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Prefilled Syringes & Parenteral Manufacturing: Differentiation Is Critical

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

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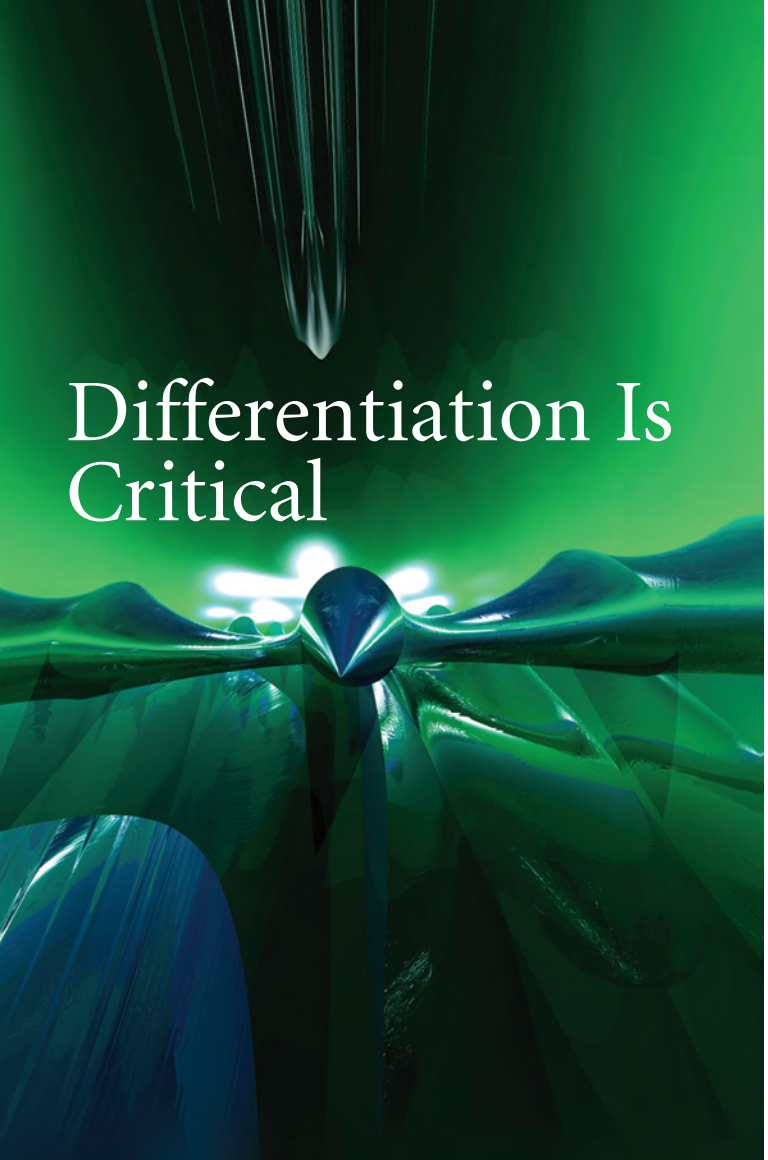

Differentiation Is Critical

"The various advantages associated with prefilled syringes over conventional delivery systems, such as vials and ampoules, have been the primary foundation for their success to date and are expected to continue to drive market growth during the forecast period 2013 to 2019. These advantages include ease of administration, improved safety, reduced risk of contamination, and accurate dosing. Estimates show that the global prefilled syringes market is likely to achieve sales of $6.9 billion by 2018, growing at a compounded annual growth rate of 13.8% from 2012 to 2018."

p.40

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p.58

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Market News and Trends

SMARTT e-Patch: A New Electronic Transdermal Patch

Rhenovia Pharma recently announced that its SMARTT e-Patch project has won an award at the World Innovation Challenge founded by the President of France to identify future champions in the French economy.

The innovative patch caters to the need for controlled administration of medicinal products in treating chronic conditions, such as Alzheimer's disease. Support from the French State's program of investment for the future will help to industrialize the production of the patch within 5 years. The world market in this field is estimated to exceed $31.5 billion by 2015 (MarketsandMarkets, April 2013).

A combination of population aging and various environmental factors are leading to the proliferation of chronic conditions, such as vascular, inflammatory, and neurological disease. Currently, about 50% of patients fail to take orally administered drugs correctly (WHO, 2012). The use of chronobiological polytherapies and controlled dosages is therefore essential for a growing majority of patients. Rhenovia's electronic transdermal patch offers a solution that can automate the administration of essential medicinal products.

The SMARTT e-Patch is a transdermal patch, which allows the controlled administration of up to seven medicinal products through the use of an in-built electronic system programmed by the treating physician. Initially designed to make it easier for patients suffering from nervous system disorders, such as Alzheimer's, to take medicinal products, Rhenovia's patch can be extended to support a significantly larger range of conditions.

By enabling the chronobiological administration and controlled dosage of medicinal products, it has the effect of increasing efficacy, improving bioavailability and minimizing side effects. The transdermal patch also prevents doses being missed or taken erratically by patients who are confused, or who require third-party assistance.

A patent was filed in 2012 for Rhenovia's intelligent transdermal patch. It combines a number of technological innovations, including an ultra-slim battery, a printed electronic circuit on a flexible substrate, UV-LED ink, a novel photolabile ligand, transdermal nanovectors, and non-contact programming.

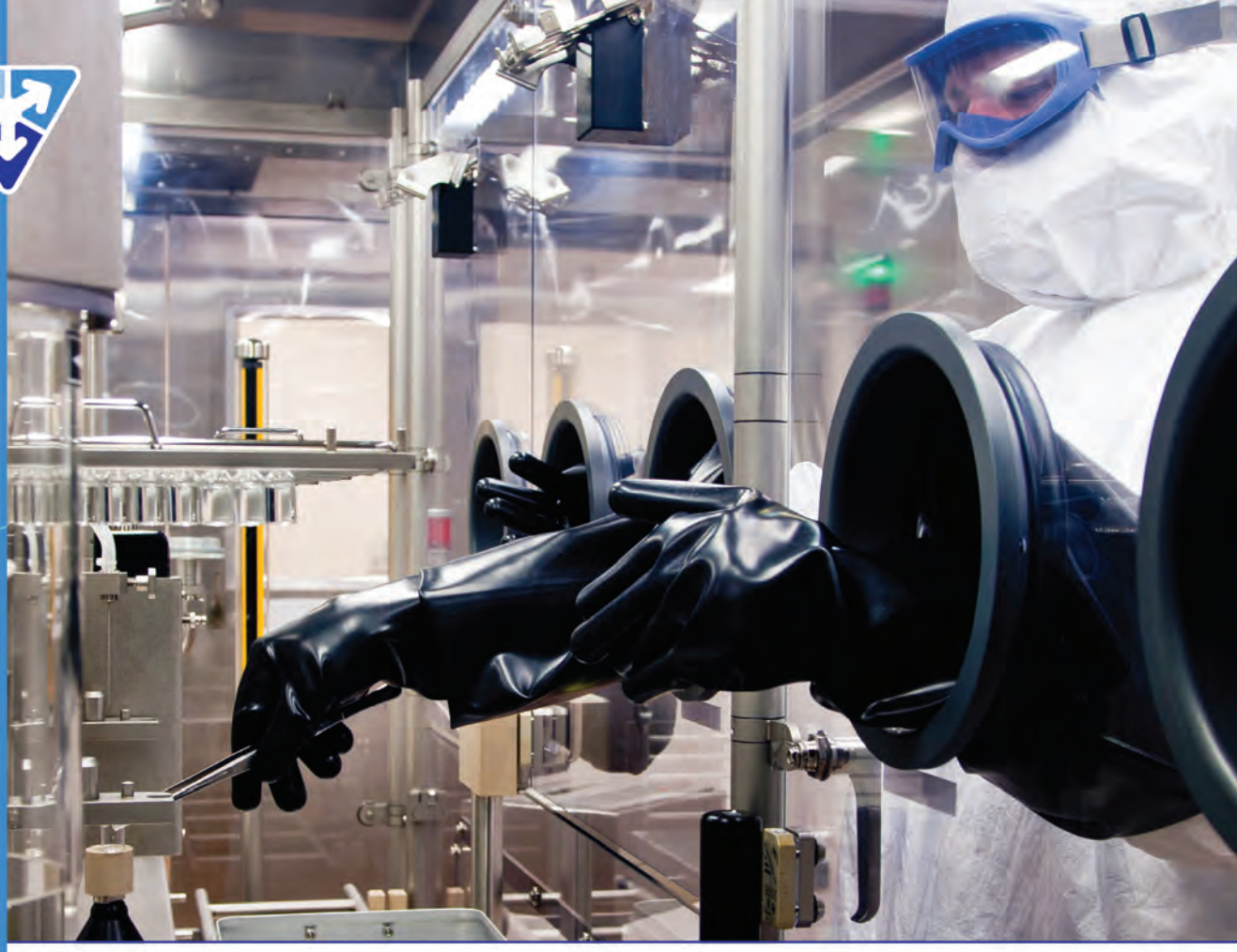
The development of Rhenovia's transdermal patch will result in the creation of a new entity to raise the funds required for its development and secure strategic partnerships with industry players in the health care sector. Meanwhile, Rhenovia, a world leader in central nervous system biosimulation, will continue its development in the research and development markets for medicinal products, agri-food and defense.

Novozymes' Half-Life Extension Technology Reaches Landmark Milestone Approval

The US FDA has granted marketing approval to GlaxoSmithKline's new type 2 diabetes drug, branded Tanzeum in the US and Eperzan in Europe, which uses Novozymes' Veltis technology to achieve an extended half-life that means patients are only required to inject their medication once a week. The FDA approval follows GlaxoSmithKline's announcement in March that albiglutide received marketing authorization in Europe.

"This is yet another important market approval for a drug based on Novozymes' Veltis technology," said Dermot Pearson, Marketing Director, Novozymes Biopharma. "The versatile capabilities of our solution are being continually demonstrated by our customers. Not only has Novozymes developed a platform that helps medicines achieve optimum therapeutic effect, but that also improves the day-to-day management of conditions by extending drug half-life and, therefore, reducing the frequency at which patients need to inject."

Veltis is a half-life extension platform based on engineered albumins that enables manufacturers to define and optimize the therapeutic window of their drug candidate to control dose frequency, dose quantity, and improve drug tolerability. The platform also offers Novozymes' partners, such as the recently announced collaboration with Janssen, the ability to provide once-weekly, once two-weekly, or once-monthly peptide or protein dosing, and, as a result, offers the potential for enhanced patient compliance and improved therapeutic impact.



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UPM Signs Long-Term Agreement With Amerigen

UPM, a division of Gregory Pharmaceutical Holdings, Inc., has reached an agreement with Amerigen Pharmaceuticals, Inc. to commercially manufacture two ANDA products for a 10-year supply term. In addition, the agreement allows for UPM to develop and potentially commercially supply several additional ANDA products for Amerigen over the next few years. UPM acquired the 475,000-sq-ft Pfizer manufacturing facility in Bristol, TN, in July of 2013 and, eventually, all of these products will be made at this new facility.

"UPM has been working with Amerigen for the past 3 years providing development services for their significant pipeline of ANDA products," said Dr. John M. Gregory, Chairman and CEO of Gregory Pharmaceutical Holdings, Inc. "We have a strong working relationship with their company and are impressed with their technical team and their business development approach. We believe this agreement cements our partnership with Amerigen. Also, it is another example of UPM's transition from a company that formerly focused on only early stage development, but now provides a full range of solid dose commercial services for our clients."

"Amerigen looks forward to a long relationship with UPM," added Jonathan Embleton, Chief Business Officer of Amerigen. "We are excited about our upcoming product portfolio and the role UPM will play in providing products to market."

Amerigen is a privately held company founded in 2007 and is located in central New Jersey and has additional manufacturing facilities in China. Their focus is the development, manufacture, and sale of high quality generic pharmaceutical products for the United States and China.

UPM Pharmaceuticals is a Bristol, TN-based independent contract development and manufacturing organization (CDMO) serving the pharmaceutical and biotechnology industries. UPM provides high-quality pharmaceutical drug development services that include formulation development, cGMP manufacturing and packaging, analytical method development, and testing from concept through commercialization.

Link Technologies Announces New Modifier for Improved Oligo Delivery

Link Technologies Ltd. recently announced it has expanded its range of lipophilic modifiers for the effective delivery of oligonucleotides into cells. As oligos continue to be of interest in drug discovery, offering exciting potential as therapeutic agents, there is an increasing demand for improved oligo delivery techniques. Link's proven collection of lipophilic oligo modification reagents, which include cholesterol and tocopherol modifiers, now also includes 5'-Palmitate-C6-CE Phosphoramidite. As a derivative of palmitic acid, a physiologically common fatty acid, the new palmitate modifier is the first palmitate phosphoramidite available commercially, and provides scientists with an ideal approach to improve the cellular uptake and utilization of oligos.

In the cell, palmitic acid is known to conjugate to proteins via cysteine residues and, in doing so, is believed to aid the movement of proteins between intracellular compartments. It is also known that improved cell delivery is achieved when an oligonucleotide is modified with palmitic acid, and that modification at the 5'-end results in more efficient uptake than modification at the 3'-end. However, until now, modification of the 5'-end of the oligo with palmitic acid has proved inefficient. For this reason, Link has developed 5'-Palmitate-C6-CE Phosphoramidite, the first of its palmitic acid-derived phosphoramidites, as a dedicated delivery reagent. When incorporated during oligo synthesis, the use of this novel palmitate modifier can result in more efficient uptake of the oligonucleotide by the cell, offering important value particularly for therapeutic applications.

Link Technologies Ltd is a leading kilo-scale supplier of speciality reagents for oligonucleotide synthesis and modification, all to ISO 9001:2008 quality certification. The company's main markets are university and commercial research departments, plus, increasingly, larger Contract Manufacturing Organizations (CMOs) in the biotech sector.

Mucosis Announces Strategic Partnership With Changchun BCHT Biotechnology

Mucosis B.V. recently announced it entered into a long-term collaboration and license agreement with China-based Changchun BCHT Biotechnology Co (BCHT) and raised EUR 5 million, in a new financing round.

Under the agreement with BCHT, Mucosis will receive an equity investment along with customary payments, including royalties in return for a license to its SynGEM prefusion F vaccine candidate for prevention of RSV and the Mimopath platform for other disease targets within the People's Republic of China on an exclusive basis and non-exclusively in certain other Asian countries. Further details of the agreement were not disclosed.

Changchun BCHT Biotechnology Co. was established in 2004 and is a 600-person biopharmaceutical enterprise engaging in research, development, production, and marketing of vaccines, biologics, and peptide drugs. BCHT has a well-established innovative organization led by talented researchers and supported by state-of-the-art facilities. The management team consists of members with broad international background along with extensive experience in China's biopharmaceutical industry.

Mucosis B.V. is a clinical-stage Dutch biotechnology company with a proprietary platform technology, Mimopath, on which it develops novel vaccines using various routes of administration, including those that provide additional protection in the mucosa, the site where over 90% of pathogens enter the human body. Mucosis's lead product is SynGEM, a stabilized prefusion F protein recombinant vaccine to prevent RSV infection in various target groups. In addition, the company has developed PneuGEM, a vaccine to prevent diseases caused by pneumococcal bacteria and FluGEM, a vaccine to prevent influenza which served as a successful Mimopath platform proof-of-concept through human clinical testing.

Oval & Solize to Collaborate on Injection Device Development

Oval Medical Technologies Ltd. and SOLIZE Corporation have agreed to collaborate together in support of Oval's development program of state-of-the-art autoinjectors.

Oval has been developing injection systems since its establishment in 2009 and it has strong IP, know-how, and capabilities in the delivery of high-viscosity biologics and in device development. Currently, Oval is developing a number of small light-weight autoinjectors with a plastic drug container, providing excellent usability for the patient, and enabling maximum drug efficacy and high safety levels.

SOLIZE has been providing engineering and consultancy services since 1990, which covers the entire development processes from product design through pilot stage of tooling and molding. SOLIZE has been supporting development of many new medical device products, especially for European customers. SOLIZE can accelerate the development process by offering high-quality prototypes with very short delivery time, which are enabled by an in-depth know-how of Design For Manufacture, tool design, and plastic injection expertise.

Oval and SOLIZE will collaborate by utilizing strengths of both companies to support Oval's development programs, resulting in highly reliable autoinjectors customized to meet the needs of individual biopharmaceutical products in an expedited manner, and secure a strong presence in the autoinjector market, which is expected to expand also in Japan in near future.

