Drug Development & Delivery

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Optimizing Combination Cancer Therapies

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

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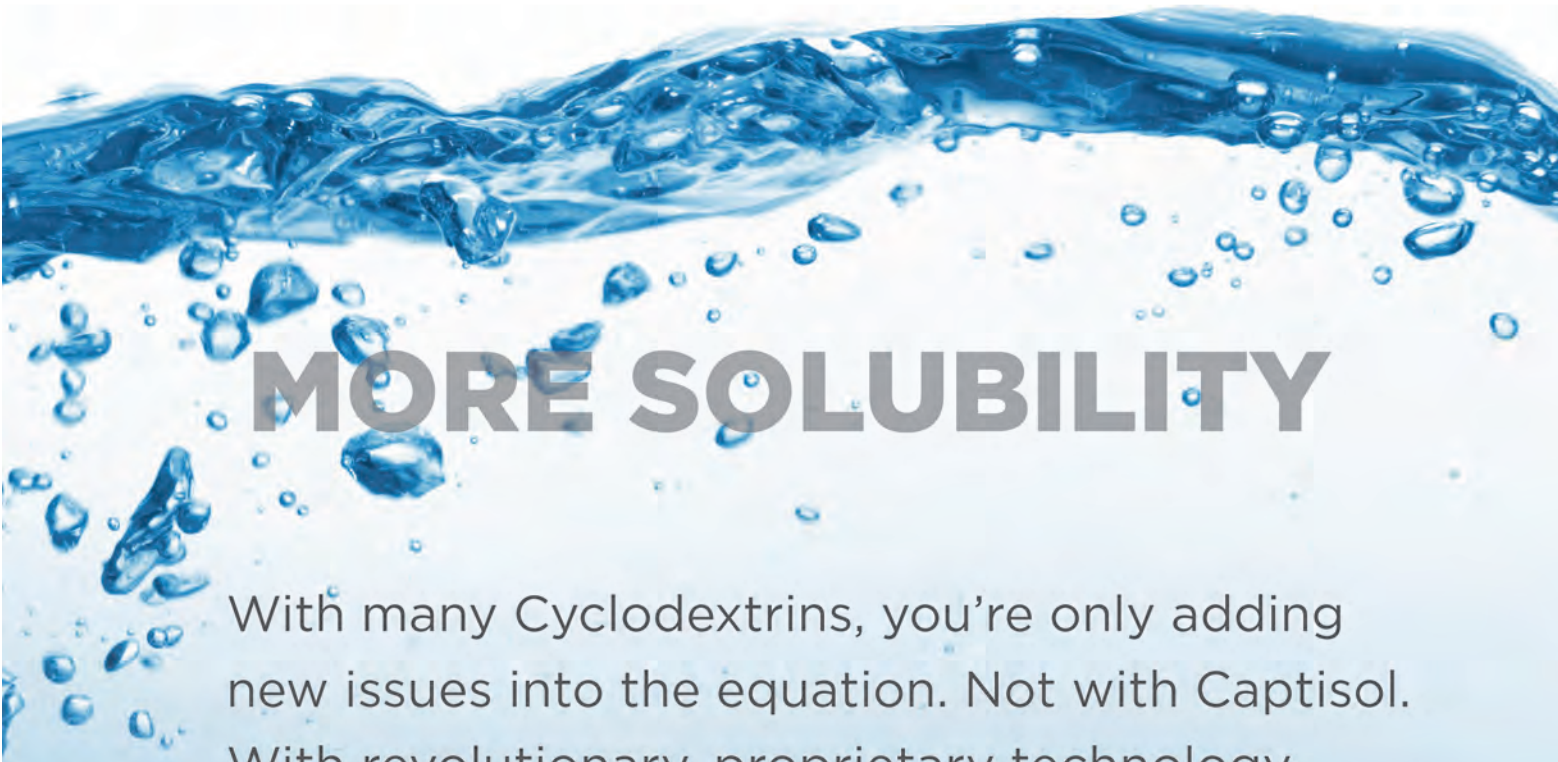

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Optimizing Cancer Therapies

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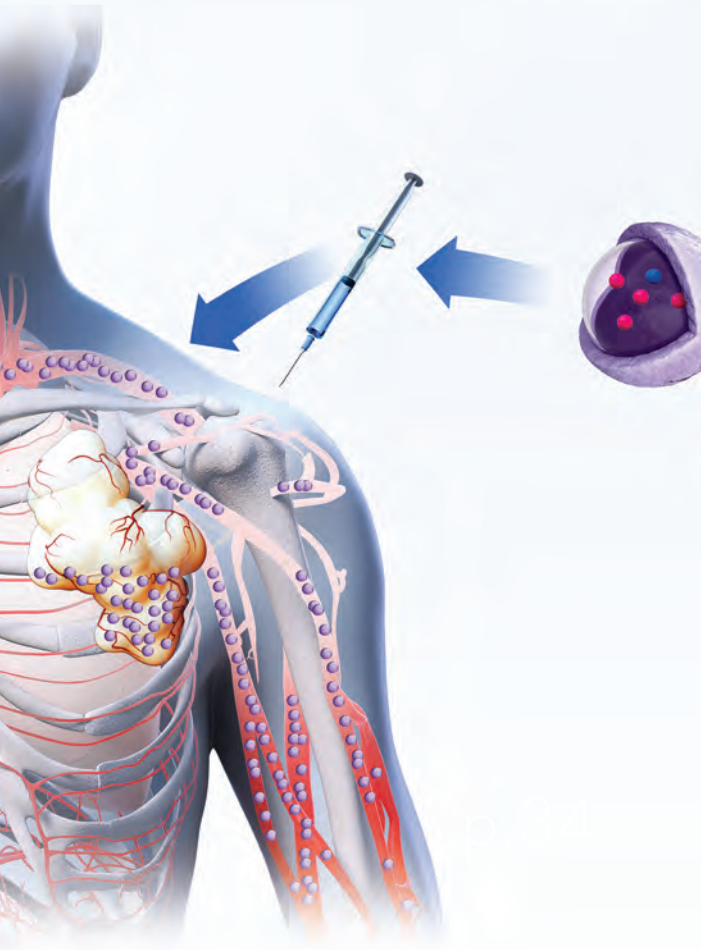

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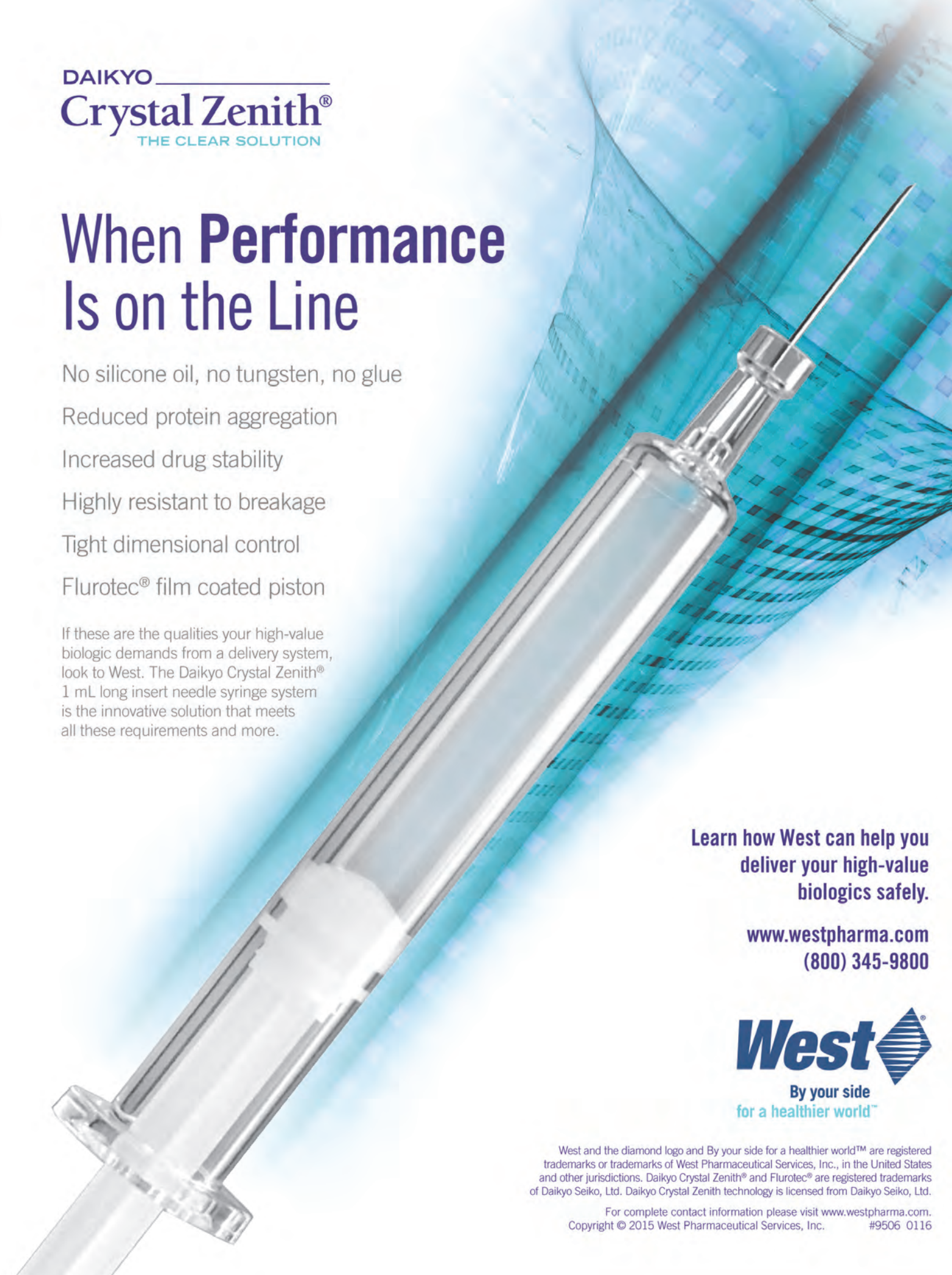

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Analytical Testing Trends

"For large molecules, the areas of analytical testing to support CMC activities that are on the rise include surfactant and process impurity testing, glycan analysis, and high-resolution analysis of macromolecules. There has also been an industry shift from slab gel to capillary analysis for electroseparations, and a call for more robust effector function assays for monoclonal antibodies and kinetic binding assays (both surface plasmon resonance and biolayer interferometry)."

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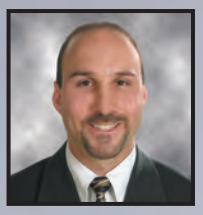

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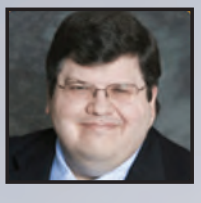

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Protea Announces Biopharm Industry Collaboration With Agilent

Protea Biosciences Group, Inc. recently announced it is collaborating with Agilent Technologies, Inc. to address customer challenges within existing Biopharma bioanalytical workflows in order to meet the emerging needs of the growing biopharmaceutical industry.

Under Terms of the Agreement, a Memorandum of Understanding (MOU), Protea, using Agilent instrumentation combined with its technology, will develop workflows that focus on developing new methods for the field of metabolomics.

"The field of biotherapeutics is advancing rapidly, and is in need of new, innovative solutions that identify changes in the 'metabolic profiles' of cells due to disease processes and drug interactions," said Greg Kilby, PhD, Protea's Vice President & Chief Operating Officer. "To accelerate the pace of drug development, we need to know how a new drug interacts with the body as a whole - as completely and as early in the drug development process as possible. We believe new metabolomics workflows, including use of our LAESI mass spec imaging technology, will help address the challenges of the ballooning costs and widespread failures endemic to the drug development processes today."

"To meet the needs of the biopharmaceutical industry, Agilent looks forward to working with Protea to develop mass spectrometry based solutions across a wide range of biopharm applications, including innovative solutions for metabolomics," commented Tiffani Manolis, Agilent's Biopharm/Pharm Marketing Manager.

Metabolites are the molecular products of living cells. All cells produce them, and they are essential to all bodily functions. A cell's metabolic profile can change due to health, nutrition, or environmental factors. Metabolomics represents the goal to identify all the thousands of metabolites being produced by specific cells, and to identify changes that take place in the "metabolic profiles" of cells due to disease processes and drug interactions. Metabolomics also is being used to improve cellular processes that support high production and quality of recombinant protein in biopharmaceutical manufacturing.

Protea Biosciences Group, Inc. provides innovative bioanalytical solutions to the pharmaceutical and life science industries by applying the company's proprietary technology to identify and characterize the proteins, metabolites, lipids, and other biologically active molecules, which are the byproducts of all living cells and life forms. Protea is the leader in mass spectrometry imaging services (MSI), providing a revolutionary capability that enables the identification and spatial display of biologically-active molecules in tissue and cells. MSI can be performed without sample preparation, labeling or antibody techniques, thereby integrating for the first time direct identification of molecules with anatomic pathology.

Agilent Technologies Inc. is a premier laboratory partner for a better world. Agilent works with customers in more than 100 countries, providing instruments, software, services and consumables for the entire laboratory workflow. The company generated revenue of $4.04 billion in fiscal 2015 and employs about 12,000 people worldwide.

ProQR Announces R&D Day; Provides Update on Innovation Portfolio

ProQR Therapeutics N.V. recently announced an update on the innovation pipeline and an R&D day for investors. ProQR has been investing in its Innovation Platform to discover RNA medicines for severe genetic disorders. Under the leadership of Chief Innovation Officer, Gerard Platenburg, this team has made significant progress in multiple therapeutic areas, which will be presented at the R&D day in more detail.

"We founded ProQR with the goal of developing a drug for CF based on a unique RNA technology that was invented at Massachusetts General Hospital. In the 3 years since incorporation, this early invention is developed into a product that is now being investigated in two global clinical studies in CF patients. During this time, we have launched our second development program for LCA and have significantly expanded our understanding of the potential of RNA therapeutics. We are just starting to scratch the surface of what RNA technologies can mean to the future of medicine," said Daniel de Boer, CEO of ProQR. "Our innovation platform has been very efficient and has yielded a wealth of new opportunities, establishing ProQR at the forefront of this novel therapeutic approach. We are laying out a strategic path forward for these core and non-core programs to maximize the potential."

The R&D day will be led by the company's Chief Innovation Officer Gerard Platenburg, Co-founder of ProQR. Under his leadership, ProQR has initiated a broad effort to apply existing and novel RNA technologies to other severe genetic diseases to discover new potential therapies.

"We have seen the field of RNA therapies mature significantly over the past decade. To unlock the promise of this field, we initiated our Innovation Platform in mid-2014," said Gerard Platenburg, Chief Innovation Officer at ProQR. "With the broad experience in the field at our disposal, I believe we are at the verge of a new range of possibilities to treat genetic diseases. At ProQR, our innovation platform is focused on delivering the potential of this new class of therapeutics in several disease areas, including respiratory, CNS, ophthalmology and skin disorders. Within these areas, we target diseases with a good understanding of the causality, a feasible delivery route and a high unmet medical need. At our inaugural R&D day, we will present the progress made on a selection of the innovation programs we are pursuing, including programs targeting epidermolysis bullosa, Usher syndrome, Friedreich's ataxia, Fuchs endothelial corneal dystrophy (FECD), Huntington's disease and Alzheimer's disease."

On March 14, 2016 ProQR will organize its first R&D day in New York, NY. The day will feature a presentation from key executives in ProQR and Key Opinion Leaders in some of the therapeutic areas. We request people that are planning to attend to register at www.proqr.com/rd-day.

MedPharm Announces Formation of US Subsidiary & First Appointment

MedPharm recently announced the formation of its new US-based laboratories, MP Pharma Services Inc. With a targeted operational date in Q1 2016, the services offered in the US will initially focus on topical and transdermal formulation performance testing. Among other services, the facility will provide access to MedPharm's unique, validated in vitro models, complementing the UK based operation and offering a significant increase in capacity, as well as new services to the company's clients. It is an important expansion for MedPharm with US-based business accounting for 50% of company revenues. The operation will be led by Jon Lenn who has been recruited as the first of a number of new appointments to join the new facility in RTP, North Carolina.

"MedPharm is already the leading company in this field, and we continue to cement this reputation by adding new services and bringing in the latest know-how to the company. The expertise that Jon brings to the table is of incredible value as we expand the company into the US. As well as offering an increase in services and capacity to all of our partners, our clients in North and South America will now also benefit from having the opportunity for even closer contact with MedPharm,"said Dr. Andrew Muddle, CEO.

Jon brings with him an extensive and impressive portfolio of experience in topical and transdermal drug delivery. Jon has held senior positions in Stiefel and GSK, specializing in skin biology and topical and transdermal formulation development. During his career, he has been instrumental in numerous successful NDA and ANDA regulatory submissions including EVOCLIN, VERDESO, OLUX-E, EXTINA, VELTIN, SORILUX, FABIOR, & DUAC LD.

"We are all delighted to be able to bring Jon on board. He brings with him a vast wealth of experience from his time in industry, and we are certain that our clients will benefit enormously from his input in their projects at MedPharm," added Prof. Brown, CSO states.

MedPharm is the leading topical and transdermal pharmaceutical development company. It is recognized internationally for its expertise in transdermal and topical (skin, nail, nose, lungs, and other mucosal membranes) formulations and drug delivery systems. Established in 1999, MedPharm has built a worldwide reputation for its unique and highly specialized service in contract research, development and manufacturing. The company offers a complete suite of development options from simple feasibility tests, formulation and dosage form design, optimization and testing through to preparation of GMP clinical supplies for Phase I/II. The company operates a hybrid business model, with a CRO business and a development program with a substantial patent portfolio of novel topical and transdermal drug delivery systems, including MedSpray, MedRo, and AquaRMed. It has produced these innovations by exploiting its internal product development expertise.

Ashland Aids Pharmaceutical Manufacturers With Formulation Services

Pharmaceutical scientists at Ashland understand how polymers interact with complex drug molecules. These experts presented at CPhI India to explain how Ashland is providing formulation services to manufacturers in the region that require assistance in tailoring polymer-based drug delivery systems for optimal bioavailability, stability, and patient compliance.

"The pharmaceutical market in India is now the third largest in the world," said Nelson Corda, General Manager, Rest of Asia, Ashland Specialty Ingredients. "Last year, Ashland opened a Pharmaceutical Center of Excellence in Hyderabad to conduct oral solid-dosage form research and to assist manufacturers with novel therapeutics through polymeric drug delivery systems. With this facility, we recognize the importance and vitality of the Asia Pacific pharmaceutical market and the particular relevance of India within this market."

At the exhibition, Ashland also showcased a series of polymer excipients that enable manufacturers of oral dosage forms to produce finished products with relative ease and efficiency. Among the products on display will be Klucel hydroxypropyl cellulose (HPC), a premier tablet binder that makes tablet preparation easy. Polyplasdone crospovidone, a super disintegrant for immediate-release oral dosage forms, will be presented as a core technology proven to enhance dissolution.

Natrosol hydroxyethylcellulose (HEC), a non-ionic water-soluble cellulose ether, will be spotlighted as a technology to control the rheology of solutions and gels. AquaSolve hypromellose acetate succinate (HPMCAS), a solid dispersion polymer, will be presented as a novel technology for bioavailability enhancement of poorly soluble active pharmaceutical ingredients. Direct compression grades of Benecel hypromellose will be offered as a technology to control the release of complex drug molecules in solid-dosage forms.

"Ashland brings to India an unparalleled excipient portfolio and a global research and development (R&D) team focused on all of the major formulation trends," said Thomas Durig, Senior Director, Pharmaceutical and Nutrition Specialties R&D, Ashland Specialty Ingredients. "Our Pharmaceutical Center of Excellence in Hyderabad is a world-class resource, completely secured, inspected, and certified to India's highest regulatory standards. At this facility, we conduct formulation development, respond to technical service requests, perform customer trials, and create new technologies for our customers in India and the Asia Pacific region."

Ashland Specialty Ingredients is the leading global producer of cellulose ethers and a global leader in vinyl pyrrolidones. It offers industry-leading products, technologies and resources for solving formulation and product-performance challenges. Using natural, synthetic and semisynthetic polymers derived from plant and seed extract, cellulose ethers and vinyl pyrrolidones, as well as acrylic and polyurethane-based adhesives, Specialty Ingredients offers comprehensive and innovative solutions for today's demanding consumer and industrial applications. Key customers include: pharmaceutical companies; makers of personal care products, food and beverages; manufacturers of paint, coatings and construction materials; packaging and converting; and oilfield service companies.

Vetter Receives Internationally Recognized AEO-F Certificate

Vetter has received the status of Authorized Economic Operator Full (AEO-F) from the European Union confirming Vetter reliability, solvency, and high safety standards in international trade. Vetter's customers worldwide will now benefit from shorter transit times and lower costs with the usual high product quality.

The internationally accepted AEO-F certification (Authorized Economic Operator - Customs simplifications/ Security) will facilitate the import of drugs in third countries. The certificate confirms the compliance of high safety requirements throughout the entire supply chain of a company. Customs procedures of consignments will be simplified and accelerated, all of which results in shortened transport durations, as well as improved fulfillment of pharmaceutical requirements for transit times. Another advantage is the facilitation of regulatory proceedings for security reviews and audits. Thus, Vetter and its customers benefit from additional time and cost savings in international supply chains.

"With the recognition afforded by the granting of the AEO-F certificate, we can enable our customers not only a fast and smooth international customs clearance, but more importantly, a very high standard of safety," said Carsten Press, Senior Vice President Supply Chain Management. "The certification is important for Vetter, and at the same time, it is also further evidence of the high service and product quality we offer to our customers." With the extended certificate, the benefits of the previous AEO-C status for the European movement of goods also apply at the global level.

The AEO-F certificate is currently accepted by the US and Japan, the EU Member States, Switzerland, Norway and China. The aim of the World Customs Organization is to continue to expand the agreement to additional countries. By expanding the Authorized Economic Operator (AEO) concept, they will establish a uniform customs and security standard in the international movement of goods within the framework of the SAFE (Standards to Secure and Facilitate Global Trade) program. The European Union commends the recognition of the concept in international agreements with third countries in order to protect the supply chain from manufacturers to end users.

Vetter is a premier contract development and manufacturing organization (CDMO) and a global leader in the fill and finish of aseptically prefilled syringe systems, cartridges and vials. Headquartered in Ravensburg, Germany, with facilities in Germany and the United States, the company provides state-of-the-art manufacturing, from early clinical development through commercial filling and packaging of parenteral drugs. The CDMO's extensive experience covers a broad range of complex compounds, including monoclonal antibodies, peptides and interferons. Vetter supports its customers every step of the way, guiding their products through development, regulatory approval, launch and lifecycle management. Known for quality, the company offers a foundation of experience spanning more than 35 years, including dozens of customer product approvals for novel (bio-)pharmaceutical compounds.

Adaptimmune & Universal Cells Announce Collaboration & License Agreement

Adaptimmune Therapeutics plc and Universal Cells Inc. recently announced they have entered into a collaboration and exclusive license agreement for the development of allogeneic T-cell therapies.

With Universal Cells' proprietary gene-editing technology, Adaptimmune intends to develop affinity enhanced donor T-cells that are universally applicable. The enhanced T-cell technology involves selective engineering of cell surface proteins (TCRs and class I and class II HLA proteins), without the use of nucleases, to develop universal T-cell products. Adaptimmune and Universal Cells are planning to develop these off-the-shelf allogeneic affinity-enhanced T-cell therapeutics to treat large patient populations.

"Our proprietary platform for TCR identification, affinity enhancement, and safety testing is already best in class, and we set high standards for collaborations," said Dr. Helen Tayton-Martin, Adaptimmune's Chief Operating Officer. "We believe that Universal Cells' platform for generating universal donor cells is also best in class and provides us with a great opportunity to test the feasibility of a longer term allogeneic product, thus allowing large numbers of patients to be treated from a single cell line."

"We are very excited about working with Adaptimmune. By partnering with the world leader in TCR engineered T-cell immunotherapies, we are poised to develop a scalable, safe, and efficacious product with the potential to revolutionize cancer immunotherapy," added Claudia Mitchell, Chief Executive Officer of Universal Cells. "This partnership will combine Universal Cells' nuclease-free genome-editing platform with Adaptimmune's unique expertise in TCR engineering to develop a first-in-class therapeutic product based on our universal donor cells."

Under the terms of the agreement, Universal Cells will grant to Adaptimmune an exclusive, sub-licensable, worldwide license to use, sell, supply, manufacture, import, and develop products and services utilizing Universal Cells' technology within the T-cell immunotherapy field. Universal Cells will receive an upfront license and start-up fee of $5.5 million, and will be eligible for up to $41 million in milestone payments for certain development and product milestones. Universal Cells would also receive a profit-share payment for the first product, and royalties on sales of other products utilizing its technology.

Adaptimmune is a clinical-stage biopharmaceutical company focused on novel cancer immunotherapy products based on its T-cell receptor (TCR) platform. Established in 2008, the company aims to utilize the body's own machinery – the T-cell – to target and destroy cancer cells by using engineered, increased affinity TCRs as a means of strengthening natural patient T-cell responses.

Adaptimmune's lead program is an affinity-enhanced T-cell therapy targeting the NY-ESO cancer antigen. Its NY-ESO TCR affinity enhanced T-cell therapy has demonstrated signs of efficacy and tolerability in Phase I/II trials in solid tumors and in hematologic cancer types, including synovial sarcoma and multiple myeloma.

Universal Cells Inc. is a private biotechnology company developing proprietary nuclease-free genome-editing technologies that allow efficient and accurate editing of any gene without off-target effects.

BioCellChallenge Obtains Unprecedented In Vivo Results

BioCellChallenge SAS recently announced its positive results from in-vivo tests of a therapeutic antibody. The results confirm the efficacy of BioCellChallenge's ImmunoCellin technology, which allows the antibody to pass through the cell membrane. No toxicity was observed at the administered doses.

The tests were conducted in 18 animal models, from January through July 2015. They showed that the intracellular delivery of a specific monoclonal antibody directed against the Ras oncoprotein, which is implicated in many cancers, significantly reduces the proliferation of tumor cells. In all cases, the animals' lives were prolonged by up to 30%. Recovery was observed in 33% of cases. No toxicity-related mortality or inflammation was observed, or any abnormal change in the growth of the animal.

