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September 2012 Vol 12 No 7 www.drug-dev.com

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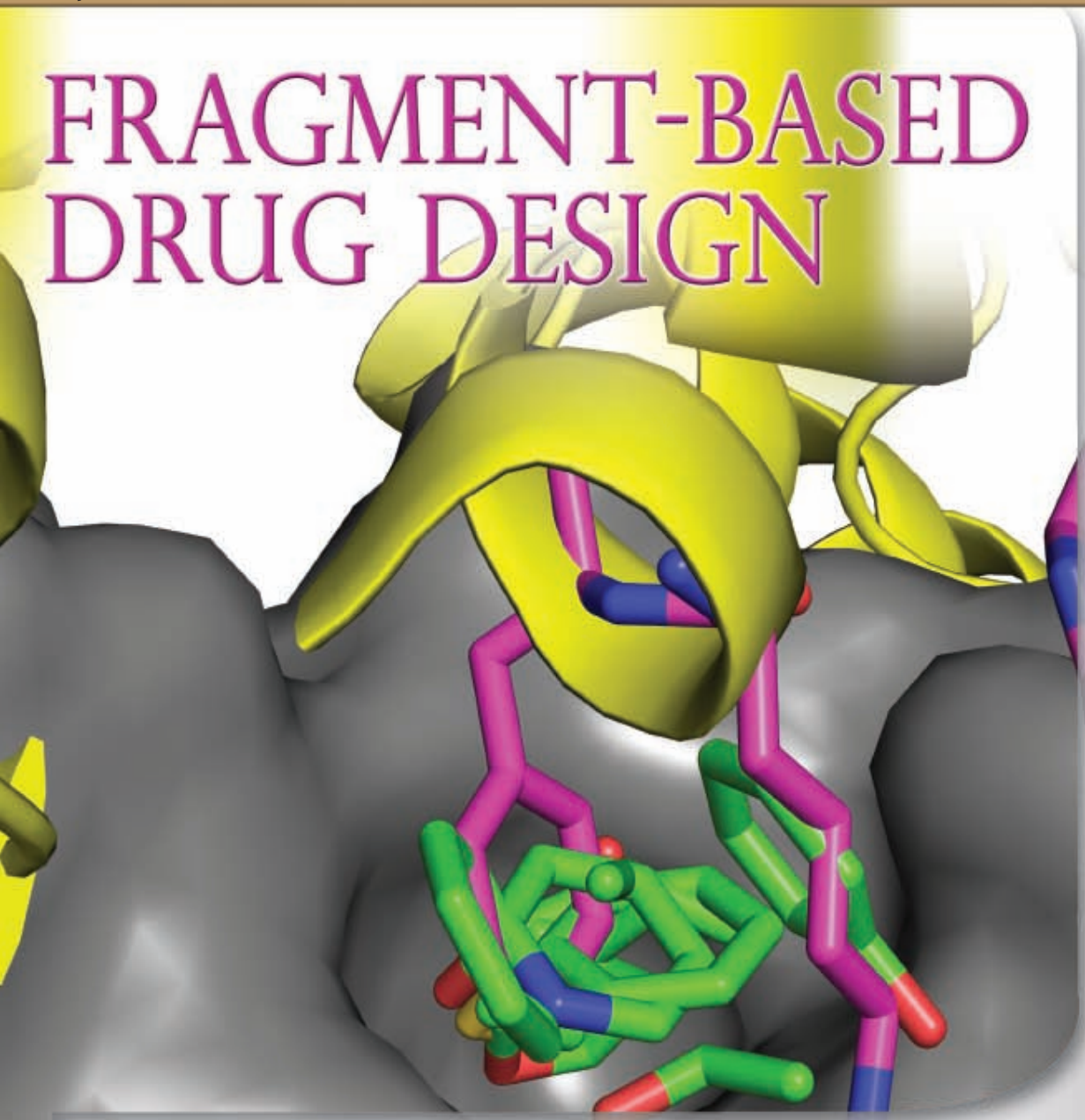

The science & business of drug development in specialty pharma, biotechnology, and drug delivery

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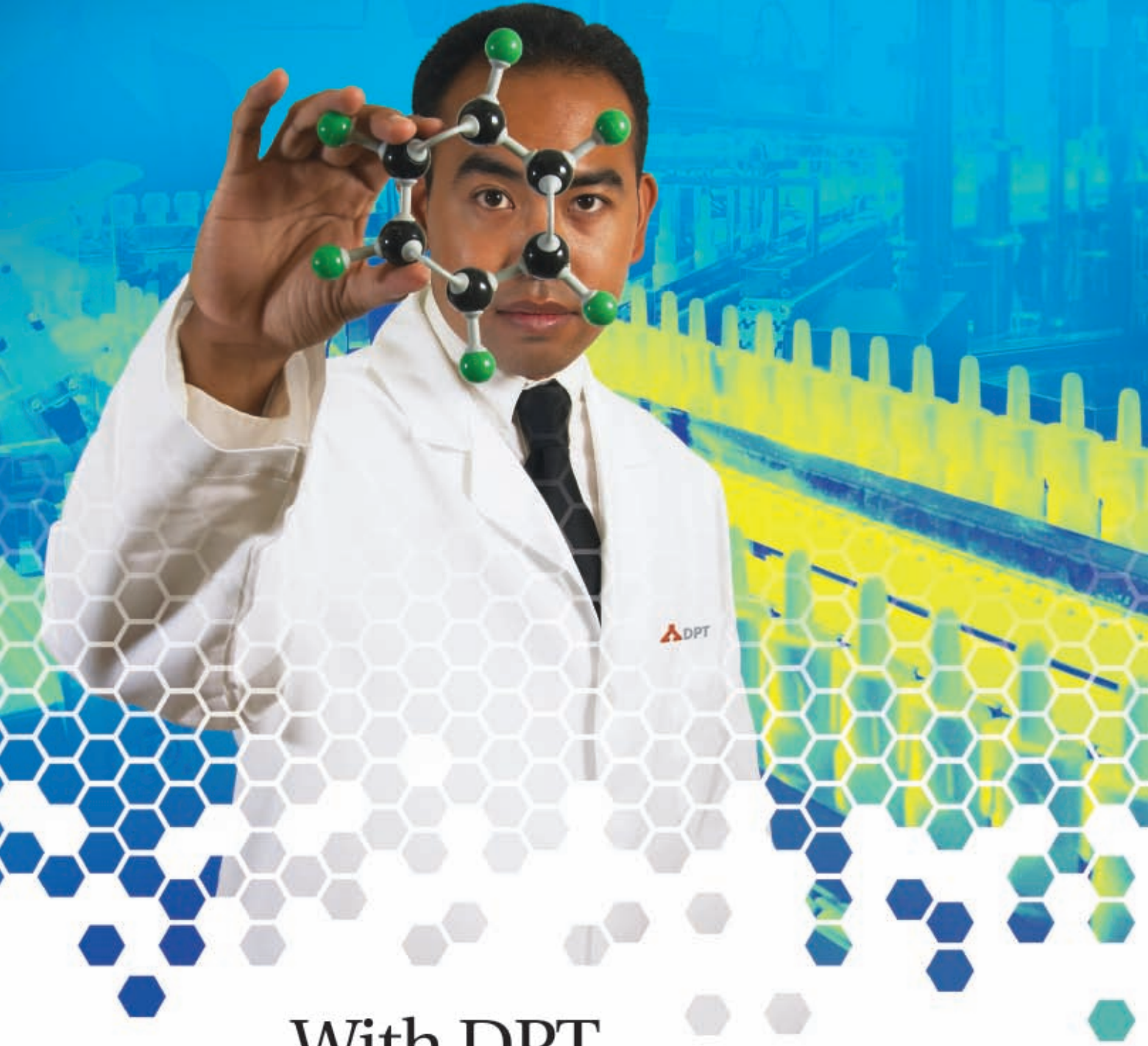

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"The biopharmaceutical industry is one of the most research-concentrated industries. The expenditure on biopharmaceutical research and development has showcased a dependable growth. Thus, the global biologics market was valued at an estimated $149 billion in 2010 and is expected to reach $239 billion by 2015, a compound annual growth rate (CAGR) of 9.9% from 2010-2015, states ReportLinker. As most biologics are proteins and hydrolyzed in the gut by digestive enzymes, most new biologics are being introduced for IV administration. However, some biologics may later be reformulated into other handheld drug delivery systems, such as prefilled syringes, needle-free injectors, autoinjectors, and traditional needle-and-syringe delivery."

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TRANSDERMAL TRANSCENDENCE

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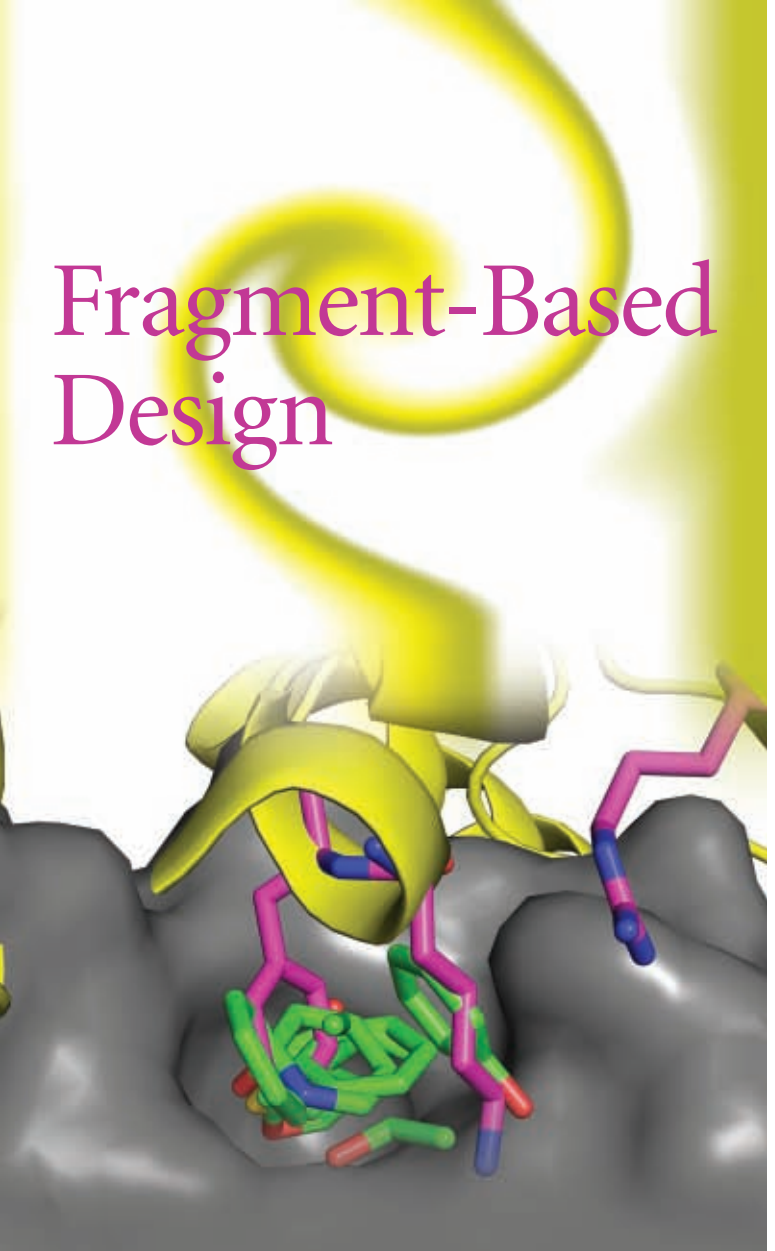

"Based on reliable predictions of where, and with what binding affinity, small chemical fragments interact with disease targets, such as enzymes and cell receptors, drug designers can assemble new drug-like molecules. The fragments, once linked together synthetically, are much more active biochemically. And the entire progression from fragment identification through lead optimization can be performed using predictable software models. Delivering on this vision is fraught with obstacles, given the difficulty of modeling molecular interactions. But computational chemists must take on the challenge."

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Researchers Discover New Mechanism Behind Resistance to Cancer Treatment

Developing resistance to chemotherapy is a nearly universal, ultimately lethal consequence for cancer patients with solid tumors - such as those of the breast, prostate, lung, and colon - that have metastasized throughout the body. A team of scientists led by Fred Hutchinson Cancer Research Center has discovered a key factor that drives this drug resistance - information that ultimately may be used to improve the effectiveness of therapy and buy precious time for patients with advanced cancer. They describe their findings online in advance of print publication in Nature Medicine.

"Cancer cells inside the body live in a very complex environment or neighborhood. Where the tumor cell resides and who its neighbors are influence its response and resistance to therapy," said Senior Author Peter S. Nelson, MD, a member of the Hutchinson Center's Human Biology Division.

Dr. Nelson and colleagues found that a type of normal, noncancerous cell that lives in cancer's neighborhood - the fibroblast - when exposed to chemotherapy sustains DNA damage that drives the production of a broad spectrum of growth factors that stimulate cancer growth. Under normal circumstances, fibroblasts help maintain the structural integrity of connective tissue, and they play a critical role in wound healing and collagen production.

Specifically, the researchers found that DNA-damaging cancer treatment coaxes fibroblasts to crank out a protein called WNT16B within the tumor microenvironment, and that high levels of this protein enable cancer cells to grow, invade surrounding tissue, and resist chemotherapy.

The researchers observed up to 30-fold increases in WNT production - a finding that was "completely unexpected," said Dr. Nelson. The WNT family of genes and proteins plays an important role in normal development and also in the development of some cancers but, until now, was not known to play a significant role in treatment resistance. This discovery suggests that finding a way to block this treatment response in the tumor microenvironment may improve the effectiveness of therapy.

"Cancer therapies are increasingly evolving to be very specific, targeting key molecular engines that drive the cancer rather than more generic vulnerabilities, such as damaging DNA. Our findings indicate that the tumor microenvironment also can influence the success or failure of these more precise therapies. In other words, the same cancer cell, when exposed to different neighborhoods, may have very different responses to treatment," said Dr. Nelson.

The major clinical reason that chemotherapy ultimately fails in the face of advanced cancer, he added, is because the doses necessary to thoroughly wipe out the cancer would also be lethal to the patient. "In the laboratory we can 'cure' most any cancer simply by giving very high doses of toxic therapies to cancer cells in a petri dish. However, in people, these high doses would not only kill the cancer cells but also normal cells and the host."

Therefore, treatments for common solid tumors are given in smaller doses and in cycles, or intervals, to allow the normal cells to recover. This approach may not eradicate all of the tumor cells, and those that survive can evolve to become resistant to subsequent rounds of anti-cancer therapy.

For the study, the team of researchers, which also involved investigators at the University of Washington, Oregon Health and Science University, the Buck Institute for Research on Aging, the Lawrence Berkeley National Laboratory, examined cancer cells from prostate, breast, and ovarian cancer patients who had been treated with chemotherapy.

"This study is an example of collaborative, translational research that capitalizes on years of federally funded investments into the development of tissue banks and clinical trials in which we were able to track long-term patient outcomes. Investing in this type of infrastructure is critical but may take many years to see payoff," said Dr. Nelson, who serves as Principal Investigator of the Pacific Northwest Prostate Cancer SPORE, a federally funded, multi-institution research consortium led by the Hutchinson Center.

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GeNO LLC Receives Two Additional Patents for Inhaled Drug Delivery

GeNO LLC recently announced it has been awarded two new US patents on its proprietary nitric oxide (NO) generation and delivery technology. This brings to 12 the number of US patents that have been awarded to GeNO.

US patent No. 8,173,072 describes the conversion of nitrogen dioxide (NO2) to nitric oxide (NO) in a gas stream using the GeNO cartridge technology. The output gas is highly purified NO intended for inhalation therapy for the treatment of acute and chronic forms of pulmonary arterial hypertension and other medical uses. This patent expires in 2030.

US Patent No. 8,187,544 describes a unique method for scavenging traces of toxic nitrogen dioxide (NO2) from a gas stream prior to inhalation by a patient. The patent on this new technology expires in 2029.

"These two new patents are important additions to our company's strong intellectual property portfolio, and extend the company's patent protection into year 2030," said GeNO LLC Founder and President Dr. David Fine. "It is unusual for a drug company already in Phase II clinical trials to have 18 years of patent protection on its key chemistry."

GeNO is developing three unique nitric oxide delivery platforms: a stand-alone gas cylinder system for hospital and outpatient use, a ventilator-based platform for Intensive Care Unit use, and a pocket-sized ambulatory system for chronic outpatient use. All of the platforms are designed to deliver extremely low levels of the toxic by-product nitrogen dioxide that are undetectable by conventional means, while also addressing the cost, complexity, and lack of portability of approved inhaled nitric oxide treatment systems. GeNOnitric oxide gas has the potential for treatment of a multitude of serious pulmonary and cardiac diseases, and potentially could reach a much larger group of patients.

GeNO recently completed a Phase II pilot study of its nitric oxide for use as a diagnostic in Pulmonary Arterial Hypertension (PAH). The company is currently performing a dose-escalation trial for the Treatment of Pulmonary Hypertension in patients with PAH and Pulmonary Hypertension secondary to Idiopathic Pulmonary Fibrosis (PH-IPF).

NanoViricides Reports Orall Administration of Drug is Effective

NanoViricides, Inc. recently announced that an anti-influenza drug candidate under its FluCide program is effective when given orally. The company has received information that a FluCide drug candidate designed for oral administration has shown very strong efficacy in corresponding animal studies. The studies involved the same highly lethal animal model the company has continued to use for its influenza drug development program. The company is awaiting data from the studies and intends to release additional information as the data are analyzed and studied.

"An orally administered drug is highly desirable for treating out-patient influenza," said Anil R. Diwan, PhD, President of NanoViricides. "We are pleasantly surprised that the modifications that we have been studying for the development of a nanoviricide that can be orally effective have indeed succeeded. Molecules that nanomedicines are composed of are notoriously difficult to develop into orally available drugs. This is indeed a coup for our nanomedicine technologies."

Nanoviricides, Inc. has been working on the development of an orally available nanoviricide for several years now. The essential chemistries were finally worked out during the CMC studies for its current FluCide drug candidate. An initial feasibility study to determine whether a nanoviricide anti-influenza drug candidate would work when administered orally was undertaken perviously and had shown positive indications. The company continued further development and has now completed a definitive animal model study to determine whether one of the FluCide anti-influenza drug candidates was effective when administered orally.

The study was conducted by KARD Scientific, Inc. Dr. Krishna Menon, President of KARD and consulting Regulatory Officer for NanoViricides, Inc., has advised the company that some of the orally administered drug candidates provided by NanoViricides showed efficacy in combatting highly lethal influenza H1N1 infection in mice. This was a double-blind study. Until the data are received and the code is broken by the company scientists, the identity of the FluCide drug candidates that were orally active will not be known. The company expects to receive information from the various analyses in this study over the next several weeks, as the data are compiled and returned by analytical laboratories. The company intends to provide additional information as the data become available and are analyzed by its scientific staff.

Quintiles Acquires Company to Advance Personalized Medicine

Quintiles recently announced the acquisition of Expression Analysis, Inc. (EA), a premier provider of genomics testing and analysis to biopharma, academic, government, and non-profit customers, to help biopharmaceutical companies significantly improve drug development productivity and deliver greater value.

"The addition of EA's Genomic Know-How to Quintiles is another step forward in our efforts to bring personalized medicine into mainstream drug development," said Thomas Wollman, Senior Vice President, Quintiles Global Laboratories. "Its expertise in genetic sequencing and advanced bioinformatics is essential to understanding diseases and drugs at the molecular level. That's a huge step in creating more value across the healthcare spectrum."

"The combination of Quintiles Global Laboratories and EA genomic technology excellence will facilitate worldwide access to resources and expertise to drive improvements in the diagnosis, treatment, and management of complex disease," added Steve McPhail, EA President and Chief Executive Officer. "EA can now play a global role in helping biopharma succeed in the New Health. This is the right move for our company and our employees. Our mission perfectly fits Quintiles' strategy to use genomic data and advanced informatics to yield actionable insights and more effective personalized treatments."

Protalix BioTherapeutics Receives Clearance to Initiate Study

Protalix BioTherapeutics, Inc. recently announced it has received clearance of its IND application from the US FDA to initiate clinical trials of PRX-102. The company plans to commence enrollment of Fabry disease patients for a Phase I/II trial in the fourth quarter of 2012.

PRX-102 is a proprietary plant cell-expressed, chemically modified, recombinant alpha-galactosidase-A in development as a long-term enzyme replacement therapy (ERT) for the treatment of Fabry disease. The Phase I/II clinical trial is designed as a multi-center, open label, dose ranging study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of PRX-102 in adult Fabry patients.

"We are very excited to begin the clinical development of PRX-102, which we believe may prove to present an important improvement to the well being of patients with Fabry disease, a rare, genetic lysosomal storage disorder affecting approximately 8,000 people globally," said Dr. David Aviezer, Protalix's President and Chief Executive Officer. "We have designed PRX-102 as a potentially improved version of the currently marketed enzyme replacement therapies for Fabry disease given its potential to be a more stable, potent, and specific enzyme. This enzyme is expressed through ProCellEx, our proprietary, plant cell-based protein expression system. We are also excited that another biotherapeutic protein evolving from our ProcellEx platform technology is anticipated to enter clinical development shortly."

Eighteen adult Fabry patients will be enrolled in one of three dosing groups. Each patient will receive intravenous infusions of PRX-102 every 2 weeks for 12 weeks, and will be infused sequentially and stepwise in order to evaluate safety. Exploratory efficacy parameters will be evaluated as a preliminary assessment. Following the end of the trial, the company intends to offer patients the option to continue to receive PRX-102 in an open-label extension study.

Oculus Innovative Sciences Announces Licensing Agreement

Oculus Innovative Sciences, Inc. recently announced the exclusive licensing of the company's Microcyn-based human healthcare products in Mexico, South/Central America, and the Caribbean to More Pharma Corporation.

"Since our founding in 2007, More Pharma has established a track record of strong growth because of our ability to identify and partner with cutting-edge pharmaceutical technologies," said Guillermo Ibarra, More Pharma's CEO. "We believe the Microcyn Technology - already proven and with a dominant share of the Mexican market - is a compelling addition to our product portfolio, allowing us to build upon Oculus' established success in the Mexican market and affording us the opportunity to achieve similar commercial success throughout the South and Central American and Caribbean countries."

Under the terms of the agreement, More Pharma will pay Oculus an up-front $5.1-million licensing fee. The transition of the marketing and sales effort in Mexico to More Pharma will begin immediately, while expansion into other South/Central American and Caribbean countries is dependent upon securing the needed regulatory clearances in those regions. More Pharma will oversee and underwrite all costs for regulatory review and approval.

"We are excited about partnering with More Pharma and their rapidly growing sales and marketing teams in Mexico, the Caribbean, Central, and South America," added Hoji Alimi, CEO of Oculus. "We believe this positions us for accelerated long-term unit sales growth in Mexico and also provides us with a terrific partner to introduce our portfolio of Microcyn-based products throughout South and Central America - new territories that are large, untapped markets with a growing middle class."

Theorem Clinical Research & Gallus BioPharmaceuticals Announce Exclusive Partnership

Theorem Clinical Research has entered an exclusive partnership with Gallus BioPharmaceuticals in which Gallus will provide process development and clinical and commercial supply for mammalian cell-based biopharmaceutical products to Theorem's customers. In return, Theorem will offer contract research services to Gallus' customers to increase both companies' global reach and accelerate their customers' products through the clinic to market.

Gallus and Theorem have indicated their collaboration is aimed at addressing various time and cost issues in the current working relationship between sponsor companies and service providers by supporting the needs of their customers to outsource the research, development, and ultimate commercial production of products more cost effectively and to accelerate the path to market.

"Our intent is to make the process as seamless as possible," said Gallus President and CEO Mark Bamforth.

Theorem is one of the industry's leading full-service, global CROs providing core clinical research and development services. The company provides core CRO services for Phases I to IV, but with niche business units in the areas of clinical analytics, medical device, and pharmaceutics. Gallus is a world-class CMO, operating a commercially licensed manufacturing site in St. Louis. With more than 25 years of experience in process development and a decade of commercial manufacturing, the company's facilities are designed to support the development of early phase processes through scale-up and full clinical and commercial production.