This collaboration enables Oval to expand its unique business with the autoinjector both in Japan and globally and provides SOLIZE with an opportunity to further expand its development support business in the medical device field.

Management Insight

The Biotech Bubble: What Goes Up Must Come Down

By: Derek Hennecke, CEO & President, Xcelience LLC

Physicists know it. Coffee drinkers live it. Roller coasters capitalize on it. Yet stock market investors - even coffee-drinking physicist-investors strapped into roller coasters - routinely deny it. What goes up, must come down! How much? How fast? How hard? When? These are the relevant questions.

In the past 12 months, the Nasdaq biotech index has skyrocketed 80%, borne aloft on a wave of new drug approvals. The overall stock market climbed just 20% in the same period. This is far from normal. Last year, we saw more biotech IPOs in a single calendar year than we saw in the previous 5 years combined.

Biotech is delivering. Landmark approvals abound. In December, California biotech Gilead saw the FDA approve Solvadi, a treatment for Hepatitis C, which could earn the company $3 billion this year if they don't have a large backlash on the reimbursement. Biogen Idec is expected to see $1 billion in revenues for Tecfidera, a multiple sclerosis treatment approved last year.

Biotech is the spigot that feeds our pipeline. Everyone in this industry wants to hear that biotech is booming. Right now, the spigot is wide open. But will this continue? Or is it just a blast of activity that comes from taking the kinks out of the hose - kinks created during 5 years of pent up recessionary pressure.

The biggest threat to the industry going forward may be the stock market itself, which is a major source of capital. Investing in biotech is always highly speculative, and with the recent peaks and dips it may feel more like a gamble than ever. At one point, biotech was up 40 percent for the year. It's cut those gains since then, but remains solidly up for the last twelve months. As of this writing, the IBB index has fallen 20% which is officially bear market conditions. Is further correction in sight?

There are some very real reasons behind the past year's growth, and if those reasons remain strong and steady, we may be able to hold off a precipitous downward plunge, though it may be wise to buckle up for more loops just the same. Let's start by looking at three of the engines behind biotech's amazing last year.

ENGINE 1: HARVESTING THE GENOME

All those years of unraveling the human genome are finally paying off with a surge in new drugs. Vertex has a drug that treats a subset of patients with cystic fibrosis, made possible because of improved understanding of the malfunctioning gene that causes it. Bluebird Bio, a small Celgene partner, is making progress toward a treatment for sickle cell anemia that inserts a properly functioning version of the bad gene into the patient's blood cells.

There is every reason to believe there will be more of these exciting discoveries, and yet implications of the unraveling of the human genome go beyond more and better medicine. Because we can now identify precisely which patients have the genetic markers that make them candidates for a particular treatment, clinical trials can be smaller, cheaper, and show better results. Cheaper clinical trials make it more economical to research treatments for rare diseases and for those that have proved immune to existing treatments.

The FDA gives special treatment to these drugs, allowing them a speedier path to approval. Witness NPS Pharmaceuticals (NPSP), which developed a treatment for a rare disease known as short bowel syndrome. Hyperion Therapeutics (HPTX) is developing a drug for another rare illness known as hepatic encephalopathy, a decline in brain function that results when the liver is unable to remove toxins from the blood. The stock is up 20% this year. This is a solid development that gives industry growth legs.

ENGINE 2: OPTIMISM OVER OBAMACARE

Optimism fuels markets, and at least in the biotech market, there is a lot of optimism about Obamacare. More Americans than ever will have insurance in the future, meaning more people than ever will be able to afford expensive drugs. The fact that it's too soon for most of these people to have actually begun buying these drugs is irrelevant. The stock market acts not on what is, but on what it anticipates. For the past year, the market has been

SIDEBAR

Patently Dangerous: *Alice Versus CLS Bank*

Biotech's future could be profoundly affected by a software patent lawsuit before the Supreme Court right now. *Alice v. CLS Bank* will set the legal framework for future patent of all kinds; a matter in which the biotech industry takes a very keen interest. The contention revolves around subject matter eligibility. Every country excludes some things from patent law eligibility. In the States, literary works, musical compositions, data compilations, and legal documents such as insurance policies cannot be patented. Biotech benefits from tough patent laws. Without patents, all that hard work and research goes to the public domain and there is no chance to recover the investment. For biotechs creating a new drug, patent law is in biotech's favor, but in many cases, such as the development of better processes and methods, patentability is far from certain. The precedent on the books right now is not one biotech likes. In 2012, in the case *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, Prometheus was forced to defend a patent law it had obtained for correlations between blood test results and patient health that could be used to determine the appropriate dosage of a specific medication for the patient. The Supreme Court ruled that this process could not be patented because the correlation was in fact a law of nature. Biotech would rejoice were *Alice v CLS Bank* to counter the Mayo precedent, but the not insignificant risk is that the case will reinforce a landscape in which biotech patents for processes and ideas are harder to obtain. In the meantime, the uncertainty itself can be expected to form a negative drag on the industry, particularly as the summer decision approaches.

anticipating that more people than ever will be able to afford expensive drugs in 2014. Hence the growth. Can we expect more growth based on this optimism? It may be baked in at this point.

ENGINE 3: BIOTECH AS THE ENGINE FOR PHARMA GROWTH

Biotech is benefiting from a shift in large pharma thinking. Internal R&D used to be a major part of any large pharma operation. Biotech is the engine of large pharma R&D today; big pharma cherry picks promising candidates from biotech's field of dreams.

There are a few companies that still rely heavily on internal R&D, and they're taking a hit for it. Merck poured a massive $8.16 billion into its R&D department last year. To put this in perspective, the XBI, the largest biotech ETF, contains 44 companies and is worth just slightly less than $8 billion, even after the massive recent run-up in stock prices.

What results did Merck see? Precious few. Perhaps Merck's R&D department failed to produce any juicy cherries, forcing the company to throw support behind a few Craisins. The FDA gave Merck countless sleepless nights over Suvorexant, a new sleep drug, forcing it to revise its NDA to limit use to small doses. Progress with the osteoporosis drug Odanacatib has been extremely fragile, plagued by delay after delay. And the embarrassing failure of the cholesterol drug Tredaptive, the latest iteration of Niacin, once marketed in Europe, was a major cardiac event for the company. Tredaptive didn't cut the risk of vascular events while it raised several side effects, such as diabetes, bleeding, and infections.

Sanofi, meanwhile, has staked its fortunes on biotech with a very different result. Sanofi depends increasingly on its American biotech partner Regeneron to stoke the ovens that fire the pharma giant's growth. This year, the massive French company will pump about $1 billion into Regeneron's research program. That's a sizable amount, though nothing like Merck's $8 billion. Interestingly, Sanofi isn't trying to absorb Regeneron and make it into an internal R&D department. Rather the company prefers to keep it at arms length, allowing Regeneron to do what it does best - breaking new ground in research, while allowing Sanofi to exercise its considerable skill and experience in bringing the new treatments to market. The trend of large pharma looking to biotech for innovation is a mature trend, but it still has room to grow.

BIOTECH MARKET FUTURES: ENGINE FAILURE?

The biggest threat I see to biotech's upward momentum in the near-team future is the stock market itself. As the industry's primary source of funding, the gyrations of this market could temper the near-term future of a very promising industry.

Whether or not you agree with me depends on how you answer this question: Would you put your investment dollars into a biotech ETF right now?

Your gut reaction may be, why not? Biotech is delivering profits, saving lives, and furthering science. The fundamentals are strong, and as we've just outlined, positive.

But the market is not a perfect reflection of fundamentals. The fortunes of a particular drug develop slowly, yet individual stocks generally languish on the ocean floor then skyrocket based on a single news story. Karyopharm Therpeutics stock doubled in January from $16 to $32, reaching a company value of $950 million when the company reported Phase I data on Selinexor as a treatment for metastatic colorectal cancer. Keryx doubled from $8 to $16 over the past half year when Zenerex, under review by the FDA, showed favorable efficacy as a treatment for chronic kidney disease associated with hyperphosphatemia. Such erratic leaps and crashes are the norm of the biotech stock market. For every one that skyrockets, 8 or 9 smolder and fail. It's a risky business.

If you're a savvy investor, you may believe you can better your odds by choosing only biotech ETFs with favorable P/E ratios. This is a basic tenant of investing. Except when it comes to biotech. *Most people don't realize that you can't analyze P/E ratios in the biotech industry like you do most other industries.*

P/E is the ratio of the Price of the Stock, divided by its Earnings (profits). The lower the positive number, the better. If the price of a stock is $10 and it earns $1 a year, it has a P/E of 10 and you can expect to earn profits at a rate that you could recover your initial investment in 10 years. That's good.

The P/E of the SPDR Biotech ETF is 34. That's high, but most of the market is a little pricey right now, so you might surmise that because biotech is actually growing at 20% a year, 34 is not bad. You'll recover your investment sooner than 34 years.

The problem is that P/E ratios are only a

good measure of an ETF when most of the companies in it are making money. When this is the case, the cumulative P/E ratio for the index will be positive. Negative P/E ratios throw the entire measure off.

Bear with me. Let's say you have a company with a price of $10 and earnings of negative $1. The P/E is negative $10. Next door, is another company that also has a price of $10, but a negative earnings of $2. That yields a P/E of negative $5. But that makes no sense! Negative $5 is a better number negative $10. You see how negative P/Es are misleading? You also can't just add them up like positive numbers. The result would lead you in the wrong direction.

Generally, when grouping large numbers of stocks and averaging them, sites like Morningstar and Yahoo just toss out the negative P/Es, or assign them a very high positive number, like 300. If you have only a few negatives, this doesn't affect your ETFs total P/E much. But in biotech, three-quarters of all P/E ratios in a given ETF may be negative. The result of this strategy gives, for example, the XBI ETF a P/E of 34, when in fact the ETF is losing money hand over fist.

If you want a better way to calculate an ETF's true P/E, try this. Add up all the prices of the component companies in the ETF. This is your price. Then total the actual losses of all the component companies. This is your earnings. If you do this with the XBI ETF, instead of a P/E of 34, you will get a far more accurate P/E of negative $21.

A P/E of negative $21 tells you nothing. It can't possibly take negative 21 years to recoup your investment. My point is that you must base your biotech investment decisions on factors other than P/E. If you are in a privileged position to understand (without insider information) how well a particular company's dual-specificity kinase inhibitor effecting the serine-threonine and tyrosine kinases of the MAP kinase cascade might perform, then that is something that might give you an advantage over Wall Street.

I've emphasized the riskiness of biotech investing, but I'd be remiss if I didn't mention that biotech has come a long way toward learning to make a profit. They've been selling for high prices, and that's good for the industry as a whole. Every time a biotech company commands a noteworthy price, a few more venture capitalists wade into the investment pool. Investment stimulates R&D spending, and that benefits everyone reading *Drug Development & Delivery magazine.*

While such progress buoys my spirits as an industry player, the steep 80% upward growth of the past year makes me steel my gut for a fall.

After reading this, have you changed your answer to my question? Do you believe a biotech ETF is a good place to invest your money right now? If you say no, I suspect you're probably in a growing majority, and that's not a good sign for the market's upward trajectory. Because the market provides capital fuel for the industry, we could see some downside in the near to mid-range future. But the underpinnings are strong enough that I believe we will all weather another dip. ◆

To view this issue and all back issues online, please visit www.drug-dev.com.

BIOGRAPHY

Derek G. Hennecke is President and CEO of Xcelience, a CDMO in formulation development and clinical packaging located in Tampa, FL. Mr Hennecke launched Xcelience as a management buyout in 2006, and the company has more than doubled in size. Prior to starting Xcelience, Mr. Hennecke worked for DSM as a turn-around manager in the global drug development community, managing an anti-infectives plant in Egypt, technical and commercial operations in a JV in Mexico, and a biologics facility in Montreal. He developed the formulation and business strategy of several drug compound introductions such as clavulanic acid, erythromycin derivatives and Tiamulin. A Canadian, he covets the Florida sun, but can't be kept away from the rink for long. He is an avid fan of the Tampa Bay Lightning.

Wearable Bolus Injectors - A New Class of Patient-Friendly Drug Delivery Systems

By: Michael D. Hooven, MSME

Injectable drugs are projected to be the largest growth category of drug delivery throughout the next decade. The majority of the new injectables are biologics, which now account for $161 billion in sales and are predicted to gain market share, growing to $215 billion in sales throughout the next 5 years, according to a Roots Analysis. The analysts further predict that approximately 50% of the top 100 drugs will be biologics by 2016.

Biologics hold tremendous promise for advancing treatment of numerous cancers, various immunologic disorders, such as Rheumatoid Arthritis and MS, and a number of other disease categories, including rare genetic disorders.

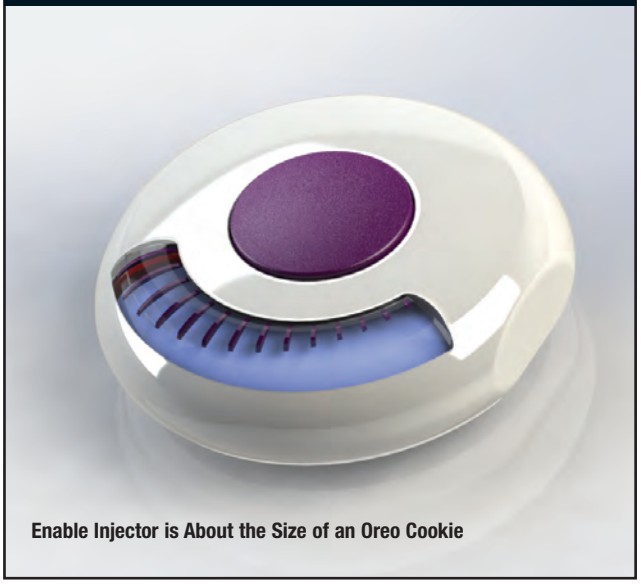
Many of these drugs (biologics, monoclonal antibodies, and immunoglobulins) are characterized by large molecules that cannot be absorbed into the digestive tract. Because they require direct injection into the tissue or bloodstream, they raise multiple drug delivery issues that cannot be addressed with today's injectable systems.

ADDRESSING THE CHALLENGES OF DELIVERING LARGE DOSE OR VISCOUS DRUGS

Biologic drugs are often viscous or high volume formulations and are thus developed primarily as intravenous formulations or, in some instances, as intramuscular or subcutaneous formulations. Such parenteral drugs, however, require specialized training to administer, which often necessitates a patient visit to a hospital, outpatient clinic, or specialty pharmacy solely for drug therapy. Not only do these issues raise health care costs, but also decrease patient satisfaction and compliance.

Further, a significant number of large-dose drugs currently on the market or in development require more than 1 mL per dose,

FIGURE 1



Enable Injector is About the Size of an Oreo Cookie

which is generally considered near the upper limit for subcutaneous administration using a syringe or autoinjector. The subcutaneous tissue cannot comfortably handle a bolus injection of more than 1 mL delivered in this way.

Pharmaceutical companies have attempted to address these various issues by decreasing the frequency of dosing, converting intravenous to subcutaneous administration, and most recently, by rapidly adopting (and adapting) drugs to more patient-friendly drug delivery systems.

One of the most promising drug administration systems is the Bolus Injector, a new class of drug delivery device that can be customized to subcutaneously inject doses far larger than today's syringes or autoinjectors. Bolus injectors are wearable injectors that have the capability to deliver more than 1 ml of a drug subcutaneously in a simple, reliable, and inexpensive manner.

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BOLUS INJECTORS MAY REVOLUTIONIZE TREATMENT REGIMENS FOR CHRONIC CONDITIONS

There is a compelling need for this simple-to-use, low-cost disposable device that allows at-home self-administration of high-volume drugs. Minimizing the need for patients to travel to a healthcare facility, these new injectors could potentially revolutionize treatment regimens for many of the most prevalent chronic conditions, from cancer to autoimmune disorders to blood diseases and others that now require multiple, repeated doses of drug at frequent intervals.

Bolus injectors allow patients to easily and comfortably self-administer injectable drugs. In addition, drug delivery with bolus injectors may enable additional treatment advances by making it possible to safely, conveniently, and cost effectively deliver many of the more than 900 biologics and biosimilars in development today.

WHAT IS DRIVING ADOPTION OF BOLUS INJECTORS?

