duration of action and/or suppress the immunoreactivity of therapeutic agents ranging from low-molecular-weight

FIGURE 5



Competitive ELISAs show that rabbit anti-PEG antibodies raised against a diPEGylated conjugate of human interferon-alpha ($mPEG_2$-IFN-alpha) have c. 5,000 fold higher affinity for conjugates of human serum albumin with 19 molecules of 10-kDa mPEG than for analogous conjugates with 10-kDa HO-PEG.

drugs to whole cells, a growing body of evidence supports the conclusion that mPEG is both antigenic and immunogenic when conjugated to a protein or larger carrier, such as a liposome.[2,12,13,16] This report includes our analysis of data published by others showing strong inverse correlations between the circulating levels of an oncolytic enzyme (asparaginase), following administration of mPEG-asparaginase, and the relative titers of anti-PEG antibodies in the same human sera.[8] We have demonstrated the analogies between the latter data of Armstrong et al, based on studies of mPEG conjugates of an enzyme used for treatment of ALL, and the data of Sundy et al, based on studies of mPEG conjugates of recombinant porcine-like uricase used for the treatment of refractory chronic gout (Figure 1).[1,5,8]

A comparison of the molecular models of human serum albumin and multi-PEGylated HSA provides a visual rationale for the expected (and observed) decrease in the vulnerability of the protein to proteolysis, as well as its prolonged circulation time, when administered as a PEG conjugate (Figure 2). The model of PEG_{17}-HSA also provides a visual image of the expected accessibility of the methoxy group at the remote terminus of each mPEG molecule to the immune system in vivo and to antibodies present in the sera of immunized laboratory animals or humans.

The results of direct ELISAs provide compelling evidence that immunization of rabbits with mPEG conjugates of HSA elicits the production of higher titers of antibodies that bind to mPEG conjugates of an unrelated protein, SOD, than of antibodies that bind to HO-PEG-SOD (Figure 3A). In contrast, antibodies formed against HO-PEG-HSA have indistinguishable titers measured on mPEG-SOD or HO-PEG-SOD (Figure 3B). The results of competitive ELISAs provide compelling evidence that antibodies elicited in rabbits by HSA conjugates with mPEG, but not HO-PEG, have higher affinity for mPEG than for PEG diol (Figure 4), and that antibodies elicited by mPEG conjugates of recombinant human interferon-alpha have higher affinity for mPEG-HSA than for HO-PEG-HSA (Figure 5). While the relative titers of antibodies raised against mPEG-HSA and measured by binding to mPEG-SOD versus HO-PEG-SOD differ by factors of 2 or 6 in two rabbits, respectively (Figure 3A), the affinities of antibodies elicited by mPEG-HSA for unconjugated molecules of 10-kDa mPEG or PEG diol differ by a factor of 30 in serum from the illustrated rabbit (Figure 4A), and the affinities of antibodies elicited by $mPEG_2$-interferon-alpha for multi-PEGylated mPEG-HSA and HO-PEG-HSA differ by more than three orders of magnitude (Figure 5).

The ensemble of data presented here and in our previous publications suggests that clinically important decreases in the immunoreactivity of a next generation of PEGylated drugs (PharmaPEG® conjugates), including proteins, liposomes, nucleic acids, viruses, and red blood cells, may be attainable by the use of monofunctionally activated hydroxyPEGs instead of methoxyPEGs in their synthesis.[2,16] Such decreases in immunoreactivity are likely to result in better tolerated PEGylated drugs, more durable clinical benefits, and fewer dropouts caused by accelerated clearance with loss of efficacy. ◆

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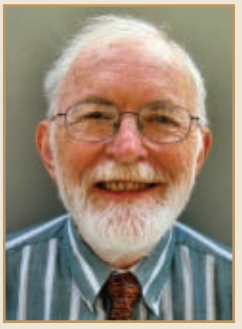
BIOGRAPHIES

Dr. Merry R. Sherman is the CEO and President of Mountain View Pharmaceuticals, Inc. (MVP), of which she was a Co-Founder with Drs. Mark Saifer and L. David Williams. She previously directed research in Endocrine Biochemistry at Memorial Sloan-Kettering Cancer Center and was a Professor of Biochemistry at Rutgers University. She is an inventor on 8 issued US patents and 154 granted foreign patents, including >100 patents on pegloticase.

Dr. Mark G. P. Saifer, Vice President and Scientific Director of MVP, served as Corporate Vice President and Scientific Director of DDI Pharmaceuticals, Inc., for more than 12 years and has received 22 US patents and >300 international patents on the chemistry, production, and analysis of proteins, viruses, synthetic polymers, and polymer-linked proteins. He is a co-inventor of pegloticase.



Dr. L. David Williams, Vice President and Laboratory Director of MVP, is a co-inventor of pegloticase and the recipient of 21 US patents and >300 international patents. After earning his PhD in Organic Chemistry from Harvard University and Post-Doctoral training, he joined DDI Pharmaceuticals, Inc., where he served as Laboratory Director for 15 years before co-founding MVP.

Shawnya J. Michaels is an Associate Scientist at MVP. She previously directed the Discovery Department at ChemGenex Pharmaceuticals, with additional responsibilities in IP management and KOL development. She has an MS in Biotechnology Management from the University of Maryland, University College, and more than 20 years of experience in the development of pharmaceutical products, primarily for cancer indications.

Monika A. Sobczyk has been a Research Associate at MVP for nearly 9 years. She earned her BS in Biotechnology and MS in Biotechnology, with a specialization in Bioinformatics, from the University of Wrocław, Poland. Before joining MVP, she was a bioinformatics specialist at Genmatrix Inc., in Livermore, CA.

A Topical Tacrolimus Microemulsion for Plaque-Type Psoriasis Therapy

By: Johannes Wohlrab, MD; Alexandra Goebel, PhD; Dieter Scherer, PhD; Debra Bingham, and Reinhard H.H. Neubert, PhD

INTRODUCTION

Tacrolimus is a macrocyclic lactone that complexes intracellularly with immunophilin of the Rotamase family (FKBP12) and inhibits the calcineurin phosphatase as well as the MAP kinases JNK and p38, thereby hindering the activation of the nuclear transcriptional factors NFAT and AP-1 to cause an arrest of T cells in the G_0-phase. The resulting reduction of proinflammatory-signaling substances produces an immunosuppressive effect.[1]

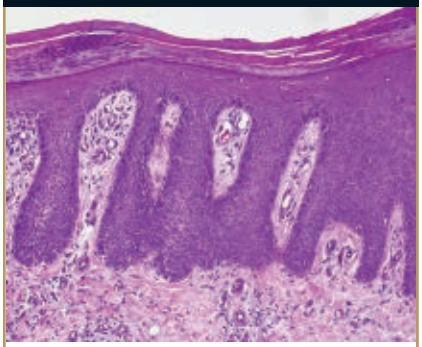
Tacrolimus is mainly used in transplantation medicine and for the epicutaneous application in atopic dermatitis. However, the spectrum of the clinical use extends far beyond the mentioned indications. There are clinical data showing efficacy in other chronic inflammatory dermatoses, eg, psoriasis, lichen planus, sarcoidosis, and pyoderma gangrenosum.[2-4] There is remarkable clinical evidence particularly for the use of topical Tacrolimus in facial and flexural psoriasis inverse.[5-18] Early studies for systemic Tacrolimus have shown efficacy even for plaque-like psoriasis vulgaris.19,20 Admittedly, there are also studies involving the commercially available lipophilic Tacrolimus ointment (Protopic® 0.1%), which do not show efficacy for the indication of plaque-like psoriasis vulgaris.[21] Tacrolimus is a lipophilic, high-molecluar weight (822,05 Da) molecule formulated as a lipophilic ointment.[22] The data show that a sufficient bioavailabilty in the upper dermis is essential for the efficacy of Tacrolimus. Both the nuclear hyperparakeratosis, which can be detected micromorphologically, as well as acanthosis as part of the pathological condition of the psoriatic epidermis, alter the conditions for diffusion fundamentally (Figure 1). To overcome this galenic problem, a colloidal preparation, a microemulsion, has been developed that meets the specific conditions for penetration of the psoriatic skin, and achieves the required bioavailability of the drug in the underlying tissue, which cannot be achieved by conventional formulations.

EXPERMINENTAL METHODS

Development & Characterization of Microemulsions

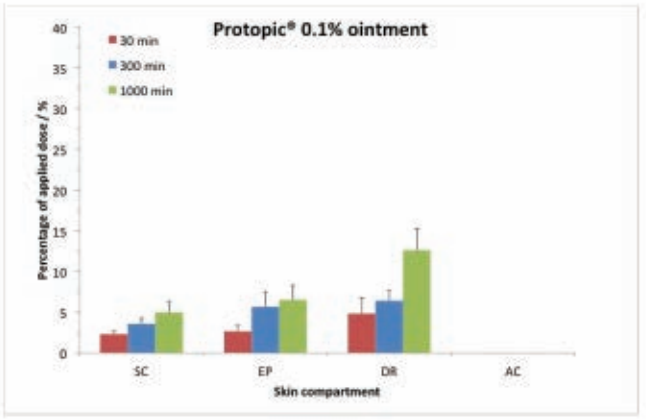
0.1%-m/m Tacrolimus was added to a microemulsion system containing 1,2-propylene glycol (20.0% m/m), Tween 80 (15% m/m), Brij 30 (10.0% m/m), isopropyl myristate (10.0% m/m), and water (45.0% m/m) with 60 microliters tartaric acid (10% m/m). The physico-chemical characterization was performed using the following equipement: rotational rheometer (Anton Paar GmbH, Graz, Austria) for determination of the dynamic viscosity, Cyberscan CON 11 instrument (Eutech Instruments Europe B.V., Nijkerk, The Netherlands) for determination of the electric conductivity, differential scanning calorimetry DSC 200 (Netzsch-Gerätebau GmbH, Selb, Germany) for identification of a free aqueous phase, dynamic light scattering by a compactgoniometer ALV/SP 86 (ALV-Laser Vertriebsgesellschaft mbH, Langen, Germany) equipped with a Nd:YAG-Laser (ADLAS GmbH, Weil im Schönbuch, Germany) for determination of the hydrodynamic radius.[23]

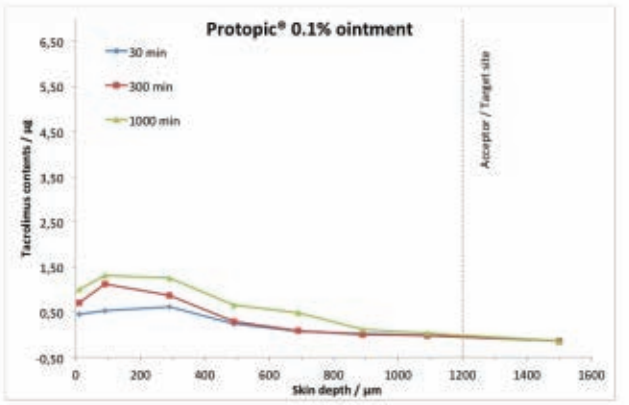
FIGURE 1

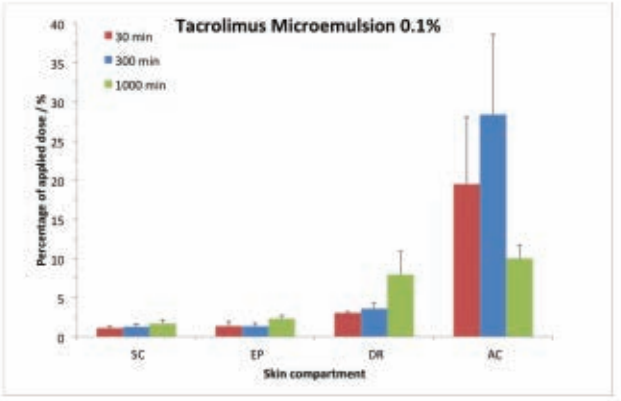


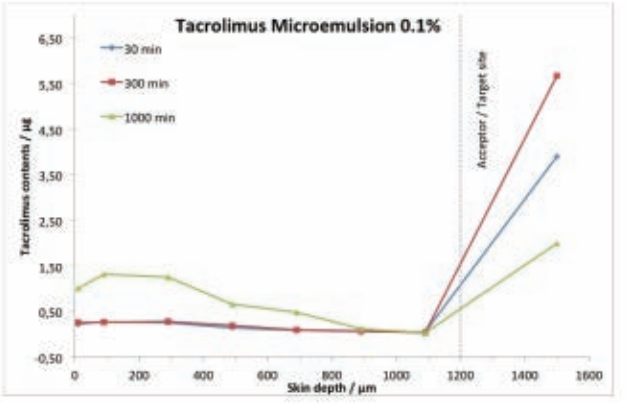
Typical histologic morphology in plaque-type psoriatic skin with confluent parahyperkeratosis, acanthosis, superficial perivascular lymphocytic infiltration, and dilated vessels in papillary dermis. (H&E)

FIGURE 2









Penetration profile of tacrolimus after epicutaneous application of Protopic® 0.1% ointment (above) and the microemulsion system (below). The bar charts show the percentage of the applied dosis in the respective layers (SC=Stratum Corneum; EP=Vital Epidermis; DR=Dermis; AC=Acceptor Phase). The line charts show the absolute concentration of tacrolimus in micrograms correlating the penetration depth in micrometers.