The therapeutic antibody is specific to a given protein. When it is delivered into the cancer cell, it blocks the function of the protein and weakens or even leads to the death of the cell. The lipid-based formulation encapsulates the antibodies, making it easier for them to pass through the cell membrane. Without an appropriate transport mechanism, the antibodies are unable to cross the plasma membrane of living cells and reach their intracellular targets. The formulation and properties of the BioCellChallenge technology help to deliver the antibodies directly into the cytosol of living cells, with no specific prior preparation and without the need for chemical modification of the antibodies. Antibody activity is not affected in any way.

"So far, there is no solution for efficiently transporting antibodies into living cells. The existing drugs are largely directed at targets that are on the surface of the cells. Antibodies are proteins that circulate in the blood, remaining outside the cells. In the case of cancers, though, over 90% of the deregulated targets that lead to the disease are inside the cells," said Dr. Laurent Meunier, Founder of BioCellChallenge. "Therapeutic antibody internalization offers huge potential by allowing them to reach many new targets."

In October 2015 BioCellChallenge sold its reagents business to Eurobio and is now focused on collaborative projects and out-licensing. The next step for the company will be to test the delivery of an Antibody Drug Conjugate (ADC), which combines an antibody with a cytotoxic component to kill the cancer cell.

The BioCellChallenge technology offers a new or complementary approach for most ADC antibodies currently in development or already on the market. Delivering the ADC directly into the cytosol would both reduce the required amounts of toxins, and significantly limit their spread throughout the body. For pharmaceutical companies, the use of this technology could help to relaunch some ADC programs. It could also help CROs in optimizing the results of preclinical phases.

OncoMed Achieves $72.5-Million in Milestone Payments From Celgene

OncoMed Pharmaceuticals Inc. recently announced the achievement of two milestones from Celgene Corporation and pre-announced its 2015 year-end pro-forma cash balance and key anticipated events for 2016.

OncoMed achieved the $70-million safety milestone from Celgene based on an analysis of available Phase Ib and blinded interim Phase II clinical trial safety data associated with the demcizumab (anti-DLL4, OMP-21M18) program. The data from the pancreatic, non-small cell lung and ovarian cancer clinical trials showed no demcizumab-related Grade 3 or higher cardio-pulmonary toxicities among 155 patients treated with truncated dosing. Of those, 68 patients have received at least two cycles of demcizumab at the Phase II dose or higher and have been followed for at least 100 days. OncoMed also achieved a $2.5- million milestone for clinical candidate designation of an undisclosed preclinical immuno-oncology program, "IO#2". This is OncoMed's second immuno-oncology program to reach clinical candidate designation, and both programs are advancing in IND-enabling studies.

Including the Celgene milestones, OncoMed ended 2015 with approximately $227.2 million in pro-forma cash, representing approximately 1.5 years of cash, without taking into account future potential milestone payments from partners, and exceeding its 2015 guidance predicting a year-end cash balance of greater than $120 million. Full-year operating expenses for 2015 are anticipated to be approximately $110 million, in accordance with previous guidance. OncoMed plans to provide full-year 2016 guidance during its 2015 fourth quarter earnings call in the first quarter of 2016.

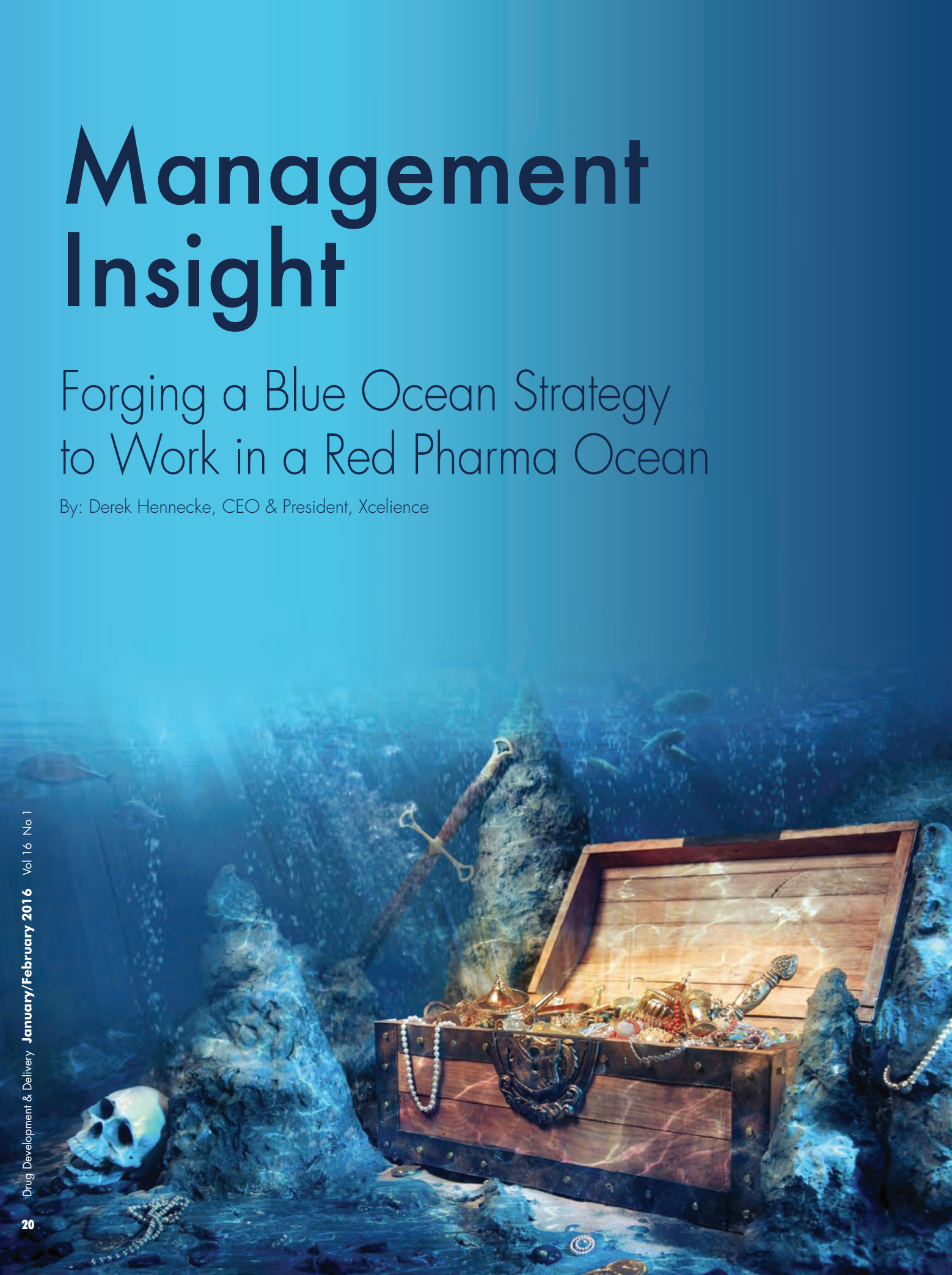
"The achievement of the demcizumab $70-million safety milestone is based on extensive Phase Ib and blinded Phase II data, and positions OncoMed to rapidly enroll its Phase II randomized YOSEMITE and DENALI clinical trials, as well as the Phase Ib demcizumab plus pembrolizumab (anti-PD1) trial, and also to explore the potential of demcizumab in ovarian cancer," said Paul J. Hastings, OncoMed's Chairman and Chief Executive Officer. "We enter 2016 in a strong cash position to support all seven internally discovered programs through clinical trials, including four randomized Phase II clinical studies, and to advance two immuno-oncology candidates toward IND filings while maintaining ongoing discovery efforts. Over the course of this year, we anticipate completing and reporting on our first randomized Phase II clinical trial, the tarextumab ALPINE study in pancreatic cancer, presenting additional data from our ongoing clinical- and discovery-stage programs, filing at least one new IND and achieving additional milestones related to our collaborations."

The next potential financial milestone for demcizumab is an opt-in payment from Celgene that may occur through the end of either of the Phase II pancreatic cancer or NSCLC trials. Following option exercise, OncoMed and Celgene will co-develop and co-commercialize demcizumab in the US, sharing profits 50/50, while Celgene would lead development and commercialization outside the US.

Management Insight

Forging a Blue Ocean Strategy to Work in a Red Pharma Ocean

By: Derek Hennecke, CEO & President, Xcelience



I used to hate the circus. Crowds, sticky cotton candy fingers, poodles utterly failing to take the place of lions and bears, candy-overdosed children, and blasé, predictable stunts.

And then came Cirque du Soleil. Montreal's Cirque catapulted onto the scene in the 1980s, translating the circus to an adult audience, without losing the kids. It sidestepped the complications of dealing with animals, added edgy opera and ballet elements, and elevated the human acrobatic and artistic performances to jaw-dropping levels. It was something no one had ever seen before, and it created a new market.

Cirque du Soleil is the ideal business model; the golden ticket, the American dream, the thing we business types are all looking for. In modern management parlance, it's the *Blue Ocean Strategy*, a book by W. Chan Kim and Renee Mauborgne, professors at INSEAD.

The thinking goes something like this: in a crowded market space, prospects for profit and growth are marginal, and competition turns cutthroat. The oceans become bloodied; hence the term "red oceans." True growth is to be found by seeking out blue oceans — those unknown market spaces where demand is untapped and competition non-existent. They are hard to find.

Percy Spencer, while working at Raytheon in 1945, noticed that his chocolate bar was melting when he worked on radar. This observation led to the discovery of the microwave – a completely new cooking method. While testing a potential insecticide, Shashikant Phadnis tastes it and finds that this test subject is surprisingly sweet. This leads to Sucralose. The anti-cancer drug cisplatin was discovered in the 60s, when researchers were looking at the effect of electricity on cell growth and found that a byproduct from one of the platinum electrodes was to blame. We like these stories, but how frequent are they? And can you work to find a blue ocean, or is it something that just happens to people by chance?

THE BLUE OCEAN REVOLUTION

Blue Ocean Strategy made waves. Published in 2005, it quickly became a *Wall Street Journal*, *Business Week*, and *Amazon.com* bestseller. It was named best book of the decade by 800-CEO-READ. Translated into 43 languages, it was selected by the China Daily and the China Research Institute as one of the 40 most influential books in the history of the People's Republic of China, along with Adam Smith's *Wealth of Nations*, under the category Economics and Finance. It was named one of the 15 Best Business Books of the past decade in Russia by *Kommersant.ru* magazine. *Forbes* named it one of the 10 business trends for 2013 claiming that blue ocean strategies are "more influential than ever."

If you work in a business, you should know about blue ocean strategy. At the very least, it will give you something to drop into conversation with your CEO at the company Christmas party. At best, it might help you come up with the next Big Idea.

The key concept behind the strategy is the value innovation. A value innovation is something novel that, once introduced, unlocks demand that wasn't there before. It is achieved by pursuing both differentiation and low cost at the same time. The result is a new, uncontested market space, effectively making competition irrelevant. You no longer have to grow by reducing competitor market share. Payoff possibilities are higher in this scenario than in any other.

Much of the body of the *Blue Ocean Strategy* contains analyses and exercises to help your company find the blue ocean strategy that plays on your company's strengths and is just waiting to be discovered.

DOES IT WORK?

You're probably a scientist. You had to ask that question. The analyses in this book would not meet our industry's standards for scientific rigor. The book used no control groups. There is no way to know how many companies attempting a blue ocean strategy failed; no insights at all into why some ideas belly-flop into the big blue ocean and others grow and

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expand. It is descriptive rather than prescriptive, identifying businesses that appeared to have created value innovations, and then working backward to fit those cases into the blue ocean blueprint.

In some examples, it isn't even the proven cause of its own success. NYPD Commissioner Bratton's success in reducing crime in New York is given as an example of public sector blue ocean strategy. But did the decline in criminal activity truly come as a result Bratton's ideas, or was the drop a result of a nationwide decline in crime, as many social scientists contend?

It's not even a new idea. It's a really slick branding of some concepts that have been out there for a long time. Ideas like competing factors, the consumer cycle, non-customers, etc. Tools like this were used by Six Sigma practitioners and proposed by other management theorists for many years before this book.

WHY YOU SHOULD TRY IT ANYWAY

And yet, I'm going to suggest that you take it seriously anyway. Don't see this book as a formula for finding new blue ocean opportunities. See it as an exercise that will help you recognize one when it hits you in the face. Because quite honestly, that's how most blue ocean opportunities come to light. The only company I could find that claims to have had a value innovation epiphany as a direct result of a blue ocean strategy process is Nintendo, which successfully used the book's techniques to create the Wii. The Wii, however, was a one-hit wonder. When the initial success began to wane, Nintendo failed to repeat the win.

Pharma is a very red ocean business. We tweak medications to extend patents, we combine medications, we extend release, and we offer maximum strength. In drug development, we fine-tune our equipment lists trying to offer the latest and the best, adjusting capacity to maximize revenue and flexibility.

Which is not to say pharma hasn't had its blue ocean moments. Fleming's discovery of penicillin is an obvious example. The most famous recent example is the little blue pill – Viagra. Developed to treat pulmonary artery hypertension, for which it didn't work particularly well, doctors noticed a most interesting side effect. They stumbled across this happy fact by complete accident – but they knew a blue ocean moment when they had one. By 2012, the little blue pill was earning $2 billion in annual sales.

Latisse, the popular cosmetic that causes extra growth and thickening of eyelashes, began life as Bimatoprost, a prostaglandin analog/prodrug used topically to control the progression of glaucoma and to manage ocular hypertension. That patients grew long luscious lashes was a serendipitous

side effect, which now earns Allergen in excess of $90 million annually.

Anyone can find a blue ocean. Many management textbooks will tell you it takes a visionary — someone in the company, usually at the top, with that rare ability to think outside the box. Honestly, these ideas may equally come from anywhere in the company, as with the 3M employee who famously thought of another application for an adhesive that failed to permanently bond paper, inventing the Post It note.

It is hard to figure out how much chance plays in this invention process. It is probably underreported as everyone wants to believe his or her discovery came from hard work. There was a study way back in the 80s by Jaun Miguel Campanario that looked at 200 papers and found that about 8% of them mentioned luck in their scientific discovery.

Is it really just luck, though? Maybe it's just about looking at things from a different angle. Maybe instead of taking a problem and looking for an invention or solution, most innovation comes from the reverse: you have an invention or discovery and then look for a problem it could solve. It is far easier to work backward.

Blue oceans are pseudo-serendipitous. There does seem to be an element of serendipity, and yet, these ideas only seem to happen to people through hard work. That's the pseudo part. If you sorted all of Thomas Edison's 1,093 patents in chronological order, you would see that the more subjects he worked on the higher the output of patents. Cross-pollination fueled his discoveries. If you search for more ideas from different places you will get more ideas.

HOW TO FIND A BLUE OCEAN

Blue oceans don't have to have the size and impact of Cirque du Soleil. They may be small and even fleeting. Think about your company's strengths. Then think about what those strengths could do that you and your competition aren't already doing. In my business, I have seen four. They are small oceans, and none of them will last. But all were/are/will be springboards for truly substantive growth.

THE XCELODOSE

Ten years ago, my company's best-known strength was formulation services. Around this time, I came across a little known company called Meridica. They had invented a capsule-filling machine that claimed to bypass steps of the formulation process, getting products to market faster. This was their blue ocean, not ours, but they were going about it wrong. They were marketing these machines to big pharma, thinking that, at $500K a pop, only these companies could afford them. In fact, even for big pharma, $500K is a big purchase, particularly for a machine that is destined to be mothballed for months or years at a time. The Xcelodose was perfect, however, for a service provider that could push dozens of projects through it every year.

I brought the first one to America and for a short time, the ocean belonged to us. Today, that ocean is red, though our history as the first gave us a solid reputation within that market.

CLINICAL SUPPLY SOLUTIONS

This blue ocean play came from a different strength: flexibility and adaptability. Before 2012, companies with a viable drug candidate looked to large pharma for their blister packs, their bottles, and their distribution services. Even if they only needed a few tablets, they would have to book a room that was meant to produce 10,000 tablets a day, reconfiguring it to produce small batches at large batch prices. There was no flexibility for urgent or unpredictable demand.

What if there was a facility that could produce small runs in small rooms, using pre-establish protocols to enable quick turnarounds? What if you could book such a room on a few days or even a few hours notice? Here was an uncontested market space, and we developed a dedicated plant to meet a new

demand.

Others are making moves to establish similar operations that will bloody the waters. In the meantime, we have begun swimming into deeper blue waters. Orphan drug sponsors can rarely find enough patients on our own shores; they are forced to go global to get the necessary patient numbers. It took 2 years to establish our UK facility and get MHRA certification, and we figure that gives us a 2-year license to fish in this ocean alone.

DEDICATED SHOPS

Quality and regulatory excellence are two of our company strengths. So when a colleague in an unrelated field – bioprocessing – ran into quality and regulatory issues, I came up with the idea of working with him to create a dedicated shop inside our facility. This bioprocessing shop will launch by the end of the year, and two more very different shops are in the pipeline.

FULL SOLUBILIZATION SERVICES

Here's a blue ocean we're still scouting: full solubilization services. Imagine one company that can offer the full range of solubilization services. With our recent strategic acquisition of the Pennsylvania-based company Powdersize, we are almost there. Powdersize is one of two contract companies capable of micronization, the other having been bought by a competitor. We are missing one piece of the puzzle: spray drying.

THE OCEAN VIEWED FROM 30,000 FEET

Stringing all of these services together into Suite Services creates yet another blue ocean. No other company with revenue under $1 billion offers this combination of services. Of course, anyone can put together a unique combination of services. The key is to choose your pieces not at the 30,000-foot level, but at the 5,000-foot level.

If you were designing a city from the window of a jet plane at 30,000 feet, you might choose to put your city near the river, to dam the river for hydroelectric power, and to cultivate farms on the flatlands behind the city. But when you get closer you might see that the river is too small to dam, the soil to unstable to support skyscrapers, and the flatlands are too rocky to farm.

If you looked at the drug development pipeline from 30,000 feet, you'd start with API development, add formulation, and string it together with analytical. You've seen this combination before. It makes sense from a distance. But if you get in closer you'll see what the customer really needs, even if he or she doesn't yet know it. Adding micronization was like that. You would never see the need for this piece from 30,000 feet, and our clients never asked us to bring this service in house. But we realized that when packaged together with our analytical and formulation services, micronization creates a much stronger value proposition for our customers by allowing them to develop drugs under a single corporate roof.

None of these blue ocean strategies from our industry created a jaw-dropping Cirque moment for our customers. None will go down in history as game-changing plays. But every time we get out of the red ocean, creating untapped, uncomplicated markets, our books see a nice little crescendo that our investors truly appreciate. ◆

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Derek G. Hennecke
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Advanced Delivery Devices

How Data Hubs & Smart Devices Are Enabling the Rise of Therapeutic Ecosystems

By: Stephen Allan

INTRODUCTION

It seems everyone is getting into digital health. As just a few recent examples, Philips has teamed up with Amazon, Sanofi with Google, JNJ with IBM, and Medtronic with Apple. In each case, there has been one common goal - to sync drugs, devices, and data to better monitor patient health. These collaborations between tech and biotech reflect a new paradigm in how therapeutics are being commercialized and marketed under the new pay-for-performance healthcare model. Industry participants that ignore these converging trends risk being left behind as innovators leverage smart technologies to create therapeutic ecosystems that create long-term, value-driven relationships with patients, prescribers, and payers.

CHANGING TIMES

You've probably heard about a "war on drug pricing" where the battle lines have been clearly drawn. On the one side, politicians and payers are demanding lower costs and regimented pricing controls. On the other side, patients and prescribers are seeking widespread access to the most effective treatments with maximum reimbursement. In the middle are the pharmaceutical companies, who are seeking to advance patient care whilst delivering an attractive return on their R&D investment.

Although this might be a simplistic view of things, it gets to the heart of a debate surrounding how much drugs should cost and who should pay for them. While drug pricing, reimbursement rates, and market share will always be determined by competitive market dynamics, the factors being used by healthcare stakeholders to make financial decisions are changing.

Traditionally, a volume-based model has been used to balance the upfront price of a drug against the number of units purchased. However, this model is being gradually replaced by a value-based model in which the upfront drug pricing must be balanced against the long-term socio-economic outcomes it can generate amongst patients, prescribers, and payers.

In particular, payers and large healthcare providers are investing heavily in systems that enable them to better understand the comparative value of the different therapeutic options available. Many have established dedicated research units that mine data from various sources, such as health claims, medical records, social media, and real-world patient preference studies. Increasingly, this information is being used by healthcare providers to allow its members to only access a single, preferred brand of therapy.

In one of the most recent examples, CVS Health selected Amgen's Repatha® as the only PCSK9-inhibitor on its commercial formularies, in a move designed "to get the best price possible for clients and preserve our commitment to deliver the best care available." In its press release, Amgen described the arrangement as a "value-based partnership."

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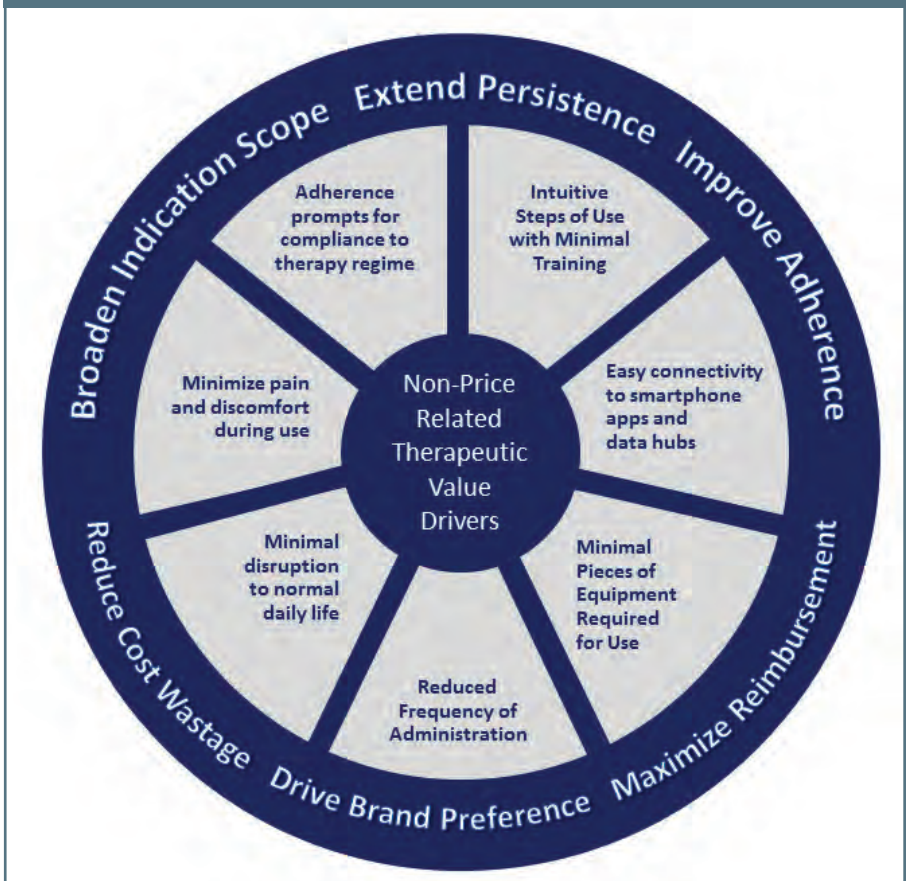
DEFINING VALUE

But how can a pharmaceutical company best showcase the competitive value of their therapies, particularly when there is limited pharmacological or pricing differentiation between competing brands? Pharmaceutical companies are increasingly utilizing an array of innovative technologies and practices to demonstrate how a therapy can save time, money, or lives.

By reducing steps of use or the number of pieces of equipment required, a therapy can eliminate complexity and reduce preparation time. By reducing frequency of administration, for example, from once a week to once every month, a therapy can minimize lifestyle disruption and potentially reduce the number of prescriptions to be filled. By shifting the place of administration from the clinic to the home, a therapy can reduce the burden on healthcare facilities and improve patient quality of life. By minimizing the pain or discomfort of administration, or providing medication reminders, a therapy may boost adherence rates and plug value leakages across the healthcare system. And by leveraging technologies, such as smartphones, Bluetooth, and data hubs, a therapy can efficiently bring patients and prescribers closer together to enhance the provision of care.

Such outcomes represent attractive value propositions that can be leveraged by pharmaceutical companies to optimize therapy pricing, maximize brand differentiation, and build or protect market share. As one health executive recently stated in a PWC report, "Tomorrow, drugmakers may not get paid for the molecule…they may only get paid for the outcome."

SLIDE 1



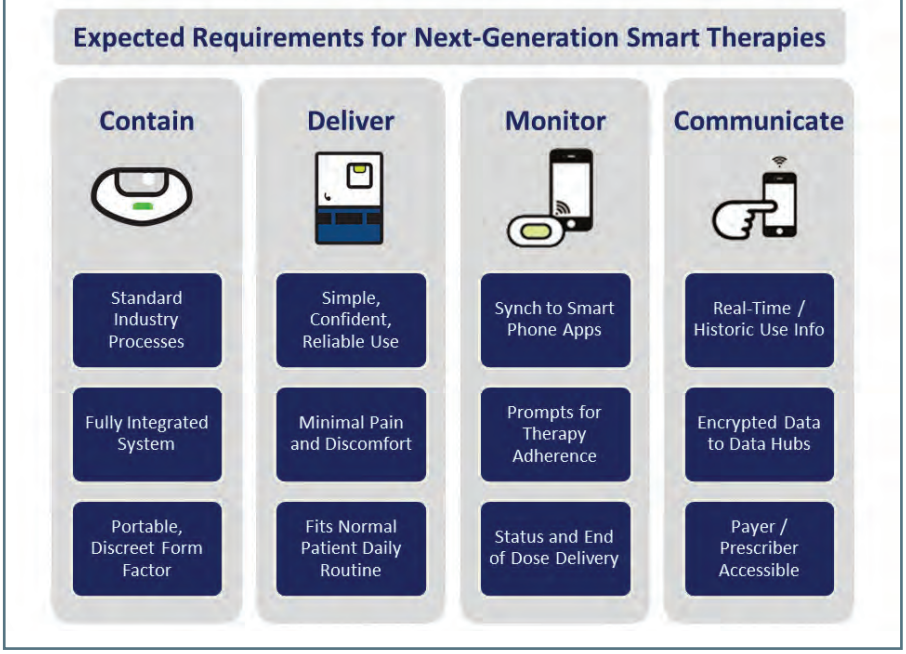
In one clear recent demonstration of a value-based drug strategy, Gilead Sciences successfully justified the cost of Harvoni® and Solvadi®, which cure the vast majority of people with the most common type of hepatitis C within 3 months, based upon the long-term savings the products are projected to generate compared to the future treatment of acute liver disease. However, for most drugs targeting chronic diseases, the determination of a drug's true value can be less black-and-white and more difficult to quantify using conventional processes.