There are several drivers for adoption of the new bolus injectors, including the following:

- FDA regulations requiring the use of a device in drug clinical trials
- New safety and needle-stick standards
- Lifecycle management
- Brand differentiation
- The overall drive to lower healthcare costs by moving therapy from office and healthcare professional to home self-administration
- Patient convenience
- Increased patient comfort for greater compliance
- Cost containment

A SOPHISTICATED, PATIENT-FRIENDLY BOLUS DRUG DELIVERY SYSTEM

Enable Injections has developed a fully automated drug delivery system that allows the user to self-administer any volume of drug from 1 to 20 mL. The patient simply inserts the drug vial or cartridge into the system, places the device on the body, and presses a button. The drug is automatically and comfortably delivered at a pre-programmed flow rate into the subcutaneous tissue over a timeframe that can range from minutes to hours. After delivery is complete, the needle is automatically retracted and locked out, and the user is notified with audible, visual, and tactile feedback. The needle is never seen or exposed, and the device is fully recyclable with no electronic components.

FIGURE 2

A Single-Vial Enable System

THE PRIMARY CONTAINER: NO CHANGE REQUIRED

In developing any drug/device combination, the greatest development challenge and risk is validation that the drug is stable and compatible with the primary container for the storage life of the drug. Modifying a primary container involves long-term stability testing with the drug, as well as extensive manufacturing process development and validation designed to incorporate the drug and primary container into the device. Any material compatibility issues or processes that affect the stability or integrity of the drug or container must be addressed.

Enable's system is unique in that it requires no change to the primary container and can utilize any standard vial or cartridge. This minimizes the risk, cost, and time associated with development of a new delivery system because the long-term container closure testing and manufacturing process and equipment changes have been validated with the original container. The vial or cartridge can then be

FIGURE 3

A Dual-Vial Enable System

combined with the Enable system at any point in the supply chain.

COMPATIBLE DRUG PATH

In addition, short-term material compatibility testing must be performed with all materials in contact with the drug during delivery. The Enable system minimizes the risk, time, and cost of this testing by using only standard IV materials in the drug path. Therefore, any drug that is approved for IV administration should be exposed to the same materials, minimizing the short-term material compatibility risk.

HUMAN FACTORS ENGINEERING – DELIVERING WHAT PATIENTS WANT

The FDA is placing an ever-increasing emphasis on Human Factors testing for drug-device combinations. The agency recognizes that it is not enough to simply ensure that the device is safe and efficacious if used properly, particularly as home self-injection has become more prevalent. This emphasis on patient self-administration of injections challenges drug and device manufactures to show that the device delivers the proper dose of the drug when used by the patient in a home environment. A device that is shown to be highly reliable in laboratory bench testing may be prone to user confusion or errors, and as a result, may not perform reliably in actual use. Devices must be designed with the assumption that the user is one of the primary variables. To address these concerns, Enable has put intense effort into Human Factors, from the earliest concept through the final design.

Enable's primary emphasis during design was to focus on a safe, reliable device that minimizes user error and confusion.

To address the fact that few users read instructions, the entire Enable injection process is printed on the inside cover of the box in six simple, consecutive, numbered steps with single-word descriptions and accompanying pictures.

In testing, those users with compromised dexterity or eyesight had difficulty "peeling" the cover off the adhesive backing. Holding the device in one hand while pulling at the adhesive cover with the other created the opportunity to drop the device on a hard floor, potentially damaging it. The Enable system was designed to eliminate this step with automatic removal of the adhesive cover on the tape as the injector is being removed from the package.

COUNTERINTUITIVE RESULTS: PATIENTS PREFER ONE-BUTTON FUNCTIONALITY – NO PROGRAMMING

"Programmability" is a buzzword that most would assume is a benefit in an injection device. It turns out to be the opposite. Rather than having a number of features, indicators, functions, alarms etc., users wanted minimal interaction with the device. They did not want to have to make decisions on programming or which button they needed to push. Consequently, the Enable Injector gives them one thing to do after inserting the vial - press the central button. With one press of the button, the needle is automatically inserted to the proper depth, and a controlled flow of the drug begins.

DISCRETION IS KEY FOR PATIENTS

Another issue encountered again and again throughout 15 Human Factor studies was the word "discreet" - the user did not want to see, feel, or hear the device. So Enable designed a small, low-profile device about the size of an Oreo cookie that makes a subtle click that only the user can feel, hear, and see when the dosing is completed. The patient then makes the decision when and where to remove and dispose of the device.

PRELOADED VERSUS PATIENT LOADED: PATIENT PREFERENCES

When presented with the alternative "preloaded" or "patient-loaded," most people's initial reaction is that a preloaded device is

preferable. With a non-refrigerated drug, this may be true. However in the case of a refrigerated drug, encompassing the vast majority of biologics, every patient surveyed preferred the patient-loaded system for a number of reasons. For every injector that uses a refrigerated drug, the patient must wait 30 minutes or more for the drug/device to warm to room temperature. At colder temperatures, the drug viscosity can increase by more than threefold, and a cold drug is more painful to inject. Additionally, an electronic system requires a battery. As everyone knows from starting their car in the winter, both battery life and power are significantly decreased when cold. Battery-powered devices are designed for room temperature use.

With the non-electronic Enable system, patients need only refrigerate the drug vial or cartridge and when ready, insert it into the Enable system. The system automatically warms the drug during the transfer to the injector, and the injector is ready to use immediately upon transfer, eliminating the 30-minute wait and saving patients valuable time. When given a choice of a preloaded or patient-loaded Enable Injector, all of those surveyed chose the patient-loaded system. Among the reasons given were: "the vial doesn't take up room in the refrigerator," "the vial is childproof, an injector isn't," "once I start something, I want to finish it," and "if I have to leave it out, I might forget about it." And of course, patients want an injector that is ready when they are.

ENABLE'S S.E.T. DRIVE SYSTEM ELIMINATES DRAWBACKS OF CARTRIDGE/PLUNGER INJECTORS

In a wearable injector, the drug primary container, specifically a cartridge or vial, is not the ideal container for use in delivering the drug, and this can result in some significant compromises in design. A typical system using a cartridge with a plunger driven by a motor or spring has two major drawbacks - it is relatively large, and the force required to drive the plunger increases as the volume of the drug increases. This increase in force means either an increase in delivery time or an increase in the cannula size as the volume of drug increases.

For example, take a standard 1cc syringe, fill it with water, and attach a small-gauge needle. Push the plunger as hard as you can and time how long it takes to deliver the 1 cc. Then take a 10-cc syringe with that same needle. Pushing just as hard on the plunger, it will take 10 times longer to deliver that 1 cc of water.

To eliminate these significant technical challenges, the Enable Injector uses a proprietary S.E.T. drive system that is optimized for wearable injectors. The force required to deliver the drug does not change with the volume, and the delivery rate and cannula size remain the same.

The Enable system is, consequently, unique in its ability to deliver volumes and viscosities significantly higher than cartridge/plunger-based systems (10 mL of 100 cP through a 29-g needle at 1 mL/min). In most cases, the needle size can be reduced to 30 g or less for patient comfort. The S.E.T. system allows for devices with volumes of 1 to 10 mL and 1 to 20 mL with a very small size and low profile.

Having the same device for volumes ranging from 1 to 10 mL provides for great flexibility in studies where the dosing may not yet be determined. Having a small device with volumes of 20 mL or more could allow subcutaneous delivery of currently approved IV drugs without a change to the formulation. This unique capability to deliver higher volumes and viscosities in a very small size enables patient-focused, reliable delivery of new and existing drugs.

MINIMIZING INJECTION PAIN YIELDS THE MOST COMFORTABLE PATIENT EXPERIENCE

One of the primary challenges of delivering a high-volume drug through a wearable injector is making the experience comfortable for the patient. If the injection is painful, or even uncomfortable, the patient will be resistant to use of the product or might attempt to remove it during the injection. This could have a major impact on patient compliance and affect the device's ability to consistently deliver the proper dose.

Enable Injections was founded with a focus on painless injection technology, a concept originally developed and evaluated in multiple clinical studies at Children's Hospital in Cincinnati. Enable has partnered with CHMC to gain a deep understanding of the causes of injection pain. The Enable Injector addresses each of these causes, resulting in the most comfortable possible injection experience.

AUTOMATED MIXING PROVIDES CONSISTENT, RELIABLE THERAPY

Many drugs are first introduced in lyophilized form because of increased stability and quicker time to market. Enable has developed an automated mixing system that provides fully automated mixing of two vials of up to 10 mL each. The system can be customized to mix powder/liquid or liquid/liquid for up to 1 hour or more.

The mixing capability of the Enable Injector completely removes the user from the mixing process and provides consistent, reliable results that could allow for therapies to be moved from the clinic or hospital to in-home administration. Not only is this a great

convenience for patients, but it can also help reduce treatment and facility costs. The entire mixing and injection process is completed using the same six simple user steps as with a standard liquid vial.

ENVIRONMENTALLY FRIENDLY

Since its inception, the Enable system has been designed to be compatible with the ennvironment and integrate easily into the recycling process. The system uses only standard IV component materials, and contains no electronics or batteries that must be removed for recycling. The total volume of the material and packaging is less than what would be used in an IV system.

SUMMARY

Bolus Injectors represent one of the most exciting new opportunities in the field of medical devices. Enable injections' focus on developing innovative technology in combination with an intense emphasis on Human Factors has resulted in a system that is unique in a number of ways. It is the only Bolus Injector that utilizes a standard container closure. It has very high volume and viscosity capability and can be customized to automatically mix lyophilized solutions. Additionally, it provides the patient with a product that is small and low profile, simple, environmentally friendly, and ready to be used immediately. With this unique technology, a highly experienced Board and staff, manufacturing facilities in place, and agreements in negotiation with major Pharma/Biotech companies, Enable Injections is poised to help pharmaceutical and biotech companies develop and market exciting new therapies that benefit and delight patients while lowering the cost of drug administration. ◆

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BIOGRAPHY

Mike Hooven is President and CEO, Enable Injections, LLC. Mike has over 30 years of experience in the medical device industry in a broad variety of business, technical, and clinical areas. He is the Founder of five medical device companies and holds over 100 issued and pending US patents. Mr. Hooven is the Founder, and a Director of AtriCure, Inc. (NASDAQ:ATRC), where he previously held positions as the Chairman and CEO. He is also Founder and Chairman of Enable Medical, a surgical device manufacturer that was acquired by AtriCure in August of 2005. Prior to Enable Medical, he was Director of Product Development at Ethicon Endo-Surgery from 1988 to 1994, where he had responsibility for all in-house product development and supervised a staff of 200 engineers. He held Engineering positions in pacemaker and lead development at Siemens/Pacesetter from 1986 to 1988 and at Cordis Corporation in neurosurgical products from 1981 to 1986. In addition, he is Director and past Chairman of BioOhio, a state-funded organization to accelerate life-science startups in Ohio. He earned a Bachelor of Science in Physics and a Master of Science in Mechanical Engineering from the University of Michigan. Mr. Hooven was recently appointed by the Governor to the Third Frontier Advisory Board, a $2.1-Billion initiative to create new technology-based companies and jobs in Ohio.

Formulation of Poorly Soluble Drugs: A Modern Simulation-Based Approach

By: Sanjay Konagurthu, PhD, and Alexander McVey, MS

ABSTRACT

Leading companies in other industries have shown that designing for quality and manufacturability from the earliest stages can positively impact the outcomes for a product. In addition, predictive modeling and directed product analyses can significantly reduce time-to-market and overall product costs.

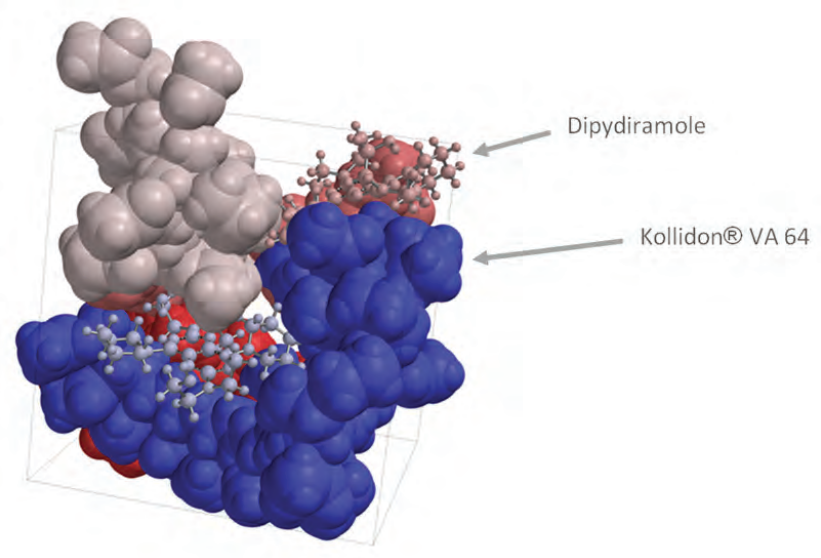
To enable such approaches in pharmaceutical formulation development, there is a strong need for deeper mechanistic understanding to support efficient and robust formulation activities for poorly soluble molecules. To meet this need and the demands of clients seeking solubilization solutions, Agere is taking a modern approach to solubilization formulation development that incorporates Quality-by-Design (QbD) principles at the preclinical stages of the drug development process. We have developed a platform, Quadrant 2™, that is based on a comprehensive understanding of multiple proven solubilization technologies coupled with materials science and a targeted application of molecular modeling. The primary advantage of this approach is that it enables a faster, more informed formulation development process that promises to minimize costly iterations and reformulations as drug products proceed into the clinic.

This following presents a case study in which a model BCS Class II compound, dipyridamole, was evaluated as an amorphous dispersion using molecular modeling combined with experimental data. All work described was conducted using Agere's Quadrant 2 platform.

INTRODUCTION

Solubilization formulation design has traditionally been a stage of product development that takes place long before QbD guidelines are applied. One reason for this is that pharmaceutical unit operations naturally lend themselves to the use of well-established tools, such as design of experiments. A second reason is that prediction of the behavior of materials is complex, and no comprehensive materials science modeling tools had been developed directly related to drug delivery. To address this need, Agere has undertaken

FIGURE 1



Molecular model of dipyridamole interactions with Kollidon® VA 64 in the solid state. Dipyridamole is shown in ball and stick format, and PVP-VA is shown in space filling format. The colors are indicative of differing intermolecular energies.

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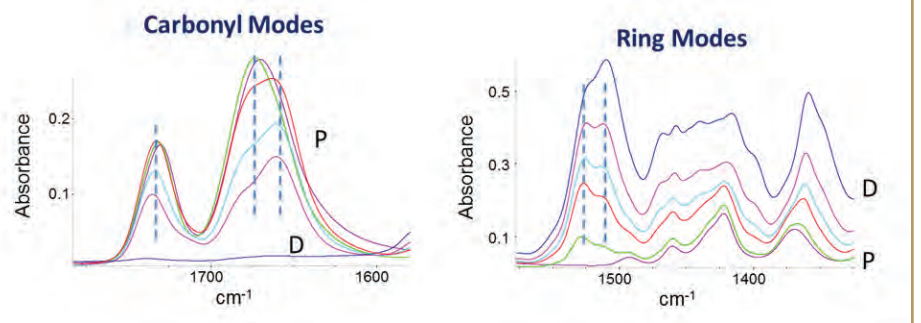
the development of a set of tools that combine physical measurements and simulations to fully understand the fundamental materials science of formulation design.

IN SILICO MODELING

The in silico modeling phase of Quadrant 2 is a crucial first step in dispersion development and manufacture. It provides the context and constraints needed to screen candidate excipients and solvent systems for a given chemical entity. Modeling starts at the molecular-level and progresses through thermodynamic and kinetic analyses. Each stage of analysis is designed to explore and refine interactions and relationships among APIs, excipients, and solvents resulting in a pre-optimized formulation. This powerful tool leads to informed selection of finalist systems prior to full laboratory evaluation.

A representative molecular model of dipyridamole with Kollidon® VA 64 (PVP-VA) as the dispersion polymer is shown in Figure 1. The modeling of dipyridamole:PVP-VA dispersions show strong non-covalent interactions between the hydroxyl groups of dipyridamole (H-bond donating) and carbonyl groups of PVP-VA (H-bond accepting). In addition, it is informative to visualize the molecular environment of the drug in the polymer matrix. Specifically, comparison of the molecular configuration of the drug in its crystalline form (not shown) with that in the polymer clearly demonstrates there are significant steric conformation changes between the two states. In fact, it is these specific changes that are, in large part, responsible for the free energies of mixing that ultimately lead to the bulk properties of the solid dispersion.