Penetration Studies Ex Vivo

The penetration tests were performed in a Franz diffusion cell using ex vivo human breast skin. Beforehand, the cryo-preserved skin was subjected to an integrity test. For each setting, skin of three different donors had been examined after 30, 300, and 1000 mins, respectively. The quantification of tacrolimus was performed using LC-MS (Agilent, Waldbronn, Germany).[24] As a reference for the microemulsion system, Tacrolimus 0.1% ointment (Protopic® 0.1% ointment, Astellas Pharma Europe B.V., Leiderdorp, Netherlands) had been examined.

Preclinical Tolerability Test

For the evaluation of tolerability, the hen's egg chorioallantois membrane test (HET-CAM) was performed.[25,26] The test criteria had been defined according to the recommendations of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM).[27]

RESULTS

Characterization of Microemulsions

The microemulsion system had a dynamic viscosity of 100.75 ± 0.14 mPas, an electric conductivity of 11.17 ± 0.05 microScm-1, and a hydrodynamic radius of 10.77 ± 0.61 nm. There was no evidence of a free aqueous phase. The stability of Tacrolimus within the microemulsions had been verified by LC-MS for 100 d.

Penetration Profile of Tacrolimus

For the two systems examined, the concentration-time-profiles of Tacrolimus in human skin after epicutaneous application differ significantly. The active substance from the reference diffuses slowly and reaches only the upper layers of the skin, the microemulsion, however, allows a strong flow of the active substance into the intended skin compartment. Given that the concentration measured in the dermis and in the acceptor equals the bioavailable part of the active substance, the microemulsion reaches a bioavailability 2 to 5 times higher than the reference. This is highly relevant for the clinical practice because these high penetration rates can be observed even after a short application time of 30 and 300 mins (Figure 2).

TABLE 1

Test Preparation	Irritation Score	Severity Grade			Irritatives Potential ICCVAM Criteria
		h	I	c	
Sterile water	0	0	0	0	none
1% SLS	10.81	1.5	0.3	2.8	hight
Protopic® 0.1% ointment	0	0	0	0	none
Microemulsion 0.1% tacrolimus	0.17	0.1	0	0	none

Single parameters according ICCVAM criteria for determination and evaluation of the irritation scores via HET-CAM (SLS=Sodium Lauryl Sulphate; h=haemorrhage time; I=lysis time; c=coagulation time).

Preclinical Tolerability Test

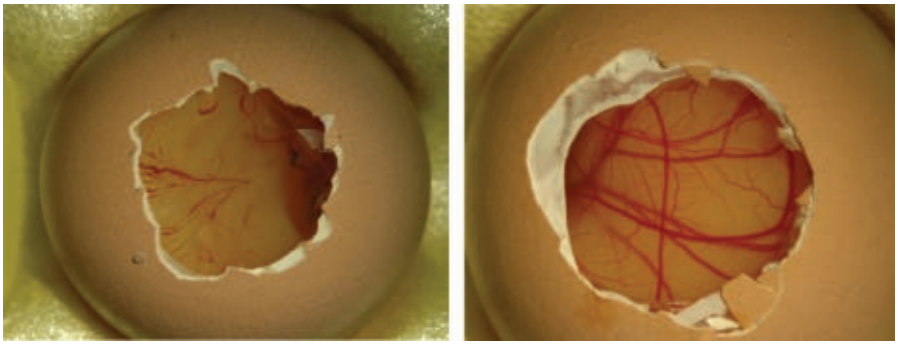
No evidence of local incompatibility could be found in HET-CAM tests (Figure 3), thus there are no concerns regarding potential irritations after cutaneous or mucocutaneous application of the microemulsion (Table 1).

CONCLUSION

The available data show a significantly higher bioavailability of Tacrolimus in the intended skin compartment for the developed microemulsions than for the commercially established reference preparation. This is primarily due to the high level of thermodynamic stability and the dynamic microstructure of the microemulsions.[28] The empirically determined, isotropic mixture of hydrophilic and lipophilic phases, emulsifiers, and co-emulsifiers forms spontaneously and acts like a Newtonian fluid allowing for a good solubility for Tacrolimus.[29] The high mobility of the active substance is caused by the spontaneous and continuous fluctuation of domains within the system and allows the high penetration rate via solvent drag effect. Because of its low interfacial tension and low viscosity, the preparation shows excellent spreading properties. These properties allow the administration of the formulation as a spray. This is advantageous over conventional topical formulations like ointments, in particular, if hairy areas like on the scalp have to be administered. The applied dose reaches the underlying skin and does not stick to the hair as it is well known for ointments. There is also a safety and a cosmetical aspect. This formulation is less visible and thereby less stigmatizing compared to ointment preparations in the hair. In addition, there is no highly potent active on the finger tip that can be spread unintentionally to the environment, eg, infants. Although the microemulsions feature a higher content of emulsifiers compared to standard vehicles, it has been designed to be inert by strategic selection of skin-friendly surfactants. The preclinical tolerability tests (HET CAM) do not indicate any irritative properties. Also, the characteristics of psoriatic skin must be taken into account because its pathologic structure reduces the bioavailability of potential irritants anyway, there are no concerns regarding local tolerability particularly for the indication of plaque psoriasis. Safety concerns regarding the topical application of calcineurin inhibitors expressed by the FDA in a black box warning have been discussed at length in the literature and have been widely dispelled.[30]

Within this context, the international patent rights have been secured, and a concept for a clinical trial for the indication psoriasis has been agreed on with the German approval authority. All planning preparations for a pivotal study in the indication psorasis capitis have been finalized. The results will show to what extent the significantly higher bioavailability of Tacrolimus makes the immuno-suppressant effect of the developed microemulsion therapeutically relevant for the indication psoriasis in comparison with Calcipotriol (Daivonex® solution, Leo Pharmaceutical Products Ltd. A/S, Ballerup, Denmark) and with the combination of Calcipotriol/Betamethasone diproprionate (Xamiol® Gel, Leo Pharmaceutical Products Ltd. A/S, Ballerup, Denmark). ◆

FIGURE 3



Representative examples of HET-CAM tests 3 mins after application of test substance (left=sodium lauryl sulphate; right=tacrolimus 0.1% microemulsion).

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BIOGRAPHIES

Prof. Dr. Johannes Wohlrab is a dermatologist at the Department of Dermatology and Venereology at Martin Luther University Halle-Wittenberg (Germany). In addition to his clinical activities, he is involved in the development in preclinical and clinical validation of new cosmetic and pharmaceutical products or medical devices for topical use.

Dr. Alexandra Goebel graduated as a pharmacist specializing in the development, production, and quality testing of colloidal systems by Skinomics. She has now been working in a research laboratory of Allmiral.

Dr. Dieter Scherer joined Novaliq in April 2009 as its Chief Business Officer. His 20 years of experience covers the gamut from business development and licensing to product development in the field of drug delivery. His experience covers a wide variety of dosage forms, with his speciality in working with the delivery of poorly soluble drugs. After filling various staff and line functions with increasing responsibilities at LTS Lohmann in Germany and SkyePharma in Switzerland, he set up his own consultancy (Apis Pharma AG) in 2003 advising drug delivery companies throughout Europe. Dr. Scherer graduated as Pharmacist at the J.W. Goethe University in Frankfurt and later earned his PhD in Pharmaceutical Technology from the same faculty.

Debra Bingham is a life science partner with the Washington, DC-based consulting firm Valeo Partners. Valeo provides business development, licensing, and market strategy advisory services. Ms. Bingham has more than 18 years of experience working with clients in the pharmaceutical and chemical industries. Her clients include multinational pharmaceutical, biotech, medical device, and chemical companies as well as medium-to-small specialty pharma and drug delivery companies. Valeo Partners is working with Novliq to license its proprietary products and technologies.

Prof. Dr. Dr. h.c. Reinhard H.H. Neubert is a pharmacist at the Faculty of Pharmacy at Martin Luther University Halle-Wittenberg (Germany). He is an expert in drug transport, dermal drug delivery, colloidal drug carrier systems, biosensors based on quartz microbalance and molecular structure of the stratum corneum lipids.

Focused Ultrasound - A Novel Tool for Liposome Formulation

By: Srikanth Kakumanu, PhD, and Avi Schroeder, PhD

INTRODUCTION

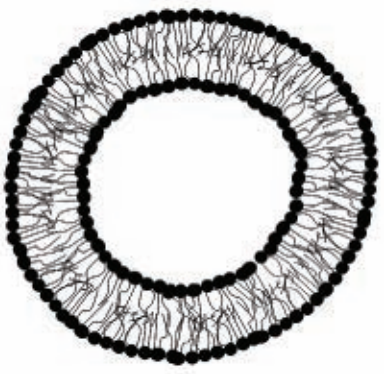
Liposomes are excellent carriers of active pharmaceutical ingredients and cosmetic agents. Their vesicular structure, housed by lipid bilayers, resembles that of natural cells and is shown in Figure 1. The building blocks of liposomes, ie, lipids, can be tuned to enhance the bioavailability of an active compound in specific tissues, improve the therapeutic index, and decrease side effects, such as toxicity. Clinically, liposomes are already FDA approved for delivering a wide scale of small molecule drugs, and their development for the delivery of more sophisticated macromolecules, such as DNA, siRNA, proteins, and peptides, is being sought by industry and academia. Producing liposomes at the nanoscale is of great interest; current technologies, such as extrusion, high-pressure homogenization/ultrasonication, and microfluidic chambers, are either non-suitable for delicate compounds or difficult to scale up. Herein, we describe a novel technology - Adaptive Focused Acoustics™ (AFA) - capable of efficiently producing nanoliposome formulations at the bench or in a pilot plant. The technology eliminates the need to heat the lipids or to dissolve them in a co-solvent during the formulation process. The computer-guided process ensures batch-to-batch repeatability, and the disposable closed flow-system prevents inter-batch contamination and alleviates the need for exhaustive wash cycles.