Consider as one hypothetical that a new oncology drug is approved tomorrow. It comes in a convenient injectable formulation that enables intuitive once-monthly subcutaneous administration outside of the clinic. What proportional increase in price could such a product support compared to equivalent rivals that alternatively require slow IV infusion, and incur thousands of dollars in add-on costs relating to specialty care facilities, staff, and equipment?

Alternatively, consider auto-immune diseases, in which it's common that half of a patient population does not maintain compliance with prescribed therapy regimens. It's estimated that up to $300 billion is wasted every year in the US alone through patient non-compliance, with prime examples including missed or incorrect doses due to several factors, such as injection pain, preparation complexity, and the non-collection of prescriptions.

So, as another hypothetical, what

SLIDE 2



type of value-based pricing strategy could be deployed by a pharmaceutical company with a therapy facing biosimilar competition if it introduced a new proprietary version that improved patient compliance or persistence rates by 20% or more over a 12- to 24-month period? Furthermore, how could such enhancements to the combination product, particularly those of a proprietary nature in which it may be difficult to generate equivalence according to regulatory processes, help to extend the commercial lifecycle?

CAPTURING VALUE

As prescribers, payers, and government agencies all begin to prioritize the use and reimbursement of therapies that deliver the best socio-economic healthcare outcomes, pharmaceutical companies recognize they must be able to precisely quantify why their therapeutic brand represents the most attractive, long-term competitive value.

Within this new age of healthcare, a simple rule is fast gaining traction - the drug with the best data wins. Given how influential value-based information will be in the decision-making processes of patients, payers, and prescribers, it is not hard to see why data informatics is poised to become a primary healthcare battleground throughout the next decade.

But how does a pharmaceutical company make the collection of data accurate, reliable, and above-all, patient-proof? Especially when much of the data must come directly from patients who will be self-administering high-value biologics on an infrequent basis while they are otherwise pursuing normal daily routines around the home, work, or other social environments, such as the gym or café?

Furthermore, how should such information, once captured and encrypted, be securely transmitted from the patient to data hubs and stored for real-time or historic access by authorized personnel without breaching HIPAA regulations and other privacy laws? And finally, how should all of this data be structured and stored, and by who, for efficient analysis and comparison to generate quality insights on either a single-patient basis, or for an entire patient population?

To address such issues, many pharmaceutical companies are seeking to create therapeutic ecosystems that not only capture and process data, but also build and maintain long-term trust amongst consumers and purchasers. Within each ecosystem, a therapy will be provided with a range of value-adding technologies and related services, including mobile apps, devices, cloud computing, biosensors, and diagnostic tools. Many, if not all, of these technologies will be adherence data-enabled.

To ensure each component of an ecosystem works seamlessly with all the other parts, long-term collaborations between drug, device, and data specialists will commence early during the clinical development of a therapy and then extend across its regulatory approval and commercial lifecycle will prove critical.

From the perspective of a pharmaceutical company, the synchronization of these smart technologies under one fully integrated ecosystem can fundamentally transform the nature of how they interact with patients, prescribers, and payers. Instead of just selling a drug, a pharmaceutical company can become a healthcare solutions service-provider that is fully engaged across the continuum of care.

As has been demonstrated in other markets being redefined by data, such as music by Apple, or books and retail by Amazon, such one-stop ecosystems are highly coveted by consumers and

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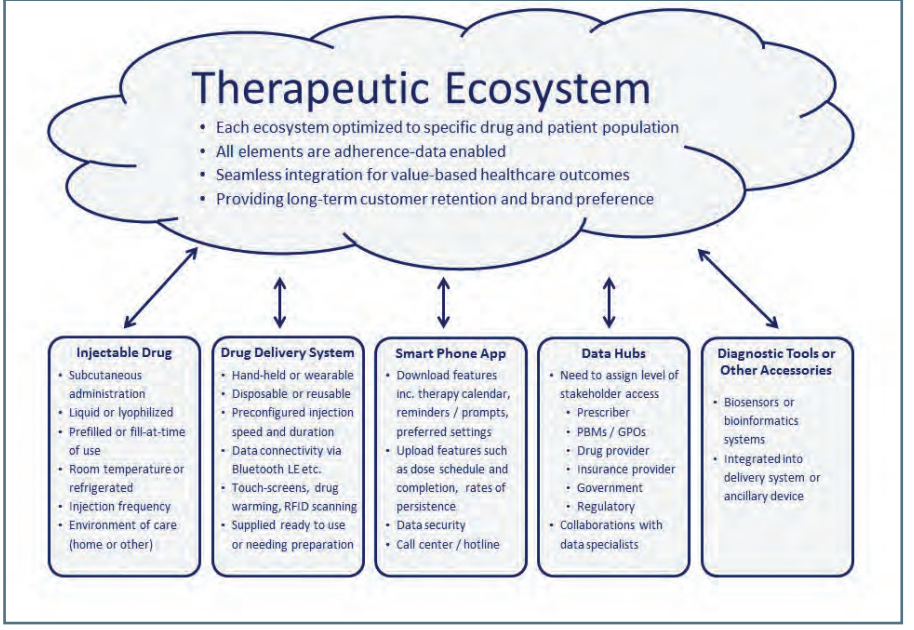
can inspire strong brand loyalty.

The use of smart-phone apps, such as health and wellness teaching aids and patient medication adherence programs, or ancillary wearable devices, such as smart watches and fitness bands with Bluetooth LE connectivity, have already started to be utilized in the creation of these therapeutic ecosystems.

In one example of what's already possible, a diabetes industry leader has created a system that links a durable insulin pump to an app on a person's iPhone®, enabling them to easily view pump and glucose information, including active insulin levels, calibration time, insulin in reservoir, connection status, and battery level. An authorized physician can also view the patient's information online to monitor adherence and adjust a regimen if necessary.

However as with any early generation new technology, there are limitations. An additional uploader device must be separately purchased by the user at extra cost to enable communication between the smartphone and the pump. Perhaps due to potential regulatory or technical challenges, the system also does not enable the user to control the rate or timing of insulin delivery via their smartphone, which could potentially provide benefits in some social environments.

SLIDE 3



With every secondary piece of equipment that is required, extra cost that must be incurred, or additional website or app that must be visited, complexity is added to the user experience, and the overall value proposition for a therapy is diminished. A seamless therapeutic ecosystem experience will therefore only truly exist

once future generations of smart technologies become available that not only monitor therapeutic outcomes, but deliver them as well.

This next wave of change will bring drug, device, and data hub together into one fully integrated package to provide a seamless user experience. Such ready-to-use products, where the device will serve as an primary interface between the drug, patient, and data hub, will be capable of doing it all…contain, deliver, monitor, and communicate.

SMART TECHNOLOGIES

Over the coming decade, these therapeutic ecosystems will be enabled or enhanced by a new wave of smart technologies with a range of embedded features and user-centric functionality. Each will have been developed and refined during the clinical development and regulatory approval process for a therapy to ensure it not only addresses the specific needs and expectations of a well-defined patient population, but also provides attractive benefits for prescribers and payers.

SLIDE 4

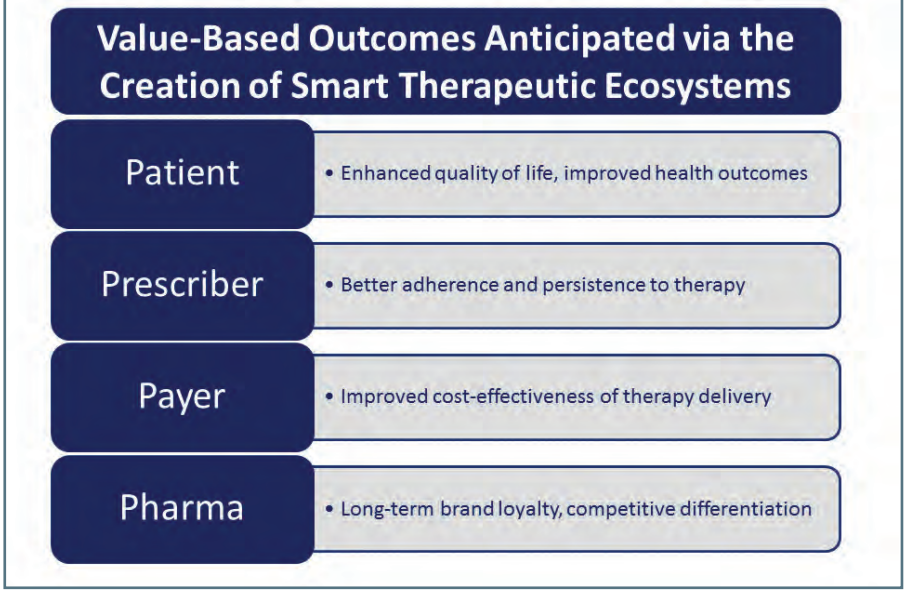


FIGURE 1

To help shift the place of treatment from the clinic to the home, or anywhere else the patient happens to be during a normal day, they will be commonly supplied in a prefilled or ready-to-use format that saves time, reduces bulk, and encourages portability. To fully empower patients to maintain long-term compliance with their prescribed therapy regimen, they will be intuitive to use and discreet in appearance. Some may not look like a traditional therapeutic product at all, but instead more closely resemble an electronic device or cosmetic product. And to enable the automatic uploading or downloading of data, they will feature Bluetooth LE or some related technology for seamless connection to therapy-specific apps that have been downloaded onto the patient's smartphone or tablet.

Outside of insulin, where durable insulin pumps are expected to continue growing in popularity, or novel concepts, such as smart contact lenses, there are two new categories of adherence-enabled devices that are expected to play a key role in the acceleration of this market shift to smart therapeutic technologies.

HAND-HELD SMART REUSABLE AUTOINJECTORS

For therapies designed for the patient, self-administration of a small dose volume on a frequent to semi-frequent basis, such as every day, week, or fortnight, smart reusable autoinjectors that minimize the average cost per injection will be utilized with prefilled syringes.

An early taste of things to come is the BetaConnect® autoinjector that has recently begun to be marketed across various international regions by Bayer with its Betaferon® therapy for the treatment of multiple sclerosis. The system

has been configured for use with the myBETAapp to upload data to a smartphone or computer using a Bluetooth or USB connection. The app can set reminder alerts for the next injection, with a calendar of all injections that have been scheduled, recorded, or missed. This injection history can be emailed directly to the patient, as well as the healthcare provider.

Such emerging technologies, particularly when synched with intuitive smartphone apps, can remind patients when to collect or take their dose, monitor health throughout the continuum of care, and alert healthcare stakeholders to potential issues before they become serious. In addition to leveraging the benefits of data informatics, these smart devices, which are designed for use up to hundreds of times before disposal or replacement, can further drive value by significantly reducing the average cost per dose over a multi-year period when compared to standard disposable autoinjectors.

Future generations of smart reusable autoinjectors may also be equipped with other features that can provide value-based healthcare outcomes in areas, such as therapy adherence, drug security, and data management. For example, through the inclusion of an automatic heating system, smart reusable autoinjectors will quickly warm a refrigerated biologic to room temperature to reduce patient pain or sensitivity during the injection process, and improve pre-injection waiting times from between 20 to 30 minutes to less than a minute.

Alternatively, autoinjector features that allow users to pre-select and store preferred settings for the speed or depth of an injection can help to reduce pain and improve rates of user preference. This may be especially important with therapies in which it is common to rotate the site of subcutaneous injection.

FIGURE 2

The integration of RFID/NCC tag readers within the autoinjector will also allow devices to scan each dose of prefilled therapy to confirm it has not expired, that it is the prescribed strength, and that it is has not been tampered with prior to use.

When specifically designed for use with proprietary prefilled syringes, such as those provided by Unilife with automatic needlestick retraction, smart reusable autoinjectors also create opportunities for a pharmaceutical company to follow a marketing strategy similar in many ways to the well-known Gillette razorblade model. Under such a strategy, the smart reusable autoinjector could be provided to patients either for free or at a subsidized price. As the autoinjector would be configured only for use with a specific brand of therapy, through the use of a bar code reader or the custom design of the prefilled syringe, the device would restrict use with other competing generic or biosimilar brands. Such practices create opportunities for a pharmaceutical company to build strong rates of user preference for the prefilled brand of therapy, and encourage long-term customer retention.

WEARABLE SMART DISPOSABLE INJECTORS

While patient-monitoring devices, such as biometric sensors that can be worn on the body, are already helping to redefine the boundaries of patient self-care, even greater healthcare outcomes are anticipated once wearable smart disposable injectors become common in the subcutaneous administration of injectable therapies across therapy areas such as oncology and autoimmune diseases.

Outside of disposable or durable insulin pumps, many wearable injectors will be supplied ready to self-administer biologics between 1 mL and 15 mL in dose volume over pre-set periods between 20 seconds and several hours on an infrequent basis, such as every 2 weeks, month, or quarter. These devices will enable convenient, comfortable, and discreet patient wear during the period of dose delivery, as well as compact disposal.

In addition to many of the same features that will be available with smart reusable autoinjectors, smart wearable injectors also create a number of other opportunities to unlock healthcare value due to the nature by which they can be worn on the body for extended periods of time.

For example, early generations of smart wearable injectors will have the capacity to be stuck onto the body, and then leverage the patient's own body heat to quickly warm a drug to room temperature prior to the automatic initiation of dose delivery to minimize patient pain and sensitivity. When integrated with smartphone apps, they will also be able to discreetly inform the user regarding injection status and the expected time until the completion of dose delivery.

In the longer-term, closed-loop systems, such as next-generation insulin pumps with integrated continuous glucose-monitoring technologies, create opportunities for a device to adjust the administration of a therapy regimen to the patient's specific health requirements in real-time. These therapy-specific outcomes may be feasible either via biosensors and bioinformatics programs embedded into the device or smart-phone app, or by allowing some level of control by the user. Such advances, which would extend the device's role well beyond the simple monitoring or pre-set delivery of a drug at a designated rate or duration, is however likely to be the subject of rigorous scrutiny by regulatory agencies.

OPPORTUNITIES FOR BIOPHARMA

The convergence of big pharma, big data, and smart devices will be instrumental in improving rates of therapy adherence, enhancing patient quality of life and creating financial efficiencies across the healthcare spectrum. In particular, the creation of cohesive therapeutic ecosystems will enable patients, prescribers, and payers to make informed decisions about the comparative value and effectiveness of competing brands of therapy.

Pharmaceutical companies that can remain at the leading edge of this wave will be strongly positioned to justify the competitive value of their therapy brands, build long-term patient relationships, and maximize revenue. In addition, the value of this data is expected to further reduce costs by shortening clinical development timelines for pipeline drugs, and providing enhanced patient information that can maximize the likelihood of regulatory approval and expanded indications for use. ◆

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BIOGRAPHY

Stephen Allan is a communications, marketing, and strategic planning specialist for injectable drug delivery systems with more than a dozen years of international industry expertise. As Senior-Vice President of Strategic Planning at Unilife, he is responsible for the assessment of unmet industry needs and emerging market trends relating to the containment and delivery of injectable therapies, and the development of differentiated brand marketing strategies for advanced drug delivery technologies. He can be reached at stephen.allan@unilife.com or (717) 805-8607.

NANOSCALE COMPLEXES

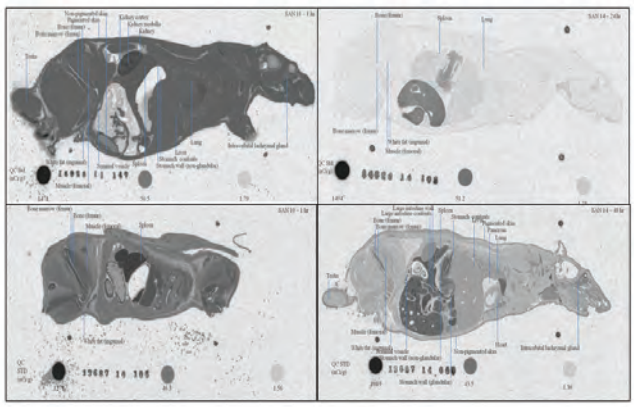
A Novel Nanotechnology-Based Platform to Optimize Combination Cancer Therapies: Rational Development & Improved Delivery Using CombiPlex®

By: Barry D. Liboiron, PhD; Arthur C. Louie, MD; and Lawrence D. Mayer, PhD

INTRODUCTION

Combination treatments for cancer continue to be developed in a manner largely unchanged since the inception of this approach over 50 years ago, where agents with non-overlapping toxicities are typically escalated to the highest dose possible based on their clinical use as single agents. This is done with the expectation that maximum efficacy can be achieved at the maximum tolerated doses (MTD) of the individual drugs. Emerging evidence indicates that this approach fails to recognize the critical role that drug-drug interactions, enabled by coordinated tumor cell exposure to multiple drugs, can play in enhancing efficacy by promoting synergy and reducing antagonism. In fact, the therapeutically optimal exposure of many combined agents may not be equivalent to their maximum tolerated exposure. Also, optimal efficacy of many combinations requires temporal control of tumor drug exposure to ensure that the degree of target inhibition/interaction is coordinated for interrelating pathways and processes. Taking advantage of these relationships in vivo requires that drug ratios be controlled following administration by coordinating the pharmacokinetics of the combined agents so that optimal ratios are exposed to tumor cells while avoiding antagonistic ratios.

FIGURE 1



QWBA images of radiolabeled (^{14}C) cytarabine (top) and daunorubicin (bottom) 1 hour (left) and 24 hours (right) after intravenous administration to Sprague-Dawley rats. Darker shades represent increased concentration of drug.

Nanoscale drug carriers, such as nanoparticles and liposomes, are well suited for this application because they can be designed to synchronize the release of drug combinations following injection such that synergistic drug ratios can be maintained and delivered to tumors. We refer to this approach of controlling drug combination exposure in vivo as CombiPlex®, a technology in which drug development activities focused on specific combinations are prospectively integrated

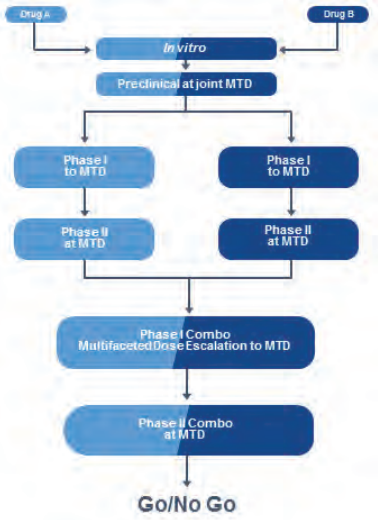
much earlier in the drug development process. The sections below describe how CombiPlex addresses the challenges facing the traditional development path of many contemporary drug combinations and provide clinical proof-of-principle evidence that this approach can yield marked improvements in efficacy and patient outcomes.

CHALLENGES FACING THE TRADITIONAL APPROACH FOR DEVELOPING DRUG COMBINATION REGIMENS

The early advent of front-line cancer treatment regimens were composed of multiple cytotoxic agents designed to indiscriminately overwhelm, disable, or disrupt multiple cellular processes that are more active in tumor cells compared to healthy cells. More recently, the development of molecularly targeted agents (MTAs) has expanded at a rapid pace, with high expectations for breakthrough treatments in a broad range of cancer types. Initially, this class was predicted to provide improvements in patient outcomes due to highly specific targeting of tumor cell-signaling processes and decreased non-selective systemic toxicity. While there have been promising signs of activity in previously difficult-to-treat tumor types (eg, B-Raf inhibitors used to treat melanoma), responses to single agent treatments have often been transient.[1] Cancer cells use multiple signaling pathways to both grow and resist therapies; consequently, it is not surprising that single MTAs often have modest or transient activity due to inter-pathway communication and feedback loops that compensate for loss or blockade of a targeted signaling pathway. These types of compensatory intracellular signaling networks create a situation in which many combinations require simultaneous target inhibition to be effective.[2] Due to MTA target specificity, combination therapy is of even greater importance because of the need to target multiple pathways in order to contend with the biological heterogeneity of human tumors. As a result, increasing efforts have focused on combinations of MTAs, and for certain indications, this has led to FDA approvals.[3,4]

The traditional drug development path focuses the majority of early stage (preclinical and Phase I/II) activities on the identification and development of new individual therapeutic agents aimed at targets that are believed to be important drivers in cancer progression. The effectiveness of any drug therapy is largely dictated by its pharmacokinetic and pharmacodynamic (PK/PD) properties. Consequently, these attributes are extensively studied and optimized to produce the most efficacious single agent treatment regimen possible within the drug class and for a particular clinical indication. However, this diligence does not typically extend to the development of drug combinations in which large differences in PK/PD properties can lead to markedly different biodistribution and tumor exposure between two combined drugs. These differences are readily seen in the quantitative whole body autoradiography (QWBA) images of rats administered the combination of cytarabine plus daunorubicin (Figure 1). The differences in the in vivo behavior of the two drugs administered in their conventional forms are striking. Both drugs rapidly distribute throughout the entire body within 1 hour following administration that may present toxicity implications. After 24 hours, virtually no cytarabine remains within the body, yet daunorubicin persists with higher concentrations in several organs. Both the rate of elimination and the biodistribution profile of these two drugs are substantially different, such that the ratio of drug concentrations in various organs changes greatly over time.

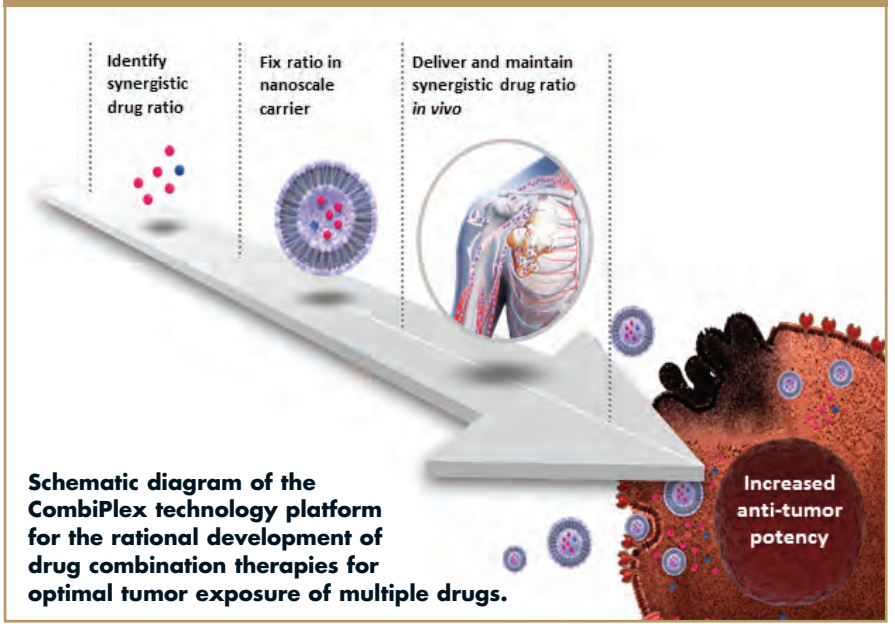
FIGURE 2



Traditional pathway for preclinical and clinical development of anti-cancer drug combination treatment regimens.

Although drug combinations are widely used within oncology because they are typically more efficacious than each agent administered on its own, the current approach for developing combination therapies (Figure 2) is inefficient in terms of the ability to identify and optimize the dose and schedule of each agent within the combination and the time and patient resources needed to develop each agent to registration. While there may be in vitro and preclinical studies supporting the utility of two drugs in combination, each drug is developed

FIGURE 3



Schematic diagram of the CombiPlex technology platform for the rational development of drug combination therapies for optimal tumor exposure of multiple drugs.

individually until registration before combination studies are initiated. This usually results in quite different treatment schedules for each agent and consequently, a significant amount of effort and experimentation must be performed in patients when the agents are eventually combined for use in a Phase I combination trial. A multifaceted trial is typically required to determine the dose of each agent and the schedule of the combination, frequently conducted by clinicians employing an empirical approach. Often, the more active agent is used at high doses, while the less-active agent is substantially dose reduced. Only at that point can the proposed combination regimen be evaluated for efficacy in humans, and it is generally not known whether the optimal tumor exposure of the multiple agents is achieved due to differences in PK/PD properties of the individual agents. Drug interactions affecting efficacy are almost never considered or exploited. Furthermore, it is often unknown whether the degree of target inhibition associated with regimens for the combined drugs based on safety profiles will, in fact, be most efficacious.

Conventional combination dosing regimens are unable to coordinate combination drug exposure to tumor cells due to large differences in PK/PD properties of the individual drugs, and consequently, the approach commonly used is to saturate the body continuously with high doses of each agent in an attempt to achieve simultaneous and prolonged inhibition of the intended targets. This can lead to excessive and often dose-limiting toxicity due to the extensive exposure of healthy tissues to the drugs that compromises the utility of the combination and, if doses must be reduced, limits target inhibition. An example of this effect is the combination of MEK inhibitors with Akt inhibitors. When agents of these two classes were combined in a Phase I trial using repetitive and prolonged oral dosing schedules, significant GI and dermal toxicities were experienced that necessitated additional dose escalation/de-escalation schemes.[5] While there was some evidence of anti-tumor activity, it was unclear whether these results reflected the optimal efficacy achievable due to the underlying tumor biology or if toxicities associated with uncoordinated PK and biodistribution precluded exposing the tumor cells to the optimal concentrations (ratios) of the two agents. Lack of certainty about drug delivery and maximal biological effect may cloud the interpretation of clinical outcomes.

