Drug Development & Delivery

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Hand-Held Injection Market Drivers

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

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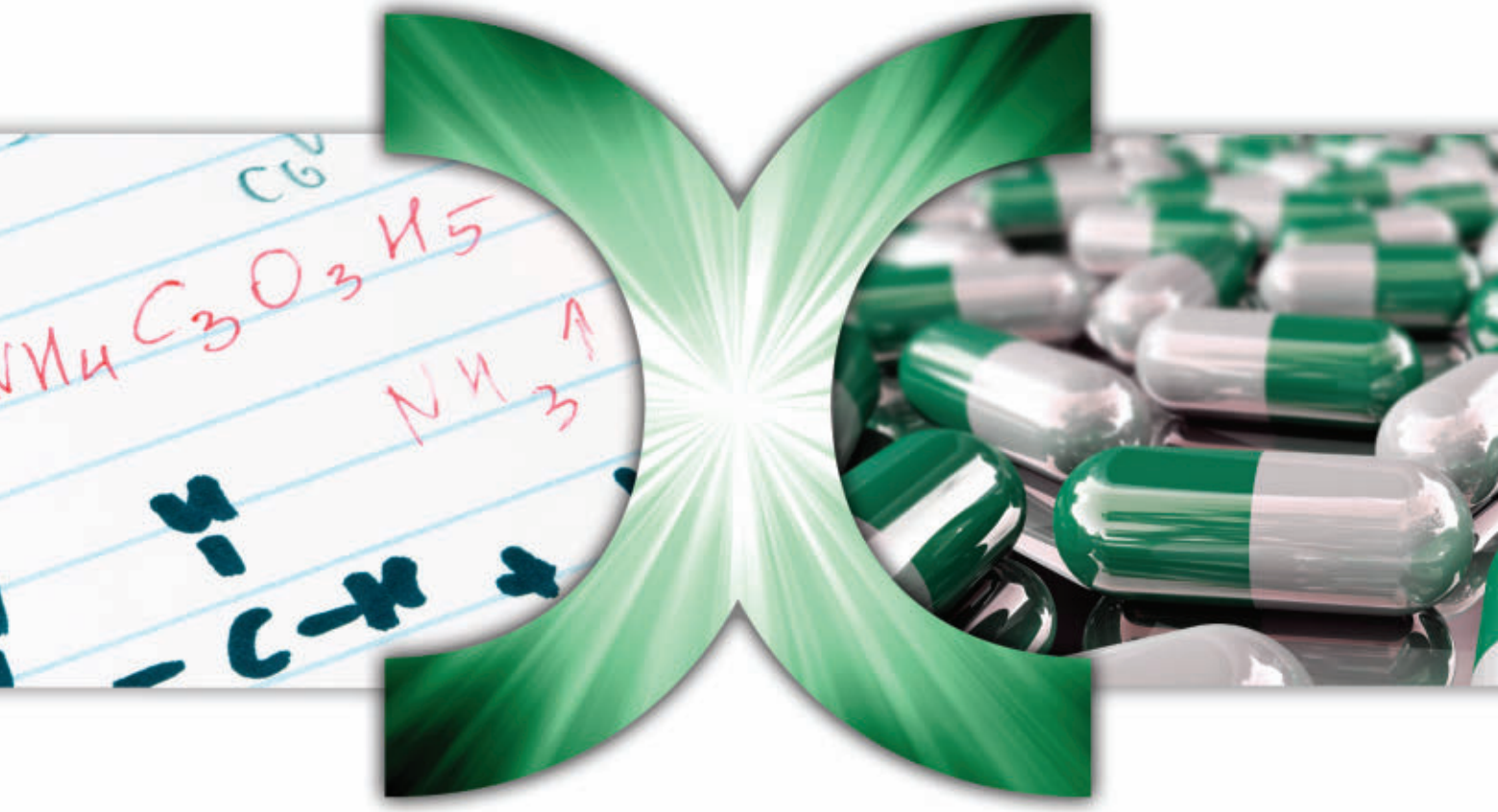

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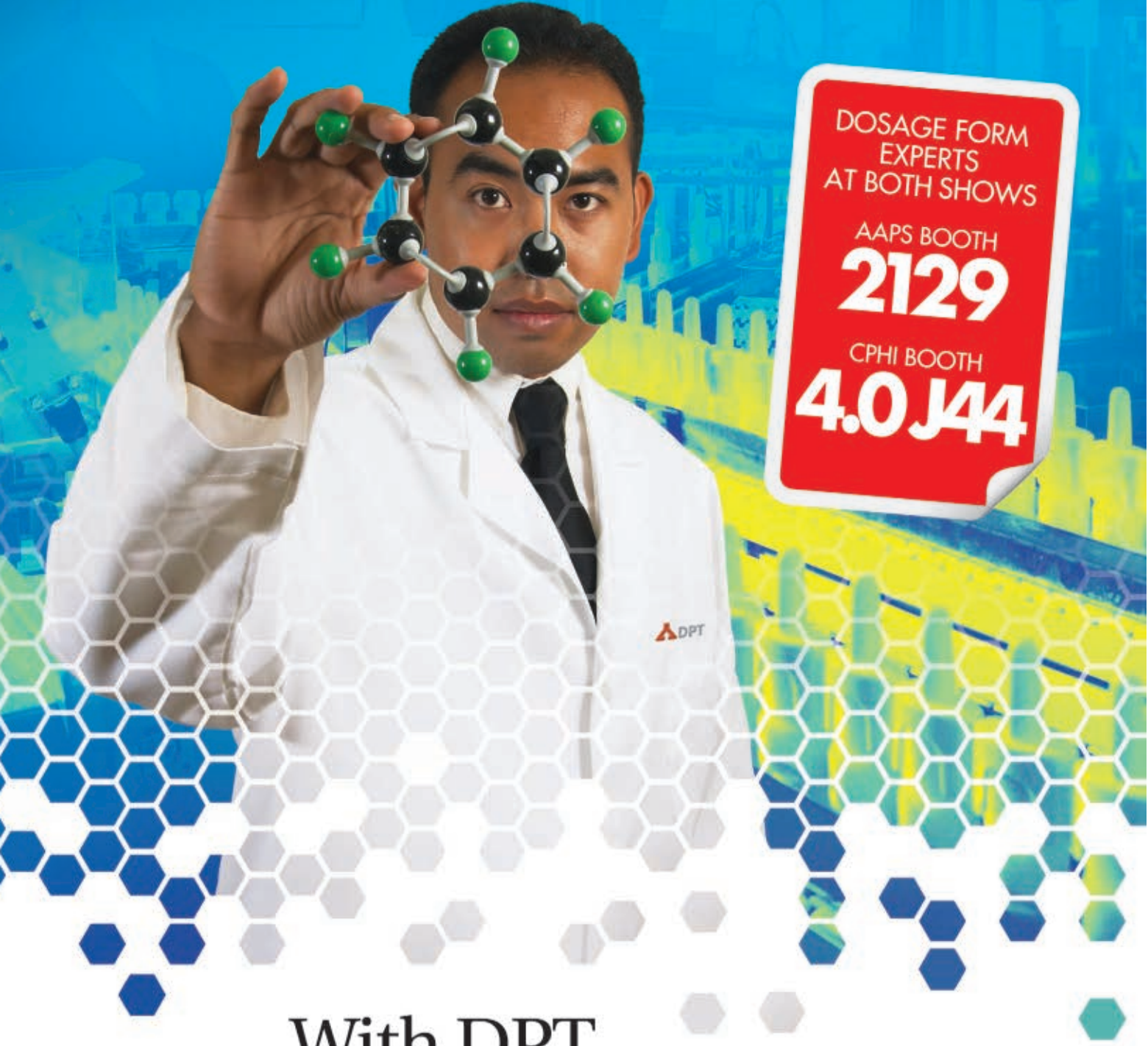

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Biosimilar Development

"The comparability exercise for biosimilars should be very extensive at each step of the development. Phase I PK/PD studies are a key step in which innovative study designs and rigorous methods should be used. They should allow sensitive detection of any difference between the innovator and the biosimilar, if exists, in well-controlled testing environments and standardized clinical conditions."

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Market Drivers

"The market for prefilled syringes has achieved positive growth in recent years. In 2009, an estimated 2 billion prefilled syringe units were sold, and the market for that technology was estimated to be worth up to $2.5 billion, forming one of the fastest-expanding sectors in the pharmaceutical industry. Due to the expanding use of biologic drugs and vaccines, worldwide prefilled syringe technology market revenue is expected to reach $3.9 billion in 2015."

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FDA Tentatively Approves Intellject's Lead Product e-cue

Intellject, Inc. recently announced the US FDA has granted tentative approval for the company's NDA for a novel epinephrine auto-injector, e-cue, for emergency treatment of allergic reactions, including anaphylaxis.

The tentative approval of e-cue following a first cycle, 10-month review by the FDA provides validation of Intellject's vision of developing patient-centric products and of the company's ability to execute.

"e-cue's tentative approval is another important step along our journey to empower patients living with serious medical conditions," said Spencer Williamson, President and CEO of Intellject

Obtaining a tentative approval means that the product review is complete and the submission met the FDA's requirements to be approved. The FDA reserves final approval of the product, however, until all exclusivity or patent challenges have been resolved, specifically the current patent litigation brought against Intellject by King Pharmaceuticals, Inc. (King) and Meridian Medical Technologies, Inc. (Meridian). Final FDA approval is required before a product can be marketed in the United States.

Intellject is confident that the pending patent disputes with King and Meridian will be favorably resolved and looks forward to obtaining final FDA approval and to e-cue's subsequent availability.

Intellject is a specialty pharmaceutical company dedicated to developing drug/device combination products that empower patients to gain freedom from their medical conditions. Each Intellject product combines an established drug with an innovative delivery platform with the goal of achieving superiority, patient preference, and cost effectiveness.

Intellject applies rigorous selection criteria to identify areas where its patient-centric approach and proprietary technology will offer superior solutions. The company only proceeds to an active development program once it has established that incremental clinical and economic benefit is achievable.

Array BioPharma, Genentech Ink $713 Million Oncology Pact

Array BioPharma recently announced an oncology agreement with Genentech, a member of the Roche Group, for the development of each company's small-molecule Checkpoint kinase 1 (ChK-1) program. The programs include Genentech's compound GDC-0425 (RG7602), currently in Phase I, and Array's compound ARRY-575, which is being prepared for an INDA to initiate a Phase I trial in cancer patients.

Under the terms of the agreement, Genentech is responsible for all clinical development and commercialization activities. Array will receive an up-front payment of $28 million and is eligible to receive clinical and commercial milestone payments up to $685 million and up to double-digit royalties on sales of any resulting drugs. Full financial terms have not been disclosed.

"We're delighted to expand our long-standing relationship with Genentech, a leading innovator of important new cancer therapies," said Robert E. Conway, Chief Executive Officer, Array BioPharma. "Combining both companies' programs will maximize our chances for success in developing and commercializing this novel cancer therapy. We believe ChK-1 inhibition is a key strategy for enhancing the efficacy of chemotherapeutic and other agents in cancer patients."

ChK-1 is a protein kinase that regulates the tumor cell's response to DNA damage often caused by treatment with chemotherapy. In response to DNA damage, ChK-1 blocks cell cycle progression in order to allow for repair of damaged DNA, thereby limiting the efficacy of chemotherapeutic agents. Inhibiting ChK-1 in combination with chemotherapy can enhance tumor cell death by preventing these cells from recovering from DNA damage. Both GDC-0425 and ARRY-575 are highly selective, oral ChK-1 inhibitors designed to enhance the efficacy of some chemotherapeutic agents.

Genentech and Array have worked together since 2004 to advance certain oncology programs into clinical development. In 2010, one resulting drug, GDC-0068, an AKT inhibitor, entered Phase I clinical testing. GDC-0068 is currently advancing into a Phase Ib trial. Array researchers continue to advance other preclinical programs under Array's collaboration agreement with Genentech.

Array BioPharma Inc. is a biopharmaceutical company focused on the discovery, development, and commercialization of targeted small-molecule drugs to treat patients afflicted with cancer and inflammatory diseases. Its proprietary drug development pipeline includes clinical candidates designed to regulate therapeutically important target proteins and are aimed at significant unmet medical needs.

Market News and Trends

Evonik Establishes New Health Care Business Line

Evonik Industries AG recently announced it will combine its business in custom manufacturing of APIs (exclusive synthesis), pharmaceutical amino acids (Rexim) and pharmaceutical polymers in the new Health Care Business Line effective September 2011. The newly formed business line will be part of the Health & Nutrition Business Unit, headed by Dr. Reiner Beste.

"The merger strengthens our distribution, research, technical service, and production network. This means our products and services will be equally represented in key pharmaceutical markets in Europe, America, and Asia, and that we can respond more comprehensively to customer requirements," explained Dr. Beste.

Success factors for specialty chemical companies in the pharmaceutical market include global market access, a broad innovation platform, and production in accordance with the cGMP pharmaceutical standard.

"By concentrating our pharmaceutical activities in the Health Care Business Line, we enhance our performance in all three areas," noted Dr. Beste. "This creates the framework for further strategic developments and the targeted advancement of partnerships with key customers."

The Health Care Business Line will be divided into three product lines: Pharma Polymers with the brands EUDRAGIT and RESOMER under the management of Dr. Thomas Riermeier, Exclusive Synthesis under the management of Dr. Klaus Stingl, and Rexim under the management of Dr. Thomas Hermann.

The Pharma Polymers Product Line is a leading developer and manufacturer of functional pharmaceutical excipients for oral and depot formulations and a provider of solutions to the healthcare industry for drug and medical device functionality. The Pharma Polymers portfolio includes acrylic copolymers marketed under the brand name EUDRAGIT, bioresorbable poly(lactic-co-glycolic acid) copolymers marketed under the brand name RESOMER as well as advanced formulation services for oral and parenteral dosage forms.

The Exclusive Synthesis Product Line focuses on the manufacture of custom-tailored, high-quality advanced GMP-intermediates and patented API and high-potency APIs (HPAPI) for the pharmaceutical industry, from clinical stage all the way to commercialization. The global production and research network of the product line offers a seamless service portfolio, ranging from the development of syntheses at the laboratory-scale to commercial-scale production in facilities certified by the US FDA.

The Rexim Product Line is a significant producer of amino acids, peptides, and amino acid derivatives, supplied in pharmaceutical and food-grade qualities. These products are primarily used in the pharmaceutical industry, including in infusion solutions, in cell cultures, and to manufacture APIs for the treatment of high blood pressure and diabetes, but also have applications in the cosmetics and food industry. The strengths of Evonik include its global distribution network and cGMP-compliant manufacturing across the entire supply chain, ranging all the way to cGMP-compliant amino acid purification.

Affymax Receives $10-Million Milestone Payment From Takeda

Affymax, Inc. recently announced it has received a $10-million development milestone payment from Takeda Pharmaceutical Company as part of the companies' exclusive global agreement to develop and commercialize peginesatide (formerly known as Hematide), Affymax's investigational drug for the treatment of anemia in chronic renal failure patients. The payments were triggered by the acceptance and filing of the NDA for peginesatide by the FDA.

If approved, peginesatide will be the first once-monthly erythropoiesis-stimulating agent (ESA) available for the treatment of anemia associated with CKD patients on dialysis in the United States.

Affymax and Takeda Pharmaceutical North America are collaborating on the development of peginesatide and plan to co-commercialize the product if approved in the United States. The product, upon approval, will be commercialized outside the United States by Takeda. The peginesatide Phase III clinical program was the largest to support the registration of an ESA for the treatment of anemia in CKD and the first to prospectively evaluate the cardiovascular safety of an ESA via an analysis of independently adjudicated cardiovascular events.

Anemia is a common complication in CKD because the impaired kidneys are not able to produce enough erythropoietin, the hormone that promotes the production of oxygen-carrying red blood cells. Research has shown that anemia impacts the overall health and well being of CKD and dialysis patients and is associated with increased rates of hospitalization and mortality. In severe or prolonged cases of anemia, the lack of oxygen in the blood can cause serious and sometimes fatal damage to the heart and other organs. ESAs, which stimulate red blood cell production, are commonly prescribed to treat anemia of CKD. According to the Centers for Medicare and Medicaid Services, more than 95% of patients on dialysis in the United States are currently receiving ESA treatment for anemia of CKD.

Affymax, Inc. is a biopharmaceutical company committed to developing novel drugs to improve the treatment of serious and often life-threatening conditions.

Bohai Pharmaceuticals Acquires Yantai Tianzheng Pharma for $35 Million

Bohai Pharmaceuticals Group, Inc. recently announced it has consummated a significant acquisition of a complementary Traditional Chinese Medicine (TCM) company in China, Yantai Tianzheng Pharmaceutical Co., Ltd. Like Bohai, Yantai Tianzheng produces, manufactures, and distributes modernized herbal medicines based on TCM in China.

Based in Yantai City (where Bohai is also located), Yantai Tianzheng achieved audited revenue of $37.9 million and net income of $6.3 million in its fiscal year ended December 31, 2010. For the 3 months ended March 31, 2011, Yantai Tianzheng achieved unaudited revenue of $11.3 million, an increase of 67% over the same period last year, and net income of $1.9 million, a 56% increase over the 3 months ended March 31, 2010. As of March 31, 2011, Yantai Tianzheng had working capital of $2.1 million and net tangible assets of $5.9 million. In terms of relative size, the acquisition represents a significant add-on to Bohai's existing TCM business, which achieved unaudited net sales of $74.5 million and net income of $14 million for the trailing 12 months ended March 31, 2011.

Under the terms of a share purchase agreement, Bohai will acquire 100% of the outstanding shares of Yantai Tianzheng from its three shareholders for $35 million in an all cash transaction consisting of four installment payments over 18 months. Notwithstanding the installment payment structure, Bohai will obtain full ownership of Yantai Tianzheng immediately, with an effective transaction date of July 1, 2011. Mr. Jiangbo Chi, Yantai Tianzheng's majority owner and CEO, will remain with Bohai to oversee the Yantai Tianzheng business. Bohai expects to fund this acquisition from cash on hand, future cash flow, and from third-party debt and/or equity sources. Additional details of the transaction will be available in Bohai's Form 8-K to be filed with the Securities and Exchange Commission.

Yantai Tianzheng markets five primary products: Fangfengtongsheng Granule; Zhengxintai Capsule; Maitong Granule; Bezoar Antipyrotic Tablet; and Sanqi Shang Tablets. Yantai Tianzheng has annual production capacity of 400 million tablets, 300 million capsules, and 250 million bags of granules respectively, which adds to Bohai's current capacity of 1,350 million tablets, 370 million capsules, and 30 million bags of granules and other product categories.

Bohai and Yantai Tianzheng have collaborated in the past. In 2008, Bohai granted Yantai Tianzheng a non-exclusive license to market and sell Yantai Tianzheng's products under the Bohai brand and trademark for five years. No other relationship existed between the two companies prior to the acquisition.

Bohai Pharmaceuticals Group, Inc. is engaged in the production, manufacturing, and distribution of modernized herbal pharmaceuticals based on Traditional Chinese Medicine in China. Bohai's medicines address common health problems, such as rheumatoid arthritis, viral infections, gynecological diseases, cardiovascular issues, and respiratory diseases.

Boehringer Ingelheim Licenses ProBioGen's GlymaxX Technology

Boehringer Ingelheim and ProBioGen AG recently announced they have signed a non-exclusive Licensing Agreement regarding ProBioGen's GlymaxX technology. Boehringer Ingelheim's Contract Manufacturing Business will apply the technology to enhance ADCC (Antibody-Dependent Cell-Mediated Cytotoxicity) activity of antibodies.

The GlymaxX technology for production of afucosylated proteins is universally applicable, simple, and potent. As a unique feature, differentiating it from other approaches, the GlymaxX technology can also be applied to already existing antibody producer cell lines without altering their productivity. The technology can easily be integrated into Boehringer Ingelheim's high expression CHO-based BI-HEX system. Both Parties agreed to jointly market the technology and to offer it to customers royalty free.

"We are very pleased that Boehringer Ingelheim has decided to integrate our GlymaxX technology into their technology portfolio for customer and in-house projects. This is an additional milestone in our long-standing business relationship," said Volker Sandig, Chief Scientific Officer of ProBioGen AG.

"The GlymaxX technology is another demonstration of ProBioGen's core expertise, understanding animal cell biology, and converting this knowledge into pioneering solutions in process development and product design," added Wieland Wolf, ProBioGen's Chief Executive Officer.

"With the combination of the BI-HEX platform and ProBioGen's GlymaxX technology, we can offer our customers tailored solutions for high titer expression of highly potent antibodies," explained Simon Sturge, Corporate Senior Vice President Biopharmaceuticals of Boehringer Ingelheim. "This is another step to continuously invest in our technology leadership and to provide flexible solutions, addressing our customer's needs."

ADCC (Antibody-Dependent Cell-Mediated Cytotoxicity) activity is an important antibody function leading to selectively killing target cells, ie, cancer cells or pathogen-infected cells. Several therapeutic antibody drugs on the market rely on ADCC as a mechanism of action. ADCC enhancement has the potential to increase the therapeutic effect and/or to greatly reduce antibody dosage requirements, resulting in fewer side-effects and treatment costs.

The GlymaxX technology, developed by ProBioGen, prevents the addition of the sugar "fucose" to the N-linked antibody carbohydrate part by antibody producing cells. The absence of fucose enhances ADCC. The GlymaxX technology is based on the introduction of a gene for an enzyme that deflects the cellular pathway of fucose biosynthesis. The GlymaxX technology is universally applicable, simple, and potent, and can be rapidly applied to any existing antibody producer cell line, or can be included into any new cell line development. ProBioGen offers this technology royalty-free to third parties.

ProBioGen is an internationally operating Contract Development and Manufacturing Organization (CDMO) with almost 20 years of experience in mammalian cell culture, process development, and GMP-manufacturing. The Boehringer Ingelheim group is one of the world's 20 leading pharmaceutical companies. Headquartered in Ingelheim, Germany, it operates globally with 145 affiliates in 50 countries and more than 42,000 employees. Today, Boehringer Ingelheim is one of the world's leading companies for contract development and manufacture of biopharmaceuticals.

Xcelience to Expand, Plans to Hire 45 Employees

Xcelience, a Tampa, FL-based contract research organization, recently announced it is expanding its footprint and more than doubling its employment over the next 3 years.

"We have weathered the economic crisis and feel honored by the confidence our long-term clients have shown in us throughout. Now, as our business experiences a strong rebound, we are poised to ensure that we have the capacity and staff to maintain the highest level of quality for our rapidly expanding customer base," said CEO and President Derek Hennecke.

Xcelience will be expanding its 24,000-sq-ft existing facility with the addition of nine rooms (1,000 sq ft), as well as developing a new 24,000 sq-ft facility a short distance away to help accommodate 45 new employees. The new jobs made the company eligible for a Florida Qualified Targeted Industry Tax Refund incentive award of $135,000. To qualify for QTI, the new jobs must pay average salaries meeting or exceeding 115% ($46,833) of the Tampa-St. Petersburg-Clearwater MSA's average annual wages.