To date, among the approved liposomal drugs, liposomal doxorubicin (known as Doxil in the US and Caelyx in the EU), is the leading drug on the market, with annual sales that exceed $650 million. Doxil liposomes are composed of three major lipids (HSPC, PEG-DSPE, and cholesterol). In order to achieve proper liposome construction, traditional preparation methods call for high-temperature extrusion or other mechanical down-sizing processes. We tested the ability of AFA to formulate Doxil-like liposomes at 4°C. In addition, we used AFA to co-formulate nanoliposomes with the highly hydrophobic drug paclitaxel (Taxol) at 4°C and without the need for any co-solvent.

CURRENT PROCESSES & LIMITATIONS

Traditional liposome preparation methods include detergent depletion, ethanol injection, reverse-phase evaporation, and emulsion methods. Processing methods include high-pressure homogenization, extrusion, and ultrasound. One disadvantage of the preparation methods is the usage of large amounts of volatile organic solvents, multiple lengthy steps, and heat/degradation of the sample. These issues become even more problematic when scaling from small lab scales to those needed for volume manufacturing. The use of organic solvents can affect the chemical integrity of the active ingredient intended to be encapsulated and requires purification and separation steps, not to mention the environmental impact and associated

FIGURE 1



Representation of liposome structure showing a lipid bilayer with an aqueous core.

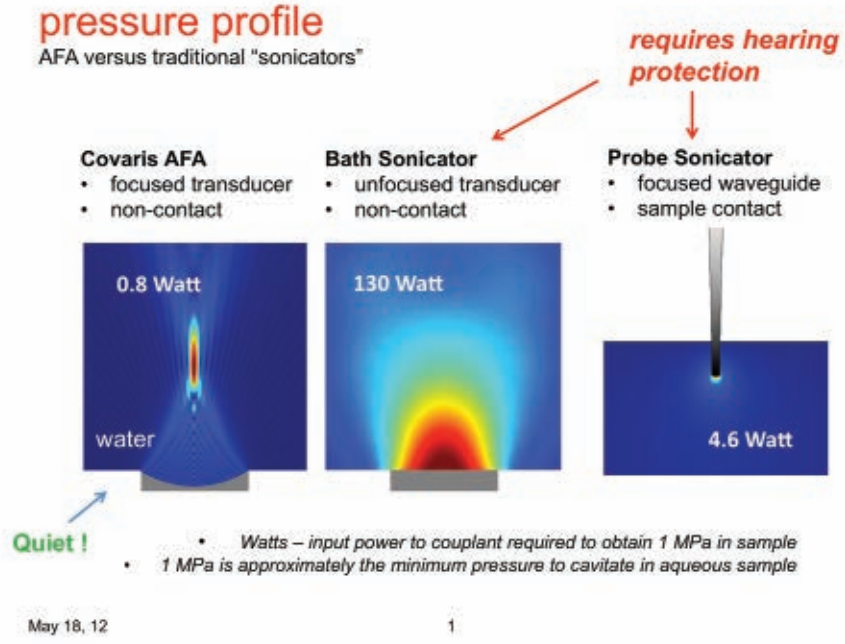
costs. New techniques, such as dense gas liposome production, are not widely employed because of the high operating pressures required for these processes.

High-pressure homogenization, in which the lipid emulsion is passed multiple times through a confined nozzle at speeds of 400 m/s and high shear rates, can generate heat and sample degradation, even when active cooling is implemented in the system.

Probe sonicators can be used to form liposomes; however, because the probe is in contact with the lipid/water during processing, concerns over contamination and scalability are inherent, and with a relatively low efficiency, the probe tip and adjacent sample material can experience extremely high temperatures. A model of pressure/temperature distribution of a probe sonicator is presented in Figures 2 and 3. In the case of a bath sonicator, the energy diverges away from the source, which reduces the intensity thus lowering the efficiency. With a broad divergent energy field, the acoustic waves can reflect and converge or diverge on a given area, thus creating "hot" or "cold" spots of uneven energy distribution.

Figure 4 represents how a sample is processed to form liposomes using AFA technology. A concave transducer directs the energy to a focal point, where the sample is placed inside of a closed vessel. Temperature is controlled by a surrounding water bath, allowing isothermal processing during liposome formation. The non-contact nature of this process ensures no contamination, and enables a sterile and disposable processing chamber.

FIGURE 2



Comparison between Covaris Adaptive Focused Acoustics (AFA), bath sonicater, and probe sonicater.

MATERIALS

Phospholipon 90G (Lipoid, Ludwigshafen, Germany), Egg Lecithin (Lipoid), HSPC: L-alpha-phosphatidylcholine, hydrogenated (Soy) (Avanti Polar Lipids, Alabastar, AL), PEG-DSPE: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (ammonium salt) (Avanti Polar Lipids), Cholesterol (Sigma), Paclitaxel (LC Laboratories, MA, US).

AFA Technologies (Covaris, MA, USA): S220x, Vessel: 12x24 sample vessel P/N 520056, Holder: 12x24 sample holder P/N 500199, Flow Cell, Flow Cell Holder, Flow System SF220X, Particle Sizing: Malvern Zetasizer S90/ZS90.

METHODS

To prepare 2 mL of Phospholipon 90G-based blank liposomes, 20 mg of dry Phospholipon was added to 2 mL DI water. The vessel was loaded into the instrument and processed at AFA conditions of 300 PIP, 50% Duty Factor, and 200 Cycles per Burst for 30 seconds. Particle size was measured using a Malvern Zetasizer using volume distribution analysis. Similarly, other natural lipids, such as Egg lecithin, can be processed to produce liposomes. Egg lecithin at 10 mg/ml with the same protocol produced 105-nm particles of liposomes. The concentration of lipids can be varied so it can be increased or decreased according to the needs.

Adding 20 mg of the hydrophobic anti-cancer drug Paclitaxel to 40 mg of Phsopholipon (both in their dry form, into 2-mL phosphate buffered saline) increased the particle size to 400 nm, even after 20 minutes of AFA processing. This is explained by stabilization of the particles by the drug and by the extremely high drug-to-lipid ratio. Increasing the lipid content will enable further reduction of particle size, while maintaining stability over time.

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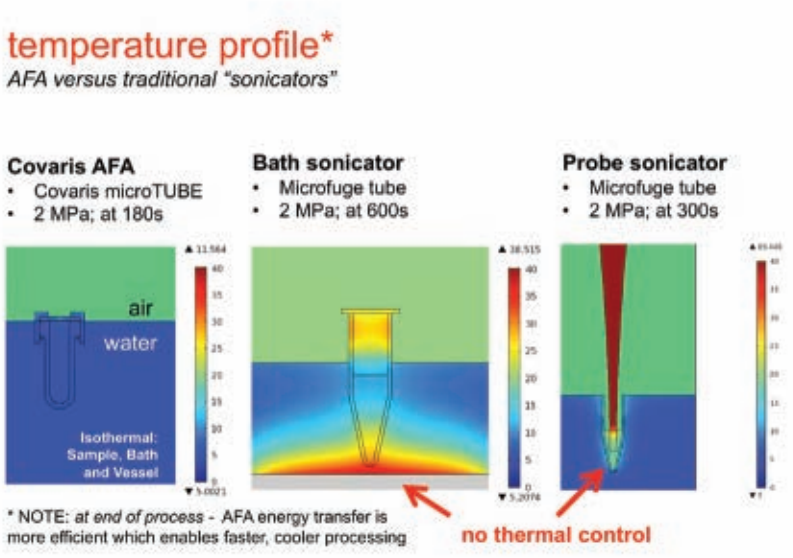
FIGURE 3



Temperature profile comparison between Covaris Adaptive Focused Acoustics (AFA), bath sonicator, and probe sonicator.

Pilot-Scale Production

The ability to scale up the lab system was tested using an AFA flow system. Here, the processed solution can be pumped through the AFA apparatus one or more times, depending on the target size of the particles. The smaller the particle size, the longer the needed exposure to AFA. A 250-mL batch was processed with 2.5 g of dry Phospholipon 90G in PBS. The dispersion was allowed to mix for 20 minutes before recirculation started. The flow rate through the acoustic field was adjusted to 65 mL/min. Figure 5 presents the particle size as a function of AFA processing time. As expected, as the processing time increases, particle size converges and the polydispersity index (PDI) decreases. It should be noted here that "over processing" can occur, in which samples reach their target size and then start agglomerating due to the continuation of the acoustic process. This highlights the need for the integrated control unit that indicates the real-time particle size by measuring absorbance in the system. In the current process, particles reached a uniform size of approximately 200 nm after 30 minutes of processing.

Low-Temperature Doxil Liposome Formulation + Taxol Formulation

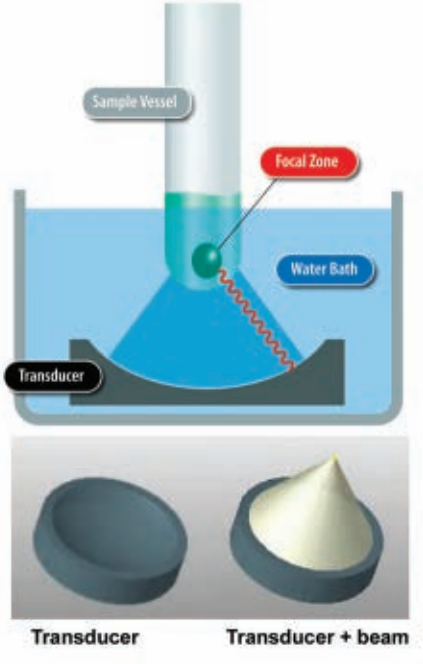
To prepare a 2-mL sample of Doxil liposomes, HSPC (11.4 mg), PEG-DSPE (3.8 mg), and cholesterol (4.2 mg) were placed dry in the sonication vessel, and PBS was added to fill the vessel to the lid (~2 mL). The vessel was processed at 200 PIP, 50% Duty Factor, 200 Cycles per Burst for 25 minutes, and particle size was measured. The particles reached a homogeneous size of < 100 nm. Doxil preparation is by remote loading, ie, the drug is loaded via an osmotic pumping mechanism post liposome formulation; thereby, these liposomes resemble those currently used in industry.

SUMMARY & CONCLUSION

Adaptive Focused Acoustic (AFA) technology was demonstrated to be a promising and novel tool for the formulation of lipid-based drug delivery systems. With the ability to formulate at low temperatures , non-contact, and without the use of solvents, AFA allows liposome formation across a variety of lipid compositions. The ability to form a Doxil liposome blank is demonstrated in small 2-ml batches while recovering 100% of the material. A Phospholipon 90G-based blank processed for 30 seconds produces a high- quality liposome distribution.