Comparative Analysis

Whiteboard Walls & Open Doors: Creating an Environment for Pharmaceutical Innovation

Part 5 of a 6-part series on lessons learned from other industries.

By: Derek Hennecke, President & CEO Xcelience LLC

Go forth and diversify. If there was a Bible for business, this would be a commandment. Diversify to spread risk. Diversify to dilute exposure. Most importantly, diversify to innovate. When the Canon Camera Company moved into copiers and later printers, that was diversification into an existing business segment. When Hallmark began the first mass production run for a new invention called gift wrap near the turn of the century, the young greeting card company diversified into a whole new market that never existed before, thereby creating even more opportunities, including 3M's invention of Scotch Tape in 1930. So, good company, *Go forth and diversify*.

If only this commandment were as easy as *Go forth and multiply.* From GE to J&J, most companies struggle to formulate a workable recipe for diversification. Many manage to cook up solutions that taste okay, barring a few real nose pinchers. The Japanese company Toto famously diversified from heated and self-cleaning toilets into toilets that test your urine and measure blood sugar and body fat. Consumers ruled this innovation TMI, even for a toilet.

Most diversification failures, however, are more subtle - a gradual splintering of product offerings, for example, that fails to grow the pie.

The May *Harvard Business Review* produced a thought-provoking article called *Managing your Investment Portfolio*, about what works and what doesn't work in diversification. According to authors Bagji and Tuff, a well-balanced innovation strategy balances three types of innovation: core, adjacent, and transformational. Different industries successfully balance the three differently.

From Bell Labs to Google, companies have long sought to create the ideal environment to foster ground breaking innovations.

Core innovation initiatives form the majority of all innovations. A core innovation tweaks an existing product for an existing client. McDonald's comes out with a new line of chicken burgers that are grilled instead of fried. In our industry, a core innovation might involve reformulating a diabetes drug from a twice-a-day tablet to a once-a-day version. For the top performing consumer goods companies, core innovation formed 80% of all innovations within the company. These companies can keep interest in burgers and bicycles high with a few small changes. A mid-stage technology firm, on the other hand, would flounder with 80% core innovations. Tweaking won't cut it for long in a market that reinvents itself every couple of years. Successful tech companies churn out just 40% of their innovations in this category.

Tech companies are far more active in seeking more daring *adjacent* innovations. Bagji and Tuff describe adjacent innovations as drawing on companies' existing capabilities and putting them to new uses. We're talking here about using what you have on hand to enter a business that's new to the company. McDonald's moves into lattes. Delta Airlines, which spends $32 million/day on fuel, buys a refinery. That's adjacent.

Sticking with the diabetes example for our industry, an adjacent innovation would involve creating a new drug to treat diabetes that uses a completely different method of action. Consumer companies usually put about 18% of their innovation efforts into adjacent developments, and industrials 20%. Technology firms generally need about 40% adjacent innovations to generate solid returns.

The third type of innovation touted by Nagji and Tuff is the *tranformational* breakthrough. This is the big kahuna, the great gamble, the lottery winner, the ground breakingly new invention for a market that doesn't exist yet. Think of the television or the computer. In our industry, a transformational strategy might involve the purchase of a new platform, such as a screening mechanism, which might lead a company specializing in diabetes treatments to develop a completely new drug for leukemia.

FROM BELL LABS TO GOOGLE

When we think of transformational innovation today, we think of Apple, Microsoft, or Google, but in the halls of innovation, the ultimate transformational lab of all time predates these companies by decades. From efforts to connect New York to San Francisco by telephone before WWII, the legendary minds of Bell Labs went on to invent radar, fiber optics, mobile phones, and satellite communications. This one lab produced 13 Nobel prize winners. Bill Gates once said, “My first stop on any time-travel expedition would be Bell Labs in December 1947.”

Replicating the creative environment of Bell Labs is the Holy Grail of businesses everywhere. Companies emulate Bell's flat organizational structure, its open doors, and long corridors. Google, which aims for 20% transformation innovation, copied Bell with its policy of encouraging workers to spend as much as 20% of their time on whatever project piques their interest.

I had an opportunity to visit a Google office in Montreal last Christmas. Glass-walled offices faced sprawling cushioned meeting areas, and whiteboard paint covered entire walls. Off the gleaming cafeteria, stocked with healthy snacks, drinks, and take-home lasagnas for working parents, was an old-fashioned arcade. Just down the hall from the gym and washing machine was, by employee request, a sound-proofed music room complete with drums and keyboards. The *pièce de résistance* - alongside a staircase to the second floor, was a two-story rock climbing wall. Don't try this with your morning coffee in hand.

Most attempts to discover transformational innovations fail. That's why stable, slow-moving consumer companies are successful even when they throw only 2% of their innovation budgets into transformational strategies. Industrial companies generally need to put more like 10% of their innovation budgets into this category, while technology companies must invest at least 15% of their resources into this type of innovation if they are to produce industry-leading returns.

BIOTECH: THE INDUSTRY'S INNOVATORS

I'd love to see Nagji and Tuff turn their lens to our own industry, because any small biotech company is, by its nature, 100% transformational. These people are the risk takers, the all-in poker players. They are our industry’s equivalent of cliff divers and parkour traceurs. Danger is their middle name. These folks are the innovative engine of our industry, and I for one wouldn't be here without them.

We rely more on these guys for innovation every year. In days gone by, many biotech innovators might have worked in large pharma - where they could confidently support a spouse and kids. But big pharma has been downsizing its in-house R&D. I believe if Nagji and Tuff were to analyze big pharma today, they would say most successful large pharma

companies split their innovation budgets as follows: 80% core, 18% adjacent, and it's only 2% transformational nowadays, when big pharma embraces a breakthrough innovation, it's usually through purchasing an existing company that's already brought the new treatment through some of the riskiest stages of development.

Maybe big pharma's conservatism isn't a bad thing. It's arguable that big pharma doesn't have the right atmosphere to foster creativity. Not that it couldn't - Bell Labs had 12,000 scientists working in the heyday of its productivity. But I don't see any big pharma companies building rock climbing walls right now. Correct me if I'm wrong, but big pharma neither has nor is striving to foster an environment conducive to transformational or adjacent innovation.

THE FDA POLICY ON ME-TOO DRUGS UNDER ATTACK

Which makes it all the more important that we free up the biotech companies to innovate as much as possible. If ever there were an industry the world would like to see innovating in the transformational category on a regular basis, it's pharmaceuticals. And yet there are still those out there arguing to reign innovation further in.

An essay in the *Journal of the American Medical Association* published in February of last year argued that drugs seeking FDA approval should demonstrate not just non-inferiority, but superiority compared to available drugs. The article lambasted the FDA for approving pitavastatin (Livalo), resulting in eight statins approved for use in the US. The author contends that eight is too many, and that new drugs should be at least safer, more efficient, or suitable for other populations, such as the elderly or children.

Such a move would hamper innovation further. No drug company ever sets out to develop a me-too drug. They always start with a molecule they believe is better. When it turns out the drug's efficacy is similar to an existing drug, does that really mean this new molecule should be thrown out with the bathwater? There are so many reasons to let these drugs come to market. Doctors, for one, are always on the lookout for precisely the kind of options these drugs present. When a patient doesn't respond to one drug, or perhaps reacts with a nasty side effect, doctors need options to be able to match the patient to the drug that performs best for him or her. Perhaps even more importantly, shutting down promising new molecules closes an entire avenue of potential innovation. The

SIDEBAR

Patently Offensive?

International pharma has just cause for concern after a company official of India's Natco Pharma was quoted in *LiveMint* saying that "certain products" have been declared eligible for compulsory licensing by the Indian government. Compulsory licensing occurs when a government allows a company to produce a patented product without the permission of the patent owner. Natco was not forthcoming on which drugs are on this list, but the company's claim has the ring of truth. Earlier this year, Natco received permission from the Indian Patent Office to produce a generic of a Bayer kidney and liver cancer medication called Nexacar. The Indian government justified the decision saying that Bayer had failed to make the drug available in India at an affordable price, and the license is for the domestic market only. This was the first time that India had taken such a step, and big pharma is keenly aware that the rules of the game have just been rewritten.

On the subject of India, I reported last fall about the shocking increase in the number of reported deaths of participants in clinical trials in India. From 137 deaths in 2007 to 668 in 2009, the numbers had tripled. Now, it appears, those numbers are on the decline. Last year saw 438 deaths, according to the Business Standard. With no significant changes in the regulatory procedures governing the trials, we are left to speculate as to why they are declining. Are trials moving away from India, either back to our own soil or another third-world country? Does the decline reflect a reduction in the total volume of trials? I'd like to believe that the numbers reflect safer studies, but the cynic in me suspects that reporting procedures in India are simply unreliable.

availability of any one new molecule could lead to untold transformational discoveries that would never otherwise see the light of day.

Eight statins does increase the possibility that pitavastatin will usurp lovastatin, but after a quarter of a century, is that necessarily a bad thing? What if we legislated that no more companies should waste resources on developing new operating systems unless they can prove they are better that what's out there? If the computing industry required new companies to demonstrate superiority before allowing a new operating system on the market, we might still be using DOS. Apple might have suffocated from lack of ability to innovate at its very infancy.

Innovation thrives by getting new ideas out there, viewing them from all angles, and seeing where they take us. A policy against me-too drugs would present yet another hurdle for new molecules to overcome, effectively throwing water on the sparks of innovation at their very source.

CHEMIATICA: NO ONE CAN PREDICT WHERE UNBRIDLED INNOVATION WILL LEAD

Often it isn't until an idea is out there for a while that it's true potential comes to light. Take for example Chemiatica. Chemiatica is to our industry what the internet was to computers. This massive database essentially wires together seven million different substances and the knowledge associated with them. "Think about it as a collective chemical brain," says inventor Bartosz Grzybowki from Northwestern University in Evanston, IL.

Chemiatica began as a tool to help chemists find cheaper and more efficient ways to make existing drugs. A mind-numblingly big interconnected database of chemicals, it took 5 years to develop and another 2 to program it with 86,000 rules, such as the required balance between acids and bases, or the compatibility of solvents.

Only when Chematica was out there did its other uses become obvious. The database can be used to find and create new substances without the intermediate stages of isolating and purifying compounds. But it can also be used to spot potentially dangerous chemicals before criminals do. Today, Homeland Security is looking at how the database might be exploited to identify potential terrorists building chemical weapons using seemingly harmless chemical components. Who could have foreseen this use at its inception?

SIZE MATTERS

There does seem to be a critical organizational size, beyond which innovation is increasingly difficult to achieve. This is a theme of *Antifragile: Things That Gain From Disorder*, to be published this fall by Nassim Taleb, author of *The Black Swan*. The book aims to provide advice to help companies protect themselves from random events, and sometimes even profit from them. Taleb points to size itself as a source of fragility. He follows the case of Societe Generale SA's forced sale of $70 billion in stock market bets for a crippling $6 billion loss. Sales of one-tenth that amount, he argues, might have been absorbed by the market without losses, even at fire sale prices.

Companies everywhere seem to be heeding this advice about the perils of growing too large. Monolithic GE is poised to split itself up. Abbott, Pfizer, and Covidien have all undertaken major spin-offs. Rubin, the Goldman analyst, is now advising J&J to deal with its declining sales growth by dividing its three divisions into three separate companies.

CROS & INNOVATION

How do CROs best diversify to maximize innovation? CROs, as service providers, don't follow the

same rules as either small or large pharma. We need to be more agile than large pharma, on top of the latest developments, experimenting with and perfecting new methods of service delivery in a way that large pharma, by virtue of its sheer size, can't. That's how we justify our existence. Yet obviously, we can't emulate small pharma either, and be 100% transformational.

Applying Nagji and Tuff's rules to my own business, Xcelience seeks to have 60% of our innovation core, 38% adjacent, and 2% transformational. This would probably be a good time to mention a major adjacent diversification, which Xcelience will be launching on September 14, 2012: *Xcelience Clinical Supplies*. We are hard at work right now finalizing SOPs, plumbing compressed air, and laying sheet vinyl for a brand new 25,000-sq-ft facility for primary and secondary packaging in Tampa, FL.

This is a step we have taken with a great deal of care and forethought. It is a natural extension of the business we already do: formulation. We are going to great pains to ensure that we add this business not just as an afterthought - an adjunct tacked on for profit making (though a little of that would be nice too) - but as an extension of ourselves into another field that our existing clients have asked us to move into.

What defines Xcelience is our customer care. Our clients have access to our experts in every phase of their project. This is who we are, and any diversification we undertake must respect who we are. Following our own advice to customers, we have made full use of the experts available to us in clinical supply packaging to design a facility that would provide the most up-to-date, comprehensive service possible. We have hired experts with years of packaging experience behind them.

That said, we won't tell customers that we know everything there is to know about clinical packaging. What we do say is that we are growing and listening and learning, and we want to give our customers an opportunity to help shape our new organization to meet their own ideals.

We are optimistic this new business will reflect who we are as an organization that listens and learns, molding itself through every project to be an extension of our customer's own organization. We hope you will share in our excitement as we learn and grow in the coming months. And yes, there is a whiteboard wall in the conference room. (No rock-climbing wall just yet.) ◆

BIOGRAPHY

Derek G. Hennecke is a Founding Member, CEO, and President of Xcelience. He has a long history of growing strong businesses around the world. Blending a scientific and business background, he has nearly 2 decades of international experience in the healthcare industry and a track record as a highly successful international turn-around manager in the global drug development community. Xcelience is the first company Mr. Hennecke has managed as an owner, having launched a management buy-out from MDS Pharma Services in 2006. The newly-formed company immediately embarked on a robust pattern of growth. Before founding Xcelience, Mr. Hennecke spent more than 10 years abroad working for the Dutch-based conglomerate DSM. In Montreal, he was GM of a 250-staff Biologics plant for more than 2 years. In Cairo, Egypt, as GM, he oversaw a turn-around in an anti-infectives plant that had been slated for closure. He spent 2 years in Holland developing new Pharma intermediates, and two years in Mexico as Commercial Director covering Central and South America. He also worked for Roche, both in Canada and Germany. Mr. Hennecke has a BSc in Microbiology from the University of Alberta and an MBA from the Erasmus University in The Netherlands.

Understanding the Role of Excipient Functional Category & Performance-Related Tests in a Quality-by-Design Framework

By: Catherine Sheehan, MS

Pharmaceutical inactive ingredients or excipients are essential to a drug product's performance. Pharmaceutical-grade excipients are manufactured and supplied in compliance with standards established by the US Pharmacopeial Convention (USP) and published in its compendia - *US Pharmacopeia* and *National Formulary* (*USP-NF*).[1] However, while conformance with compendial standards is necessary, USP standards alone are not sufficient to ensure suitability for use or compliance with regulatory requirements. Not all essential physical and chemical properties of an excipient may be identified or evaluated by tests and procedures listed in *USP-NF* monographs or relate to its *NF* functional category.[2,3] Excipient function or functionality is the general purpose or utility of an excipient in a drug product formulation (eg, as a diluent, lubricant, or glidant).[4] Of greater importance are the quantitative performance properties or critical material attributes (CMAs) (eg, particle size, particle size distribution, or specific surface area) of an excipient that must be identified, and control strategies in place to ensure the drug product critical quality attributes (CQAs) are achieved and maintained throughout the drug product's life-cycle.[5] The International Conference on Harmonization (ICH) guidance for industry on pharmaceutical development links material attributes and process parameters to drug product CQAs.[6] This article is an overview of USP General Chapter <1059> *Excipient Performance*, describing how the chapter provides a framework for applying Quality-by-Design (QbD) principles to excipient quality and performance.[7] It also discusses the upcoming revision proposals to General Chapter <1059> and to the *USP* and *NF* Excipients, listed by category reference table, both targeted to appear in *Pharmacopeial Forum* (*PF*) 38(5) [Sept.-Oct. 2012] for public comment, which will include additional dosage forms, *NF* functional categories, and updates of several existing excipient *NF* functional categories.[8]

INTRODUCTION

Pharmaceutical excipients are defined in USP General Chapter <1078> *Good Manufacturing Practices for Bulk Pharmaceutical Excipients* via the following:

"Pharmaceutical excipients are substances other than the active pharmaceutical ingredient (API) that have been appropriately evaluated for safety and are intentionally included in a drug delivery system. For example, excipients can:

- aid in the processing of the drug delivery system during its manufacture;
- protect, support, or enhance stability, bioavailability, or patient acceptability;
- assist in product identification; and
- enhance other attributes of the overall safety, effectiveness, or delivery of the drug during storage or use."[9]

Unlike APIs, excipients usually are not manufactured specifically for use in drug products, but may be used in multiple industries, such as food, cosmetics, or personal care. Given the increasing globalization of the pharmaceutical industry, frequent challenges arise with sourcing of excipients from multiple suppliers. This can lead to batch-to-batch, lot-to-lot, or supplier-to-supplier variability that sometimes creates issues with performance inequivalence.[10,11] Manufacturing a quality pharmaceutical product requires well-defined excipients and processes that yield consistent results. In addition, an excipient may have several intended uses depending on the formulation, manufacturing process, and dosage form, and consequently, there are

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many excipient applications. As a result, selecting performance tests requires understanding the excipient's role and the CMAs relevant to a dosage form. Thus, requirements for one excipient and formulation may not be suitable for the same excipient in another formulation.

USP-NF excipient monographs establish a minimum set of specifications (tests, analytical procedures, and acceptance criteria) for identity, quality, and purity with very few requirements for CMAs that relate specifically to excipient function or performance (Table 1). Excipients manufactured to comply with compendial standards may, therefore, not have all the CMAs identified using compendia monograph test methods and specifications. USP General Notices 4.10 states:

"[Monograph requirements include a specification that] consists of tests, procedures, and acceptance criteria that help ensure the identity, strength, quality, and purity of the article [for general requirements, see section 5, Monograph Components]. Because monographs may not provide standards for all relevant characteristics, some official substances [eg, excipients] may conform to the *USP* or *NF* standard but differ with regard to non-standardized properties that are relevant to their use in specific preparations. To assure interchangeability in such instances, users may wish to ascertain functional equivalence or determine such characteristics before use."

However, performance and functional characteristics of an excipient are important aspects of its quality, as the development, manufacture, and performance of pharmaceutical dosage forms depend heavily upon excipient physical and chemical properties. Thus, the selection of tests and specifications necessary to ensure reliable excipient performance requires a complete understanding of the physical and chemical properties of each excipient in the final drug product. As a result, excipient suppliers and pharmaceutical users should identify and control excipient CMAs for the intended drug application use that goes beyond monograph specifications.[12] Drug product manufacturers should also anticipate lot-to-lot and supplier-to-supplier variability in excipient properties and have controls in place to ensure consistent excipient performance.

TABLE 1

USP Some Important Physical /Chemical Properties Affecting Excipient Function/Performance

• Particle Shape	• True Density	• Molecular Weight
• Particle Size	• Bulk Density	• Mol. Weight Distribution
• Size Distribution	• Tapped Density	• Degree of Substitution
• Surface Area	• Moisture Content	• Viscosity
• Thermal Properties	• Porosity	• Swelling
• Polymorphic Form	• Flow	
• Crystallinity	• Compactibility	
• Amorphous Content		

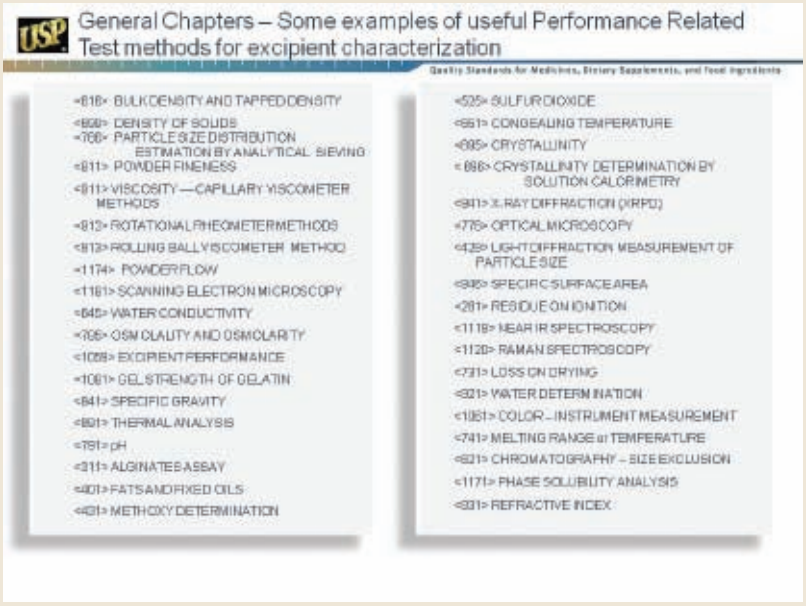
HOW DOES USP ADDRESS PERFORMANCE TESTING IN EXCIPIENT MONOGRAPHS?

Throughout the past 20 years, USP has developed different approaches for introducing references to performance-related testing into the monograph without making such testing mandatory. USP's first approach employs the monograph's labeling section, which specifically addresses grade differentiation. Excipients developed and manufactured specifically for pharmaceutical use sometimes have several grades available, examples of which are Microcrystalline cellulose (MCC) and Magnesium stearate. Excipient suppliers have identified physical and chemical properties as important and perhaps as CMAs by reporting this information on their Certificate of Analysis (CoA). For example, tests for particle size and distribution, moisture content, specific surface area (for lubricants), density (true, bulk, tapped), degree of substitution, viscosity, and molecular weight may appear on the CoA (Table 1). Magnesium stearate's labeling section serves as a basis for alerting the user to the fact that "where Particle Size Distribution (PSD) is stated in the labeling," the test should be performed. It also notes that if PSD is not a CMA for the excipient, the PSD test can be omitted. This approach integrates test procedures into excipient monographs where appropriate and without specifications. Several *USP-NF* monographs have a labeling section that contains test procedures relating to excipient performance; examples are:

- 12 refer to General Chapter <786> *Particle Size Distribution Estimation by Analytical Sieving*
  - [8 actives, 4 excipients (MCC, Lactose Monohydrate, Soda Lime, Sugar Spheres)],
- 4 refer to General Chapter <846> *Specific Surface Area*
  - [3 actives, 1 excipient (Magnesium Stearate)],
- 1 refers to General Chapter <616> *Bulk Density* (Microcrystalline Cellulose).

These general chapters provide useful performance related test methods for excipient characterization and facilitate the selection of suitable excipients using a QbD approach in formulation development that is aligned with the Food and Drug Administration's Center for Drug Evaluation and Research critical

TABLE 2


General Chapters – Some examples of useful Performance Related Test methods for excipient characterization

<616> BULK DENSITY AND TAPPED DENSITY
<699> DENSITY OF SOLIDS
<786> PARTICLE SIZE DISTRIBUTION ESTIMATION BY ANALYTICAL SIEVING
<811> POWDER FINENESS
<911> VISCOSITY—CAPILLARY VISCOMETER METHODS
<912> ROTATIONAL RHEOMETER METHODS
<913> ROLLING BALL VISCOMETER METHOD
<1174> POWDER FLOW
<1181> SCANNING ELECTRON MICROSCOPY
<645> WATER CONDUCTIVITY
<785> OSMOLALITY AND OSMOLARITY
<1088> EXCIPIENT PERFORMANCE
<1061> GEL STRENGTH OF GELATIN
<841> SPECIFIC GRAVITY
<891> THERMAL ANALYSIS
<791> pH
<311> ALGINATES ASSAY
<401> FATS AND FIXED OILS
<431> METHOXY DETERMINATION

<525> SULFUR DIOXIDE
<651> CONGEALING TEMPERATURE
<695> CRYSTALLINITY
<696> CRYSTALLINITY DETERMINATION BY SOLUTION CALORIMETRY
<941> X-RAY DIFFRACTION (XRPD)
<776> OPTICAL MICROSCOPY
<429> LIGHT DIFFRACTION MEASUREMENT OF PARTICLE SIZE
<846> SPECIFIC SURFACE AREA
<281> RESIDUE ON IGNITION
<1119> NEAR IR SPECTROSCOPY
<1120> RAMAN SPECTROSCOPY
<731> LOSS ON DRYING
<921> WATER DETERMINATION
<1061> COLOR—INSTRUMENT MEASUREMENT
<741> MELTING RANGE or TEMPERATURE
<621> CHROMATOGRAPHY – SIZE EXCLUSION
<1171> PHASE SOLUBILITY ANALYSIS
<831> REFRACTIVE INDEX

path initiative (Table 2). Several of these general chapters have reached sign-off stage 6 in the *Pharmacopeial Discussion Group* (PDG) international harmonization process.[13]

The second approach is to include the information in an above <1000> general chapter. Above 1000 chapters are intended to be informational unless they are specifically called out in a monograph. The joint advisory panel on General Chapter <1059> *Excipient Performance*, under the excipient general chapter and excipient Expert Committees, developed the informational General Chapter <1059> *Excipient Performance*, official in *USP* 33 – *NF* 28, 2nd Supplement, February 2011. Given that the *European Pharmacopoeia (Ph Eur)* operates under a different regulatory framework than that of USP, it follows a different approach to addressing performance-related tests. A *Ph Eur* monograph contains a non-mandatory section called functionality-related characteristics (FRCs) that comprises physical and chemical characteristics critical to the typical uses of an excipient.[14] USP monographs do not have non-mandatory provisions; monographs and general chapters apply, although above-1000 chapters (such as <1059>) are intended to be informational only unless specifically called out for more than informational purposes. While *USP* and *Ph Eur* monographs are structured differently in this manner, neither approach to performance-related tests for excipients is mandatory.