Xcelience's headquarters is located in Tampa, where there is a good base of talented workforce to build upon. "Our goal is to remain in this community", says Mr. Hennecke. "We are excited to be a part of the local economic turn-around that we see beginning to occur in the Tampa Bay area."

Xcelience is poised to begin hiring, and is currently seeking Chemist-II and Manager positions for Preformulation/Formulation. Jobseekers may find more information and apply for open positions on the Xcelience website at www.xcelience.com/formulation-development-careers/.

Nycomed & Orion Corporation to Collaborate on Easyhaler

Nycomed recently announced it has entered into a collaboration agreement with Orion Corporation for the co-marketing of Easyhaler combination products for the treatment of asthma and COPD in the major European countries and an exclusive license and distribution arrangement for the Middle East and North Africa region (MENA). Both companies will commercialize Easyhaler combination products under their own brands accompanied by the Easyhaler umbrella brand.

The agreement covers Orion's new Easyhaler combination products for treatment of asthma and COPD. Orion is developing a budesonide-formoterol formulation that combines budesonide as an anti-inflammatory agent and formoterol as a long-acting bronchodilator. In addition, Orion has another Easyhaler research program in progress to develop a fluticasone-salmeterol formulation. In this formulation, fluticasone acts as an anti-inflammatory agent and salmeterol acts as a long-acting bronchodilator. Both these combination products are included in the co-marketing agreement.

Respiratory is a key strategic area for Nycomed, including the COPD treatment Daxas (roflumilast), Alvesco (ciclesonide) for asthma, and Omnaris (ciclesonide) for allergic rhinitis. The collaboration with Nycomed reinforces Orion's presence throughout Europe and is in line with Orion's strategy to strengthen its marketing position in Europe and the sales coverage through partnerships. The co-marketing area - in which both companies present their own product brands under the Easyhaler umbrella brand - covers the major European countries, including Austria, the Benelux countries, France, Germany, Greece, Italy, Poland, Portugal, Spain, and Switzerland. Orion will retain exclusive marketing rights for the Nordic countries, UK, and Eastern Europe, where the company is currently promoting single molecule Easyhaler products. Orion will exclusively manufacture the Easyhaler combination products covered by the agreement.

Orion's portfolio of proprietary products includes Easyhaler, an in-house developed dry-powder inhaler. Orion has developed Easyhaler-adapted dry powder formulations of several well-known generic active substances (salbutamol, beclometasone, budesonide, formoterol) used in the treatment of asthma and COPD. At the moment, under development are new combined formulations of budesonide-formoterol, and fluticasone-salmeterol for the treatment of asthma and COPD.

Orion is an innovative European R&D-based pharmaceutical and diagnostic company with a special emphasis on developing medicinal treatments and diagnostic tests for global markets.

Nycomed is a privately owned global pharmaceutical company with a diversified portfolio focused on branded medicines in gastroenterology, respiratory, and inflammatory diseases, pain, osteoporosis, and tissue management. A range of OTC products completes the portfolio.

Recovery Strategies

Beyond the Headlines: AstraZeneca, Pfizer, Asia & Strategic Alliances

Part 5 of a 6-part series on how not to blow the recovery.

By: Derek Hennecke, President & CEO Xcelience LLC

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Most people see and react to the headlines. Others probe further, searching for deeper understanding before forming opinions. Below are four industry headlines you've probably already seen. A glance beyond the headlines may reveal a different take on the same old story.

FAT MARGINS FOR A NEW BLOOD THINNER?

Astrazeca's new blood thinner Brilinta will cost about 19% more than the current price of Plavix, the leading blood thinner. It's a pricing decision many believe is outrageous given that Plavix will face generic competition in May, effectively reducing the average price of a generic blood thinner to pennies a pill.

Adding to this seemingly inflated pricing strategy is the fact that Brilinta will enter the market handicapped by a black box warning that may give physicians pause. The warning requires doctors use only low-dose aspirin with Brilinta. This could be a problem given that most American doctors prefer high-dose aspirin, and other blood thinners carry no such caveat.

So why the the fat margins for the new blood thinner? Is AstraZeneca really just throwing a price at the wall and hoping it will stick? Are they afraid that because they might sell less, they will have to increase their pricing to make up the difference?

Beyond the Headline

Companies don't make pricing decisions that way. It's Business 101: raising prices in the face of lack of demand gives you even fewer customers. You can bet AstraZeneca has a different angle.

Ideally, AstraZeneca would like to tackle the blood thinner market head on without the black box warning, but you go to war with the armor you have on. Instead, AstraZeneca is going after a lower volume, higher-priced niche market.

They're banking on the possibility that Plavix may be contraindicated for some patients. Several studies have shown that the use of Proton Pump Inhibitors (PPIs) for acid reflux, such as Prilosec and Nexium, actually reduce the effectiveness of clopidogrel, the active ingredient in Plavix, and increase the chance of cardiovascular events.

The data has yet to be proven clinically significant, but the FDA released an early communication about the ongoing safety review of clopidogrel in January 2009. AstraZeneca is looking seriously at potential overlap of these and other drugs to determine the actual market for Brilinta, and price it accordingly.

INSIDE PFIZER: THE DECLINE & FALL OF JEFF KINDLER

Pfizer's ex-CEO Jeff Kindler made blistering headlines as the Captain who steered the Wall Street icon into the iceberg. His departure capped a decade of declines that saw Pfizer's share price collapse from $49 to $17, and the company's drug pipeline went down with the ship.

Beyond the Headline

August's Fortune magazine features a provocative and gossipy story called What Happened at Pfizer, which goes inside the corporate boardrooms under his leadership. Not all is bad; positive lessons abound in this story, including how to build a good team, delegate, work hard without micromanaging, and his experience that trial prosecutors can be good compliance officers but are not necessarily CEO material.

The article also delves deeply into the less-fortunate legacy of what a leader should not do, accusing him of an indecisive approach that created an atmosphere of confusion and chaos:

After more than a year of on-and-off debate, Kindler just couldn't make up his mind. "Jeff was really afraid of making a mistake," says one person who worked on the deal (buying Wyeth). "Everything had to be analyzed and re-analyzed. You'd close a meeting and he'd say, 'Okay, here's what we're going to do.' You'd sharpen your swords. And the next morning, it'd be off."

In another example, he split the research operation in two - setting up a separate unit for biologic drugs and launching a new facility in San Francisco - only to reverse the decision 30 months later after taking on Wyeth's big biotech operation.

What I learned from Pfizer: plan, load your gun, and don't forget to fire. Once your shot is discharged, you're done. Above all, don't say anything you wouldn't want to see on the cover of Fortune magazine. Even a boardroom with the door closed and only one person in it is not a private place.

GO EAST YOUNG MAN /WOMAN

The drive to outsource development and production to Asia has been a headline for the past decade.

Beyond the Headline

According to Mangesh Sai at PharmExecBlog, a routine inspection carried out by the FDA in the state of Maharashtra, India, noted an increase in the number of sub-standard drug samples. Officials found 26 samples that were not what they purported to be. This followed a finding of 16 sub-standard quality samples in May and 20 in April. According to the report, some ampicillin and amoxycillin formulations contained no active ingredients whatsoever. Others contained between 6% and 30%. Thiamine tablets with vitamin B1 and diclofenac sodium, paracetamol, and magnesium trisilicate tablets were also found to be below standard.

BIG PHARMA BUOYS BELEAGUERED CROS

Eli Lilly set off a wave of 3- to 5-year strategic partnerships when it linked with Covance in 2008 in the depths of the recession. Such deals were touted as salvation for CROs providing a much-needed revenue stream in the face of economic adversity.

Beyond the Headline

2011 marks the beginning of a first wave of strategic partnership contract renewals. The result is that some CROs who have spent much of the past 3 years revamping their business around the demands of a major partner and are just starting to see the first projects come down the pipeline, must now realize that these contracts will be re-negotiated.

"We expect pharma to turn the pricing screws another revolution, either explicitly or implicitly via higher resource utilization targets or additional investments," David Windley, Equity Analyst at Jefferies & Company told Nick Taylor of Outsourcing-Pharm.com. Given that this renewal period overlaps with the patent cliff, Windley says CROs can expect pharma to "extract a fresh pound of flesh" from CROs in the renewal process.

Windley argues that a standard 3-year strategic deal is "borderline unreasonable." He argues that getting the deals up and running is in some cases challenging and costly and raises the question of their ultimate value. He recommends CROs push for longer contracts to be sure they receive some payback from their up-front commitment.

For most companies, Windley predicts the renewals will come, albeit at a cost, if only because there are enough joint projects in the works that it would be costly to start over.

In cases of outright incompetence or unsatisfactory performance, the alliances will end, and that in turn will present opportunities for other CROs. Should the CROs be lining up? Not necessarily. Windley argues that for those who believe the good old days are on their way back, CROs should take them. Too many CROs have reported that the trials of these deals outweigh the triumphs.

PAREXEL might be one such CRO. PAREXEL shares suffered after Icon reduced it's 2011 financial guidance citing weighty up-front investments to support a deal with Pfizer. Pfizer has a deal with PAREXEL as well, and some analysts claim to be growing increasingly uncomfortable with the level of risk involved.

It's easy to jump to a conclusion with only a cursory look at the headlines. The information we need to make informed decisions is rarely found in the initial reporting of events. The Roman Emperor Marcus Aurelius advised his subjects: "To read with diligence; not to rest satisfied with a light and superficial knowledge, nor quickly to assent to things commonly spoken of." Then again, if you've read this far, you already knew that! ◆

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.

EXCIPIENT UPDATE

The New Era of Functional Excipients: An Innovative Approach in Dosage Form Design

By: João T.A. Correia, António J.A. Bica

ABSTRACT

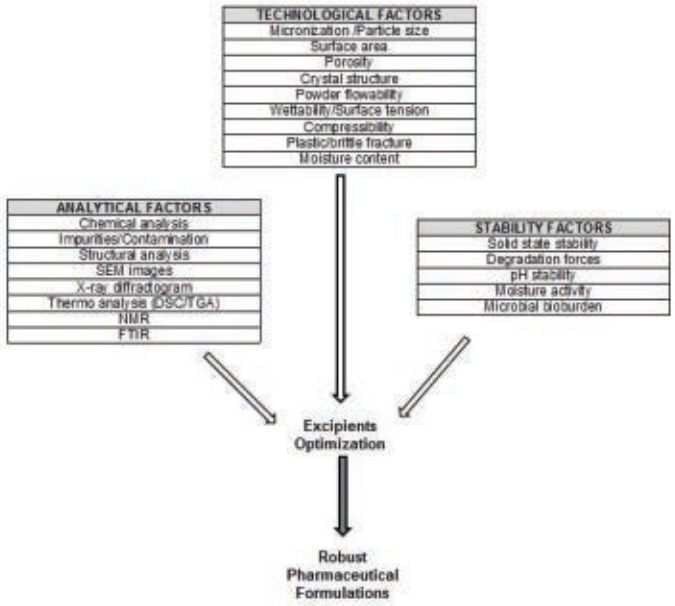
The concept of Quality by Design in the pharmaceutical development and manufacture of drugs has contributed to more robust formulations, with less time and cost of development and in which a single ingredient can be a solution for many challenges. However, these more efficient and less variable scale-up processes must still adhere to the regulatory requirements for drug formulation marketing approvals. Nevertheless, the potential of functional excipients is continuing to revolutionize the pharmaceutical industry.

INTEREST IN FUNCTIONAL EXCIPIENTS

In the industrial production of drugs, active substances rarely have the physical requirements needed for processing. An example is the compression of drugs in solid forms, in which the addition of adjuvants in formulations becomes a requirement. In tablets, the API and excipients alone almost never have the physical and mechanical properties suitable for a compression technology. The excipients can also be found in variable amounts for active substances, contributing to the functionality of formulations.[1] Success of pharmaceutical development is conditioned by a wide variety of factors. From even a traditional concept of "passive" and "inert" excipients, we have steadily progressed toward more complex (highly functional and highly specific) substances.

With current novel interest in producing tablets, direct compression is regarded as an easy, economical, and flexible technological process. High technological value excipients will enhance the flow characteristics of solid mixtures and their compaction, leading to the establishment of cohesion/adhesion forces between materials. Eliminating granulation, sometimes critical, the production is simplified, and disintegration of tablets is improved. Unlike with classic ingredients, even at small quantities, the high-functional performance is transmitted to the entire formulation, facilitating production of large batches. The easy mixing, dilution with other components, and the resulting density and compaction of powders reflects on the flow of mixture during compression, which is essential for mass uniformity of tablets, even at high-compression speeds. These new ingredients are synergistic optimized combinations of fillers, binders, lubricants, disintegrants, and glidants that reduce segregation by enhancing flowability. In finished products, hygroscopicity may be changed, improving stability over time or minimizing degradation reactions. When designing these particles, it is imperative to know their surface area; irregular shape;

FIGURE 1



Assessment for pharmaceutical formulation development based on excipients properties.

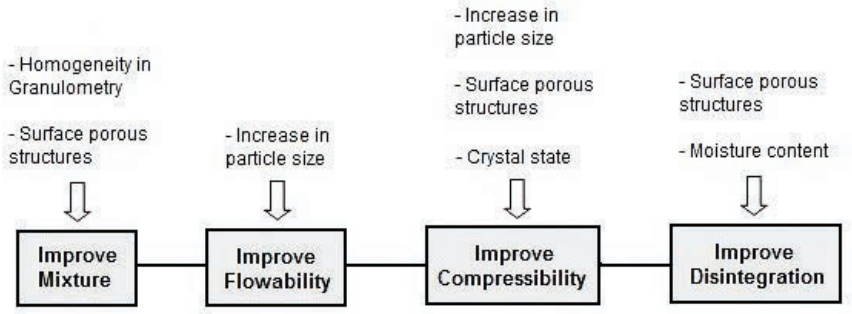
roughness; and intrinsic porosity, polarity, wettability, and surface energy.[2] There are three ways to functionalize pharmaceutical excipients: (1) through physical changes, (2) through chemical modifications, or (3) through co-processing with drugs or excipients.[3]

In the case of physical changes, making materials less crystalline or even amorphous allows the formulation to present better dissolution and bioavailability, based on thermodynamic factors and molecular interactions, giving them the functional advantages compared to traditional excipients.[2] This material engineering introduces different degrees of functionality due to polymorphism and isomerism. For example, the amorphous forms of lactose have better compaction behavour. In general, the functionality of excipients is directly related to changes in theirr particles.[3]

Chemical modifications in cellulose derivatives improves solubility, viscosity, and different coating properties (due to substitution reactions, polymerization, acid hydrolysis, or alkaline oxidative degradation of vegetable fibres), resulting in various types of microcrystalline cellulose with different residual moisture and apparent densities, good flow characteristics, and standardized particle size distribution.

Co-processing allows for the combination of two or more materials by processes (such as fluid bed drying), resulting in highly functional and more stable materials.[2] Variables, such as the processing temperature, presence of inhibitors or catalysts, pressures, mixture systems, or activation by solvents atomized, allows for the control of diameter, size, and shape of resulting particles. Products with more favorable properties are obtained compared with a simple mixture of individual components.[3] A significant advantage of co-processing is that it induces mostly physical changes rather than altering the chemical structure or the stability of excipients. However, bonds breaking, reorientation, a stereochemical environment, and the intermolecular forces established are responsible for the new shapes that determine the formation of a new material.[4] Several interactions result from the combination of particles: hydrogen bonding, van der Waals forces, polar and ionic interactions, covalent links, or even chemisorption complexes by absorbing carriers. The greater the number of ingredients involved, the more complex these interactions will be, which must be controlled and monitored. In addition, the moisture in these excipients is of particular importance as it influences the balance of water adsorption and disintegration in solid dosage forms.[4] Co-processing can occur among or between excipients and active substances, improving the dissolution profiles of the latter. The optimum ratio for the components results from experimental studies and compatibilities, targeting the development to products with less variability between batches.[3] Co-processing usually occurs by combining ingredients that create plastic deformation with those with brittle behavior, a symbiosis required for the best compression performance.[1]

FIGURE 2

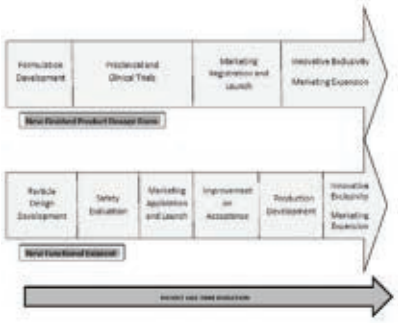


Influence of changes in the excipient particles on the resulting functionality in a technological process.

MANAGING REGULATORY WITH MONOGRAPHS

The official pharmacopoeias define quality tests for analytical characterization of individual excipients, but regarding determination of their functionality, methods are mostly omitted. In such combinations, the biggest challenge however is the gap of a

FIGURE 3



Comparative development timelines for a finished pharmaceutical product and a new functional excipient.

unique official monograph analysis. To approve the use of these functional adjuvants, there is no uniform global strategy. The harmonization has significant importance to the general acceptance of these new ingredients.[5] Compared to their classical relatives, the analytical techniques focus on the characterization of particle size distribution, SEM images, the specific surface area, and X-ray diffractograms obtained for these materials.[6] In addition, HPLC, DSC, NMR, and FTIR techniques are used to aid and control their structural properties.[2] For new excipients to be accepted by regulatory authorities, demonstration studies are required for chronic and acute toxicity, pharmacokinetics, toxicology, and reproductive effects as they are considered new entities. The co-processed excipients may be GRAS granted if the excipients from which they are obtained are also certified by regulatory authorities, with well-documented toxicological studies.[1]

According to the European Medicines Agency, in pharmaceutical development, the use of an excipient should be well reasoned, its role explained, and the amount justified for inclusion.[7] Compatibility and safety studies must be observed, especially if using a new route of administration or a higher amount than previously described. Despite some regulatory issues that still exist, widespread use could be accepted based on an Excipient Master File (EMF) document that relates the properties of the product, supported by its physico-chemical characterization and safe use basis.

In Europe, this process has been very restrictive compared to other countries. The safety profile must be obtained medicine by medicine, not based on all the results accepted for a given innovative excipient for another pharmaceutical product. Due to high development costs, many pharmaceutical companies will eventually continue to prefer the traditional ingredients listed on the international database of non-active ingredients. The US is more flexible for companies requesting approval to launch a product on the market, working within the ICH safety guideline requirements of a technical committee of qualified persons (IPEC, International Pharmaceutical Excipients Council).[8] This Council is a tripartite organization with representatives from the US, Europe, and Japan, all working toward the harmonization of regulatory requirements for these materials.[1] Following a favorable pronunciation, the FDA may already accept some of these ingredients as approvable, encouraging the benefits of new drugs and innovative therapeutic methods.[8] Such approval is not based upon individual evaluations of the excipient, but on drug products in which it has already been used, along with other safety information and data on the EMF.

In parallel with the companies developing these new products, a committee of experts in toxicology pronounces on the knowledge of the new excipient, considering the route of administration, and prepares an impartial report on the substance based on all related existing knowledge. It prepares CTD format documentation on safety of the excipient (and later data within the FDA) to shorten and simplify regulatory approval. Also, due to the nature of changes made on the classic excipient, and based on its use in the food or cosmetics industry or even in other countries, it may be excessive and unnecessary to perform some of the extensive range of tests required by the FDA safety standards.[8] The co-processed excipients presented with minor molecular changes undoubtedly results in the best regulatory acceptance within the medicines authorities.

Some major world-known companies have been dedicated to innovation in these functional excipients obtained in accordance with the latest technologies, quality standards, and cGMP requirements. Combinations of ingredients mixed with certain drugs of common use have also emerged on the market in the form of premixes, allowing in many cases a simple technological step to obtain the final product. Aware that these products require a long period of time from conception to commercialization, a continuous investment in developing these materials is required, along with new challenges for drug delivery. Development of these excipients is a relatively new area, particularly in oral dispersible tablets, in formulations for controlled release, and in inhalers devices. It is estimated that in future, nanotechnology and biotechnology can bring significant changes to this field.

SELECTING AVAILABLE MARKETING OPTIONS

The most common combination of co-processed excipients consists of mixtures of microcrystalline cellulose; lactose monohydrate; corn starch; crospovidone; colloidal anhydrous silica; and lubricants such as magnesium stearate, stearic acid, or sodium stearyl fumarate. Economically, these premixes may have a higher cost compared to traditional excipients but offset with lower production times.[1]

The combination of corn starch with

lactose allows for matching the smooth flow and deformation of spray-dried lactose with the elastic deformation and rapid disintegration of starch.[6] Combinations of cellulose and lactose with similar purposes are available. Enhanced features have also been made with materials such as sorbitol and mannitol, converting them into materials with better rheological characteristics better suited for direct compression.

During processing, testing of compressive strength, hardness, disintegration time, and dissolution profiles are most often used to make comparisons with the procedures using the traditional ingredients.

One of the newest and most popular applications of these excipients has been in orodispersible products in which the previously mentioned features are added to the high-solubilization capacity of the oral mucosa; the pleasant taste and texture resulting from the disintegration. Published studies compare the properties of several commercial alternatives for rapidly dissolving oral formulations.[1,9] The alternatives marketed differ in the time of disintegration with slight differences distinguishing between mixtures of co-processed excipients, mannitol, and modified derivatives of the modified sugars, which are all competing for the same effect on immediate release, but with different specificities also depending on the target public to whom they are intended.

In the future, new approaches and concepts of functionality will be discovered. Property rights and patents of several of these associations can bring economic benefits to companies who bet on their development and use. The particular characteristics of functional excipients, along with their physical and chemical properties, are significant factors when choosing between conventional excipients and co-processed ones. Some populations, such as those who are diabetic, hypertensive, or intolerant to lactose or sorbitol, will also benefit from the development of co-processed excipients. The ability to develop safe and highly effective drugs using simple production processes results in reduced costs of finished drug forms that are easier and more efficient to administer.[10] ◆

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BIOGRAPHIES

João Correia earned his MSc in Pharmaceutical Technology and Biogalenics from the Faculty of Pharmacy, University of Coimbra, Portugal. His current job is focused on pharmaceutical development and production technology at LEF, a Portuguese CRO. He plans and acts on several projects for galenic development process, production, optimization of formulations, and delivery strategies of drugs for pharmaceutical industry costumers. He has past experience on regulatory affairs and quality control of drugs.

António Bica is the Technical Director of LEF, Infosaúde and also a Board Member. He is a Pharmacist, graduating from the Faculty of Pharmacy, University of Lisbon, and earned his Masters in Management from Instituto Superior de Economia e Gestão, Lisbon, Portugal. He has several years of experience in pharmaceutical projects, leadership, and managing activities on analytical methods, biopharmaceutics, regulatory affairs, and pharmaceutical development.