Scaling of AFA is accomplished using the same equipment utilizing a flow cell configuration. This was demonstrated to effectively produce a 250-ml batch of Phospholipon 90G-based liposome, again without contact or the use of solvents. The particle size distribution is controllable by adjusting AFA process settings and time,

FIGURE 4

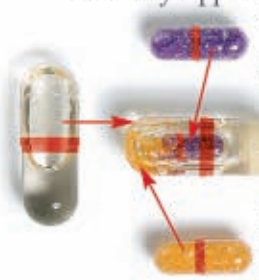


Covaris Adaptive Focused Acoustics (AFA) Technology

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
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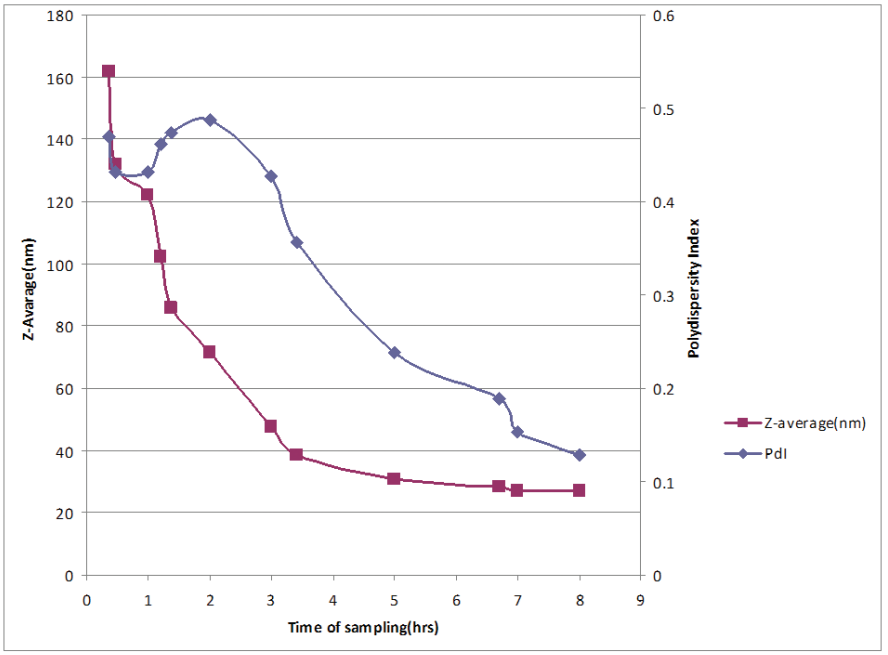
FIGURE 5



Lipsome Upscaling 250 ml (10 mg/ml of Phospholipon 90G)

with a distribution of approximately 30-nm size particles achievable. We thus conclude that the AFA technology is a promising and novel tool for the formulation of lipid-based drug delivery systems at the bench and pilot scale. ◆

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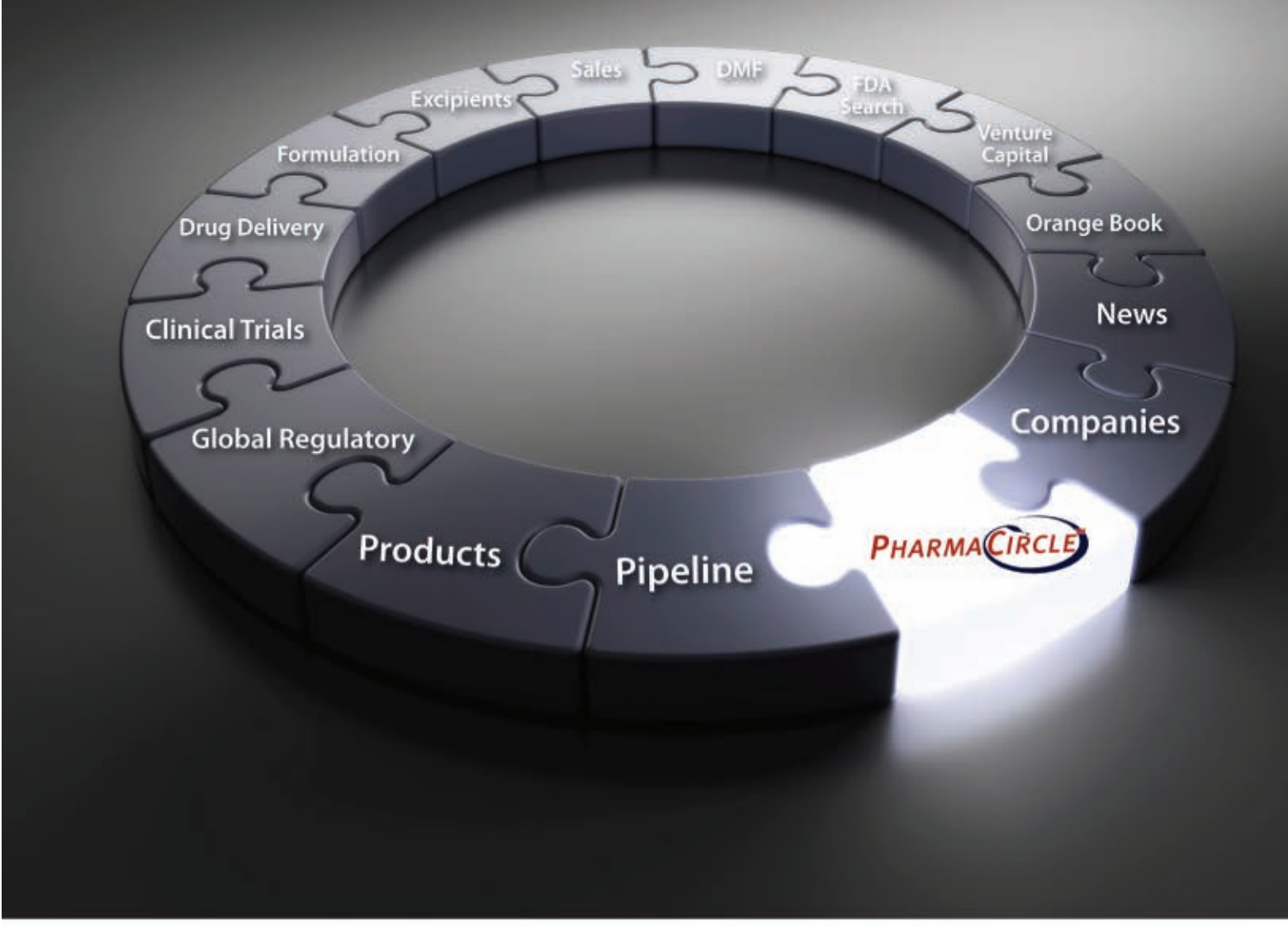
BIOGRAPHIES

Dr. Srikanth Kakumanu earned his PhD from the Department of Biomedical Engineering and Biotechnology at University of Massachusetts in 2010. Since June, 2010 he has been working as a Research Scientist at Covaris Incorporated, where he heads the research in the application of Adaptive Focused Acoustics in formulations (dissolution, micronization, nano-suspension, and liposome production) and cell lysis. His major focus of research is scaling the AFA process to pilot scale and continuous flow sample volumes.

Dr. Avi Schroeder is a Post-doctoral Fellow in Robert Langer's Lab at the Department of Chemical Engineering and Koch Institute for Integrative Cancer Research, the Massachusetts Institute of Technology. Previously, he earned all three degrees in Chemical Engineering from the Ben Gurion and Hebrew Universities, Israel. Dr. Schroeder is an author of 19 peer-reviewed papers and inventor on 9 patents. He is a recipient of the Intel Nanotechnology, TEVA Pharmaceuticals, Hebrew University Nanoscience and Nanotechnology, and the Wolf PhD Awards.



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MARKET BRIEF

Drug Development for the Management of Type 2 Diabetes - Glucose Control Is No Longer Enough

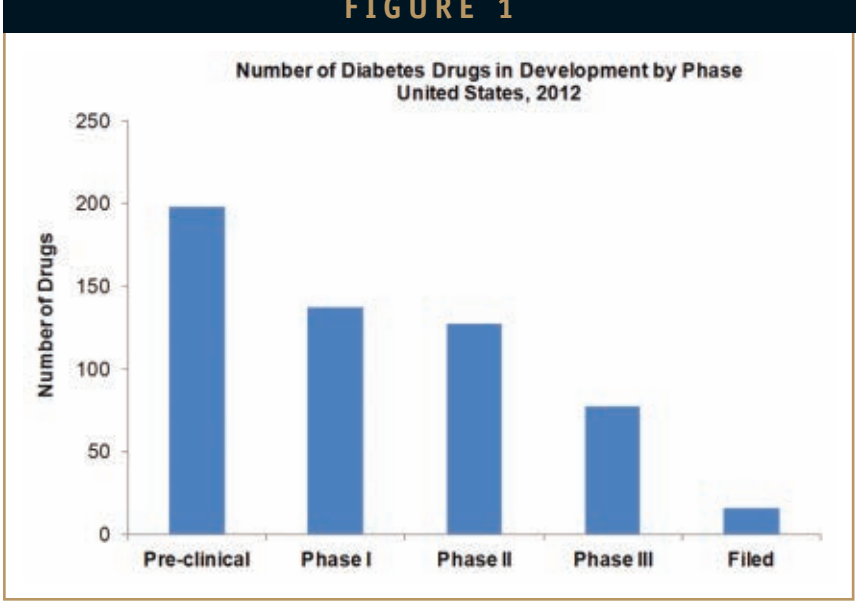
By: Debbie Toscano, Senior Industry Analyst, Frost & Sullivan

INTRODUCTION

Diabetes mellitus has been recognized as a human disease for thousands of years. According to the American Diabetes Association, the total prevalence of diabetes in the US in 2011 was 25.8 million children and adults, or 8.3% of the population. Although it presents itself in several distinct forms, the basic pathology revolves around a defect of the pancreas to produce enough insulin, an essential hormone for moving glucose from the blood into the tissues where it is needed, giving rise to the hallmark feature of high blood sugar. The large majority of cases (approximately 90%) are type 2 diabetes mellitus, also known as adult onset diabetes or non-insulin-dependent diabetes (NIDDM), as opposed to type 1 diabetes, or juvenile onset diabetes, an autoimmune disease targeting the pancreas. Type 2 diabetes is rapidly becoming a global epidemic, alongside obesity. As compared to type 1 diabetes, which is essentially the inability of the pancreas to produce insulin, type 2 diabetes has a different pathology but essentially results from a combination of the body's resistance to the effects of the insulin along with the gradual inability of the pancreas to produce enough insulin. Left uncontrolled, type 2 diabetes eventually leads to numerous complications such damage to the nerves, kidneys, and retina, which can lead to amputation of the feet, kidney failure, and blindness, respectively. However, the most common cause of death from diabetes is cardiovascular disease. Having diabetes increases the chance of dying from a heart attack to the same degree as having previously suffered from a heart attack.

The association between obesity and the development of type 2 diabetes is becoming increasingly strengthened with epidemiological research and can no longer be ignored. Obesity and overweight is a primary risk factor for diabetes, along with age and a family history of diabetes. Largely considered a preventable lifestyle disease, the incidence of type 2 diabetes continues to increase despite substantial public health efforts to message the importance of making healthy lifestyle choices, such as proper nutrition and adequate physical activity. With nearly 2 million new cases of diabetes diagnosed each year, development of novel treatments for the pharmacological management of type 2 diabetes remains a high priority pursuit of numerous pharmaceutical and biotech companies. There are more than 500 new drugs currently in development for the treatment of diabetes.

FIGURE 1



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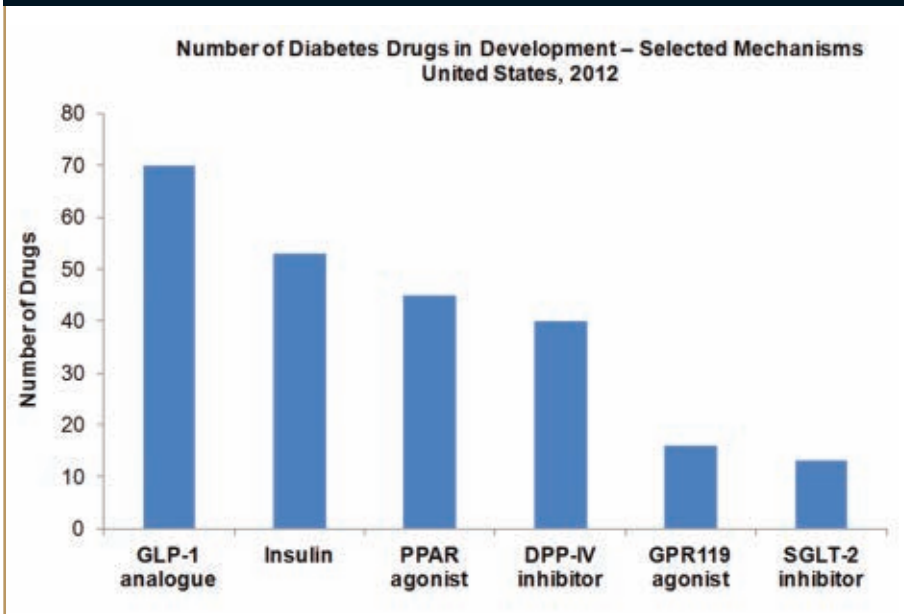
Although there is currently a wide variety of therapeutic options for physicians and patients to choose from, the trend in drug development is moving away from simply controlling blood glucose, toward addressing the other important risk factors and co-morbidities, primarily obesity and cardiovascular disease. This market brief will address the main diabetes therapies commonly in use, as well as discuss some of the novel mechanisms in the drug development pipeline. Figure 1 depicts the number of drugs in development by mechanism, with a focus on some of the more promising targets.