THE COMBIPLEX ADVANTAGE: RATIONAL DEVELOPMENT OF COMBINATION PRODUCTS

Improving the effectiveness and efficiency of drug combination development requires changing the focus from developing single agents to registration prior to combining them in the clinical setting, to the rational development of drug combinations starting at the research and preclinical stage (Figure 3). CombiPlex offers the ability to optimize drug combinations for efficacy preclinically, rather than in the clinic, and in a manner that can be translated more predictably into the clinic. In vitro testing is used to identify drug-drug interactions and to establish the relationship between drug ratio and the degree of synergy/antagonism for simultaneous drug exposure in a broad range of tumor cells. Nanoscale drug carriers are then iteratively engineered to coordinate the PK/PD of the combined agents such that the optimal drug ratio for the combination identified in vitro is maintained over extended times following injection (Figure 3). Furthermore, nanoscale (eg, 20 to 100 nm diameter) particulate carriers, such as liposomes and nanoparticles, direct the distribution of drugs away from

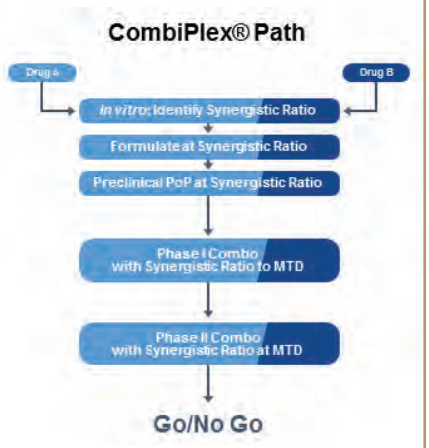
the majority of healthy tissues, while enabling preferential accumulation into sites of tumor growth due to increased vascular permeability of tumors. These features help overcome many of the problems associated with conventional combination regimens (in which the therapeutic window between efficacious and toxic doses is often very narrow) while at the same time also ensuring that optimal drug ratios are maintained with target cells exposed to sufficient concentrations of each drug to be maximally efficacious.

CombiPlex therefore minimizes the potential uncertainty of treatment outcomes due to the uncoordinated PK/PD properties of the combined drugs, as these properties are now dictated by the nanoscale carrier that maintains the drugs at the administered ratio. Drug ratio and tumor exposure are optimized at the preclinical stage, which allows starting clinical studies directly with the optimized drug combination product. Thus, CombiPlex (Figure 4) presents two major advantages over the traditional drug combination pathway (Figure 2). First, because CombiPlex introduces the combination in the clinic at the first-in-man stage, this avoids the redundant loop of Phase I/II testing of individual agents followed by re-evaluation in Phase I and Phase II trials as a combination. Second, CombiPlex nullifies the confounding influence associated with uncoordinated PK/PD of conventional combination regimens by ensuring that tumor cells are exposed to the combined agents at the optimal ratio. Therefore, CombiPlex-derived combination products will arrive at a more definitive Go/No-Go decision much earlier than the traditional model of combination drug development.

COMBIPLEX CASE STUDY: VYXEOS™ (CPX-351)

Combination chemotherapy incorporating cytarabine plus an anthracycline, such as daunorubicin, has remained the standard-of-care for newly diagnosed AML for over 40 years despite many attempts to improve this treatment regimen by altering drug dose and schedule or incorporating new cytotoxic and molecularly targeted agents. This situation provided an opportunity to directly test the impact of the CombiPlex approach versus the traditional combination approach head-to-head in a clinical setting. VYXEOS is a CombiPlex-derived liposomal formulation of cytarabine and daunorubicin at a 5:1 molar ratio. The PK/PD impact of the CombiPlex approach is readily demonstrated through QWBA images of rats treated IV with VYXEOS compared with conventional administration of the same drugs (Figure 1). When encapsulated within a rationally designed nanoscale carrier designed to coordinate in vivo drug exposure, the QWBA images of cytarabine and daunorubicin for VYXEOS (Figure 5) show significant differences in both biodistribution and pharmacokinetic properties compared to the free drugs. At 1 hour (left side images), both VYXEOS-delivered cytarabine and daunorubicin show less systemic distribution to tissues than the free drugs (Figure 1) and demonstrate preferential localization to the bone marrow (the site of leukemia growth), as evinced by the higher concentrations of both drugs in the femur. In contrast to the observations with the free-drug combination, both drugs in VYXEOS remain present at the same ratio in the images taken at 24 hours and continue to localize within the marrow at the tumor site (Figure 5). Extensive preclinical testing demonstrating drug ratio-dependent efficacy and significant improvements in efficacy for VYXEOS compared to the free-drug cocktail supported the evaluation of VYXEOS in a clinical setting.

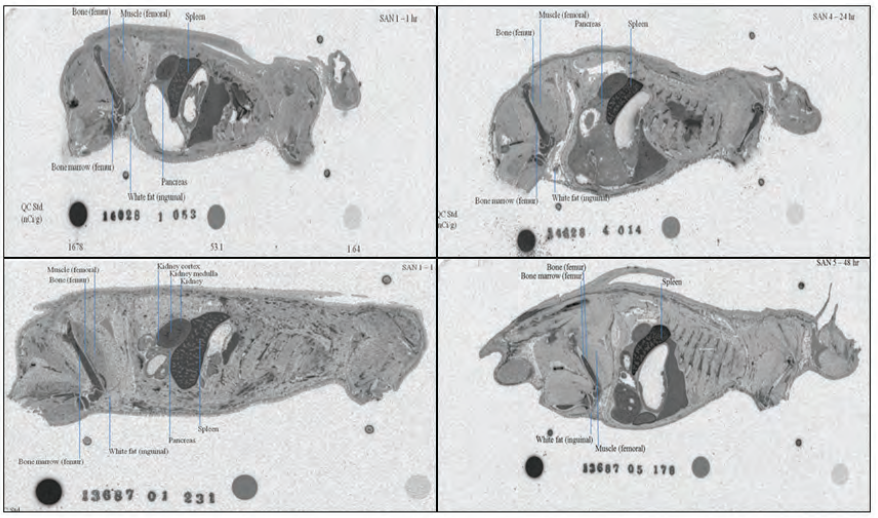
FIGURE 4



Rational development of a drug combination using the CombiPlex approach.

Multiple clinical trials have demonstrated the translation of CombiPlex combination development to improved clinical efficacy. Promising anti-leukemic activity was observed in the Phase I trial of VYXEOS in patients with advanced acute leukemias, most with relapsed AML following prior cytarabine and daunorubicin treatment. VYXEOS produced multiple responses (4 out of 12) at sub-MTD doses as low as 32 units/m^2 (32% of MTD), with 9 responders at or below MTD, 8 of whom had previously received cytarabine and daunorubicin. These encouraging results led to two randomized Phase II trials in which VYXEOS was evaluated against the 7+3 regimen of cytarabine and daunorubicin in newly diagnosed elderly AML patients and against investigators choice salvage

FIGURE 5



QWBA images of VYXEOS-derived radiolabeled (^{14}C) cytarabine (top) and daunorubicin (bottom) 1 hour (left) and 24 hours (right) after intravenous administration of VYXEOS to Sprague-Dawley rats. Darker shades represent increased concentration of drug.

therapy in first relapse AML patients. VYXEOS provided improvements in complete remission rate, 60-day mortality and overall survival in subsets of high risk patients. For newly diagnosed secondary AML patients, VYXEOS nearly doubled the median overall survival from 6.3 to 12.1 months (Figure 6). In the first relapse trial, the median overall survival increased from 4.2 months for salvage treatment to 6.6 months for VYXEOS. The survival improvements in high risk patient subsets were statistically significant in both trials.[6,7]

The Phase II trial in newly diagnosed elderly AML patients identified the high risk (secondary) AML population as one with a high unmet need for which VYXEOS appeared to provide the largest efficacy improvement and survival benefit. Subsequently, a Phase III trial evaluating VYXEOS versus 7+3 in this population resulted in a 43% relative improvement in CR+CRi rates for VYXEOS (47.7% vs. 33.3%). Final results are expected in the first quarter of 2016. Taken together, the clinical trial results reported to date provide compelling validation of the CombiPlex approach for the rational development of drug combination products.

COMBIPLEX COMBINATIONS ON THE HORIZON

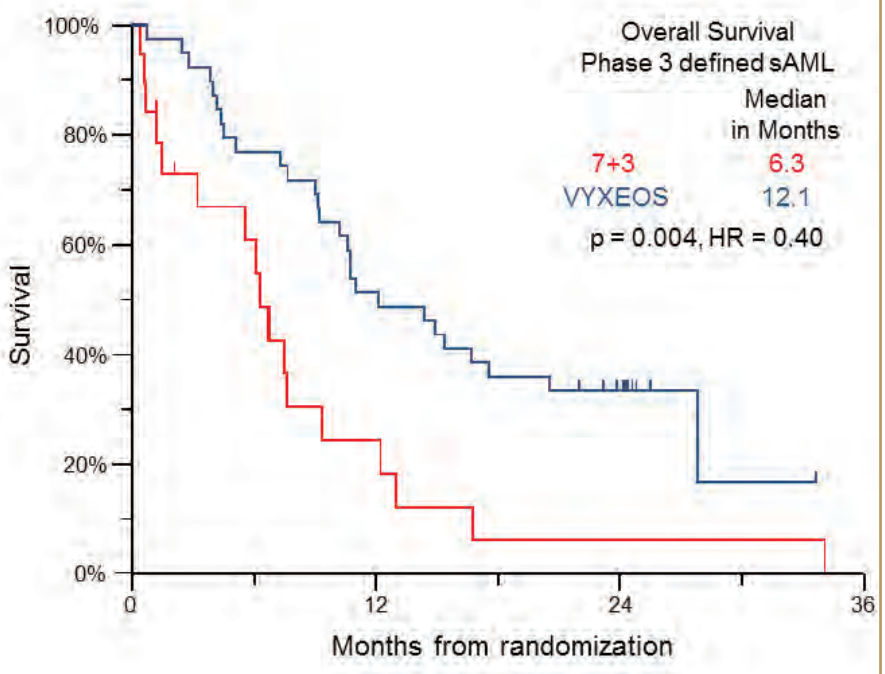
With strong clinical data providing proof-of-principle, CombiPlex was recently expanded to combinations of MTAs using Celator's hydrophobic prodrug nanoparticle (HPN) delivery technology.[8] The HPN concept is broadly applicable: MTAs from diverse classes, including inhibitors of MEK, Akt, HSP90, B-Raf, and FGFR as well as docetaxel, were all successfully formulated in polymer nanoparticles. In all cases, HPN delivery eliminated the early distribution phase observed for conventional formulations of these agents, which has been associated with significant exposure and toxicity to normal tissues. This was reflected by the fact that HPN co-formulated combinations of docetaxel plus the HSP90 inhibitor AUY922 as well as the MEK:Akt inhibitor combination of selumetinib plus ipatasertib could be administered at much higher doses.

For both combinations, the CombiPlex formulations provided significant improvements in efficacy over the free-drugs in human xenograft cancer models. Furthermore, evidence of strong drug ratio-dependent efficacy and in vivo synergy was observed in which the largest improvements were observed in models that were more resistant to the drugs administered in their conventional forms. Once HPN formulation conditions were optimized for these first two combinations, the approach was readily extended to the B-Raf and FGFR inhibitors. Both were successfully co-formulated with the MEK inhibitor selumetinib, resulting in coordinated drug exposure in the plasma. In addition, prodrug components could be "mixed and matched." This versatility was exploited to generate a 3-drug combination, a co-formulation of selumetinib, AUY922, and docetaxel prodrugs in a single HPN that exhibited a plasma half-life of 10 hours in mice with no early distribution phase.

CONCLUSION

The traditional drug development path may limit the ability to capture the full efficacy potential of combinations composed of chemotherapeutics as well as highly potent molecularly targeted agents due to the uncoordinated PK/PD properties of the individual drugs and the presence of drug ratio-dependent synergy/antagonism. CombiPlex provides an avenue to develop and optimize combinations prior to approval

FIGURE 6



Survival curves for patients with secondary AML in a two-arm, randomized Phase II trial of VYXEOS against the standard 7+3 therapy regimen.

of individual agents in a manner that controls drug ratios and coordinates in vivo drug exposure through the use of nanoscale drug carriers. Optimizing combinations as early as possible in the development process may enhance efficacy, improve safety, and reduce the time and patient resources required to create effective combination therapies. ◆

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BIOGRAPHIES

Dr. Barry D. Liboiron joined Celator Pharmaceuticals in 2006, as a Research Scientist in biophysics, and was promoted to direct the department as Director, Biophysical Characterization and Advanced Solutions in 2008. Dr. Liboiron earned his BSc with distinction from the University of Guelph, his PhD degree in Inorganic Chemistry from the University of British Columbia, and completed a post-doctoral fellowship in Bioinorganic Chemistry at Stanford University.

Dr. Arthur C. Louie is Chief Medical Officer at Celator Pharmaceuticals. He is a board-certified Oncologist with more than 25 years of experience in Pharmaceutical Research and Development. Dr. Louie earned his BA in Biology with honors from Haverford College and his MD from New York University. He completed oncology fellowships at the National Cancer Institute and Stanford University.

Dr. Lawrence D. Mayer is the President, Chief Scientific Officer, and Founder of Celator Pharmaceuticals. He has played a lead role in the discovery and development of numerous anti-cancer drugs, several of which achieved market approval. Dr. Mayer has authored over 250 publications and has more than 35 patents either awarded or pending. Dr. Mayer earned his BSc summa cum laude from Wartburg College and his PhD from the University of Minnesota.

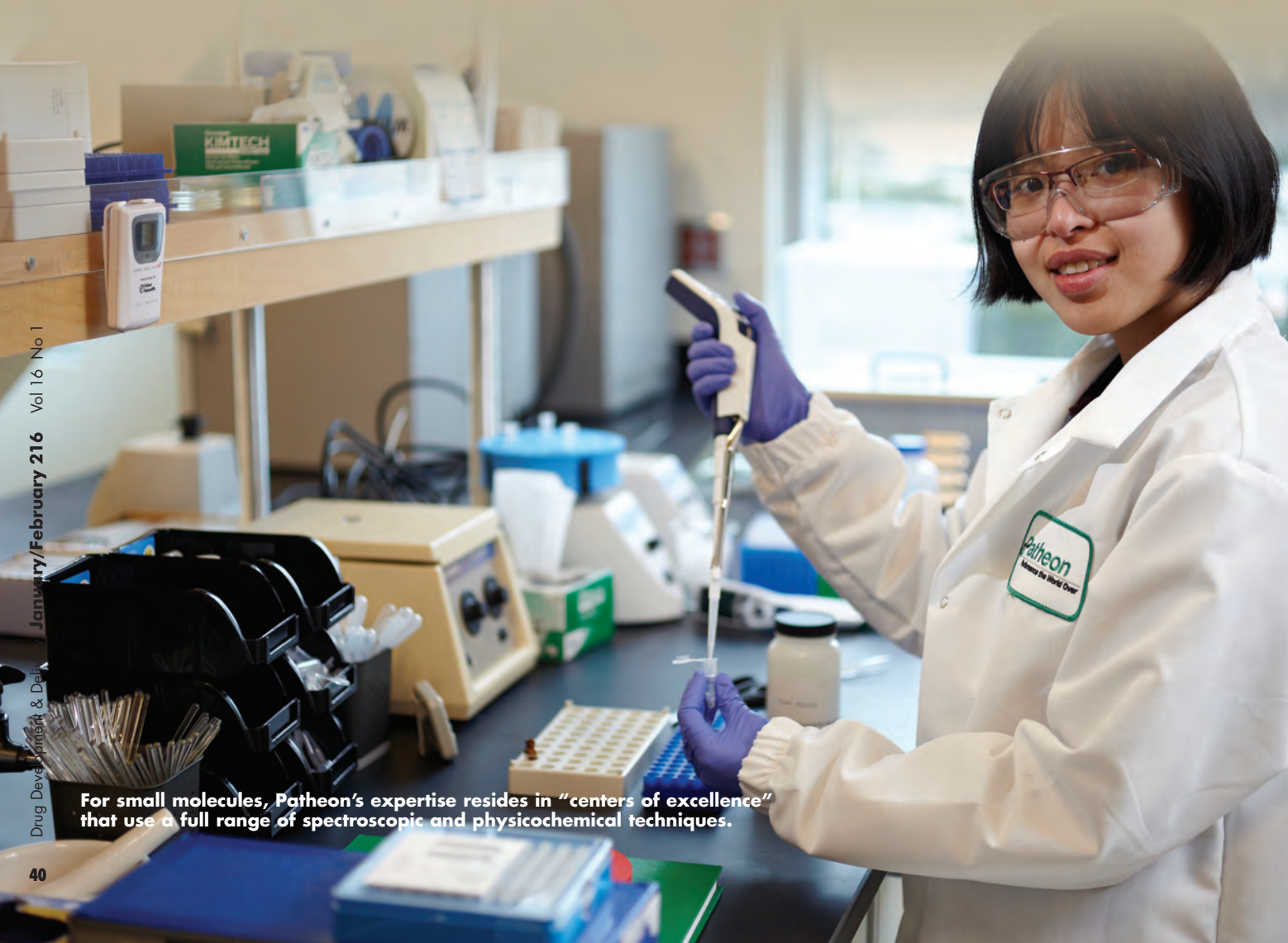
Special Feature

Analytical Testing: Using More Sophisticated Tools to Support Small & Large Molecule Projects

By: Cindy H. Dubin, Contributor

As pharmaceutical companies increasingly demand more integrated solutions from fewer vendors, contractors are adding capabilities. One area where this is becoming evident is in analytical testing, where contract labs are procuring more analytical tools to handle increasingly complex multinational clinical trials on an accelerated basis, according to Capstone Partners.[1]

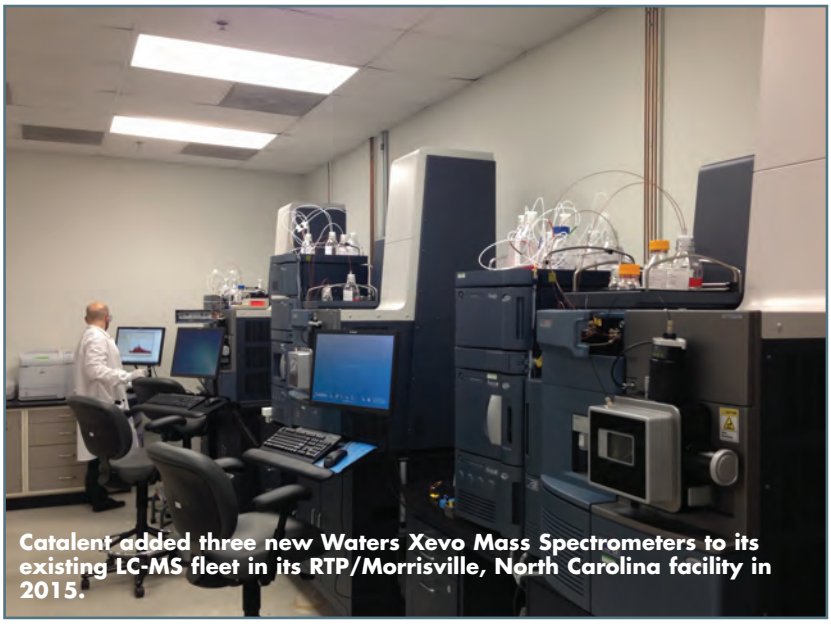
"Analytical testing plays an important role in all phases of pharmaceutical development and is the most outsourced among all CMC activities," says Chris Gregory, General Manager of Catalent's Morrisville, NC facility. Gregory says new trends in the pharmaceutical and biotech industry are driving innovation and creative outsourcing solutions.



For small molecules, Patheon's expertise resides in "centers of excellence" that use a full range of spectroscopic and physicochemical techniques.

First, the pharma outsourcing model has changed in recent years. Traditionally, big pharma outsourced late-phase and routine programs to analytical testing labs and retained early-phase method development projects and problem-solving activities in house. Recently however, big pharma is transitioning bench scientists from laboratory work to direct management of outsourcing activities. Additionally, companies are outsourcing their analytical work much earlier in the product development phases. Occasionally, contract analytical labs are engaged when dealing with some of the most challenging projects so scientists from both labs can work through the problems together.

The second trend, according to Wei Pan, PhD, Director Strategy and Analytical CMC at Catalent, is a result of a recent FDA guidance, "Abuse-Deterrent Opioids – Evaluation and Labeling." The FDA now expects development programs that study abuse-deterrent technologies to include data from three categories: laboratory-based *in vitro* manipulation and extraction studies (Category 1); pharmacokinetic studies (Category 2); and clinical abuse potential studies (Category 3). Category 1 testing is exclusively laboratory-based and proper design of studies is essential. Results from Category 1 studies identify the methods of manipulation that yield the greatest release of opioid. This is critical because it influences the design of both Category 2 and Category 3 clinical studies.



Catalent added three new Waters Xevo Mass Spectrometers to its existing LC-MS fleet in its RTP/Morrisville, North Carolina facility in 2015.

"For companies without experience designing and conducting Category 1 abuse-deterrent studies, outsourcing these studies to analytical labs with expertise in this area will save money and time, and ensures that proper data is generated in support of pharmacokinetic and abuse potential clinical studies," says Dr. Pan.

For large molecules, the areas of analytical testing to support CMC activities that are on the rise include surfactant and process impurity testing, glycan analysis, and high-resolution analysis of macromolecules. There has also been an industry shift from slab gel to capillary analysis for electroseparations, and a call for more robust effector function assays for monoclonal antibodies and kinetic binding assays (both surface plasmon resonance and biolayer interferometry). These changes are mainly driven by increased regulatory expectations as advances in analytical resolution/sensitivity and capacity increase, and more becomes known about the increased complexity of biological molecules (e.g. fusion proteins, conjugated, bispecifics).

"As the industry has matured, there are greater expectations for analytical details to fully understand the molecule, especially in the ever-advancing field of biosimilarity, and the requirements that are needed to prove equivalence," says Rekha Patel, Large Molecule Analytical Chemistry at Catalent.

Drug Development & Delivery Magazine recently spoke with leading analytical testing providers to find out what services they offer and what equipment they use to handle both small and large molecules for their pharma clients.

Catalent—Finding Solutions for Development Challenges

Catalent provides a full range of analytical services to pharmaceutical and biotechnology companies to support both drug development and manufacturing. As drug product pipelines fill with molecules that are becoming more complex and challenging, the instrumentation and technologies needed to support clients and satisfy regulators have to evolve. Catalent has invested in increasingly sophisticated instrumentation to assist its clients in solving the most challenging analytical problems for large and small molecules.

In addition to basic analytical services, Catalent offers more complex analysis such as mass spectroscopy (including Orbitrap, Triple Quad Mass Spectrometry, Q-TOF Mass Spectrometry, and Ion Trap capabilities), bioassays, kinetic binding assays (Octet and Biacore), and characterization tools such as analytical ultracentrifugation (AUC), circular dichroism, Fourier Transform Infrared (FTIR) Spectroscopy, and MicroFluid Imaging (MFI). Catalent can undertake complex and challenging chromatographic assays to support peptide map analysis including glycan and excipient analysis. Assays can be transferred from clients for optimization to Catalent's large molecule analytical service, or developed from scratch to be used for a multitude of purposes such as characterization, stability testing, release testing, in-process testing, and all levels of phase-appropriate validations.

For companies developing small molecules, poor solubility/bioavailability is a challenge. Catalent has developed the OptiForm® Solution Suite to accelerate development and reduce risks at the early screening phase. This analytical screening solution follows a three-step approach: 1) application of high throughput screening tools to collect pre-formulation data to assess the molecule's characteristics; 2) evaluation of multiple bioavailability enhancement technologies in parallel (e.g., particle size reduction, polymorph or salt form selection, hot melt extrusion, lipid-based softgel capsules); and 3) delivery of the optimal formulation. This integrated service helps the molecule progress to animal pharmacokinetic studies and Phase I clinical trials.

The Catalent analytical scientist team recently helped a client solve a challenging problem at a critical time. A softgel capsule manufacturer observed a new impurity peak that was out of specification in all batches during process validation. Laboratory investigation performed in the customer's QC lab suggested that the peak was real and needed to be fully identified and characterized. With stock build-up and product launch in jeopardy, the customer reached out to Catalent for help. Utilizing LC-MS, the team quickly identified the unknown peak as two co-eluting phthalate peaks. Phthalates are common plasticizers used to make plastics more flexible and hard to break. The Catalent scientists worked with the softgel manufacturer to gain knowledge of the production line, and eventually traced the phthalate's source to a piece of PVC tubing used in the production line. With the information Catalent provided, the customer made the necessary change and moved forward with its product launch plan.

"This analytical and investigative mindset is typical of Catalent scientists who are in the business of finding solutions for challenges in drug development, for both small and large molecule formulations," says Chris Gregory, General Manager of Catalent's Morrisville, NC facility.

Patheon—Focused on Three Areas of Analytical Capability

Most technical decisions made during development and manufacturing are based on analytical testing results. Analytical development laboratories don't get to select the compounds they work on, so the key to project success is having an analytical team with strong scientific capabilities, good instrumentation, deep and broad problem-solving experience, and a large network of experts to provide a specialized focus when needed.

There are three critical areas where analytical capability plays a crucial role in long-term project success. First, characterization of the active ingredient and a thorough

understanding of its interaction in the expected formulation environment are vital to developing good formulations. For small molecules, Patheon's expertise resides in "centers of excellence" that use a full range of spectroscopic and physicochemical techniques. The real value comes in not just rote application of instrumental techniques, but also integrating the information into a comprehensive assessment of formulation approaches for low-solubility compounds.

"Our formulation agnostic approach combines analytical characterization and parallel screening of formulation options, such as lipid emulsions in soft or hard-gelatin capsules, solid dispersions (spray-drying), and particle size reduction to rapidly identify the most promising outcomes," says William E. Weiser, PhD, Executive Director, Global Head of Analytical Sciences, Patheon.