PERFORMANCE TRENDS

Performance 2010, Trends of the Future

By: Josef Bossart, PhD

How did the US market treat drug delivery products in 2010? Did the introduction of newer DDEP (drug delivery enabled/enhanced pharmaceutical products) offset the overall loss of branded pharmaceutical sales and prescriptions to generics? In this discussion, we will look at the some key trends that defined 2010 and try to understand how these figures may impact business going forward.

Let's start with the qualifications and key references. Unless otherwise noted, sales and prescription data were sourced from the SDI Vector One® Top 200 reports published online by Drug Topics (www.drugtopics.com). These reports are updated annually and are available at no charge. The data in these reports refer to prescription pharmaceutical products sold in the US retail market and exclude hospital, direct, and institutional sales. Product sales figures are based on the average wholesale (AWP) or average selling (ASP) prices. As we'll see further on, these figures can differ substantially from actual net product sales.

The products listed in the Top 200 retail brand sales report represent the top products sold in the US on the basis of sales. These products account for about 84% of all sales of brand pharmaceutical products at the retail level and do not include the sales of retail generic prescription products. The Top 200 prescription report provides the same information, but with products ranked by prescriptions. The top 200 brand products by prescription account for about 82% of all branded product prescriptions in the US.

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BRANDED DDEP SALES & PRESCRIPTIONS – 2010

Table 1 summarizes the overall sales and prescription figures for 2009 and 2010. These figures cover products that were included in the SDI Vector One® Top 200 product lists for each of those years. Not all products in the SDI's Vector One® Top 200 lists were drug delivery products, nor were the same products included in both lists. For example, a relatively low-volume (prescription) product with a high price could have made the Top 200 Sales list but not the Top 200 Prescription list. And a high-volume, low-priced product would have had the reverse situation.

The products included in Table 1 do not include products that solely depend on simple formulation or delivery devices; formulation- and device-enhanced pharmaceutical products (FDEP). The FDEP incorporate formulation tools like enteric coating, and devices such as auto injectors. The difference may seem subtle upon first consideration but FDEP represent a major departure from DDEP. The FDEP are analyzed separately in Table 2.

A quick look at Table 1 reveals that while sales for DDEPs were basically flat from 2009 to 2010 (about $32 billion), there was a precipitous drop in prescriptions in this period. The drop in prescriptions could not be offset by the larger number of DDEP, that managed to break into the Top 200 list. This implies the average price per DDEP prescription increased in 2010, due to a combination of price increases and a greater number of higher value DDEPs. From these figures, it can be extrapolated that total dollar sales of DDEPs in 2010 at the US retail level was about $39 billion. This total for DDEPs represents about 21% of all branded pharmaceutical prescription sales at the retail level in 2010.

In the case of FDEPs, both sales and prescriptions dropped substantially in 2010. This was largely due to a continuing drop in prescriptions filled for the very popular enteric-formulated proton pump inhibitors resulting from the introduction of generics of Prevacid and the switch of patients from branded products to Prevacid generics.

TABLE 1

	2009	2010	Change Y/Y
Total DDEP Sales	$32,116,000,000	$32,329,000,000	+1%
# of Products	60	56	-7%
Total DDEP Prescriptions	226,748,000	203,152,000	-10%
# of Products	58	60	+3%

*extracted from SDI's Vector One®: National 2009 and 2010 Top 200 branded drugs by retail dollars

Sales & Prescriptions, Retail DDEPS 2009 & 2010*

be about 20% less than these figures. In some cases, there can be an even larger discount. At an early 2011 Reuters Health Summit, the CEO of AstraZeneca stated, "The price in the Red Book is probably between $4 and $5 per capsule. I can tell you we get less than $2." This is an extreme case but provides an important reminder that when preparing forecasts and market opportunity assessments, one fully understands the source and basis of the figures used. In the case of the SDI/Vector One figures, the prescription figures are estimated from their proprietary audits and validated extrapolation. The sales figures though are generally calculated by multiplying these prescription figures by the average wholesale price (AWP), or more recently, the average selling price

TABLE 2

	2009	2010	Change Y/Y
Total FDEP Sales	$9,754,000,000	$8,819,000,000	-10%
# of Products	12	15	+25%
Total FDEP Prescriptions	56,570,000	46,775,000	-17%
# of Products	12	13	+8%

*extracted from SDI's Vector One®: National 2009 and 2010 Top 200 branded drugs by retail dollars

Sales & Prescriptions, Retail FDEPS 2009 & 2010*

(ASP). Differences in price can be large and arise from rebates associated with Medicaid, co-pay offsets, indigent patient programs, and negotiated pharmacy benefit discounts. In general, prescription figures are the most reliable resource for building forecasts and estimating market trends.

LEADING BRANDED DDEP – 2010

The leading retail DDEPs for 2010 in terms of sales are presented in Table 3. Summed together, these 10 DDEPs account for about half of all Top 200 retail product sales and a bit more than a third of the prescriptions. CNS products dominate the list, accounting for about 55% of sales and prescriptions. The two inhalation targeted DDEPs, Advair Diskus and Spiriva, captured some 31% of sales of sales and prescriptions.

The implied price per prescription figures are worth a quick reflection. These prices for the most part reflect average wholesale price. In many but not all cases, the actual prices received by the company will

TABLE 3

Product	2010 Sales	Sales Chg. 2010/2009	2010 Prescriptions	Rx Chg. 2010/2009	Implied $/Rx
Advair Diskus	$3,655,206,486	0.0%	16,580,931	-4.7%	$220.45
OxyContin	$3,554,751,453	17.7%	6,869,557	7.5%	$517.46
Spiriva	$1,593,593,745	19.1%	7,738,168	5.3%	$205.94
Effexor XR	$1,431,042,602	-40.0%	7,603,949	-44.6%	$188.20
Concerta	$1,407,962,235	19.2%	7,949,409	2.7%	$177.12
Suboxone	$1,164,872,171	30.3%	6,476,241	24.2%	$179.87
Ambien CR	$951,108,005	-3.3%	5,687,633	-16.7%	$167.22
Lidoderm	$934,418,905	-0.3%	3,402,179	-2.6%	$274.65
Vyvanse	$931,421,098	41.1%	6,604,632	31.3%	$141.03
Nasonex	$886,446,374	-0.8%	8,834,010	-7.9%	$100.34
Total	$16,510,823,074		77,746,709		$212.37

*extracted from SDI's Vector One®: National 2009 and 2010 Top 200 branded drugs by retail dollars

Leading DDEP Retail Sales & Prescriptions, 2010

ANALYSIS

With sales up slightly and prescriptions down, 2010 was at best a so-so year for companies selling branded DDEPs at the retail prescription level. So then, where are we headed from here?

Relative to all branded retail pharmaceuticals (sales down 2.4%, prescriptions down 12.1%), DDEP performance looks good. This is due in large part to device-dependant DDEPs, notably inhalation products, for which there is no simple regulatory pathway to approval of directly substitutable generics. This largely "protects" the prescription and sales base for these products from generics. This may well change as Advair Diskus loses regulatory and patent exclusivity throughout the next couple of years and companies attempt to introduce lower priced non-interchangeable generics. Widespread cannibalization will depend on regulatory changes that provide for a simple path to substitutable inhalation products.

A few DDEPs showed good prescription and sales growth in 2010 that will positively impact the group as a whole for the next few years and at least partially offset continued generic erosion. Most notable are OxyContin, which may have established extended exclusivity with the introduction of a tamper-resistant formulation of controlled-release oxycodone. The growth of Spiriva will depend on addressing concerns about cardiovascular events. The leading ADHD products, Concerta and Vyvanse, will need to get around the challenges of impending generic competition if they hope to continue their considerable growth.

Beyond the top 10 DDEPs, there is growth to be found in several inhalation products, notably Ventolin HFA, Flovent HFA, and Symbicort, all of which had strong prescription growth in 2010. Two oral controlled-release products, Pristiq and Seroquel XR, enjoyed exceptional growth in 2010. Their continued growth will depend on beating back expected generic challenges.

REFLECTIONS

To answer the opening questions: the market for branded DDEPs in 2010 was not great, but it could have been worse. Not only did DDEPs contribute to the overall sales of branded retail prescription pharmaceuticals, they provided a boost to both the sales and prescription performance of the sector. Companies that had not invested in drug delivery products in general missed an important business opportunity.

Going forward, the true value of DDEPs will not be realized because of the unreasonably limited amount of market exclusivity these products receive. It's "three and out" for too many products; that is, 3 years of market exclusivity and a fully substitutable generic is approved. This not only hurts the commercial returns of a DDEP; current legislation acts as a disincentive for companies to develop new and therapeutically valuable products based on drug delivery technologies. But nothing will happen until companies active in the Drug Delivery sector work together to secure legislative support for a more reasonable duration of regulatory exclusivity for DDEPs. "In business as in life, you don't get what you deserve, you get what you negotiate."[1] ◆

Next month we will discuss the other side of the coin, the performance of generic DDEPs in 2010.

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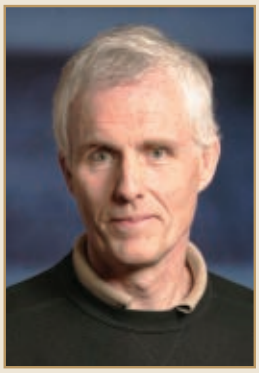


Dr. Josef Bossart is Managing Director of The Pharmanumbers Group, a boutique research and consulting group providing the biopharmaceutical industry with analysis and insights that improves business outcomes. In addition to issuing industry reports, such as DDEP2011 - Drug Delivery Product Success Rates,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

PATIENT COMPLIANCE STUDY

New Data Shows Drug Delivery Has Positive Impact on Patient Compliance

By: Steven Hamlen, MBA, Karen MacGregor, PhD

INTORDUCTION

Patient non-compliance in America is a major medical problem with an estimated cost in excess of $290 billion a year, according to a report from the New England Healthcare Institute.[1] While researchers have identified improved patient education about disease management and medications, pharmacist and physician assistance, and simplified drug regimens as means for improving compliance, many in the pharmaceutical community are recognizing that drug delivery may also be an influential factor.

A recent study of longitudinal patient records at Catalent Pharma Solutions supports the theory that drug delivery can improve patient medication compliance. The 1-year study compared the compliance rates of two oral delivery methods for delivery of selegiline: standard pill and an orally disintegrating tablet (ODT) formulation that achieved pre-gastric absorption. Results showed a 98.5% compliance rate with the ODT formulation compared to 81% with the standard oral treatment in US Medicare patients.[2]

Medication compliance (adherence) refers to the degree or extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency. It may be defined as the extent to which a patient acts in accordance with the prescribed interval, and amount of a dosing regimen.[3]

A lack of compliance (adherence) can lead to false diagnoses or a change in dosing, which can prove harmful or even result in hospitalization. Medication non-compliance (adherence) can cost about $8.5 billion in emergency room visits due to various complications.[4]

THE ROLE OF DRUG DELIVERY IN NONCOMPLIANCE

Multiple factors impact a patients' compliance to their prescription medications. Treatment-related factors include route of administration, pattern of dosing, length of treatment, side effects, and cost of treatment to patient. Patient-related factors also contribute to non-compliance, such as age, cognitive impairment, and gender. Children are also dependent on adult supervision to follow their medication treatment plan.

According to Harris Interactive, a market research and consulting firm, more than 40% of adults in the US general population reported problems with swallowing pills.[5] As a result, 14% delayed

TABLE 1

Selegiline vs. Zelapar Fast-Dissolve Tablets

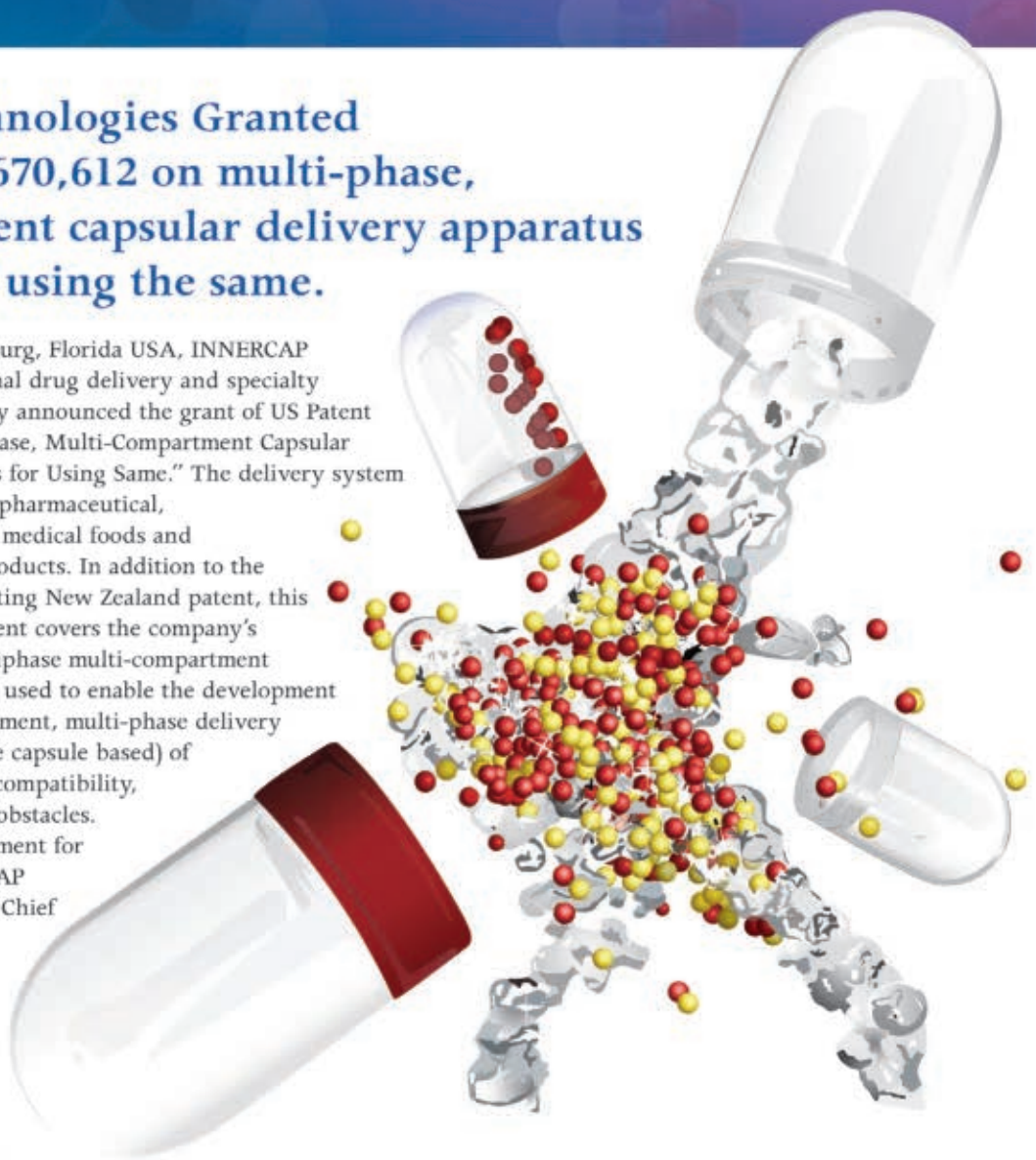
	Tablet/Capsule Selegiline (Traditional Formulation)	Zelapar Formulated With Zydis Fast-Dissolve (Innovative Formulation)
Lower Dose & Less-Frequent Dosing	5-mg doses, take twice a day (BID). Pill or capsule that must be swallowed.	1.25-mg or 2.5-mg doses, taken once a day (QD). Tablet that dissolves in mouth within seconds without water.
Increased Bioavailability/Faster Onset of Action	Tmax = 1 hour. Digested in the gut, absorbed through small intestine, processed by liver.	Tmax = 15 minutes. Innovative transmucosal drug delivery absorbed through the lining of the mouth directly into the blood.
Lower Side-Effect Potential	Processed through liver, producing undesirable metabolites.	Significantly bypasses the liver, producing lower undesired metabolites.

Product profile comparison of Zydis® ODT formulation and conventional selegiline tablets.

THE ADVANTAGES

OF MULTI-PHASE, MULTI-COMPARTMENT CAPSULES ARE CLEAR

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



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

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

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

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

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

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

INNERCAP™ TECHNOLOGIES, INC

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

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taking their medication, 8% missed or skipped their dose, and 4% discontinued their medicine.

While there has been an underlying perception that drug delivery does not play a role in noncompliance as critical as the safety and efficacy of the drug itself in development, in fact, drug delivery has a significant impact as seen in new data from Catalent Pharma Solutions' study of its Zydis ODT formulation.

The market for ODTs could exceed revenues of $13 billion by 2015, based on upward global growth trends, according to Technology Catalysts International, a technology-transfer and business-consulting firm based in Virginia. The report explains that ODTs have continued to expand as dysphagia (ie, difficulty swallowing), patient compliance, and consumer convenience issues gain prominence.[6]

According to the Harris Interactive study of 679 adults age 18 and over (513/age 18 to 64 and 166/age 65 and older), nearly 1 in 5 who have taken oral medications have hesitated because they thought they might have trouble swallowing them. Most people who have hesitated attribute their hesitation to the size of the pill (84%), followed by its shape (29%). To facilitate swallowing, more than half (55%) of those who have had difficulty swallowing pills drink plenty of liquids. Other coping strategies include trying more than once to swallow the pill (30%), splitting the pill in two (17%), and taking a deep breath before taking the pill to minimize a gag reflex (13%). About twice as many women (51%) as men (27%) experienced pill-swallowing problems.[5]

After swallowing, a standard pill disintegrates in the stomach, and the drug is absorbed through the small intestine, processed through the liver, and can produce undesired metabolites. ODTs are placed on the tongue and disintegrate quickly in saliva, resulting in a fine dispersion that is easily swallowed without water, or in some cases, the drug dissolves and is absorbed through the oral mucous membranes, entering the bloodstream faster than traditional pills and bypassing the liver, potentially reducing undesired metabolites. Controlled-release formulations can reduce dose frequency, pill burden placed on the patient, and increase compliance, leading to potentially better treatments.

TABLE 2

Disease	Study Type	Patient Number	% Patients Preferring ODT vs. Standard Tablet	Compliance: ODT vs. Standard Tablets
Parkinson's Disease[2]	12-month longitudinal patient records	1520	NA	98.5% vs. 81% Medicare patients
Parkinson's Disease[8]	12-week investigator study	197	86% preferred ODT	NA
Allergy Rhinitis[8]	Patient preference survey	420	83% preferred ODT	NA
Schizophrenia[10]	16-week investigator study	149	NA	92.9% vs. 78.5% (P = 0.015)
Allergy (Antihistimine)[11]	Patient preference study; patients told they were given active dose, but was ODT placebo	>7500	94.3% ODT convenient to use 95.3% ODT easy to take 87.7% would change current antihistamine for ODT formulation	NA

Zydis® data showing improved patient preference and/or compliance.

CASE STUDY

New compliance data from SDI Health, a division of IMS, has shown that Zelapar®, a Zydis fast-dissolve ODT formulation of selegiline that achieves pre-gastric absorption, resulted in higher patient compliance rates in Medicare patients than alternative pills, capsules, and other ODT formulations. A 12-month longitudinal patient records study measured patient compliance for Selegiline pills versus Zelapar.[2]

Zydis fast-dissolve technology-enabled Zelapar (1.25 mg or 2.5 mg) to deliver more drug where it is needed, in a faster and safer way. This was achieved due to transmucosal adsorption, significantly bypassing the stomach and liver, and avoiding first pass metabolism. This resulted in a better treatment profile as shown in Table 1.

Selegiline is a class of dopaminergic antiparkinsonism agents, used in addition to carbidopa/levodopa agents, in the treatment of Parkinson's disease. According to the package insert, patients using this product take a 5-mg pill or capsule twice a day (BID). Eldepryl®-branded selegiline launched into the market in 1989, with several generics entering from 1997-2006. In 2006, Zelapar, a once-daily dosed selegiline HCL formulated with Catalent's Zydis fast-dissolve technology, was launched and marketed by Valeant Pharmaceuticals International, Inc.

The impact of the Zydis fast-dissolve formulation versus the traditional capsule and tablet formulations showed that the Zydis fast-dissolve technology has the potential to improve product bioavailability (Table 1). Zelapar also showed compliance differences when compared to other dose forms of selegiline. After 1 year, there was a 98.5% compliance rate for Zelapar prescriptions compared to an 81% rate for standard tablet formulations in all Medicare patients studied. Compliance improvements were demonstrated in additional patient cohorts: all ages, female, all payer type cohorts (91.6% compliance for Zelapar prescriptions versus 83.7% for standard tablet formulations). Age 19 to 65, all genders, all payer type cohorts (87.3% compliance for Zelapar prescriptions versus 83.8% for standard tablet formulations).[2]

By applying Zydis fast-dissolve technology, Zelapar achieved pre-gastric absorption and an improved and differentiated product profile. This has translated into a positive market impact for the product in the US market. Launching into a mature, already generic selegiline market, Zelapar sales growth rates have outperformed other branded and generic oral formulations. Moreover, Zelapar has gained the dollarized market share leader position in the overall Anti-Parkinson treatment market for ODT formulations, and retained this position even as alternative loosely compressed ODT formulations have been launched in the overall class. As of 2010, Zelapar holds a 50.1% dollar market share in the anti-Parkinson treatment ODT market and 39.3% of the total selegiline market.[7]

Zydis fast-dissolve products have achieved market share and sales growth as well

as share retention for both over-the-counter and prescription drugs in other therapeutic areas, including central nervous system, gastrointestinal (nausea and diarrhea), migraine, pain, and allergy.

Even where transmucosal adsorption and improved product profiles are not possible, Zydis fast-dissolve products, which are taken without water and disperse instantly in the oral cavity, are preferred by patients and support adherence, as shown in Table 2, offering better treatment. In fact, 83% of patients preferred Zydis fast-dissolve versus traditional tablets in an antihistamine patient preference study.[8]

SUMMARY

Patient medication non-compliance has become one of the most expensive and under addressed problems in healthcare. Educating patients and improving physician-patient relationships is helping ease the burden of noncompliance for the healthcare industry. However, the pharmaceutical industry can do its part by seeking out alternative drug delivery regimens that facilitate convenience and ease of dosage administration. One type of drug delivery form meeting the challenge of noncompliance is the orally disintegrating tablet. New research has demonstrated that Zydis fast-dissolve is an ODT that is patient preferred, easy to self-administer, easy to swallow, and can support the buccal delivery of drugs and enhance pharmacokinetics, reducing pill burden, dosing frequency, and limiting adverse effects from metabolites. In addition, pharma companies that have launched ODT formulations of drugs have realized improvements in market share. ODTs have been proven to reach across multiple therapeutic areas as a convenient and patient preferred drug delivery solution and in this case, have shown to be particularly effective in an older patient population in which dysphagia is prevalent.