FIGURE 2



INSULIN

Administration of exogenous insulin has been the mainstay of diabetes therapy since the 1920s when one of the most important Nobel Prizes for Physiology or Medicine was won for the discovery of the treatment of diabetes with insulin. While insulin is not a cure, it is still the most effective therapy for managing blood glucose. However, it carries several important drawbacks, such as the necessity to inject, sometimes several times daily, and the risk of hypoglycemia (dangerously low blood sugar) if an incorrect dose is accidentally administered or the patient fails to eat properly.

Insulin is currently available in several forms that can be used alone or in combination with other forms depending on the needs of the patient. For example, some patients require rapid-acting insulin to control mealtime glucose spikes along with longer-acting insulin (basal insulin) for all-day control. As diabetes patients are very heterogeneous with regard to individual blood glucose profiles, the availability of a variety of insulins is important in order to prescribe tailored therapy. The introduction of Lantus (insulin glargine) in 2000 was a major improvement to insulin therapy due to its 24-hour glucose-lowering effect and convenient once-daily dosing regimen. Further advancements in insulin development primarily aim to reduce the frequency of administration. Degludec, an ultra-long-acting insulin being developed by Novo Nordisk, has the potential to be used less than once daily and could reach the market by mid-2012 pending approval by the FDA in July. Attempts to successfully bring inhalable insulin to the market have thus far met with failure. In 2007, less than 2 years after approval, Pfizer pulled its inhaled insulin Exubera from the market due to risk of lung cancer. Mannkind is developing Afrezza, an inhaled insulin drug-device combination product, currently in late-stage development. The first attempt to win FDA approval resulted in a Complete Response Letter in January 2011. Pending the successful completion of two additional pivotal clinical trials, diabetes patients could potentially see the first non-injectable insulin in the near future.

Advancements in delivery devices have also made the self-administration of insulin easier for patients. Next-generation pen injectors that can administer a dose with the push of a button have simplified the process and have the potential to greatly improve patient compliance. The most popular pen injectors are prefilled disposable pens, which are simply used until the insulin cartridge inside is empty and the entire unit is discarded. Patient-friendly features of more advanced pens include smaller needles for less discomfort, an audible click to signal when the dose is complete, and greater dose accuracy.

GLUCAGON-LIKE PEPTIDE-1 (GLP-1)

One of the most exciting recent discoveries in diabetes therapeutics has been that of the benefits of GLP-1. This intestinal peptide is secreted in response to a meal and helps the body process the food by stimulating insulin secretion as well as suppressing appetite, among other physiological functions. However, it has a very short half-life in the blood. Therefore, GLP-1 analogues were developed to have a longer half-life, providing therapeutic benefits of glucose control with a low risk of hypoglycemia, a key advantage of

this therapy. Whereas drugs such as insulin lower blood sugar regardless of the level in the blood (hence the inherent risk of hypoglycemia), GLP-1 analogues essentially only work under conditions of elevated blood sugar and therefore have a much lower risk of inducing hypoglycemia.

In addition to glucose control, GLP-1 analogues also typically have a modest weight loss effect and may even have a curative effect on the pancreas as well as preventing cardiovascular disease, making this class one of the most beneficial diabetes therapies on the market. However, there are several class-associated disadvantages, such as the need for injection and gastrointestinal side effects such as nausea and vomiting. There are three GLP-1 analogues currently on the market. Byetta (exenatide injection, Amylin) is a synthetic version of exendin-4, a protein found in the saliva of the Gila monster that is highly similar to human GLP-1 but has a longer half-life. Byetta was the first commercial GLP-1 analogue approved for the management of type 2 diabetes. Victoza (liraglutide, Novo Nordisk) is a long-acting GLP-1 analogue that is more similar to human GLP-1 and needs injection only once daily, whereas Byetta must be injected twice daily. The newest addition of the GLP-1 class to the market is Bydureon (Amylin), approved by the FDA in January 2012, which provides all of the benefits of Byetta with once-weekly injection. Another significant advancement was the approval of the use of Victoza in combination with basal insulin in April 2012. The combination of basal insulin and a GLP-1 analogue is considered by many to be the optimal therapy for long-term disease management. Next-generation GLP-1 analogues aim for less-frequent administration or oral delivery and better safety and tolerability, particularly with respect to nausea and vomiting. Demonstration of greater weight loss and cardiovascular benefits will also be major advancements for this class.

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR AGONIST

The peroxisome proliferator-activated receptor (PPAR) agonists are oral therapies that target a family of nuclear receptors. The main drug classes targeting PPAR receptors are PPAR-gamma agonists (also referred to as thiazolidinediones, or TZDs), PPAR-alpha agonists (also referred to as fibrates), and PPAR-delta agonists. Depending on the specific target, these drugs control blood sugar by increasing the sensitivity of the tissues to insulin ("insulin sensitizers"), improve the lipid profile, spur weight loss, or a combination of actions. PPAR-gamma agonists are a well-known class, with two approved drugs in the US - Actos (pioglitazone, Takeda) and Avandia (rosiglitazone, GlaxoSmithKline). While these drugs are very effective at controlling blood sugar by reducing insulin resistance, they are also associated with potentially serious side effects such as cardiovascular disease (Avandia) or cancer (Actos). PPAR-alpha agonists are effective lipid-lowering drugs and have a good safety profile. A well-known example of a PPAR-alpha agonist is Tricor (fenofibrate, Abbott), typically prescribed for high triglycerides. Dual PPAR-alpha/gamma agonists, which could have the ideal profile of normalizing both blood sugar and lipids, have been in development for some time, but many have met with failure due to risk of serious side effects, such as liver toxicity or cancers. PPAR-delta is a receptor largely found in adipose tissue, and drugs that stimulate this receptor have the potential to induce weight loss by accelerating fat burning as well as having favorable effects on blood glucose and lipids; however, none have yet progressed beyond Phase II. Several PPAR agonists in development are designed to selectively target both PPAR-alpha and gamma (dual agonists) or all three receptors (PPAR pan agonists). Drug design also incorporates differential targeting of each receptor in order to achieve the desired balance of safety and efficacy as well as clinical effect. For example, aleglitazar (Roche), currently in Phase III of development, is a dual PPAR-alpha/gamma agonist designed for balanced control of both glucose and lipids with potential for cardiovascular benefits as well.

DIPEPTIDYL PEPTIDASE-IV (DPP-IV) INHIBITOR

Glucagon-like peptide 1 owes its short half-life in the blood to the enzyme dipeptidyl peptidase-IV (DPP-IV). Inhibition of this enzyme extends the half-life of GLP-1 in the blood resulting in increased blood levels, similar to GLP-1 analogues. DPP-IV inhibitors have a very clean safety profile, including a low risk of hypoglycemia and no weight gain, with convenient once-daily oral dosing and thus have quickly been adopted into widespread use, typically on top of standard first-line therapy, metformin. Although similar in mechanism to the GLP-1 analogues, DPP-IV inhibitors have the main advantage of oral administration. However, they do not have an effect on weight loss, primarily because while they enable the body to maintain blood levels of GLP-1 for a longer time period, they do not raise the levels above normal as do GLP-1 analogues. There are currently three DPP-IV inhibitors available in the US: Januvia (sitagliptin, Merck); Onglyza (saxagliptin, Bristol-Myers Squibb/AstraZeneca); and Tradjenta (linagliptin, Boehringer Ingelheim).

All three are also available as a fixed combination product with metformin. Januvia is also available as a fixed combination product with simvastatin (Juvisync, Merck), providing glucose control and cholesterol lowering with the convenience of a single pill. Next-generation DPP-IV inhibitors stand to differentiate by demonstrating improvements in pharmacokinetics (many are cleared by the kidney, necessitating dose adjustments for patients with compromised kidneys), greater potency, or cardiovascular benefits.

SODIUM-DEPENDENT GLUCOSE CO-TRANSPORTER-2 INHIBITOR (SGLT2)

The sodium-glucose transporter 2 is located in the kidney and is responsible for the re-absorption of glucose back into the blood. Inhibitors of this transporter lower blood glucose by increasing the disposal of glucose through the urine. This mechanism has the additional benefits of convenient once-daily oral administration as well as a modest weight loss effect due to the disposal of excess calories in the form of glucose. Concerns with this class include risk of urinary tract infections as well as the unknown long-term effects, particularly on the kidneys. There are currently no approved products in the US. Dapagliflozin (Bristol-Myers Squibb/AstraZeneca), the most advanced product, was submitted to the FDA in 2011. However, eventual approval will depend on submission of additional data as per the FDA's Complete Response Letter issued in January 2012. The drug recently received a positive opinion by the European Medicine Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP) in April 2012, where it will be marketed under the trade name of Forxiga if approved by the EMA.

GPR-119 AGONIST

G protein-coupled receptor 119 (GPR-119) is a receptor found in the pancreas and intestines. Agonists of this receptor have great potential as diabetes therapeutics due to favorable effects on glucose control, body weight, and preservation of the pancreas. The most advanced product in this class is GSK1292263 (GlaxoSmithKline), currently in Phase II clinical trials.

SUMMARY

The diabetes therapy area is a challenging and crowded space for drug developers. However, there remain significant unmet needs to fulfill. Therapies that are convenient for patients and provide effective glucose control with low or no risk of hypoglycemia on top of important additional benefits for this patient population, such as weight loss and cardiovascular risk reduction without compromising safety, are greatly needed. Besides being important for market uptake, these additional key benefits will be increasingly important for regulatory approval by the conservative FDA. The requirement for diabetes drugs to demonstrate cardiovascular safety with an outcomes trial adds significant expense to the drug development process, and new entrants will face an uphill battle. However, the size of the market and the potential to capture a slice of the pie represents a lucrative opportunity for successful participants. ◆

BIOGRAPHY

Debbie Toscano is a Senior Industry Analyst with the Frost & Sullivan North American Healthcare practice. Utilizing more than 20 years of life sciences industry experience, she maintains particular expertise in analysis and interpretation of scientific data as well as preparation of deliverables with attention to technical detail. Mrs. Toscano has an experience base covering a broad range of sectors, including focus on diabetes and metabolic diseases, cardiovascular diseases, and preclinical animal modeling and pharmacology. Prior to joining Frost & Sullivan, she conducted preclinical research with Novartis Pharmaceuticals. Mrs. Toscano earned her BS from Delaware Valley College in Biology and her Master's Certificate from Thomas Edison State College in Clinical Trials Management.

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

Biopharma Solutions

BioPharma Solutions, a business unit of Baxter, partners with pharmaceutical companies to support their commercialization objectives by providing scientific expertise, sterile manufacturing solutions, parenteral delivery systems, and customized support services needed to meet the unique challenges that parenteral products face. Experience makes the difference: with nearly 80 years of parenteral expertise, we can help to navigate the pathway of success for your molecule. BioPharma Solutions provides our clients with confidence of delivery, service, and integrity - we know the work we do is ultimately vital to the patients you serve. BioPharma Solutions offers resources to help solve the high-stakes challenges you face in today's complex parenteral marketplace. For more information, contact Baxter BioPharma Solutions at (800) 4-BAXTER or visit **www.baxterbiopharmasolutions.com**.