USP AND NF EXCIPIENTS, LISTED BY CATEGORY

A listing of excipients grouped by *NF* functional category summarizing the most typically identified purposes these excipients serve in drug products is included as a reference table under *USP* and *NF* Excipients, Listed by Category, in *NF*, under Contents. The list of excipients included in each *NF* functional category is not comprehensive and is not intended to limit the choice or use of the excipient. In addition to updating the current list of excipients under existing *NF* functional categories, it is proposed to rearrange the reference table to highlight the dosage forms in which these excipients are commonly used. The reference table is an extension of General Chapter <1059> *Excipient Performance* and considered a useful tool to navigate through the list of *NF* functional categories and dosage forms.

EXCIPIENT QUALITY & PERFORMANCE: A LINK TO QUALITY-BY-DESIGN PRINCIPLES

Drug product manufacturing requires ingredients and processes that consistently yield a quality result. General Chapter <1059> provides a framework for applying QbD principles to excipient quality control by drawing a direct link between excipient properties and drug product performance. The general chapter expands the scope of *USP-NF* in an informational sense by considering excipient quality and performance as being made up of three components: monograph specifications, functional category, or role that the excipient performs in a dosage form, and performance-related tests.[15] The ICH Q8 R2 Pharmaceutical Development guidance for industry links CMAs and process parameters to drug product CQAs.[16] Where an excipient plays an essential/functional role in the performance of a drug product (eg, drug release), it is important to evaluate the impact of lot-to-lot and supplier-to-supplier variation in excipient performance on CQAs and finished drug product performance.[17] The effect in some cases may in fact be due to trace levels of impurities in the excipient that impact product performance. For example, if a drug product is prone to oxidation, (eg, elevated peroxide levels) it may significantly impact drug product stability and subsequently its purity/impurity profile.[18] Once the user has a good understanding of the CMAs of the excipient that contribute to its functional performance, a control strategy can be developed to either control the key excipient CMAs and/or modify the formulation and process parameters to accommodate the variation in the excipient and consistently produce the drug product of desired quality.

USP EXCIPIENT PERFORMANCE CHAPTER <1059>

The purpose of General Chapter <1059> is to provide an overview of the key functional categories and related dosage

forms of excipients identified in *USP-NF*. The general chapter describes which properties might be important for a particular excipient in a particular application, standard test methods to assess excipient performance, and test procedures that may not be presented in *USP-NF* monographs. The *NF* functional categories have been organized by their most typical use in common pharmaceutical dosage forms to provide a greater level of specificity for each *NF* functional category. Each *NF* functional category includes a general description; the mechanisms by which the excipients achieve their activity; physical properties common to these excipients; chemical properties; and a list of pharmacopeial general chapters that may be useful in the development of specific tests, procedures, and acceptance criteria, and that help ensure that the CMAs are adequately monitored and controlled. Most important is the non-mandatory nature of General Chapter <1059>, in that it avoids possible confusion with mandatory tests and labeling requirements specific to a *USP-NF* excipient monograph. Chapter <1059> does not impose limits or specifications as the required excipient properties will vary and depend upon the drug product, manufacturing process, quantity, and the excipient's intended function.[19] Thus, General Chapter <1059> serves as a tool box of performance test methods not typically included in compendial monographs that can be used by both pharmaceutical users and excipient suppliers. General Chapter <1059> may help formulators identify and monitor excipient properties that they determine are important to excipient function and performance.

SUMMARY

Pharmaceutical excipients are manufactured and supplied to comply with *USP-NF* compendial standards. However, not all the CMAs of an excipient may be identified or evaluated by tests and procedures listed in *USP-NF* compendial monographs related to its *NF* functional category use. Performance and functional characteristics of an excipient are important aspects of the quality of the excipient. An excipient may have different functional purposes and may require different CMAs depending on its intended use in the final drug product. Understanding excipient CMAs that contribute to consistent performance is critical to the overall quality control strategy to accommodate excipient variability and consistently achieve final drug product CQAs. The ability to assess these performance and functional characteristics can allow the manufacturer to determine the likelihood that an excipient will perform as intended in the drug product. General Chapter <1059> *Excipient Performance* provides an informational tool box of performance tests and procedures not typically included in *USP-NF* compendial monographs that can be used by both excipient suppliers and pharmaceutical manufacturers.

On September 18, 2012, USP will host a workshop in Boston on *Food Ingredient Functionality and Its Correlation with Pharmaceutical Excipient Performance*. Preceding USP's Science & Standards Symposium on Functional Foods and Dietary Supplements, the workshop will address topics, such as raw material variability and its challenges; a comparison and contrast of food ingredient functionality and pharmaceutical excipient performance; excipient variability in a QbD setting; and a round-table discussion on food ingredient functionality and its relevance to pharmaceutical excipient performance. A full workshop agenda and registration information can be found at: http://uspgo.to/excipient-ws. ◆

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BIOGRAPHY

Catherine Sheehan is Director of Excipients in the Science and Standards Division, United States Pharmacopeial Convention (USP). In her current role, she is responsible for development and modernization of excipient monographs and related general chapters and provides support to the Excipient and General Chapters Expert Committees in addition to four expert panels, Povidones, Talc, <1059>Excipient Performance, and <1197> GDP for pharmaceutical excipients. She also provides support to the Pharmacopeial Discussion Group's compendial harmonization of excipient monographs and excipient general chapters. Ms. Sheehan earned her BSc from University College Cork, Ireland. She also earned an MS in Bioscience Regulatory Affairs and an MS in Biotechnology from The Johns Hopkins University, Baltimore, MD.

Trends in Pharmaceutical Primary Packaging for Injectables - Solutions for New Challenges

By: Claudia Petersen

INTRODUCTION

With a share of approximately 27%, injectables were No. 2 in the $860-billion dollar drug delivery market in 2010, preceded only by oral medication. Double-digit growth rates, mainly triggered by biotech-derived products, and the rise of injectable generics show that the importance of this segment is still on the rise. Still, prefillable glass syringes and vials are still the most common primary packaging containers for modern injectables.

However, end user requirements and even marketing related reasons have led to a growing market for innovative devices, such as safety syringes, pen systems, and needle-free or intradermal injectors.

Various glass container systems are traditionally used for the storage of parenterals. All of them are standardized to facilitate processing on automated filling lines (eg, ISO 11040-4 for prefillable syringes).

With the exception of ampoules, all glass containers have pharmaceutical rubber closures. The so-called container closure systems (c/c system) are designed to protect the drug product from quality-diminishing environmental influences (eg, light, moisture, microbial contamination). However, the c/c system is not just a container. Throughout the product shelf-life, it also has to ensure that functionality and drug delivery accuracy always comply with the specifications.

Available container closure systems/devices include vials, reconstitution kits, disposable or prefillable syringes, ampoules and auto-injectors or pen systems. Several factors have to be considered when choosing the right c/c system, such as drug product formulation properties, dosage, type of application, and end-user friendliness. Examples of drug product formulation-related factors observed especially with prefillable syringes are high metal ion sensitivity and viscosity. A high sensitivity to metal ions may necessitate the use of new alternative primary packaging materials. In the case of high-viscosity drug products, syringe features such as needle inner diameter, have to be considered.

Furthermore, the dosage regime can influence device decisions, driven by the type of application, frequency and volume, and fixed or variable dose. In connection with end-user friendliness factors, such as the place of application (clinic, home, or emergency setting), the length of therapy, the target patient group and the dexterity of the operator have to be considered. It may be necessary to develop different packaging solutions for one product to satisfy different patient group needs.

FIGURE 1

A selection of the most common glass containers for parenterals.

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TREND 1: OUTSOURCING OF CLOSURE PRODUCTION STEPS

A dominant trend in primary packaging is the evolution from simple bulk packaging materials toward ready-to-sterilize (RTS) or even ready-to-use (RTU) primary packaging components and systems. Process steps in the pharmaceutical production process, such as washing, siliconization, and sterilization of container system components, are outsourced to suppliers that have to ensure these processes are qualified and validated in accordance with current global regulatory requirements. When pharmaceutical manufacturers opt for ready-to-sterilize products, they have a significantly lower investment in machinery and qualification/validation. Because the requirement of washing and siliconizing equipment is eliminated, and products are supplied with a certified endotoxin, bioburden, and particle load. For rubber components and prefillable syringe systems, this also includes the necessary siliconization process.

RTU quality is the next logical step. Pharmaceutical manufacturers outsourcing RTU components can thereby also eliminate the need to invest in sterilization equipment and the regular revalidation of this process. The sterility and shelf-life of the products are certified by the primary packaging supplier. While prefillable syringe systems are always ETO-sterilized, plunger stoppers undergo mainly gamma irradiation. A validated gamma sterilization process has to provide a minimum sterility assurance of 10. Dose mapping and setting have to conform to ISO 111337-2. In general, a package transport simulation and integrity validation should be performed on the sterilized goods, and an expiration date has to be stated (Figure 2).

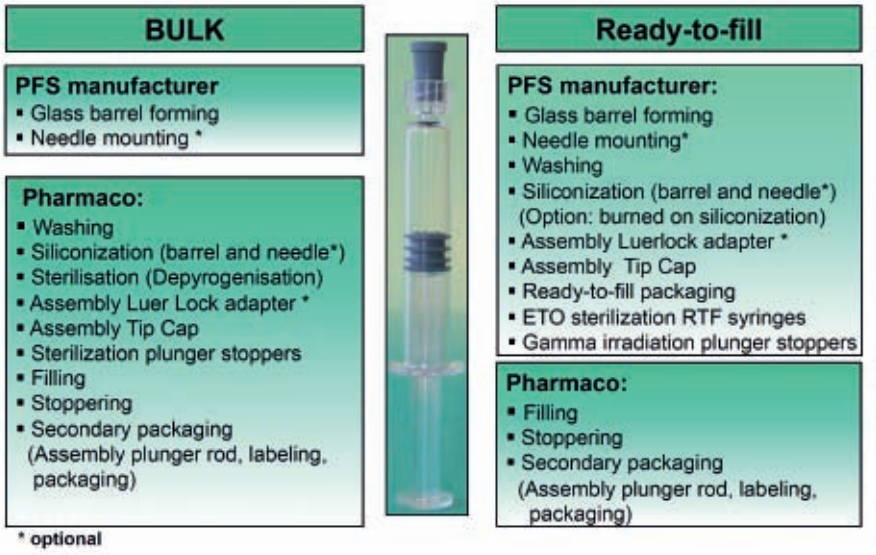
RTF syringe systems, including sterile plunger stoppers, have already been available for many years. In recent years, pharmaceutical rubber suppliers have recognized this trend and now offer a broad range of RTU (either gamma or steam-sterilized) rubber components on their own. Glass suppliers have now begun working on RTU glass vials. Also in recent years, customer interest regarding RTU glass vials did increase. The first glass suppliers did address this developing RTU glass vial offerings.

TREND 2: INCREASINGLY STRINGENT QUALITY REQUIREMENTS

Regulatory authorities all over the world are paying greater attention to the use of appropriate primary packaging materials with the consequence that standards have become very comprehensive and detailed. In 1997, the European pharmacopeia included 19 pages on primary packaging materials. Eight years later, the number of pages had nearly tripled to 53. Within the same time frame, regulatory authorities around the globe issued new guidelines dedicated to primary packaging materials, such as the Container Closure Guideline published by the FDA in 1999 and the EMA Guideline on Plastic Immediate Packaging Materials dated 2005.1,2 Another example is the DIN ISO standard 15378 “Primary packaging materials for medicinal products – Particular requirements for the application of ISO 9001:2000, with reference to Good Manufacturing Practice (GMP)” dated 2006. The primary packaging industry has coped with these increasingly tough regulatory requirements by enlarging quality departments, installing dedicated regulatory affairs functions and intensifying technical support. ISO 15378-compliant production is nowadays standard practice in the European and US primary packaging industry.

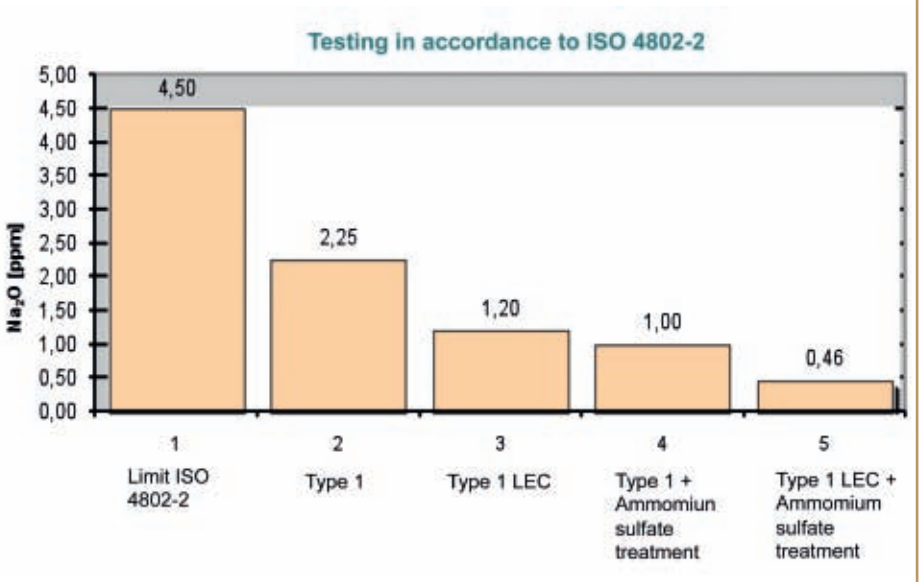
Quality requirements for glass containers, which are likely to be tightened up, include specifications regarding the particle load, lower rates of cracks or cosmetic defects, and smaller dimensional tolerances. Prefillable syringes are associated with specific requirements, such as low hold-up volumes and reduced tungsten or siliconization levels. The tungsten oxide contamination resulting from the forming process of the bore inside the syringe cone can, for example, be avoided using pins made from other metals in the forming process. No official tungsten limit exists as yet. An upper limit of 500 ppb is under discussion. Superior quality requirements on the cosmetic and dimensional side can be met by improved manufacturing processes, the introduction of comprehensive process control with camera

FIGURE 2



Comparison of bulk versus ready-to-fill prefillable syringes.

FIGURE 3



Influence of ammonium sulphate treatment and low extension glass (LEC) on pH-shift.

systems, and packaging inside clean rooms. Automated visual inspections to check for dimensional and cosmetic defects allow constant sorting performance with high reliability and output. Inevitable negative side effects are the cost of the equipment and a proper sorting process qualification to avoid an excessive scrap rate due to false rejects. Rubber component suppliers have developed similar visual inspection procedures.

TREND 3: GROWING SYSTEM COMPLEXITY

Relentless progress in medical technology, the cost pressure of increasingly expensive healthcare systems, and the necessity to operate profitability in a globalized economy all contribute to the complexity of decisions in the primary packaging market. Medical factors that have to be taken into consideration are demands for simpler and safer administration and increased dosage accuracy. Economic factors include the total cost of a system and the retail price of drugs. It is also necessary to consider that developed nations face an aging population that will double the percentage of people aged 60 and older by 2050. Other factors are demands for optimized production processes or enhanced product value, specific regulatory frameworks, or a company's IP position.

Currently, four major drug delivery market trends can be observed, which in some respects are controversial:

- More standardized, simpler, and more robust packaging solutions to address the increasing cost pressure.
- Modern drug delivery systems as a means of differentiation from competitors.
- Modern drug delivery systems as a reflection of modern lifestyle.
- New regulatory and legislative requirements, such as dose counting for metered dry powder inhalers and needle stick legislation to be considered during device development.

In this complex situation, the requirements of the drug product, syringe/container, and device are all interlinked, which necessitates the close collaboration of all project participants. Pharmaceutical and primary packaging/drug delivery device manufacturers should share their expertise to specify system requirements and achieve a common understanding.

TREND 4: NEW MATERIALS

There are a number of reasons why packaging and device suppliers should develop enhanced primary packaging solutions or even use new materials. New, complex devices may require primary packaging that cannot be made from glass due to the limitations of its technical and material properties. As mentioned previously, modern biopharmaceuticals that are mostly based on large proteins are more likely to interact with traditional c/c system components. Also, biopharmaceuticals are often quite expensive, so low overfills and excellent container drainability are essential.

Primary packaging manufacturers are responding to these challenges with new or modified materials. For example, elastomeric components, such as plunger or injection stoppers can be coated with fluoropolymers. The FluroTec® system manufactured by West/Daikyo is partially coated, while Omniflex® by Daetwyler has a completely coated closure surface. Acting as a barrier, the coating improves compatibility with drugs and minimizes extractables/leachables. This eliminates or significantly reduces the need for additional siliconization of plunger stoppers for lubrication purposes while maintaining the functionality of the syringe system.

In cases where the technical limitations of glass prevent its use, modern plastics, such as cyclic olefins, can be a solution. They offer far greater design flexibility, facilitate tighter dimensional tolerances, and are more break-resistant than glass.

Surface treatments, such as ammonium sulfate treatment, can be applied to glass containers to minimize sodium ion leaching and a subsequent pH shift. The use of low alkali glass, called low extension glass, has the same effect (Figure 3).

Another approach is based on thin film technology. Pure silica (SiO_2) coatings are applied to the inner surfaces of glass containers. The silica layer acts as a diffusion barrier, preventing interaction of the glass matrix with the drug without impairing compatibility with standard filling lines and

sterilizing procedures.

In the past, the high cost and complexity of meeting regulatory requirements discouraged manufacturers from considering other materials than the well-established combination of borosilicate glass and pharmaceutical elastomers. Now that new types of drugs with unique properties are entering the market, innovative materials are being scrutinized more closely. The polymers of choice are cyclic olefin polymers/copolymers (COP/COC), which have some properties comparable to those of glass. Both materials are transparent, durable, and solvent-resistant. Cyclic olefins also have some properties, which are superior to glass, such as higher break-resistance, broader pH-range tolerance, and no leakage of metal ions. One particularly important feature relating to the storage of biotechnological drugs is the excellent drainability of cyclic olefin containers, which limits the need for excess overfill. However, cyclic olefins also have some downsides. Compared to glass, they are more susceptible to scratching and, with few exceptions, compendia standardization does not exist. Another parameter to consider during primary packaging material selection is the gas and water vapor permeability of cyclic olefins. Compared to other plastics, such as polyethylene or polypropylene, they have much lower permeation values, though glass is gas impermeable.

Prefillable plastic syringes, such as ClearJect™ by Taisei Kako Co. Ltd, are manufactured in "lights out" factories. Specifically, the entire production process, providing highest injection molding accuracy, is fully automated and takes place inside clean rooms. Camera inspection systems are used for 100% quality control of dimensions, cosmetic defects, and other product parameters, such as the siliconization. These syringe systems are gamma-sterilized. They offer the advantage over glass prefillable syringe systems that the tip cap and plunger stopper are made of the same modern latex-free, chlorobutyl-based pharmaceutical elastomer.

OUTLOOK

Current trends indicate the future of pharmaceutical primary packaging will be characterized by continuous change. Although traditional disposable syringes with vials or ampoules will remain in use, the trend in biopharmaceuticals toward prefillable syringes, auto-injectors, and pen systems as well as customized delivery systems will continue. Primary packaging containers will be made from either glass or plastic. Alternative coatings to standard siliconization are being developed and will gain in importance.

For the primary packaging industry, this means an expanding market for more convenient and easier-to-use injectable products. This trend is closely related to rising demand for complex services that cover more stages in the supply chain. Primary packaging suppliers will assume an increasing number of production steps relating to closure preparation for the fill & finish process. As a result, they will evolve from component providers to system suppliers and product development project partners. ◆

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BIOGRAPHY

Claudia Petersen completed her education from 1990 to 1996 in Bioprocess Engineering at the Technical University of Berlin. Following 2 years post-graduate work in the field of Oncology Research, she joined in 1998 Life Sciences Meissner & Wurst working finally as a Lead Validation Engineer mainly on projects for biopharma customers. From 2000 to 2007, she held different positions at West Pharmaceutical Services, including European Technical Support and Marketing finally as Senior Manager Biotechnology. Since 2007, she has been working as Director, Business Development for the Tubular Glass Division at Gerresheimer Bünde. Ms. Petersen is a member of several pharmaceutical organizations, including the PDA and APV. She is a frequent speaker at international congresses and seminars related to primary packaging and drug delivery devices for injectable drug products.

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Analytical Tools & Techniques in Hot Melt Extrusion & Case Studies on Formulation Development & Process Scale-Up

By: Tony Listro, MS, MBA; Mike Borek, Michael Crowley, PhD, MBA; and Kathrin Nollenberger, PhD

INTRODUCTION

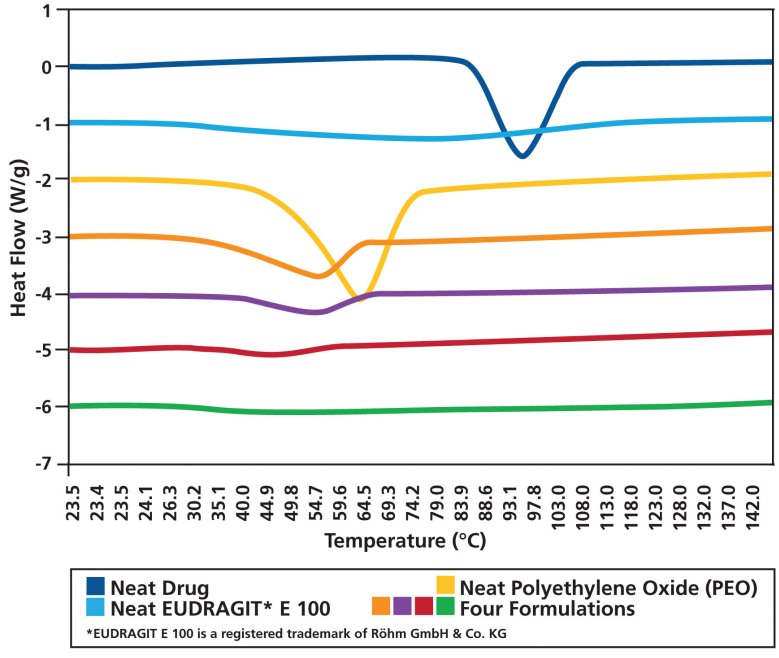
Hot melt extrusion has been widely used as a processing method for many purposes, including formation of a solid molecular dispersion to increase the bioavailability of poorly soluble drugs.[1] Analytical tools and techniques can greatly reduce time and improve success rates in development of hot melt extrusion formulations. In the formulation development stage, analytical characterization of molecular dispersion simplifies the process to compare and contrast different hot melt formulations. In the scale-up phase, analytical characterization techniques ensure similar solubility enhancement occurs on larger extrusion equipment as with the lab-scale equipment used for formulation development.

ANALYTICAL TECHNIQUES FOR HME FORMULATION DEVELOPMENT

With the advent of smaller extrusion equipment, melt extrusion processing of drug substances can now be performed on the gram scale. Solid molecular dispersions of nifedipine, nimodipine, and itraconazole have been successfully produced using melt extrusion technology.[2-4] Analytical characterization of dispersions prepared by melt extrusion is necessary to assess its physical and chemical properties and performance in the final drug product. Interpretation of the analytical data can be challenging. A step-wise approach for characterizing a molecular dispersion simplifies the process to compare and contrast different formulations. Testing a formulation at the next step only occurs if acceptable results are obtained.