Considering drug delivery formulation options, such as ODTs, is among the factors that should be considered as a means to deliver a treatment option that both meets the needs of patients and manages healthcare costs by supporting compliance. ◆

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BIOGRAPHIES

Steven Hamlen has 19 years experience in the life sciences industry, including Hoffmann-La Roche and Johnson & Johnson. While at Johnson & Johnson, he was a Director of Global Strategic Marketing, leading global teams in the development of life cycle strategies for new molecules and also compounds approaching loss of exclusivity in the anemia and oncology supportive care therapeutic areas. This included the creation of differentiated product profiles for numerous new products, line extensions, and licensing opportunities. He was also a Product Director for PROCRIT, leading sales and marketing for the US nephrology business at Johnson & Johnson's Centocor Ortho Biotech division. During his time at Hoffmann-La Roche, he was an Engineer in the vitamins new product forms group, where he was responsible for developing new vitamin and antioxidant formulations, and technology transfer from laboratory to production. His experience transcends emulsification, milling, granulation, spray drying, fluid bed drying, and tableting. Mr. Hamlen has a BS in Chemical Engineering and an MBA from Lehigh University. He is currently in global marketing for Catalent Pharma Solutions' Modified Release Technologies business, leading teams in the launch of new technologies and identification of new opportunities for Zydis®, Lyopan®, OSDrC® OPTIDOSE™, and controlled-release technologies to help pharmaceutical and consumer healthcare companies address unmet needs and develop better treatments through drug delivery.

Dr. Karen MacGregor, as a pharmacist with a PhD in topical cytotoxic drug delivery, has more than 17 years experience in the pharmaceutical industry with the past 10 years being in outsourcing pharma services and a provider of innovative solutions to the industry. Dr. MacGregor has had functional and leadership roles in Rhone Poulenc Rorer, Aventis, CCL Pharmaceuticals, and Cardinal Health, involved in oral, topical, and inhalation dosage forms. Throughout this time, Dr. MacGregor has led technical teams both in the areas of formulation and process development and in operational technical support. Working for Catalent for more than 7 years, as Director Product Development, she is responsible for leading multifunctional teams in the development of new and existing ODT products.

Importance of Phamacokinetic/Pharmacodynamic Studies During Biosimilar Clinical Development

By: Fethi Trabelsi, PhD

ABSTRACT

The development of biosimilar/follow-on biologic products has become a reality throughout the past decade, evidenced by the significant number of "similar" biologic products brought to the market globally and in particular in Europe. Important challenges have been identified that are significantly different to those faced during small chemical molecule product development. Although the regulatory pathway has not yet been completely defined by the US FDA, progress has been made elsewhere, where a variety of guidelines for the development of biosimilar products have been successfully implemented.

The challenges faced with biosimilar development are product specific; however, there seems to be a consensus that the drug development process needs to be scientifically driven to ensure the quality, safety, and efficacy of pharmaceutical products by using state-of-the-art technologies. The establishment of "similarity" as opposed to standard bioequivalence follows the so-called "comparability exercise." This includes the characterization of the physicochemical and analytical properties of the product, comparative bioassays and in vivo animal testing, and comparative immunogenicity and in vivo clinical studies, which typically include pharmacokinetics/pharmacodynamics (PK/PD) studies, as well as Phase III efficacy/safety trial(s).

The clinical development process starts with the assessment of the PK/PD characteristics of the biosimilar product as compared to the already marketed reference product. The Phase I PK/PD step is a very important stage in clinical development in order to determine any differences to the reference product that may exist. This could be in terms of the rate and extent of the systemic exposure to the test product, as well as its biological activity; provided that validated biomarkers or surrogate markers of the clinical activity exist. The purpose of this discussion is to highlight the importance of PK/PD studies in the "similarity assessment" during biosimilar clinical development.

INTRODUCTION

Throughout the past decade, the development of biosimilars/follow-on biologics has grown rapidly as many biologic patents expire. From 2008 to 2015, approximately 45 patents of innovator biologic patents will expire, and these biologics will become open to the development and manufacture of a biosimilar by other companies. This introduces competition in the market that can result in more affordable biologic drugs. From a sales perspective, biologic drugs reached some $130 billion in 2009, and even though the global biosimilar sales might have doubled each year since 2007, the global market for biosimilars represents only $235 million in mid-2010.[1]

Biosimilars are typically complex molecules produced in living systems as opposed to small chemically synthesized traditional generics. They should not be treated as generics and therefore, the traditional principles of bioequivalence could not be systematically applied, although some of the principles could be used and maybe adjusted to biosimilars. Their development should be scientifically driven, and the development plan should be accomplished on a case-by-case basis. The three-dimensional structure of recombinant protein products is complex, and any difference between the biosimilar and the reference product may result in

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significant differences in terms of in vivo behavior of the product, which has raised a number of concerns since the beginning of biosimilar history. It is believed that a difference in purity of a recombinant protein product may impact the safety (eg, immune response) and efficacy of the biosimilar.

A THOROUGH COMPARABILITY EXERCISE IS NEEDED

Because of the inherent complexity of the biologics, the manufacturing process and the physicochemical and biological characterization should be thoroughly designed to ensure quality and safety of the product. This characterization is a key step of the "comparability exercise," and extensive data should be generated using advanced analytical methods and bioassays before moving ahead with the non-clinical and clinical testing. Even though some biosimilars could be as highly purified as insulin, interferon, and granulocyte colony-stimulating factor (G-CSF), it is admitted that these products are too complex to conclude similarity only on the basis of physicochemical and biological testing. A clear demonstration of the safety and efficacy of the product will require extensive non-clinical and clinical studies to ensure that a safety and/or efficacy concern would not arise either from the product or any other factors, such as some degradation elements or some impurities during the manufacture process.

In vivo animal studies are another step in the "comparability exercise." Before initiating the clinical part of any biosimilar program, non-clinical studies should be designed in a way to capture any relevant and meaningful difference with the comparator product that will be used in the clinical trials. Relevant species, state-of-the-art technology, and properly designed studies to assess in vivo PK/PD characteristics in animals are key in this step. A repeated-dose non-clinical toxicology study is usually required to assess toxicokinetic profiles as well as antibodies titration, cross-reactivity, and neutralizing capacity as appropriate. This type of non-clinical study should be long enough to detect any immune response difference and therefore the associated potential risk for the safety of the biosimilar.[2]

The clinical development program for biosimilars starts with the assessment of the PK and, whenever possible, the PD characteristics against the reference. The comparability of the critical PK parameters is essential to demonstrate systemic exposure similarity in terms of rate and extent of the drug bioavailability, as well as the elimination of the product. The comparability of the PD characteristics, when validated and relevant PD markers exist, should bring more insights to the expected therapeutic response during the clinical efficacy demonstration and for some rare cases could be even used as surrogate markers of efficacy. It would be ideal to design combined PK/PD studies to explore the relationship between both PK and PD parameters as demonstrated in the literature.[3]

Most of the time, the product efficacy and safety evidence of biosimilars is not based only on PD data in healthy volunteers but rather on Phase III clinical data in patients where the clinical endpoints and the acceptance margins are defined based on the targeted indication. In addition, post-marketing pharmacovigilance studies are mandatory to continue to provide further evidence on the quality, safety, and efficacy of biosimilars.

The following will highlight the importance of PK/PD studies in the clinical development phase and focus on three major questions to consider when designing these studies.

WHY PK/PD STUDIES ARE SO IMPORTANT

PK and PD studies are an important step in the comparability exercise as highlighted in the aforementioned sections. Many key study design elements are essential and should be investigated when designing Phase I trials to generate reliable data to support drug development and to provide direction regarding the objectives to be achieved in the Phase III efficacy trials. Usually, the PK/PD studies would not be sufficient for the efficacy and safety comparability unless there are validated PD markers that could be used as surrogates for efficacy. There are a few exceptions in which Phase III trials were not required, and when conducted, they were considered supportive. For example, the approval of Zarzio® G-CSF relied mainly on the PK/PD studies, and the clinical trial conducted in breast cancer patients undergoing cytotoxic chemotherapy was a supportive one.[4]

HOW MANY STUDIES ARE REQUIRED?

The number of PK/PD studies will vary from one biosimilar program to another, depending on the knowledge of the product PK

characteristics (eg, PK parameters, linearity), the extent of available PK/PD data in the literature, the relevance of the non-clinical data, etc. Each biosimilar development is unique; however, the Phase I PK/PD program could differ in terms of study designs from one sponsor to the other, which may still lead to similar conclusions with the assumption that biosimilars are of a high quality and the study design is adequate. The ultimate goal would be to avoid repeating unnecessary clinical trials, but rather focus on what would be scientifically sound to perform the best comparability exercise. Robust and successful Phase I PK/PD studies would certainly increase the level of confidence of the developer to move to a subsequent development phase, and may limit the extent of clinical efficacy and safety data required in Phase III.

The number of PK/PD studies performed in the development of the Zarzio® G-CSF product was a total of four two-way crossover design trials. Comparable PK and PD profiles were demonstrated using different doses from 1 to 10 mcg/kg given either subcutaneous (sc) or intravenously (iv) and following either single- or multiple-dose design.[4] Absolute Neutrophil (ANC) and CD34+ cell counts were used as surrogate markers of efficacy. Overall, the primary (AUCs) and secondary PK parameters (Cmax and half-life) met the acceptance criteria for almost all doses and routes of administration. The design of these PK/PD studies were optimal and have given the assurance to the regulatory agency that ANC and CD34+ could be used as surrogate markers of the product efficacy. Hence, only one additional Phase III efficacy study was conducted in patients with breast cancer receiving cytotoxic chemotherapy to support the PK/PD data.[3,4]

The development of the TevaGrastim® G-CSF Phase I program was a bit different; it was based on two large single-dose crossover studies to establish PK/PD similarity in normal healthy volunteers.[5] In the first study, two groups of healthy volunteers were given a single dose of either 5 or 10 mcg/kg sc of both the test and the reference in a crossover fashion. In the second study, the duration of the sampling was longer; there were four groups of healthy volunteers, and each group received both products as either 5 or 10 mcg/kg, sc or iv. Similarity on PD was demonstrated based on ANC and CD34+, while the PK comparability used AUCt as primary and Cmax, AUCinf, Tmax, and half-life as secondary parameters. The Phase III clinical program was more elaborated with three clinical trials; one for efficacy comparability and two for safety. These studies were performed respectively in breast cancer, lung cancer, and non-Hodgkin lymphoma patients, along with chemotherapy.[5]

Therefore, the number of Phase I clinical trials would be dictated by the product PK/PD specificities, and the question is how much data should be generated to be confident with the comparability. The use of the most appropriate design for each study should be looked at on a case-by-case basis. The choice of the study design for single dose, steady-state studies, or repeated determination of PK parameters, should be justified. For example, crossover design might not be that appropriate for therapeutic proteins with a long half-life, such as therapeutic antibodies and pegylated proteins.[2]

BEST STUDY POPULATION FOR PK/PD EVALUATION?

One of the first questions that needs to be addressed when designing PK/PD studies is: which population would be most suitable to adequately assess the key PK parameters and PD responses? The appropriate population should enable the detection of any potential differences between the innovator and the biosimilar products. Usually, normal healthy volunteers are considered adequate populations, and the most sensitive model to demonstrate biosimilarity, unless there is a safety risk to the subjects. Healthy volunteers are usually appropriate as we avoid any interference or bias caused by the disease itself. Indeed, for G-CSF, healthy subjects are considered more appropriate to evaluate its haematopoietic effect, as their bone marrow is more responsive to G-CSF compared to cancer patients undergoing chemotherapy.[6]

WHICH ACCEPTANCE CRITERIA SHOULD WE USE?

The acceptance margins defining the clinical comparability of PK/PD parameters should be pre-defined and justified based on clinical grounds from safety and efficacy stand-points. The acceptance criteria for traditional generics are well-defined as the 90% confidence interval (CI) for key

parameters falling within 80% to 125% is used. These standard acceptance criteria may not be appropriate for biosimilars depending on the products' characteristics and the relevance from a clinical application. By default, the standard criteria should be used, but in case a widened acceptance range (eg, 90% CI within 75% to 133%) could be justified, other criteria may be proposed and discussed with the regulatory agency. Usually, the primary PK parameter used for biosimilars is the AUCt, but other parameters such as Cmax, AUCinf, Tmax, half-life, and clearance should also be explored.[2]

The challenge is to define what would be acceptable from safety and efficacy standpoints. In the Zarzio® G-CSF application, the primary PK parameter (AUCt) was comparable to the reference product as shown by the 90% CIs within 80% to 125% for all doses and both administration routes.[4] The primary PD endpoint AUEC (Area under the effect curve) of ANC and the secondary endpoint AUEC of CD34+, met the acceptance boundaries using the 95% CI approach. For Omnitrope®, the 90% CIs of the AUCinf and Cmax fell within 80% to 125%, while the PD results did not meet the pre-defined acceptance criteria.[7]

SUMMARY

The comparability exercise for biosimilars should be very extensive at each step of the development. Phase I PK/PD studies are a key step in which innovative study designs and rigorous methods should be used. They should allow sensitive detection of any difference between the innovator and the biosimilar, if exists, in well-controlled testing environments and standardized clinical conditions. The number of studies should be limited and specific to each biosimilar program in order to give the assurance to the developers, the regulators, the physicians, and ultimately, the patients that the product is of high quality, safe, and effective. ◆

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BIOGRAPHY

Dr. Fethi Trabelsi is currently the Director of Scientific and Regulatory Affairs at PharmaNet Canada, Inc., heading the protocol design and the pharmacokinetics teams involved with Phase I clinical trials, including bioequivalence pharmacokinetic/pharmacodynamic studies as well as first-in-man single- and multiple-ascending dose, drug-drug-interaction, and QTc prolongation clinical trials for new entities. Dr. Trabelsi is the key expert leading the early stage clinical development of biosimilars/follow-on biologics as part of a multi-disciplinary team at PharmaNet. Dr. Trabelsi has more than 12 years of experience in contract research organizations, mainly in pharmacokinetics and protocol design development for early stage programs. He earned his PhD from the University of Montreal in Exercise Physiology and completed his post-doctoral research training at the Faculty of Pharmacy of the University of Montreal in the Pharmacology/Physiology field. Before joining the pharmaceutical industry, Dr. Trabelsi was a lecturer in the Department of Physiology at the University of Montreal for more than 8 years, and he continues to lecture at the University of Laval in Quebec City. He has published numerous scientific papers in peer-reviewed journals and has presented at national and international scientific symposiums, conferences, and workshops. He is a member of many scientific associations, including the Generic Pharmaceutical Association (GPhA) and the Canadian Generic Pharmaceutical Association (CGPA). Dr. Trabelsi also maintains professional relationships with many key scientists and regulatory officials at the FDA, Health Canada, and various EU agencies.

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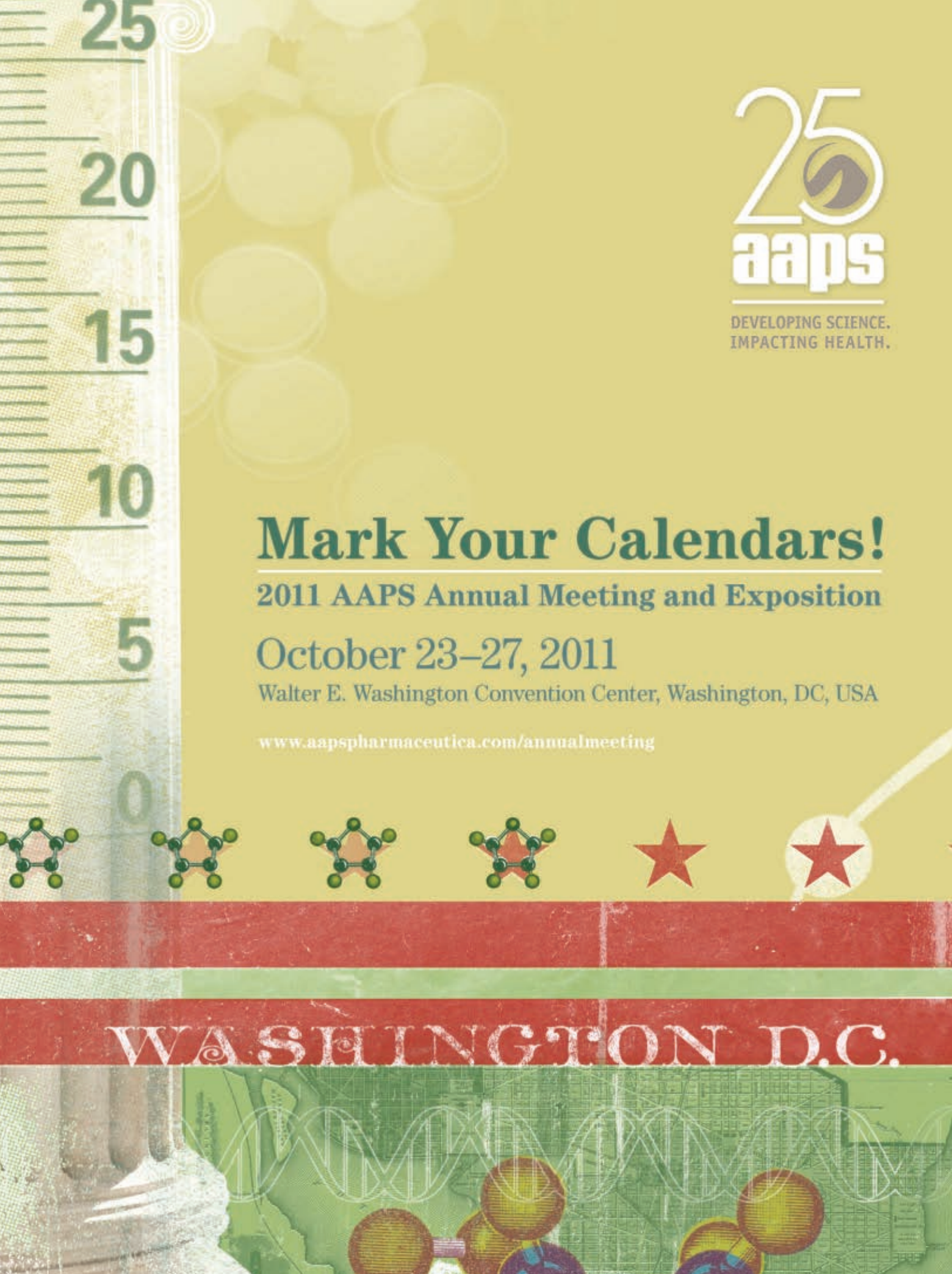

DRUG DEVELOPMENT Executive

MacuCLEAR, Inc: Discovering & Developing a Novel Solution for Dry Age-Related Macular Degeneration

Philip Ralston
CEO
MacuCLEAR, Inc.

"The competitive advantage of MacuCLEAR's approach is the unique way MC-1101 treats and prevents the progression of Dry AMD by targeting the underlying problem of decreased choroidal blood flow. Another major advantage comes from the fact most competitors are developing new chemical entities and as such, will be subject to the full FDA approval process required under a 505(b)(1) new drug approval (NDA) application."

Age-related Macular Degeneration (AMD) is the leading cause of blindness in the world for people over age 50. There is currently no approved treatment for 90% of these 30 million AMD sufferers. This huge unmet need represents a market potential of greater than $5 billion. (The remaining 10% who have late-stage, or wet AMD, spent $3 billion on treatments). MacuCLEAR, Inc., a clinical-stage specialty pharmaceutical company focused on discovering and developing novel solutions for vascular disorders of the eye, is developing a unique, preservative-free eye-drop treatment for this pandemic problem. MacuCLEAR's treatment for Dry AMD (early stage AMD), MC-1101, was invented by George Chiou, PhD, who led the discovery of Timolol, the pioneering treatment for glaucoma and the most successful ophthalmic drug to date. While novel in this ophthalmic application, the active ingredient of MC-1101 has been previously approved by the FDA as an oral antihypertensive (or high blood pressure) drug. MC-1101's safety and toxicity profile is well characterized, has been granted 505(b)(2) status, and has formal Fast Track designation by the FDA. Drug Development & Delivery recently interviewed Philip Ralston, CEO of MacuCLEAR, to discuss the company's unique, yet practical approach to treating Dry AMD.

Q: Can you explain to our readers the significance of Age-related Macular Degeneration (AMD) and what causes it?

A: AMD is the leading cause of blindness in the world in people age 50 and older. This disease affects one in three people. That's nearly 5,500 cases each day, and this number is growing as the population ages.

In its early stages, AMD will cause patients to have a noticeable decrease in their ability to see sharply or use focused vision. It is hypothesized this is a result of decreased blood flow to the back of the eye that causes subsequent damage to the macula, the area in the retina responsible for central vision, which is required for reading, driving, and watching television.

As aging occurs, a reduction in blood flow causes an accumulation of metabolic waste products, including a build-up of yellow subretinal deposits in the macula called drusen and a thickening of the Bruch's membrane, a critical blood barrier separating the retina tissues and the choroidal blood vessels in the back of the eye. The first stages of AMD are indicated by these deposits.

Q: MacuCLEAR's lead product, MC-1101, is a treatment in development for Dry AMD. What is the difference between Dry AMD and Wet AMD?

A: Dry AMD is the earliest stage of AMD. As the disease progresses, it eventually leads to the later stage, known as Wet AMD. The fundamental difference between Dry AMD and Wet AMD is the integrity of the Bruch's membrane. When the disease has progressed to Wet AMD, the Bruch's Membrane is ruptured, bleeding into the retina occurs, and the patient loses central vision.

For approximately 90 out of every 100 patients with AMD, the loss of vision is a gradual process. Patients who show this initial and gradual decrease in vision have Dry AMD. Studies have shown that eyes with lower choroidal blood flow at baseline are at a greater risk of developing this initial stage of AMD. Presently, there is no approved drug treatment available for patients with Dry AMD, and limited treatments are available for patients with Wet AMD. As a result, 90% of AMD patients cannot be treated with current methods.

Q: What makes MC-1101 different from other AMD treatments in development?

A: MC-1101 is the first therapy for AMD to be based on a well-researched vascular model. Blood brings nutrients to tissues and takes waste away. Normal aging can cause a reduction of blood flow, especially in the eye. Reduced blood flow can cause retinal waste products to accumulate in the eye, ultimately causing a thickening and rupture of the Bruch's membrane. New blood vessel formation, always present when the body experiences reduced blood flow, can now get through these ruptures and leak into the retina causing the wet form of AMD and ultimately, legal blindness.

MC-1101 works by restoring blood flow in the choroidal vessels, removing accumulating waste and stabalizing the Bruch's Membrane before it ruptures, preventing the leakage into the retina and blindness. MC-1101 is the first therapy to address the restoration of blood flow.

Q: You mentioned that MC-1101 treats Dry AMD by increasing the choroidal blood flow in the back of the eye. How does MC-1101 reach the back of the eye to treat this problem?

A: MC-1101 is administered in an eye-drop formulation that has been proven to travel to the back of the eye through well-researched pathways, including the suprachoroidal space between the sclera and the vitrious. Preclinical animal studies and human clinical trials, using sophisticated laser Doppler flowmeter technology, proved MC-1101 got to the back of the eye, and when it got there, significantly increased choroidal blood flow.