FIGURE 2



Solid Dispersion: Representative Molecular Model of Dipyridamole:Kollidon® VA 64.

INFRARED SPECTROSCOPY

Fourier transform infrared spectroscopy (FTIR) is a powerful technique for the study of molecular interactions. In addition, the vibrational energies measured experimentally are directly comparable to those calculated from high-level quantum mechanical simulations. To aid our understanding of the drug-polymer interactions, FTIR spectra were collected for dipyridamole, PVP-VA, and dispersions thereof.

Spectra were recorded for pure amorphous dipyridamole, PVP-VA, and spray-dried dispersions of dipyridamole:PVP-VA (10:90, 50:50, and 70:30 wt%) on a Nicolet iS10 FTIR spectrometer in the range from 4000 to 500 cm-1 at 25°C. Select regions of the spectra are shown in Figure 2.

PVP-VA has no hydrogen bond-donating capability; however, there are two types of hydrogen bond-accepting carbonyl groups on the pyrrole ring, and one on the acetate group. The characteristic vibrational peaks are centered at 1729 cm-1 and 1670 cm-1. Dipyridamole contains four hydroxyl (-OH) groups that can act as hydrogen-bond donors, and these –OH-stretching modes appear as a broad band spanning from ca. 3000 to 3600 cm-1 (data not shown). The ring modes of dipyridamole span the region from ca. 1500 to 1525 cm-1 with peaks centered at 1510 cm-1 and 1524 cm-1.

As shown in Figure 2, IR spectra of spray-dried dispersions of dipyridamole:PVP-VA show distinct spectral changes with respect to the pure components (D indicates pure amorphous dipyridamole, and P indicates pure PVP-VA). They were identified in two different regions associated with the carbonyl modes of PVP-VA and the ring modes on dipyridamole.

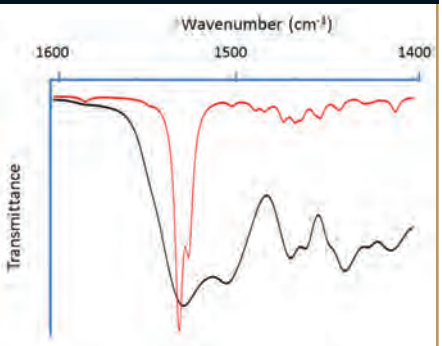
Upon interaction with dipyridamole, the carbonyl band of PVP-VA centered at 1670 cm-1 is split into two discernible bands with peaks at ca. 1660 cm-1 and 1680 cm-1, and the band at 1729 cm-1 shifts slightly to 1738 cm-1. Concomitantly, upon interaction with PVP-VA, the hydroxyl bands of dipyridamole undergo a shift from a maximum of 3260 cm-1 (pure dipyridamole) to 3440 cm-1 (70% dipyridamole) [data not shown]. The ring modes of dipyridamole also undergo a slight shift and change in intensity upon interaction with PVP-VA. Molecular modeling suggests that as the drug becomes more dilute in the polymer, the intra-molecular hydrogen bond on the dipyridamole ring system rotates outward and hydrogen bonds preferentially to a carbonyl group on PVP-VA. The combined spectral changes observed in the spray-dried

dispersions are indicative of hydrogen bonding interactions that occur between the hydrogen bond acceptor groups of PVP-VA and the hydrogen bond donor groups on dipyridamole.

IR spectra were also calculated in silico using density functional theory (DFT) and used to assign the fundamental modes of vibration for the dipyridamole, PVP-VA, and specific drug-polymer interactions. With these methods, we are able to reasonably predict the major features of the experimental IR spectra.

A representative IR transmittance spectra for crystalline dipyridamole is shown in Figure 3, illustrating the region of the oscillating ring modes. The calculated spectra are shown in red, and the experimental spectra are shown in black. Peak positions of the calculated vibrational modes allow assignment of the fundamental vibrational modes in the experimental data. Note that exact fits of experimental to calculated spectra are not expected due to a number of factors in the quantum mechanical calculations. Specifically, the calculated spectra contain only the 3N-6 fundamental vibrational modes of the molecule in vacuum. In comparison, the experimental spectra unavoidably have numerous intermolecular interactions that result in additional vibrational energies and intensities. In addition, the calculated vibrational spectra do not include hot bands or the various allowed combination and difference transitions that are present in the experimental results. To address these differences, we are developing methods to enhance the modeling and predictive aspects of the calculations.

FIGURE 3



Calculated IR transmittance spectra (red) versus experimental spectra (black) for dipyridamole ring vibrations in the crystalline state.

FUTURE DIRECTIONS

Agere's approach in developing a methodology for drug formulation design involves expanding Quadrant 2 to encompass a comprehensive set of in-depth tools that combine physical measurements with a variety of calculation modules to fundamentally understand and predict drug and polymer interactions.

As can be seen, the use of quantum mechanical methods to elucidate the fundamental properties of drug and polymer interactions has particular utility. Statistical mechanics methods are then used to transform the molecular-level interactions into macroscopic-level interactions via the partition function. In conjunction with the modeling, highly directed experimental measurements are used to confirm and refine the predictions from the simulations. Using this approach, we are able to not only efficiently select and develop an optimum set of materials for use in a solid dispersion, but also able to inform why these formulations are most optimal. ◆

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BIOGRAPHIES

Dr. Sanjay Konagurthu is Senior Director of Formulation Sciences at Agere Pharmaceuticals, Inc. and has over 15 years of experience managing the development of compounds from the discovery interface through clinical manufacturing. His expertise spans a broad spectrum of therapeutic areas, all involving formulation and process development of novel drug delivery technologies. With extensive experience in oral solid dosage forms, including solubility enhancement and modified release, Dr. Konagurthu has performed and managed the formulation and process development for a broad range of NCEs and lifecycle management of marketed products. He has 7 patents/patent applications to his name, and has authored more than a dozen publications. Dr. Konagurthu earned his Bachelors of Technology from the Indian Institute of Technology (IIT), Madras, and his PhD from the University of Colorado, Boulder, both in Chemical Engineering.

Alexander McVey is a Research Scientist at Agere Pharmaceuticals, Inc. He joined the company in 2012 upon completing his MS in Chemistry from the University of Oregon, where he specialized in polymers and coatings. In his current position, he is involved in research and development focusing on analytical support and formulation development for spray-dried dispersions, other amorphous dispersion technologies, and immediate-release solid dosage forms. Past positions include QC chemist in Quality Control at Agere, and Chemist at Absorption Corp. (now J. Rettenmaier & SÖhne Group). Alexander completed his undergraduate work at Western Washington University, where he earned his BS in Chemistry with a minor in Materials Science.

Application & Effectiveness of Daikyo Crystal Zenith® Container Closure Systems for Radiopharmaceuticals

By: Lloyd Waxman, PhD, and Vinod Vilivalam, PhD

INTRODUCTION

The use of radiolabeled compounds in medicine has had a long history dating back at least to the 1940s. Today, protein- and peptide-based radiopharmaceuticals are increasingly employed diagnostically as well as for the treatment of disease, most notably in certain types of cancer. However, the synthesis and purification of these radioactive agents can be a difficult and costly process. Often, peptides used in the synthesis of radiopharmaceuticals can adsorb to the walls of container closure systems such that drug product cannot be fully recovered after the synthetic reaction has been terminated. In instances where the labeled peptide or protein must be stored prior to use, additional losses of valuable product can occur that could also affect potency. Consequently, the choice of the proper container closure system is critical for the recovery, transport, and storage of drug product. The use of a material such as Daikyo Crystal Zenith® cyclic olefin polymer may reduce losses due to adsorption while mitigating other problems associated with glass, including delamination and the potential risk of contamination to healthcare providers because of breakage when handling radioactive materials.

Nuclear medicine uses nuclear tracer and radiopharmaceuticals to diagnose and treat diseases. Radionuclides are typically combined with existing pharmaceutical compounds to produce radiopharmaceuticals, which once administered to a patient, will become localized to a specific organ or cellular receptor. The radiation emitted by the radiopharmaceutical can be detected and used diagnostically to provide information about the extent of a disease process. Monoclonal antibodies (mAbs) along with tyrosine kinase inhibitors are currently the most rapidly expanding classes of anti-cancer drugs.[1] A small number of mAbs have been labeled with toxic payloads like the radionuclides yttrium-90 or iodine-131. Ideally, these will bind selectively to receptors on malignant cells and destroy them by short-range ionizing radiation. However, a far broader application has been to label mAbs with a positron emitter for use in understanding the in vivo behavior and efficacy of these targeted drugs in individual patients and for more efficient drug development.

SELECTING CONTAINER CLOSURE MATERIALS FOR RADIOPHARMACEUTICALS

The process of selecting container closure materials compatible with a radiopharmaceutical product and its intended use is an important aspect of delivering safe medicines to patients. The materials used in container closure systems can have physical and chemical properties with the potential to compromise the drug product. Glass has traditionally been used as a primary container for pharmaceuticals since it has characteristics that enable generally safe and effective drug delivery, including good chemical resistance, impermeability to gases, and the fact that it is easily cleaned and sterilized. However, issues such as breakage,

delamination, leachables, and physical and chemical compatibility can affect the safety and efficacy of the drug product. Glass delamination can result in the formation of visible glass flakes (lamellae) in parenteral drug products. Delamination originates from an unstable layer on the inner surface of a glass vial and has been attributed to the chemistry or composition of the glass, processing of the glass vial after manufacture, or the use of certain solvents and buffers used to formulate the drug product, including those with high pH or ionic strength or containing citrate or phosphate. In the case of radiopharmaceuticals, such issues may not only harm the patient, but the use of glass could also put the healthcare provider at risk should breakage or other contamination occur. Newer containment alternatives, including cyclic olefin polymers, are now being widely investigated for use with sensitive drug products, particularly biologics (therapeutic proteins).

Low molecular weight compounds as well as peptides intended for use as radiopharmaceuticals or as tracers are frequently lipophilic and will avidly absorb to the walls of a glass container closure system. Adsorption will prevent recovery of costly precursor materials and the resultant synthesized labeled product. In addition, high molecular weight ligands used in nuclear medicine, such as radiolabeled antibodies also tend to adsorb to the primary containment system.

GLASS VS. PLASTIC CONTAINER CLOSURE SYSTEMS: A STUDY

Positron Emission Tomography (PET) imaging makes use of radionuclides including ^{68}Ga, ^{18}F, ^{86}Y and ^{64}Cu. Due to the short half-lives of these positron emitters, the radiolabeled product is typically used shortly after synthesis and purification.

A recent investigation conducted by Massachusetts General Hospital (MGH) compared the adsorption of a radiopharmaceutical for use in PET imaging to glass and Daikyo Crystal Zenith vials and evaluated which material allows for greater recovery of radiopharmaceutical product. The goal of the Study, "A container closure system that allows for greater recovery of radiolabeled peptide compared to the standard borosilicate glass system," was to quantify how much 1) labeled drug product and 2) total reaction activity adhered to the container closure system.

As noted previously, many peptides are lipophilic and have a tendency to become adsorbed onto the walls of a container closure system. Several methods that have been shown to mitigate surface adsorption include the addition of a surfactant, such as bovine serum albumin (BSA) or Tween 20, coating the system with polyethylene glycol (PEG) or siliconizing agents, and the addition of organic modifiers to improve the solubility of peptides.[2-4] Surfactants and modifiers, such as ethanol and acetic acid, are solvents that have been used to reduce the amount of adsorption to a container closure system; however, the addition of these agents is often undesirable for the synthesis of radiopharmaceuticals. All of the previously discussed methods may require additional purification steps to isolate the labeled product but still fail to remove impurities that have the potential to render the radiopharmaceutical unfit for human use.

Alternatively, a container closure system with inherently reduced surface adsorption, such as one made from a cyclic olefin polymer, could improve the product recovery without the need for modifying the container closure system surface properties or by adding other chemicals to the reaction mix.

Edeotreotide, also known as DOTAC,

is a peptide-based molecule which, when bound to various radionuclides, is used in the diagnosis and treatment of certain types of cancer. The peptide contains the chelating group DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), which is capable of complexing with various lanthanide ions, such as ^{68}Gallium.

Researchers at MGH selected a USP Type 1 borosilicate glass container closure system and a resin-based Daikyo Crystal Zenith containment system to compare the synthesis and recovery of ^{68}Ga-chloride and ^{68}Ga-DOTATOC (^{68}Gallium-DOTA-D-Phe1-Tyr3-octreotide) from each type of reaction vial after radiolabeling the peptide. In all experiments using a sodium acetate buffering system and various amount of DOTATOC, the Crystal Zenith container closure system retained less of the total activity than the glass containment system. Over a range of different peptide amounts in a HEPES buffering system, less radioactivity remained in the Crystal Zenith system than the glass with respect to both the percentage of total activity and the percentage of ^{68}Ga-DOTATOC labeled peptide.

Overall, the MGH study concluded that an advantage of the Crystal Zenith container closure system is that one can achieve higher recoveries without the addition of other surfactants that may require extra purification steps as well as have negative effects on the reaction chemistry. Approximately 10% more drug product was recovered from the Crystal Zenith containment system when compared to glass, and approximately 2.5% more of the total reaction activity was recovered from Crystal Zenith compared to glass vials. While the improvement in recovery in this study was relatively modest, such recovery can be critical to the cost of radiopharmaceuticals. Radionuclides and peptides are expensive, so that greater recovery of labeled product will result in a cost savings for the pharmaceutical manufacturer and more drug product available to treat patients.

THE CASE FOR CYCLIC OLEFIN POLYMERS

Several other factors associated with the unique properties of a cyclic olefin polymer support the suitability of Crystal Zenith vials for use with radiopharmaceuticals. In order to accurately measure and adjust the right radiolabel to the right dose, the product must be synthesized, placed in a container, and the amount of ionizing radiation measured using a dose calibrator or similar instrument. The thickness of a vial has an impact on the accuracy and precision of the dose being measured. While glass has variable thickness, cyclic olefins are injection molded, so overall consistency of the vial walls ensure a more precise measurement.

Crystal Zenith's exceptional transparency and high resistance to most organic solvents, as well as its history of commercial use for contrast media and magnetic resonance imaging fluids, suggest that it may also be an attractive option for radiopharmaceutical containment. Like all plastics, Crystal Zenith is highly resistant to breakage and possesses excellent temperature characteristics. Solutions can be frozen at -20°C to -80°C in containers made of CZ for storage and transport without breakage. Cyclic olefins are compatible with a wide pH range, and in contrast to glass offer greater design flexibility for device integration. However, unlike many other plastics, Crystal Zenith exhibits low levels of leachable molecules and metal ions.

Selection of a container closure system for any drug product should be based on conditions required to maintain stability

and ensure recovery of the protein or peptide used in the final drug product. For many radiopharmaceuticals, concentration of the drug product can be an issue. High concentration products, such as mAbs may not require special packaging because the loss of a small amount of product due to adsorption will be negligible. However, many radiopharmaceuticals are formulated at very low concentration. Consequently, the loss of 10 micrograms may be most of the radioactive material, so adsorption can become a major concern. A head-to-head comparison can often provide the most immediate answer to the best container closure system for the peptide or protein drug product, and pharmaceutical manufacturers should not rule out cyclic olefin materials, such as Daikyo Crystal Zenith, without first testing the material as an alternative to glass. In addition to providing a potential solution to losses due to adsorption, the use of Crystal Zenith can mitigate risks associated with breakage and delamination of glass while helping to ensure that the drug product is delivered to patients safely and effectively and at the correct dose.◆

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BIOGRAPHIES

Dr. Lloyd Waxman joined West in 2008 as a Principal Scientist. He has spent the past 6 years supporting the use of the Daikyo Crystal Zenith® polymer in primary containers used to store and deliver biologics. Dr. Waxman earned his BA and MA in Physics from Temple University and his PhD in Biophysics from Harvard University. He spent 6 years as a Research Scientist at Harvard Medical School in Boston, holds three patents, and has contributed to more than 60 publications.

Dr. Vinod Vilivalam is a Senior Director for Global Technical Marketing of Daikyo Crystal Zenith® and elastomers products at West Pharmaceutical Services, Inc. He provides scientific and technical support and leads various research alliances with academic and commercial institutions to characterize and develop solutions for unmet needs, and has published various peer-reviewed papers. Dr. Vilivalam earned his MS and PhD in Pharmaceutics in 1993 and 1996 from Duquesne University, Pittsburgh, and successfully completed a 2-year business management program in 1999 at The Wharton School, University of Pennsylvania.