Pharmaceutical Solutions

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

Technology & Services Showcase

Hormone Delivery Technology

OraSorb™ hormone delivery technology provides the convenience of a pill with a metabolic profile similar to a patch. CIMA's new delivery system combines solubilization and permeation enhancing technologies into one buccal tablet. The solubilization technology ensures the hormone is in solution when it comes in contact with the buccal mucosa. The buccal permeation technology provides for rapid absorption. The high bioavailability of the buccal delivery means that efficacious drug levels can be obtained with lower doses. Buccal delivery also reduces first-pass hepatic metabolism, which results in reduced hepatotoxicity. This resulting formulation has a more favorable "patch-like" metabolite profile with the convenience of a buccal tablet. If you would like to learn more about OraSorb, please contact CIMA Labs at (763) 488-4975 or visit **www.cimalabs.com**.

Biopharmaceutical CDMO

Cook Pharmica is a biopharmaceutical contract development and manufacturing organization (CDMO) with process development, clinical and bulk drug substance manufacturing, formulation development, clinical and commercial parenteral drug product manufacturing (including liquid and lyophilized vials, prefilled syringes, and secondary packaging), and an array of supported services all at a single facility in Bloomington, IN. Founded in 2004, Cook Pharmica is a division of Cook Medical, the world's largest privately held medical manufacturing company. For more information, contact Cook Pharmica at (877) 312-2665 or visit **www.cookpharmica.com**.

Development & Manufacturing

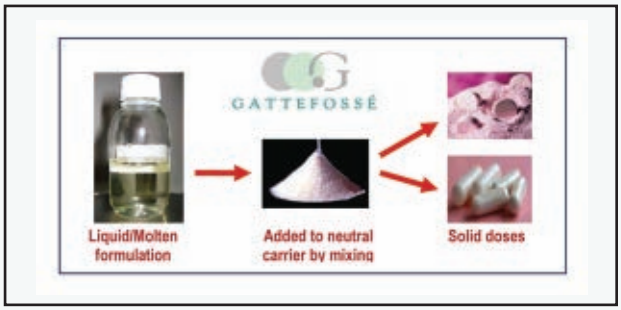
DPT is a contract development and manufacturing organization (CDMO) specializing in semi-solid and liquid dosage forms. DPT provides fully integrated development, manufacturing, and packaging solutions for biopharmaceutical and pharmaceutical products. DPT is the industry source for semi-solid and liquids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

Analytical Testing & Consulting

Gateway Analytical provides analytical testing and consulting services that can help ensure product quality throughout your product development lifecycle. Specializing in advanced characterization and pharmaceutical forensics, we support provide unique services, such as chemical imaging for layer thickness analysis, ingredient-specific particle-size analysis, polymorph characterization, as well as investigation of deviation and nonconformance issues. With more than 15 years of experience, you can rely on our expertise in analytical testing and consulting to help you solve your toughest challenges. Our scientists have the diverse industry expertise and the technical know-how to meet your unique needs quickly and efficiently. For more information, contact Gateway Analytical at (724) 443-1900 or visit **www.gatewayanalytical.com**.

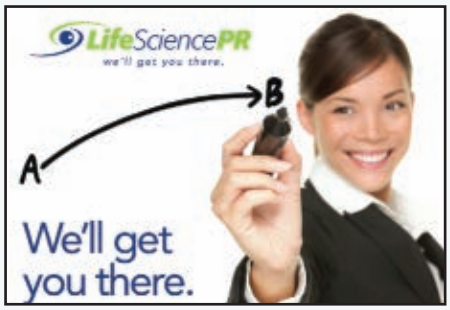
Technology & Services Showcase

Solvent-Free Adsorption



Designed for enhancing the solubility of poorly soluble drugs in solid dosage forms, this technique allows the transformation of liquid or semi-solid lipid formulations into solid particles that can subsequently be filled into hard shell capsules or alternatively compressed into tablets. The active may be dissolved or dispersed in the formulation prior to adsorption onto a solid neutral carrier, such as calcium silicate, with the aid of conventional mixers. The success of the technique depends much upon the properties of the carrier, notably its flow characteristics and capacity to absorb the desired amount of formulation. Our laboratory has successfully loaded up to 68% liquid SELF onto solid support. For more information, contact Ron Permutt of Gattefosse at (201) 265-4800 or visit **www.gattefosse.com**.

Marketing & Communications



Get Noticed. Get Funded. Grow Faster. When you need to connect with investors, business partners, and regulatory agencies, LifeSciencePR can make that happen. Our integrated communication strategies and well-established industry contacts will help your life science company achieve its short- and long-term corporate objectives. We work seamlessly with your senior management team to develop the most effective communication initiatives to reach your prospective investors and partners. Our experienced staff knows what it takes to break through with your breakthroughs, powering your engine in your continued drive toward your success. LifeSciencePR will get you there smarter, faster, and easier than any other marketing and communications firm in the industry. For more information, contact LifeSciencePR at (800) 724-2372 or visit **www.LifeSciencePR.net**.

Specialty Pharma

CAPTISOL®

Ligand is a specialty biotech company that develops and acquires technology and royalty revenue-generating assets that are coupled to a lean cost structure. Our formulation technology, Captisol® has enabled five FDA-approved products, including Pfizer's VFEND® IV and Baxter's Nexterone®. Captisol is patented and designed to improve solubility, stability, bioavailability, safety and/or dosing of a number of APIs. Deep industry experience with an extensive drug master file (DMF), technical expertise, and worldwide collaborations make the Captisol®-enabling technology a solution to advancing a product toward commercialization. For licensing opportunities, contact Jessica Smith at **(913) 402-3521**.

Ocular Drug Delivery

Unique Drug And Oxygen Delivery Systems

NOVALIQ

Novaliq GmbH, Heidelberg, Germany, offers a new drug delivery technology for poorly soluble drugs, semi-fluororinated alkanes (SFA). SFAs offer very unique features as a drug delivery platform, aside from dissolving poorly water-soluble compounds, they also offer excellent spreading and wetting properties and are chemically and biologically inert, thus causing no irritation to ocular tissues. This patented, non-aqueous, and preservative-free formulation represents an interesting alternative to aqueous-based ophthalmic formulations. A prominent example is our proprietary cyclosporine A formulation, CyclASol. In contrast to the current state-of-the-art aqueous-based formulations that require complicated emulsions with all their drawbacks, SFAs dissolve cyclosporine A and can therefore be administered as a solution. For more information, contact Novaliq GmbH at +49 6221 502590, or info@novaliq.de, or visit **www.novaliq.de**.

Technology & Services Showcase

Recombinant Human Albumin

Manufactured specifically for the biopharmaceutical and medical device markets, Novozymes Biopharma's animal-free, recombinant human albumins (rAlbumins) are applicable in formulation, drug delivery, and medical device coating. Proven to stabilize proteins by preventing aggregation, oxidation, or adsorption of the active drug, Novozymes' rAlbumins are pure, high-quality ingredients that can help customers deliver safer products to the market faster. Albucult® is supplied as an ingredient for the manufacture of pharmaceutical drugs, medical devices, and advanced cell therapy products. Approved for use in the manufacture of human therapeutics, Recombumin® is the world's first commercially available, GMP-manufactured, animal-free rAlbumin developed for drug and vaccine manufacturing. Novozymes' rAlbumins are manufactured to regulatory standards to deliver a secure supply of batch-to-batch consistency and increased efficiency for customers looking for a compliant albumin alternative. For more information on Novozymes' rAlbumins, visit **www.biopharma.novozymes.com**.

Silicone Materials

NuSil SILICONE TECHNOLOGY

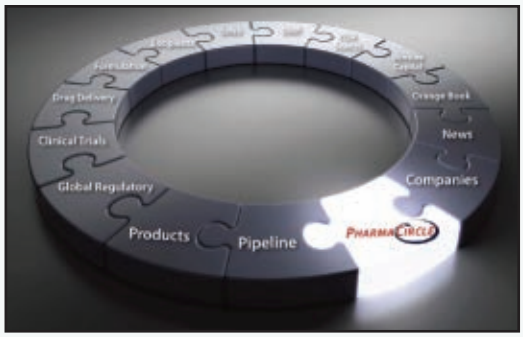
When it comes to drug delivery, NuSil provides numerous solutions that fit a variety of device needs. While most silicone products are customized for individual delivery systems, all are developed with FDA regulatory concerns in mind. In addition to its role as a supplier, NuSil offers research and development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

Development & Delivery Solutions

PARTICLE SCIENCES
DRUG DEVELOPMENT SERVICES

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

Knowledge Management



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

Technology & Services Showcase

Contract Diagnostics

ResearchDx is the leading Contract Diagnostics Organization (CDO) for the biopharmaceutical and diagnostic industries. As a CDO, ResearchDx integrates in vitro diagnostics (IVD) non-clinical and clinical research, CAP/CLIA laboratory assay discovery, development and testing, GMP manufacturing of test kit components, and end-to-end consulting to achieve the fastest path to market for your IVD/companion diagnostic. With experts managing the entire development process from initial assay concept and discovery through clinical research to regulatory approval, ResearchDx employs a proactive project management approach with the availability of resources to ensure appropriate attention to timelines every step of the way. By offering the complete range of CDO services without owning a proprietary testing platform, ResearchDx ensures its clients' diagnostics are developed with the methodology and platform that best optimize its characteristics and commercialization strategy. For more information, contact ResearchDx at (866) 225-9195 or visit **www.researchdx.com**.

CRO Services

Theorem Clinical Research is a foremost provider of comprehensive CRO services with offices in more than 30 countries and a customer base composed of some of the world's leading pharmaceutical, biotech, and medical device companies. Theorem converges Phases I-IV solutions with specialized therapeutics expertise to execute perfectly aligned trials. Supporting business units include Clinical Development, Clinical Supply, Clinical Analytics, Biopharmaceutical, and Medical Device and Clinical Combination Studies. For expert guidance and custom solutions to streamline your trials, think Theorem. Learn more about Theorem's extensive capabilities by calling (800) 290-5766 or visiting **www.theoremclinical.com**.

Development Services

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 40,000-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**.

West PFS Solutions

You need prefillable syringe systems and components designed to compete in an evolving industry. You need the management, expertise, and support of a manufacturer capable of creating systems and components that will mitigate risk and differentiate your product. You need West. Pharmaceutical and biopharmaceutical customers trust West to provide prefillable syringe systems and components that help bring products to market safely, reliably, and with the integrity you've come to expect from West. Our global technical expertise and services provide solutions that are true to our core goal of reducing regulatory risk while ensuring quality and patient safety. So you can rest easy. Pictured above is West's prefillable syringe solutions that include the Daikyo Crustal Zenith® 1-mL long insert needle syringe system. For more information, contact West at (800) 345-9800 or visit **www.WestPFSsolutions.com**.