In addition, Patheon's Quadrant2™ technology is a hybrid computational and empirical tool that identifies appropriate formulation technologies, defines valid excipient choices, and produces acceptable drug-loading expectations for the company's formulation processes supported by Patheon.

The second critical area for long-term analytical success is the development and validation of robust methods for determining assay and related substances. This activity is accomplished through a combination of chemical knowledge and method development context. Knowledge development is based on the continuum of information developed for the API, formulation, manufacturing process, and stability assessment stages, and even during troubleshooting activities.

"Our OneSource™ program can streamline development by sharing compound-specific knowledge, developing testing methods in parallel, sharing method development responsibilities, and facilitating seamless hand-offs throughout a project," explains Dr. Weiser. "Method development context is an understanding of the starting point for an incoming method and how the method is going to be used. We use a phase-sensitive risk assessment for all methods that quantitatively ranks the risk of the method. We can then judge the value of any needed method development relative to the stage of the project. Further optimization is accomplished in a structured fashion using automated systems to map out the method design space. This approach is aligned with recently issued guidelines from the FDA ("Analytical Procedures and Methods Validation for Drugs and Biologics – Guidance for Industry," FDA, July 2015)."

The third critical area is developing and executing methods with long-term robustness and reliability. In early stages of projects, method development may be done quickly with the goal of just getting something to work. An example of a poorly designed method is an extended gradient HPLC method (40 minutes) used to test dissolution or content uniformity samples. While this approach may work for a Phase 1 program, in later stages, the impact may be dramatic. For example, during process validation or QbD studies, the sample load can quickly become onerous (thousands of samples equating to weeks of run time). With emerging emphasis on continuous manufacturing, the ability to generate samples may completely outstrip analytical capacity for an inappropriate method.

To demonstrate the value of an integrated analytical/formulation approach to problem solving, consider this example of a poorly soluble, small molecule NCE formulated in a soft-gelatin capsule. Although developmental formulations were demonstrated to be stable, a small change in the capsule fill concentration was required for clinical needs. According to Dr. Weiser, formulated product that used API from a different supplier generated undesirable precipitates in the filling matrix. A combination of XRPD, DSC, hot-stage microscopy, and particle size analysis was used to characterize the API, while IR was used to verify the non-API nature of the precipitates. In this case, the analytical testing and knowledge of the formulation fill matrix was required to advance the product and generate an acceptable formulation for clinical trials. "Blind application of even highly advanced analytical techniques does not solve formulation

SGS Life Science Services uses post-column derivatization with ninhydrin for raw material testing and deformulation projects.

challenges; integration of project and product knowledge in parallel with analytical science is the key to success," says Dr. Weiser.

SGS Life Science Services—Using New Methods to Address Client Needs

Outsourcing of analytical testing to the cGMP contract research organization gives pharmaceutical companies peace of mind that laboratory testing integrity is in the hands of experts. Although the majority of analytical tests for well-known APIs and excipients are performed following USP and other pharmacopoeial procedures, there is high demand for highly sensitive, specific, and high throughput techniques for analytical testing of newly discovered potential drugs in both API and final formulations.

SGS Life Science Services deploys established and conservative analytical procedures, as well as the latest technology and methodologies. "For example, instead of monitoring impurities of amino acid raw materials (ninhydrin positive substances) by thin layer chromatography (TLC), modern post-column derivatization with further detection in visible range by HPLC is being used at our lab," explains Natalia Belikova, PhD, Analytical Services Director, SGS Life Science Services.

Post-column derivatization with ninhydrin has been used successfully by SGS for raw material testing, as well as for deformulation projects, where individual components of a formulated product needed to be separated, identified, and quantified.

"For example, we have had requests to analyze Histidine, Arginine, Lysine, and other amino acids (both in base and hydrochloride forms) for ninhydrin-positive substances tests (EP 2.2.56, Method 1)," explains Dr. Belikova. "We have also executed a study for a patent prosecution group for Arginine Monohydrochloride."

Xcelience—Ensuring the Final Dosage has the Right Properties

Testing capabilities that can help move a client's product through the development process begin at the pre-formulation stage. By building a good base of data with the API, problems that might be encountered later during the developmental process can be more easily identified and overcome. This includes using XRD to determine the polymorphic structure, running pH solubility profiles, and particle size/distribution analysis. This data will help ensure that when the API is made at a larger scale, the physical and chemical properties of the API do not change. During manufacture, the testing can include determining moisture content to ensure there is good content uniformity, and monitoring tablet hardness that can change the dissolution profile. Additional testing could include instrumentation such as Accupyc and GeoPyc, which will provide true density of the ribbons produced during roller compaction. A ring shear tester can be used to measure the potential of granulation to stick to dosator or tablet punches. The analysis on the finished dosage form will include dissolution, assay by HPLC or UPLC, moisture content, and polymorph testing.

"The goal is to ensure that throughout the manufacturing process, appropriate properties are monitored to establish that the final dosage form has the desired properties," says Paul Skultety, PhD, Vice President, Pharmaceutical Development

Services, Xcelience.

A trend in the pharmaceutical business is to build quality into the product. With this in mind, the analytical method development process is also being adapted. Techniques include not only generating appropriate data, but also developing equipment that can generate the data faster. Examples include UPLCs, applying automation to disintegration apparatus to determine disintegration times for each tablet or capsule automatically, and developing better or more sensitive analytical techniques to provide the requisite data in a timely manner.

The biggest challenge associated with analytical testing is to determine what properties of the dosage form need to be monitored and what specifications should be put in place to maintain the desired properties. Once these are determined, the analytical tests need to be developed with enough sensitivity to adequately monitor these properties. This can include ensuring such things as the correct polymorphic structure is maintained, and particularly for controlled-release products, that the right dissolution profile is maintained.

Developing the right dissolution test method for poorly soluble, high-dose compounds also can be a challenge. The method must show that the API will be completely released in the desired time frame. Often, clients are using API in capsule for Phase I clinical trials. For low-dose compounds, it can be a challenge to develop a technique for an assay or determine moisture content for a capsule shell containing less than one milligram of API, says Dr. Skultety.

Xcelience has 28 HPLCs, 2 UPLCs, 9 dissolution baths, and more.

Another challenge is with combination products, which can sometimes have a larger number of degradation compounds that must be separated. Two examples come to Dr. Skultety's mind. The first was a problem that arose with a capsule product. The capsule shell was cross linking and the product would not dissolve. After lengthy evaluation, it was determined that the problem was due to the presence of an aldehyde in part per million quantities.

"The product was saved by limiting the specification for the amount of aldehyde," he says. "Once this was established, the stability of the product was fine."

The second example was the use of XRD to monitor the appropriate polymorph. The product was a wet-granulated tablet. It was determined that the amount of water added and the wet massing time could change the API to a different polymorph or cause the API to become amorphous. A technique was developed to measure the quantity of different polymorphs in the granulation. This allowed for a granulation process to be developed that ensured the finished dosage form had the correct polymorph. ◆

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Reference

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DRUG DEVELOPMENT

Human Challenge Studies in Vaccine Development

By: Bruno Speder and Adrian Wildfire, MS

ABSTRACT

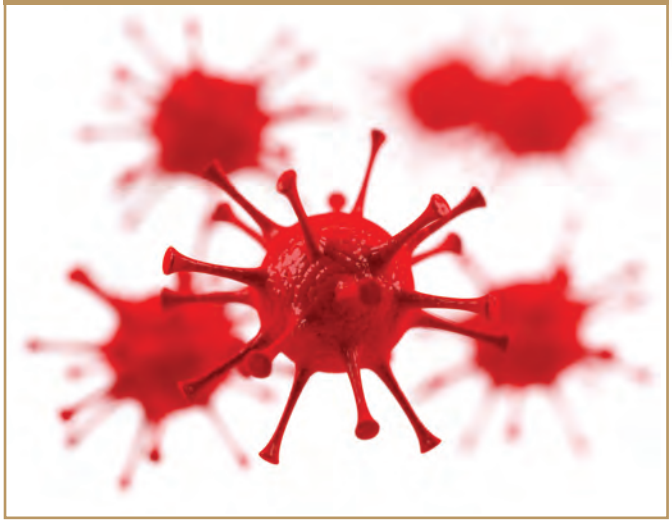
The human challenge model (HCM) for the study of pathogenic organisms comprises the deliberate exposure of humans to known or putative disease-causing material. The following review describes how the concept is being applied to help develop vaccines against a number of common diseases, including influenza, rhinoviruses, respiratory syncytial virus (RSV), cholera, malaria, dengue, and *Salmonella typhi*.

INTRODUCTION

Since the 1990s, the human challenge model (HCM) has been used to provide early performance data through proof-of-concept (PoC) and mode of action (MoA) studies to accelerate the clinical development of vaccines. Governmental and commercial organizations are developing challenge models to accelerate vaccine development programs, eg, for siRNA and mAB trials in respiratory tract infections (influenza and RSV), and to gain a better understanding of the underlying pathological processes that drive immune responses. Such exploratory models started gaining favor in regulated clinical trials in the early 1990s and were first mentioned in regulatory guidance in 2010.

Users of HCM frequently emulate previous protocol designs, as these have proven value and offer a route toward a standardized model. To ensure statistically significant data, it is essential to employ previously characterized human

FIGURE 1



challenge stocks with known attack rates, consistent symptomology, and predictable adverse event (AE) rates, i.e. Virus Emergent Adverse Effects (VEAEs). However, despite the many years of use, there are still no agreed guidelines referencing the quality requirements for the challenge agent or performance of a human challenge study (HCS). It is generally accepted that challenge agents should be manufactured under cGMP conditions when used in the framework of a clinical trial; however, for experiments that are not considered a clinical trial, there is no formal advice. The FDA has published an expectation regarding challenge agents, and the EMA and several EU national agencies have indicated that a virus should comply with the quality requirements of an investigational medicinal product (IMP), but there are, as yet, no references to human challenge in the ICH-GCP regulations. It would assist

the HCS community if an agreement could be reached as to quality requirements for challenge agents and its classification [IMP /Non-Investigational Medicinal Product (NIMP)]. The International Association for Biological Standardization has debated this subject, and some consensus was reached but no "white paper" or other draft guideline has, to date, been issued.

Regulatory-wise, HCS are accepted for the following:

- as PoC studies for influenza and other upper respiratory tractinfections. In such Early Phase studies, protective (vaccine) or curative (vaccine/drug) efficacy is being assessed. There are currently no specific guidelines regarding efficacy markers (correlates of protection) for PoC in HCS studies, although the FDA guideline on influenza studies mentions haemagglutination and tissue culture infective dose 50% (TCID50)

- as a method for determining optimal dosage (to identify the correct individual dose, dose range, or schedule for field studies)

INFLUENZA CHALLENGE CONSIDERATIONS

For a challenge study to prove effective, it is essential that subjects are confirmed to be susceptible to the challenge agent prior to entering a trial to ensure a high attack rate (rate of infection). Unfortunately, despite a general agreement that measurement of the haemagglutination antibody (HA) is an effective method for assessing immunity to influenza, variabilities in the sensitivity of the HA assay, and changes in agglutination potential of viruses currently circulating worldwide, may serve to lower the predictability of attack rates from 100% to 80% or less. Prior to enrollment in a challenge trial, subjects should be pre-screened in order to assess the relative naivety of the cohort to the challenge agent. Subjects should also be quarantined for at least 48 hours prior to admission to avoid cross-contamination by concomitant diseases, or the entrance of a secondary infectious agent into the unit. Subjects are usually kept separated and are tested for adventitious agents prior to enrollment to reduce the chance of drop-outs or failures due to infection control failures.

Interventions in an HCS may be drug-related (dosing post-inoculation with the challenge agent), preventative-vaccine-related (vaccination up to 3 months prior to challenge), or therapeutic-vaccine-related (vaccinated just prior or at the time of inoculation). Other considerations affecting dose-response may be the dose or titre of the challenge virus, or the type/suitability of the virus to the model being tested, eg, strain-specific interventions.

Identifying the most appropriate outputs (objectives) may be crucial to the success or failure of an intervention, eg, are the correlates of protection (CoP) known? Can the assays be standardized against a World Health Organization (WHO) or other recognized control? What bioavailability requirements are there, and can they be related directly to the therapy/challenge agent, eg, cytokine stimulation? Are the symptoms or any AEs because of VEAEs or treatment emergent (TEAE)?

Wider ethical considerations concerning the HCM (extant to the subject informed consent) come into play when potential threat(s) to the subject, staff and the public collide. For example, can subjects be released into the community following a challenge study if they are still qRT-PCR or antigen positive? What is the relative risk associated with such subjects? Further work is required to assess the relative transmission rates of differing challenge agents and the mechanisms underpinning infectivity. To date, safety parameters are largely based on theory or observational studies and the principles of barrier nursing.

From a regulatory point of view, appropriate quarantine measures (isolation and supervision) are required to be put in place to assure the authorities that not only are trial staff and the community safe from immediate disease, but also that the likelihood of long-term sequelae within the subject cohort are low. Quarantine conditions are also part of the quality envelope, protecting subjects and staff from cross-infection, ensuring observation and interventional analyses may be performed in a timely manner, thus optimizing the accuracy or purity of measurements.

RELATIONSHIP BETWEEN HCM & INFLUENZA FIELD TRIAL RESULTS

Late phase field trial data demonstrating the relative efficacies of the two predominant influenza vaccines

– trivalent, cold-adapted influenza vaccines (CAIV-T - live) and trivalent influenza vaccines (TIV - lyophilized) – has been proven to be reproducible in the HCM. Measurements of efficacy (attack rates, incidence and severity of disease and antibody response) are similar for vaccine classes and viral serotypes.

Influenza, rhinoviruses, respiratory syncytial virus (RSV), cholera, malaria, dengue, and *Salmonella typhi* amongst others have all been trialed in Human Challenge Trials (HCTs) against potential vaccine candidates. The only limiting factors have proven to be the availability of a suitable agent (cGMP) and the potential for adverse events or long-term sequelae associated with certain agents.

The general regulatory principles that apply for influenza challenge trials also apply for other pathogens and vaccines. The agent of disease must possess the necessary characteristics, i.e., high attack rate, short (acute) disease state, consistent symptomology, and available therapeutics or support measures to be considered as a challenge agent. An additional regulatory complication, depending on the virus and its GMO classification (type II/III), may be the difficulty in finding a suitable clinical pharmacology unit (CPU) with the appropriate quarantine facilities.

POTENTIAL USE OF INFLUENZA CHALLENGE MODELS IN HUMANS

In the field of influenza, susceptible populations or cohorts may be challenged with differing strains or serotypes of influenza to enable the performance of PoC studies for antiviral drugs and vaccines; the establishment of relevant etiology/ies; assessments concerning the immunogenicity of candidate vaccines; and the kinetics of immune responses as well as the development of correlations between clinical trial data and resistance to infection. The development of such correlates has proven pivotal in the rapid evaluation of vaccine efficacy against seasonally variant influenza strains.

Thus, the HCM model may be used to accelerate both validation and discovery programs through concepts related to protective antibody levels and insights into novel mechanisms of immunity.

Regulators have voiced criticisms concerning the limitations of the HCM, including the fidelity of manufactured challenge agents to wild-type stains; reduced pathogenicity and symptomology; high viral counts in inocula and the volumes applied and route of inoculation; excessive attenuation of agents during the manufacturing process (passage associated); and the potential for mutations in surface proteins and genomic sequences. However, to ensure subject safety and to comply with infection control measures, subject/pathogen balance must be maintained in favor of the subject. Should challenge agents cause significant morbidity or long-term sequelae, the value of the model as a reliable and safe model would be diminished and the willingness of subjects to participate would suffer.

To try to address some of the issues raised by regulatory authorities, circulating and naturally attenuated strains of organisms are used as far as is possible (for example in malaria studies and *Plasmodium falciparum*) to best represent the naturally occurring disease state. However, both regulatory and ethical considerations may ultimately serve to limit the use of highly pathogenic or chronic disease-causing agents. It may also be the case that challenging subjects with replication defective agents, eg, HIV or HCV, may not be an acceptable solution for investigating such viral diseases until other *in vivo* models have been exhausted.

POTENTIAL ROLE OF HCS IN THE MARKETING AUTHORIZATION APPLICATION

HCS may play a significant role in the Marketing Authorization Application (MAA) for both vaccines and drugs. PoC and limited safety data from HCS may also serve to accelerate and enhance later clinical trial applications (CTAs). However, regulators are rightly wary of placing too much emphasis on HCS data due to the limited cohort sizes (approx. 80 subjects); restricted safety database (inherent to studies with limited subject numbers and short timelines); a controlled study environment not strictly representative of the "natural habitat;" and the manner of transmission [large volumes of virus may have the potential to overwhelm natural (innate) immunity processes].

It has been suggested that performing larger challenge studies (200+ volunteers) or supplementing the HCS with an early phase safety study, would increase the statistical significance of the data. However, emulating natural routes of infection is currently limited by our knowledge of viral epidemiology

and the relative significance of droplet versus contact transmission rates.

Although it is inherent to the model that HCS studies should take place in a controlled environment, it may be possible to make subject inclusion/exclusion criteria less stringent in order to better mimic natural populations. Also, where correlates of protection demonstrate strain or intra-assay variability [the predominant strains of influenza A circulating since 2010 demonstrate poor haemagglutination in haemagglutination inhibition assays (HAI) – a primary marker for immunity], it may be an appropriate strategy to use HCS as a direct in vivo efficacy model. Finally, for some indications in which the population to be challenged is similar to the population that will receive the vaccine, eg, vaccines for travelers, HCS could be considered for use as a pivotal study.

FURTHER DEVELOPMENTAL WORK

More work is required to identify and define more effective/predictive correlates of protection. The lack of understanding behind some vaccine models must serve to lessen the impact of many studies, both early and late phase, if such poorly understood or inconsistent correlates alone are used as the primary outcome. Although it has been stated that "efficacy trumps all," that efficacy cannot be later translated into advances in knowledge or understanding if the CoP can only be defined as "it worked" and not directly related to a measurable marker. Both the academic and commercial sectors require improved correlates to measure the effect of therapeutics of all types on disease states.

A STEP IN A LONG ROAD

It is becoming widely accepted that HCMs can tangibly accelerate certain pipelines and add directly to the body of knowledge relating to a product and its interactions, both with the challenge agent and the host. As the HCM becomes popularized as part of the route to licensing, accessibility to the model and relevant challenge agents may become more of an issue than acceptability. Efforts to make cGMP challenge agents more widely available are being supported by the NIH; however, historically, private investors have funded and thus driven the model, bridging the transition of HCM from academia to industry. Given the considerable investment required, it is unlikely that many new players will enter the field in the short-term and that the challenge will remain a premium service with limited access.

With a global need for new antibiotics and antivirals and a low take-up rate by industry for less-rewarding avenues and indications, it may fall to state institutions, including regulators alike to promote novel means of bringing investigational products rapidly to market, where safety is not compromised, and early efficacy data can enable the rapid prioritization of promising candidates.

In conclusion, although further evolution of the model may be required before it can address all the regulatory strictures, the HCM has already provided efficacy data for a large number clinical trials, principally for upper-respiratory tract infections, and has been instrumental in providing timely non-inferiority data for a range of new anti-influenza drugs. Requests for HCS continue to increase year over year, and it is to be expected that as early phase trials are potentiated, the number and size of late-phase studies may be reduced in accordance with the value of the EP data. Human challenge studies are a relatively new phenomenon in EP trials, and their contribution has still to be fully realized. ◆

BIOGRAPHIES

Bruno Speder holds a degree in Bio-engineering and a degree in Business Economics from the University of Ghent, and has an additional degree in Health Economics from the EHSAL Management School. He joined SGS Life Science Services in 2008, and has held several positions in the regulatory group before assuming his current position as Head of Clinical Regulatory Affairs. In this role, Mr. Speder is involved in all the regulatory aspects of drug development, with a focus on regulatory support to sponsors in early development phases.

Adrian Wildfire is Project Director, Infectious Diseases and Viral Infection Unit, at SGS Life Science Services and has nearly 30 years of experience in communicable diseases. He has trained and worked within the fields of bacteriology, virology, parasitology, and mycology, obtaining his Fellowship in Medical Microbiology in 1990 and a Masters in Parasitology in 1998. He is the author of numerous papers and has been employed by a range of infectious disease key opinion leaders in tuberculosis, HIV, and influenza/upper respiratory tract infections at various hospitals, academic institutions, and CRO organizations. These include the Royal Postgraduate Medical School (Imperial College), the St. Stephen's Centre (Chelsea and Westminster Hospital) and Retroscreen.

Drug Development
EXECUTIVE

Anthony Macci
SVP,
Global Operations
Capsugel

CAPSUGEL®

Capsugel: Choosing the Right Pharmaceutical Design, Development & Manufacturing Partner

Pharmaceutical companies today increasingly require specialized design, development, and manufacturing partners to help bring new and improved drugs to market. These companies need partners of varying degrees throughout the drug development process, from preformulation, formulation, and development, through to clinical trial supply and commercial manufacturing. However, many pharmaceutical companies are challenged with how to effectively select and then manage such partners in order to achieve successful outcomes.

Anthony Macci, SVP of Global Operations at Capsugel, offers his perspective to *Drug Development & Delivery* on what pharmaceutical companies should keep top of mind when working with trusted design, development, and manufacturing partners. For more than a century, Capsugel has been the global leader in the technology and supply of empty, two-piece hard capsules to the healthcare industry. Today, with the emergence of its Dosage Form Solutions business unit, the company has also become a leading provider of innovative drug delivery technologies to the pharmaceutical industry. Capsugel is leveraging its science and engineering core to develop new technologies, an expanded set of capabilities throughout the drug development process, and increased production capacity in both capsule technologies and specialized finished dosage forms. Mr. Macci also highlights how these investments enable the company to offer integrated, high-quality, highly customized solutions spanning design through to clinical and commercial manufacturing.

Q: Can you provide our readers with insights into the leading trends in global pharmaceutical design, development, and/or manufacturing today?

A: From my vantage point, three key developments are driving a great deal of change within the global pharmaceutical design, development, and manufacturing space. First, the industry has traditionally developed and introduced high-volume, blockbuster drugs that targeted large patient groups and diseases. This trend has shifted more and more toward a demand for medicines designed to address the needs of smaller patient groups, such as pediatric dosage forms and orphan drugs. As a result, pharmaceutical companies are increasingly working with specialized partners on the design, development, and manufacture of innovative drugs, to accelerate the development process as well as contain the up-front investments and costs associated with the ramp-up of smaller volume projects.

Second, given that an estimated 60% of pharmaceutical compounds in early development have poor solubility, there is a continuing need for more advanced technologies in the design stage to improve compound bioavailability. For example, solid amorphous dispersion technologies – based on either spray-dried dispersion (SDD) or hot-melt extrusion processing – lipid-based formulations, and nanotechnology are being used to address the bioavailability challenges associated with certain compounds. The percentage of highly potent APIs (HPAPIs) in the pipeline is also growing, which requires specialized dosage forms and sophisticated, high-containment capabilities both in development as well as commercial facilities to ensure safe handling of such compounds. Pharmaceutical companies are more often relying on specialized design, development, and manufacturing partners who have invested in these advanced technologies and manufacturing capabilities to effectively and safely advance their compounds and ultimately bring new medicines to market.

Third, there is greater emphasis by pharmaceutical companies in achieving value through the selection and management of trusted, integrated partners with proven experience. Pharmaceutical companies recognize that working with the right partner – with enabling technologies, specialized facilities, as well as experience and know-how in design, development, and scale-up – can deliver major benefits in successfully bringing products to market faster. Companies understand the importance of developing a mutually beneficial, win-win relationship with these partners to achieve their product objectives.

Q: What would you say are the biggest challenges your customers face in managing pharmaceutical design, development, and/or manufacturing partners in this new environment?

A: The most significant challenge is that pharmaceutical companies increasingly do not own or manage the commercial manufacturing of their medicines. Specialized, smaller companies, and even virtual companies with single or a few compounds, are taking more compounds through the clinical process and account for an increasing percentage of new product approvals. These companies have less direct control of the manufacturing processing, making them more reliant on partners to successfully execute their projects. That is why choosing the right partner and developing trusting and transparent relationships throughout the process is so important today.

Additionally, and tied to that, are the more stringent regulatory and industry manufacturing quality standards being implemented globally. Because pharmaceutical companies are not developing and manufacturing all their medicines, they are increasingly reliant on trusted partners to ensure their products are meeting global regulatory and quality standards. Any failure in quality standards could result in delays in product approvals, costly recalls, or failure to supply patients with needed products, damaging the company's reputation with consumers and investors.

"From a high-level perspective, pharmaceutical companies should work with partners who have demonstrated – through both track record and continued investment – that they place quality at the forefront of everything they do. In searching for such partners, these companies should confirm that continuous quality improvement is an integral component of their drug design, development, and manufacturing process."

Q: As manufacturing technologies for dosage forms continue to advance, what qualities should pharmaceutical companies, virtual companies, and biotechnology companies be looking for in design, development, and/or manufacturing partners?

A: There are two key questions companies need to be asking themselves. First, is this potential partner committed to the core concepts of trust, transparency, and collaboration? Further, do this potential partner's goals align with our company's goals and core values? At Capsugel, we stress the importance of cultivating each customer relationship with an "alliance mindset" – an approach in which we view ourselves as seamless extensions of our customers' project teams in advancing their compounds. We focus on fostering honest and open dialogue with our customers, and are quite flexible in our contractual approach, so that we can together deliver an innovative and high-quality product to market as fast as possible.

Second, does this potential partner have the technology breadth, expertise, and infrastructure needed to ensure an optimized design for meeting our compound's target product profile and commercial objectives? At Capsugel, we differentiate ourselves with a solutions-driven approach grounded in science and engineering expertise that we bring to every customer project. By continuously expanding and enhancing our portfolio of enabling technologies and capabilities, and employing science-based technology selection methodologies, we are well positioned to help customers choose the solution best suited for their specific needs. We take pride in being completely unbiased in both technology or finished dose form presentation. This ensures that our customers move forward with the technology that makes the most sense for their compound, and ensures a partnership basis for future collaboration.