Fixed-Dose Combination Products – What's in the Clinic? (Part 3 – Pipeline)

By: Tugrul T. Kararli, PhD, MBA; Kurt Sedo; and Josef Bossart, PhD

INTRODUCTION

In the first two parts of this series, we looked at the past and present situation with regard to fixed-dose combination (FDC) products. In this concluding article, we will take a peek at what's in the pipeline. In the first two parts of this series (Drug Development & Delivery, March and April 2014), we defined what we meant by FDC products and provided an overview of the products that had been approved by the FDA throughout the past 2 decades. A review of these articles will provide a useful introduction to the analysis offered here. Unlike the first two articles that looked only at FDC products approved in the US between 1990 and 2013, this FDC pipeline review examines products worldwide. This analysis doubtlessly overestimates the number of products in development; many companies are more eager to announce product trials than their termination. Data was sourced using the PharmaCircle Product & Pipeline module, as of the end of March 2014.

THE PIPELINE

Collecting, collating, and editing the raw pipeline information provided by the PharmaCircle Product & Pipeline module suggests there are about 250 "announced" FDC products either in Phase I, Phase II, or Phase III development. This figure does not include simple generics of currently approved FDC products, and products targeted to OTC indications. This is a global figure.

THERAPEUTIC TARGETS

The Central Nervous System (including Neurology) was the top therapeutic target for FDC pipeline products, accounting for 22% of all products. This was followed closely by products targeting Infectious Disease (15%), Endocrinology (15%), and Cardiovascular Disease (14%). Second tier indications included Respiratory (8%), Oncology (5%), Dermatology (5%), and Ophthalmology (4%). This

TABLE 1

Therapeutic Category	Pipeline Products	FDA Approved Products
Central Nervous System	22%	8%
Endocrinology	15%	21%
Infectious Disease	15%	12%
Cardiovascular	14%	26%
Respiratory	8%	7%
Oncology	5%	0%*
Dermatology	5%	4%
Ophthalmology	4%	4%
Allergy	2%	5%
All Other	10%	13

* - don't meet the criteria for fixed-dose combination, see notes in text.

Pipeline & FDA Approved (1990-2013) FDC Products by Therapeutic Category

distribution differs from that seen with FDA-approved FDC products, which had a much lower proportion of approved Central Nervous System products (Table 1). At the same time, there is a lower proportion of Cardiovascular products in the pipeline. The increase in Endocrinology pipeline products is largely accounted for by a greater number of products targeted to the treatment of Diabetes. The paucity of approved Oncology products reflects the reality that when approved, most oncology products are not physically combined into a single dosage unit, or a fixed ratio, and don't meet our strict criteria of a FDC product.

PHASE OF DEVELOPMENT

In some cases, individual FDC products are at more than one stage of development where they are being studied for different indications. In all cases, the most advanced stage of development was used as the basis for this analysis. Using this criteria, 36% of pipeline products had reached Phase III, 38% were in Phase II, and 26% had not advanced beyond Phase I. These numbers may be a little misleading. A cursory inspection of the products listed at each stage of development identified several that most likely were no longer in development but had not yet been so listed by the sponsoring company.

Just a few years ago, it might have been safe to conclude there were additional Phase I and Phase II products in development that hadn't been disclosed because of their early stage of development and a company's desire for confidentiality. This would be particularly true for Big Pharma companies. This is much less likely to be the case now with requirements for companies to file clinical trials with American and European regulatory authorities, which are then subject to online listing and discovery.

MOLECULES IN DEVELOPMENT

A total of 340 different therapeutic actives were noted as being incorporated in the 250 or so FDC products in clinical development. The most commonly used actives were: amlodipine (10 products), carbidopa (8), and rosuvastatin (8). An expanded list is presented in Table 2.

TABLE 2

Therapeutic Active	Pipeline Products
Amlodipine	10
Carbidopa	8
Rosuvastatin	8
Oxycodone	7
Estradiol or Ethinyl Estradiol	7
Fluticasone	7
Formoterol	7
Levodopa	7
Atorvastatin	5
Betamethasone	5
Dexamethasone	5
Naloxone	5
Progesterone	5
All Others (<5)	254

Most Common Pharmaceutical Actives in Clinical Stage FDC Products

DELIVERY ROUTES

It will come as no surprise that the majority of products are being developed for oral administration (55%). This was followed by injection (14%), topical/transdermal (11%), and inhalation (8%).

NEW CHEMICAL ENTITIES

The majority of FDC products in development, 81%, incorporated only previously approved actives. The remainder incorporated one, and more rarely two, non-approved actives. Among pipeline products incorporating approved actives, some of these actives are only approved in non-Western markets.

NOVELTY & CREATIVITY

There appear to be few products with the potential for the same therapeutic outcome changing impact we have seen with the antiviral combination products targeted to the treatment of Hepatitis C and HIV. Unsurprisingly, most products in development follow one of several well-validated strategies, a combination of complementary cardiovascular agents, estrogen and progestin combinations, and of course, antihistamines plus phenylephrine.

There are a couple of combination trends worth noting:

1. The combination of a vaccine with an antibody for the treatment of Cancer and Infectious Disease. There are also combinations in development incorporating two antibodies targeted to Cancer indications. These probably don't qualify as FDC products; they most likely will not be administered as a single dosage form, and it's to be expected that the dose of each component will be adjustable. Nonetheless, they represent exciting new combination product strategies that follow in the well validated path of a multi-drug approach to the treatment of Cancer..

2. Combinations of a statin with a separate class of cardiovascular product. This seems to be a variation on the commercially and therapeutically successful strategy of combining an antianginal with an antihypertensive to improve efficacy and compliance. With the increasing use of statins as a baseline therapy for cardiovascular disease, the combination of one or more antihypertensive or antianginal agents with a statin can offer a "one-pill" therapeutic regimen that should improve compliance and outcomes.

FINAL THOUGHTS

There are surprisingly few FDC products when one considers the number of approved pharmaceutical actives and the common practice of combining pharmaceuticals to achieve improved therapeutic outcomes. A couple of reasons for this come to mind. The first relates to the regulatory environment. In the US at least, there is limited regulatory exclusivity, typically 3 years, provided for a new FDC product. This is a sufficiently short period to deter companies from investigating new combinations in the absence of extended patent protection on one or more of the actives, or a patent on the particular combination.

The second reason is the competition provided by "best practice" use of the same agents as separate dosage units. Rather than prescribing an FDC of a beta-blocker and hydrochlorothiazide, a physician may prescribe the same beta-blocker and hydrochlorothiazide as separate dosage forms, in an identical dosage, to reduce the cost of the medication or avoid a formulary restriction. Often, the strategic decision to develop a new FDC product comes down to something as simple as dollars and cents at the patient level.

Fixed-dose combination pharmaceutical products have much to offer in the ongoing task of improving therapeutic outcomes. Future success will depend on the alignment of creative therapeutic insights and commercial incentives. In their absence, we will see more situations in which patients are faced with the reality of remembering to take more pills that are too easily forgotten. The result too often is missed doses and reduced efficacy.

The industry's challenge going forward will be to find the right combination of clinical benefit and commercial return. That would be the sweet spot. ◆

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BIOGRAPHIES

Dr. Tugrul T. Kararli earned his PhD in Pharmacology from the University of Florida and his MBA from DePaul University. Dr. Kararli worked at Searle/Pharmacia for 18 years and held various positions and responsibilities within the Pharmaceutical Sciences department, participating in pharmaceutics, product development, and drug delivery activities. As the Chairman of the Global Drug Delivery Technology Team at Pharmacia, he was responsible for identifying, planning, and executing the drug delivery technology strategies for marketed and development products. Dr. Kararli has authored numerous articles on various aspects of pharmaceutics and drug delivery and holds more than a dozen US and international patents. Currently, he is the Founder and President of PharmaCircle LLC, a knowledge management service company in the drug delivery and pharmaceutical/biotechnology fields.

Mr. Kurt Sedo is Vice President of Operations at PharmaCircle LLC. He earned his BS in Chemistry and Mathematics from the University of Wisconsin Stevens Point. Prior to joining PharmaCircle in 2003, he held various R&D Scientist positions within Searle/Pharmacia's Pharmaceutical Sciences Department in Analytical Development and Drug Delivery.

Dr. Josef Bossart is Managing Director of The Pharmanumbers Group, a boutique research and consulting group providing the biopharmaceutical industry with analysis and insights that improve business outcomes. He has more than 3 decades of experience in the biopharmaceutical sector, including senior sales, marketing, business development, and management positions within Big Pharma, Specialty Pharma, and Emerging Pharma companies. He earned his PhD in Medicinal Chemistry from The Ohio State University, College of Pharmacy.

SPECIAL FEATURE

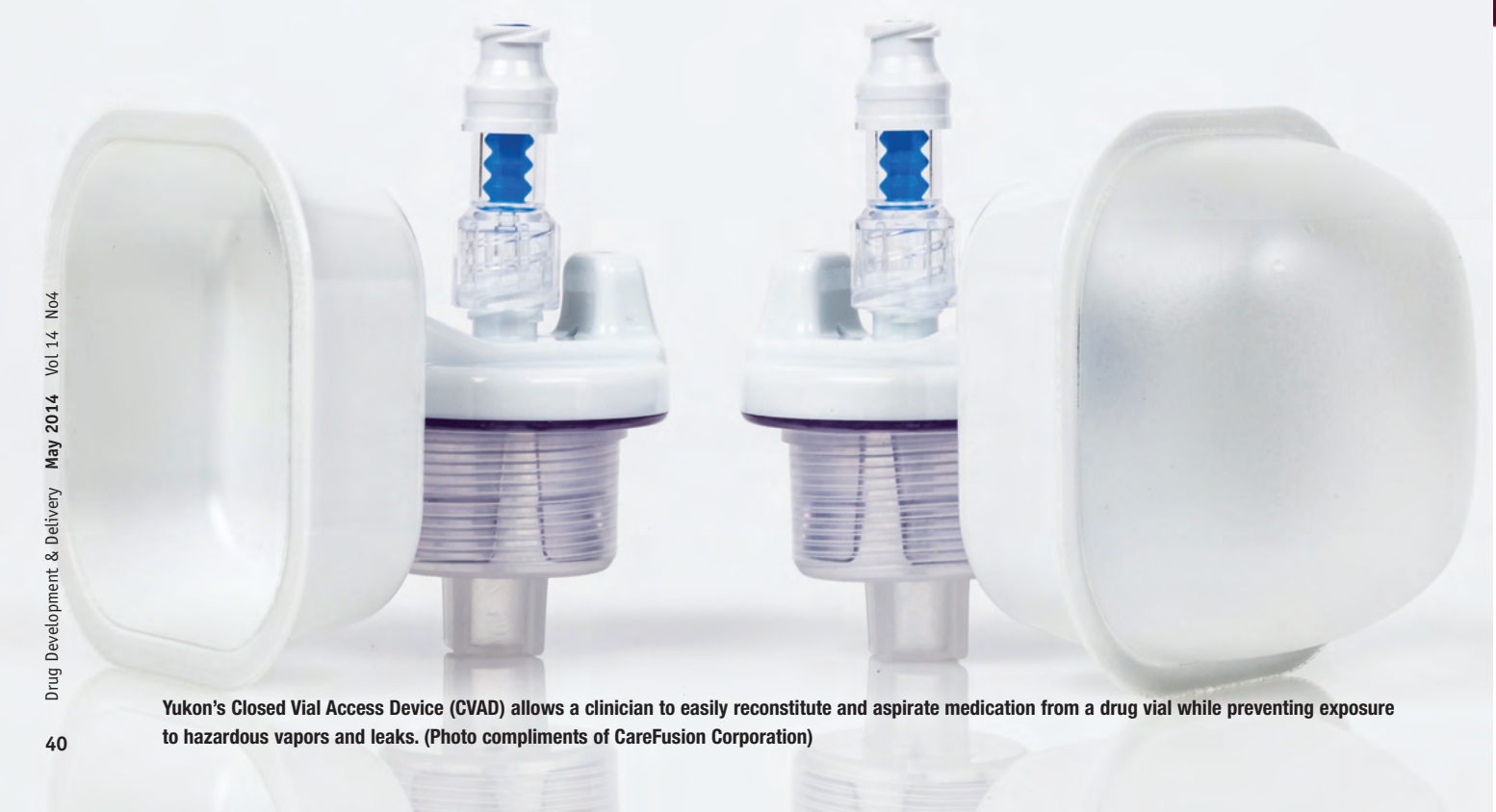
Prefilled Syringes & Parenteral Contract Manufacturing—Product Differentiation Is Critical

By: Cindy H. Dubin, Contributor

After oral drug administration, parenteral delivery is the second most applied route of drug administration. A steady increase in the number of parenteral drugs has led to rise in demand for various advanced drug delivery devices that ensure ease of administration as well as cost containment. Prefilled syringes (PFS) constitute one of the fastest growing segments of the injectable drug delivery devices market. The various advantages associated with prefilled syringes over conventional delivery systems, such as vials and ampoules, have been the primary foundation for their success to date and are expected to continue to drive market growth during the forecast period 2013 to 2019.[1] These advantages include ease of administration, improved safety, reduced risk of contamination, and accurate dosing. Estimates show that the global prefilled syringes market is likely to achieve sales of $6.9 billion by 2018, growing at a compounded annual growth rate of 13.8% from 2012 to 2018.[2]

Depending on the type of material used to manufacture the syringe barrel, prefilled syringes are available mainly in two types, glass prefilled syringes and plastic (polymer) prefilled syringes. Although the industry is witnessing increasing use of polymer by many manufacturers for plastic syringe manufacturing, and plastic syringe use is expected to increase with the development of improved polymers that offer better leachables and extractables profile, glass is still considered the gold standard and will continue to lead the market in terms of revenue and volume. The market for glass prefilled syringes is expected to lose some of its share at the end of the forecast period, which will be eaten up by the market for plastic syringes that will grow at a CAGR of 25% from 2013 to 2019, states the report.

Rapid growth in the biologics market, technical advances in the sector, and rising preference for self-administration using prefilled syringes, autoinjectors, and pen injectors are the major



Yukon's Closed Vial Access Device (CVAD) allows a clinician to easily reconstitute and aspirate medication from a drug vial while preventing exposure to hazardous vapors and leaks. (Photo compliments of CareFusion Corporation)

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factors driving growth of the global market for prefilled syringes. Currently more than 60% of the drugs under clinical development are biologics and are likely to be approved for parenteral administration. This is because most of the biologics including monoclonal antibodies, vaccines, and anticoagulants, are large molecules that need to be administered via parenteral route to achieve the desired therapeutic effect. Likewise, technical advances related with siliconization and needlestick safety and prevention are also expected to drive growth of the market for prefilled syringes.

Based on the promise of the market, there is an increasing number of delivery system companies that provide ready-to-fill/sterile prefilled syringes as well as a rise in contract manufacturers developing the drug for those devices. Several of these suppliers and manufacturers spoke to *Drug Development & Delivery* about the importance of customization and differentiation as the key to pharma companies staying competitive in the prefilled syringe space.

BATTELLE MEDICAL DEVICES—DEMONSTRATING USABILITY

Battelle has extensive experience designing and executing formative and summative usability studies for prefilled injection devices. The company provides turnkey support including: use failure modes and effects analysis (uFMEA) support; protocol development; Institutional Review Board (IRB) coordination; recruiting; data collection; data analysis; and a full range of settings from low- to high-fidelity simulated testing environments. In the past 24 months, Battelle has recruited and tested more than 1,800 subjects and has successfully completed drug delivery device usability testing to help clients achieve two device approvals, with eight more currently under FDA review.

"Usability is no longer a "nice-to-have" concept related to product preference," says Alexa Konstantinos, Director of Business Development, Battelle Medical Devices. "The FDA requires companies to document that they have considered the needs, capabilities, and limitations of the specific user populations who will utilize their injection devices throughout the device development process, and ultimately demonstrate that the device users can safely and effectively administer their specific therapeutics."

To achieve "usability," Battelle incorporates human centric design into all aspects of its work, beginning with an end-user perspective and incorporating the insights of behavioral and cognitive psychology with design and research elements. "Clients utilize our extensive human factors experience in usability testing to mitigate the risks of their injection devices and ensure that they are meeting regulatory requirements for safe and effective use," she explains.