DRUG DEVELOPMENT
ZOSANO PHARMA Executive

Zosano: A Differentiated and Clinically Validated Transdermal Technology

By: Cindy H. Dubin, Contributor

The worldwide market for drugs delivered transdermally has been valued at $5.6 billion in 2009, with the US being the largest individual market, according to Research and Markets. The immense size of this market can be attributed to the ability of transdermal delivery to fulfill unmet needs in the marketplace, such as the ability to deliver large-molecule therapeutics. Methods for administration of these products are often problematic. Active transdermal drug delivery solves many challenges associated with parenteral and oral drug delivery by allowing large molecules, such as antibodies and vaccines, to be self-administered painlessly. Active transdermal technologies use some form of added energy to increase the drug flux across the skin. Such technologies include iontophoresis (low voltage electrical current), electroporation (short electrical pulses of high voltage), thermal energy (heat), and microporation (microneedles to create micropores in the outermost skin layer without causing pain or bleeding). Microneedles are proving to be one of the most cost-effective and user-friendly of the active transdermal technologies. Zosano is one company exploring the benefits and advantages of microneedles. Formerly known as The Macroflux Company, Zosano was as an internal venture within Alza (J&J), a pioneer in the field of drug delivery systems. In 2006, the internal venture became an independent company. Zosano aims to develop products independently and is also actively pursuing strategic licensing and co-development arrangements, an example of which is the recently announced exclusive licensing agreement in Asia for a phase 3 ready weekly patch formulation of PTH for osteoporosis that was recently signed with Asahi Kasei Pharma Corporation (see press release of October 10, 2011). Zosano is a fully integrated development company, including a recently launched cGMP manufacturing capability. Much of the company's core staff came from Alza. Zosano's patent portfolio includes more than 19 patent families in the US, 12 in the EU, and 20 patent applications pending. Zosano (meaning safe zone) is advancing a pipeline of drug candidates based on the ZP Patch Technology–a proprietary, microneedle-based technology capable of delivering peptides, proteins, small molecules, and vaccines by permeating the skin's outer layer. The technology has been clinically tested in more than 400 patients with five different peptides and a vaccine. Gail Schulze, CEO and Executive Chair of the Board, recently spoke with Drug Development & Delivery about her plans for the spin-off company since taking the reins in 2008.

Gail Schulze

CEO & Executive Chair of the Board

Zosano

"Our recently-signed partnership with Asahi Kasei Pharma for a weekly PTH patch in Asia is an important validating step for Zosano. Beyond PTH, in the past year, Zosano has collaborated with several other major pharmaceutical/vaccine companies. In addition, our demonstrated capabilities in successful Phase II clinical trials and advanced worldwide regulatory discussions should make Zosano a partner of choice for companies looking for both differentiation and proven GMP manufacturing."

Q: What challenges does Zosano face as an emerging company in the transdermal drug delivery landscape?

A: Even though we are an emerging company, we brought the technology and people from Alza following the spin-off. So, we are technically a somewhat new company with an established team and technology. This is quite different from the challenges that a start-up company faces.

Zosano is the most clinically validated microneedle company in the world today. Zosano has developed the ZP Patch Technology, which has been proven to offer several key benefits, including efficacy and safety comparable to approved injectables, needle-free delivery, a self-administered patch, rapid onset of action, and room temperature storage. The versatility of the technology has been validated–all molecules attempted thus far have been successfully coated onto the patch.

Q: What has been the biggest announcement to come out of your company in the past year as it relates to transdermal drug delivery?

A: The most important announcement has been the exclusive licensing agreement in Asia with Asahi Kasei Pharma we signed earlier this year for a weekly PTH patch being developed for osteoporosis patients with a serious, generally untreated, severe condition. We feel this partnership further validates the potential of ZP Patch Technology, showing not only its versatility and commercial promise, but also its potential to improve the lives of patients in need. As part of the agreement, AKP has paid Zosano $7.5 million in upfront consideration. In addition, AKP will pay over $25 million in milestone payments, and Zosano will receive sales royalties as well as reimbursement for all development and manufacturing costs. AKP and Zosano plan to continue discussions regarding the extent of their strategic collaboration, including potential joint development of the patch in other territories.

Beyond this transaction, in the past year, Zosano has solidified its position in the transdermal market through two important advancements. First, we have created a cost-effective commercial cGMP manufacturing facility with per-patch costs that are on-par with the leading autoinjector pens. A cGMP manufacturing process is critical to getting a drug approved. This is where our investors are putting their money. Having document and quality systems will allow our product to become real.

Second, we have had advanced discussions with worldwide regulatory bodies (including the FDA) to clarify and simplify the steps needed for the ZP Patch Technology to reach the market.

Q: Where will the ZP Patch Technology make the most difference in the transdermal market?

A: The applications of ZP Patch Technology are numerous. Aside from being compatible with parenterally delivered, potent biomolecules, it is well-positioned to capitalize on two dominant trends in today's healthcare environment: The emergence of biobetters and the increasing importance of payers.

First, ZP Patch Technology is ideally suited as a biobetter platform that provides the potential for forward-thinking companies to leapfrog biosimilars and other biobetter competitors. The ZP Patch Technology allows for "biobetters on a patch" by providing concrete upsides for all stakeholders (patients, physicians, payers, and manufacturers) in a single, flexible platform. Importantly, the ZP Patch Technology is compatible with further differentiation of the molecule itself (eg, new PEGs, superior manufacturing technologies, etc). To date, Zosano has successfully coated such molecules as GCSF, EPO, and HGH onto our proprietary microneedle system.

Second, the growing influence of payers is driving the shift of drug administration from the hospital or clinic (where it is expensive) to the home (where it is less costly) and raising the bar for new therapies to show improved outcomes, cost effectiveness, and superior compliance.

At the same time, payer pressures have ignited a renewed interest in vaccines (along with several other aspects of preventative care) and antibodies (given several inherent advantages they possess in development efficiency and safety). The ZP Patch Technology provides cost-effective self-administration of antibodies and vaccines and has proven this with compelling data to date.

Phase II clinical results for daily ZP-PTH (where we enrolled 165 patients) have demonstrated a significant gain in bone mineral density of the lumbar spine and hip following 24 weeks of the ZP-PTH 40 mcg patch. All tested ZP-PTH doses were well tolerated with no systemic adverse events different from the currently marketed standard of care, Eli Lilly's Forteo daily injection. The ZP-PTH product has also demonstrated greater than 2-year shelf-life without the need for refrigeration.

Q: What is your strategy for attracting funding from venture capitalists?

A: Zosano is funded by New Enterprise Associates, Nomura Phase4 Ventures, HBM BioVentures and ProQuest Investments, all well-recognized leaders in the venture capital healthcare arena. To date, Zosano has raised more than $100 million. Our message is that our lead product, a PTH hormone for osteoporosis, is a great product, and that is what investors want, great products that make a difference in the market. Our lead PTH product is compelling to investors because it satisfies an unmet need and will have profit potential of about $1 billion to $2 billion within 10 years after it becomes commercially available in 2015. PTH is a very well-established molecule being put into a new delivery system. The only alternative treatment is a self-administered injection the patient takes daily for 2 years. This is an onerous treatment. Patients wear the ZP Patch Band-Aid-like solution for just 30 minutes per day. Investors like the technology. It is highly differentiated from any treatment in the pipeline for this patient segment, and it is low risk. Of course, there is no such thing as no risk.

Q: Where have your investors made the most impact on your business?

A: Our drug delivery platform requires a complex manufacturing and engineering infrastructure. Our investors stepped up to invest a significant amount of money in manufacturing facilities outfitted with complex, expensive equipment. This engineering, rather than chemical, component to our platform requires that the mechanics are developed consistently. Each device has 1,300 microneedles placed on a patch the size of a quarter. The challenge is to coat each microneedle with the same amount of drug each time to make sure the drug delivers reliably, and to do this all cost effectively.

Q: Please describe the Zosano business model going forward.

A: Simply put, we want to be successful with our PTH lead product and build a drug delivery company that is validated on the basis of that product. We feel the recently-signed AKP partnership for PTH is an important step in this direction. The PTH product should reinforce validity that our ZP Patch Technology platform works. Beyond PTH, in the past year, Zosano has collaborated with several other major pharmaceutical/vaccine companies. In addition, our demonstrated capabilities in successful Phase II clinical trials and advanced worldwide regulatory discussions should make Zosano a partner of choice for companies looking for differentiation of their biosimilar programs. We believe strongly that the forces are lined up for an acceleration of the growth of the microneedles delivery sector, with Zosano at the forefront. ◆

Executive Summary

Mathew W. Moore, PhD

Principal & Co-Founder
ResearchDx

Philip D. Cotter, PhD

Principal & Co-Founder
ResearchDx

The Contract Diagnostics Organization: Revolutionizing Management for Co-Development of Companion Diagnostics

The use of companion diagnostics in conjunction with custom pharmaceuticals is expected to expand as the promise of personalized medicine continues to be realized. However, a concurrent development cycle of both diagnostic and therapeutic components requires a complex synergy of both diagnostic and drug development, and represents a significant deviation from the current pharmaceutical model. In response, ResearchDx, LLC of Irvine, CA, launched the first-ever Contract Diagnostics Organization (CDO) in February 2011. This new business model facilitates simple, straightforward options to initiate the parallel development of companion diagnostic tests in synergy with drug development. Specialty Pharma recently interviewed Mathew W. Moore, PhD, and Philip D. Cotter, PhD, Principals and Co-Founders of ResearchDx, to discuss the concept of a CDO and how this new business model stands to impact personalized medicine and revolutionize management of the co-development of companion diagnostics.

Q: ***ResearchDx is the first-ever Contract Diagnostics Organization (CDO); what is a CDO?***

A: With a shared passion for, and experience in, the field of personalized medicine, ResearchDx created the concept of the Contract Diagnostics Organization in response to the numerous pitfalls we have personally experienced in the companion diagnostics development process. With our team's extensive experience in managing clinical laboratories, designing and managing clinical research, and navigating the complex regulatory environment specific to diagnostics, we saw the opportunity to fill an unmet need for partnership with the biopharmaceutical and diagnostics industries. As a result, ResearchDx provides all of the services necessary to develop a companion diagnostic in an integrated, technology-independent manner that stays focused on our customers' business objectives. As a CDO, ResearchDx offers clinical research, a clinical laboratory, manufacturing, and consulting all in one organization - eliminating the need for outsourcing to multiple partners. This also builds in flexibility as well as the ability to implement an efficient, nimble strategy that may naturally shift as development continues.

Q: ***Can you speak to the uses of companion diagnostics in today's healthcare environment?***

A: Broadly speaking, companion diagnostics can be used in one of three categories: (1) Patient Stratification; (2) Drug Dose Determination; or (3) Monitoring Treatment. In the case of Patient Stratification, companion diagnostics can assist in identifying patients who will - and perhaps equally as important, who will not - benefit from a particular therapeutic treatment. With regard to Drug Dose Determination, biomarker information derived from companion diagnostics can be used to calculate appropriate drug dosage. In the area of Monitoring Treatment, companion diagnostic assays are used to monitor the effectiveness of a given therapeutic treatment. All of these applications - patient stratification, drug dose determination, and monitoring treatment - are integral to the overall concept and emerging era of "personalized medicine."

Q: ***The regulatory environment regarding diagnostic development seems to be rapidly changing; can you tell us more about this and how a CDO can help companies navigate this changing regulatory landscape?***

A: The US FDA's guidance document The Drug-Diagnostic Co-Development Concept was drafted in 2005 to help outline a process to prospectively co-develop a therapeutic product and diagnostic test in a scientifically robust and efficient way. This document identified and outlined the recommended multi-step path from basic research to, ultimately, FDA filing and/or approval and product launch.

Following this, the FDA's Guidance on Pharmacogenetic Tests and Genetic Tests for Heritable Markers document was released in 2007 and intended to recommend a basic framework for the types of data and regulatory issues that should be addressed in a genetic test submission and provide a common baseline from which both manufacturers and scientific reviewers can operate.

In June 2011, the FDA issued Draft Guidance regarding In Vitro Companion Diagnostic Devices. This document further emphasizes the importance of companion diagnostics and speaks to the co-development of drugs and companion diagnostics.

As evidenced above, the regulatory initiatives and guidance documents are numerous. As such, the need for specific expertise in the diagnostic industry throughout the companion diagnostic co-development process is paramount. Use of a CDO fills this need by bringing expertise in the area of diagnostics and diagnostic assay development to the companion diagnostic co-development process. To navigate the changing regulatory environment requires a depth of knowledge with regard to diagnostic assay development, and a CDO brings that level of knowledge and expertise.