MC-1101 dilates blood vessels in the back of the eye and increases blood flow by stimulating nitric oxide production, which relaxes the epithelial lining of the vessel walls. This is the same principle of how such notable health issues as angina are relieved by nitroglycerin tablets and Viagra treats erectile dysfunction.

Q: Is there clinical data that suggests MC-1101 is safe and effective?

A: MacuCLEAR has successfully completed a Phase Ib/proof-of-concept human trial that confirmed MC-1101 was safe and well tolerated by all study subjects. Previously, MacuCLEAR conducted an Acute Ocular Toxicity Test in animals that also showed the safety of MC-1101. The drug has a long history of safe use as an antihypertensive, and has been given 505(b)2 status, which allows MacuCLEAR to use the historical safety data. Because reduced choroidal blood flow has been identified in patients with Dry AMD, it is logical that restoring choroidal blood flow will stop waste accumulation, prevent rupture of the Bruch's Membrane, preventing blindness. MacuCLEAR is poised to begin a novel Phase III human trial to prove efficacy once a funding pathway is secure.

Q: Who do you see as MacuCLEAR's chief competitors?

A: Most large, unmet markets attract competition; however, none have achieved FDA approval for treating Dry AMD. The therapies being developed by other companies focusing on Dry AMD are new chemical entities, none of which have progressed beyond Phase II clinical trials. These therapies in clinical development for Dry AMD appear to only address one of the many metabolic waste pathways in the retina, while none address the overall problem of reduced blood flow. Focusing on only one metabolic pathway still leaves others to accumulate on the Bruch's Membrane and contributes to potential thickening and build-up. Few companies are focused on just Dry AMD. Among the companies working on Dry AMD are Acucela and Resolvyx. Two others have failed.

Q: What would you say to our readers who are experiencing the symptoms of Dry AMD or who have loved ones with Dry AMD?

A: Those who currently have Dry AMD or who have friends or family with Dry AMD should keep themselves up-to-date on cutting-edge research developments, such as the ones we discussed. Although there is currently no definite date for bringing MC-1101 to market, we are all looking forward to a day in the not-too-distant future when MC-1101 may provide effective treatment for Dry AMD that can help those 90% of AMD patients who currently have no treatment to prevent their disease from progressing.

Q: What message do you have for potential investors in MacuCLEAR?

A: To potential investors, I stress the fact that MacuCLEAR is on track to pioneering the first treatment for Dry AMD, and its therapeutic approach has significant advantages compared to competition currently in developmental stages.

The competitive advantage of MacuCLEAR's approach is the unique way MC-1101 treats and prevents the progression of Dry AMD by targeting the underlying problem of decreased choroidal blood flow. Another major advantage comes from the fact most competitors are developing new chemical entities and as such, will be subject to the full FDA approval process required under a 505(b)(1) new drug approval (NDA) application. This process is very complex. Most drugs that fail, often do so late in the clinical process because of safety findings when toxicities or adverse drug reactions related to the new drug are uncovered. The safety profile of our lead compound, MC-1101, is already approved and on the market for other diseases. MacuCLEAR's initial drug candidate (a new use for an existing drug) will be subject to the abbreviated FDA approval process for a 505(b)(2) NDA application, thereby reducing the overall amount of work, associated time, and costs required for FDA approval. Finally, MC-1101, as well as all other compounds in MacuCLEAR's pipeline, are topically administered as eye-drops; the safest, most cost-effective and preferred drug delivery method for vision-impaired patients.

Q: Can you tell us more about yourself and how you started MacuCLEAR?

A: I have spent more than 35 years in the life science industry as a senior executive, inventor, company founder, venture capitalist, and business coach. During those 35 years, I have represented companies in the public, private, and non-profit sectors.

Founding MacuCLEAR has been an exciting endeavor for me. MC-1101 has the potential to help a huge number of people with Dry AMD that currently have no treatments for their condition. MacuCLEAR was formed in 2006 after securing a worldwide license for a proprietary platform technology for treating and preventing the progression of Dry AMD. The company was initially funded in April 2007. This technology was developed by George Chiou, PhD, at Texas A&M University. Through this worldwide license, MacuCLEAR obtained its lead drug, MC-1101, and 11 other compounds aimed at treating diseases of the eye. ◆

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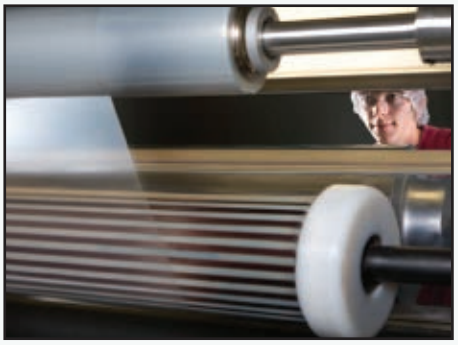

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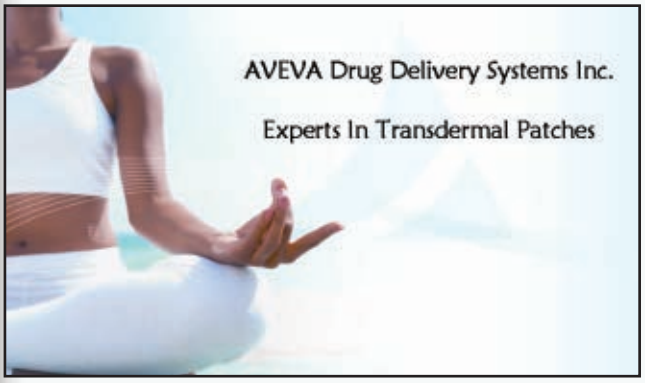

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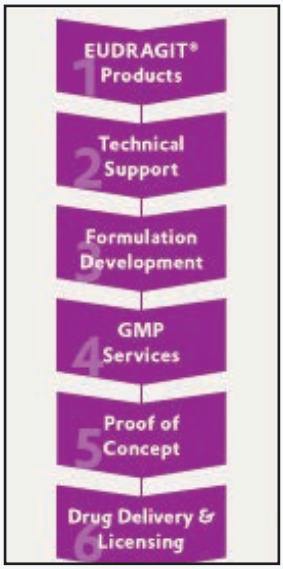

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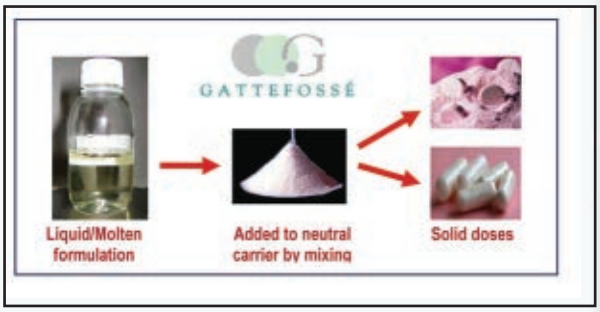

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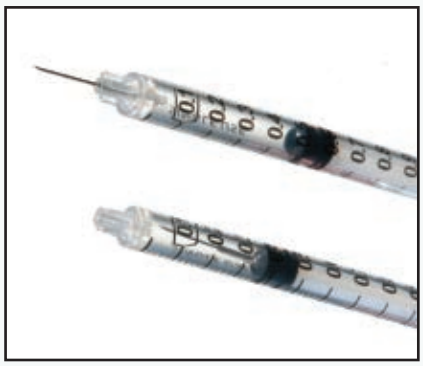
Rexam Healthcare has received 510(k) approval from the FDA for Safe'n'Sound™, its passive safety device for staked prefilled syringes. The approval is the crowning achievement of significant investment and design efforts by the Rexam teams. The aim of the project was to design a safety device that meets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

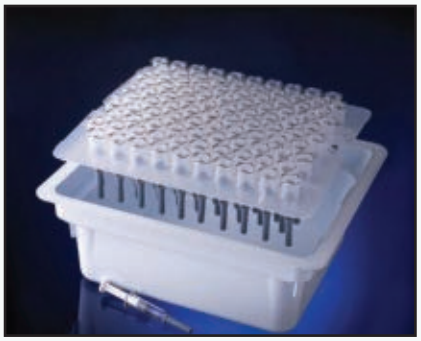
Technology & Services Showcase

Prefilled/Clinical Safety Syringes



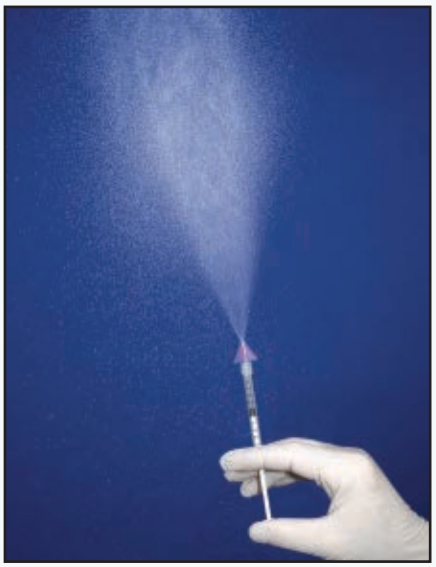
Unilife Medical Solutions has a range of prefilled and clinical safety syringes suitable for pharmaceutical companies, healthcare facilities, and patients who self-administer prescription medication. Our products incorporate passive and fully integrated safety features that can help customers comply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

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**.

Intranasal Vaccine Device



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

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FROST & SULLIVAN

ZETA POTENTIAL

The Zeta Potential & its Use in Pharmaceutical Applications - Part 2: Measurement Techniques & Uses

By: David Fairhurst, PhD; Robert W. Lee, PhD

INTRODUCTION

In Part 1 (July 2011 issue) of this review, we covered charged interfaces (in both polar and non-polar media) and introduced the concept of the zeta potential (ZP). In this concluding Part 2, we discuss techniques to measure ZP and illustrate the utility of its measurement.

MEASUREMENT OF ZETA POTENTIAL: ELECTROKINETIC PHENOMENA

An electric double-layer (EDL) exists between a surface and solution. Any relative motion between the rigid and mobile parts of the EDL will result in the generation of an electrokinetic potential. There are four fundamental ways (Figure 1) that electrokinetic potential can be produced: electrophoresis, electro-osmosis, streaming potential, and sedimentation potential.[1] The parameter used to describe this real, measurable potential is the ZP, introduced in Part 1, in which the theoretical model for the EDL was discussed.

Measurements made using techniques based on the four effects should give the same value for ZP. However, owing to a variety of contributing factors, this is not necessarily the case. These include assumptions in the model for the EDL, inadequacies in the theory, experimental limitations in the design and construction of instrumentation, and differences in sample preparation.[2] The choice of method should be based on the specific application under investigation.

FIGURE 1

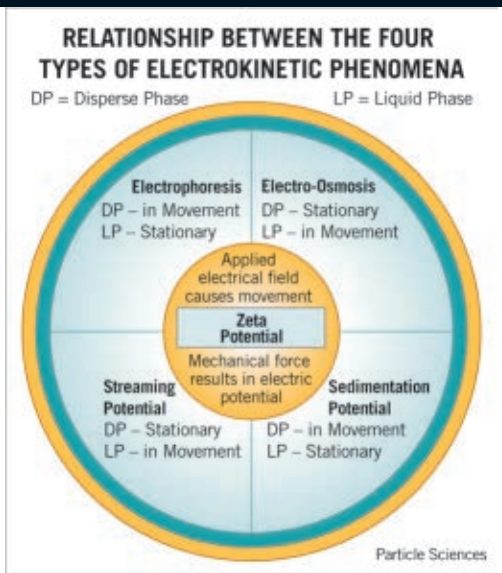


TABLE 1

Material	ZP (mV)
O/W Emulsions	>15
Polymer Latices	>20
Metal Oxides	>40
Metal Sols	>70

Rule of Thumb for Electrostatic Stabilization

Particle Electrophoresis

The most common technique based on microelectrophoresis is electrophoretic light scattering (ELS), sometimes called laser-Doppler electrophoresis (LDE). It is fast, and the latest commercial devices are fully automated, requiring little input from the user. ELS/LDE instruments yield a histogram of the ZP of the particles within the sample suspension, and most devices also measure the particle size distribution.

ZETA POTENTIAL REFERENCE MATERIALS

There is no accepted universal standard for ZP measurements. However, there are a number of reference materials supplied by the various instrument manufacturers. These are well-characterized suspensions whose ZP has been established over hundreds of measurements over many years; it is typically some stated value for ZP ± 10% of that value.

The nearest "official" reference material is a sample of Goethite, α-FeO(OH), manufactured and distributed by NIST (Gaithersburg, MD), which when prepared under standard conditions, has a certified electrophoretic mobility value of +2.53 x 10^{-8} ± 0.12 x 10^{-8} $m^2V^{-1}s^{-1}$, equivalent to a ZP of +32.5 mV ± 0.12 mV.[3] Unfortunately, the Goethite suspension has to be freshly prepared before each use, and the protocol is not without travail. Further, being positively charged, the Goethite particles tend to coat the walls and surfaces of an instrument measurement cell; clean-up can be very tedious.

SYSTEMS HAVING VERY SMALL ZETA POTENTIALS

The ELS method works very well for aqueous systems in which the solution ionic conductance is moderate. However, human red blood cells (RBC) and microorganisms, such as bacteria and viruses, are suspended in water under physiological (isotonic) conditions (0.145 M NaCl, pH 6.8) in which the ionic strength and conductance are high.[4,5] As the electrolyte concentration increases, the value of ZP falls owing to the shielding effect of the ion atmosphere around the particle (see Part 1, July 2011). Consequently, the ZP of RBC in isotonic solution is almost an order of magnitude smaller than in distilled water.[5,6] Some body fluids can exceed the isotonic ionic strength by an order of magnitude, and salt levels in environmental systems, such as brine and sea water, can be very high (~ 2 M).[7] Obtaining reliable data in when the solution conductivity is so large poses a challenge for ELS/LDE devices because of Joule heating and other undesirable effects.[8,9]

Particles that are sterically stabilized by adsorbed non-ionic surfactants, macromolecules, and synthetic polymers all have ZP values at or near zero; making reliable, reproducible measurements on such systems almost impossible.[2]

Non-aqueous systems also pose a challenge because the viscosities of many organic liquids are higher than water, and the dielectric constants are invariably lower. For example, PEG 200 (at RT) has a viscosity of ~ 100 cP and a dielectric of ~ 12; ZP measurements by ELS in this fluid would be impossible.

Phase Analysis Light Scattering

The aforementioned difficulties can be overcome by using phase modulation in place of frequency spectrum analysis.[10,11] Termed phase analysis light scattering

FIGURE 2

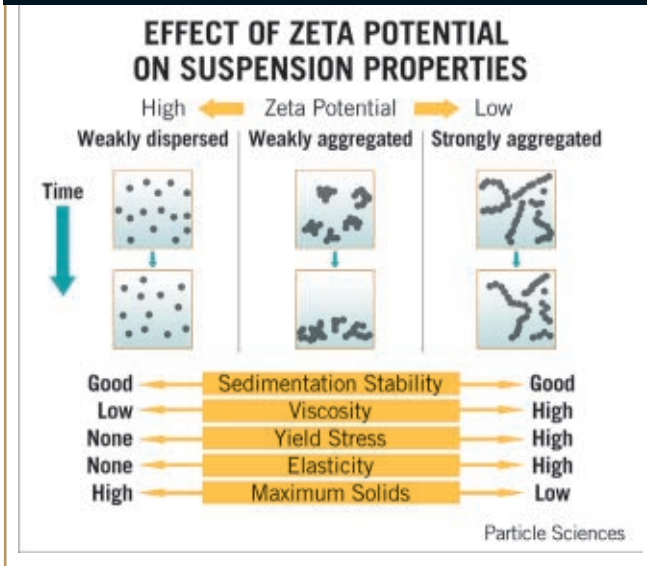
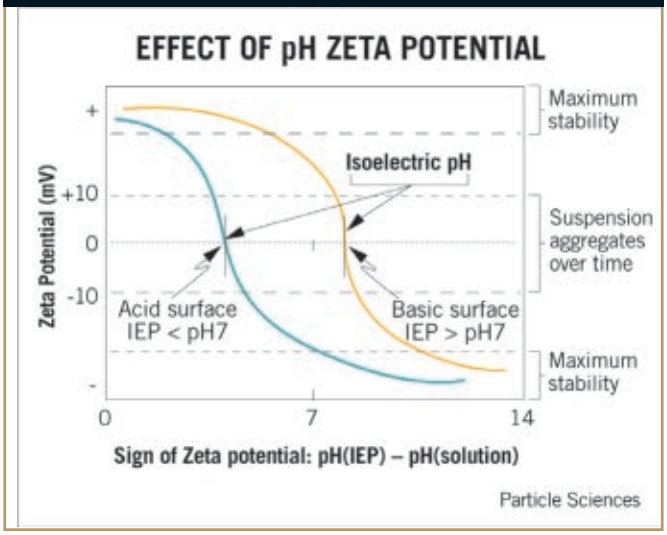


FIGURE 3



(PALS), this methodology has much superior sensitivity compared to conventional ELS/LDE. At 37°C, the viscosity of PEG 200 is ~ 30 cP, and a sample of casein dispersed in it has a measured ZP of ca -0.3 mV in contrast to a typical literature value for casein in water of ca -75mV.[12]

The limitation of the PALS method is that it will only give an average value for ZP, ie, there is no histogram. Hence, it cannot be used for systems in which mixtures of materials are used.

CONCENTRATES & OTHER UNUSUAL DISPERSIONS

Instrumentation based on ELS/LDE or PALS require that the system under measurement be initially diluted, but there is always a potential concern that the dilution process can produce instability; one classic example is emulsions. Another issue is the subsequent extrapolation of data from exceptionally dilute suspensions to the practical relevant concentration of the formulation. For biological systems, the problem of small amounts of contaminants in dilute systems can be overwhelming, whereas in concentrates, this can be almost ignored. Finally, ELS and PALS are light scattering techniques and so have limitations with opaque (ie, light absorbing) materials (ie, carbon black) or light sensitive materials (ie, selenium or silver compounds) or systems in which the particles have motility (ie, sperm).

Electroacoustic Attenuation

In sedimentation potential measurements (Figure 1), the disperse phase moves through a stationary liquid under the influence of gravity (the mechanical force) to produce an electric potential.[13] The gravitational force can be replaced by an acoustic field to give an AC equivalent of the DC sedimentation potential. Termed electroacoustic attenuation (EAA), there are two principal methods: colloid vibration potential (CVP) and electrokinetic sonic amplitude (ESA); a comprehensive review of ultrasound techniques has been made by Dukhin.[14-17]

A major advantage of EAA is that the sample under investigation need not be stationary, a necessary requirement of ELS and PALS instrumentation. The prime disadvantage of the EAA technique is interference from the presence of air bubbles.[17] The lower limit of concentration that can be reliably measured is about 1%, and at high concentrations (> 50%), technical issues limit its usefulness.

It should not be expected that the value of ZP determined at high concentration using EAA should be the same as that determined under dilute concentrations using ELS or PALS. At very high solids concentration, interpretation of experimental measurements is complicated because of possible EDL overlap.[18]

Thus, if a suspension is prepared at one concentration but used at some other lower concentration, it is critical that measurements be made at the use concentration; measurements of ZP as a function of suspension concentration can often be illuminating.

MASSIVE & IRREGULAR SHAPE SOLID MATERIALS

There are applications in which the surface under investigation is not a particle. Examples include hair, bone, skin, polymer films, fibers, membranes, filter and porous materials, paper pulp, and metal foil. In addition, coarse and massive solids that are of irregular shape are simply not amenable because of their physical dimensions to be measured by ELS/PALS and EAA techniques.

Streaming Potential

Measurements on such systems can best be made using the streaming potential (SP) method.[19] A major advantage of the

SP technique is the ability to investigate adsorption/desorption phenomena *in situ*; the flow-through nature of the method makes it ideal for the study of long-term processes. However, there are very few commercial manufacturers of SP instrumentation.

THE USEFULNESS OF ZETA POTENTIAL MEASUREMENTS

The Relation of Zeta Potential to Suspension Behavior

All suspensions are inherently thermodynamically unstable and will over time, through random motion of particles, aggregate unless sufficient repulsive forces are present. The repulsive force between particles, V_R, which keeps particles from aggregating, is illustrated in the following equation:

Equation 1.

$$V_R = D\ a\ \psi_d^2\ [\text{Geometric term}]$$

Where, D is a dimensionless constant related to the permittivity (dielectric constant) of the suspension medium, a is the particle size, and ψ_d is the Stern potential. The Geometric term is a function of particle radius, the Debye length, and the distance of separation between particles.

ZP is related to surface charge and can be substituted for the Stern potential, ψ_d. Thus, we can see that for a fixed medium, particle size and ionic strength, V_R will increase as ZP gets larger. Hence, a widely used application of ZP is to monitor the stability of electrocratic suspensions. It is particularly useful to predict the resistance of such dispersions to coagulation by electrolytes, by determining the critical ZP, ie, the value of ZP below which the suspension is coagulated. Table 1 lists the approximate minimum values of ZP needed to electrostatically stabilize materials of different dielectric constant in neutral (ie, pH 7 at 25°C) water.

The values of ZP in Table 1 are meant as guides only. APIs can be considered similar (in this regard) to polymer latex

TABLE 2

Material	pH Value of IEP
Oxides	
Silicon Dioxide	2
Titanium Dioxide (Anatase)	4
Titanium Dioxide (Rutile)	6
Iron Oxide	8
Aluminum Oxide	9
Zinc Oxide	10
Magnesium Oxide	12
Proteins	
Ovalbumin	4.0
Casein	4.6
Gelatin	4.8
Streptavin	5.0
BSA	5.0
Lactoglobulin	5.3
Rapeseed 12S	7.0
Ribonuclease	9.5
Avidin	10.5

Isoelectric Point of Materials

particles. ZP measurement is often used in determining the critical coagulation concentration (CCC) of an electrolyte (the minimum concentration required for the onset of coagulation); the CCC is proportional to ZP^4/z^2 (where z is the electrolyte counter-ion valence).

A variety of products require rheological control as an integral part of product requirements. Effective control of rheology relies on knowledge of the effect of formulation and process variables. Figure 2 illustrates the relation between ZP and the rheological characteristics of suspensions. A high ZP produces a well-dispersed suspension. This in turn results in good sedimentation stability and high solids loading capacity. This type of suspension will have fluid-like characteristics, ie, low viscosity, extremely low elasticity, and relatively linear viscoelastic behavior as a function of shear or strain. In contrast, a low ZP results in particle association. The formation of a strong network structure provides good sedimentation stability but greatly reduced solids loading capacity. Here, the rheological behavior would be characterized by a high viscosity, a high elasticity, and a yield point at some critical strain.

DETERMINATION OF THE ISO-ELECTRIC POINT OF MATERIALS

All charged materials will have an isoelectric point (IEP), defined as the condition when the ZP is zero. This is usually achieved by addition of potential determining ions (PDI), which for many materials, means H^+/OH^- (ie, a function of pH). It can also be attained by specific adsorption of charge modifying agents (CMA).