Q: Quality manufacturing is a hot topic in the industry today. What are key approaches that pharmaceutical companies should be looking for in their design, development, and/or manufacturing partners to ensure they are meeting quality manufacturing guidelines?

A: From a high-level perspective, pharmaceutical companies should work with partners who have demonstrated – through both track record and continued investment – that they place quality at the forefront of everything they do. In searching for such partners, these companies should confirm that continuous quality improvement is an integral component of their drug design, development, and manufacturing process.

In the late 1990s, benchmarking by the pharmaceutical industry of its development and manufacturing processes against other industries led to the concept of Quality by Design (QbD) for drug products, which has since been broadly

adopted in both regulatory and industry circles. Pharmaceutical sponsors now typically demand QbD methods be used for their projects with development partners, and the FDA's use of Question-based Review (QbR) processes necessitates the need for QbD-type data.

Instead of focusing quality controls on testing completed products and discarding those that fail to meet specifications, QbD principles highlight the importance of assuring quality through proper design and risk management. The understanding and control of critical quality attributes (CQAs) and critical process parameters (CPPs), from the concept stages of dosage form design, helps ensure high-quality and consistent manufacturing of finished dosage forms. Implementing QbD effectively requires significant investment to understand the CQAs and CPPs at each process phase for a given technology and process train, utilizing design of experiments (DOE), and scale-up studies.

At Capsugel, we have built a successful track record of using QbD principles with our hard capsules to achieve desired product characteristics. My colleague Sven Stegemann recently led a study that examined the CQAs within and between different batches of empty hard capsules to better understand their variability and impact on the desired quality and performance of the final dosage form. The study, which provided the first comprehensive collection of relevant QbD data for hard capsules, confirmed that Capsugel capsules are suitable "excipients" for QbD-based product development and manufacturing.

We have also incorporated QbD principles into our product design, development, and manufacturing processes for specialized dosage forms utilizing SDD, lipid-based/liquid-filled hard capsules, soft gels, and other technologies. We design dosage forms with "manufacturability" in mind, and utilize QbD-based development to streamline scale-up and regulatory approval in bringing compounds to market. Significant investment over the past 20+ years has been made in developing "formulation maps," which consider an API's physical and chemical properties, and can be used in conjunction with the target product profile (TPP) to identify a formulation that is likely to produce physically stable formulations with the desired performance early in development.

The TPP that is created during initial screening can guide the entire development process and be refined with additional product and process information for specific projects. Predictive testing can be combined with risk assessments to identify CQAs for further study, and physical stability maps can be used to predict whether parameters, such as drug loading, humidity, or temperature, represent a risk to stability during manufacture or long-term storage. For SDD manufacture, as an example, common CQAs include physical state, particle size, bulk density/morphology, residual solvents, water content, and assay/related substances/potency. Potential TPP impact, important SDD formulation parameters, and important SDD process parameters have been thoroughly studied and modeled in order to facilitate QbD-based development and scale-up.

Six Sigma is another approach that focuses on a continuous improvement process to achieve a level of performance for capsule manufacturing that is very consistent and highly reproducible. Six Sigma calls for the manufacture of capsules at quality levels that are far higher than those measured by a traditional, less-stringent Acceptable Quality Level (AQL) approach. In 2013, Capsugel launched our Coni-Snap® Sigma Series capsules to offer quality performance that significantly benefits our customers at each stage of the production process. Our customers using Coni-Snap Sigma Series capsules tell us that the higher quality increases production cycle time, reduces deviations and investigations, and has lowered inventory levels. This gives them the opportunity to focus on other aspects of their business.

In addition to implementing QbD and other methods, design, development, and manufacturing partners are adopting their own approaches to improve the quality of their products. At Capsugel, we incorporate our manufacturing know-how into the design and build our own, proprietary manufacturing equipment – for example, for capsules and drug product intermediates based on SDD technology – enabling us to achieve quality levels and throughputs that "off-the-shelf" equipment cannot achieve. We have also used "science of scale" and our deep understanding of process technology to develop specialized lab-scale equipment for feasibility studies that speed the overall development process while minimizing the use of valuable active ingredients.

Q: What investments is Capsugel making to expand its footprint to better meet the needs of its customers as a specialized solutions provider?

A: In 2013, we formally established Capsugel Dosage Form Solutions, our business unit focused on developing innovative drug delivery products by integrating our formulation R&D expertise, proprietary technology platforms, and commercial manufacturing infrastructure. Later that year, we acquired Encap Drug Delivery and Bend Research to further expand our technology platforms and capabilities.

Since then, we have transformed into a leading solutions provider through integration, investment, and growth. In 2015 alone we unveiled a new SDD commercial manufacturing facility at our Bend, OR, site. The facility builds upon Capsugel and Bend Research's proven, more than 20-year record with SDD technology and unparalleled experience in the formulation of more than 1,000 compounds. It includes the installation of two new specially designed commercial-scale spray dryers, which complement and expand the commercial-spray drying capacity at the facility, including one SDD unit designed to accommodate high-potency compounds. With the completed facility, we now offer the largest integrated SDD technology capability in North America.

We also announced plans to double the size of our Edinburgh, Scotland, facility to increase our liquid- and semi-solid-fill hard capsule manufacturing capacity for drug products utilizing lipid-based technology to address low solubility and/or high-potency compounds. The expansion will also further diversify our technology platforms offered at the facility, including the addition of SDD formulation and development capabilities. Eventually, our SDD offering in Europe will be expanded to also include development through commercial-scale capabilities.

In addition, we installed additional isolator technology at our Ploërmel, France, facility for the development and commercial manufacturing of soft gel and liquid-filled hard capsule dosage forms containing high-potency compounds. We also added new laboratories to support our growing pharmaceutical product development activities. These developments come following a successful US FDA inspection of the facility earlier in the year.

Q: What are examples of Capsugel's new capabilities being put into action?

A: A few recent examples come to mind, citing the ultimate objective – advancing our customers' drug compounds to clinic and on to commercialization. One is our work in patient-centric product development. Recently, we collaborated with a start-up European pharmaceutical company to improve the taste of a pediatric epilepsy medication that was only available in high-sugar form. While taste masking was necessary to improve the drug's taste so children would take it, the addition of sugar actually exacerbated the condition by increasing the risk for inducing seizures. Our formulation scientists tapped our broad technology portfolio to pinpoint the right solution for the needs of this compound. Using our proprietary lipid multiparticulate technology, we developed a sugar-free, yet taste masked formulation, delivered in a child-friendly dosage form that could be "sprinkled" on soft food like yogurt, or in a drink like orange juice. As a result, our partner was able to introduce a patient-centric dosage form with an improved bioavailability profile and acceptable dosage form that will have a direct and positive impact on the experience of young patients with epilepsy.

Another example area is innovating existing compounds often using the NDA 505(b)2 regulatory pathway for improved efficacy and/or new indications. To that end, we are increasingly using our bioavailability-enhancement platform to enhance the bioavailability for compounds with low solubility. In one case, we are using an amorphous dispersion to improve the performance and cost effectiveness of a hepatitis C vaccine. In another, we are using SDD technology to improve the bioavailability of an existing blockbuster drug for prostate cancer to deliver patient convenience through reduced pill burden.

Through these and other examples, we are leveraging our expertise in science and engineering to help our customers bring better medicines to the marketplace. ◆

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IMMUNOASSAY PLATFORM

Accelerating Drug Development & Clinical Validation With Single Molecule Counting

By: Steven Suchyta, PhD

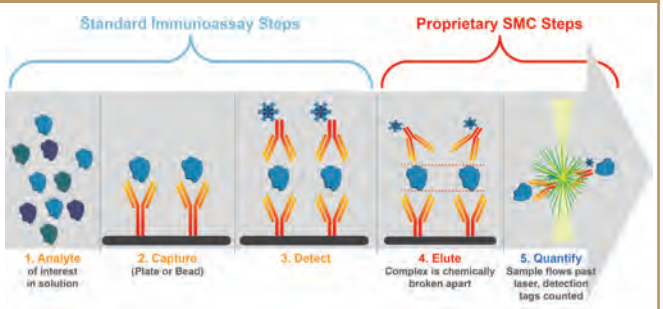
INTRODUCTION

Ultrasensitive Single Molecule Counting (SMC™) technology provides an indispensable tool in the researcher's arsenal to help move novel biology forward, fueling the discovery and development of new therapeutics. This technology is now available to leading pharmaceutical R&D laboratories, clinical research organizations (CROs), and academic institutions around the world through the Research-Use-Only Erenna® Immunoassay System, immunoassay kits, reagents, and custom services.

Enzyme Linked Immunosorbent Assays (ELISAs) are the traditional approach to protein biomarker quantification due to target specificity and ease of operation. However, ELISA methods often fail to quantify the target of interest if present in low abundance, which leads researchers to create more complex studies to produce the data they need, change their sample matrix, or stop investigating a putative marker entirely. Addition of patented digital SMC technology to the traditional immunoassay workflow enables detection of low-abundance, previously undetectable biomarkers, such as proteins and nucleic acids, with unparalleled sensitivity and accuracy, capturing concentrations down to the femtogram/mL level. This combination of digital counting and standard immunoassay processing allows quantification of biomarkers at sensitivities of 10- to 1,000-fold over other commercially available technologies.

With the addition of SMC technology to plate- and bead-based immunassay formats, researchers and clinicians can now detect and monitor changes of established disease biomarkers that are present at extremely low levels, such as cardiac troponin I and cytokines. New molecular insights can be gained and greater utility can be achieved with disease biomarkers, such as those for cardiovascular, Alzheimer's, Parkinson's, rheumatoid arthritis, Crohn's disease, certain cancers, and inflammatory- and autoimmune-based diseases. Even the smallest changes in biomarker levels can be measured, allowing researchers to gain unprecedented insights into complex disease biology, drug efficacy, and drug safety, and providing clinicians with a broader assessment of patient risk to enable proactive health management.

FIGURE 1



The SMC™ workflow.

HOW IT WORKS

The Singulex® platform couples SMC technology with robust microparticle-based immunoassays to provide higher sensitivity and broader dynamic range over traditional

immunoassay and ELISA platforms (Figure 1). The steps unique to SMC technology include concentrating the detection area (improves signal) and removing the detector from the assay plate (reduces background). This results in reproducible signal at low analyte concentrations, and better quantification of proteins, including those at very low abundance.

During the capture and detection steps, specific antibodies translate each biomarker into a signal. During final elution, fluorescent dye-labeled detection antibodies are released from the immune complexes and separated magnetically from the paramagnetic microparticles. These detection antibodies are the source of signal. The Erenna® Immunoassay System uses a robust digital SMC module to count photons, allowing precise measurement of low-abundance biomarkers with high statistical confidence. The instrument's capillary tube contains a very small interrogation space that is illuminated by a laser. Single fluorescently labeled molecules are detected as they generate intense flashes of light when passing through the interrogation space. Detected signals with peak intensity above the threshold of background fluorescence are counted as digital events. The instrument also records the sum of all digital events counted. At high concentrations, a proprietary algorithm computes the total sum of all photons recorded. Thus, the SMC technology improves assay sensitivity and extends dynamic measuring range one to three orders of magnitude greater than possible with traditional immunoassay technologies (Figure 2).

The SMC process enables digital detection at the lower end of the dynamic range. The signal is specific to individual antibodies passing through the confocal laser point. This decreases the background and reduces the lower limit of quantification. At the upper end of the range, the signal is more analog, and the instrument uses a proprietary algorithm and total photons to measure against a standard curve.

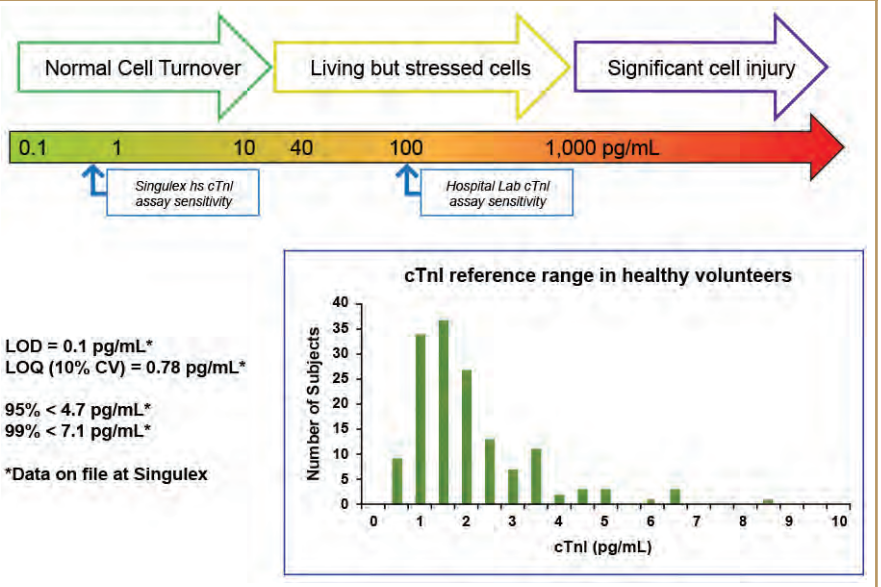
IDENTIFYING CLINICALLY RELEVANT BIOMARKERS

Several considerations must be taken into account when establishing a biomarker for translational research, including the demonstration of disease specificity, the ability to measure the biomarker in "normal" healthy states, demonstration of low biological variability, as well as the ability to predict future disease and/or clinical outcomes. Traditional technologies often lack the requisite specificity and sensitivity to address these critical considerations, presenting challenges to establishing the clinical utility of a potential biomarker.

SMC technology can help to overcome the many challenges associated with the biological qualification of protein biomarkers for clinical and translational research. With improved assay precision and sensitivity, SMC technology has enabled the measurement of endogenous biomarker concentrations at femtogram/mL levels and precise monitoring over time. For example, this technology has established high definition cardiac troponin I (cTnI) as a physiologically relevant biomarker for cardiovascular disease (CVD) risk characterization and chronic disease management.

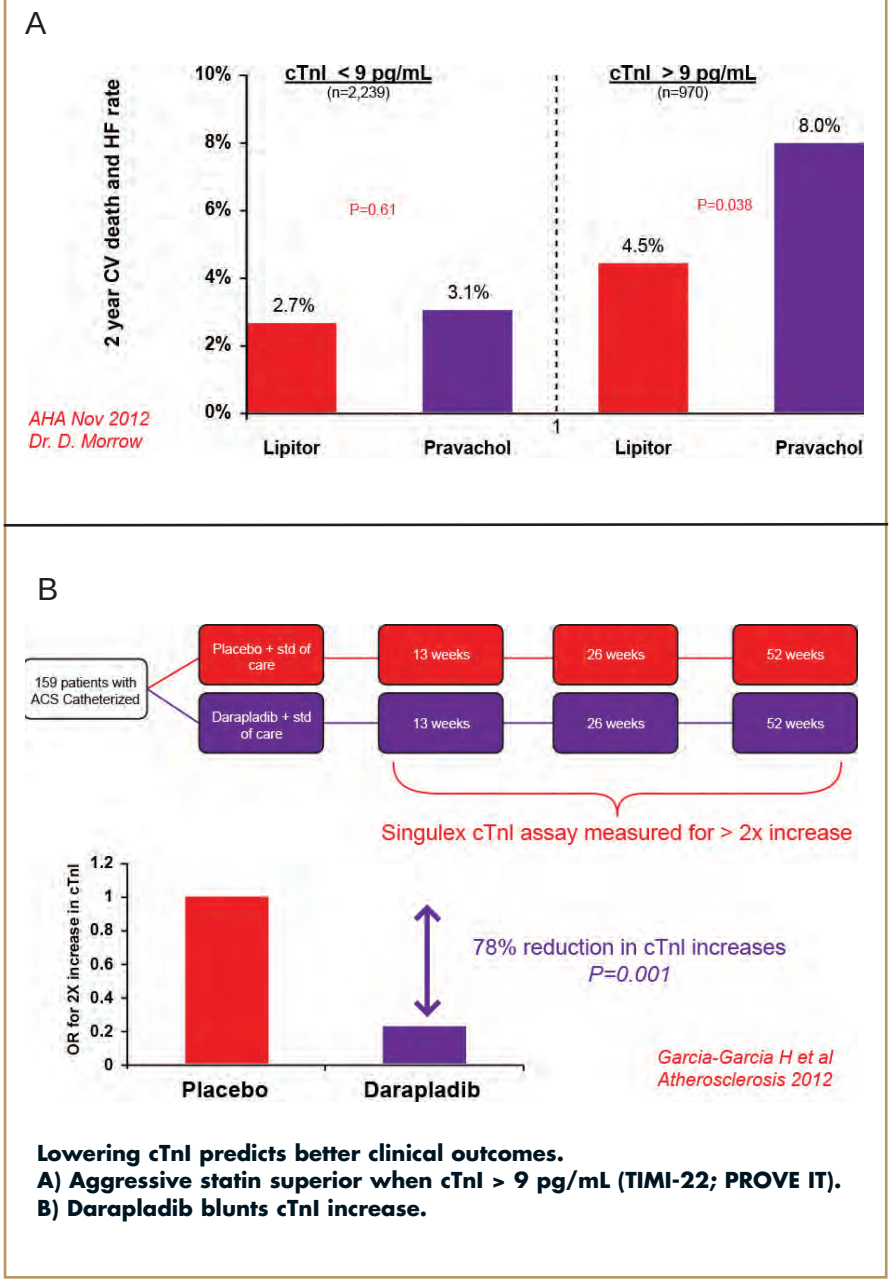
cTnI is a contractile protein that is specific to cardiac monocytes and is released at very low levels through normal cell turnover (0.1 to 10 pg/mL). However, damage to the cardiac monocytes during acute myocardial infarction (AMI) releases cTnI into the circulation at significantly higher levels

FIGURE 2



SMC™ technology can measure the complete range of cTnI.

FIGURE 3A&B



Lowering cTnI predicts better clinical outcomes.
A) Aggressive statin superior when cTnI > 9 pg/mL (TIMI-22; PROVE IT).
B) Darapladib blunts cTnI increase.

(1,000 pg/mL +). The early identification of AMI is vital for limiting myocardial damage and preserving cardiac function. According to the Minnesota Heart Survey and Framingham Heart Study, cTnI predicts cardiovascular (CV) death and the gradient of risk for heart failure (HF) in primary prevention, respectively. This biomarker also predicts CV death and HF in secondary prevention. Therefore, the ability to measure the full range of cTnI and monitor changes over time enables the use of this biomarker in clinical research studies of chronic disease management.

SMC technology can measure the complete range of cTnI concentration in circulation with a sensitivity of 0.1 pg/mL, allowing this biomarker to stratify clinical research subjects for immediate vs. longer term risk of cardiovascular disease (Figure 2). In addition, low biological variability of this biomarker combined with high precision of the assay allows for monitoring of disease progression as well as response to therapy (Figure 3). cTnI is a relevant cardiac biomarker that can be used to manage and monitor subjects of clinical research through the use of SMC technology.

COMPLETE PK/PD PROFILING

The use of SMC technology also offers new perspectives for low therapeutic index drug development. Traditional methodologies offer limited capacity for pharmacokinetic/pharmacodynamic (PK/PD) profiling and are often unable to show the full clearance profile of some drugs. In addition, they often have limited ability to measure the low concentrations of a given drug, such as used in micro-dosing studies. New digital high-definition immunoassays allow for the detection of lower levels of a drug to provide a more complete PK/PD profile, as well as allow for the identification of unpredictable clearance patterns undetectable by traditional immunoassay methodologies. These data can inform Go/No-Go decisions in Phase I/II of drug development and thereby reduce attrition and development costs.

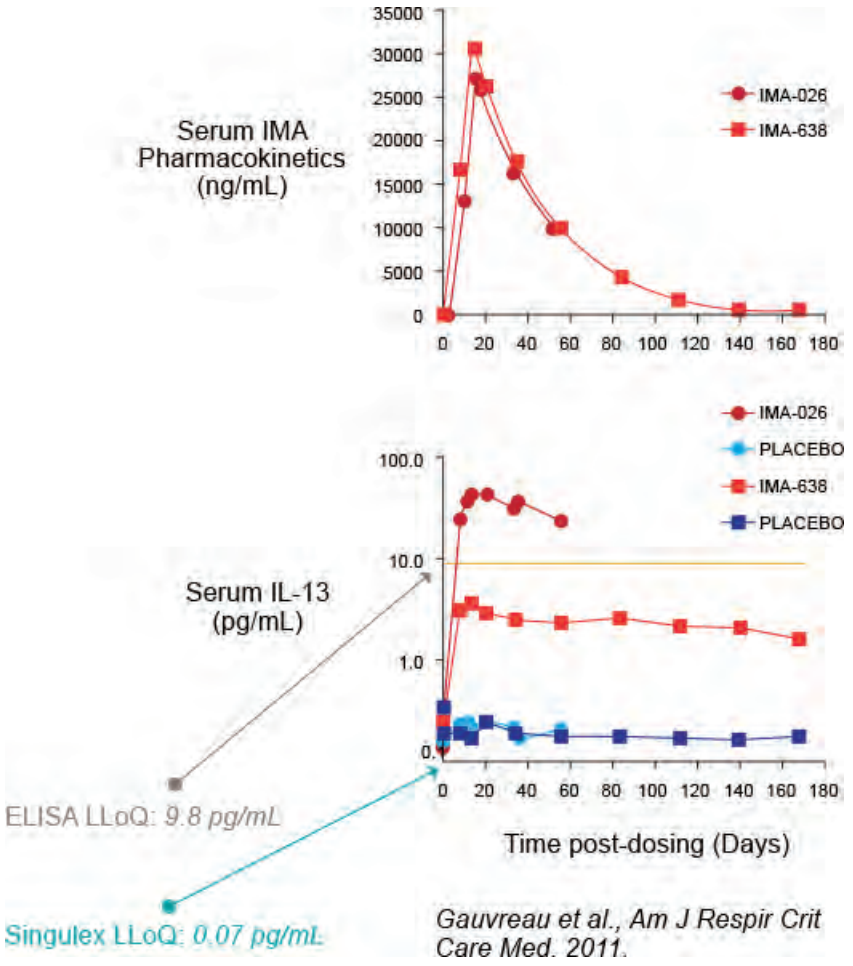
Interleukin-13

IL-13 is a Th2 cytokine implicated in asthmatic inflammation, and anti-IL-13 therapeutics are in development to counter autoimmune diseases. Accurate measurement of circulating IL-13 levels is therefore needed for PK/PD and mode of action (MOA) studies to support these drug development efforts. However, IL-13 quantitation requires greatly improved

sensitivity over traditional immunoassay or ELISA techniques, as circulating levels of this molecule are ≤ 1 pg/mL.

Improved assay sensitivity has been achieved using SMC technology, which offers up to a 140-fold improvement in the lower limit of quantification (LLoQ; pg/mL) over traditional ELISA methods. Anti-IL-13 monoclonal antibodies, IMA-026 and IMA-638, each of which competes with different receptors for IL-13 binding, were evaluated for anti-IL-13 treatment in patients with mild atopic stable asthma. The Singulex proprietary IL-13 assay (LLoQ = 0.07 pg/mL), but not traditional ELISA (LLoQ = 9.8 pg/mL), enabled quantification of baseline measurements of the clinical study population (n=182). All 99th% cut-off values for healthy and asthmatic subjects at baseline were less than 1 pg/mL. The assay also enabled longitudinal measurement of serum IL-13 levels from antibody- and placebo-treated subjects (Figure 4). An ELISA assay would be unable to measure the full profile for antibody- or placebo-treated subjects.

FIGURE 4



Monitor pre- and post-dosing of anti-IL-13 mAbs in subjects with mild atopic stable asthma.

Serum cTnI

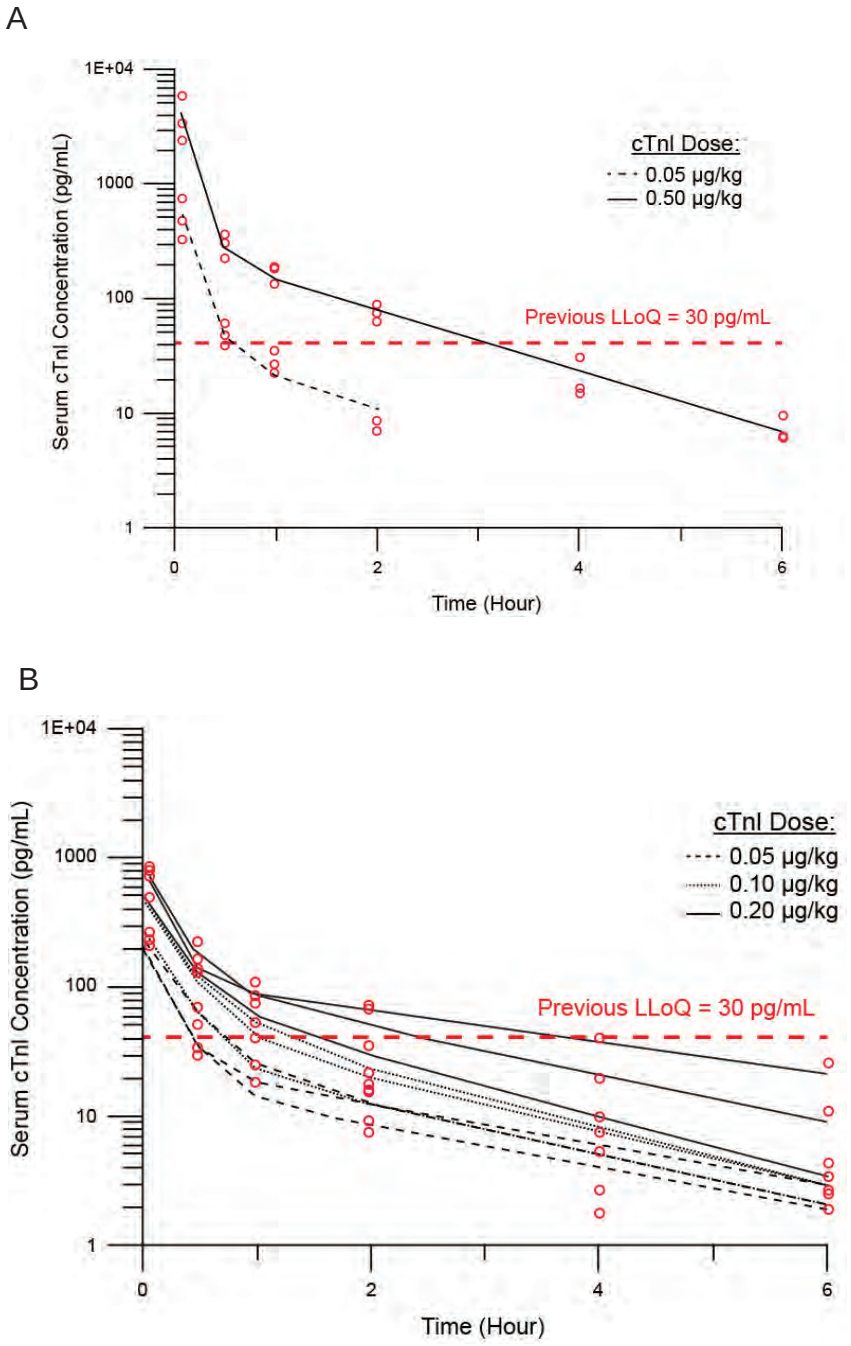
The effect of minor serum cTnI elevations, independent of extensive cardiomyocyte damage, has not been evaluated thoroughly because traditional assays (LLoQ ~30 pg/mL) have not been sensitive enough for this purpose. Transient or slight cardiomyocyte damage may not generate a large and persistent release of cTnI, making it difficult to identify a treatment-related transient increase using limited sampling times. However, recent evidence suggests that even small elevations of serum cTnI above baseline are correlated with an increased risk of myocardial-related mortality in humans. Therefore, the ability to establish and monitor baseline concentrations of serum cTnI in the rat or dog is essential to assessing the cardiovascular safety of therapeutic compounds in development.