Q: ***You mentioned experiencing pitfalls, or challenges, in your own experiences in the companion diagnostics development process; what are some of these issues and how can ResearchDx help companies combat these challenges?***

A: The challenges faced are numerous, and may include any or all of the following:

- Knowledge-base: need for in-depth diagnostics knowledge
- Strategic: consideration regarding restriction of assay platform options
- Need for an accredited clinical laboratory partner
- Timeline management: coordination of parallel timelines for therapeutic and diagnostic development
- Management of multiple partnerships

In short, ResearchDx offers all of these services - all within one organization, and there is no need to manage multiple R&D partners because we do it all. As a CDO, ResearchDx can build, validate, and perform any assay that a business demands, or alternatively work with competing technology vendors to ensure the best fit for the application. Clients can trust that the focus and motivation from ResearchDx as a CDO are solely on the diagnostic development, with no competing interests. Our partnerships are based on flexibility, allowing us to either build and validate any assay without bias toward existing product platforms, or to work with emerging technology to ensure the best solution.

As a CDO, ResearchDx takes contract R&D for diagnostics to the next level. Our partners trust ResearchDx to provide everything they need to develop a diagnostic product, and that we will make their business objectives our priority.

Q: ***Your description of a CDO sounds similar to that of a Contract Research Organization (CRO); how do you distinguish between the two?***

A: CROs have been traditional choices for outsourcing partnerships with pharma in the management of clinical trials for pharmaceuticals. However, CROs cannot provide the in-depth diagnostics knowledge, and many CROs do not have an accredited clinical laboratory solution for clients. A CDO provides all of the services and expertise needed from biomarker identification to submission for regulatory approval to manufacturing all from one partner.

Q: ***You describe ResearchDx as a non-competitor provider to pharmaceutical & diagnostics companies; what do you mean by that?***

A: Because ResearchDx does not own a proprietary testing platform, we are able to ensure our clients' needs are met using the platforms and methodologies that best meet the commercialization strategy and needs of the client. ResearchDx provides all the necessary components of the companion diagnostics development process in an integrated, technology-independent manner that keeps the focus on the clients' business needs and objectives. ResearchDx can build, validate, and perform any assay that a business demands, or work with competing technology vendors to ensure the best fit for the application. Because ResearchDx has no competing interests, clients can trust that the focus and motivation is on the companion diagnostic development process.

Q: ***Describe the services offered by ResearchDx?***

A: ResearchDx offers services in three key areas of focus: (1) Companion Diagnostics Services, (2) Clinical Laboratory Services, and (3) Manufacturing Services. Within our Companion Diagnostics Services, we offer independent and unbiased guidance, as well as expert and seamless integration of all the services pharma needs to develop a companion diagnostic assay. ResearchDx can design, manage, and coordinate all aspects of clinical trials for the development of a diagnostic product from assay concept to assay development, through to regulatory submission and commercialization.

Our Clinical Laboratory is CLIA-certified and CAP-accredited, in which we perform high-complexity, esoteric laboratory testing. We are an ideal laboratory partner for companies looking to outsource high-complexity laboratory testing. We allow our clients to confidently offer a broad range of genetic testing and provide outstanding service to their ordering physician clients. Through our Clinical Laboratory Services, we offer seamless integration into our clients' lab operations and industry-leading turnaround times.

As part of our Manufacturing Services, we offer clients a GMP manufacturing partner that will meet the unique specifications of a project, stay on target with the development timelines, and put our clients' business first. Services include manufacture of a range of products including reagent kit components and IVD kits for clinical trials or product commercialization. Our Manufacturing Services division offers clients unparalleled flexibility, focus, and experience.

While offering services in these seemingly distinct areas, we are able to deliver these services in a seamless manner to the client, in such a way that that the client experiences an integrated services approach, with integration of all the services needed to develop a diagnostic product. We also pride ourselves on operating in a flexible manner that allows us the ability to adapt in order to meet clients' complex and constantly evolving needs during the diagnostic development process. We focus on our clients' business needs - our sole focus is our clients' diagnostic development needs.

Q: ***In closing, what do you see as the future of personalized medicine?***

A: The basic science behind personalized medicine will continue to offer a myriad of choices for pharmaceutical companies to create companion diagnostics in healthcare, further driving the demand for companion diagnostic assays. In addition, there is already more attention being given to the field of personalized medicine due to the changing regulatory environment. The downstream market for custom therapeutics has significant untapped potential. Yet, the traditional bench-to-bedside development of such therapeutics can be arduous and inefficient. Opportunities to advance the practice of healthcare via personalized medicine may be lost in the development process due to the obstacles and challenges we have discussed. Yet, there is a solution. ResearchDx, as the first-ever CDO, can seamlessly provide everything a company needs, from start to finish, to develop a successful diagnostic product and impact the future of how medicine is practiced. ■

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Ask for the Order

By: John A. Bermingham

My career path has navigated through sales and marketing. I'm still in sales and marketing, even though I have additional responsibilities these days and my title is different.

During my "salad days" I became a student of the art and science of selling. I read books and articles, attended seminars, listened closely to what top sales people had to say about selling, and attended the Dale Carnegie and American Management Association Sales Courses. I also took a sales course and a negotiation course at Harvard Business School. I learned many principles of selling. Some of them include the following:

- The most basic tenet of selling is to solve a problem or fulfill a desire.
- Never deal with a buyer's objection at the beginning of a sales presentation, always defer it to the end of the meeting.
- Great sales people understand why they have two ears and one mouth. They understand that they should listen twice as much as they talk.
- Always attempt a trial close or two so that you can determine how well you are doing with the buyer.
- Never give something to a buyer, such as a better price or more advertising support, without getting something in return, such as a larger order or a wider product assortment.
- You must ask for the order.

This last principle is one of the most important principles because it pertains to everyone throughout their career. Here's why. When I was Vice President of Sales and Marketing for Sony's Magnetic Products Group, we grew revenue from $30 million to $1.2 billion in 7 years. We had a superior sales force, and our Group received many awards from Sony Corporation, both in Japan and the United States.

The level above Vice President of Sales and Marketing was Senior Vice President of Sales and Marketing. This was not just a title change, it meant a serious raise in salary and bonus, an increase in perks to include going from a standard company car to a luxury company car, use of the corporate jets, and a higher status at Sony as there were many Vice Presidents but few Senior Vice Presidents.

At the close of each fiscal quarter, Sony America held a quarterly business review for Vice Presidents and above. At this meeting, promotions and key position changes were announced, and I noted there would usually be one person promoted to a Senior Vice President title.

Because our Group's performance was so strong, I kept wondering why my boss never promoted me to a Senior V.P. title. I had a great boss, and we worked extremely well together, so I was very quizzical.

I decided to meet with my boss and ask him why he did not promote me to a Senior V.P. title. He told me that he just never thought about it. So I asked him to put me in for a promotion to Senior Vice President of Sales and Marketing, and so he did. My promotion was announced at the next Sony quarterly business meeting. I had asked for the order!

I found from that point on that if you don't ask, you may not receive. You have to make your desires known because those in a position to give you what you want may not know or be thinking about what you want in your career or business. Ask vendors for lower prices and better credit terms. Ask bankers for a larger line of credit and more liberal advance rates. Ask angel investors, venture capitalists, or private equity firms to invest in or to acquire your company. Ask your boss (if you deserve it) for a raise, a better bonus plan, a company car, a larger office, your own admin, stock options, etc. Ask and you may receive! The worst that can happen is that you are told no or not at this time. But at least you have planted the seed and you can go back later and ask again.

I mean if you are selling to a buyer and he or she says no, do you take the position of never calling on that buyer again? No. You go back in a few weeks and ask for the order again with your understanding as to why the buyer said no the last time that you called on them and how you can solve their problem or fulfill their desire.◆

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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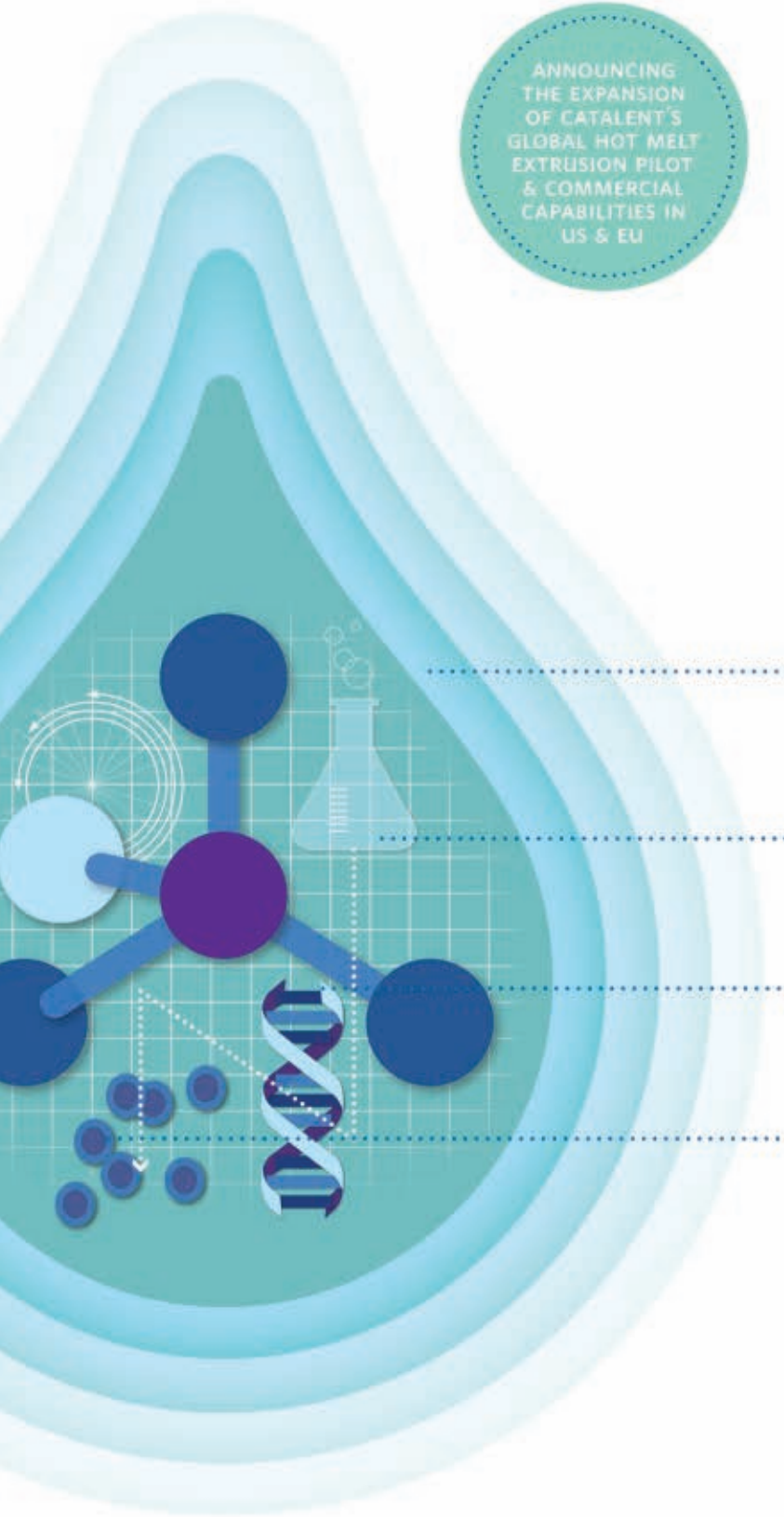

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