Microscopy, thermal analysis, spectroscopy, and non-sink dissolution test methods are frequently used to characterize formulation candidates and provide product performance and stability information.[5] Characterizing the dispersion formulations in three steps can reduce evaluation and development time. The first step is to evaluate the quality of a molecular dispersion prepared by melt extrusion using microscopy (light or scanning electron microscopy) and thermal analysis methods (differential scanning calorimetry). Microscopy is used for a visual assessment of the

FIGURE 1



Differential Scanning Calorimetry (DSC) of the Neat Drug, Neat EUDRAGIT E 100, Neat Polyethylene Oxide and the Four Formulations

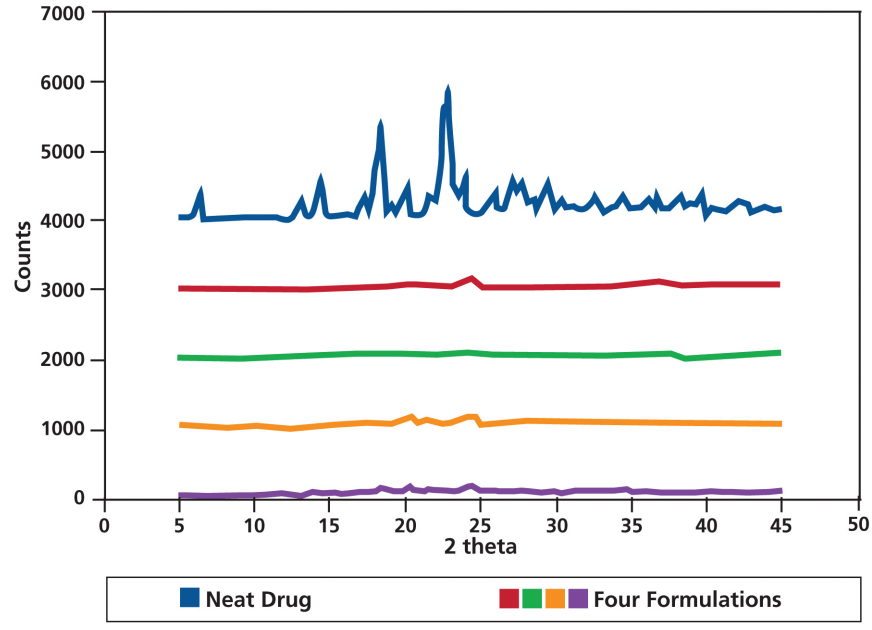
dispersion to detect the presence of drug crystals on or within the dispersion, and is usually the most sensitive method to identify crystals. Crystals can seed formation of other crystals, and ultimately a reduction in product performance. The presence of a small number of crystals may be due to exceeding the carrying capacity of the polymer. A formulation with a lower drug loading may provide an improved molecular dispersion.

Modulated differential scanning calorimetry (mDSC) is used to qualitatively confirm that the dispersion has a single glass transition temperature (T_g) and identify a value for the T_g, and the lack of a melting point corresponding to the drug substance. It is important to run a physical blend of the formulation as a control. Often, the drug may dissolve into the polymer as the temperature is increased during the test.

The second step completes the assessment of dispersion quality using methods to determine crystallinity, eg, x-ray powder diffraction (XRPD) and or Raman spectroscopy, and evaluates performance using a non-sink dissolution test. XRPD or Raman can be used to identify the presence of crystals within the sample. Again, it is important to analyze a physical blend of the formulation. Formulations with low drug loadings may be below the sensitivity of the method to detect crystals. Non-sink dissolution testing evaluates each dispersion formulation for enhancement and sustainability of supersaturation over the crystalline drug form, and can be used to rank-order formulations.

The third step encompasses tests to evaluate physical and chemical stability of the dispersion, generally by mDSC and high performance liquid chromatography (related substances). DSC is used to analyze how the T_g changes as a function of humidity. This test is used to rank-order formulations based on the value of the T_g at a constant equilibrated humidity, such that the highest T_g formulations would have the best predicted physical stability for miscible mixtures of drug and polymer. The related substance test by HPLC determines, under the processing conditions used to manufacture the dispersions, no chemical degradation of the drug substance occurred.

FIGURE 2



X-Ray Diffraction (XRD) of the Neat Drug & the Four Formulations

FORMULATION DEVELOPMENT CASE

An example of the third step analytical characterization approach is presented further. Melt extrusion of a poorly water-soluble drug substance was evaluated in two different polymers (EUDRAGIT E 100 and polyethylene oxide) at two different drug loadings. DSC analysis of the neat drug, neat EUDRAGIT E 100, neat polyethylene oxide (PEO), and the four formulations is presented in Figure 1. Melting points associated with the drug substance are absent from the formulations. Melting points corresponding to PEO are present, and depressed, in the two PEO formulations, indicating the drug is plasticizing the polymer. A single glass transition was observed in the two EUDRAGIT E formulations.

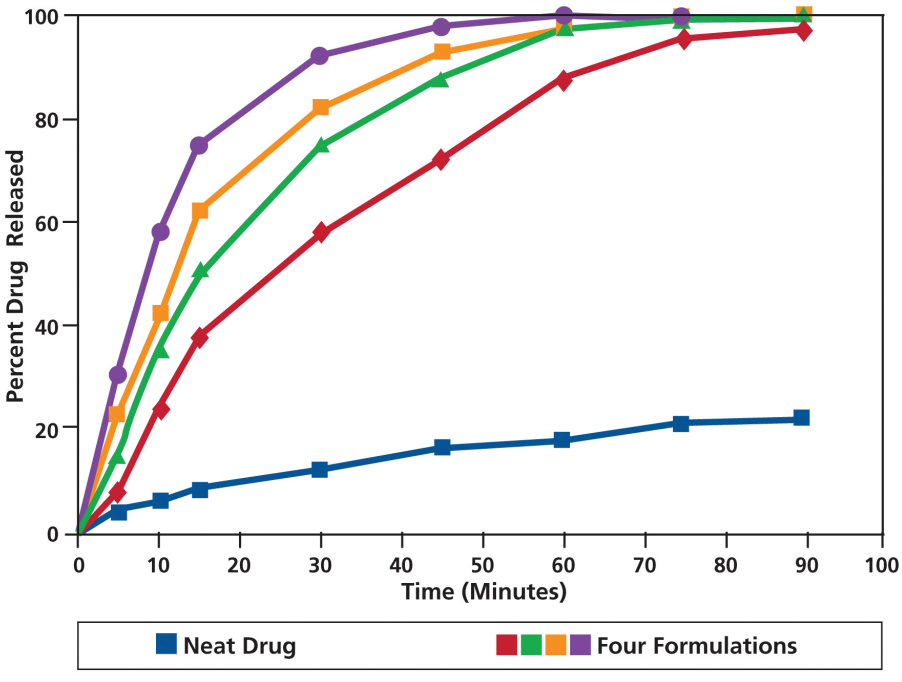
Light and scanning electron microscopy was performed on the neat drug (needle shaped), the polymers and four formulations (data not shown). Crystals were absent in the EUDRAGIT E formulations, but crystals were visible in the PEO formulations. The crystals in the PEO formulations were consistent (size and shape) with the polymer, reinforcing the presence of the PEO melting transition observed in the DSC results.

All four formulations were advanced to Step 2 testing. X-ray powder diffraction of the neat drug and the four formulations are presented in Figure 2. Physical blends of each formulation (data not shown) indicated the presence of crystalline peaks associated with the drug substance, and peaks associated with PEO in those respective formulations. Crystalline peaks associated with the drug substance are absent in the melt extruded formulations.

Non-sink dissolution testing of the neat drug and the four formulations is presented in Figure 3. All four formulations achieved a supersaturation of the drug substance within the 90-minute time frame of the test. Samples were also taken at 4-, 8-, 24-, and 36-hour time points to assess the sustainability of supersaturation (data not shown). Three formulations maintained supersaturation at the 8-hour time point. All four formulations were unable to sustain supersaturation at the 24-hour time point.

Three formulations were advanced to Step 3 testing. HPLC analysis of the molecular dispersion prepared by melt extrusion demonstrated the maintenance of chemical stability. Degradants were not

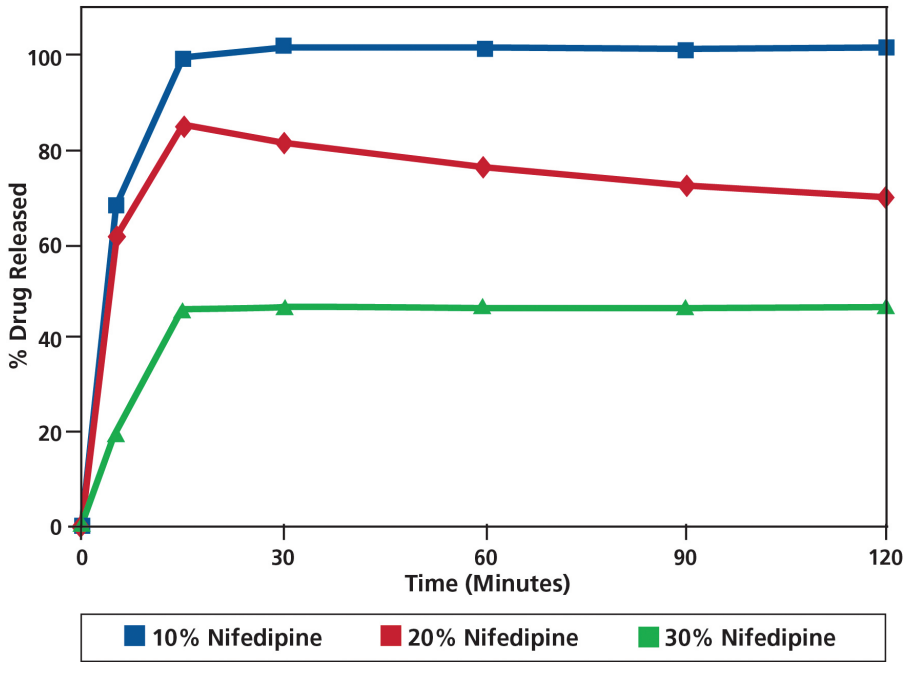
FIGURE 3



Non-Sink Dissolution Profile of the Neat Drug & the Four Formulations

observed in the three formulations. The formulations were also placed into a stability chamber at 40°C and 75% for 4 weeks in open containers. The samples were analyzed by DSC at 1-, 2-, and 3-week time points (data not shown). The EUDRAGIT E formulations maintained the glass transition temperature observed initially, indicating a stable formulation. The PEO formulation adsorbed a significant amount of water and softened, but the presence of a thermal event associated with the drug substance was not observed. A thermal event associated with the boiling point of water was observed.

FIGURE 4



Dissolution Results of Different Drug Loadings on an 18-mm Extruder

CONCLUSION

Melt extrusion processing is a technique widely used to form solid molecular dispersions of a drug in a polymer to enhance bioavailability. Extrusion experiments and analytical tests may be performed on a small scale to conserve costly active pharmaceutical ingredients (API). A step-wise approach to characterizing formulation prototypes using microscopy, thermal analysis, spectroscopy, non-sink dissolution testing, and chromatography can be used to rapidly rank order formulations.

ANALYTICAL TECHNIQUES FOR HME PROCESS SCALE-UP

Formulation development using hot melt extrusion is generally performed using small, laboratory equipment. Scale-up of these developed formulations by achieving similar properties of the dosage forms is always a challenge in pharmaceutical industry. There is limited information available in the literature for scale up of solubility-enhanced formulations prepared by melt extrusion processing. Analytical characterization and techniques are critical in the scale up of these melt extruded solid dispersions in order to ensure similar products are produced, specifically in obtaining similar solubility enhancing effect.

When attempting to achieve similar solubility for a formulation on a large extruder to that of the lab scale, the first step is to match process energies between the extruders, both mechanical and thermal. Mechanical energy influences the degree of mixing achieved in the process, and thermal energy determines the amount of heat the formulation experiences in the process. Matching energy input of the extruders ensures good mixing without degrading the formulation.

Computer-aided process simulation is used to match energies between the small and large extruder. This requires thermodynamic and rheological characterization of the formulation. The simulation provides an initial

screw design and process conditions for the larger extruder that provides similar mechanical and thermal energies to the small extruder.

Once initial a screw design and process conditions are established for the large extruder, extrusion trials provide samples that can be analytically characterized and compared to the original samples. Iterative trials to fine tune process conditions may be required to achieve optimal results.

PROCESS SCALE-UP CASE

A stable, solid dispersion of EUDRAGIT E/nifedipine and EUDRAGIT NE 30 D formulation was required to be scaled up from an 18-mm twin screw extruder to a 27-mm twin screw extruder. Consistent physical and chemical properties of the scaled up solid dispersion were required.

Different drug loadings (10%, 20%, and 30% nifedipine) were extruded with EUDRAGIT E PO/NE 30 D (90%:10% dry polymer). EUDRAGIT E PO and EUDRAGIT NE 30 D were extruded in a first step to prepare a pre-blend and cut into granules. Nifedipine and the granular polymer blend were fed with separate doses into either an 18-mm or 27-mm co-rotating twin-screw extruder (Leistritz, Nuremberg, Germany).

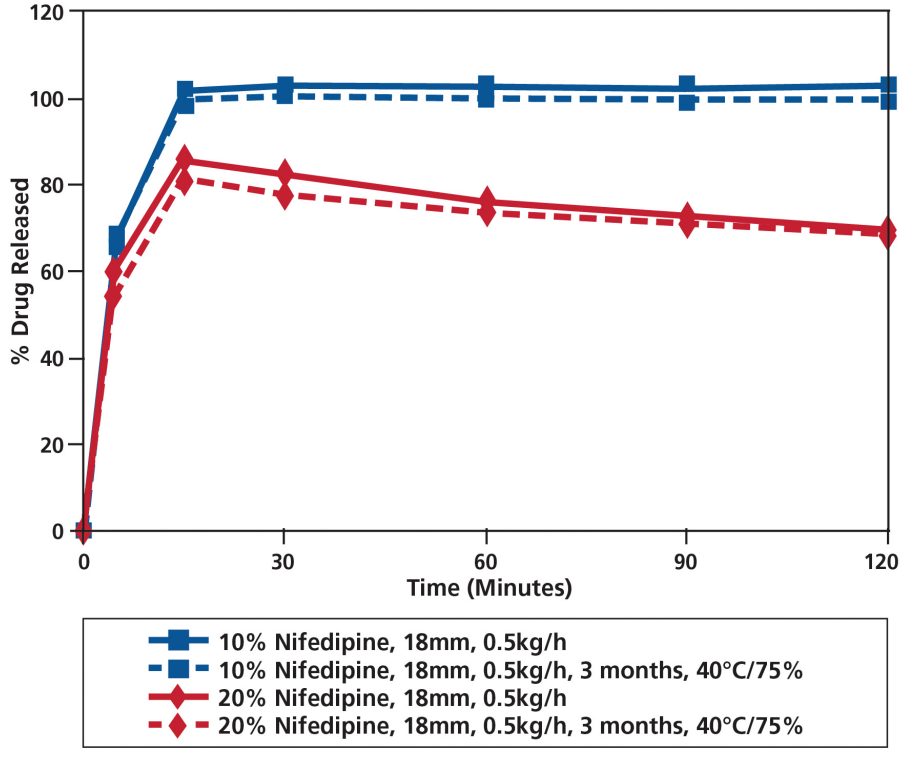
Scale-up parameters were calculated with software to determine all important parameters. Scale-up parameters on the 27-mm extruder were based on the process parameters from the 18-mm extruder. Screw configuration in both extruders consisted of conveying and mixing elements. The screw speed of the 18 mm was set to 140 rpm. Based on the mass throughput, the output of the 27-mm extruder was calculated to be 100 rpm. Screw configuration on both extruders were similar. The melt was cooled as a strand on a conveying belt and subsequently cut into cylindrical granules. The granules were milled prior to analysis.

Visually, the extrudates were completely transparent, indicating a transformation of crystalline nifedipine into an amorphous state. XRPD analyses for extrudates were performed on an X´Pert Pro (PANalytical) using an X´Celerator as detector. The instrument is equipped with a Cu tube as X-ray source. Each diffractogram was recorded between 4°C and 74°C (2θ). Crystallinity was not observed.

Dissolution testing was performed under non-sink conditions using a USP apparatus II in 900-ml 0.1N HCl pH 1.2, 100 rpm. Samples equivalent to 45-mg nifedipine were analyzed.

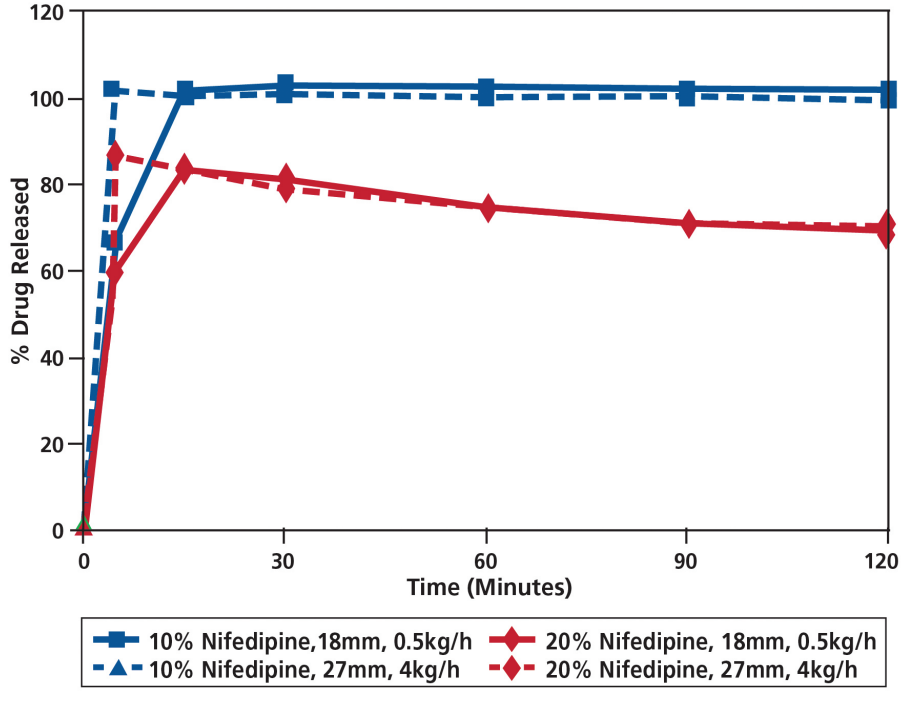
The extrudates were stored in HDPE

FIGURE 5



Storage Stability of Extrudates with 10% & 20% Nifedipine

FIGURE 6



Comparison of Extrudates with 10% & 20% Nifedipine Prepared on 18-mm & 27-mm Extruders

bottles at 40°C/75% relative humidity. Formulations prepared with 10% and 20% drug loading were stable over 3 months. The formulation containing 30% drug loading demonstrated a decrease in dissolution rate of 20% to 25%.

Initially, a faster release rate of the extrudates prepared with the 27-mm extruder was observed. The faster release rate was due to the differences in granule particle size. The granules from the 27-mm extruder were smaller than the granules prepared with the 18 mm. The formulation with 20% drug loading demonstrated a slight re-crystallization after dissolution testing. This observation can be attributed to small crystals present in the extrudate that could not be detected by XRPD, seeding re-crystallization.

CONCLUSION

XRPD and dissolutions studies were used to confirm formulations with EUDRAGIT E/NE 30 D containing different loadings of nifedipine demonstrated an increase in solubility and a stabilized dissolution profile. 10% and 20% drug loading were stable up to 3 months at accelerated conditions. Trials on the 18-mm and 27-mm extruder led to similar dissolution behavior of nifedipine from the extrudates. This study demonstrated that scale up of a solubility-enhanced formulation containing EUDRAGIT from an 18-mm to a 27-mm extruder could successfully be performed. EUDRAGIT polymers proved to be suitable carriers for storage stable solid dispersions, enhancing the solubility of poorly soluble drugs. ◆

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BIOGRAPHIES

Tony Listro, Managing Director, Foster Delivery Science, is an expert in the areas of polymer formulations and polymer processing, such as injection molding, extrusion, and coating. In addition, he has substantial experience in formulating polymers with various functional additives/ingredients and polymer compounding, including twin screw extrusion. He has worked on such applications as oral dosage, anti-counterfeiting, controlled release, and other technologies. Mr. Listro earned his BS and MS in Plastics Engineering from the University of Lowell, and his MBA from the University of Massachusetts at Amherst.

Mike Borek is the Project Engineer for Foster Delivery Science. He has extensive experience in the area of biocompatible materials, including over 9 years developing implantable devices and drug device/combinations. Mr. Borek has also been Lead Engineer in developing Delivery Sciences' Analytical Laboratory. He earned his BS in Chemical Engineering from Worcester Polytechnic Institute.

Dr. Michael M. Crowley is the President of Theridian Technologies, LLC. He has worked in the field of drug delivery and pharmaceutical research for more than 19 years and has previously been employed in senior management roles with PharmaForm, Monsanto Company, Warner-Jenkinson Company, and Mission Pharmacal. Dr. Crowley earned his BS in Chemistry from the University of Missouri at St. Louis, his MA in Organic Chemistry from Washington University, and his PhD in Pharmaceutics from The University of Texas at Austin, where he studied under Professor James McGinity. His research interests include physical pharmacy and pharmaceutical technology focused on novel drug delivery.

Dr. Katherin Nollenberger is currently the Director Technical Services for Europe, Middle East, and Africa at Evonik Industries AG, Pharma Polymers in Darmstadt, Germany. She earned her degree in Pharmacy and her PhD in Pharmaceutical Technology from the University of Frankfurt, Germany. Dr. Nollenberger has 7 years of experience on the research and development of oral solid dosage forms and has published several research papers and patents and attended scientific seminars as guest speaker.

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Hyaluronic Acid: An Ideal Ingredient for Slow-Release Formulations for Osteoarthritis Treatment

By: Morten J. Maltesen, PhD; and Ole M. Dall, MSc

INTRODUCTION

Osteoarthritis (OA) is the most common degenerative joint disorder, affecting more than 60% of the world's population over the age of 65.[1] Characterized by symptoms such as subchondral bone sclerosis, progressive articular cartilage loss, and synovial fluid viscosity decrease, OA causes bone surfaces to come into contact under ordinary load and can lead to severe pain and disability. The total economic burden of arthritis has been estimated to be 2.5% of the gross national product of western nations, and OA accounts for a large portion. In the United States alone, the costs have been estimated to be more than $60 billion per year.[2]

Although current medical therapies reduce the symptoms of OA, no disease-modifying drugs are approved for its treatment. For moderate-to-advanced OA, two types of local intra-articular (IA) treatments are available. The first approach is treatment with intra-articular injected anti-inflammatory drugs, which have been shown to relieve pain and other symptoms of cartilage degradation. Injections of steroids into joints and into the synovial sac have a local anti-inflammatory effect, and systemic side effects can often be avoided. A second strategy has been to inject hyaluronic acid (HA) preparations to restore the viscoelastic properties of the synovial fluid and increase the lubricant properties of the joint. By doing this, symptomatic pain can be reduced and joint functionality significantly improved. In addition, exogenously administered HA can reduce the production of pro-inflammatory cytokines, yielding a longer effect than the actual residence time in the joint.[1]

In addition to its physiological and biological effects in the joints, HA exhibits significant structural and rheological properties that make it an attractive carrier for drug delivery applications. HA can act as a depot matrix, where it slowly releases the active substance locally and, as a result, prolongs the therapeutic period of the active pharmaceutical ingredient (API) in the formulation. By adding HA into a formulation with steroid drugs, therapeutic effects can be achieved, potentially leading to more effective treatment of symptoms.