Over the last few years, the industry has witnessed increase intensity of the regulatory requirements for demonstrating usability, particularly in devices for self or caregiver administration. For example, devices such as prefilled syringes, which previously did not require demonstration of usability, now must demonstrate usability for the specific user population based on the therapeutic that they deliver. And while the FDA is expecting human factors studies to be as close as possible to "real use," most studies involve simulation of actual patient application of drug utilizing injection pads on themselves or mannequins. "Battelle sees a need for testing paradigms that more accurately reflect the administration use case," says Chris Muenzer, Principal Research Scientist, Battelle Medical Devices. "We believe that future usability testing requirements will drive human factors studies to have users apply, inject, inhale or ingest a placebo using the proposed delivery system to get an authentic representation of real life use. Such "clinical usability" will be a hybrid of a human factors study and a clinical trial. It will require the standard operating procedures (SOPs) and medical oversight of a clinical trial, but will study usability of the delivery system only and not the clinical effect of the therapy."

Battelle recently worked with a company to support the submission of a generic version of a marketed, combination product. Battelle designed and executed a human factors validation study to evaluate the equivalency of the safety and usability of its customer's device compared with the marketed product. "Because only one step was different between the two

devices, our study determined that intended users could perform the unique step without making errors that had potential for clinical impact," describes Mr. Muenzer. "Another unique aspect of this study was an expected-use scenario where both devices could exist in the same home, potentially causing confusion. Battelle also assessed whether injection-naïve and current users could visually distinguish between different devices and their corresponding instructions-for-use."

Considering the continued upward trend in combination products for self administration, Battelle can foresee a need for higher-fidelity summative studies that include administration of placebo. "While the FDA is not requiring clinical usability testing at this stage, we expect such studies may become necessary in the future to demonstrate usability in cases where the identified use errors are associated with anxiety or nervousness about giving injections," states Mr. Muenzer. "As a result, Battelle is preparing to launch clinical usability services. Our IRB, ISO 13485-compliant quality system for human subjects, and experience designing and executing complex human factors and clinical studies, allow us to take on such studies. We have developed SOPs and infrastructure to capture clinical data, have trained our staff, and have outfitted our usability test facility (uLAB) with the required clinical equipment. We are prepared to capture and analyze clinical human factors data from users' application of placebo to the subcutaneous or intramuscular region, topical application on the skin, ocular application, and oral application."

In the last year, Battelle has partnered with Zogenix to re-envision its 0.5mL DosePro® instantaneous, subcutaneous injection technology for high-viscosity and/or high-volume applications. DosePro is a needle-free, FDA-approved technology with demonstrated delivery bioequivalence to needle-based injection and capability to deliver biological drugs. Battelle has generated a development plan for a next-generation device incorporating the needle-free injection engine of the DosePro system with novel patient interfaces.

"Needle-free injections have a unique capability to deliver high-viscosity formulations into the subcutaneous tissue nearly instantaneously," says Ms. Konstantinos. "This has a tremendous impact on patient compliance when compared with the long injection times of typical auto injectors. With a proven ability to delivery viscosities in 100s cP, this technology can solve both human factors and delivery challenges that are preventing drugs from coming to market."

BAXTER BIOPHARMA SOLUTIONS—STERILE MANUFACTURING ASSURES COMPLIANCE

BioPharma Solutions, a business unit of Baxter, partners with pharmaceutical companies globally to support their commercialization objectives by providing formulation development, lyophilization development/optimization, sterile contract manufacturing solutions, parenteral delivery systems, and customized support services to meet the unique challenges that parenteral products face. Additionally, the company can handle liposomals, highly potent, and cytotoxic material. And, according to Tom Tsilipetros, Product Manager, Baxter BioPharma Solutions, this is the only company worldwide certified by SafeBridge doing both parenteral drug substance synthesis and parenteral drug product manufacturing and testing.

Mr. Tsilipetros explains that Baxter's sterile contract manufacturing business, BioPharma Solutions, has several initiatives to address safety, accuracy, and compliance. "For example, as potential pharma and biopharma customers approach us with the desire to fill product in a vial at our facility, we take the time to educate them on the benefits of considering a prefilled syringe delivery system instead." These potential benefits include less steps and decreased risk of needle stick injury to the product administrator, decreased risk of contamination for the patient, greater dose accuracy, and less overfill required resulting in less product waste (i.e. decreased API cost per unit). Additionally, if a customer decides to

Baxter BioPharma Solutions offers high-speed, high-volume syringe filling and mirrors filling capacity with automated inspection, labeling, and packaging equipment.

launch in a prefilled syringe, BioPharma Solutions offers services to aid clients in making a seamless transition of their products from vials to prefilled syringes.

As an example, he explains how one client was already in a proprietary syringe, but looking to transition into a newer, superior syringe. To help ease the transition, Baxter's R&D group designed a study to evaluate 4 different polymer syringes from different suppliers. The study consisted of a lab fill followed by a variety of terminal sterilization cycles and testing both before and after stability storage. Based on the results that were generated from the study, the client selected the polymer syringe that was most appropriate for its product in terms of compatibility as well as meeting quality standards.

During projects like this, Mr. Tsilipetros says clients tend to express their needs. Due partly to shortages in the market, many customers expressed a desire for diluents. In response, BioPharma Solutions expanded and rolled out a "diluent in a prefilled syringe," which allowed a client to pick a customized fill volume in a 1, 1.25, 2.25, or 3mL size syringe while leveraging BioPharma Solutions' drug master files with expiry dating up to 5 years

"The diluents in prefilled syringes provide increased value and safety for pharmaceutical clients, the end users, and for patients compared to the more common diluents in vials that are available in the market," says Mr. Tsilipetros. "In addition, the diluent prefilled syringes have up to 5-year expiry dating, which is longer than the typical 2-3 years for other diluents in the market. Finally, BioPharma Solutions incorporated a tip cap into our Drug Master Files that has a cleaner extractables profile and does not contain natural rubber, allowing it to be used with more products."

One clear trend that Baxter has identified is parenterals that are biologics. "Upon looking at the pipeline of products that are in development and clinical trials, we estimate that ~70% of them are biologics," says Mr. Tsilipetros. "Because of the concern that some industry experts have with rotary piston pumps potentially causing shearing and aggregation of biologics, BioPharma Solutions has added peristaltic pumps to be used for filling of biologics into syringes to minimize any potential concerns."

He explains how one client with a high-concentration monoclonal antibody wanted to deliver in a glass syringe with a staked needle. The R&D group designed a study to evaluate the product's sensitivity to tungsten and any propensity to aggregate in the presence of silicone. The experiment provided the client with the data to proceed with filling the product in the glass syringe with a staked needle.

Baxter continually evaluates how to enhance/evolve its products and services. One area of enhancement being pursued is in packaging assembly. "As many of the items to be packaged are product specific, we have ensured that we have enough space in our packaging area to add custom packaging capabilities," Mr. Tsilipetros explains.

Additionally, the scientific team at Baxter's Lyophilization Center of Excellence is in the process of developing lyophilization technologies, such as GAP lyophilization, to reduce and optimize lyophilization cycles.

CATALENT PHARMA SOLUTIONS—EXPANDING PFS OFFERINGS

Catalent Pharma Solutions has more than 70 years of experience in providing specialized scientific and manufacturing expertise in complex injectable treatments. In sterile manufacturing, Catalent offers a customizable range of prefilled syringe products, fill-finish processes, and specialty delivery vehicles such as auto injectors. The contract developer and manufacturer offers drug formulation services to aseptic and/or sterile filling, visual inspection, and customized packaging for clinical and commercial scale supply, as well as regulatory advice and support.

In March, Catalent launched its ADVASEPT™ technology for the advanced aseptic filling of injectable drugs. The new platform provides a glass-free, aseptically filled, primary container that reduces or eliminates many concerns associated with traditional glass vials, including the risk of injuries to treatment providers and patients, and the potential for glass particulate contamination and accidental breakage in transit and subsequent product wastage, explains Rutger Vandiest, Commercial Operations Director for Catalent Pharma Solutions in Belgium.

ADVASEPT vial production leverages Quality by Design (QbD) manufacturing techniques that have optimized the blow-fill-seal manufacturing process. Leveraging this form of aseptic processing, a stopper is inserted during the blow-fill-seal process to create a glass-free injectable solution, minimizing the risk of contamination by reducing particles, process steps, and human interaction. Significant reductions in controlled space requirements also drive out

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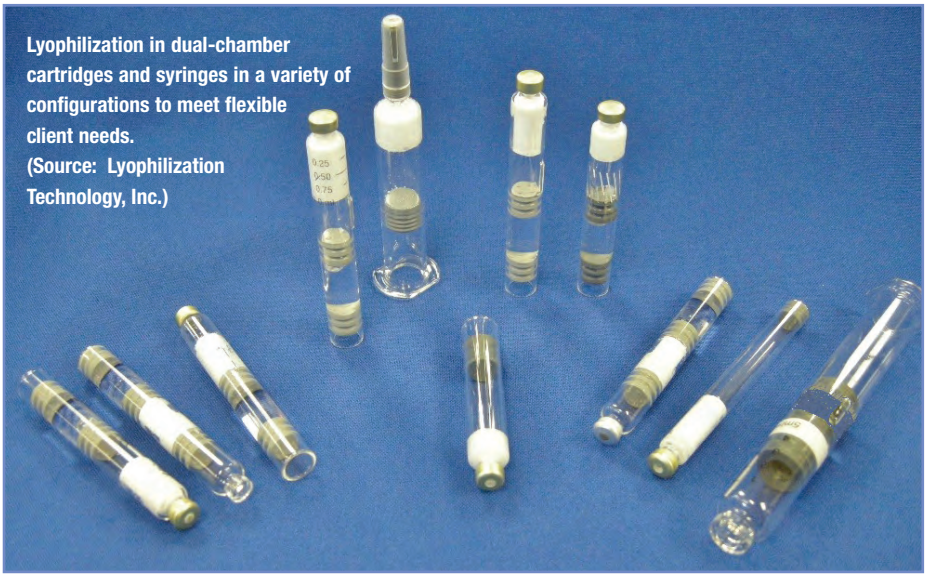
the operational and fixed costs of traditional vial filling while decreasing the risk of contamination, explains Mr. Vandiest. Available with safe, easy-to-open pop-off or twist-off tops, the ADVASEPT vial is currently produced in 10, 50, and 100mL sizes.

Catalent is also expanding its auto-injector platform to enable assembly and packaging of auto injectors from different suppliers in full automatic lines. Mr. Vandiest explains how one client wanted to launch a biosimilar in a prefilled syringe assembled in an auto injector. "We reduced the timelines of the initial project lines to make sure the client would be first to market. That was achieved by a very close and intense cooperation between different departments, such as project management, regulatory support, R&D, and operations and close cooperation between cross-functional teams to coordinate the analytical and technical methods for development."



Lyophilization in dual-chamber cartridges and syringes in a variety of configurations to meet flexible client needs. (Source: Lyophilization Technology, Inc.)

LYOPHILIZATION TECHNOLOGY, INC.—EASING THE HANDLING OF LYOPHILIZED PRODUCT

Lyophilization Technology, Inc. (LTI) provides development, technical support, and Phase I/II clinical supply services. In addition to conventional presentations of product in vials, LTI has the capabilities to develop product formulation and lyophilization process engineering services, as well as offering production of aseptic clinical trial material in cartridges and syringes.

With the emerging trend of home drug administration and the push for patient independence and compliance, lyophilization process engineers can take the process of a traditional container closure system, vial, and stopper, and apply it to the future of drug delivery: the dual-chamber or single-chamber cartridge or syringe. "Being able to successfully apply these concepts to multiple drug delivery formats will benefit the pharmaceutical industry and patient by reducing the time to market, lowering processing costs, and achieving the highest level of product quality," says Michael S. Thomas, Senior Research Scientist for LTI.

Another trend that Mr. Thomas identifies is pharmaceutical suppliers seeking packaging alternatives to suit diverse and complex product portfolios. "This desire for improved product presentations that benefit the health care practitioner and patient is addressed by providing flexibility to drug and device companies by investigating alternative container closure and product combination formats," he says.

To advance its work in alternative packaging, LTI recently collaborated with LyoGo, a design and development company of primary package containers for lyophilized therapeutics. LyoGo invented a drug reconstitution and delivery system that offers an alternative to an internal or external bypass, which Mr. Thomas says transforms any standard primary syringe or cartridge container into a dual-chamber reconstitution system. "This system provides for greater ease of handling and yield for lyophilized pharmaceutical products."

LyoGo was in need of consultation, product development, and production of samples to be used as a platform for promoting the delivery system technology. LTI worked with LyoGo to improve product functionality, develop the appropriate lyophilization cycle, and establish processing techniques.

On its own, LTI has designed a custom cartridge holding device and a semi-automated plunger insertion device for completing development and clinical manufacturing activities. The custom holding device is suited for increasing heat transfer to the product and minimizing edge effect during lyophilization. This holder also allows for ease of washing, filling, and capping of the containers in aseptic manufacturing. The semi-automated plunger insertion device was designed for ease of aseptic plunger insertion both before and after lyophilization, allowing for various configurations of the cartridge or syringe during processing, as needed.

Pfanstiehl's HPLE products are processed under cGMP conditions suitable for the manufacture of Regulated Injectable Formulation Grade Ingredients.

PFANSTIEHL, INC.—USING QUALITY EXCIPIENTS FOR PARENTERAL FORMULATIONS

Pfanstiehl is addressing patient safety by manufacturing high-purity, low-endotoxin (HPLE), multi-compendial excipients for use in parenteral formulations. cGMP production of excipients provides a higher level of control and quality assurance for customers and patients. The company is also executing a program of extensive analytical testing of elemental impurities in advance of evolving industry requirements. In particular, excipients such as sucrose, mannitol, trehalose, and maltose are being subjected to rigorous analysis.

With increasing focus on addressing stability issues in liquid formulations, and on using platform approaches to expedite development, Pfanstiehl has been working with its customers to provide highly consistent excipients for these parenteral platform formulations, while also looking to expand its offerings to address customer challenges that exist in sourcing cGMP-produced components. Typically, high-purity low-endotoxin sucrose or trehalose is used in these formulations for protein stabilization. The versatility of these two excipients has provided the basis for many customers to develop a platform upon which all of their liquid formulations can be built. Cynthia Kerker, Pfanstiehl's President, states: "We are focused on delivering solutions to the challenges brought to us by our customers. We believe that by smartly expanding our high-purity excipients portfolio, we will enable our clients to achieve their formulation goals without compromising on quality."

Pfanstiehl recently introduced new high-purity, cGMP-produced mannitol and maltose excipients for therapeutic formulations. Typically, mannitol is used in combination with sucrose or trehalose in lyophilized formulations. However, there are some clients who use mannitol across multiple platforms, in combination with other excipients. Maltose has been historically used in blood fractionation, but has also found utility as a protein stabilizer in liquid formulations.

The primary advantage of Pfanstiehl's mannitol and maltose excipients is the fact that they are produced under cGMP, in a US-based ICH Q7-compliant facility. This provides assurance to developers that each lot of every product is of high quality, consistency, and is fit for purpose, she says.

Pfanstiehl will be launching several new products for application in prefilled syringes within the next year. While the details are still not public, they will be a combination of cGMP-quality protein stabilizers and solubilizing excipients.

UNILIFE— DIFFERENTIATING INJECTABLE DRUGS

Unilife has created a portfolio of platform-based technologies to address unmet customer needs and emerging market trends for injectable drug delivery. Product platforms include prefilled syringes with integrated needle retraction, drug reconstitution (dual-chamber) delivery systems, auto injectors, wearable injectors, ocular delivery systems, and novel devices.

Stephen Allan, Vice President, Marketing & Communications, Unilife, says the market is shifting from a one-size-fits-all approach to flexible platform-based technologies that can deliver the right drug to the right patient at the right time.

"We've created a broad, highly differentiated platform of prefilled syringes and many other device platforms that enable us to develop customized products that address specific customer, drug, and patient requirements. Our prefilled syringes are designed to minimize steps of use, eliminate the risk of needlestick injuries, and cater to

specific user preference needs. By creating drug delivery systems that are more patient-centric and driven by user preference, we can also help to minimize non-compliance among patients."

Complementing Unilife's strategy is the rise of biologics, the shift to patient self-injection, and the use of devices to differentiate drugs in competitive markets. These trends are amongst those according to Mr. Allan that are driving pharmaceutical investments toward a new model for device innovation. "We call this 'Innovation within a Standard Footprint.' Under this model, pharmaceutical companies are seeking innovative, highly customizable devices that can be integrated with standard fill-finish processes and equipment, and utilize standard materials within the primary drug container. We expect this new paradigm will become the preferred way to commercialize and market injectable therapies moving forward."