The pharmacokinetics of cTnI in the Wistar Han rat and beagle dog was analyzed with a two-compartment model; blood samples were collected at multiple time points, and cTnI concentration was measured (Figure 5). For each animal model, single-digit pg/mL baseline concentrations of cTnI were detected, which were previously undetectable by other cTnI assays. Biphasic disposition of serum cTnI was observed after intravenous (IV) injection. The complete cTnI profile was exposed using select low dose cTnI concentrations estimated to be equivalent to cTnI levels expected after slight cardiomyocyte damage. The cTnI levels observed fall below the LLoQ for previous assays within 1 hour of dosing.

SUMMARY

Traditional ELISA methodologies have limitations in sensitivity and quantification, sample volume

FIGURE 5A&B



The complete PK profile of serum cTnI in rat and dog.
A) PK profile of serum cTnI in rat.
B) PK profile of serum cTnI in dog.

requirements, dynamic range, and matrix effects. These factors reduce the utility of the traditional microplate-based immunoassay for sample stratification, endogenous level quantification, and determination of appropriate dilutions for sample measurements. Minimal changes made to a traditional ELISA assay that incorporates SMC technology can make the difference between a particular biomarker being undetectable and being a viable research target. In addition, SMC technology accelerates biomarker research by providing femtogram/mL biomarker detection across multiple disease areas and drug states.

The use of SMC technology enables researchers to attain greater sensitivity, use less sample, and, in some cases, reduce costs, while still retaining the ease of use and familiarity of the traditional ELISA method. The performance improvement can allow, for example, the tracking of small changes in previously undetectable analytes to better understand disease progression and stratify patient populations, to gain insights into novel biological mechanisms, and/or to employ better biotherapeutic monitoring strategies, such as microdosing for assessing safety and efficacy. ◆

BIOGRAPHY

Dr. Steven Suchyta is a Senior Global Product Manager at MilliporeSigma, the life science business of Merck KGaA, Darmstadt, Germany. He is responsible for all of the company's single protein detection immunoassay technologies, including Singulex SMC™ technologies, Gyromark HT™ assay, and ELISA kits. Dr. Suchyta earned his BS and MS from The University of Georgia and his PhD in Genetics from Michigan State University.

CRO MARKET

CRO Sector: Sales & Margins Remain Healthy

By: Adam Dion, MSc, Senior Industry Analyst, GlobalData

INTRODUCTION

The total combined peer group revenue from these leading CROs increased 11.3% year to year from $24.5 billion in 2013 to $27.3 billion in 2014. Largely fueling this growth was Patheon, which independently contributed approximately $685 million to the $3-billion increase. GlobalData believes growth in the sector continues to be mainly driven by acquisition, as outsourcing providers look to add capabilities and expand resources and infrastructure globally. Figure 1 displays the combined peer group revenue and average operating margin for leading public CROs from 2010–2014.

Margin growth remained strong in the CRO sector, increasing 80 basis points to 6.4% in 2014. Sector leader Quintiles posted nearly $591 million in operating income in 2014, which is a testament to the company's large revenue base allowing it to comfortably cover its operating expenses. Quintiles benefited from a cost-reduction program it instituted in 2014, which resulted in a decrease of approximately 250 positions, which translated into annual cost savings of about $20 million. Table 1 summarizes the key sales drivers for the leading CROs in 2014.

LARGE M&A DEALS DRIVE PHARMA OUTSOURCING SECTOR

As of October 2015, the number of pharmaceutical outsourcing deals decreased by 36.4% from 143 in 2014 to 91 in 2015. However, deal values skyrocketed by more than 76% from $9.9 billion in 2014 to nearly $17.6 billion in 2015. This value was driven higher from both clinical trial and contract drug manufactures. Figure 2 shows the total number of deals and deal values in the pharmaceutical outsourcing services sector from 2005–2015.

GlobalData attributes the rise in value to primarily a significant increase in M&A deals, which has nearly doubled from $5.5 billion in 2014 to nearly $12 billion through October 2015. This year has seen a number of high-valued transactions, including LabCorp's $6.1-billion purchase of Covance, and WuXi being sold for $3.3 billion to a Chinese private equity group. Contract manufactures were also busy in 2015. Siegfried Holding AG, an API maker based in Switzerland, bought BASF's pharmaceutical supply business, and Lannett acquired Kremers Urban Pharma (a subsidiary of UCB), a specialty generic drugmaker for $1.2 billion. Figure 3 illustrates the total deal values for M&A and capital raisings from 2005–2015.

MERGERS & ACQUISITIONS

The pharmaceutical outsourcing services sector has seen a sharp rise in M&A activity over the past few years. LabCorp shook up the central lab testing market when it inked a deal to purchase Covance in February 2015. Other notable deals include Parexel building out its safety and assessment services with the purchase of QSI, and Siegfried buying BASF's pharma supply business which will expand capacity in Europe.

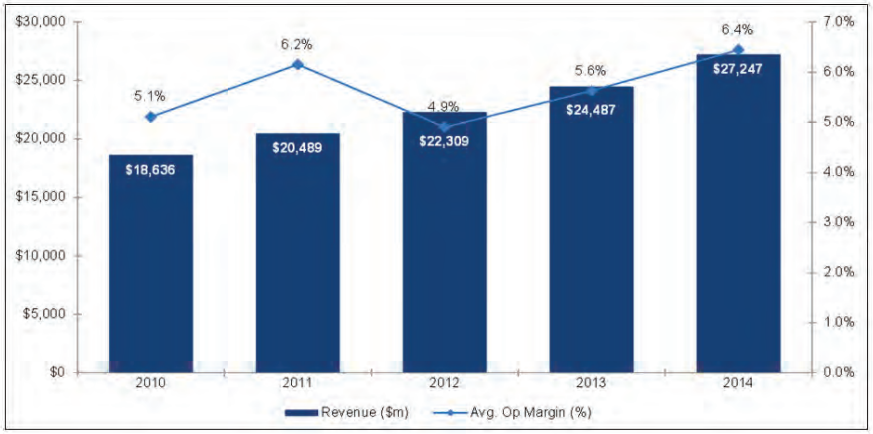
LabCorp's Purchase of Covance Diversifies Revenue Base

LabCorp closed on its acquisition of clinical trial contractor

Covance under a cash and stock deal valued at approximately $6.1 billion. Covance shareholders received $75.76 in cash and 0.2686 LabCorp shares for each Covance share they own. The transaction was valued at $105.12 per Covance share, representing a 32% premium above the company's closing share price of $79.90 on October 31, 2014, a multiple of approximately 13.3 times Covance's earnings over the past 12 months at the time of purchase. News of LabCorp's purchase caused Covance's stock price to shoot up by 25%, in line with the premium LabCorp agreed to pay. Shares of Covance's main competitors, Charles River Labs, Quintiles, and Parexel, also traded higher once the news broke on renewed speculation of consolidation in the pharmaceutical contracting sector.

The combined business will now have pro forma revenue of nearly $8.4 billion, vaulting it ahead of closest rival Quest Diagnostics, establishing a new leader in the medical testing space. LabCorp's intentions seem pretty clear – it wants a larger piece of the CRO market, which has enjoyed impressive growth over the past few years, as plummeting sales from the loss of exclusivity branded drugs and the high cost of pharmaceutical R&D, along with the globalization of clinical trials have led to a surge in demand for outsourced clinical trial work. It will be interesting to see how these two companies meld their business operations together. Historically, LabCorp has been a diagnostic testing partner to industry, payer, and hospital segments, not a manager of clinical trials. To this end, GlobalData expects that Covance will act as a separate entity under the LabCorp moniker, where

FIGURE 1



CRO Sector, Combined Peer Group Revenue (Millions) & Average Operating Margin (%), 2010–2014.

Source: GlobalData Pharma eTrack (Accessed on: October 14, 2015); Company Data.
Note: Includes peer group of 17 publicly traded CROs.

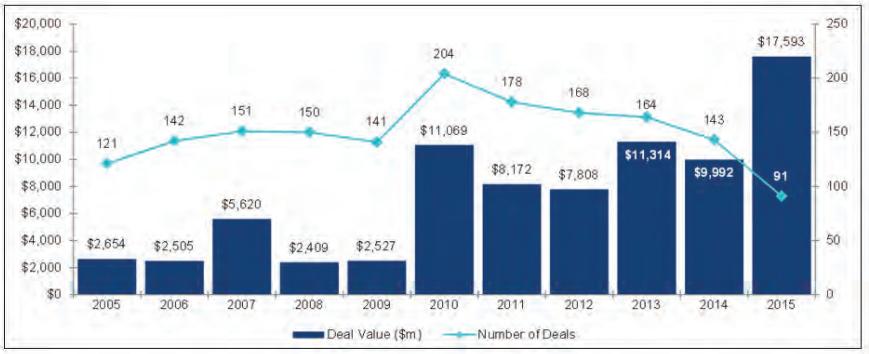
TABLE 1

Company	Revenue	YoY (%)	Key Growth Drivers
Quintiles	$5.5	7.1%	Novella Clinical and Encore Health acquisitions. Growth in Product Development and Integrated Healthcare Services. Renewal of two five-year contracts for clinical and data management services.
Covance	$2.5	4.9%	Strong organic volume growth in the company's managed care and toxicology testing businesses.
Parexel	$2.3	13.5%	Clinical Research Services segment grew in both Phase II-III and Peri/Post approval services. Consulting Services and Perceptive Informatics segment revenue increased due to new revenue from the acquisitions of Heron and Liquent, respectively.
Catalent	$1.8	1.5%	Sales higher across all business segments, led by the company's Oral Technologies segment, particularly modified release technologies and soft-gel offerings.
Patheon	$1.7	67.1%	Transaction to buy Banner Pharmacaps. Stronger than expected results in North America.
Icon	$1.5	12.5%	Growth outside of European markets. BeijingWits Medical purchase bolstered operations in Asia.
PRA	$1.4	47.2%	RPS acquisition provided PRA with a more diverse client mix, including 16 of the 20 largest pharmaceutical companies. Increase in billable hours and backlog.
ChRiver	$1.3	11.3%	Discovery Services segment revenue increased due to Argenta and BioFocus acquisitions, as well as higher revenue from safety assessment services.
INC	$1.2	18.5%	Increase in contract awards over the past year along with lower cancellation rate of previously awarded business during 2014. Oncology and CNS therapeutic areas posted strong revenue growth.
WuXi	$675m	16.6%	Expansion in the US and Iceland for genomics and bioinformatics services. Both Manufacturing Services and Laboratory Services segments witnessed higher order backlog in anticipation of deferred revenue from projects expected to begin in the near future.
CMIC	$550m	(4.2%)	Negatively impacted by softer sales from its Healthcare Information Services business, and currency fluctuations. This was off-set by better than expected gains in CRO business, including analytical chemistry services (JCL Bioassay).
AMRI	$276m	12.2%	Growth in CMO business due to acquisition of Oso Biopharmaceuticals, a contract manufacturer of complex injectable products.

Source: GlobalData, Pharma eTrack, [Accessed October 14, 2015].
Note: Revenue includes reimbursable out-of-pocket expenses.

CRO Sector, Revenue (Billions) Leaders, 2014

FIGURE 2



Pharmaceutical Services Sector, Total Deals & Deal Values (Millions), 2005–2015.

Source: GlobalData Pharma eTrack (Accessed on: October 14, 2015); Company Data.
Note: Deals include all pharmaceutical contracting services sector deals. Deal Values included wherever disclosed.

LabCorp can leverage Covance's leadership in clinical trials monitoring, patient and sponsor recruitment, and study site selection through its proprietary Xcellerate technology platform.

Beyond the compatibility of service offerings, the Covance acquisition shifts LabCorp's revenue base to a more favorable mix of pharmaceutical and biotech clients, and away from the managed care and payer markets, which have been challenging of late. The managed care market has been negatively impacted by payment reductions on the Medicare physician fee schedule and delays in payments and denials of coverage for existing tests by some payers after the implementation of new molecular pathology codes. This has squeezed LabCorp's revenue-per-acquisition, which has led to stagnant earnings generation and has eroded investor confidence. However, the combined company will now have relationships with all of the top 20 pharmaceutical companies, including Bayer, Eli Lilly, and Sanofi, with each drugmaker having multi-year contracts with Covance for central lab services, creating a consistent revenue stream for the new company.

TABLE 2

Acquirer	Target	Value	Synergy
LabCorp	Covance	$6.1bn	Broadens LabCorp's revenue base into pharma, biotech, and genomics testing.
WuXi Life Science	WuXi PharmaTech	$3.3bn	WuXi PharmaTech was purchased by WuXi Life Sciences, a management buyout group consisting of a number of Chinese private equity investors, including Ping An Insurance and Temasek Holdings.
Siegfried	BASF (API business)	$301m	Acquisition gives Siegfried additional capacity, and new services to secure more business.
Parexel	Quantum Solutions	$94m	QSI business adds scale to meet growing demand for safety services.
JSS Medical	Max Neeman	$1.5m	JSS acquired India's leading CRO with six regional offices, expands global footprint into Asia.
Accelovance	Altair Clinical	N/A	Accelovance purchased Altair Clinical, a full-service European CRO with offices in the UK, Russia, Central and Eastern Europe (CEE), and the Middle East and North Africa (MENA). Altair specializes in oncology and vaccine clinical trials.
BioClinica	MediciGroup	N/A	The MediciGroup is a leading global patient recruitment and retention firm. Medici also provides a lost-to-follow-up (L2FU) patient locate service that finds missing patients globally. Together with Medici, BioClinica will offer pharmaceutical companies more comprehensive patient recruitment services and improve the speed and efficiency of global clinical trials.
Clinipace	Accovion	N/A	Accovion is based in Germany and is active in over 20 countries, including CEE territories.

Source: GlobalData, Pharma eTrack, Deal Analytics [Accessed October 14, 2015]
Notes: Includes all deal values wherever disclosed. N/A = Not Available.

Key M&A Deals, Table Summary, 2015

Siegfried Acquires Pharma Supply Business From BASF

The Siegfried Group signed a $300-million agreement with the German company BASF with the aim of acquiring significant segments of BASF's pharmaceutical supply business and connected chemical production units in Germany, France, and Switzerland. The combination represents an attractive base for sustained profitable growth and greater flexibility in acquiring new business through capacity expansion, which will have a positive effect on sales. BASF's pharmaceutical supply business contributes complementary technological platforms, such as azide chemistry, phosgenation, and low-temperature chemistry. As a result, new products and customers can be secured. Moreover, cost synergies will be achieved in the areas of overhead, IT, and procurement, as well as through consolidation of global production supply networks. Table 2 summarizes the key M&A deals in the pharmaceutical outsourcing services sector during 2015.

"GlobalData attributes the rise in value to primarily a significant increase in M&A deals, which has nearly doubled from $5.5 billion in 2014 to nearly $12 billion through October 2015. This year has seen a number of high-valued transactions, including LabCorp's $6.1-billion purchase of Covance, and WuXi being sold for $3.3 billion to a Chinese private equity group. Contract manufactures were also busy in 2015. Siegfried Holding AG, an API maker based in Switzerland, bought BASF's pharmaceutical supply business, and Lannett acquired Kremers Urban Pharma, a specialty generic drugmaker for $1.2 billion."

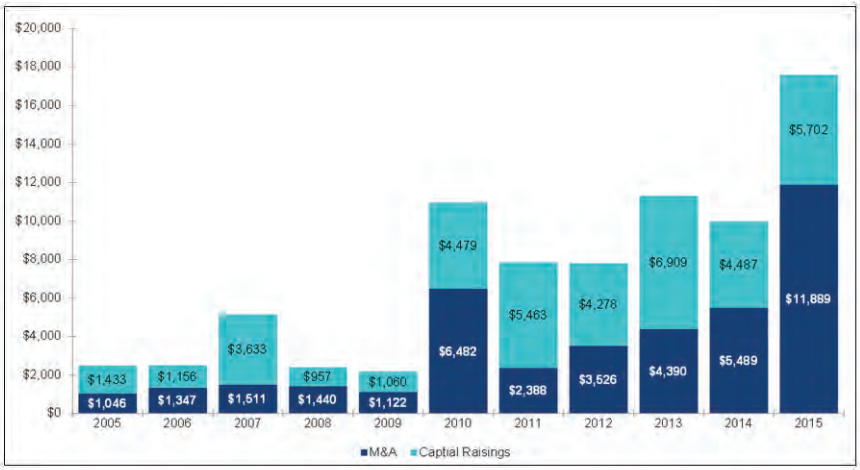
Parexel Strengthens Pharmacovigilance Services

Parexel paid $94 million for all of the business assets of privately owned, India-based Quantum Solutions (QSI), a leading provider of specialized pharmacovigilance services. QSI was established in 2004, and delivers a complete range of safety and assessment services, including individual case safety report processing, brand physician activities, affiliate support, report writing, literature reviews, and signal detection. QSI serves pharmaceutical, medical device, and consumer clients across the globe and had approximately 900 employees. The QSI business will be integrated into Parexel's peri/post-approval services group, which is part of the company's Clinical Research Services segment. It is also expected to have strong synergies with Parexel's regulatory and outsourcing services business within Parexel's consulting segment.

CAPITAL RAISINGS

Equity offerings and venture financing are common sources of deals activity among CROs to raise funds for the repurchasing of stock, corporate transactions, hiring key talent, and expanding operations and services. These funding sources include IPOs, private placements, and debt issuances. Quintiles announced the private placement of senior notes due 2023 to raise gross proceeds of $800 million. The company intends to use the net proceeds to refinance its existing credit facilities, as well as for general corporate purposes, including corporate transactions and equity repurchases. Clinipace Worldwide raised $50 million in a venture financing round. The financing was led by Virgo Investment Group and Crestline Investors. The company intends to use the proceeds to continue building its therapeutic expertise and further expand its capacity to deliver services to its clients. GlobalData expects that Clinipace also used a portion of these funds to acquire Accovion, a Germany-based CRO that provides back-end services, such as biostatistics, IT, and medical writing services to the pharmaceutical, biotechnology, and medical devices sectors. The combined company will now have clinical operations in 39 countries and nearly 1,000 staff. Meanwhile, Syngene International, a subsidiary of Biocon, went public in July 2015. Table 3 summarizes the key capital raisings in

FIGURE 3



Pharmaceutical Services Sector, M&A and Capital Raising Deal Values ($m), 2005–2015.

Source: GlobalData Pharma eTrack (Accessed on: October 14, 2015); Company Data.
Note: Deal Values included wherever disclosed.

TABLE 3

Company	Deal Type	Value	Financial Advisors/Investors
LabCorp	Debt offering	$2.9bn	Laboratory Corporation of America Holdings
PPD/Jaguar Holding	Private placement	$1.2bn	Jaguar Holding Company, Pharmaceutical Product Development, LLC.
Quintiles	Private placement	$800m	Quintiles Transnational Holdings, Inc.
Envigo	PIPE	$125m	Envigo, Ltd.
Patheon	IPO	$100m	Patheon B.V.
Syngene	IPO	$87m	Syngene International, Ltd.
Hangzhou Tigermed	PIPE	$81m	Hangzhou Tigermed Consulting, Ltd.
Clinipace	Venture financing	$50m	Crestline Investors, Harbert Venture Partners, Hatteras Venture Partners, Mario Family Partners, Morgan Stanley Expansion Capital, and Virgo Investment Group.

Source: GlobalData, Pharma eTrack, Deal Analytics (Accessed October 14, 2015).
Notes: Includes all deal values wherever disclosed.

Key Capital Raisings, Table Summary, 2015

the pharmaceutical outsourcing services sector during 2015.

Syngene International Raises $87M in IPO

Syngene International issued 22 million shares at a price range between $3.78 and $3.94, raising maximum gross proceeds of $87 million. In connection with the offering, the Government of Singapore Investment Corporation subscribed worth of $3.94 million, while the other funds managed by Goldman Sachs, Morgan Stanley, and Deutsche Bank, along with other foreign and domestic mutual funds subscribed a total of $19.71 million shares in the offering. The company intends to use the proceeds to fund its R&D programs.

Syngene International is one of the leading CROs in India offering a suite of integrated, end-to-end discovery and development services for novel molecular entities across the pharmaceutical, biotechnology, agrochemical, and animal health markets. During FY2015, Syngene reportedly serviced 221 clients, including eight of the top 10 global pharmaceutical companies. Syngene has several long-term relationships and multi-year contracts with large pharma, such as BMS, Abbott Labs, Baxter, and Merck, as well as biotechs, including Achillion, Aquinox, and Saniona.

CRO SECTOR WELL-POSITIONED FOR FUTURE GROWTH

GlobalData continues its bullish outlook on the CRO sector. Declining R&D productivity and increased development costs have negatively impacted biopharmaceutical companies. We believe that the need for biopharmaceutical companies to maximize productivity and lower costs in their commercial operations will cause them to look to CRO partners as they enter into outsourcing arrangements to improve efficiency, sales force utilization, and improve clinical success rates. ◆

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BIOGRAPHY

Adam Dion is a Senior Industry Analyst at GlobalData. He covers the competitive strategy, financial, and deal landscape of the pharmaceutical, biotech, and contract outsourcing markets. Prior to joining GlobalData, he was an Analyst with Technology Business Research, a leading market research and consulting firm covering blue-chip hardware, software, and business process outsourcing companies. Mr. Dion earned his BS in Neuroscience and MSc in Marketing from the University of New Haven.

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Drug Development
EXECUTIVE

Enable Injections: Revolutionizing Treatment With a New Class of Devices

Michael Hooven
CEO
Enable Injections

A large number of injectable biologic drugs - more than 900 - are currently in development with a market potential of $215 billion in the next 5 years, according to market analysts. Because many of these large molecule drugs are required in doses up to 20 times larger than today's injectables, they cannot easily be administered with legacy injection systems. Privately held Enable Injections is taking advantage of this rapidly growing development by introducing their line of a new class of devices to deliver these drugs subcutaneously, by patients, at home, with the potential to help revolutionize treatment of cancer, auto-immune deficiencies, blood disorders, and a range of other conditions. Drug Development & Delivery recently spoke with Michael Hooven, CEO of Enable Injections, to discuss his vision for the company and how Enable Injections intends to create market-leading biologics delivery devices that meet the most pressing needs of pharmaceutical companies while enabling easy patient self-administration for significant cost-savings.

Q: To what extent has drug delivery become more of a challenge for the pharmaceutical and biotech industries?

A: By 2016, it is expected biologics will account for approximately 50% of the top 100 selling drugs. These biologics and biosimilars hold tremendous promise for advancing treatment of numerous cancers, immunologic disorders, cardiovascular and rare diseases, and other chronic disease categories - but only if new drug delivery devices are developed in conjunction with these large-dose, viscous drugs. The subcutaneous layer cannot absorb significantly more than 1 ml of drug using a conventional syringe injection. Yet, the majority of biologics are being formulated in volumes ranging up to 20 ml. Such large-volume dosage must be delivered over longer times and with greater force than patients can be expected to tolerate.

Consequently, finding the right balance between volume and viscosity is one of the biggest challenges facing the pharmaceutical and biotech companies developing biologic drugs.

To address these challenges, Enable Injections has developed a new class of drug delivery devices - the bolus injector, capable of delivering higher volumes and viscosities with minimal discomfort. Enable's Bolus Injector can deliver up to 20 ml subcutaneously at a customizable drug delivery rate and duration.

It can deliver 1 ml of a drug as viscous as motor oil (100 cP) in just 1 minute. By comparison, water has a viscosity of 1 cP.Beyond the formulation issues and physics of taming injection forces, the pharmaceutical industry is challenged to reduce costs, and the new bolus injector may help in that regard. For example, the biologic drug Herceptin for the treatment of HER2-positive breast cancer currently must be infused intravenously by a healthcare professional, typically at a hospital. Healthcare costs could be significantly reduced, compliance increased, and patient convenience vastly improved if patients could safely and easily self-administer such drugs subcutaneously at home without the aid of a healthcare provider.

Q: Why did Enable Injections decide to change direction and create a bolus injector?

A: Enable Injections began as a painless injection company, licensing work, technology, and results of a number of clinical studies of a painless injection technology developed at Children's Hospital in Cincinnati. Enable gained a deep understanding of the sources and causes of injection pain and conducted extensive research to validate particular device features that would create the most comfortable injection experience for patients required to self-administer large-volume drugs. Although most of this work could be applied to any type of injection device, Enable saw a compelling need in both the healthcare system and the pharmaceutical industry for a better and more cost-effective way to deliver these large-volume/high-viscosity drugs. We also recognized that compliance is a major issue, and having done numerous Human Factor studies, we had a very good idea of what patients want and need in order to be more compliant. So Enable decided to focus this knowledge and technology on the development of a unique Bolus Injector system and the Enable Injector was born.