CURRENT CHALLENGES OF THE USE OF HA FOR OSTEOARTHRITIS APPLICATIONS

Commercially available HAs traditionally used in OA applications are produced from rooster comb extraction or various attenuated strains of *Streptococcus* bacteria, which have the potential to pose contamination risks from animal proteins, endotoxins, or viruses. Due to their secretion of toxins and resulting haemolytic properties, Streptococci are inherently pathogenic to human beings. This is a particular concern for regulatory bodies, such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). In addition, both extracted

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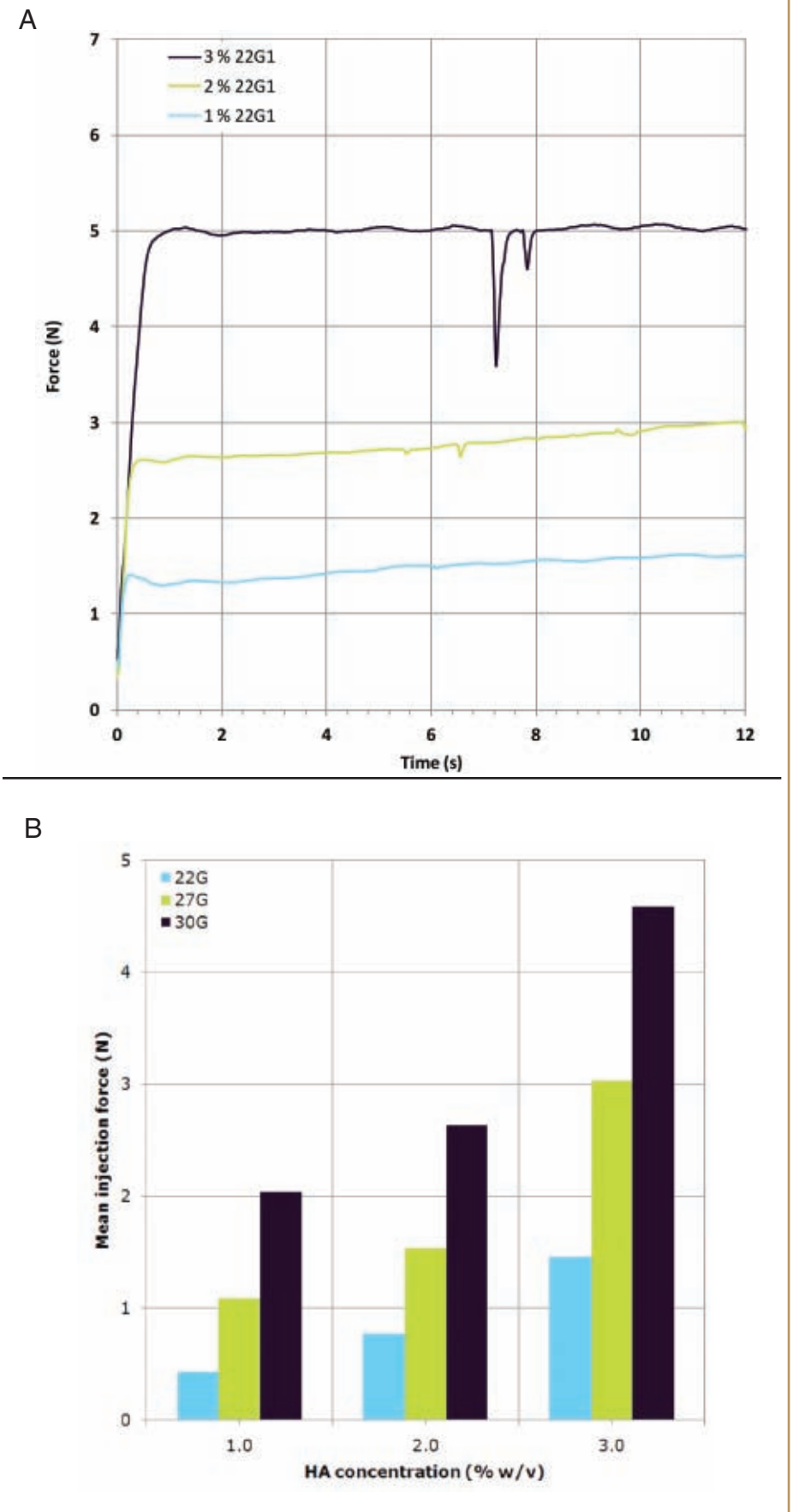
HA and Streptococcus-based HA are purified using harsh organic solvents which pose further health issues to patients.

Until recently, the source of a specific HA product has not been considered to be a clinically important point of differentiation amongst competitive products available to the market. However, with its increased use in medicinal treatments and the regulatory spotlight on potential contamination risks, demand is growing for a safer alternative to current commercial sources of HA.

THE INTRODUCTION OF BACILLUS-DERIVED HA

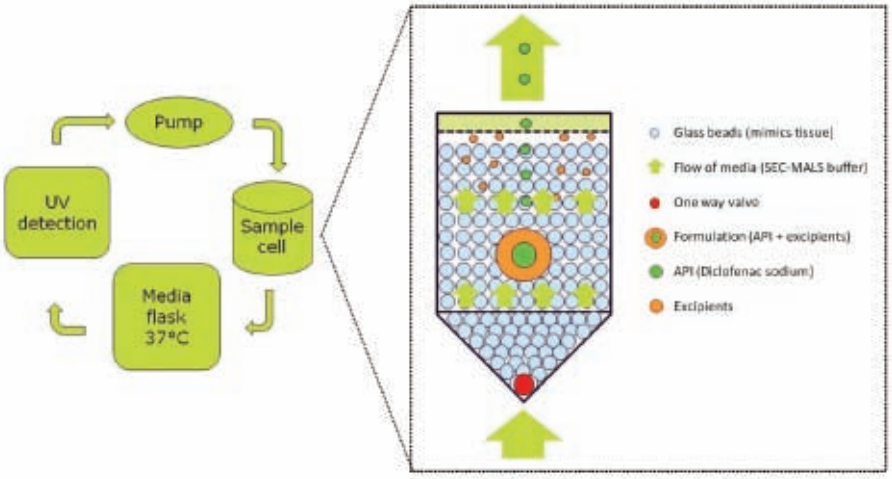
In response to growing concerns across the industry toward the use of animal-derived ingredients, Novozymes Biopharma has introduced Hyasis®, the next generation of high-quality hyaluronic acid, which has been developed using a *Bacillus subtilis* fermentation process to improve safety and minimize risks to patients. As a non-pathogenic host, *Bacillus subtilis*' products are Generally Recognized as Safe (GRAS) by the FDA. The process uses minimal medium, no animal-derived raw materials, and a water-based technique, which removes the use of organic solvents at any stage during the manufacturing process. Hyasis is characterized by low amounts of nucleic acids, proteins, bacterial endotoxins, exotoxins, and microbial contamination, which reduces hypersensitivity reactions when the material is injected. It also confers a number of disease-modifying properties, including analgesic, anti-inflammatory, and chondroprotective properties. The development of the Bacillus-derived production process means that Hyasis has a reproducible molecular weight and narrow

FIGURE 1A&B



Effect of HA concentration on (A) injection force over the entire injection period at 4 mL/min. and (B) mean injection force of HA solutions at both 4 and 6 mL/min.

FIGURE 2



Schematic diagram of the release method using an USP apparatus 4 in a closed loop configuration with online UV absorbance detection.

size distribution. In addition, this HA offers improved processability due to the porosity and reduced size of its spray-dried particles and can dissolve much faster than HAs of streptococcal origin. This reduces filtration time at large scale and as a result, reduces manufacturing costs. A high degree of purity of the material also permits sterilization by autoclaving without significant loss of product viscosity. A recent study was conducted to evaluate the effectiveness of HA in combination with three model APIs resembling combination products for OA treatment.

EVALUATING THE EFFECTIVENESS OF HA IN COMBINATION WITH APIs

To demonstrate the efficacy of Novozymes' Hyasis in the formulation of OA therapies, 1%, 2%, and 3% HA solutions were prepared using a molecular weight of 0.85 MDa. Three model APIs were used in the release studies: diclofenac, dexamethasone phosphate, and triamcinolone hexacetonide. The diclofenac used was the commercial injectable Voltaren® (Novartis International AG) with a diclofenac concentration of 25 mg/mL, while both the dexmethasone phosphate and triamcinolone hexacetonide were pure API. Dexamethasone phosphate was dissolved in phosphate buffered saline (PBS) pH 7.4 yielding a 4-mg/mL solution. A 10-mg/mL triamcinolone hexacetonide suspension was made with 10% propylene glycol, 10% ethanol, and 0.1% sodium lauryl sulphate (SLS) in PBS buffer pH 7.4. All three APIs were in addition prepared with 1%, 2%, and 3% HA in the formulation.

The injection forces needed to inject the HA solutions were evaluated with a texture analyzer. Syringes containing HA samples were placed in the texture analyzer and exposed to constant injection speeds of 4 and 6 mL/min. This is equivalent to an injection of 1 mL over a period of 10 to 15 seconds. The average force needed to inject the material at 4 and 6 mL/min was measured, and 22G 1" needle sizes were tested.

The release of API from the HA formulations was assessed by dissolution method using a closed loop system configuration and a USP apparatus 4 equipped with 22.6-mm cells at 37°C. Glass beads were added to fill the sample cells, and 1 mL of each formulation was added with a syringe. PBS buffer pH 7.0 was used as the medium for diclofenac and dexamethasone phosphate, while 1% SLS and 1% ethanol was added to the medium for triamcinolone hexacetonide, all equilibrated at 37°C. The flow rate was set to 4 mL/min, and a high stirring speed was used. The released API was measured online with UV absorbance. Three replicates were performed for each formulation, and a drug release above 95% was considered complete.

RESULTS & DISCUSSION

One of the most striking properties of HA solutions is its rheological properties and when used for treating OA, the viscous and elastic behavior of HA-based formulations is crucial.[3] Novozymes has developed an HA product in which the viscoelastic properties can be altered and adjusted by changing the HA concentration, which makes it suitable for treating OA. The viscous properties of HA solutions may pose a problem for the force needed to inject the solution. In addition, flow curves show that HA solutions behave as non-Newtonian fluids with shear thinning properties. To further investigate the shear thinning effect on the ease of injection through a syringe, the force needed to inject HA solutions of different HA concentrations was measured in a texture analyzer. When Novozymes' Hyasis was injected the injection force was constant over the entire injection period indicating a homogenous HA

solution (Figure 1A). Two different injection speeds (up to 6 mL/min) were tested; all of them showing average injection forces below 6 N even at 3% HA concentrations and 6 mL/min (Figure 1B).

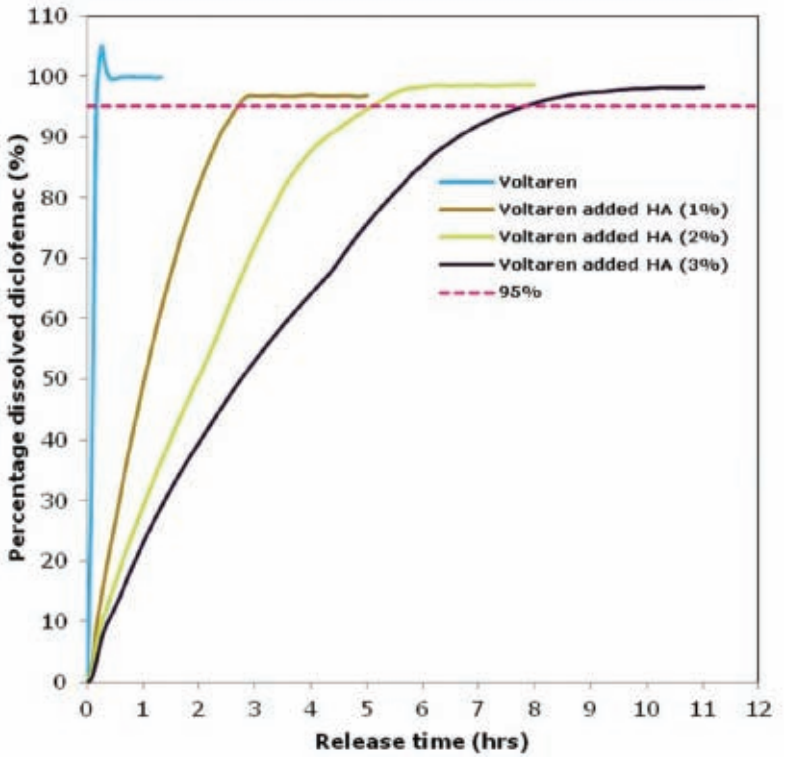
Dissolution testing is a critical parameter in the development of new formulations. It was initially developed for solid oral dosage forms but has in recent years expanded to other formulations, such as novel parental formulations designed as controlled-release formulations in which in vitro drug release is pivotal.[4] Among the different in vitro methods available for dissolution testing, the flow through system (USP apparatus 4) offers the best characteristics for parenteral formulations and is considered a state-of-the-art method for drug release from injectable controlled- release formulations (Figure 2).[5]

Diclofenac (Figure 3A) is a non-steroidal anti-inflammatory drug (NSAID) given orally, intravenously, or ocularly to reduce inflammation and pain in conditions such as arthritis and acute injury. Here, the sodium salt of diclofenac was used. The cumulative in vitro release profiles of diclofenac determined using the USP apparatus 4 method are given in Figure 3B. For the commercial injectable diclofenac formulation, a complete release was obtained after 10 minutes reflecting a reasonable water solubility and fast distribution in the dissolution system. This is the typical profile of fast-release formulations that are mostly used when administrating small molecular drugs such as diclofenac in simple formulations. By adding HA to the formulation, the release time was extended to 3, 6, and 9 hours in an HA concentration-dependent manner. This is attributed to the increased viscosity

FIGURE 3A&B

A

B



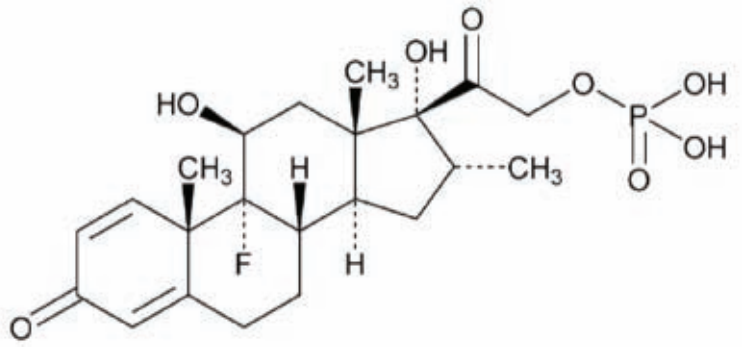
Structure of diclofenac (A) and effect of HA concentration on in vitro release of diclofenac using USP 4 (B).

of the formulations containing HA, resulting in a slower diffusion of the API. No initial burst release of diclofenac was observed for all three HA concentrations. As a result, the diclofenac formulation containing 3% HA showed a steady release profile with a 50 times slower release compared to a formulation without HA.

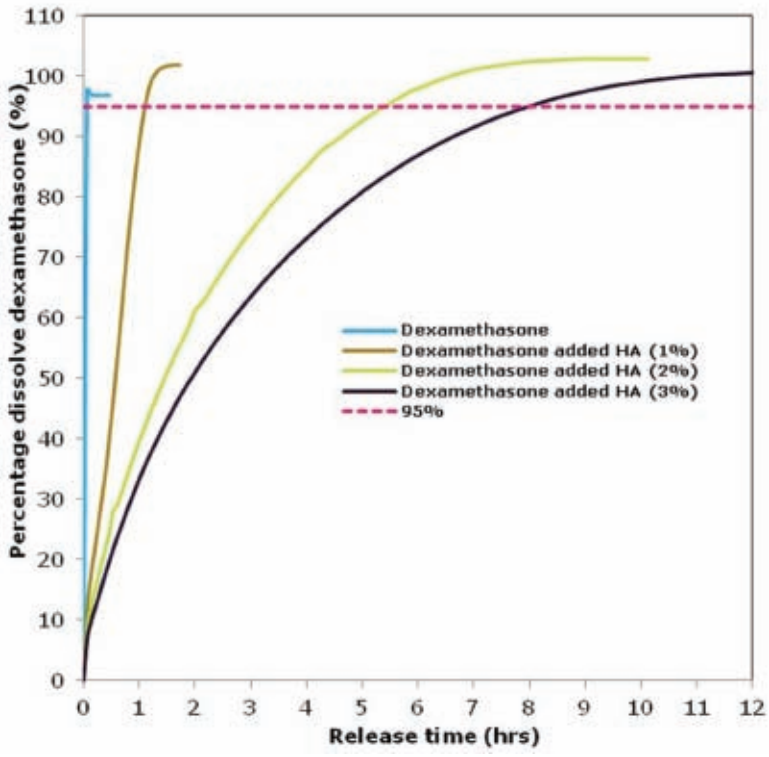
Dexamethasone phosphate (Figure 4A) is a corticosteroid that has an anti-inflammatory effect. The cumulative in vitro release profiles of dexamethasone phosphate determined using the USP apparatus 4 method are given in Figure 4B. Again, the API dissolved in PBS showed a fast distribution in the dissolution system, and a complete release was obtained after 10 minutes. The effect of HA in the formulation was similar to that of diclofenac, in which a complete release of dexamethasone phosphate was obtained after 9 to 10 hours when formulated with 3% HA. No burst release was observed, although the release profile of dexamethasone phosphate showed

FIGURE 4A&B

A



B



Structure of dexamethasone phosphate (A) and effect of HA concentration on in vitro release of dexamethasone phosphate using USP 4 (B).

greater curvature when compared to diclofenac.

Triamcinolone hexacetonide (Figure 5A) is another corticosteroid used to treat arthritis and designed for a slow release due to its low aqueous solubility. This effect was observed when triamcinolone hexacetonide was formulated as a suspension without HA. Here, the in vitro release profile was significantly different from diclofenac and dexamethasone phosphate (Figure 5B). 80% API was released after 2 hours in an initial relatively fast-release period followed by a slower-release phase in which 95% was released after 6 hours and 100% after 12 hours. By adding HA to the formulation, the release rate in the initial phase decreased, while the rate in the second phase remained constant. Subsequently, the initiation of the second phase was shifted from 2 hours without HA to 10 hours with 3% HA in the formulation, and a 95% drug release was not achieved during the 12 hours.

CONCLUSION

As the future of OA treatments lies in the development of more effective therapies, the market will most likely see a rise in advanced and multifunctional solutions utilizing combinations of HA and APIs. Three suitable APIs were formulated with Novozymes' Hyasis as models for future combination products. Formulating all three tested APIs with HA resulted in slower release time in an HA concentration-dependent manner. The effect of HA on diclofenac and dexamethasone phosphate release was similar, leading to 50 times slower release. For triamcinolone hexacetonide, the effect was smaller but resulted in the longest total release time of the three APIs. As a result, combining HA and an API could lead to a more effective OA treatment in which the viscoelastic properties of HA and the anti-inflammatory effect of the API are combined in a controlled-release formulation.

Bacillus-derived HA offers new possibilities to the industry by providing a pure and biocompatible source that confers numerous advantages to both practitioners and patients. The innovative technology offers unmatched ease of administration, effectiveness, and an unequalled safety profile, which make it highly suitable for drug delivery applications. ◆

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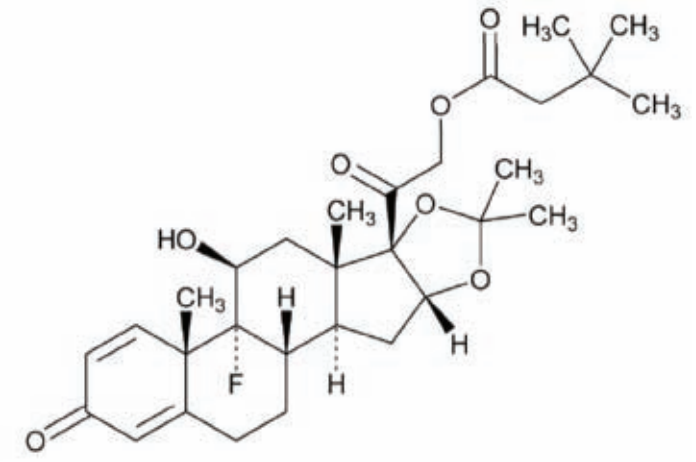
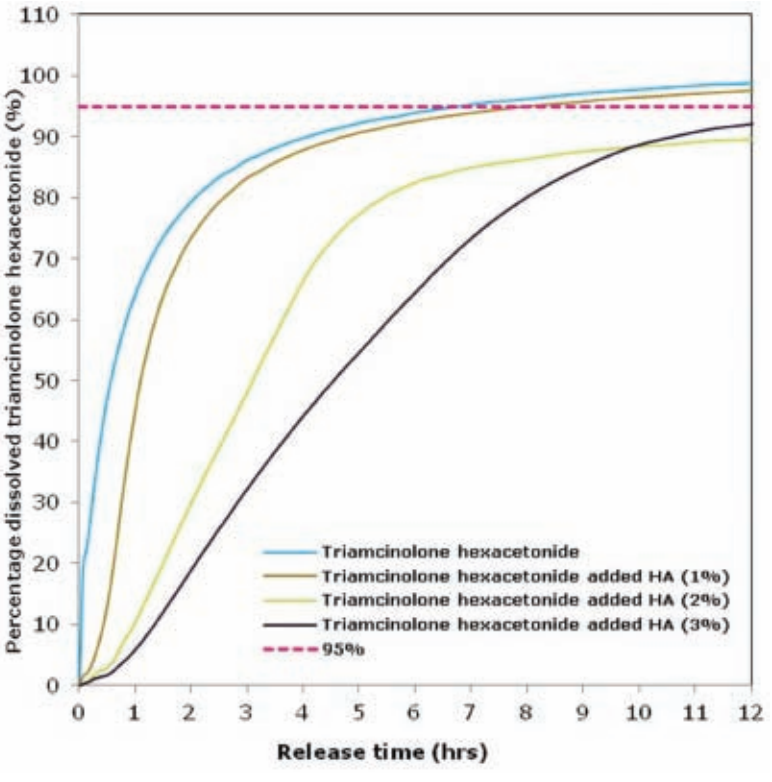
FIGURE 5A&B





Structure of triamcinolone hexacetonide (A) and effect of HA concentration on in vitro release of triamcinolone hexacetonide using USP 4 (B).

BIOGRAPHIES

Morten J. Maltesen joined Novozymes Biopharma in 2010 as a Research Scientist. He earned his MSc in Engineering (specialized in Biotechnology) from the Technical University of Denmark combined with his PhD in Pharmaceutical Sciences from the University of Copenhagen. In his current role as project manager, Dr. Maltesen works on slow-release formulations based on recombinant hyaluronic acid. Before joining Novozymes Biopharma, he worked as a research scientist in early drug development.

Ole M. Dall is a Formulation Scientist and Pharmacist from the University of Copenhagen. He joined Novozymes Biopharma in 2009 as a Customer Technical Solution Scientist. In this role, he works with customers and partners that are using and evaluating Novozymes' hyaluronic acid and technologies within this field. Prior to this position, Mr. Dall worked as a Formulation Pharmacist at a generic drug development company and as a Medical Consultant in the Danish pharmacy association.

SPECIAL FEATURE

Handheld Injection Devices: Safer, Simpler, and More Customized

By: Cindy H. Dubin, Contributor

The biopharmaceutical industry is one of the most research concentrated industries. The expenditure on biopharmaceutical research and development has showcased a dependable growth. Thus, the global biologics market was valued at an estimated $149 billion in 2010 and is expected to reach $239 billion by 2015, a compound annual growth rate (CAGR) of 9.9% from 2010-2015, states ReportLinker. As most biologics are proteins and hydrolyzed in the gut by digestive enzymes, most new biologics are being introduced for IV administration. However, some biologics may later be reformulated into other handheld drug delivery systems, such as prefilled syringes, needle-free injectors, autoinjectors, and traditional needle-and-syringe delivery. The technology and devices for needle-free delivery of drugs/vaccines has been available in the market for several decades. Although their market penetration has been low, the recent years have seen an increase in adoption, driven by the need for pain-free delivery, according to a March 2012 report from ReportLinker.com, *Needle-Free Delivery: Technology and Market 2012-2022*. As a result, the report claims that the global needle-free delivery devices market will be worth $2.1 billion by 2016.

Currently, the market for needle-free delivery devices is dominated by small medical device companies and academic researchers. These small-scale companies are developing innovative needle-free delivery technologies, with the pharmaceutical companies entering into partnership with the device developers to use the technology for delivery of the company's drug, states the Reportlinker.com report.