Figure 3 is a plot of ZP versus pH from which a number of important points can be noted. The first is that at the IEP, a particle suspension will have no resistance to aggregation. This is used in applications such as waste water treatment. If the ZP is in the range about ±10 mV, a suspension will be unstable and will aggregate over time. If the IEP is known, then the sign of ZP can be determined from the solution pH.

The second is the magnitude of the ZP increases (either side of the IEP) but eventually plateaus. The condition of maximum dissociation of any surface functional groups and can be used to great effect when dispersing particles; the greater the magnitude of ZP, the less the need for any additional dispersing aid. For proteins and charged macromolecules, the ZP value at this plateau generally increases with increasing MW. For example, at pH 9, the ZP of different gelatins can range from as low as -15 mV to more than -50 mV. Materials that carry a negative charge can be made to be positive by adding PDI or CMA.

Finally, particles with an IEP < pH 7 have acidic character, while those with an IEP > pH 7 are basic. An example of this is carbon black. Acidic carbon blacks have an IEP in the pH range of 3 to 4, while basic carbon blacks have an IEP in the pH range of 8 to 9. Table 2 lists the typical IEP of some common oxides and proteins.

CONCLUSION

ZP measurement is a very useful but often under-utilized technique that can provide information about the material surface-solution interface. Knowledge of ZP can be used to predict and control the stability of suspensions and emulsions; measurement of ZP is often the key to

understanding dispersion and aggregation processes. The presence, or absence of charged groups/moieties on the surface of materials, as revealed by their ZP, can directly affect their performance and processing characteristics in suspension.

The sign and magnitude of ZP affects process control, quality control, and product specification; at the simplest level, it can help maintain a more consistent product and at a complex level, it can improve product quality and performance. ◆

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BIOGRAPHIES

Dr. David Fairhurst is a Corporate Research Fellow at Particle Sciences Inc. He earned his PhD in Physical Chemistry in 1968 from Liverpool Polytechnic, UK, where he was also a Lecturer (in Physical Chemistry) for 4 years. He spent 2 years as a Visiting Associate Professor in the Center for Surface and Coatings Research at Lehigh University and subsequently held senior research positions with the UK Chemical Defense Establishment, Porton Down and with Union Carbide Corporation, USA. The work encompassed exploratory and basic research, product formulations, and development and technical services. He has spent the last 40 years in using colloid and surface chemistry to solve problems in industrial and pharmaceutical applications and has published more than 100 technical papers, scientific articles and book chapters in the open literature. Prior to joining PSI in 1993, he was, for 7 years, Director of Applications at Brookhaven Instruments Corporation and is an internationally recognized authority on dispersion and emulsion technology and in the assessment and characterization of particle size.

Dr. Robert W. Lee is Vice President of Pharmaceutical Development at Particle Sciences Inc. He is responsible for product development at Particle Sciences as well as providing support to clinical manufacturing operations and business development. His responsibilities include oversight of formulation development, drug delivery, analytical sciences, quality control, and quality assurance. Before joining Particle Sciences, Dr. Lee held senior management positions at Novavax, Inc., Lyotropic Therapeutics, Inc., and Imcor Pharmaceutical Co. He has also been in research positions at élan Drug Delivery, NanoSystems, and Sterling Winthrop. Dr. Lee earned his BS in Biology and Chemistry from the University of Washington and his PhD in Physical Bioorganic Chemistry from the University of California-Santa Barbara. Dr. Lee has published articles in numerous peer-reviewed journals and three book chapters plus holds 11 issued patents and 14 provisional or PCT patent applications. He has more than 20 years of experience in pharmaceutical research and development of both therapeutic drugs and diagnostic imaging agents. He maintains strong academic ties, including an appointment as Adjunct Associate Professor of Pharmaceutical Chemistry at the University of Kansas in 1992, and serving as a reviewer for the International Journal of Pharmaceutics, Journal of Pharmaceutical Sciences, and Drug Development & Delivery.

SPECIAL FEATURE

Biologics, Self-Administration & Patient Adherence: Creating a Lucrative Hand-Held Injection Market

By: Cindy H. Dubin, Contributor

Rapid enhancements in drug discovery technologies, leading to developments in proteomics and genomics, have had a great impact on the injectable drug delivery market in the past decade. Going forward, the number of injectable drugs to be introduced in the medium- to long-term future is expected to be significant.[1]

Innovation in the injectable market has contributed to advancements in injector design, convenience, and painless injection. For drugs developed for self-administration, autoinjectors have been shown to provide a more user-friendly package and improved compliance. While autoinjectors are sometimes designed to work with a particular injectable product as a form of pharmaceutical branding, the typical autoinjector is designed to fit one or more standard sizes of prefilled disposable syringes. Until recently, autoinjectors were designed to be reused. The reason was that the injectors were too expensive to be successfully marketed as a throw-away device. Recent improvements in materials technology and device design have led to the creation of a class of autoinjectors that can be made economically in high production quantities, opening the door for the disposable autoinjector, and providing expanded opportunities for both patient and drug marketer.

The past decade has also seen a significant shift in terms of the types of approved injectable drugs, the diseases they target, and the devices used to deliver them. As a result, the injectable drug segment has seen a marked increase in the level of drug/device integration. And as prefilled syringes and specialized injection devices proliferate in response to safety and economic challenges posed by recombinant protein drugs, administration of injectables has moved increasingly from practitioner offices and healthcare facilities to patient homes.

FIGURE 1

BD Soluvia™ helps ensure accurate delivery into the dermal layer irrespective of age, ethnicity, gender, and body mass index.

The market for prefilled syringes has achieved positive growth in recent years. In 2009, an estimated 2 billion prefilled syringe units were sold, and the market for that technology was estimated to be worth up to $2.5 billion, forming one of the fastest-expanding sectors in the pharmaceutical industry.[2] Due to the expanding use of biologic drugs and vaccines, worldwide prefilled syringe technology market revenue is expected to reach $3.9 billion in 2015.[3]

The market for macromolecule biologics, which must be injected, is growing at more than 10% per year and will account for almost 20% of all global drug sales by 2015. Thus, the pharmaceutical market for injectable drug delivery devices is projected to double in size from $15 billion to $30 billion between now and 2015.

Expansion of the prefilled syringe market will depend upon developments in syringe technologies and materials. Improvements to performance, product stability, convenience of use, and cost effectiveness will stimulate increasing use of prefilled syringes and related devices this decade.

BD MEDICAL–PHARMACEUTICAL SYSTEMS: NEEDLE TECHNOLOGIES THAT IMPROVE PATIENT CARE

The market for hand-held injections is quickly changing, and solutions for drug delivery must evolve along with market need. BD Medical-Pharmaceutical Systems is addressing that need by providing customized injection solutions to serve many therapeutic areas. Designed with the healthcare worker and patient in mind, and serving diverse settings, such as hospitals, clinics, and the home, BD's solutions for primary packaging, delivery devices, and needles can be customized for optimal usage to ensure quality patient care.

Important considerations for delivery device selection are evolving. Human factor requirements are becoming more stringent; pharmaceutical companies are being pushed to show that end users can safely use increasingly complex delivery devices. Once a "nice-to-have," input on device designs by ergonomics experts is now required. Due to the internet and social networks, patients are now better informed about their disease states, and their collective voice is being better heard by pharmaceutical companies and device manufacturers. As branded therapies near the end of their exclusivity periods, drug manufacturers are beginning to seek differentiation via more convenient delivery methods. The age of blockbuster drugs is coming to an end, but strong revenues are still needed to fuel the development of innovative drugs; therefore, patient adherence to therapies is increasing in importance.

BD serves the new needs created by these trends. Patient and/or healthcare worker usage settings are extensively studied to create devices that deliver therapies consistently and safely. When it comes to delivery devices, BD works with customers to test the full system for integrity, from manufacturing to filling, assembly, shipping, storage, and delivery. Testing services offered through the BD Sensitive Drug Initiative℠ give pharmaceutical companies confidence they are selecting the right system components to protect and deliver their drug.

FIGURE 2

Bioject will be producing its Intradermal Pen to reduce risks associated with needle reuse and needlestick injuries in developing countries.

One critical, but often overlooked, factor in selecting a delivery system is the needle. As the primary conduit for drug delivery and standard point of contact with the patient, needles can have a profound effect on the patient experience. Megan Lan, Senior Product Manager for BD, says that needle design can affect the patient's perception of pain, or even the force required to complete an injection. In fact, market feedback suggests that the right needle technology can increase patient adherence and improve the overall injection experience.

BD is continually improving upon needle technologies for its hand-held injection devices. For example, the newly launched BD Ultra-Fine™ Nano pen needle is simplifying injection techniques for many diabetic patients. The BD Ultra-Fine Nano, a 4-mm 32-gauge pen needle, is the shortest and thinnest pen needle available and allows patients using insulin pens to inject without pinch-up. As a result, patients have greater flexibility in rotating their injection site, especially in areas such as the back of the arm that are hard to reach when using two hands. Clinical studies have shown that test subjects rated the BD Ultra-Fine Nano as less intimidating and less painful.

BD is also improving the injection experience for patients with chronic diseases who require biotechnology drugs that are administered using prefilled syringes. The BD special thin wall needle offered with the BD Hypak™ for Biotech glass prefillable syringe was developed in anticipation of the increasing number of highly viscous molecules in the biotech pipeline. The increased inner diameter of this 27-gauge needle enables injection of highly viscous molecules without using a thicker needle that could be more painful for the patient. The increased inner diameter also minimizes the pressure required to inject, which is critical for patients with dexterity limitations.

Anecdotal evidence suggests that advanced needle technologies can help patients adhere to their treatment regimens. BD Physiolis™ glass prefillable syringes feature a 29-gauge thin wall 5-bevel needle point geometry with a special needle shield formulation designed to maintain needle integrity. This combination of needle and needle shield technology has been clinically proven to reduce the patient's pain perception and penetration force. BD Physiolis has been marketed by multiple biopharmaceutical companies with drug therapies treating self-injecting multiple sclerosis patients.

According to Chris Del Guidice, Product Manager for BD, follow-up clinical studies performed by those companies have supported the stated benefits of BD Physiolis, and market feedback suggests this technology has led to improved patient adherence.

In the clinical setting, BD needle technologies are helping healthcare workers perform intradermal (ID) injections consistently. Historically, ID injections have not been widely used because the classical technique, Mantoux, is difficult to perform consistently by healthcare workers. To address this issue, BD developed BD Soluvia™, a

FIGURE 3

Haselmeier's i-pen is used worldwide for delivery of insulin and other biotech products.

safety-engineered ID injector featuring a 30-gauge, 1.5-mm microneedle. BD Soluvia helps ensure accurate delivery into the dermal layer irrespective of age, ethnicity, gender, and body mass index (as demonstrated in clinical studies).

BD has gained a deep understanding of patient needs when it comes to the hand-held injection experience. Armed with this understanding, BD continues to develop a broad array of clinically proven needle and drug delivery technologies to help many patient populations, including those with diabetes, auto-immune, and neurological diseases.

BIOJECT: THE POSSIBILITIES OF NEEDLE-FREE INJECTION

It is estimated there are more than 20 billion injections administered worldwide. While most are still given with a traditional needle, safety syringes and pen injectors represent a growing share, indicating a movement toward safer and easier-to-use alternative delivery systems. As needle-free represents the smallest share of the market, it is believed it has the most potential for growth and expansion, especially with newer and more technologically advanced options becoming available, such as Bioject's Iject®, Jupiter Jet™, and Bioject® ZetaJet™.

"Bioject has established a leadership role by providing a range of needle-free injection devices, all using our patented pressure profile," says Ralph Makar, RPh, MBA, President and CEO of Bioject Inc. "We have gas-powered devices that can deliver up to 1 mL (Biojector® 2000) and spring-powered devices that deliver between .05 mL and 0.5 mL (Bioject ZetaJet). In addition, we have other investigational devices, such as a single-use, prefilled, needle-free disposable device (Iject), as well as a device that can deliver multiple smaller volume injections to the same individual (Jupiter Jet). We also offer a needle-free vial adapter for use when reconstituting lyophilized powers for injection."

Mr. Makar says that one of the important differentiators for Bioject is that it has a range of published data and an extensive volume of clinical studies and experiences with many different public and private organizations. Bioject's involvement in so many clinical trials has led to an understanding of how its technology can deliver biologicals, proteins, vaccines, and other injectable agents. While Bioject is focused on needle-free injection technology, the company competes with other hand-held injection devices, including pen injectors and needle-syringe systems.

Earlier this year, Bioject announced a collaboration to provide a new needle-free pen injector for intradermal delivery clinical studies. Bioject will be producing its Intradermal (ID) Pen™–a disposable syringe jet injector (DSJI) for ID delivery–to the World Health Organization (WHO) and PATH, an international non-profit organization, to advance the use of DSJIs for use in developing countries, reducing risks associated with needle reuse, and needle-stick injuries.

Bioject's ID Pen spring-powered needle-free injector, currently under development and not yet cleared by the FDA, is intended to be used for intradermal injections for vaccinations and drug therapy. The system consists of a hand-held, user-filled device that incorporates single-use, auto-disable disposable syringes. The molded syringes have orifices about the thickness of a human hair, through which the liquid drug is forced into the skin. The ID Pen is designed to deliver 0.05 mL or 0.10 mL for each injection. The injector is entirely mechanical and is intended for administration by trained clinicians and properly trained users in the home setting. The ID Pen is intended to improve the safety and ease of ID delivery of vaccines and could enable immunization programs to stretch their vaccine supplies across a larger number of beneficiaries.

This collaboration is part of ongoing research by the Global Polio Eradication Initiative (GPEI) to prepare for the post-eradication era of polio, a disease slated for worldwide eradication in the near-term. For countries that perceive that the risks warrant continued immunization against polio after eradication, inactivated polio vaccine (IPV) is currently the only option with which to do this, and the GPEI is studying a range of approaches to establish affordable strategies for IPV use in low-income settings. WHO, PATH, and Bioject recently collaborated on a research study on fractional doses of IPV delivered intradermally using the Biojector 2000 to infants in Oman. The study results showed successful ID administration in addition to potential cost savings of the fractional dose when compared to the cost of full-dose vaccination using a traditional needle and syringe.

"The hope is this new device could make IPV affordable for developing-country use and stretch the limited supply of IPV, crucial for polio post-eradication planning. At the same time, it could go a long way to getting rid of needles altogether in routine immunization programs," says Dr. Rick Stout, Bioject EVP and Chief Medical Officer. "We believe that once this new needle-free intradermal pen is developed, it will attract the interest of other organizations and companies around the globe

seeking to leverage the significant benefits our delivery technology can provide to patients, healthcare workers, and organizations working with injectables, especially vaccines."

The Bioject ZetaJet is the device currently on the market, and the others could be on the market within 24 to 36 months, once a therapeutic agent is partnered. The needle-free Bioject ID Pen will be entering global studies shortly.

Bioject's target markets are chronic diseases or therapeutic treatment regimens in which multiple injections are needed daily, weekly, or monthly over several months to many years. Some significant injectable segments include vaccines, hematopoietics, anti-inflammatory, multiple sclerosis, human growth hormone, and fertility.

Going forward, Mr. Makar says that Bioject's greatest challenge is to ensure that it enters into the right long-term strategic partnerships. "We must focus on partnerships that aim to fully leverage the technology and capitalize on the opportunity at hand. Our long-term success depends on securing strategic partnerships that are aligned with the long-term interests of shareholders, in that they maximize the value for all partners in the relationship. How we overcome those challenges is to carefully establish the responsibilities of each partner in the strategic alliance and then commit appropriate resources and personnel to successfully meet our mutual objectives," he says.

HASELMEIER—SELF-INJECTION THAT IMPROVES PATIENT COMPLIANCE

If current trends continue, the CDC estimates that as many as 1 in 3 adults could have diabetes by 2050. With this increase in incidence and the growing number of pharmaceutical companies introducing injectable products for the control of diabetes, the need for pen injectors is expected to increase significantly. Further increasing the demand for pen injection devices is the increasing number of injectable biotech therapeutics and increasing acceptance of self-injection as convenient and cost effective by patients and providers.

FIGURE 4

SCHOTT InJentle™ offers improved drug stability and a gentle application. When the needle is on, the InJentle seal remains in the closed state. When the cap is removed, the seal opens.

Haselmeier is a leading provider of pen injection devices for self-administration and has been in business for more than 90 years. Its products include a range of pens injectors for fixed and/or variable dosing that are available in a reusable or disposable format. Its pen platforms feature patented technology, including manual and auto-injection designs.

During the last year, Haselmeier introduced the Axis-D and Axis-R pens systems featuring a sliding dose window designed to make reading the selected dose easier for the patient. Axis pens are available as a disposable pen–Axis-D or reusable pen–Axis-R.

Haselmeier also introduced i-pen^2 this year, which is an all plastic version of its metal i-pen, but provides customers more color and design options as well as the cost efficiency of an all-plastic device, says Robert J. Kilgore, VP-Marketing & Business Development, Haselmeier.

"The i-pen design has been well accepted by pharmaceutical companies around the world for delivery of insulin and other biotech products requiring a high quality reusable pen injector."

Looking ahead, Mr. Kilgore says that as the market for self-injection devices continues to grow, the need for increased testing and documentation has also increased. "Some of this is a result of increase regulatory review but it is also driven by pharmaceutical and device companies striving to ensure that patients receive a self-injection device that is accurate, easy-to-use and has a low potential for mishandling.

"Although these requirements have increased the time and cost to develop and market self-injection devices, it has also provided an opportunity for our project management team to communicate and work closely with our pharmaceutical partners," Mr. Kilgore continues. "The goal is to provide the best self-injection devise for the patient and the processes we have implemented ensure that this goal will be met."

Haselmeier will continue to focus on development and production of new self-injection devices as well as enhancing existing injection device platforms. "We will continue to focus our emphasis on patient needs and how to improve the self-injection experience of the patient, reduce potential errors and increase compliance," he says.

SCHOTT: COLLABORATION WITH PHARMA EQUALS SUCCESS

The market for hand-held injections is driven by various trends. In general terms, you can see a shift from multidose vials to single-dose applications. A side effect of this development is that more and more drugs previously packed in vials are now being delivered in syringes. Furthermore, there is a trend toward complete devices with needle protection, also driven by legislation to protect healthcare professionals, such as hospital staff from accidental needlestick injuries. Many countries have already introduced such legislation; others are expected to do so in the near future.

Continuous advancements in several therapeutic areas also foster a shift from in-patient hospital care to out-patient services and home care. This means that not only healthcare professionals are responsible for applying these therapies, but also an increasing number of patients. This trend leads to a growing demand for applications that are user friendly and results in higher demands on the packaging side.

SCHOTT offers a comprehensive product portfolio to the pharmaceutical industry that ranges from standard level up to tailor-made solutions for the highest requirements, all based on high-quality special glass tubing. This includes a wide selection of vials, insulin and dental cartridges for pen and pump systems, auto injectors and needle-free injections, and prefillable syringes of glass.

Furthermore, SCHOTT offers coated packaging solutions that address the specific needs of sensitive biotech drugs.

"The latter also represents the area where SCHOTT fits into the overall hand-held injection drug delivery market," says Christian Helbig, Product Manager Glass Syringes at SCHOTT Pharmaceutical Packaging. "Based on our long-term experience, we are able to provide our clients with customized products and solutions throughout the entire product life cycle."

SCHOTT InJentle™ is a prefillable glass syringe with an integrated needle designed to fulfill the high demands of storing and administering new and upcoming highly sensitive biotech drugs. It was developed in close cooperation with pharmacists and industry experts and offers a number of novel features for the benefit of highly sensitive drugs. During storage, the drug does not come into contact with the needle. This prevents sensitive drugs from interacting with the adhesive or the metal of the needle. The seal design prevents the drug from flowing into the needle until the very moment the syringe is opened, that is, when the needle shield is pulled off. A tamper-evident closure is integrated in the design of the syringe. As soon as the system is opened, this part will break and cannot be reconnected. This allows physicians or patients to determine easily whether or not a syringe has already been used.

SCHOTT InJentle was developed for the special need of highly sensitive drugs. The design prevents sensitive drugs from interacting with the adhesive or the metal of the needle, is completely tungsten free, and offers a protected needle that is not in contact with any materials until the injection. The new syringe also allows for the use of particularly thin needles of up to 32 gauge, which results in a reduction of pain for the patients during the injection. This especially meets the needs of upcoming biotech drugs, a market that is currently on the rise.

"It can be assumed that a number of new biotech drugs will be introduced within the next years. This will also include the manufacturing of large biomolecules with higher viscosities that are highly sensitive and therefore place specials demands on packaging. Providing safe and reliable packaging solutions for these expensive drugs therefore represents a market of the future," says Mr. Helbig.

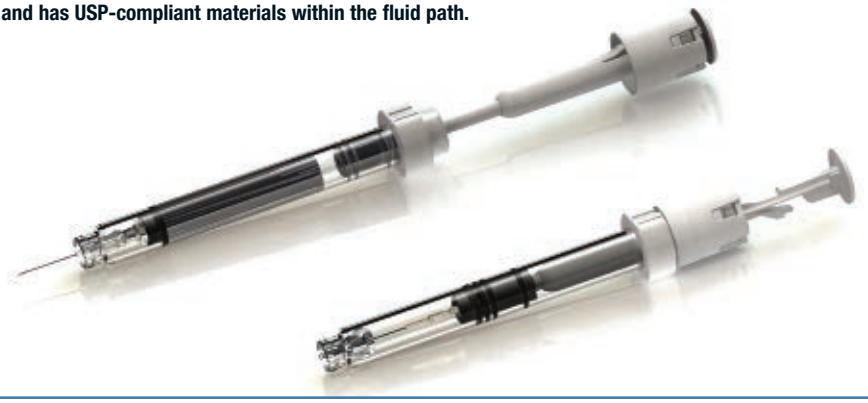
The requirements coming from the pharma market are very demanding and call for new and advanced solutions, he says. "Nevertheless, you have to take into account that changes in the pharmaceutical industry require a considerable amount of time. Extensive testing of new developments at pharmaceutical companies is required in order to reach market acceptance and usually takes several years. For supporting these processes, collaboration between packaging suppliers and pharmaceutical companies is important and a key success factor."

UNILIFE: CUSTOMIZED DELIVERY FOR HIGH-VALUE DRUGS

There are hundreds of injectable drugs within the development pipelines of top-tier pharmaceutical companies that are targeted for self-administration within highly specific patient populations. Unilife is being driven by the unmet needs of these customers to develop a rich and diversified portfolio of injectable drug delivery devices, all of which can be customized to address the specific molecular and patient requirements of injectable drugs.

FIGURE 5

The Unilife Unifill ready-to-fill (prefilled) syringe can be integrated into conventional fill-finish lines and has USP-compliant materials within the fluid path.