In the market for generic injectables, the FDA has raised patient safety concerns regarding the use of prefilled syringes for drugs requiring IV infusion. Problem areas include the spontaneous disconnection, leakage or occlusion of medication, and the lack of a prefilled syringe providing universal attachment with any ISO standard needle hub or IV connector. Unilife developed the Unifill Nexus™ and Unifill Allure™ to address these unmet needs. "With the market for generic injectables shifting rapidly to prefilled syringes, we expect our products will provide significant opportunities for customers when it comes to drug differentiation," comments Mr. Allan.

Unilife continues to invest in the research and development of technologies to enable, enhance, and differentiate injectable drugs, biologics, and vaccines. Its LISA™ auto injector is a new, smart reusable auto injector that allows users to control the speed of needle injection and provides needle-free disposal of a used Unifill syringe.

With Unilife's Unifill syringe, an audible, tactile click signals full dose delivery and users can control the speed of needle retraction.

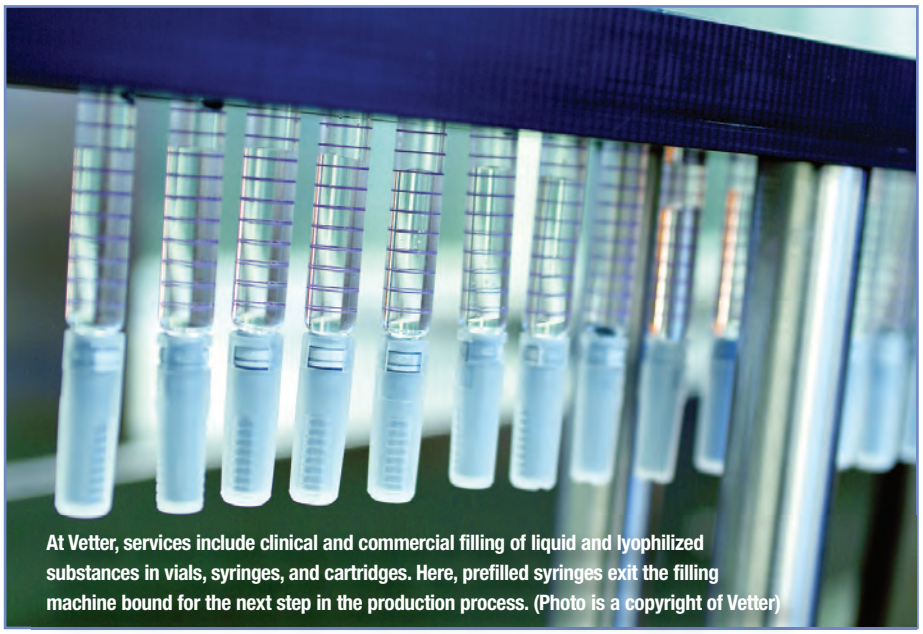
The Unifill platform of prefilled syringes provides automatic and fully integrated needle retraction, making ancillary safety products obsolete, says Mr. Allan. And, Unilife's EZMix platform of dual-chamber syringes requires only one step to reconstitute or mix a liquid or dry drug combination, eliminating the need for preparation kits or multiple pieces of inventory. Additionally, the company's wearable injectors are prefilled, pre-assembled, and ready-for-injection, requiring no terminal sterilization and accommodating dose volumes up to 30mL. Finally, the Ocu-ject system enables precise, accurate delivery of small dose volumes measured in microliters.

VETTER—SERVICES THAT ADDRESS A COMPOUND'S REQUIREMENTS

Vetter is a full-service provider and strategic contract partner to support drug manufacturers from the early phases of drug development through the approval process, and onto long-term market supply. Vetter provides clinical manufacturing of parenterals in Europe and the US, and supports pharmaceutical and biotech firms. This includes packaging material and consultation on the use of auto injectors and pen solutions. Vetter also provides regulatory compliance support. Services include clinical and commercial filling of liquid and lyophilized substances in vials, syringes, and cartridges.

Recent forecasts project a continued growth trend in the injectable sector, but the market is dynamic and continuously changing with ever-growing cost pressures, intensifying competition as well as increasing regulatory demands. "Because complex biologics will be a major contributor to this development, the need for special requirements and handling provided by novel fill and final packaging solutions will be paramount. To stay competitive, product differentiation is critical and demands high priority," says Peter Soelkner, Managing Director, Vetter Pharma International GmbH.

Mr. Soelkner explains that the increasing complexity of compounds often



At Vetter, services include clinical and commercial filling of liquid and lyophilized substances in vials, syringes, and cartridges. Here, prefilled syringes exit the filling machine bound for the next step in the production process. (Photo is a copyright of Vetter)

leads to a higher sensitivity to manufacturing processes and environmental conditions. Handling a sensitive API for one client, for instance, that also had to be filled in very small volumes in a syringe, presented challenges. Such low volumes created significant demands on all areas of the production chain, including process design, technical equipment, and packaging material. "Our manufacturing processes had to be adapted to meet the requirements of this particular product: the exact amount and proper application technique of the silicone coating of the syringe was crucial for the administration of such a low filling volume; the use of inline-weighing systems, designed to minimize API loss; filling had to be monitored; and the employees working in visual inspection required sophisticated training to detect particles in such a small amount of solution."

Biotechnology and pharmaceutical companies outsource their injectable products as a common strategy to stay competitive. The company has established validated processes to handle multi-faceted processes such as siliconization and sterilization that are involved in the prefilled syringe production. In regards to the packaging material itself, a comprehensive and reciprocal supplier management system is vital. Vetter offers a portfolio of primary and secondary packaging options, as well as production capabilities. Sharing information on critical product specifications is very important: robustness of the glass bodies, determining any distress during processing, or the forces applied by the device mechanisms when in use.

In addition to addressing these needs, Vetter sees a growing need for support in early-stage compound development. For this reason, the company has expanded its offering to support clients in early clinical-phase production. In addition to a range of small batch non-GMP and GMP filling capabilities, which include flexible and high-quality equipment, Vetter acquired sophisticated lab technology to enable better control of syringe and cartridge siliconization, improved detection of subvisible particles in drug products, and improved ability to simulate commercial-level processes in the development setting. "Taken together, these changes allow an even smoother product transfer to commercial production and market supply," says Mr. Soelkner.

Given the nature of the industry where time and cost are critical and competition fierce, if a customer is planning to launch first with a prefilled syringe rather than vial-only, the prefilled syringe can help differentiate their product. This is particularly true in a market hungry for patient-friendly systems. Moreover, it may be easier to recruit medical clinics for trials that use prefilled syringes since they require less handling and preparation than vials, and have reduced risk of needle sticks.

For these reasons, Vetter has introduced the Clinical Syringe Standard Package, which provides customers an all-inclusive service, starting with materials selection that includes the best combination of syringe, needle, and stopper to meet a compound's requirements, and continues through cGMP clinical syringe filling. A second package called the Clinical Syringe Starter Package starts with the same materials selection, proceeds through feasibility testing and regulatory consultation, and ends with a non-cGMP stability run. "Even if our customer is not planning an immediate launch in a syringe, predetermining syringe feasibility enables a nimble response to a change in market or business priorities. It may also enhance product attractiveness if they are seeking to out-license the product. Both packages are customizable to the needs of the compound and to the business goals of the innovator," he explains.

With an increasing demand for prefilled syringes, Vetter is strengthening its position as a strategic partner for both the development phase and commercial manufacturing of parenteral drugs by increasing its capacities and service portfolio. Mr. Soelkner explains: "We are currently planning the implementation of three new filling lines within the next few years, as well as further investments in innovative technologies to address regulatory requirements. To accommodate the additional

capacity, Vetter is expanding its storage volume for cold and room temperature products, as well as frozen products."

WEST PHARMACEUTICAL SERVICES, INC.—SMALL AND USER-FRIENDLY DEVICES

West offers contract manufacturing and assembly of device components, as well as collaborative development capabilities. West works with customers from early-concept phase through development, scale-up, and manufacture. Many systems require contract drug filling, so West works with contract fillers to ensure that systems can be filled using conventional equipment. West also offers the ability for secondary assembly of device components, including the potential for handling and assembly of the final drug product. A range of contract testing (both physical and chemical), as well as prescreening and extractable/leachable testing, can also be performed.

"As drug delivery systems become increasingly essential because of the growth in injectable therapies, treatments require regular injections," says Kevin E. Cancelliere, Director, PDS Marketing, West Pharmaceutical Services, Inc. "Pharmaceutical and biotech companies are working closely with drug delivery system manufacturers at an early stage to ensure that there is efficient development of an overall system to enable cost-effective drug delivery." Cost factors may include: the ability to move the product to market as quickly and effectively as possible; reducing in-process rejects caused by breakage or lack of function; and the overall cost of quality, which has to be built into a system from the start.

Prefillable syringes can aid in patient compliance, but most are still predominantly based around conventional glass materials, which may cause safety issues such as breakage. Newer drugs, including those with high viscosity or that need to be administered in high volume, can present administration challenges. To address these needs, West has introduced new materials for prefillable syringes and cartridges, including break-resistant cyclic olefin polymers, such as the Daikyo Crystal Zenith® polymer, and designs that allow for easy and safe injection. These systems are manufactured from a polymer that reduces the risks of breakage, provides freedom from silicone oil, tungsten, or adhesives, and features a FluroTec® barrier film applied to the syringe plunger to ensure that the systems provide the benefits of plastic with the features necessary to contain a sensitive biopharmaceutical.

West's SmartDose electronic wearable injector platform, designed to be small and user friendly, uses a Crystal Zenith cartridge and can hold up to 3.5mL.

After several years of development, West, along with Daikyo Seiko in Japan, scaled-up manufacturing of a 1mL Daikyo Crystal Zenith prefillable syringe system. This is a polymer syringe system with an insert-molded needle and contains no glue or tungsten. The fully validated syringe system is provided in a sterile tub and nest format, and has been designed to be compatible with existing filling equipment. West has collaborated with contract filling service companies to provide customers with a fully integrated system for obtaining a filled syringe that is ready for stability studies. "Several customers are at various stages within their marketing application processes, and we expect that this system will become a syringe of choice for many new or existing biologics where problems of quality, breakage, extractables, and drug interaction could be a challenge with glass syringes," says Mr. Cancelliere.

Also, to add to its current self-injection technologies, the SelfDose technology platform offers a design to meet patient needs for easier self injection. West recently completed the acquisition of the SmartDose electronic wearable injector system. The SmartDose electronic wearable injector platform uses a Crystal Zenith cartridge, and can hold volumes up to 3.5mL; the system has been designed to be small and user friendly. "The SmartDose system is the result of a multi-year co-development program with the innovators of this system, and we are ready to support customers' early-phase evaluation of this system through active scale up and validation programs," he says. "In 2013, we completed a successful first-in-

human study, following extensive scale-up and validation of the injector and the Crystal Zenith prefillable cartridge system. The system enables higher volumes of drug to be injected slowly, and can offer patient benefits in terms of reduced frequency of injection."

The 1mL prefillable syringe system and the cartridge for the SmartDose system are based on the Daikyo Crystal Zenith polymer. In addition to a specifically developed and proprietary polymer, the molding, inspection, and final packaging processes have been developed and validated to ensure the highest levels of quality and cleanliness to meet the requirements of customers. The molding process has been developed to incorporate an insert-molded needle, which is secured without the need for adhesives. The specially-designed FluroTec plunger does not require silicone oil lubrication. West's ConfiDose 315 technology platform with a customized, large capacity (1.5mL) Daikyo Crystal Zenith syringe offers the opportunity for a smaller, more patient-friendly injection system.

Developed more than 20 years ago, the Daikyo Crystal Zenith polymer is currently in use with more than 30 marketed drug products. However, the transition to polymer syringes has been slow in a very conservative market. Mr. Cancelliere explains: "Recent trends are driving a wider adoption, so we anticipate a strong focus on these types of syringe systems in the coming years. The design flexibility of plastic offers the ability to create more innovative syringes and containers, and to integrate these containers within devices tailored for the needs of patients."

YUKON MEDICAL, LLC—IMPROVING MEDICATION PREPARATION FOR INJECTION

Yukon Medical offers several customization services for its products, including primary container compatibility adjustments, modifications for branding purposes, private labeling, and drug kitting, as well as new concept development.

Over the past year, Yukon Medical has launched six new vial access devices that provide a safe way to accurately prepare injectable medications. "These products were designed to be easy to use, eliminate needles, minimize residual volume, increase attachment security to the vial, and minimize exposure to vapors and leaks," explains Todd Korogi, President & CEO of Yukon Medical. There are several versions of varying features and cost, depending on the need for each preparation.

Yukon's Closed Vial Access Device (CVAD) allows a clinician to easily reconstitute and aspirate medication from a drug vial while preventing exposure to hazardous vapors and leaks. The CVAD contains the vapors and fluid while preventing contaminants from entering the vial. A vapor retention bell provides a barrier to the toxic vapor that is generated during reconstitution of hazardous drugs. The CVAD also utilizes pressure equalization valves that keep the vial at neutral pressure while retaining any vapors produced in the retention bell. In addition to the CVAD, Yukon has launched the vented ViaLok® product line, which features a locking shroud and a 0.2 micron air vent to prevent ingress of microbes and is best suited for non-toxic preparations.

"As hospital pharmacies and outpatient clinics move toward closed-system transfer devices (CSTDs) for the preparation and delivery of hazardous drugs, our CVAD has been shown to be both mechanically and microbiologically closed and offers additional protection for healthcare workers and patients in the preparation and delivery of hazardous drugs," says Mr. Korogi. "Our focus is to continue to increase caregiver and patient safety while reducing the steps required to prepare medication for injection. We are working on a new product now that leverages some of our existing technology but adds new technology that will address some of the issues around pre-filled syringe connections." ◆

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DRUG DEVELOPMENT Executive

NORWICH PHARMA SERVICES: SYNCHRONIZED OUTSOURCED SOLUTIONS FOR CONTRACT DEVELOPMENT & MANUFACTURING

Kristen Arnold, PhD
VP, Product Development & Technical Services
Norwich Pharma Services

"Our ideal customer is a virtual or small- to mid-size specialty pharmaceutical company that is looking for a true partner in its drug development and manufacturing needs. We like to believe that we are not just a provider who is a "pair of hands" but a partner who will really collaborate in the process. As drug compounds move through the development phases, we work closely with customers to ensure the drug is proceeding according to the development plan, timeline, and budget."

Norwich Pharma Services, located in Norwich, NY, is a recognized leader in full-service contract pharmaceutical development and manufacturing. Norwich's predominant focus is developing and manufacturing solid oral dose tablets, and capsules. Norwich's base manufacturing capabilities include in-bin and V blending, high shear/low shear/ fluid bed granulation, fluid bed drying/top spray granulation/ bead/pellet coating, tableting, encapsulation (powder, pellet, tablet, combination, and liquid fill), pan coating, and tablet printing. Norwich's packing capabilities include both blister and bottle packaging.

Through its Synchronized Outsourced Solutions, Norwich offers customers a single-source provider with the highest level of quality and reliability from product development and Phase I-IV clinical trial materials and bio-studies, to scale-up and commercial manufacturing through clinical services. For more than 127 years, Norwich has built a reputation for dependable product supply and established an unparalleled history of regulatory compliance. Drug Development & Delivery recently spoke with Kristin Arnold, PhD, Norwich's Vice President of Product Development and Technical Services, to discuss the company's long history in pharmaceutical manufacturing, Norwich's evolution as a contract development and manufacturing organization, the "perfect" client, and Norwich's role as a service provider from start to finish.

Q: Norwich has been manufacturing pharmaceuticals for many years. Can you provide our readers some of the history?

A: Norwich Pharma Services began as Norwich Pharmacal Company in 1887. Through the years, and under various owners, it has been named Morton – Norwich Products, Norwich Eaton, and OSG Norwich Pharmaceuticals. In 2007, the site was sold to Alvogen, and the name changed to Norwich Pharmaceuticals. In October 2013, the name was changed to Norwich Pharma Services to reflect the company's role as a contract services provider. With such a long history, the site holds a very special place in the community.

Q: What services does the company offer?

A: Norwich is a full-service contract development and manufacturing organization. We offer services from Phase I product development through pilot scale, clinical production, scale up, registration, clinical services, and commercial manufacturing. In addition, we are able to help our customers with product optimization and formulation troubleshooting solutions.