The global prefilled syringes market has also been witnessing an increase in mergers and acquisitions. The global prefilled syringes market is expected to grow at a CAGR of 9% over the period 2010-2014. One of the key factors contributing to this market growth is the significant growth of pen injectors. However, sales of duplicate prefilled syringes could pose a challenge to the growth of this market, according to Reportstack.com. A report by London-based business information company visiongain predicts that world prefilled syringe technology revenues will reach $3.9 billion in 2015.

Autoinjectors have proven to be one of the most convenient and safe methods for patients to self-administer their injections. This trend has become even more noticeable as the number of combination products coming to market continues to increase and biopharmaceutical companies seek to diversify the range of drug delivery options for their products. To support this growth, auto injectors must continue to evolve in both design and functionality.

FIGURE 7

Rexam's Safe'n'Sound fully passive device offers complete protection of the needle after a smooth injection and also insures that the full dose of the drug contained in the glass syringe has been delivered.

Biologics are also driving the reconstitution market. According to ReportLinker, the inherent instability of biological drugs is a limitation that has a direct impact on the drug delivery sector. Therapeutic proteins must either be stored under special conditions or formulated to retain their efficacy from the time of manufacture until they are dispensed. Liquid protein drugs require refrigeration until dispensed. Alternatively, proteins can be formulated as powders (lyophilization). Lyophilized proteins must be reconstituted prior to injection. Lyophilized drugs are sold with reconstitution vial systems, or packaged in special injection devices (e.g., pens, needle-free injectors, two-part syringes) that allow reconstitution to take place in the device prior to injection. As biological drugs continue to grow in terms of therapeutics and total prescriptions, the impact of specialty devices will increase.

In this exclusive *Drug Development & Delivery* annual report, handheld injection experts provide their thoughts about the various factors backing the adoption of the devices including ease of use, pain-free delivery, and differentiation for product line extensions.

BATTELLE—BETTER DELIVERY OF HIGHLY VISCOUS BIOLOGICS

As a global player in healthcare R&D, Battelle has a history in designing and developing handheld drug delivery devices, particularly injection pens and autoinjectors. Battelle's cross-disciplinary approach uses multiple scientific and engineering capabilities. Through internally-funded research advances and contract R&D services, Battelle has introduced applied innovations and integrated solutions to enhance clients' injection devices and to develop new drug delivery technologies.

With a focus on Rheumatoid Arthritis (RA), Multiple Sclerosis (MS), and diabetes, Battelle is positioned to target chronic conditions that are not well-served by small molecule drugs or require regular dosing that is more conducive to at-home or ex-clinic regimens.

FIGURE 1

Battelle is exploring novel drive mechanisms and form factors to enable self-delivery of highly viscous injectable therapeutics.

Biologics are predicted to generate 60% of biopharma growth this decade, states Michael Triplett, PhD, Director of Strategic Marketing for Health and Life Sciences at Battelle. "These therapeutics treat conditions such as RA and MS, which are not well-served by small-molecule drugs, but introduce a new set of challenges such as stability, viscosity and higher dose volume," he says. "Self-administration is preferred by patients and payers alike, so injection is moving out of the clinic and into the home and other locations. This means that caregivers and patients, some with physical and other limitations, are increasingly responsible for administering their own injections in their own environments, raising the risk of injury, incomplete dosing, etc. As a result, device designs will be required to place greater emphasis on human factors to improve ease of use and usability while reducing risk."

To help improve patient acceptance, adherence, and ease of use in injectable therapies, in February, Battelle announced a partnership with Specialty Pharmaceutical firm Zogenix Inc. to market DosePro, a commercialized prefilled, needle-free, disposable, subcutaneous delivery technology, to the pharmaceutical industry and to further develop the technology for additional applications. This collaboration enables Battelle to expand its platform of drug delivery solutions to pharmaceutical customers and provides direct access of Zogenix's DosePro technology to pharmaceutical firms. "We believe DosePro will help our clients address many current delivery challenges, and we have a particular interest in moving this technology forward to enable delivery of the upcoming wave of high-viscosity therapeutics," says Alexa Konstantinos, MS, Director, Business Development for Biopharmaceuticals, Medical Devices & Diagnostics at Battelle. "We already have *in vitro* data demonstrating DosePro delivery of viscosities far exceeding anything possible by today's autoinjectors."

Battelle and Zogenix have created a center of excellence for DosePro technology development and testing of client formulations within Battelle's laboratories, and the firms are planning to complete the development and commercialization of a larger dose (1.2 mL) version of the DosePro.

In addition, the Battelle User Research Laboratory (uLab) was recently opened, which allows researchers to conduct usability studies, an activity that has become increasingly critical to medical device and pharmaceutical manufacturers trying to launch new products, explains Ms. Konstantinos. The 4,500-sq. ft. lab features 5 rooms configured to test everything from

hardware and software to full-scale interiors for home healthcare settings. The uLab also has an additional 5,000 sq. ft. that can be transformed into any environment necessary.

The new uLab will help Battelle carry out its commitment to finding better ways of administering biologics. "Battelle is applying a systems approach to solving the challenges of self-administering highly viscous biologic therapeutics," says Ms. Konstantinos. "We are funding development of devices that will enable patients with strength and dexterity challenges to self-administer highly viscous therapeutics. We are designing around the unique characteristics of the device users and are taking multiple approaches to reducing the force needed to complete injection of viscous formulations, including novel fluid flow, formulations and form factors."

Battelle's design ideas come from the divergent fields in which it conducts research–for example, alternative energy, advanced chemistry and materials, robotics, analytics, and medical devices. "This breadth allows us to harvest and apply technology adjacencies as we conceive next-generation devices for self-injection," says Ms. Konstantinos. "For example, we recently demonstrated the use of a novel fluid flow technique used in the energy industry to deliver an 85cP solution through a 27ga RW needle with reasonable force. The cross section of our formulation capabilities and device engineering expertise helps us apply innovation to make self-injection of highly viscous formulations feasible for patients with compromised hand strength."

BD MEDICAL–PHARMACEUTICAL SYSTEMS: PATIENT-CENTRIC DESIGN INNOVATION

Demand for patient administered injections is increasing within the hand held injection market. Many factors are contributing to the rise in self-administration, including increasing incidence and prevalence of chronic diseases with aging populations, increasing development of targeted injectable therapies by biotechnology companies to treat such chronic diseases, the improving access to healthcare worldwide, and the emerging shift of care from the acute setting to the home setting. With advances in information technology, patients are increasingly empowered in choice of therapy. As such, drug manufacturers aim to select and develop injectable drug delivery systems to improve patient comfort, convenience and preference, which in turn may improve compliance, control healthcare costs, increase brand loyalty, and ultimately improve health outcomes.

Today, the industry faces increasing regulatory focus on Human Factors and Ergonomics (HFE). For many years, BD has integrated principles of Patient Centric Design into all aspects of delivery system development. According to Raza Ahmed, MD, Global Medical Director for BD, "Our product development teams closely study patient interaction with self-administration systems and incorporate these results into multiple design process iterations, with the goal of reducing patient error and thus improving patient health and outcomes."

At BD, self-administration solutions are designed to address the needs of all stakeholders, including patients, pharmaceutical customers, and healthcare providers. The BD portfolio of self-injection systems include liquid pens, autoinjectors, reconstitution systems, and patch injectors for large-volume or viscous delivery. Delivery systems are customized according to the pharmaceutical company's brand differentiation strategy, clinical and therapeutic area requirements, patient and healthcare provider needs. According to Dr. Ahmed, "We adapt our established base technologies to the needs of our pharmaceutical customers, helping them to get to market as quickly as possible in a preferred self-injection device."

FIGURE 2

This is the BD Physioject™ disposable autoinjector base model; a range of look-and-feel customization options are available.

BD spends a lot of time surveying patients and health care professionals about their acceptance and preference for various delivery systems. The recently launched BD Physioject™ disposable autoinjector is a perfect example. Close to 1,000 patients and health care professionals were surveyed and their responses validated product features and design of the system. "In-depth studies helped to uncover unmet needs, identify potential solutions, and validate that the solution met product requirements," says Dr. Ahmed.

In one study, patients with limited hand dexterity and strength revealed that they experience difficulties with their current autoinjector with respect to the forces required to operate the device. In development of the BD Physioject system, operational forces and patient interaction with devices were optimized by performing usability studies testing acceptance and preference with a range of forces, shapes, and functionalities.

This resulted in an ergonomic design which overcomes patient usability challenges. A key finding eventually incorporated into the BD Physioject autoinjector design was that, among the patients tested, the smallest autoinjector design was not necessarily the preferred one, and that ease of use and reliability were rated by patients to be more important than discretion.

An issue that autoinjector manufacturers can sometimes face is delivery system malfunction. As a provider of prefilled syringes and autoinjectors, BD mitigates this risk by using quality-by-design (QbD) principles–fully integrating the autoinjector system with the primary container and the customer drug product. This approach to integration, with systematic assessment of stacked tolerances, enables a robust autoinjector offering with a very low defect rate, claims Dr. Ahmed.

To further investigate the acceptance of the BD Physioject system with patients, BD also tested the safety, efficacy and performance of the device compared to a syringe injected by a nurse. Clinical trials show that the BD Physioject autoinjector is not only safe, effective, and patient accepted, but is also perceived to be less painful in comparison.

"At every step along the development process, BD emphasizes Patient Centric Design, safety, and intuitiveness, and incorporates design-for-manufacture to facilitate scale-up for successful product launch," says Dr. Ahmed." BD partners with pharmaceutical companies to customize and develop differentiated delivery systems that help maximize the potential of their drugs with healthcare providers and patients."

DUOJECT—SAFE AND SIMPLE CARTRIDGE-BASED DEVICES

The hand held injection market is in constant evolution. What was a novelty a few years ago is now considered standard in the industry and demand for safer, simpler and more cost-effective solutions, most notably for the home care market–one of the fastest growing health sectors–has pushed drug delivery and medical device designers to come up with new innovations to address these needs.

Duoject has been addressing these needs with devices such as Vaccject and E-Z-Link. Vaccject is a cartridge-based delivery device with integrated passive needlestick protection. "It offers a safe and cost-effective alternative to prefilled syringes and provides product differentiation many pharma companies are now looking for in medical devices," explains Dan MacDonald, Vice-President, Engineering Services for Duoject.

While Duoject's focus has been to offer safe, simple, and easy-to-use medical devices, in the past few years, the company has improved on the human factors aspect of its development by introducing focus studies with end users much earlier in the design process. "This has enabled us to obtain a clearer vision of what the end-user's expectations are regarding our product and helped optimize our development time and product quality," says Mr. MacDonald.

A good example of this is when Duoject developed an improved E-Z-Link reconstitution device. He says: "End-user feedback enabled us to improve on the ergonomic aspects of the device and packaging as well as the safety features now incorporated in the device such as our patented safety disc protecting the needle before and after use and single-use locking technology."

Development of the patent-pending Vaccject was completed this past year. It is not yet on the market, but is being evaluated by a number of large pharma companies. "The product answers many market needs, such as simplified production process (the drug container is provided separate from the device), optimized cold chain storage and distribution system, and integrated passive needlestick protection," says Mr. MacDonald. The use of a cartridge rather than a staked-in needle syringe offers the ability to bake on silicone to eliminate sub-visible particles, reduce risk of glass delamination, and absence of Tungsten or needle adhesive to contaminate the drug.

FIGURE 3

Duoject's Vaccject uses a cartridge rather than a syringe and has an integrated auto-retracting needle safety feature.

"Healthcare professionals liked the fact that the needle in the device was never exposed, neither before nor after the injection and they appreciated that the device did not look like a syringe, greatly improving acceptance by end-users," he adds.

Duoject is in the process of filing a 510(k) for the device and is working with leading equipment suppliers to optimize manufacturing process for high-volume production.

Vaccject addressed the growing need for needlestick protection. "We wanted to answer the question: Does the inclusion of a

FIGURE 4

The Flexi-Q DV from Elcam Medical provides safe and simple injection, quiet injection, reduced skin reactions, and ease of drug reconstitution and aspiration.

needlestick prevention device have to increase the cost of a delivered dose of vaccine or parenteral drug? With Vaccject, the answer is no," explains Mr. MacDonald. "By using a cartridge rather than a syringe and by integrating an auto-retracting needle safety feature within an elegant form factor, we are able to offer a low-cost alternative to the current syringe and external safety system combo currently available on the market."

Duoject's primary therapeutic focus area when developing Vaccject was high-volume vaccines, but quickly realized that pharma companies could benefit by using this type of safety delivery technology for other therapeutic drugs. "It became clear that Vaccject is also a perfect solution for home care use as well as pediatric applications where the use of a standard syringe is in some cases a harder sell to the end user or patient," says Mr. MacDonald.

Duoject continues to focus on reconstitution devices and is currently completing development of PenPrep EVO, a cartridge-based reconstitution device for multi-dose applications in lyophilized drug vials, for use with standard pen injection systems. The device is an improvement over Duoject's current PenPrep XR device. PenPrep EVO will be available to the industry in early 2013.

ELCAM MEDICAL—AUTOINJECTOR LINE EASES RECONSTITUTION AND ASPIRATION

The growing use of biotech and biosimilar drugs and the global effort to reduce health care costs has driven companies that are introducing new injectable drugs or biologics to increase patient compliance and enhance sales and market success through improved drug delivery devices. The need also arises for low-cost, safe, patient compliant, and easy-to-use autoinjectors that will improve treatment efficacy.

Elcam Medical is addressing the current and future market needs with its autoinjector product line. These include ready-to-market devices like the Flexi-Q PFS autoinjector for drugs in prefilled syringes, and the Flexi-Q DV autoinjector platform for drugs in vials–either in solution form or in lyophilized form requiring reconstitution. Flexi-Q PFS is expected to reach the market in the next 1 to 2 years and has a market sales potential of more than $10 million per year. The Flexi-Q DV has received 510(k) clearance by FDA.

Both the Flexi-Q PFS and Flexi-Q DV share the same basic platform, which provides safe and simple injection, quiet injection, reduced skin reactions, and ease of drug reconstitution and aspiration. "Because they share the same platform, they provide a life cycle management tool by allowing a pharmaceutical company to launch its drug with the Flexi-QDV autoinjector even with a lyophilized (or solution) drug in a vial, and then, at short time and low investment, switch to the Flexi-Q PFS when the drug is stabilized in a prefilled syringe," explains David Daily, Director for R&D and BD, Injectable Drug Delivery Devices (I3D), Elcam Medical

One challenge Elcam Medical faced was with the Flexi-Q DV autoinjector for drugs in vials. The device allows aspiration and reconstitution of drugs from vials using a vial adaptor prior to performing the automatic injection. "These steps are not always intuitive to non-professional users and thus required iterative work on the instructional materials in usability studies," says Mr. Daily. "In addition, we implemented a plunger-lock proprietary mechanism to prevent drug spillage during use of this device."

Elcam autoinjectors in development pipeline include the Flexi-Q HV disposable autoinjector for low-to-high viscosity drugs. This proprietary platform has a mechanism

FIGURE 5

Plastic ClearJect™ prefillable syringe systems from Gerresheimer deliver drugs for patients suffering from chronic diseases.

preventing any impact on the glass prefilled syringe, enabling use of extremely strong injection springs to deliver high-viscosity drugs while using small-diameter (high gauge) needles at short injection times, explains Mr. Daily.

The second autoinjector is the Flexi-Q MU, a reusable electronic autoinjector for low-to-high viscosity drugs. It is designed to be used with various drug primary containers.

In the last year, Elcam Medical has made progress in a development project with one of the top-10 pharma companies customizing its Flexi-Q PFS autoinjector to the client's specific requirements. Other feasibility projects are on-going with large- and medium-size US-based and EU-based pharma and biotech companies, including the Flexi-Q PFS, Flexi-Q DV, and Flexi-Q MU autoinjectors. Elcam Medical is currently considering licensing and joint venture agreements, partnering with some of the leading medical device players.

GERRESHEIMER—FOCUSED ON CUSTOMIZED INJECTION SYSTEMS

Alongside the standard injection devices such as glass and plastic prefillable syringes, there is an ongoing trend towards customized injection systems and the use of autoinjectors and pen systems. This is partly driven by the fact that an increasing number of drugs to treat chronic diseases are now available to patients on a self-administration basis and these patients need solutions for simple and safe administration, says Claudia Petersen, Director Business Development, Gerresheimer Bünde GmbH.

Gerresheimer's expertise in glass and plastic primary packaging component and system manufacturing addresses that need. Its Medical Plastic Systems Division manufactures products such as pen systems for diabetes drug administration, inhalers, autoinjectors, and other customized injection system solutions. The Tubular Glass division is a leading player in the market for glass (RTF®) and plastic (ClearJect™) prefillable syringe systems. Specific accessories such as tamper-evident luer lock closure (TELC) for glass prefillable syringes satisfy market requirements of increased safety and tamper evidence features.

The glass and plastics maker is seeing growing importance for innovative solutions to improve current standard injection devices and new approaches because of the success of bioengineered drugs. "These biotech drugs often have very large molecules that are associated with specific requirements regarding the chemical and functional properties of the container/closure system," says Ms. Petersen. This market segment includes new drug classes such as DNA vaccines and siRNA-based drugs and it will continue to grow in the future. "Developing appropriate packaging solutions for each of these drug classes is associated with many exciting challenges," she says.

HASELMEIER—SELF-INJECTION DEVICES FOR GROWING INCIDENCE OF SELF ADMINISTRATION

The handheld injection market is being driven by pharmaceutical companies looking to differentiate their product and provide a patient friendly self injection experience. The increasing number of self-administered products being marketed combined with increasing incidence of diseases requiring self-injection, is rapidly expanding the need for self injection devices.

The need for pen injectors is increasing significantly as diabetes continues to be one of the leading diseases requiring self injection. If current trends continue, the CDC estimates that as many as 1 in 3 adults could have diabetes by 2050.

Haselmeier provides pen injection devices for self-administration with experience in designing and manufacturing injection devices to meet patient needs. This year, the company introduced the i-pen2, an all-plastic reusable pen based on its metal i-pen design. "By being all plastic, it provides

FIGURE 6

Haselmeier's i-pen2 is an all-plastic design for reusability and cost effectiveness.

a cost-effective pen platform when cost is an important issue," says Robert J. Kilgore, Vice President Marketing and Business Development at Haselmeier. "It features the same function, durability, and accuracy of our metal i-pen. The i-pen design has been well accepted by pharmaceutical companies around the world for delivery of insulin and other biotech products requiring a high quality reusable pen injector." The i-pen is available as an existing design platform or may be customized to meet individual customer requirements. Axis-D is Haselmeier's disposable pen platform. This is an all plastic, variable dose pen featuring a sliding dose indicator window to make dosing easier for the patient.

"Haselmeier continues its focus on the design and development of pen injectors using a 3mL cartridge as the primary drug container," explains Mr. Kilgore. These include variable and fixed-dose devices in a disposable or reusable format.

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

REXAM—MEETING A NEED FOR SAFER PARENTERAL DEVICES

In the context of increasing homecare treatments, legislations are evolving to provide more safety surrounding parenteral devices. Rexam Healthcare has developed a safety device as an add-on to glass prefilled syringes. Its Safe'n'Sound® is a fully passive device (meaning no additional gesture is necessary for the usual injection procedure from the nurses or patients). Safe'n'Sound offers complete protection of the needle after a smooth injection and also ensures that the full dose of the drug contained in the glass syringe has been delivered. A needle-shielding automatic process ensures a reliable injection while reducing non-injected volume.

Over the last year, two versions of Safe'n'Sound have received a 510(k) approval from the FDA–Safe'n'Sound for 1mL-long stacked needle syringes and Safe'n'Sound for 1mL-Luer syringes.

Rexam is focusing on large-scale industrialization of the Safe'n'Sound in currently developed versions of the system, and on the development of new versions of the safety device in different sizes. New versions will match demands for different volumes.

Safe'n'Sound is compatible with glass syringes on the market (Schott, Gerresheimer, Nuova Ompi, and BD) and can be customized for better patient handling (i.e. extended finger flanges). Safe'n'Sound is currently on the market, with a strong patent protection, positioned to respond to the increasing demand of safety from the authorities. Rexam will present new versions of Safe'n'Sound in 2013.

Ready-to-fill glass syringes are filled, labeled, and packaged on high-speed automated lines and safety devices have to fit onto these lines without disrupting the cadencies. "Safe'n'Sound can be delivered in bulk onto the assembly lines and is extremely robust on high-speed automation machines," says Isabelle Delcroix, Global Category Manager Parenteral for Rexam. "Rexam has worked upstream with assembly machine manufacturers to ensure the optimum design and robustness of the safety device for handling on pharmaceutical sites."

Safe'n'Sound is targeting all medication in prefilled glass syringes and customization has been proposed for specific pathologies such as Rheumatoid Arthritis.

SAFETY SYRINGES INC.—ANTI-NEEDLESTICK DEVICES FOR REDUCED DEXTERITY PATIENTS

The handheld injection market is being driven by the increasing need for convenience, efficiency, and safety in delivery of injectable drugs. Safety Syringes Inc. (SSI) is a leading provider of anti-needlestick safety devices for prefilled glass syringes. Its newest product developments reflect the need for more injection comfort, especially for those end-users that inject at home and have impaired dexterity, explains Sarah Baer, Marketing Product Manager for Safety Syringes Inc. The company is focused on providing innovative anti-needlestick devices that provide simplicity, intuitive ease of use, and streamlined assembly into existing packaging lines.

SSI recently launched the Add-On Finger Flange for its UltraSafe Passive®

FIGURE 8

SSI will be launching UltraSafe PLUS™ Passive Needle Guard for prefilled glass syringes later this year. UltraSafe PLUS is designed to offer improved ergonomics for self injection, support for viscous drug delivery and increased drug visibility.

Needle Guard. The Finger Flange is designed to provide improved injection comfort for self-administrating patients, especially those with reduced dexterity.

Later this year, SSI will be launching the new UltraSafe PLUS™ Passive Needle Guard. "This PLUS device combines advanced performance with built-in injection comfort," says Ms. Baer. "The UltraSafe PLUS supports the self-injecting patient by providing ergonomic support including extended built-in finger flanges, a concave plunger head, robust plunger rod, and a large inspection window to enable inspection of drugs with low fill volumes."

SSI recently completed a Human Factor user study of PLUS during which more than 500 injections were performed by self-injecting patients and nurses with a 100% success rate. Ms. Baer says: "The HF results of the user study not only validated the added design features such as the wider finger flanges but also the preference of the end-users of PLUS injecting drugs of higher viscosity."

SSI UltraSafe Devices are used in a range of therapeutic areas including immunology, oncology, vaccine delivery, anti-thrombotic, contraceptive, anemia, and more. "SSI will continue to develop advanced safety devices to support the growing needs of our customers including innovative solutions for delivery of complex biotechnology drugs and greater support for patients performing self injection," says Ms. Baer.

UNILIFE—CREATING INJECTABLE DELIVERY SYSTEMS FOR PRODUCT DIFFERENTIATION

"I don't believe the device market has evolved with sufficient speed to support the specific packaging and patient requirements of biologics," says Stephen Allan, Vice President, Marketing & Communications, Unilife Corporation. "Because every pharmaceutical customer has their own unique needs, there has to be greater flexibility from device manufacturers. One size no longer fits all when it comes to injectable drug delivery."

Thus, Unilife has made its focus the development or customization of delivery systems that can accommodate particular injectable drug and patient needs. "Our flexibility to tailor each device to specific drug, patient, and pharmaceutical requirements is being favorably received by customers," he says. Driven by the size and scope of these unmet customer needs, Unilife's technology platforms has rapidly expanded to now cover prefilled syringes, autoinjectors, large-dose volume disposable subcutaneous pumps, drug reconstitution systems, and other specialized devices.

This year, the company validated and commenced the commercial supply of the Unifill syringe to several pharmaceutical customers seeking to turn needlestick compliance into a significant competitive advantage. "The Unifill syringe is being targeted for use by pharmaceutical customers that are seeking access to innovative devices that can generate powerful brand differentiation for their injectable therapies. It's ideal for lifecycle management, the potential extension of patent protection, and needlestick compliance," says Mr. Allan.