Unilife recently completed the commercialization of its lead product, the Unifill ready-to-fill (prefilled) syringe, and commenced shipments to a number of pharmaceutical companies. The "Unifill syringe is a game-changer in the prefilled syringe market," says Stephen Allan, Vice-President of Marketing and Communications, Unilife Corporation. It is supplied as per standard handling systems, can be integrated into conventional fill-finish lines, and has USP-compliant materials within the fluid path. Furthermore, it is intuitive for use by patients or healthcare workers and has a fully automatic needle retraction system that virtually eliminates the risk of needlestick injuries.

"Our Unifill platform of primary drug containers with integrated safety features has the potential to serve as a direct substitute for virtually every prefilled drug either on the market or in development," adds Mr. Allan.

Unilife has established itself as a company to serve the needs of pharmaceutical customers who require devices that can be customized for use with their high-value injectable drugs and vaccines. "We are fast gaining a reputation as the go-to company for pharmaceutical collaborations in the development of unique drug-device combination products that are supplied in either a liquid stable form or lyophilized for reconstitution," he says. "We recognize that pharmaceutical companies are seeking higher and higher levels of quality assurance and reliability from the primary drug containers and devices that they procure for use with their macromolecule biologics."

The Unifill syringe is now in production at Unilife's facility in York, PA, and is available for shipment to pharmaceutical companies seeking to initiate compatibility and stability studies with target drugs and vaccines. Independent evaluations of the Unifill syringe against current ancillary safety products used with prefilled syringes found an overwhelming preference amongst healthcare workers for its device. Unilife is developing several additional Unifill variants, including the Unifill Select with attachable needles of up to 1.5-in lengths that will be suitable for use with drugs administered via IM injection or supplied in a lyophilized form for reconstitution.

FIGURE 6

Both of West's proprietary technologies, ConfiDose® (left) and SmartDose® (right) are designed for a standard 1-mL syringe system.

Unilife now has multiple products across a number of significant device platforms within its development pipeline that are now being commercialized in collaboration with leading pharmaceutical partners. Some of these devices are scheduled to enter clinical trials with pipeline drugs throughout the coming year.

Mr. Allan says, "We look forward to playing a lead role in redefining the industry from a place of ridged commodity offerings into one led by innovation, customization and customer service."

WEST PHARMACEUTICAL SERVICES: UNDERSTAND RELATIONSHIP BETWEEN CONTAINER & DELIVERY SYSTEM

West has a history in primary container closure and delivery components and systems. Throughout the past few years, West has focused on prefillable syringe systems for injection and has expanded its involvement in the field of delivery systems.

"While the company recognizes that it may be perceived as a new player, we know this field very well," says Graham Reynolds, Vice President, Marketing & Innovation, Pharmaceutical and Delivery Systems, West Pharmaceutical Services, Inc. "We manufacture injection devices and delivery systems for other companies, including diabetes pens, autoinjectors, and other injection devices."

In the past few years, West has also developed proprietary systems. The ConfiDose® autoinjector system, designed for a standard 1-mL syringe system with a fixed needle, is compatible with glass and plastic syringes, including the Daikyo Crystal Zenith® insert needle syringe. In the past year, West completed validation on the ConfiDose autoinjector system, so the product is now available for customers' stability testing/trials.

West also offers a system for delivery of higher volumes of drug through an electronic patch injector, the West SmartDose® system. This technology is complementary to a system for a 1-mL syringe-based dose in that it is based on a Daikyo Crystal Zenith container that enables customers to develop a unique system that can fit into the patch injector. SmartDose attaches to the body, can be programmed at the factory with different doses and dose rates, and can deliver volumes in excess of 1 mL.

"SmartDose is the result of a 2-year co-development program with the innovators of this technology, and we are ready to support customers' early phase evaluation of this system through active scale-up and validation programs," explains Mr. Reynolds.

He is confident the ConfiDose autoinjector system and the SmartDose electronic patch injector system will quickly and easily fulfill current market needs. "We're finding that many of the newer biologics are more viscous than typical drugs. Pharmaceutical companies producing such

FIGURE 7

The Ypsomed ServoPen's spring-assisted injection mechanism provides a short activation distance and minimizes injection forces for the patient.

products must determine packaging based on ease of use and patient demand. This can lead to efforts to compound the drug to a 1-mL dose, which would allow hand-held injection, but requires the product to be of a high molecular weight, affecting the performance of an autoinjector system. The other option is to deliver a larger dose, which requires dosing over a longer period of time and the need for a delivery system that can attach to the body and deliver a dose more slowly."

ConfiDose, when used with a Daikyo Crystal Zenith cyclic olefin polymer syringe system, can overcome many of the issues that may occur when glass systems are combined with viscous products. The Crystal Zenith syringe mitigates issue of breakage, delamination, and glass particulate, while the ConfiDose autoinjector is designed to minimize the force an autoinjector places on a syringe system's weakest areas. And, the SmartDose system can be easily tailored to a specific patient's needs, and through the use of Daikyo Crystal Zenith prefillable cartridges that can hold larger doses than a syringe system, is suitable for high-viscosity drugs.

West's main focus is the autoimmune arena, which includes therapies for rheumatoid arthritis, Crohn's disease, and lupus. "There are a variety of drug products currently on the market and in development for the treatment of autoimmune diseases, and we focus our efforts on working with major biotech companies who have developments in this area," says Mr. Reynolds. "Working together allows us to understand the needs of the key decision-makers, which can be technical in terms of manufacturing convenience and being able to fill a container effectively and ultimately the needs of the patient."

One of the main challenges to hand-held injection delivery is developing a system that not only meets the needs of the patient in that it is simple and easy to use, but also serves to mitigate the challenges associated with the drug product, such as viscosity and dose volume. West has met those challenges by providing a range of solutions to its customers and combining them with Daikyo Crystal Zenith cyclic olefin polymer products to create a suitable and unique container closure or delivery systems.

"Customers rely on our expertise to help design a system and on the manufacturing experience and excellence of our many global facilities to deliver a high-quality product that will help to ensure compliance, mitigate risk, and provide safety and ease of use to the patient," says Mr. Reynolds.

West is placing increased emphasis on understanding patient needs through various studies and research that will help optimize the design of West's devices to ensure they are more in line with patient needs. According to Mr. Reynolds, West recognizes the significant manufacturing challenges pharmaceutical companies face to ensure systems can be filled and validated.

"We also understand the interaction between the container and the delivery system, which ensures our customers have a partner who can create systems that not only meet the needs of the drug from development through commercialization, but also provide the patient with a safe, easy-to-use solution."

YPSOMED AG: FOCUSING ON SELF-INJECTION & CONVENIENCE

The self-injection market continues to develop in terms of platform technologies and grow significantly for insulin pens, non-insulin pens, and monodose devices, such as autoinjectors for biologicals. Pharma companies are starting to embrace the full "scale of convenience" of prefilled syringe-based devices from safety syringes to full feature autoinjectors, and there is increased interest in patch-injectors for short bolus infusions greater than 1 mL in volume.

"Ypsomed is active in all of the aforementioned areas with a full range of insulin pens, pen needles, dual-chamber devices, and disposable autoinjectors," says Ian Thompson, Vice President Business Development, Ypsomed AG.

An important milestone for the company in the past year was the launch in China of the newly developed ServoPen® reusable insulin pen in collaboration with Tonghua Dongbao, a leading pharma company and insulin manufacturer in China under the Gansulin® Pen brand. The ServoPen's spring-assisted injection mechanism provides a short activation distance and minimizes injection forces for the patient. Other features, such as the customizable light-weight aluminum housing, retractable piston rod, and easy cartridge changing, set new standards in insulin therapy in terms of patient convenience and user friendliness, says Mr. Thompson.

Ypsomed is focusing on the range of self-injection devices and is industrializing the following devices, which Mr. Thompson say will be introduced for clinical trials and commercial products throughout the next few years: the YpsoPen® Twist reusable value insulin pen, UnoPen™ disposable insulin pen, a range of LyoTwist™ dual-chamber cartridge devices compatible with the Clickfine® AutoProtect™ safety pen needle, and the YpsoJect® and YpsoMate® disposable autoinjectors. These devices will be targeted

for drugs in a range of therapeutic areas, including diabetes (insulin and GLP-1), growth disorders (hGH), fertility treatment, autoimmune diseases, and cancer therapies.

YUKON MEDICAL: A FOCUS ON LYOPHILIZATION

With the growth in the generics and biologics markets and the desire to allow patient administration in the home, the need for improved hand-held injection devices will continue to grow. As these devices continue to move into the home, safety features and ease of use will become increasingly important, so there are tremendous opportunities for advancement in delivery systems to better serve the various patient populations.

Yukon Medical is focused on point-of-delivery drug reconstitution systems, offering several devices that allow pharmaceutical companies to use standard glass drug vials, reducing the time to market. Each device has been designed with features that reduce the number of "steps to inject," minimize drug waste, or protect users from toxic vapors.

"We specialize in areas where a prefilled syringe or injector pen may not be the appropriate or complete delivery system for any one of variety of reasons," says Todd Korogi, President and CEO of Yukon.

Yukon is currently customizing its SmartMix™ delivery system for several pharmaceutical companies. SmartMix allows for one-step reconstitution using standard glass drug vials. This will enable pharmaceutical companies to reduce time to market and development costs while allowing non-clinicians to self-administer their medication.

When it comes to SmartMix, Mr. Korogi says that sterilization has been the biggest challenge.

"Some customers have asked us to allow the device to be terminally sterilized with steam or Ethylene Oxide, while others do not believe their product will be able to withstand terminal sterilization. We had to design SmartMix using materials that are medical grade, relatively inert, able to withstand a variety of sterilization processes, and still meet the performance requirements. We have also designed the product to allow users to load the lyophilized drug vial into the device for those cases in which the drug is not able to withstand terminal sterilization."

To date, Yukon has several products in development at various stages. Some products will be commercialized this year and others are being evaluated in trials next year. For example, the company expects to launch the Arisure™ Closed Medication System (for oncolytics, some antibiotics, and other medications that are considered hazardous to handle) and the ViaLok™ non-vented vial adapter later this year.

"We will be expanding our Arisure product line, leveraging new and existing technologies to reduce steps for users, improve safety, and allow more medications to be administered by patients," says Mr. Korogi.

Yukon Medical has recently partnered with a leading manufacturer of drug delivery components based in Europe, which Mr. Korogi says will allow Yukon to provide high-quality and precise device manufacturing at a reasonable price. ◆

FIGURE 8

Yukon Medical's SmartMix™ (top left), Arisure™ Closed Medication System (center), and ViaLok™ vial access devices (top right) all represent the company's focus on point-of-delivery drug reconstitution systems.

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Outsourcing Trends

Contract Research Outsourcing Market: One of the Fastest Growing Segments in the Pharmaceutical/Biotechnology Industry

By: Frost & Sullivan Industry Manager Jennifer Brice and Senior Industry Analyst Barath Shankar Subramanian

Contract Research Organizations (CROs) provide independent development services for pharmaceutical and biotechnology markets. Services offered by CROs have evolved from providing basic support services initially to providing a wide range of clinical, central lab, and analytical services that presently suit the demand of the market and the sponsors.

The Unites States continues to remain the world's largest market for drugs, accounting for nearly 50% of research and development (R&D) spending in this industry. The US market has invested in new facilities and technologies to cater to a wide range of sponsors.

CROs have also expanded globally to a large extent and account for more than two-thirds of all Phase I through Phase III trials worldwide. The rising cost of drug development and stringent regulatory guidelines have been major drivers for outsourcing of drug development by pharmaceutical and biotechnology companies. While the cost of a new drug on average was $138 million from conception stage to Food and Drug Administration (FDA) approval in 1975, the average development cost had risen to approximately $800 million by 2000 and more than $1.4 billion by the end of 2010.

Clinical trials have become significantly more expensive than preclinical testing largely due to the high cost of recruiting patients with chronic and degenerative diseases and the risk of drug failure in providing desired efficacy and safety. The CRO market is one of the fastest growing segments in the pharmaceutical and biotechnology industry. In 2010, revenues for the US CRO market were $1.14 billion, an increase of 8% over the previous year, growing at a compound annual growth rate (CAGR) of 8.4% from 2010 to 2017. Revenues are expected to reach $2 billion in 2017.

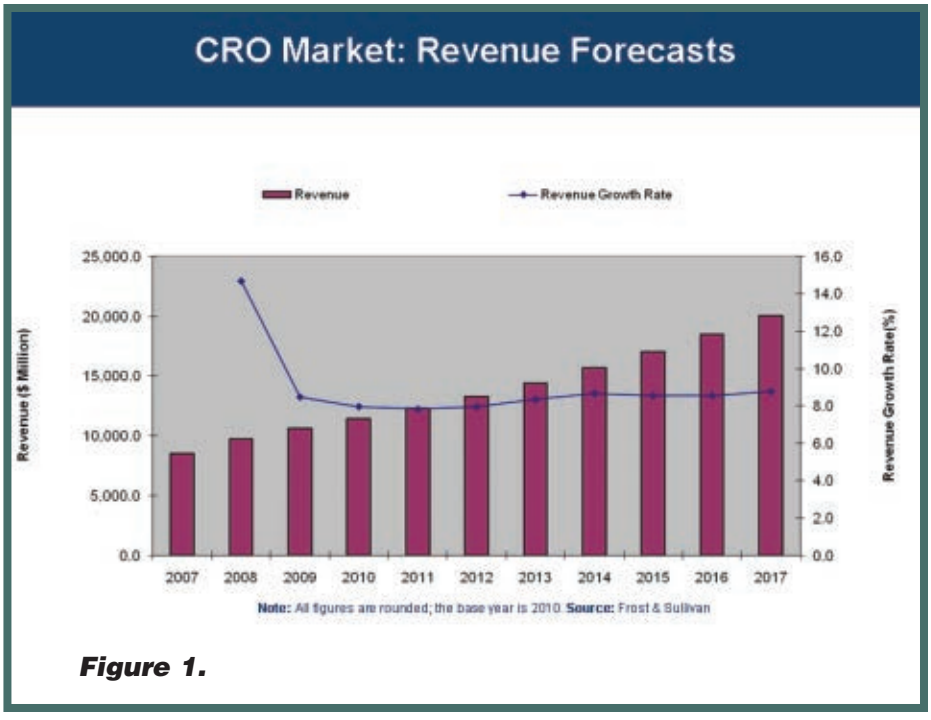

Figure 1.

Competition remains high in this growing market. CROs continue to look for new growth and expansion opportunities, while pricing pressure continues to remain a major factor that is affecting profitability. The economic recession has caused R&D cuts,

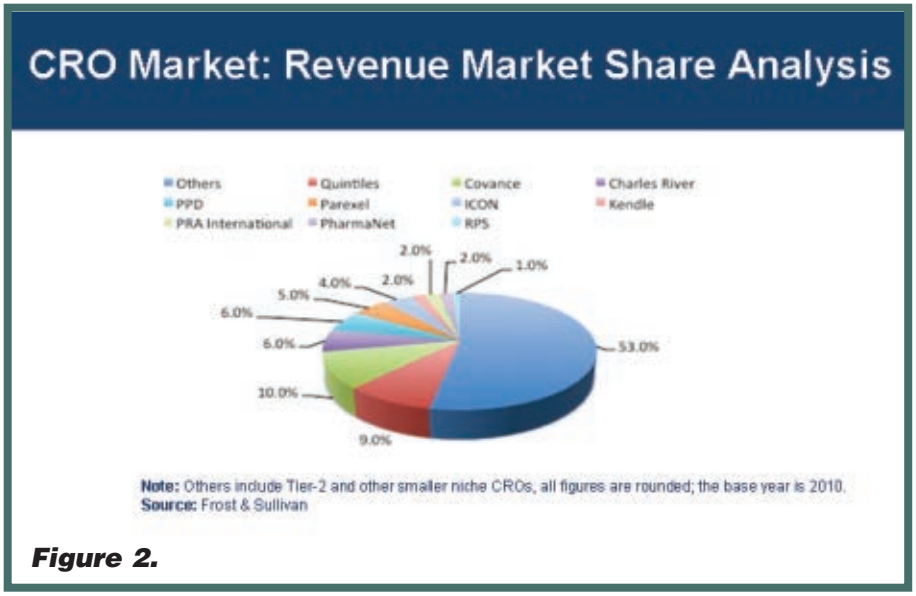

Figure 2.

causing a major impact on the CRO market.

The R&D cuts have also been beneficial to CROs as sponsors prepare to outsource more in the mid- to long-term. Tier-1 CROs continue to differentiate by expanding their offerings on a global scale.

Healthcare reform is also expected to benefit the CROs in the mid- to long-term. The proposed reform has expanded coverage to an additional 30 million plus individuals who can participate in clinical trials. CROs are also well positioned to conduct comparative effectiveness research (CER) as well as trials for biosimilars. These could be potential growth and expansion opportunities for CROs.

The top 10 market participants account for 47% of the revenues in 2010, down from 53.4% of the US CRO market revenues in 2007. The fall in market share could be attributed to the following factors:

- Expansion and increase in global trials conducted by top market participants that have resulted in lesser revenue share from the US.
- Increase in revenue contribution and business from other global regions for top CROs.
- The Tier-2 participants have outpaced the top tier CROs in volume growth, which has resulted in the decline in revenue market share of the top tier CROs. Tier-2 and Tier-3 CROs have less exposure to global businesses compared to Tier-1 CROs, which also contributed to the skewed growth.
- Covance continues to remain the market leader in the US CRO market with 10% percent share of revenues in 2010, although its share has fallen from 11.8% in 2005. Quintiles follows as the second largest, while Charles River and PPD are tied for third largest CROs in the US CRO market with revenue market shares of 9% and 6%, respectively.

The US CRO market is expected to rebound strongly in the mid- to long-term. The market is experiencing two-tiered growth from Big Pharma, which is outsourcing work to CROs to lower fixed costs, while biotechnology and specialty pharmaceutical companies outsource work to CROs due to the lack of infrastructure. Tier-1 CROs are making a shift toward pursuing long-term strategic alliances that are expected to benefit the market in the long-term in tiding over economic cycles and market volatility. Global expansion will continue to remain an area of top priority for Tier-1 CROs. ■

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Jennifer Brice currently serves as Industry Manager, Pharmaceuticals/Biotechnology at Frost & Sullivan in North America, Mountain View, California, where she devises strategies and leverages resources to deliver projects in an efficient manner from initial design to implementation. Ms. Brice has a strong ability to train, advise, and supervise analysts on project material and provide strategies for collecting primary and secondary information, as well as manages and executes quality control activities to ensure client deliverables meet top standards. Her industry expertise includes a strong network of key opinion leaders and senior executives within the pharmaceutical/biotech segments and an experience base covering a broad range of sectors within the life sciences space, including infectious diseases, biosimilars, rheumatology/inflammatory diseases, and ophthalmology. Previous experience includes both operational and project management roles in a consulting firm focused on the life sciences industry and Senior Analyst/Operations Manager at CIS Life Sciences/Business Research Group (now Prescient Life Sciences) in Mt. Olive, NJ. Ms. Brice earned her BSc from Ramapo College and her mini-MBA from Rutgers University.

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Clusters' Last Stand?

By: Andrew MacGarvey, Commercial Director & President of US Operations, Quanticate

Introduction

Pharmaceutical and biotech companies are most definitely at the pinnacle of success when they are highly innovative. The development of new medications that can work toward solving current health issues is not only critical for a pharma company's success but has the potential to make an impact into the lives of the general population. This is why advancements in drug development are vital.

Clusters of businesses in the biotech community have existed for many years, notably in Cambridge, MA, along with several other locations in the US and throughout the world. While this has been a boon for the human resources teams at the headquarters of these pharmaceutical and biotech companies, it is not necessarily in the best interest of the company as a whole, due to the innovation challenge it presents.

Challenges in Pharma & Biotech: The Innovation/Productivity Paradox

The problem of diminished pipelines for pharmaceutical and biotechnology companies is very much in the news at the moment. Many observers cannot remember a more turbulent environment in the drug development sector. The major players are scrambling to reorganize their businesses to refocus on discovery and are displacing thousands of jobs as they streamline portfolios. There are a number of factors behind this state of affairs, including the rising cost of drug development, the drive to treat rarer diseases, and biopharm's place in the global economy. To the latter point, the sector had been largely immune to recessionary economies, but the scale of the most recent global financial crisis created problems for even the largest pharmaceutical companies. It may appear difficult to identify positives for biopharm now; the sense is of companies trying to survive in chaotic circumstances. In fact, this chaos may be the lifeline the sector is looking for.

The problem for biopharm is that it is operating in an innovation/productivity paradox. Put simply, the investment in research and development is increasing, and the number of new drugs is decreasing. Those charged with bringing new drugs to market are struggling to innovate. At this point, it is worth stressing that innovation is not the same as invention. For a product to be innovative, it must return some value. In the case of biopharm, the reality is that the product must return profits. This dynamic constrains innovation because the profit imperative compresses the "space" to make mistakes. The freedom to make mistakes, learn from them, and move on is critical for innovation to thrive. Any constraints that firms apply in the discovery context will reduce innovative activity. Whether these are financial in nature or a restriction on technology or focus on a particular therapy, setting parameters brings increased order. They diminish the chaos that innovation requires. Scholars, such as Kimberly Boan and Ysanne Carlisle, have described the need for firms to operate "on the edge of chaos" to deliver innovation. I recommend readers interested in exploring this concept more deeply to read some of their work.

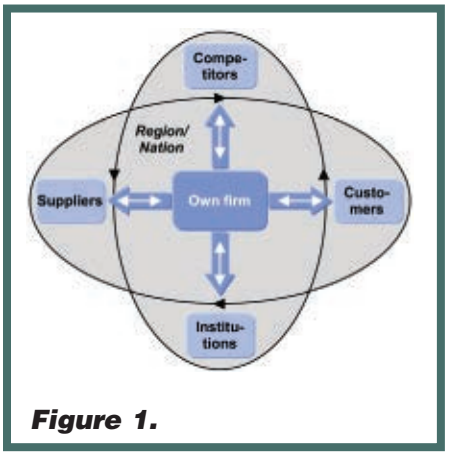

Figure 1.

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Biotech CEO Panel, Emerging Biotech Perspective on Delivery Needs & Challenges
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Controlled Release Technologies
Pfizer Global R&D

Disruptive Technologies Panel
Alcyone Lifesciences, Inc. • Novartis Pharmaceuticals • SR One Ltd. • US CEEDD, GSK

Targeted Drug Delivery
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Specialty Pharma Panel
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Figure 2.

Knowledge Spillover in Business Clusters

So, you may ask, what is a cluster, and what does the aforementioned have to do with clusters? A cluster is a way of organizing a group of competing companies in geographic proximity to one another. Perhaps the most well-known clusters in the drug development world are the biotechnology clusters in Cambridge, MA, and San Diego, CA. There are further clusters in Scandinavia and throughout Europe, and new clusters are appearing in the Asia Pacific region.

The concept of clusters is not new. Celebrated economist Alfred Marshall discussed the benefits to companies of operating in geographic proximity as early as 1890, but it was much later in the late 1980s and 1990s that Michael Porter brought the concept back into popular management theory. Researchers have studied clusters in detail and have settled into two schools of thought.