Q: How does the Enable Bolus Injector function and why is it unique?

A: The Enable Wearable Bolus Injector is a sophisticated autoinjector system that enables patients to subcutaneously self-administer, at home, the viscous or large-dose drugs already on the market or in development. It could also potentially be used as a patient home-injection for many of the drugs that are currently infused intravenously without the need for a healthcare provider. About the size of an Oreo cookie, the Enable device has been engineered to make self-injection as easy and comfortable for patients as possible. There are numerous features that make the Enable Bolus Injector unique and cost effective. First, the Enable Injector does not require any change to the primary container, ensuring drug stability. It utilizes a standard vial, cartridge or prefilled syringe, reducing development risk and time for pharmaceutical companies. For lyophilized drugs, we have a two-vial system that completely automates mixing, removing any patient variability from the mixing process. We use only standard intravenous-set materials in the drug delivery path, minimizing the time and risk of material compatibility testing. The Enable Injector has a proprietary S.E.T. (sequential elastomeric toroid) mechanical drive system that is optimized for wearable injectors - the force required to deliver the drug does not change with the volume, and the cannula size is the smallest available, typically 30 g to 33 g.

Further, the Enable system is unique in its ability to deliver volumes and viscosities significantly higher than cartridge/plunger-based systems. The S.E.T. system allows for volumes ranging from 1 ml to 20 ml in a very small-sized device with a low profile. Patients like the small size and the discrete profile. It eliminates the problems associated with adhering larger, heavier devices to the body that are the size of a deck of playing cards, which is the size currently under development by other device companies, or tethering the device to the body with the use of an infusion set and catheter.

For the most comfortable possible injection, the Enable Injector incorporates a 'Pause Feature' that allows the patient to pause the injection if they experience any pain or discomfort. They simply press the button and hold it until they are comfortable. When they release the button, the injection continues with reduced discomfort. Perhaps most unique is the elimination of the typical 30-minute or longer wait time to use the device. Once

the refrigerated vial/cartridge is inserted into the Enable transfer package, warming takes place as the Enable injector is filled. The Enable Injector is ready for use immediately after filling.

The Enable Injector was also designed in parallel with multiple human factor studies to minimize patient errors and confusion and to be easy to operate. All a patient is required to do is to insert a standard drug vial into the transfer package, remove the filled injector from the package when prompted, adhere it to the skin, and push one button.

Finally, the Enable Injector was developed to be environmentally friendly. The system contains no electronics or batteries that must be removed for recycling, and the total volume of material and packing is less than what would be used in a standard IV system.

As an advance in injectable drug delivery devices, the Enable Injector may provide greater safety for patients and healthcare workers by eliminating the risk-fraught steps involved in using conventional syringes, including removing the syringe cap, drug preparation, inserting a needle, and covering and disposing of needles. The needle is never seen or exposed to the patient. The needle is inserted to start the injection by pushing the button. At the end of the injection, the needle is automatically retracted and locked out, allowing for safe and convenient disposal of the system.

Q: Why so much anticipation about bolus injectors?

A: The market for bolus injectors is expected to grow rapidly, to over $8 billion in the next 10 years. One of the greatest promises of bolus injectors and the reason they will likely be adopted by all the stakeholders in the industry is that they have the potential to lower healthcare costs substantially as patients will no longer need to visit a healthcare facility for drug administration. Increased patient compliance is also expected to generate cost savings while increasing patient satisfaction. By enabling convenient, safe, and easy at-home self-administration of large molecule or viscous drugs and many medications that today are delivered intravenously, bolus injectors may revolutionize treatment of chronic conditions.

Yet another reason for the excitement is that these devices offer a new lifecycle management tool for pharmaceutical companies, with potential for patent extension.

For patients, time-saving is another major benefit. For example, intravenous administration of Herceptin takes 30 to 90 minutes, compared to just 2 to 5 minutes for subcutaneous administration of the same dose with a bolus injector.

Q: Who should be considering investigational use of the Enable Bolus Injector now?

A: Pharmaceutical executives in business development, product management, and lifecycle management - formulation teams - Clinical Research Organizations - R&D teams - clinical researchers - biotechnology companies - pharmaceutical brand managers - payers.

Q: What are some of the top clinical indications for bolus injectors?

A: According to a Roots Analysis, cancer and related conditions are expected to be the most researched area for bolus injectors. Other prominent target diseases are likely to be autoimmune diseases, blood disorders, and genetic disorders. The list includes, but is not limited to: Rheumatoid Arthritis - Multiple Sclerosis – Hemophilia - Myasthenia gravis - Lupus – Vasculitis - Sickle cell anemia - Numerous cancers - Crohn's Disease, ulcerative colitis, and other digestive disorders - Duchenne muscular distrophy, Pompe disease, and other genetic diseases - Infectious diseases, such as HIV, ebola, and CMV diseases - Transplantation - Inflammatory diseases - Cardiovascular diseases - Respiratory diseases - Musculoskeletal disorders - Eye diseases - Skin diseases - Neurologic disorders.

Q: What is the status of bolus injectors today?

A: The Enable Injector, like every bolus injector in development, is currently only available for investigational use pending US FDA clearance and approval by worldwide regulatory bodies. The first Bolus Injector commercial launch (subsequent to FDA clearance) is expected in 2015, according to analyst reports.

Self-injectable devices are gradually replacing conventional needle delivery systems. These new devices offer convenience, improved quality of life for patients, ease of use, and a safer option for both patients and healthcare workers compared to legacy systems. ◆

Technology & Services
SHOWCASE

ANALYTICAL SUPPORT SERVICES

ABC provides IND-enabling, registration, and post-commercialization support for the development, quality control, and lifecycle management of innovative therapies and generic medicines. Our personalized, results-based approach to development strategy is backed by decades of experience delivering GLP- and CGMP-compliant analytical testing services across all types of APIs and formulations. Through development know-how, cross-disciplinary technical expertise, and applied experience with evolving global regulatory frameworks, we help efficiently advance and manage programs for large and small molecule drugs, medical devices, and combination products. Our mission is to become a trusted extension of our client's product development teams, helping them meet the global demand for safer, more effective products. Our approach to doing business promotes relationships beyond a simple transaction. This, in turn, improves decision-making, expedites development, and reduces risk. In other words, "better insight, better outcomes." For more information, visit ABC Laboratories at **www.abclabs.com**.

OVERCOMING FORMULATION CHALLENGES

For decades, **Adare Pharmaceuticals** has successfully overcome complex formulation challenges, delivering medicines that benefit more patients. With a broad range of proprietary technologies—including taste masking and ODTs, customized drug release, and bioavailability enhancement—we have the ability to transform drug formulations, developing novel Rx and OTC products. For example, we recently partnered with Sanofi K.K. to launch Allegra® (fexofenadine HCl) Dry Syrup 5% in Japan. By using Microcaps® Taste Masking Technology, we successfully taste masked the API and delivered an oral powder formulation that can be sprinkled on easy-to-swallow foods to improve convenience of administration. To learn more about our proprietary technologies or partnership opportunities, visit **www.AdarePharma.com**.

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Aptar Stelmi is a trusted partner of leading pharmaceutical and biopharmaceutical companies throughout the world. We design and manufacture elastomeric closures: stoppers for vials, and prefilled syringe and cartridge components, such as plungers, needle shields, and tip caps for all parenteral applications. A member of the AptarGroup, we benefit from the global market presence, innovation, and technical capabilities of an industry leader. PremiumCoat™ is a novel range of elastomeric stoppers developed by Aptar Stelmi launched earlier this year. Based on an approved, pure, state-of-the-art formulation, the surface of the elastomer is coated during manufacturing with an ETFE film. This coating acts as an effective barrier to many of the extractables and leachables that can be released from the elastomer. As a result, compatibility of the drug and the closure is significantly superior with PremiumCoat™ stoppers. For more information, visit Aptar Stelmi at **www.aptarstelmi.com**.

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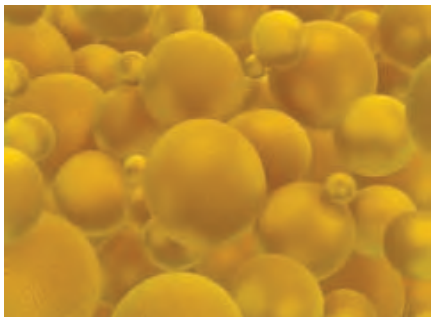

Ascendia Pharmaceuticals offers services for contract formulation development of poorly soluble drugs. Our formulation approaches include nanoemulsions, amorphous solid dispersions, and nanoparticles. These technologies are suitable for oral or injectable delivery of drugs that are challenging to formulate. EmulSol is our technology for production of oil-in-water nanoemulsions, with droplet sizes in the range of 50-500 nanometers. Ascendia's process is novel in that it uses no organic co-solvents, and minimal surfactants. Our nanoemulsions use a high-shear homogenization process to create a suspension of the oil droplets in a water phase, with the drug solubilized within the interior of the oil droplets. Thus, when the nanoemulsion is delivered to the body, the drug is more readily bioavailable. For more information, contact Ascendia at (732) 640-0058 or visit **www.ascendiapharma.com**.

Technology & Services Showcase

Excipients & Technologies

Ashland is a manufacturer and marketer of pharmaceutical-grade excipients supported by global cGMP manufacturing and R&D with expertise in polymer science, formulation development, solid dispersions, and bioavailability enhancement. Our global manufacturing sites are held to strict cGMP standards ensuring consistent production of high-quality products. Ashland meets formulators' needs by providing an unparalleled range of excipients and technologies, as well as long-standing polymer expertise and technical support from benchtop to commercialization for oral solids, liquids, topical, and parenteral dosage forms. Research taking place at Ashland is the foundation of technical solutions that will address drug delivery challenges in the future. For more information, contact Ashland at or visit **www.ashland.com/pharmaceutical**.

All Color Capsules

Commercial color decisions are rarely made before initial stability studies, which can result in costly delays if new colors are introduced. The All Color Capsule combines FD&C or Iron Oxide dyes to create capsules that can extract up to 18 built-in color options. Printed with two print bars that combine all ink colors, your stability testing can proceed before final colors are chosen. Your marketing groups will still have a flexible range of 18 colors that have undergone stability testing. Available in multiple sizes and supplied in cartons and capsule Caddies, order your All Color Capsules today or request a sample case by contacting Capsugel at (800) 845-6973.

Platform Technology

Captisol is a patent-protected, chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. Captisol was invented and initially developed by scientists in the laboratories of Dr. Valentino Stella at the University of Kansas' Higuchi Biosciences Center for specific use in drug development and formulation. This unique technology has enabled 7 FDA-approved products, including Onyx Pharmaceuticals' Kyprolis®, Baxter International's Nexterone®, and Merck's NOXAFIL IV. There are more than 30 Captisol-enabled products currently in clinical development. For more information, visit Captisol at **www.captisol.com**.

Solution Suite

Catalent's OptiForm® Solution Suite platform integrates superior technologies to match the best, most innovative, drug delivery technologies to each developmental molecule, with the goal of providing optimal animal PK materials in just 12 weeks. OptiForm Solution Suite helps enable faster development with a 3-step process: (1) ASSESS: By applying proven high throughput screening tools, detailed preformulation data are collected to characterize the molecule's potential challenges, (2) ENHANCE: Formulation technology experts determine the feasibility of the proposed formulation approaches, recommend candidate formulations and collect preliminary stability data, and (3) DELIVER: In 12 weeks, a dedicated advisor will provide a recommended path forward, based on rigorous data, accompanied by animal PK study materials to enter animal trials with optimized product faster. For more information, visit Catalent Pharma Solutions at (888) SOLUTION or visit **www.catalent.com.**

Technology & Services Showcase

Differentiated Injectable Delivery

Credence MedSystems is a medical technology company focused on delivering medications safely for the benefit of our patients, caregivers and partners. The Companion Safety Syringe System was born from Credence's core philosophy of Innovation Without Change. By providing passive safety and reuse prevention while using existing primary package components, the Companion offers best-in-class drug delivery with a vastly simplified path to market for our biotech and pharmaceutical partners. The Companion is available in luer needle, staked needle and dual chamber reconstitution configurations. In all cases, the user performs the injection, receives end-of-dose cues and then the needle automatically retracts into the syringe, which is then disabled. For more information, contact Credence MedSystems at 1-844-CMEDSYS, email info@credencemed.com, or visit **www.CredenceMed.com**.

Automated Delivery System

Insulet Corporation is an innovative medical device company based in Billerica, Massachusetts. Insulet designs and manufactures the OmniPod® Delivery System, an intelligent wearable subcutaneous pod used in a variety of therapeutic areas. This automated drug delivery system helps offer improved adherence, outcomes and differentiation throughout a drug's lifecycle. Equipped with a soft delivery cannula for a virtually painless experience and adhesive backing for extended wear, OmniPod is the on-body device that allows patients to live life uninterrupted. For more information, contact Insulet at (978) 600-7011or visit **www.omnipoddelivery.com**.

Marketing & Communications

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

Global Data & Analytics

PharmaCircle is a leading provider of global data and analysis on the pharmaceutical, biotechnology, and drug delivery industries. PharmaCircle's premier database delivers an integrated scientific, regulatory, and commercial landscape view with unprecedented access to hundreds of company, product, and technology attributes. PharmaCircle connects product and pipeline information for drugs and biologics with formulation and component details, and provides due diligence level data on nearly 6,000 drug delivery technologies and devices. Drug label comparison tools and full-text document search capabilities help to further streamline research. No other industry database matches PharmaCircle's breadth of content and multi-parameter search, filtering, and visualization capabilities. To learn more, email contact@pharmacircle.com, call (800) 439-5130, or visit **www.pharmacircle.com**.

Technology & Services Showcase

Room-Temperature Sterilization

REVOX™ Sterilization Solutions by Cantel Medical

REVOX® Sterilization uses a patented, room-temperature peracetic acid (PAA) vaporized sterilant that achieves exceptionally low chemical residuals and unsurpassed materials compatibility. With superior compatibility across a wider range of materials, engineers have more options to create products more efficiently. Companies can now create the products that will demonstrate their true potential. The REVOX™ technology eliminates inefficiencies associated with pre-conditioning and lengthy post sterilization wait times. This allows REVOX Sterilization to offer manufacturers a quick-turn, off-site sterilization service or cost efficient on-site, in-line processing. In May 2014, a Class II implantable device was granted FDA clearance with the REVOX sterilization process. The REVOX innovation is backed by a company with over 35 years of infection prevention and control advancements structured under strict regulatory compliance standards. For more information, visit REVOX at **www.revoxsterilization.com**.

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Looking for a syringe system for your sensitive compound? Vetter-Ject® offers a syringe closure system specially designed for sensitive compounds. By combining a baked-in siliconization process with a staked needle, it provides a number of significant advantages, such as Product Integrity (tamper-evident seal supports product integrity), Ready-to-Use Convenience (staked needle offers easy handling and administration), and High Product Security (baked-in siliconization process reduces product-silicone interaction). For more information visit Vetter at **www.vetter-pharma.com**.

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Intuitive and easy to use, the SmartDose® injector is designed to take patients out of the clinical setting and lets them get on with their lives. Designed for use with a Daikyo Crystal Zenith® polymer cartridge, the SmartDose injector is an ideal solution for high-viscosity formulations and for delivery volumes greater than 1 mL. Designed and manufactured by West, this single-dose disposable unit with integrated needle safety has audible and visual cues, and a pre-programmable injection rate. West works side-by-side with healthcare partners from concept to the patient, designing and manufacturing packaging, diagnostic, and delivery systems that promote efficiency, reliability, and safety. West leads the way with cutting-edge technologies, a thorough understanding of global regulatory compliance, and quality systems. West also has an unmatched knowledge of relevant pharmaceutical product testing, development, and packaging. For more information, visit West at **www.westpharma.com**.

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Xcelience offers a suite of services from preformulation and development through manufacturing and clinical distribution and logistics. Entrust all your clinical outsourcing needs by partnering with a single CDMO. Services include preformulation development, analytical services, formulation development, GMP manufacturing, and clinical supplies packaging and distribution. Xcelience's responsibility is delivering the best science and service with our commitment to quality, cost, and speed. Since 1997, Xcelience has been known for reliably expediting drug product development and clinical manufacturing for oral solid, semi-solid, and liquid dosage forms. In the past few years, Xcelience has grown exponentially, opening a facility in 2012 dedicated to clinical packaging and logistics, and in 2013, opening its first international facility in the UK. For more information, contact Xcelience at (813) 286-0404 or info@xcelience.com, or visit **www.xcelience.com**.

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External Delivery

The New Marketing Paradigm

By: John A. Bermingham

John A. Bermingham is former Executive Vice President & COO of 1st Light Energy & Conservation Lighting, Inc. and former Co-President and COO of AgraTech, a biotech enterprise. He was also President & CEO of Cord Crafts, LLC; President & CEO of Alco Consumer Products, Inc., Lang Holdings, Inc., and President, Chairman, and CEO of Ampad, all of which he turned around and successfully sold. 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 as well as turning 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.

We are 60 days past the half-way mark for calendar 2015. For those on a calendar year fiscal basis, this means their business year is almost finished as we head toward the end of the third quarter.

Business in 2015 has seen a great deal of change, refocus, and adaptation to new ways of doing business. Company CEOs have a multitude of things to be concerned with, some of them from the old school of business, and many of them from the new school.

The one big change that really caught my eye was the change from traditional product to what is now called Content Marketing. By definition, Content Marketing is the utilization of content that will attract people to your brand and turn them into brand advocates for your products. Plus, an added benefit is that while your Content Marketing is about influencing your customers, it is also about capturing those people who can influence others.

So many moons ago, when I was a Vice President of Sales & Marketing at Sony, marketing was a support function for sales. We would advertise products in various vehicles, such as magazines, radio, television, billboards, in-store merchandising displays, etc. The advertisement in its most basic form called out the feature/benefit package, specifications, perhaps a new or improved technology feature, and a headline that was a call to action, such as "Here it is, come and get it" or "Here it is, you can't live without it." Not so today with Content Marketing.

First off, today's advertising vehicles are much more diverse than they were in the old days of brand marketing. Some of the formats used today include, in addition to the standard formats of yesteryear, news, video, white papers, e-books, blogs, infographics, case studies, how-to guides, question-and-answer articles, photos, and more.

Prior to Content Marketing, most companies had a marketing strategy of advertising a brand with the intention of building that brand's reputation. Content Marketing often has the same strategy of building a brand's reputation but goes about it much differently. Content Marketing's strategy is to build an emotional relationship with its customers and with the intention of having those customers influence others to purchase the brand.

Apple is a classic brand that has obviously capitalized on the benefits of Content Marketing. Is Apple a higher quality product than its competition? Maybe, maybe not! Is Apple a more price-competitive product than its competitors? Maybe, maybe not! Is an Apple product better featured than a competitive product? Maybe, maybe not! Has Apple used Content Marketing to attach its brand emotionally to its customers who have become goodwill ambassadors for the brand? Most definitely!!!

One of the best examples of Content Marketing is Accura's TLX commercial featuring Sid Vicious singing the old classic My Way. You ask, how can Sid Vicious of the Sex Pistols sing My Way and be effective selling cars?

When you watch the advertisement and see how the company develops an emotional relationship with you by taking you through the design, engineering, testing, and real-life driving of the car, you will see what I mean. Here's the link: http://www.hondanews.com/videos/2015-tlx-my-way-commercial. Enjoy! ◆

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THE CREDENCE COMPANION

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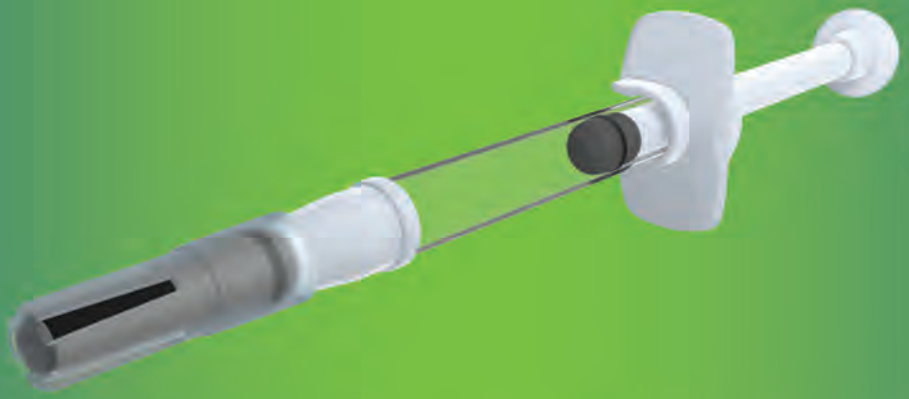

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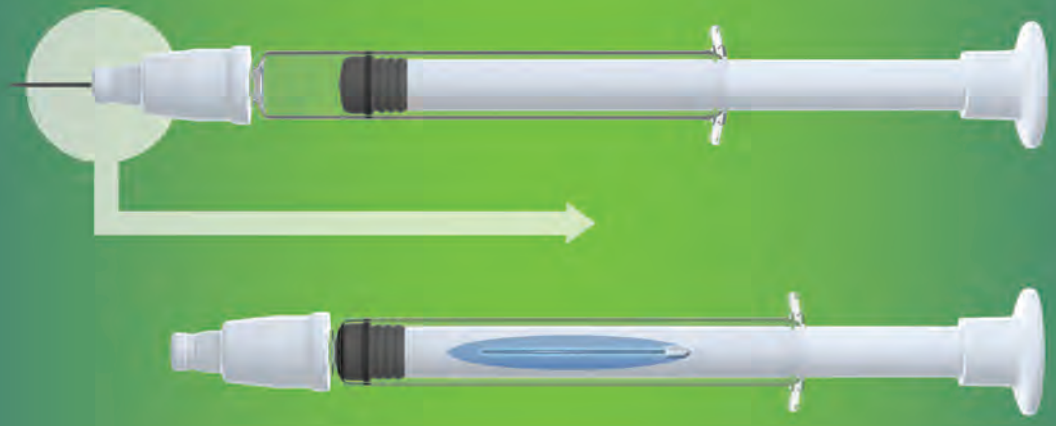

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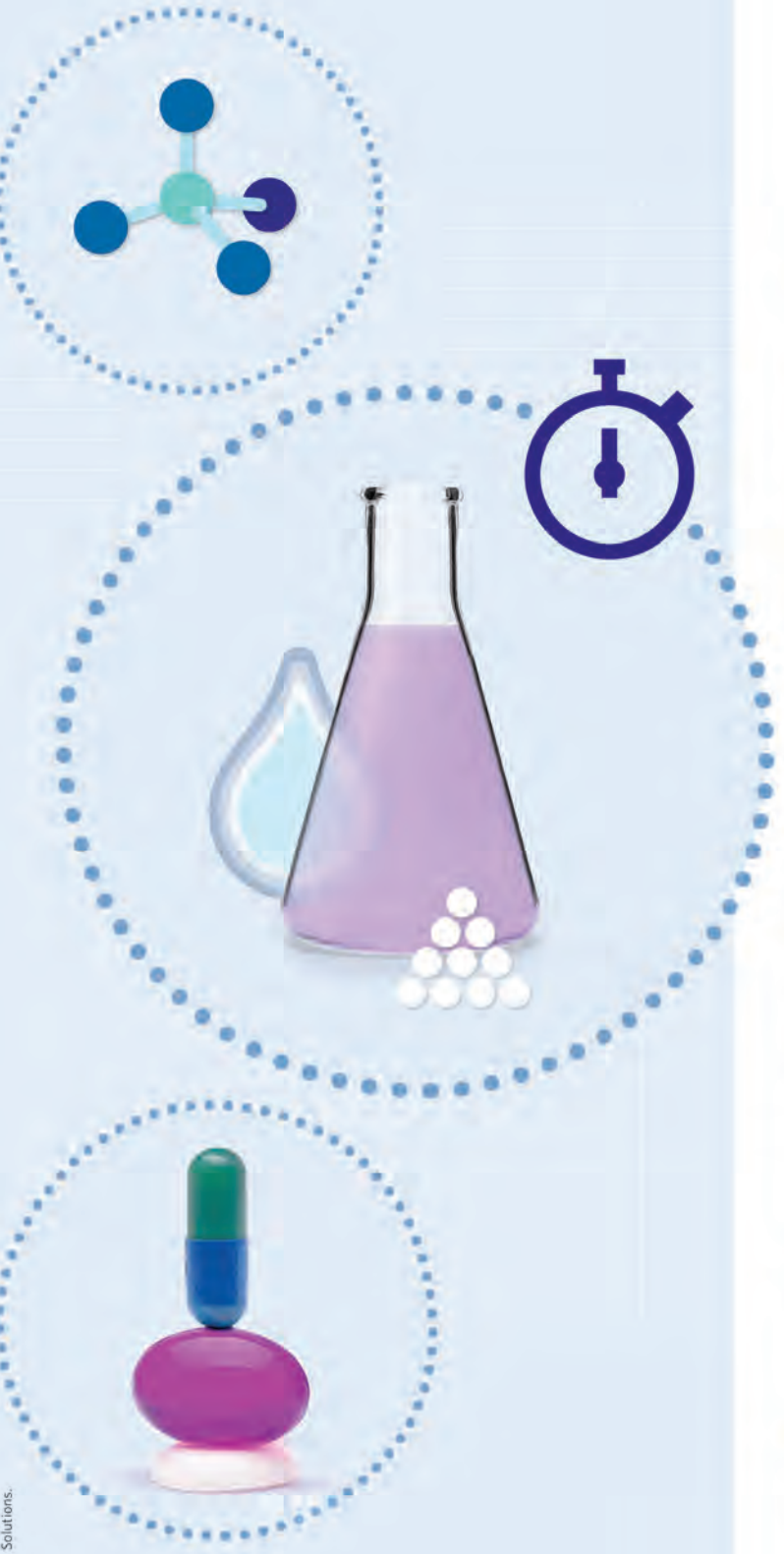

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