"Our areas of focus are those where we can enable and enhance the delivery of injectable therapies," he continues. As one example, Unilife recently developed an implantable delivery system for controlled release substances targeted for administration routes such as intravitreal injection.

The company has also added several products to its portfolio, such as the EZMix dual-chamber prefilled syringe and the Lisa Reusable AutoInjector. "Probably our most significant expansion however is the AutoInfusor family of wearable, disposable devices for the subcutaneous delivery of doses between 1mL and 30mL in volume," says Mr. Allan. "We have developed a full range including the Precision-Therapy platform for the injection of bolus-based therapies, and the Flex-Therapy platform for

FIGURE 9

The Unifill syringe by Unilife is being targeted for use by pharmaceutical customers to help generate brand differentiation for their injectable therapies.

rate-based therapies."

Several user acceptance and preference tests are now ongoing for various AutoInfusor products. Unilife is now working with a number of pharmaceutical companies seeking to use its AutoInfusors for use in scheduled human clinical drug trials.

WEST—DELIVERING DOSES IN EXCESS OF 1ML

Traditional prefilled syringes for subcutaneous injection have a typical delivery volume of below 1mL. Recently, with the advent of newer biologic drugs, the need for higher dosage concentrations has led to either higher viscosities or the need for a higher dose volume in order to ensure an effective dose. This has facilitated the development of alternative systems capable of delivering a dose in excess of 1mL.

West has a history of helping customers to package and deliver injectable drugs. In the last few years, the company has developed its own proprietary systems. The first is the ConfiDose® autoinjector system platform technology, which is designed for a standard 1mL-long syringe system with a fixed needle and is compatible with glass and plastic syringes–including the Daikyo Crystal Zenith® insert needle syringe.

"Knowing the issues in the marketplace with glass breakage and performance, West specifically designed its autoinjector system to help overcome issues associated with glass and be compatible with a range of syringes," says Graham Reynolds, Vice President, Marketing & Innovation, Pharmaceutical Delivery Systems, West. Further evolutions of the technology platform include variants capable of delivering up to 1.5mL, and enhancements designed specifically with the patient in mind. These include the development of new form factors that ease handling, designs that make device operation more intuitive, and alternative activation mechanisms for improved usability.

In order to meet the growing need for the delivery of higher-volume doses of biologics, West has continued developing the SmartDose® electronic patch injector system platform technology. It is a totally integrated system combining a novel drug container based on West's Daikyo Crystal Zenith containment system in combination with FluroTec® barrier film, and a proprietary delivery system incorporating features designed to enhance the patient experience and foster better patient compliance.

This system widens the range of possibilities for biologics, including conversion of intravenously administered products to subcutaneous self injection. Additionally, larger-volume injection may allow for less frequent dosing versus commercially available self-injection systems, which are typically limited to 1mL or less.

With regard to the ConfiDose autoinjector system platform technology, West has conducted user studies, in particular, how the system works in the hands of impaired users. User studies for the SmartDose electronic patch-injector system have also been performed. "Those studies

FIGURE 10

West's ConfiDose® autoinjector system technology platform (top) and the SmartDose® electronic patch injector system platform technology provide solutions for self-delivery of drug products.

have led us to design enhancements based on user feedback, and has improved our understanding of the balance between dose frequency and dose volume, enhancing our ability to offer a range of solutions to enable effective therapy with an optimized injection regimen," says Mr. Reynolds.

West's main area of interest is the auto-immune arena, which includes therapies for Rheumatoid Arthritis, Crohn's disease and lupus, among others. "Beyond the auto-immune area, we see burgeoning opportunities in areas such a metabolic disease, chronic pain, adjunct therapy for oncology, and other classes not historically associated with hand-held injection," he says.

Looking ahead, Mr. Reynolds says West will continue to focus on ensuring an effective integrated delivery system, "recognizing that successful drug delivery and an optimal patient outcome can only be achieved if the overall system is effective." Additionally, West will continue to build technology platforms and build on collaborative partnerships with industry partners, such as its relationship with Vetter Pharma, to enable an effective filling solution to support its technology platforms.

YPSOMED—CUSTOM PRODUCTS AIMED AT PATIENT CONVENIENCE

The self-injection market continues to develop in terms of customizable platform technologies and grow significantly for insulin pens, non-insulin pens, and monodose devices such as autoinjectors for biologicals, says Ian Thompson, Vice President Business Development,

Not only are there many new biotech drugs in development, there is also the loss of patent protection for many injectables such as insulin, human growth hormone, interferons, and TNF-inhibitors which is increasing the number of pharma companies looking for off-the-shelf device technologies in both developed and emerging markets.

"Ypsomed is active in all the above areas with a full range of custom products including reusable and disposable insulin pens, pen needles, dual-chamber devices, and disposable autoinjectors," says Mr. Thompson.

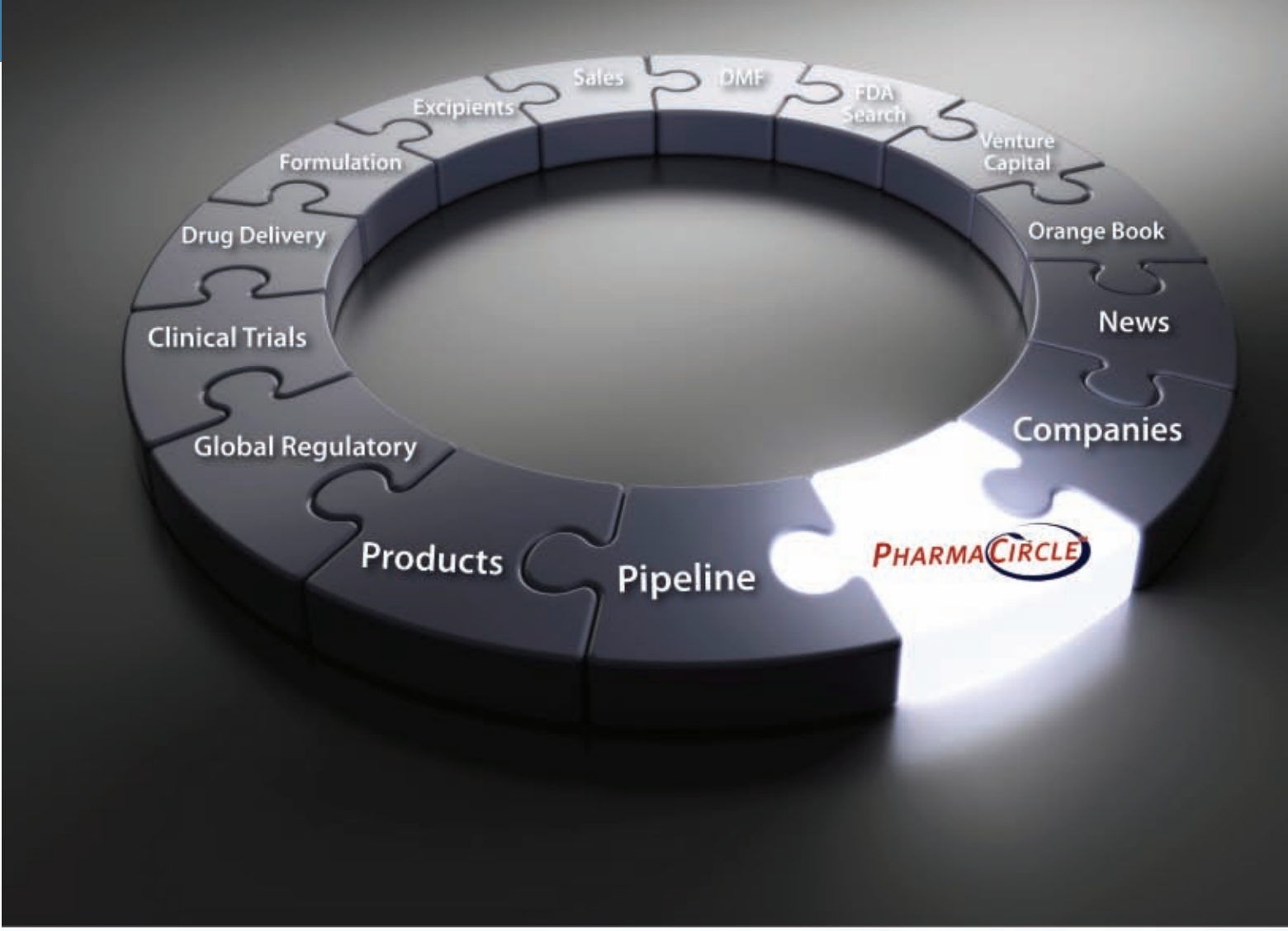
In November 2011, Ypsomed introduced the Ypsomed Delivery Systems (YDS) brand, offering services for injection systems ranging from development, through the manufacture of injection systems, to packaging them with the drug in addition to a complete range of customer products.

During the last year, Ypsomed has acquired a number of new customers in Europe and Asia for the ServoPen® reusable insulin pen. Three new custom products, YpsoPen® Twist, a reusable insulin pen, UnoPen™, a disposable insulin pen, and the YpsoMate® autoinjector are being industrialized for a number of customers. The two-step YpsoMate autoinjector, is the latest autoinjector from Ypsomed for pre-filled syringes with a volume of up to 1mL, providing ergonomic handling and enabling convenient, safe automatic injection when the autoinjector is pressed against the skin. Clearly audible clicks and a large viewing window provide the patient with a high degree of assurance, including confirmation that the full dose has been injected.

Pharma companies are starting to embrace the full "scale of convenience" of prefilled syringe-based devices from safety syringes to autoinjectors and there is increased interest in patch-injectors for bolus infusions above 1mL in volume, says Mr. Thompson. ◆

FIGURE 11

YpsoPen® Twist is a reusable insulin pen (left). The YpsoMate® autoinjector has audible clicks and a large viewing window to provide the patient with a high degree of delivery assurance.



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DPT Laboratories: Providing Solutions to Sterile & Non-sterile Development & Manufacturing of Semi-solid & Liquid Dosage Forms

Paul Johnson
Group President & COO
DPT Laboratories, Ltd.

"DPT has a stellar regulatory compliance record, and a broad reputation for our significant expertise and success in sterile and non-sterile semi-solid and liquid dosage products. Our infrastructure, including vigilant attention to quality, substantial advanced facilities, R&D, and scientific and engineering expertise, enables us to manage multiple projects at the same time. With these substantial capabilities, sponsor companies gain significant efficiency, accuracy, and reliability on the pathway to product launch."

DPT Laboratories, Ltd. is globally recognized as a leading contract development and manufacturing organization (CDMO) specializing in the sterile and non-sterile development and manufacturing of semi-solid and liquid dosage forms. DPT provides full-service solutions to pharmaceutical companies through innovation, advanced technology, scientific and technical expertise, and exceptional service. Recently, DPT launched a major expansion of its sterile capabilities and infrastructure. The company is widely known for its unmatched technical expertise, extensive manufacturing capabilities, and exemplary regulatory compliance record. Drug Development & Delivery recently interviewed Paul Johnson, DPT Group President and Chief Operating Officer, to discuss the consistent growth and success of DPT, its expansion in the sterile arena, and plans for the future.

Q: Can you briefly review DPT's capabilities and services for our readers who may be unfamiliar with them?

A: DPT has a 75-year history of developing and manufacturing drugs for the pharmaceutical industry, with an unmatched record of regulatory compliance, financial strength, stability, and technical expertise in sterile and non-sterile semi-solids and liquids. With five cGMP facilities in San Antonio, TX and Lakewood, NJ, DPT offers full-service outsourcing solutions, including pharmaceutical development, site transfers, state-of-the-art pharmaceutical manufacturing, packaging, and distribution services.

We have three *Centers of Excellence.* Our *Center of Excellence for Sterile and Specialty Products* specializes in the development and aseptic manufacturing of clinical trial material and commercial-scale products to meet sterile requirements. This center features

the newest aseptic manufacturing suites in the industry, a state-of-the-art microbiology lab, and advanced equipment, giving clients access to specialized capabilities. Aseptic manufacturing services include small-volume parenterals, ophthalmic preparations, preservative-free nasal sprays, and sterile ointments. Supported by our seasoned experts and state-of-the-art technology, we focus significant attention on regulatory compliance, which helps our clients avoid costly delays and achieve rapid time to market.

DPT's *Center of Excellence for Research and Development* is a best-in-class facility that provides pharmaceutical development services, including preformulation and formulation development, analytical chemistry and quality control testing, and worldwide product distribution. The center performs R&D activities and supports technology transfers.

Our *Center of Excellence for Semi-Solids and Liquids* in San Antonio has more than 400 employees who provide cGMP pilot, clinical, and commercial-scale manufacturing. As a CDMO, DPT gives customers the advantages of flexible batch sizes and having a central resource for process development, clinical trial materials, and full-scale commercial products without the added expense and time of site and technology transfers. The Center has a dedicated aerosol manufacturing facility, a raw material dispensing and distribution area, and a compounding and fill-and-finish area.

Q: DPT was recently acquired by Renaissance Acquisition Holdings, LLC. How will this affect DPT moving forward?

A: On July 5, we announced the acquisition of DPT by Renaissance, a portfolio company of RoundTable Healthcare Partners, an operating-oriented private equity firm focused exclusively on the healthcare industry. We believe the new business structure will have a very positive impact on the future growth and success of DPT. Renaissance and its management team bring a depth of industry experience, including a solid understanding of the contract manufacturing and development space, and a successful history of partnering with companies like ours to help them grow. This partnership provides the resources we need to accelerate our long-term strategic plans, which include maximizing our semi-solid and liquid business in San Antonio, and achieving aggressive growth in our sterile and specialty products business in Lakewood.

DPT's business is flourishing. Looking forward, DPT's world-class management team, skilled scientists, and staff at our San Antonio headquarters will continue to advance our pattern of steady growth and leadership in the industry as we strive to meet our customers'changing needs for reliable, flexible services, expertise, and quality.

Q: What specialized services does DPT offer the industry?

A: DPT focuses on sterile and non-sterile semi-solid and liquid dosage forms - creams, lotions, gels, ointments, solutions, and suspensions. The development and manufacturing of these forms can be complex, requiring collaboration between experts managing each process. We have incorporated virtually every API, including biopharmaceuticals, into these platforms. We also offer full CMC documentation services for these products. Clients benefit by leveraging our experience early in the development process to avoid duplication in formulating their product.

Q: Can you expand upon DPT's continued expansion of its sterile capabilities?

A: Our decision to expand our sterile services was based on our capabilities and experience in this area, a commitment to satisfy customer needs, and the growing market demand for sterile contract manufacturing services. We have substantial scientific, technical, and regulatory expertise in aseptic development and manufacturing of clinical trial and commercial-scale products that meet sterile requirements.

In the past 2 years, DPT has invested more than $40 million in the expansion and upgrade of our *Sterile and Specialty Products Center of Excellence*. Most recently, we are in the process of installing a Modular Aseptic

Compact (MAC) System, the most advanced, integrated, fully automated filling line in the industry. The consolidated system enables fast, reliable filling with the least likelihood of introducing microbiological contamination. These upgrades expand our capacity and most importantly, increase our ability to better serve clients with high-speed, cost-effective manufacturing runs. Continued investment at this level represents our commitment to maintain our position as the leading provider of pharmaceutical development and manufacturing services for semi-solid and liquid products.

Q: What makes the company's business model unique to its partners?

A: As a full-service, flexible CDMO, DPT offers three primary benefits. The first advantage is greater project efficiency and continuity through fewer development hand-offs. Having one partner through the entire process enables a smoother transition from development to launch, and decreased regulatory complexity. DPT is a one-stop shop, providing comprehensive services across all facets of drug development, from concept and preformulation through clinical and commercial manufacturing. Our technical specialists and management in all areas are always available to clients.

Another key benefit of a CDMO is the flexibility this business model offers drug sponsors. DPT can become a major component of a client's development and commercialization efforts, involved at various stages as technical experts, joint project overseers, hand-off specialists, advisors, and supply chain managers. As a partner, we become fully in tune with a client's objectives and integrated with its internal processes. An alternative model is utilizing the CDMO at specific times as needed.

The greatest benefit comes from the multiple linkages of collaboration between the CDMO and client, and close collaboration between development and manufacturing. DPT's R&D and manufacturing processes are physically integrated in our facilities to enhance the flow of product development, preparing a client's drug candidate for a smooth pathway to commercialization. For the complex development processes required for semi-solids and liquids, close collaboration between development and manufacturing is essential.

Beyond the technical, regulatory, and specialty expertise of the CDMO is the sponsor benefit of significantly less investment in facilities and equipment, an improved flexibility in the use of financial resources. A strategic partnership with a CDMO can also offer a link to regulatory bodies and supply chain parties around the world. As new technologies emerge, requiring changes in processes, expertise, and infrastructure, a CDMO can quickly and efficiently accommodate sponsor needs, providing development, evaluation, prototyping, testing, counseling, and manufacturing.

The day of the fully converged pharma service provider - offering discovery and early stage development support, clinical trials, drug development, formulation, and manufacturing support - may well be in our future. But it's not here yet. This is the time of the CDMO.

Q: Why should a company partner with DPT Laboratories?

A: DPT has a stellar regulatory compliance record, and a broad reputation for our significant expertise and success in sterile and non-sterile semi-solid and liquid dosage products. Our infrastructure, including vigilant attention to quality, substantial advanced facilities, R&D, and scientific and engineering expertise, enables us to manage multiple projects at the same time. With these substantial capabilities, sponsor companies gain significant efficiency, accuracy, and reliability on the pathway to product launch.

DPT also takes a proactive approach to extend product life

cycles. We focus on new technologies and innovation to bring continued value to our clients, and strive to achieve operational excellence.

Q: What is the advantage of a strategic partnership arrangement between sponsor and service provider?

A: A strategic relationship forces the service provider and client to look at the relationship in a different paradigm, from tactically for a few as-needed interventions to a far more integrated, collaborative style with greater commitment, transparency, and involvement throughout all processes. The partnership enables greater efficiency, with both partners complementing each other's capabilities. DPT has dedicated resources proactively working on multiple projects for our clients, so we are not working on an opportunity-by-opportunity basis. Also, access to scientists and senior management on both sides is more prevalent, and the information flow between partners is more consistent and frequent.

Q: What are the most common reasons companies choose to partner with DPT Laboratories?

A: Our extensive experience, our world-class experts, our technologies and capabilities, and outstanding, collaborative customer service. We understand our clients' challenges and we're here to help solve them. We can deliver more effective solutions for our partners more efficiently and help them achieve higher value results than anyone else in our specialty areas. And the earlier and more extensively we're involved in a product's development, the better the results are likely to be.

Q: What do you see as the key industry trends and issues that will impact the life science industry over the next 5 years, and what key messages do you want to convey to our readers?

A: The industry faces increased regulatory challenges and must invest more time and resources to ensure compliance. As a result, pharmaceutical companies are increasingly depending on their outsource partner to help them avoid costly regulatory delays and achieve speed to market. DPT excels in this area and continues to invest considerable financial resources in technology, infrastructure, and people to ensure that DPT's commitment to quality and regulatory compliance is maintained in today's changing environment.

With pharmaceutical companies increasingly depending on service providers, it is essential that they choose a reliable, highly competent partner. In addition to having outstanding technical expertise and needed capabilities, the CDMO must be able to execute services competently and efficiently, working flexibly as a team to achieve clients' goals and solve challenges.

Another industry trend is the need for sponsors to launch differentiated products. DPT has assisted its business partners in achieving this objective by providing innovative formula and delivery systems, such as unit-dose intranasal and aerosol foams.

Q: How do you see DPT evolving in the future?

A: Moving forward, we will continue to add capabilities that complement what we do best, bringing our industry-leading development and manufacturing competencies in sterile and non-sterile semi-solids and liquids to our pharmaceutical partners. DPT will continue to monitor market trends and intelligence, strive to understand the current and future challenges our clients face, and respond to their changing needs. Our vision is to continue focusing on our core business of semi-solids and liquids, emphasizing innovation, high-quality service, and the best technology. We will also expand into adjacent technologies that will bring value to our clients. Our goal is to be the best at what we do, with success defined by customer satisfaction. ◆

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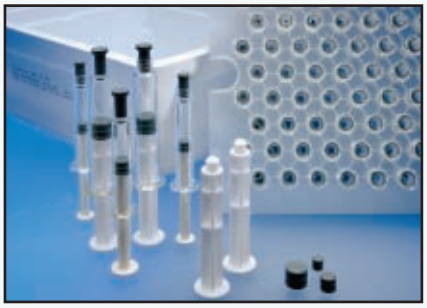

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Fragment-Based Drug Design: Delivering Drugs That Hit Multiple Targets, Leveraging Insights From Systems Biology

By: David Pompliano, PhD, CEO, BioLeap, Inc.

Introduction

Everyone says life is complicated, but systems biologists have a unique perspective thanks to computer models that probe the dense interconnections of the body's myriad cells and tissues. The field is exploding. At last count, the National Institute of General Medical Sciences was sponsoring more than a dozen systems biology centers around the country. Harvard Medical School is taking the next step: an initiative in "systems pharmacology" that puts chemists and biologists together with clinicians and computer scientists to view how drugs perform in living systems.

These many-faceted efforts to understand illness in the context of networked cellular systems will eventually yield fresh insights about drug targets. And, in the spirit of systems biology, the science will also show us how the targets interact along different metabolic pathways involved in complex diseases, such as diabetes, cancer, and autoimmune disorders.

This sophisticated view of living systems has huge implications for drug development. I believe the next generation of pharmaceuticals will have to hit more than one target simultaneously in order to fully exploit the knowledge gained from systems biology. Currently, the most effective strategy to achieve this rational design goal is computational fragment-based drug design (CFBDD). This in silico approach is not only well synchronized with the objectives of systems biology, but also sets up important signposts for the new discipline of systems pharmacology.

Based on reliable predictions of where, and with what binding affinity, small chemical fragments - organic-based moieties

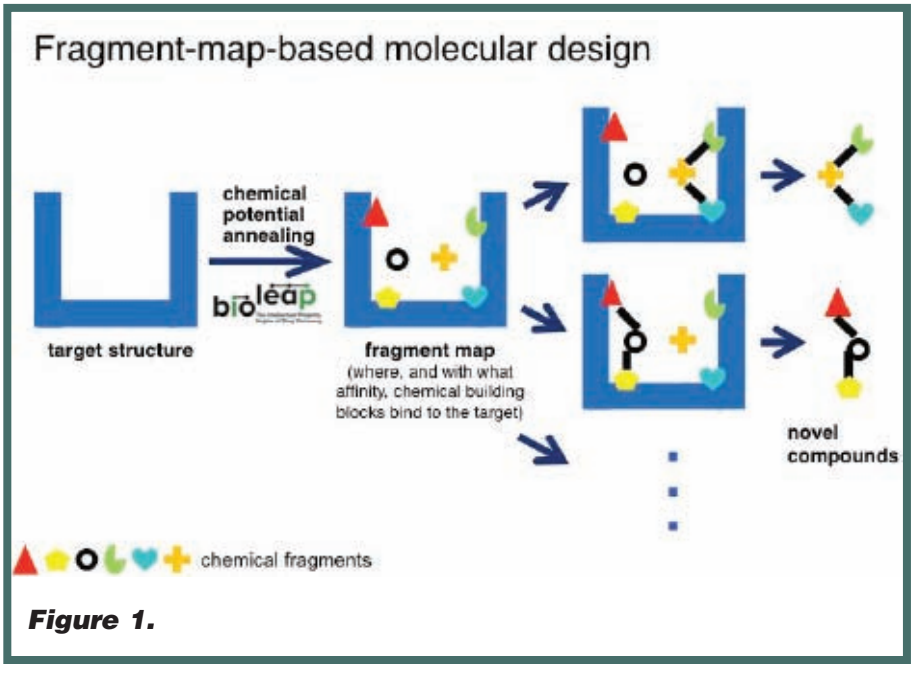

Figure 1.