The first group extols the benefits of operating in the cluster model. They perceive the phenomenon of "spillover" to be highly beneficial. Spillover occurs when one firm in the cluster can leverage a resource available at one of its neighbors. A great example of this is knowledge spillover. Knowledge gained in one company can be accessed by others through local networking events (be they formal or social) or by hiring their new staff from them. The knowledge does not necessarily need to relate to intellectual property, indeed on most occasions transfer of this knowledge will be limited contractually. Rather a person operating in a similar company in the same geography will bring useful procedural knowledge to the hiring firm.

In contrast, the second group believes the number of relationships a company has is more important than proximity of links. They cite an increasingly sophisticated telecommunications infrastructure and the shrinking of the world through affordable air travel as nullifying the competitive edge gained by companies choosing to operate in a cluster.

Whoever is right, clusters remain popular. Governments in many regions have used grants and tax breaks to encourage inward investment by firms into designated regions. As the recent financial crisis began to bite, many firms chose to take the incentives; this was particularly true for biotechnology companies. I believe this trend was a major contributor to the innovation/productivity paradox.

Risk & Benefit of Clusters

Pharmaceutical companies have been aware of the "patent cliff" for some time; they have realized they cannot sustain the blockbuster model through the traditional small molecule approach. Their hopes were pinned on the new technologies offered by biotechnology companies. Unfortunately, the biotechnology sector has been among those most affected by the recent financial crisis. As investors have grown more cautious and liquidity has become scarcer, investments in biotechnology firms have fallen significantly.

Drug development is not a good match for venture capital. The cost of developing a drug is very high, the process is lengthy, and the risk profile is prohibitive. This challenge has driven many firms to the safety of a cluster environment, where they have gratefully received grants, tax breaks, and even free accommodation as they have sought to minimize their cash burn rate.

While clusters provide many benefits to those companies that choose to operate within them, my view is that those same benefits can also harm innovation. I question whether operating in a cluster is the right decision for a drug development company, or indeed any knowledge-based organization. Access to suppliers, the power of group-buying syndicates, the ability to hire qualified staff without relocating them, and the political strength in numbers are all useful attributes for those in the cluster. But at what cost?

When a firm joins a cluster and begins to leverage knowledge spillover, the environment restores an element of order to the system. An example of this might be the head of discovery moving from one company to another and imposing similar standard operating procedures at the new company. In this example, prior to the move, two groups might have tackled a problem in different ways; now they may try to tackle it in the same way. This problem has the potential to arise in similar situations as staff at various levels move from company to company. Staff exacerbate the problem as they move to their third or fourth companies. Of course, this situation could just as easily occur when a person moves from one country to another; the difference in the cluster is that other factors increase the risk. For example, where a head of discovery moves within a cluster, the risk that their members move too is higher compared to the same person undergoing an interstate or inter country move. Furthermore, local networking events and presentations could lead to certain approaches being implemented across the cluster and becoming the "norm." As staff move between companies, these organizational routines become embedded across multiple firms, and those with new ideas can find it difficult to get them adopted.

Operating on the Edge of Chaos

An ordered approach to business drives the benefits derived by members of a cluster but can have downsides. Group-purchasing schemes increase purchasing power but limit the number of vendors in the value chain. Membership of local trade groups aligns the political views of those members but can stifle change just as easily as promote it. Joint presentations at funding events brings access to money but does introduce the members to the same potential funders. While order might be useful in terms of how easy it is for smaller firms to do business, it is not useful in helping them to innovate.

Researchers have identified that two domains of knowledge are important in stimulating innovation. They are technologically distant and geographically distant knowledge. The best example of technologically distant knowledge was probably the introduction of biotechnology techniques into a pharmaceutical-based world. The geographically distant domain is interesting; there is research that suggests introducing team members from geographically distant companies can increase innovation but that there is a limit. Studies reported that an interstate move within the US could increase innovation, but an international move could hinder innovation. The researchers attributed the results to cultural differences overriding the innovation benefit. We are back to Boan and Carlisle; managers need to "dance at the edge of chaos" to achieve innovation. If the environment is too chaotic, innovation will not thrive either.

Clusters have a place in the commercial world; I am just not sure they have a place in drug discovery. They encourage those that work within them to move away from the edge of chaos and toward an ordered environment. It is interesting to note that biotechnology firms seem to attract more investment if they sit in a cluster because the venture capitalists perceive the risk to be lower. Both government and the investment community want new drug development companies to succeed, yet both may be setting them up to fail. ■

Authors' suggested further reading:

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3. Marshall A. Principles of Economics. London: Macmillan;1890.
4. Porter ME. Clusters and the new economics of competition. Harvard Business Review. 1998;76(6):77-90.

Andrew MacGarvey, MBA

Commercial Director & President of US Operations
Quanticate

Andrew MacGarvey is the Commercial Director of Quanticate, a global Clinical Research Organization (CRO) and the President of its US operations based in Cambridge, MA. He has worked in leadership roles as well as in a technical capacity for both statistics and clinical data management for IBAH (now Omnicare), Statwood, CroMedica (now PRA), and Datatrial. He is currently completing his DBA at Walden University, where he is researching the innovation/productivity paradox.

Executive Summary

Aris Persidis, PhD
President & Co-Founder, Biovista, Inc.

Biovista, Inc: Drug Indication Expansion & Adverse Event Profiling as a Viable Business Model

Biovista, Inc. is a privately held drug discovery company focused on systematically addressing drug efficacy and safety questions. It does so in a way that is mechanistically rational, faster and less expensive than current drug development approaches. With patent expirations looming for many major pharmaceutical companies, Biovista's efforts help its partners by shortening the time it takes to move a new compound from bench to the clinic. A major added benefit is it also helps to immunize a company's pipeline against competitors who enter the same space by proactively identifying alternate indications and securing patent protection before competitors. To accomplish this goal, Biovista developed its proprietary platform, the Clinical Outcome Search Space (COSS), which is capable of matching the mechanism of action of all approved drugs worldwide, plus all drugs in development and all publicly known pharmacologically acive compounds against the mechanism of action (MoA) of all diseases and adverse events known to modern medicine. Specialty Pharma recently spoke with Dr. Aris Persidis, President & Co-Founder of Biovista, who discusses how indication expansion (also known as drug repositioning) practiced in a rational and systematic manner generates a new kind of Intellectual Property (IP), innovation, market opportunity, market barrier, and competitor differentiation.

Q: ***What is Biovista's focus and how was its proprietary COSS technology developed?***

A: While a majority of drugs are developed for a single indication, there has been little systematic effort in the pharmaceutical industry to explore alternative indications for any given drugs, leaving drug pipelines at risk for competitor exploitation. Given this reality, there is a need in the pharmaceutical industry for the discovery and development of novel and non-obvious indications for already approved drugs. Over an 11-year period, our team developed a truly novel system and methodology capable of systematically addressing safety and efficacy questions in drug development in a way that is faster and less expensive than current standard practices. The COSS platform came to be the basis of Biovista's approach to indication expansion and adverse event (AE) identification. Based on all the experimental information available, COSS explores the variation of network biology across different organs and cells in the body and also across different patient groups.

Q: ***How is Biovista's approach to indication expansion and adverse event identification unique?***

A: Biovista's COSS platform approaches indication expansion in a systematic and rational way. It matches and ranks the mechanism of action (MoA) of any of the 90,000 drugs approved worldwide and pharmacologically active compounds in the public domain, against the MoA of more than 23,000 diseases and 6,000 AEs known to medicine. This technology represents an important advancement in terms of identifying and repositioning approved or development-stage drugs for new indications and predicting

their safety profiles. It does not use any preconceived filters or weights and thus has no bias, which together with its coverage of all possible clinical outcomes, makes it unique.

Q: ***How did Biovista develop its own pipeline of repurposed drugs?***

A: Biovista utilizes COSS to develop its proprietary pipeline based on discovering and validating new indications for approved drugs. BVA-101 has been identified as a potential treatment for progressive multiple sclerosis and epilepsy, and BVA-201 as a potential treatment for progressive multiple sclerosis. BVA-501 and BVA-701 have been identified as product candidates for melanoma, gliomas and thyroid cancer. Biovista intends to develop its pipeline through proof-of-concept clinical studies in humans, at which point it would likely seek licensing partners.

Q: ***How has Biovista's technology been validated?***

A: COSS, Biovista's proprietary technology, has been validated through the company's internal work as well as through its partnerships with the FDA and four of the top 10 pharmaceutical companies, most recently with Pfizer and Novartis. Biovista is collaborating with Pfizer to find new indications for several undisclosed compounds in Pfizer's pipeline. Similarly, Biovista is collaborating with Novartis to reposition undisclosed compounds in Novartis' pipeline. The company's collaboration with the FDA's Office of Clinical Pharmacology, within the Center for Drug Evaluation and Research, is to predict severe adverse events for drugs or drug classes of significant interest to the agency.

Biovista's ability to predict efficacy and safety has also been validated by successful in vivo and in vitro experiments, as well as extensive studies of the company's approach and its ability to predict drug safety and efficacy. Biovista can predict safety and efficacy outcomes with high levels of confidence, unlocking significant potential value in a compound.

Q: ***How does Biovista help major pharmaceutical companies as patent expirations loom?***

A: With patent expirations looming for many major pharmaceutical companies, Biovista's efforts help its partners by not only shortening the time it takes to move a new compound from bench to clinic, but also by immunizing company pipelines against competitors moving into their space by expanding the use footprint of a drug and securing patent protection before competitors. COSS is an important and timely drug discovery tool for major pharmaceutical companies as the industry struggles to maintain growth in the face of patent expirations of blockbuster drugs, declining productivity, or drug discovery and development efforts and a difficult regulatory environment with increased emphasis on drug safety. In addition, pharmaceutical companies must also be vigilant against "competitor adjacency" threats wherein a competitor seeks to secure intellectual property on new uses for the pharmaceutical company's own drugs.

Q: ***As large pharmaceutical companies are trending toward the reduction of internal R&D activity, how will Biovista's role be impacted?***

A: With pharmaceutical companies facing declining R&D activity due to increasingly high attrition rates and an increasingly scrupulous regulatory environment, Biovista can help extract additional value from a company's pipeline by discovering new uses for their approved or pipeline drugs, help gain insight into the safety profile of their drugs, and help pursue offensive and defensive "competitor adjacency" strategies.

The pharmaceutical industry is beginning to see the value of systematic drug indication expansion as a complementary activity in their portfolio development efforts. With indication expansion, companies can limit safety risks as the drugs that are selected have already passed toxicity and a number of other tests. Much more is already known about repositioned drugs' behavior than any new chemical entity or new biological entity. This is a significant development advantage since approximately 30% of drug failures in clinical trials are due to safety issues. With an already well-established safety profile, pharmaceutical companies significantly save on the developmental costs and more importantly, a patient whose current therapy is not working for them will not have to wait the 10 to 15 years it takes for a new drug to come to market.

Q: ***How does Biovista's COSS platform differ from other approaches to identifying and repositioning drugs for new indications and predicting their safety profiles?***

A: Indication expansion is approached in a variety of ways by pharmaceutical companies. Many companies, such as Pfizer, Novartis, and Bayer maintain internal units focused on discovering new indications for existing drugs in the internal pipeline. Others look to third-party groups to analyze targets and pathways for new effects, to be compared against potential indications of interest to the company. CROs and vendors are also a resource for companies seeking repositioning services. Lastly, pharmaceutical companies may serendipitously observe an effect during a clinical trial that is purely accidental, which can ultimately lead to a repositioned drug. Pfizer's development of Revatio as a heart drug, which ultimately led to the development of Viagra, is a perfect example.

Biovista's COSS platform acquires and correlates all of the target-based information and matches this against all diseases, AEs, and patient sub-populations. Prior to COSS, there was effort to develop a systematic and bias-free technology aimed at finding novel and non-obvious uses for existing drugs. It is now understood that unless a company has a systematic indication expansion effort, it is at risk for competitors to develop novel indications for the original company's drug, even if that drug is patent-protected. By utilizing its proprietary COSS platform technology, Biovista can immunize a partner's pipeline by identifying novel indications and securing patent protection before competitors.

Q: ***What are the Intellectual Property (IP) issues regarding repositioned drugs?***

A: When discussing IP challenges, it is important to determine the status of the drug in question. Are there new routes of administration that open up new potential uses? Is there a novel formulation that opens up new potential uses? It is important to note the various layers involved in drug indication expansion, combining reformulations, new use patents, or different routes of administration.

Companies can proactively protect and expand the IP footprint of their drugs by engaging in systematic and rational indication expansion. Additionally, a drug does not need to be a generic to be repositioned. Take the case of Enbrel for example. Enbrel, approved for use against rheumatoid arthritis (RA) and psoriasis, is an Amgen biologic; a TNF inhibitor. The drug's patents have not yet expired. Bioassets Development Corporation (BDC) repositioned Enbrel in sciatica, and Cephalon acquired the company to combine BDC's intellectual property with Cephalon's own pipeline of TNF inhibitors. This has effectively blocked other anti-TNF developers from entering the sciatica space. The Cephalon-Enbrel deal ultimately means that even if a pharmaceutical company has a drug with patent life, anybody can obtain new-use IP on that drug in a new indication. Also, if a company's discovery, pathway, and Bio-IT efforts have missed the new indication, they will be locked out of potentially excellent new markets and revenue streams. Essentially, a company's pipeline must be protected against competitors and Biovista offers the unique ability to systematically immunize companies' pipelines against these threats.

Biovista has filed new-use IP on more than 60 drugs targeting novel, high-value indications, such as oncology, inflammation, CNS, and neglected diseases.

Q: ***What does Biovista plan to accomplish over the next two years?***

A: Biovista is currently in discussions for potential collaborations with several pharmaceutical companies. Biovista would also like to work with decision-makers at several small, publicly traded biotechnology firms to collaborate on finding and proving new safe uses for their drug candidates. Biovista also seeks to work with investors in a company that has recently had a clinical setback who want to rescue their compounds by finding new uses.

Q: ***What is Biovista's background?***

A: The company was founded as a research project in 2000 by my brother Andreas and me. Andreas has a PhD in artificial intelligence, and I have a PhD in biochemistry. Biovista was founded as a way to apply artificial intelligence techniques to problems of life sciences, notably AE prediction and drug discovery. Formally incorporated in 2005, the company is headquarted in Virginia, and its technology and R&D teams are based in Athens, Greece. Biovista currently employs 12 full-time employees, including a core team of seven MDs and PhDs to guide its discovery efforts, and five consultants. ■

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Teachers

By: John A. Bermingham

One of this magazine's readers sent me a very nice e-mail last month informing me that he is a professor of both management and accounting at an area college and uses some of my columns in his teaching. He also invited me to speak at one of his classes, which I quickly accepted. This was a wonderful invitation as my next career goal is to teach at a college when I wind down my business career. That e-mail got me to thinking about how important it is for us to understand that everyone of us is a teacher.

Think about it. You teach your children about life beginning at an early age although they stop listening to you at about age 13. You teach your dog to sit, be quiet, and fetch. My wife taught me to do the same three things. Our dogs taught our cat to think that he is a dog so our cat acts like a dog. But that is as far as it goes for the cat because our cat does whatever else he wants to do.

Where most people do not think about teaching is in the business environment. Or they think about it but never do it. I didn't think about being a teacher in a business environment until many years ago when one of my direct reports, who was leaving the company, came into my office to say goodbye. He said all of the usual things, but at the end of our conversation, he said something that had a lasting impact on me. He said the number one thing he liked was how much he had learned from me.

I had never looked at myself as a teacher. I always looked at myself as a person working in a company trying to do the best job I could and that I had an important responsibility to the people who worked for me and those I reported to. Most people meet with their direct reports, assign projects and responsibilities, and then follow up on their progress. Although there may be some limited coaching and mentoring involved, this is not really teaching.

Let me provide an example. Years ago, one of our sales managers came to me one day telling me of a problem he was having in closing a deal with a large retailer to replace one of our competitors with our product line. Every time our sales manager negotiated with this buyer, it always came down to a price issue with the buyer demanding unreasonably low prices from us on our product line. Rather than just going through the mathematics of how far down in price we could afford to go, I instead asked this sales manager to spend a couple of hours with me working through this situation.

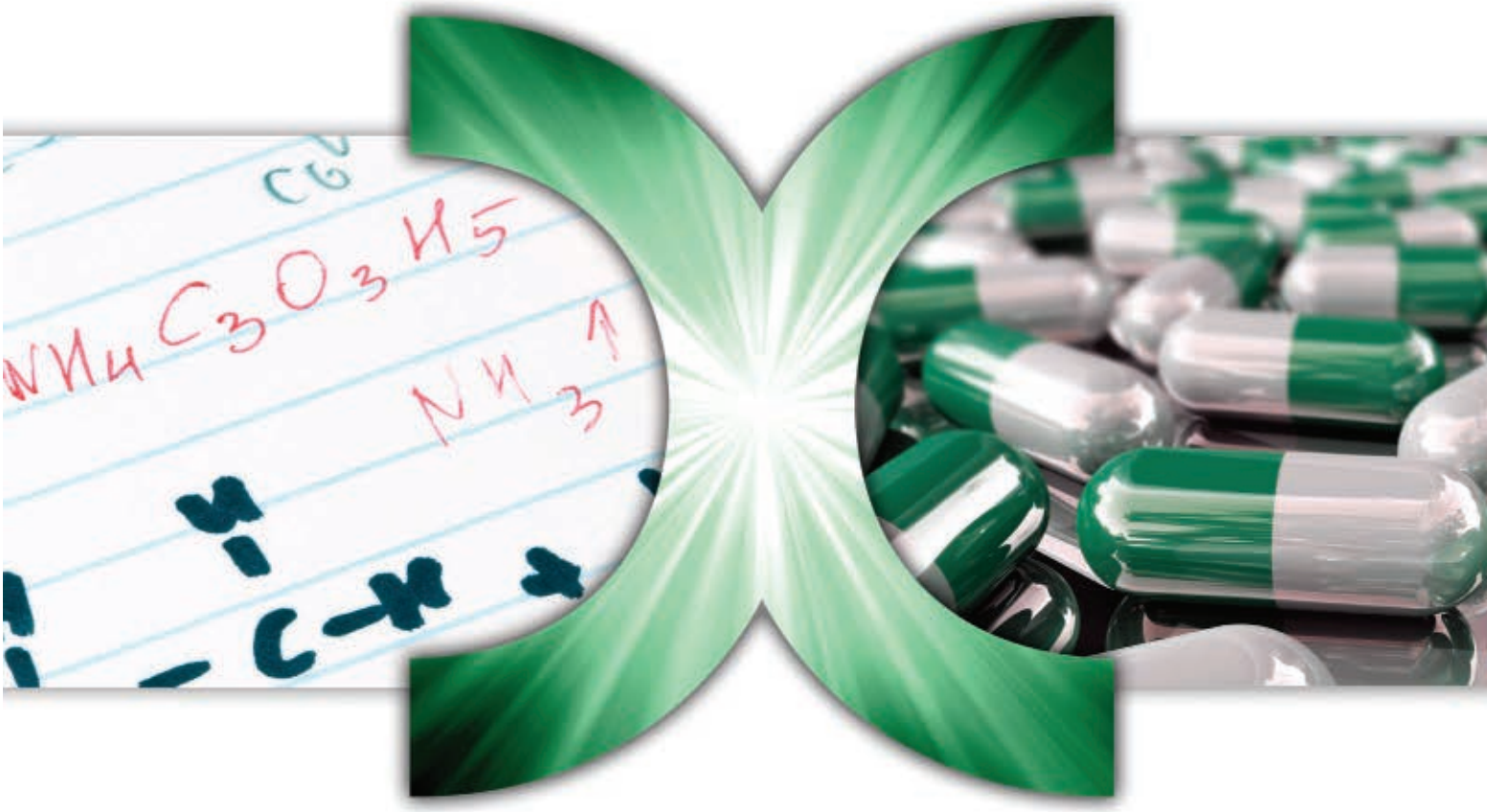
I began by saying two things: 1) That we are all order takers until the buyer says no, then we become sales people, 2) Great sales people understand the reason they have two ears but only one mouth is because they listen twice as much as they talk. I wanted this sales manager to know that having a buyer say no is normal and if you listen to what he or she is saying very closely, they will inadvertently tell you things they do not mean to tell you.

We then spent the next 2 hours on how to discover the buyer's true concerns (not just what he was telling our sales manager), strategy, and tactics, negotiations, decision trees, and how to create various deal structures. We eventually won the business because this sales manager subsequently learned by listening carefully to the buyer that his bonus was heavily weighted toward gross margin on the product lines he bought and he had no bonus incentive to switch over to our product line. The sales manager structured out a rebate program for the buyer with additional discount incentives based on purchase volume, and it was a profitable win/win situation for everyone.

The point is that this sales manager knew I was no longer just a person he reported to but also a resource he could go to at any time. And I knew he was a hard working, competent, and now a loyal sales manager. ◆

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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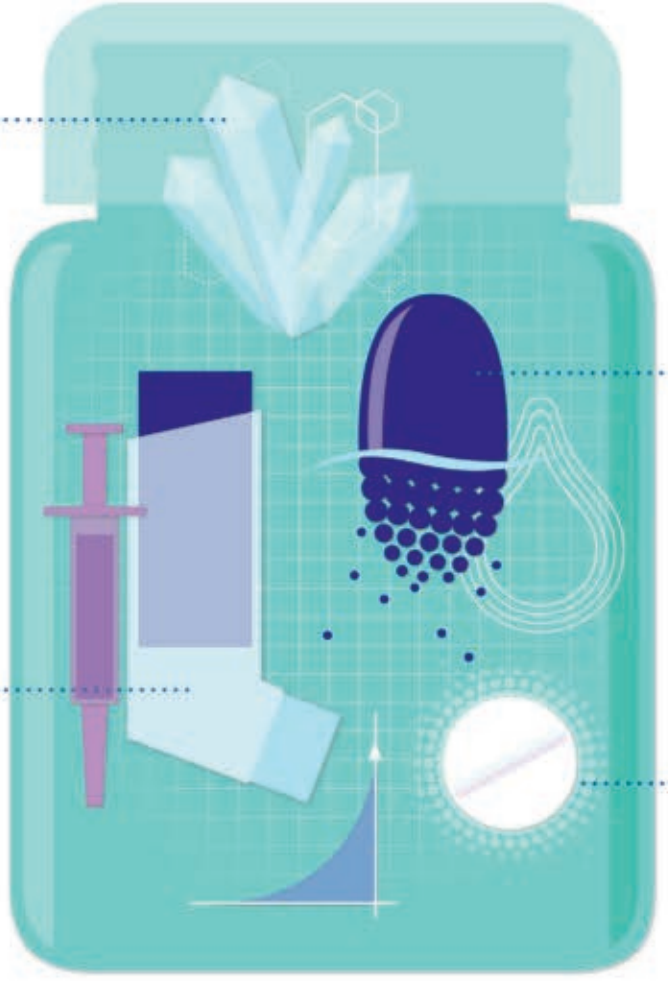

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