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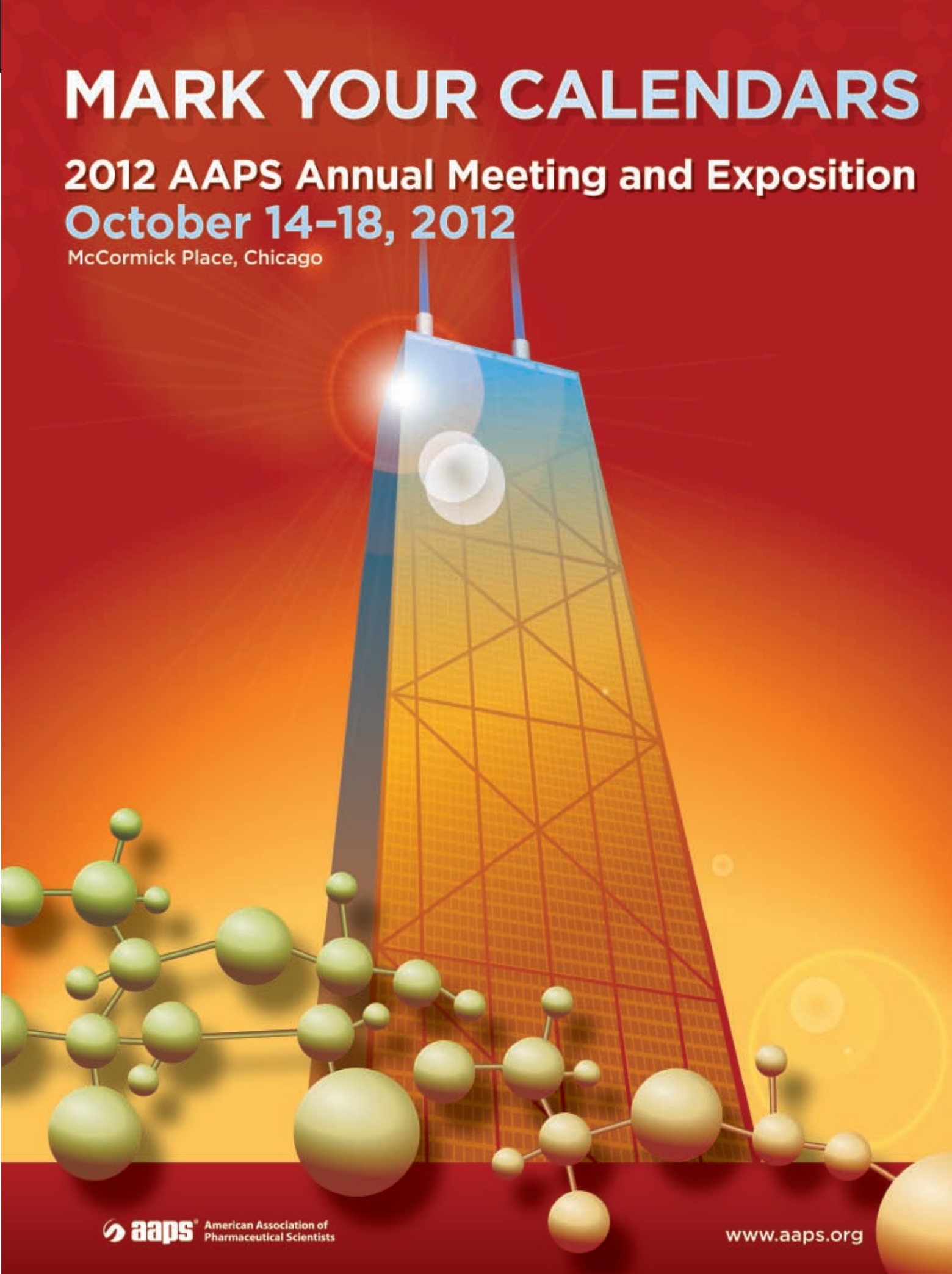

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commonly found in the drug discovery process - interact with disease targets, such as enzymes and cell receptors, drug designers can assemble new drug-like molecules. The fragments, once linked together synthetically, are much more active biochemically. And the entire progression from fragment identification through lead optimization can be performed using predictable software models. Delivering on this vision is fraught with obstacles, given the difficulty of modeling molecular interactions. But computational chemists must take on the challenge. At BioLeap, we are refining the concepts and methods that will allow CFBDD to be the standard approach of early stage small-molecule drug design.

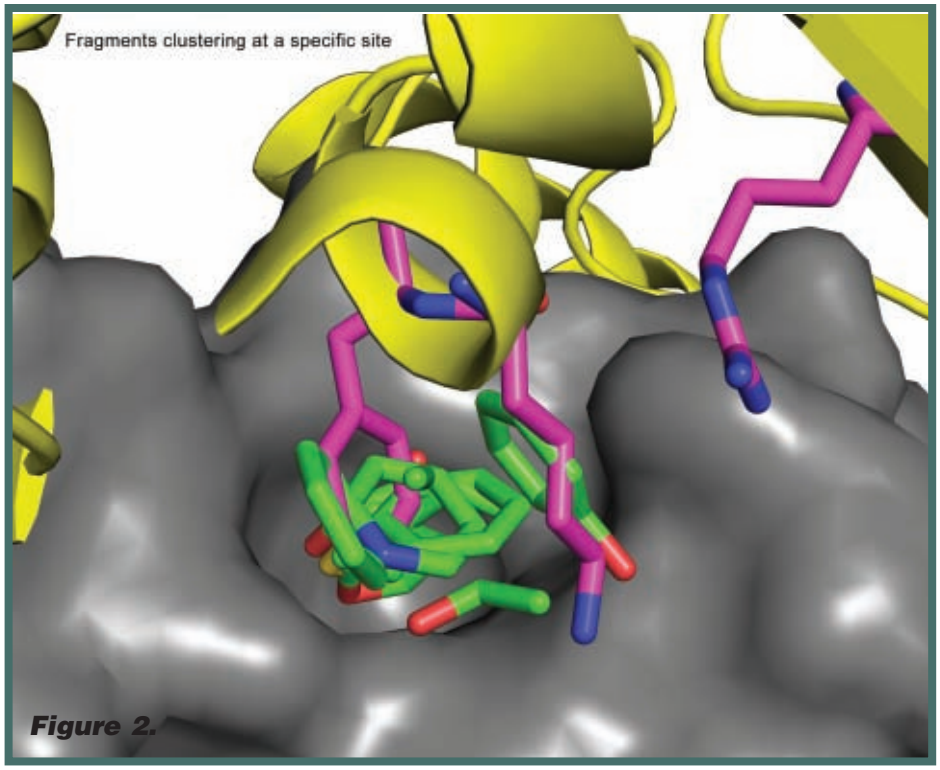

Figure 2.

Today's Tough Development Environment

Combination therapy - administering multiple small-molecule drugs - is the current standard for modulating multiple disease targets simultaneously. However, this approach faces numerous hurdles, such as matching the pharmacokinetics of multiple targeted drugs, coping with drug interactions, and navigating new regulatory obstacles. A second approach is to screen each target with the same chemical collection using high throughput screening (HTS) and looking for single compounds that hit each member of the target panel. But based on what we know today, the odds of success using traditional methods to pinpoint a single molecule that hits four or five different targets are slim, and attempts to do so are bound to be very expensive.

Even if these approaches started to yield significant results, aided by advances in pharmacogenomics, there are structural and economic issues that could stand in the way. In a sweeping study titled Beyond Borders: Global Biotechnology Report 2012, consultants Ernst & Young note that the rush of innovations in drug development hasn't lowered the cost, increased the pace, or appreciably raised the number of new drugs reaching the market each year. It still takes more than a decade and upward of $1 billion to create a novel drug, including the cost of efforts that fail, E&Y contends. Despite the new technologies: "drug development is still linear, slow, inflexible, expensive, and siloed."

The litany of familiar industry woes is even longer than this. According to the Tufts Center for the Study of Drug Development, just 3 of 10 compounds sold by pharma companies bring revenues that match or exceed development costs - and many of those will soon be off patent. London-based consultants EvaluatePharma reckon that between 2011 and 2018, more than $290 billion in prescription drug sales are at risk from the patent cliff. Meanwhile, the drug industry is shedding research jobs at an alarming pace, and funding hurdles are crimping the ability of biotech start-ups to deliver game-changing ideas. According to BioWorld, public and private biotech firms raised 40% less capital in the first half of 2012, compared with the same period in 2011.

How CFBDD Facilitates Polypharmacy

No single drug development strategy or breakthrough can address all the issues we have just enumerated. Yet there are reasons to believe that a fragment-based approach can produce superior results that genuinely make a difference. The reason has to do with the intrinsic virtues of fragments. It's not uncommon for small chemical probes to bind to more than one target. The diverse clustering of fragments finds the protein hot spots or sites of high interaction energy.[1] Finding and utilizing these sites is an important step in multi-targeting drugs. Also, by building up from small fragments, you're able to explore new chemistry and new chemical spaces that effectively map whole, and multiple, proteins. In short, by rationally combining the fragments on multiple proteins, you maximize the likelihood of generating a multi-talented drug.

While these are still early days for

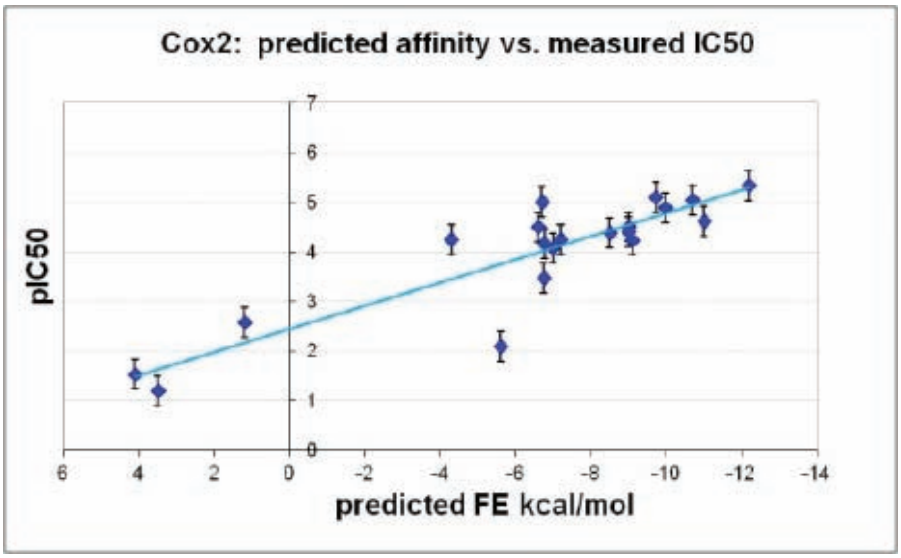

Figure 3.

CFBDD, the methodology is already proving its worth. By using predictive models, we can weed out the drug candidates most likely to fail before spending time and money synthesizing and testing them. Ultimately, the strategy of targeting multiple proteins with a single compound will eliminate the hazards of multi-drug interactions, avoid the hit-or-miss pitfalls of HTS, and simplify the regulatory review when compared with combination therapies. The result is true polypharmacy: a single small molecule drug that hits multiple targets simultaneously.

Two years ago, Drug Discovery Today published a sweeping review of the fragment-based design field, spotlighting advances at Abbott Laboratories, AstraZeneca, Roche, and Eli Lilly, as well as Vertex and other biotech startups.[2] In many cases, the research involved exploiting fragment binding data derived using x-ray, surface plasmon resonance, nuclear magnetic resonance (NMR), and other traditional tools. In just the 2 years since this review appeared, we've seen fresh evidence that the bulk of fragment-based drug design can, indeed, be executed in silico. At BioLeap, which currently possesses the only industrial-scale rational CFBDD platform, we had 45 projects on 70 protein structures underway in 2011. In just the past 3 months, we have run no fewer than 12,000 fragment-based Monte Carlo simulations and thousands of quantum mechanical calculations to further refine the assessment of ligand binding when highly polar and/or charged interactions are involved.

A Path Strewn With Obstacles

As the CEO of BioLeap, my commitment to this approach owes much to the pioneering work of Frank Guarnieri and John Kulp. More than 10 years ago, these two scientists recognized that to be adequately predictive, any model for designing drugs from chemical fragments needed to be thermodynamically rigorous. Unfortunately, at the time, methods for computing the binding affinity of a drug to a target protein (free energy) involved trade-offs: the methods were either accurate, but too computationally intensive and hard to use, or they relied too heavily on approximation and ceased to be predictive.[3] Guarnieri had developed a method that approached this issue very differently, called simulated annealing of chemical potential in grand canonical Monte Carlo simulations.[4] This represented a significant advance in closing the gap between accuracy and practicality. Kulp and colleague Richard Bryan, meanwhile, developed a robust, chemist-friendly platform that would one day make CFBDD a practical methodology for drug design.

Even with these advances, however, the path forward has been strewn with obstacles. Historically, the field of computational chemistry developed in support of the screen-and-correlate paradigm of drug discovery. Capabilities such as docking, virtual screening, cheminformatics, chemical database similarity searches, etc., helped streamline and facilitate the assessment of compounds from libraries and the synthetic expansion of screening hits. These capabilities were an operational improvement. And yet, they didn't fundamentally provide information leading to new ideas or insights that would result in higher success rates and higher quality molecules in discovery programs. Thus, the initial enthusiasm for computational chemistry waned and disappointment spread as expectations for high impact were not met.

CFBDD diverges from traditional computational chemistry, mobilizing a different set of capabilities targeted at a different paradigm. While it is a potent source of new information about protein-ligand binding interactions and chemical novelty, early CFBDD approaches from the 1990s suffered from an excessively high rate of false positives, limiting the technology's utility. There were two basic issues: the reliability of the fragment binding predictions as a starting point, and the fragment linking problem. Specifically, even if you know the location and binding affinity of the component fragments, it's difficult to tell whether ligands assembled by linking those fragments together will precisely follow suit. The fragment poses may lead you to a strong hypothesis about the location and binding affinity of the completed ligand. However, when fragments are linked, charges in the

resulting ligand are often redistributed, and the binding pose can shift to accommodate a trade-off in the binding of each component. Further, the bonds impose restrictions on motion, which changes the entropy of the fragments.

The Challenges of Ranking Ligands

New algorithms are needed to solve the fragment-linking problem. For instance, in the computer model, one or more fragments could be constrained to move in certain ways, subject to forces binding them to other fragments or ligands. This would provide a characterization of the free energy that includes changes in configurational entropy caused by the limited range of motion under the bonded constraint. Working with an approach like this, BioLeap has found that the interconnected fragments can now explore somewhat different poses. Each fragment is annealed, and the sum of the lowest free energies of the components is used for ranking.

In addition to the fragment-linking problem above, we have identified several other challenges in ranking ligands. One is the change in solvation energy between the unbound and bound states (ΔGs). The industry now has access to new, high-performance, empirical solvation models, which when combined with fragment-linking algorithms, may improve the ligand ranking.[5] One also needs to closely consider conformational stress upon ligand binding due to the difference in energy between the lowest energy unbound conformation and the bound conformation. Tools are needed that can quickly identify the global minimum conformation when the high number of rotatable bonds makes systemic exploration impractical. More extensive, and automated, use of quantum mechanics should be a priority in order to further refine the assessment of ligand binding when highly polar and/or charged interactions are involved. This is "the new frontier" of molecular interactions. By combining fragment-linking algorithms, salvation ΔGs, quantum mechanics, and conformational analysis, researchers will be able to make significant progress in ranking compounds over the sum-of-fragment free energies of previous methods. In a recent blinded computational challenge hosted by OpenEye Scientific, BioLeap demonstrated how incorporating these aspects in CFBDD significantly improves affinity ranking and pose predication, which could have a transformative impact on fragment-based drug discovery and drug discovery in general.[6]

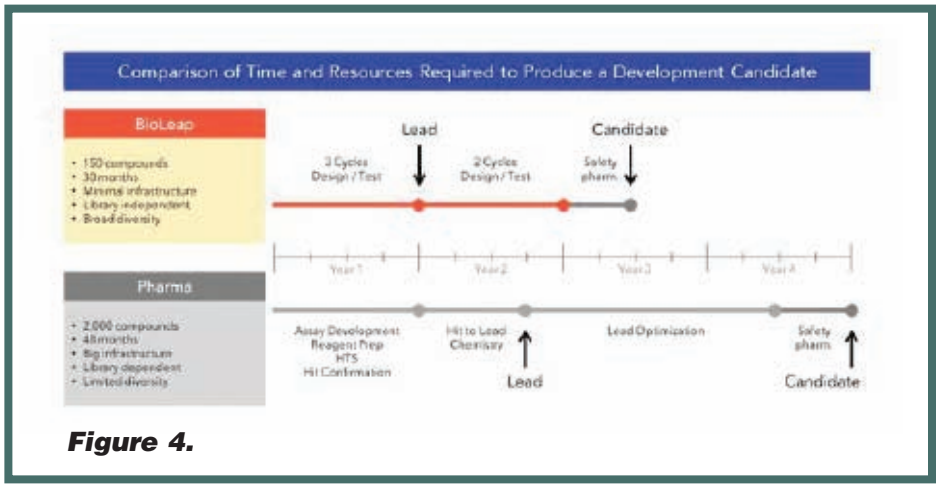

Figure 4.

It is clear that computational advances throughout the past decade have brought us much closer to accurately predicting binding affinity between, say, a ligand and an enzyme. Though more work is necessary, the CFBDD approach now seems to be the most effective way to design new molecules. Consider the limitations of other fragment-based approaches, such as experiments that rely on x-ray crystallography or NMR. If you are working with a fragment molecule that isn't water soluble, for example, it is difficult to use crystallography or NMR to test whether it binds to a protein in solution. Nor is it easy to pinpoint where the fragment binds with the highest affinity and orientation.

High-Affinity Binding & Low Molecular Weight

CFBDD solves this dilemma. Our models reveal not only the highest-affinity binding site on the protein, but every site where the fragment binds with any affinity at all. We can give the medicinal chemist something called a fragment map displaying how thousands of different fragments might bind to a protein target, and what the orientation and relative affinity is at each site. Chemists, armed with computational data, can now use an automated search to find high-affinity fragments in the right location and start linking up the fragments in any fashion they chose.

In the course of designing new drugs, digital chemists mull the problem from many angles. For drug selectivity, they'll typically want a higher binding affinity to one protein and not others. The chemists will be aiming for a low molecular weight, and will want something that has reasonable solubility in water. These and other considerations affect the choice of fragments, and may lead the chemist to settle for a weaker binding affinity as a trade-off. By turning these matters into conscious choices, our technology eliminates hunt-and-peck chemistry. One can evaluate countless potential molecules, operating at minimal cost until a decision is made as to what molecules to synthesize. Out of 200 designed candidates, we might make 20.

The technology I've described has other virtues. With HTS, the molecules you cull are likely to be large - 400 molecular weight or more. By building up from small fragments, we design significantly smaller compounds with higher selectivity. The result may be a molecular weight of 225, or even lower. Due to this context-dependent, custom-made approach, the molecules are not only smaller, but have better pharmacological properties. A typical HTS-derived drug candidate with a molecular weight of 400 will have features that don't serve your therapeutic needs, or might be toxic. You'll have to cut out the bad bits, while adding in the good bits. Why not assemble the molecule you want from the start?

Summary

In the course of this short review, I don't mean to imply there is only one way to harness computing in drug discovery. Different companies are exploring a variety of information-based strategies. Some biopharma companies search databases for molecules that closely resemble existing drugs with a proven track record. With this Google-like approach, there's no need to examine the binding sites or contemplate basic biophysics. That's very helpful if you have a target or pathway that is already well characterized. However, I submit that the approach doesn't help when you have a new target for which there is no historic database (welcome to the new terrain in systems biology!).

Due to the revolution in this field, we are moving into an era in which there will be many new targets and clusters of targets at the juncture of different disease pathways. Understanding what goes on in an organism based on computer models remains a tall order. And that understanding only points us to places in the disease process where we ought to intervene - we still have to design the molecules that affect the enzymes, receptors, and other targets to cure the disease. With marvelously good luck, scientists have already discovered a few medicines, such as the cancer drug Gleevec, that act on multiple targets simultaneously. With fragment-based drug design, our mission is to create many more. ■

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David Pompliano, PhD

CEO
BioLeap, Inc.

Dr. Pomplianohas has 19 years of leadership experience in the pharmaceutical industry with a strong track record in joint venture management, international business development, and driving strategic change in research and development. Most recently, he served as Vice President, Worldwide Basic Head, Vaccines and Infectious Diseases Franchise for Merck Research Laboratories, where he created the global antimicrobial research strategy and led the research and business development teams that integrated internal discovery activities with external shared-risk venture partners. Prior to Merck, he was Vice President, Head of Biology, Microbial Musculoskeletal and Proliferative Diseases Center for Excellence in Drug Discovery at GlaxoSmithKline. As a drug hunter, Dr. Pompliano has contributed to the discovery or development of four marketed drugs (Tykerb, Promacta, Votrient, and Altabax) and four drugs that have reached clinical proof-of- concept. He has published more than 50 research papers and is co-inventor on three patents. Dr. Pompliano earned his PhD in Chemistry from Stanford University and was an NIH Postdoctoral Fellow at Harvard University.

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Resource Allocation

By: John A. Bermingham

Driving your business forward in a fluctuating economy can be a very dicey situation. There are many issues to be considered in this circumstance, but this month's column will concentrate on budget allocation and cuts and things you can do to mitigate the issues.

First, you must quickly get your arms around the situation and then develop your contingency plans while looking at your financial resources. Aggressive action is critical at this time. All functional area budgets have to be reviewed, such as sales, marketing, product development, R&D, supply chain, operations, etc. The theme for these reviews has to be "what you must do or what you must have" rather than "what you would like to do or what you would like to have."

Constant communication throughout the company is essential at all times, but never more so then when poor economic conditions begin to affect the company negatively. You must communicate with your people to let them know the situation, what is expected of everyone, what the plans are to survive the situation, and reset your employees' thinking as to what will constitute success.

As you move into the budget allocation/budget cut process, you should realize that you are going to have a fight on your hands. Managers by their nature do not like to lose financial resources and often take the position that they are being set up for failure. So to mitigate this, it is extremely important for you to meet individually with each of your managers and carefully review the situation. You may not fully convince them of the need to reallocate or cut budgets, but at least they will understand your reasoning.

I always give each manager a revised budget target and let them decide how to meet that number. It is important that each manager develop their own plan on how to achieve the target number so that they have ownership of the process. I then have a combined meeting with all of the managers to review the new budget allocations and work hard to gain consensus. It greatly helps to stop the infighting when each manager sees what the other managers are enduring. Then I hold a company-wide town hall meeting to explain the strategy and budget allocations/cuts in order to meet the problems caused by the fluctuating economy.

All functional areas of a company are important, but in this type of situation, I always give priority to sales and marketing, assuming that we are talking about a product or services company. The reason is that in a fluctuating economy, a company is at high risk to lose customers for various reasons. It could be a competitor looking to gain market share in tough times, it could be customers deferring purchases, or it could be customers becoming more selective on who they buy from and may be reducing suppliers.

If revenue declines, then everything in the company is affected. Without adequate revenue, gross profit will decline and not be adequate enough to cover the SG&A expenses, which will result in an operating loss and negative cash flow. Then the death spiral begins!

From a marketing perspective, companies should think about co-marketing or co-promoting their products or services with other non-competing companies. Sharing costs and driving product sales or services off of each other works extremely well. Also, think and re-think about all the various forms of advertising, including the ones in which you are currently operating, to promote your products or services. The idea here is to see what types have given you the greatest impact or to change things up a little bit.

So in a fluctuating economy, you must deal with the issues aggressively, make the tough decisions that you know have to be made, and think outside of the box. You will live to fight another day! ◆

BIOGRAPHY

John A. Bermingham is currently the Co-President and COO of AgraTech, a biotech enterprise focused on chitosan, a biomaterial processed from crustacean shells (shrimp, crawfish, crab, etc). He was the President & CEO of Cord Crafts, LLC, a leading manufacturer and marketer of permanent botanicals. Prior to Cord Crafts, he was President & CEO of Alco Consumer Products, Inc., an importer of house ware, home goods, pet, and safety products under the Alco brand name and through licenses from the ASPCA and Red Cross. He successfully turned around the company in 60 days and sold Alco to a strategic buyer. Mr. Bermingham was previously the President & CEO of Lang Holdings, Inc. (an innovative leader in the social sentiment and home décor industries) and President, Chairman, and CEO of Ampad (a leading manufacturer and distributor of office products). With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona Corporation, and Rolodex Corporation. He turned around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served 3 years in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes, earned his BA in Business Administration from Saint Leo University, and completed the Harvard University Graduate School of Business Advanced Management Program.

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