Q: What type of products do you work with at Norwich?

A: We work with both immediate- and modified-release products. We have experience with standard tablets and capsules but also work with unique dosage forms, such as laser-drilled tablets, extruded and spheronized beads, Wurster coated beads, tablet-in-tablet, granules, and mini-tablets.

Q: Can you tell our readers about Norwich's development facilities?

A: Norwich's development and pilot-scale facilities are located within 8,000 square feet of space that is DEA approved, solvent, and potent compound (OEL3) capable. We have two dedicated areas, one for development and the other for GMP pilot-scale batch manufacture. We support all phases of drug development. In addition, we have an analytical laboratory dedicated to our development group. They are skilled at developing, transferring, and validating methods, and they perform all of the testing on our development batches. The development and pilot-scale facilities, equipment, and technology mirror Norwich's commercial capabilities. This allows for a direct transfer from the pilot plant to commercial operations and from the analytical laboratories to quality control laboratories, enabling a fast transition to the market.

Norwich has made substantial capital investments in its pilot-scale facilities throughout the past 3 years. In the past 12 months, Norwich nearly tripled its pilot-unit capacity to a total of 19 rooms. This expansion provided an increase in overall capacity as well as added new capabilities to handle higher potency products. Each of the 19 units has the ability to handle Occupational Exposure Limits (OELs) for drug potencies ranging from category 1 to 3.

Q: What would you describe as Norwich's "ideal" customer?

A: Our ideal customer is a virtual or small- to mid-size specialty pharmaceutical company that is looking for a true partner in its drug development and manufacturing needs. We like to believe that we are not just a provider who is a "pair of hands" but a partner who will really collaborate in the process. As drug compounds move through the development phases, we work closely with customers to ensure the drug is proceeding according to the development plan, timeline, and budget. As we progress, and the development and process learnings are realized, we work closely with our customers to make rapid response adjustments/revisions to keep the program on track.

Q: Sourcing APIs from a single source can pose a challenge for drug developers. What can Norwich do to deal with this issue?

A: Norwich had a recent experience with this challenge while preparing for a commercial launch with one of our long-term customers. The market projections on this particular product had increased causing a probable API supply issue. Our customer responded quickly and engaged another API supplier, but the physical properties of the new API were different than the current supply used for finished dosage development. The issue was further complicated by the high percentage of the API in the finished product. Norwich quickly developed a Design of Experiments (DOE), which provided operating ranges that would accommodate both sources of active. Because Norwich had partnered with this customer from the beginning of finished dosage development, Norwich had substantial experience the client was able to leverage in resolving this supply issue.

Q: What does the future hold for the industry, and what has your facility done to prepare for it?

A: Within the solid dose market, there is both good news and bad news. Overall, growth in solid dose products has been stagnant, and there is adequate capacity in the industry to handle demand for the near future. However, within certain niches of the solid dose market, there are opportunities for Norwich, due to our focus on complex solid oral dosage form delivery.

Traditionally, these specialty type products can be manufactured much more efficiently in equipment that is sized for the product demand. Norwich has put an emphasis on being just the right size in terms of equipment offerings as well as its overall service offerings, particularly for specialty pharmaceutical and virtual companies. ◆

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CLOUD COMPUTING

Enabling Better Collaboration in the Cloud

By: Peter Shaw and Yury Rozenman

INTRODUCTION

In the laboratories of today's pharmaceutical companies, pressure is building - pressure to develop drugs faster and cheaper; to comply with stringent security and compliance requirements; and to maximize the expertise of colleagues across time zones and geographies. At the same time, there is growing pressure to properly optimize, manage, transfer, store, and protect the vast quantities of data that are being created. In fact, many life sciences companies need tens of thousands of gigabytes of data for experimental runs.

Increasingly, pharmaceutical companies have steered clear of conducting drug research entirely in-house, preferring to work with a constellation of partners, such as CROs, small biotech firms, and academic groups to advance research and development breakthroughs. However, this collaborative approach requires a new way of working.

The pharmaceutical industry has reached a crucial inflection point, requiring access to new working methods and tools. But where should the pharmaceutical industry look for answers to these real-world challenges? The answer is simple - the cloud.

THE CHALLENGE

A key goal for pharmaceutical companies is to be able to identify successful and innovative drug compounds that will make it to the market as quickly as possible, as well as identify those that are likely to fail. Additionally, as the development of new clinical products becomes more complex, government compliance regulations have become increasingly complicated as well. With shrinking drug pipelines and ever-complicated regulations to follow, companies are investing in better collaboration, standardization, and analytical tools to improve R&D productivity, as well as their sales and marketing operations.

As the market for new drugs advances, reliance on efficient communication and collaboration strategies between partners is also evolving. However, to ensure patient safety, meeting compliance mandates can take priority over integrating new technologies. Coupled with the explosion of data resulting from the drug discovery and development process, companies have had to look to other industries to implement enterprise software systems that allow researchers in laboratories around the world to collaborate.

THE SOLUTION

There have been many technologies that have sworn to transform the drug discovery and development process, but many may fail to deliver on all the benefits promised. For example, high-throughput screening (HTS) promised to allow drug screening laboratories to "process" several tens or even hundreds of thousands of molecules per day. However, the results of contemporary HTS are often composed of false positives and false negatives, and relatively expensive. Another introduced technology that missed the mark is the Laboratory Information Management System (LIMS), which promised to take

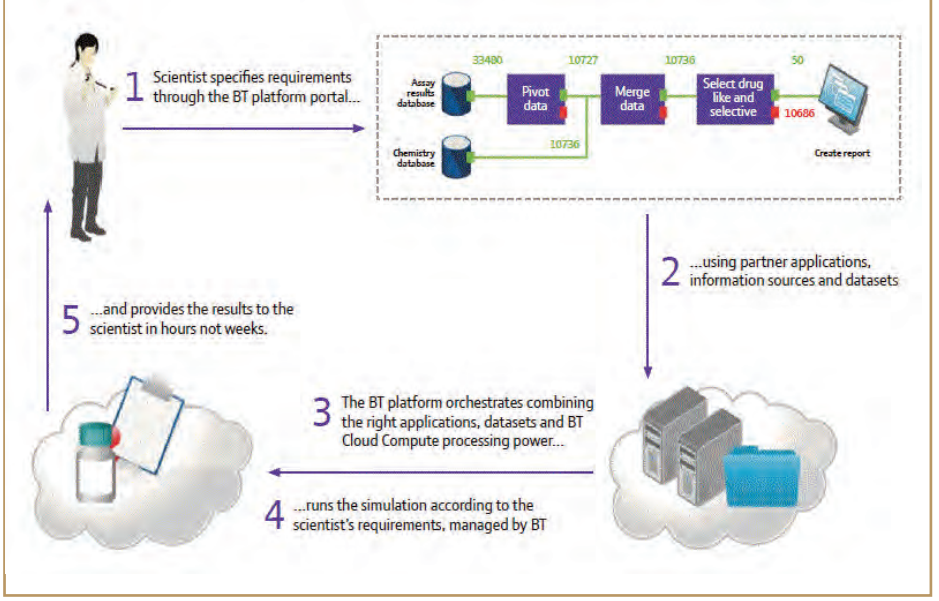
large sets of data and deliver paperless results. However, many customers found themselves unsatisfied with the difficulty of use and vast amount of training required. With these disappointments in mind, adapting to another new groundbreaking technology may seem difficult. But the reality is, cloud computing is already making it easier and less expensive for companies and clinicians to deliver new drugs and analyze data that used to take years and tens of millions of dollars to complete.

The beauty of cloud computing is it enables virtually unlimited computing resources on tap - allowing pharmaceutical researchers to scale their computing environment up or down, when they need it. With cloud computing, it's easier for companies to adapt solutions to their specific needs. For instance, BT's Cloud Compute life sciences platform can deliver specific pharmaceutical applications across the value chain all the way from discovery to commercial operations, ensuring that necessary applications can work across pipelines rather than force-fitting one application to all pipeline teams.

Beyond cost savings, there are multiple business advantages of cloud computing for the pharmaceutical industry. Cloud computing has existed for years, but it has recently experienced a boom in attention among business sectors looking to analyze and manage massive amounts of data. The main impact of cloud computing to pharmaceutical companies is that it creates a reduced dependence on internal infrastructures and streamlines operations across the globe. In some cases, the preference is to do some initial data reduction locally, due to compliance issues and data protection policies. However, a few of the primary advantages of cloud computing deliver several advantages, including the following:

FIGURE 1

How the virtual workbench empowers scientists



Scalability: As a business grows, so does the availability and capability of what can be stored and manipulated in the cloud. This is especially important given the peaks and troughs in pharmaceutical research. For example, let's say a company finishes a clinical trial in which its dataset is stored on machines that are 100% occupied, and the company needs to add two more clinical trials. With cloud computing, the company could easily access more storage and computer power, and complete the analysis of this information. It could also do more specific queries and look at cross clinical trials or look at how two competitive drugs perform in the clinical trials. In the past, the simple fact is most companies just didn't have that access to such a significant computational estate because it was too costly, and they would have had to provision it for peak usage. By leveraging cloud computing, companies now have access to much more elastic and scalable data storage options.

Flexibility: Instead of relying on one application, companies can easily build their pipeline and test different applications under different environments, simultaneously, with no concerns about data storage or demands. By freeing scientists from the boundaries presented by data processing constraints, today's laboratories can work faster and smarter. No longer do they need to spend precious time worrying about IT configurations and available server space. As a result, scientists can make earlier predictions about potential drug candidates, while also identifying earlier what drugs should be eliminated from the discovery process. Further, cloud computing allows scientists to trace what information has been used in data analysis and can be used to tackle highly parallel computational problems. Even on the commercial side, companies can use the cloud platform to evaluate trends in the industry, such as the impact of discontinuing a drug.

Global Connections: Because the cloud can be accessed anywhere and at any time, this also enables companies to share information more quickly, easily, and efficiently. Pharmaceutical companies can scale project teams up and down - based on the number of trials they are running - regardless of the location of various team members. The global infrastructure of the

cloud platform delivers connectivity, visibility, agility, and collaboration necessary for performing in a global marketplace. For example, if a lead pharmaceutical researcher is in France working on a project, at close of business, he can easily hand off his work to a scientist in the U.S., who can then pick up and access the project exactly where he left off. In turn, a colleague in China can come in later and access the results, using the same resources as colleagues in the U.S. or France. The cloud helps to essentially eliminate down time and allows companies to easily continue priority work, 24 hours a day.

Ease of Use: As we're all aware, the pharmaceutical industry can be quite unique in terms of how it operates, how it submits information to regulatory agencies, and how it complies. Using the cloud platform makes it easy for pharmaceutical companies to work collaboratively both internally and externally, providing for better integration of all the moving pieces of data associated with the life cycle of a drug.

Regulatory Compliance Adherence: A cloud platform can offer a simpler way to comply with various regulation requirements. This is because cloud-based systems are often more secure and more compliant than an on premises system, as they are designed and maintained - and continually updated - to address the latest security risks and regulations. BT even offers a GxP-compliant variant of its cloud platform.

SUMMARY

While the benefits of cloud are clear, stepping into the cloud can seem a bit overwhelming at first. When choosing the best cloud platform for your business, you should first research the type of environment you need, which applications are right for the cloud, the benefits of each platform, and how to prioritize the environment. Then, identify which applications are driving the business and which need separate, stand-alone environments, as you won't want to reengineer an entire application for a cloud strategy. At BT, a team of advisors works closely with pharmaceutical companies to help prioritize applications and determine which applications can provide the greatest return on investment and which applications are easy or difficult to transition into the cloud. Cloud computing enables pharmaceutical companies to share information in real-time, run the same program across several connected computers simultaneously, analyze results more quickly, and communicate across the globe with colleagues seamlessly. It truly allows pharmaceutical companies to maximize productivity, collaboration, and resources. This is an exciting time for the pharmaceutical industry to discover the promises that cloud technology holds.

Can cloud computing relieve the growing pressures that are building in the pharmaceutical industry? It offers elasticity and scalability for storing and processing large amounts of data, which all growing labs can find use in. It's a flexible platform that allows for simultaneous testing across applications. It enables employees to collaborate strategically, without disruption, in a global marketplace. It's cost effective and easy enough to use that it helps to reduce the dependency on internal infrastructures alone. In the drug discovery game, the cloud does more than just relieve the pressures to develop drugs faster and cheaper, remain compliant, and maximize global expertise - it spurs innovation and promotes efficiency. ◆

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BIOGRAPHIES

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Yury Rozenman is the Business Development Director for Pharmaceutical with BT Global Services since 2005, where he is responsible for marketing and sales strategy of BT's solutions portfolio and proposition development. The main four areas Mr. Rozenman focuses on are Clinical Development, Regulatory Compliance and Risk Management, Supply Chain, and Sales & Marketing. Previously, Mr. Rozenman held positions as Director of Information-Based Medicine Strategy at IBM Life Sciences and Director of Life Sciences Division at Platform Computing.

Optimizing a Full-Package Strategic Alliance for Clinical Development Services

By: Kamaljit Behera, Team Lead, Beroe Inc.

INTRODUCTION

Pharmaceutical and biopharmaceutical companies are confronting a fundamental productivity challenge. In the past two decades, R&D cost has increased significantly, yet the rate of innovation is diminishing and so is the success rate of new drugs launched in the global market. Figure 1 illustrates annual R&D spending versus new drug approvals. In addition, revenues of these companies are at risk due to current and expected patent expirations. Figure 2 illustrates the pharmaceutical industry sales at risk from patent expirations.

Analyzing the operating model of a pharmaceutical company in the late1980s reveals a fundamental error - "too much ownership" - of non-core activities within the internal operations for the drug discovery and development process. This in turn was diluting efforts toward innovation and efficiencies (ie, against the concept of core competency).

To overcome this situation and burnout effect caused due to under productivity, pharmaceutical and biopharmaceutical companies have been embracing the path of externalization; by converting their fixed costs into variable costs.

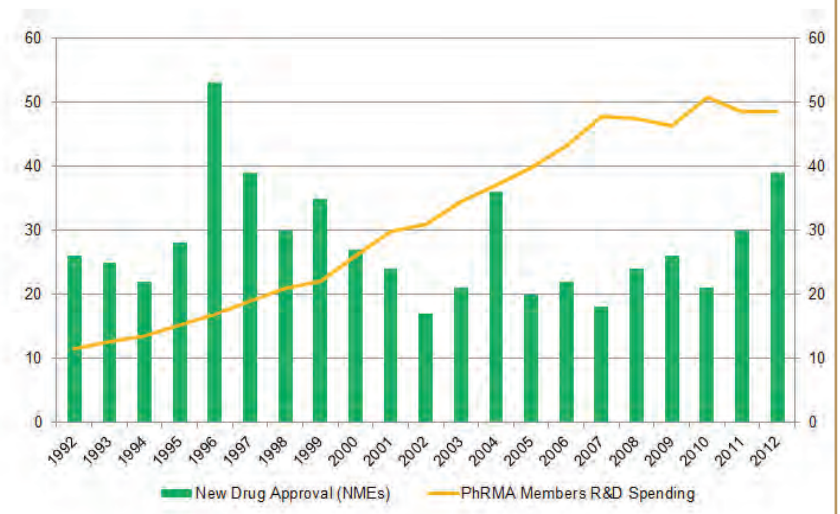
However, with increasing prevalence of outsourcing in the past decade, many sponsors have adopted the path of full-package strategic alliances (umbrella deals) with leading global CROs, most of which are falling short of their desired results.

Some of the major reasons for the failure of these full-package strategic alliances can be attributed to the following factors:

- Lack of proactive assessment of synergies across categories and functionalities and identifying the optimal level of externalization across clinical development services
- Inefficient competency assessment in the course of vendor selection process (ie, mapping vendor's core competencies)
- Alliance implementation & scale-up challenges

The following discusses these challenges, which are critical gaps to be addressed by the next-generation of clinical development category managers, specifically, deciding the optimal level of externalization rate across clinical development categories to improve operational efficiencies and flexibility, and identifying the potential vendors and the scope of engagement (functional and/or multi-functional), while leveraging their functional core competencies and

FIGURE 1



Risk due to the increasing R&D spend and diminishing NMEs in the global market.

inter-functional synergies to ensure best-in-class quality, innovation, and efficiency.

EXTERNALIZATION OF CLINICAL DEVELOPMENT SERVICES

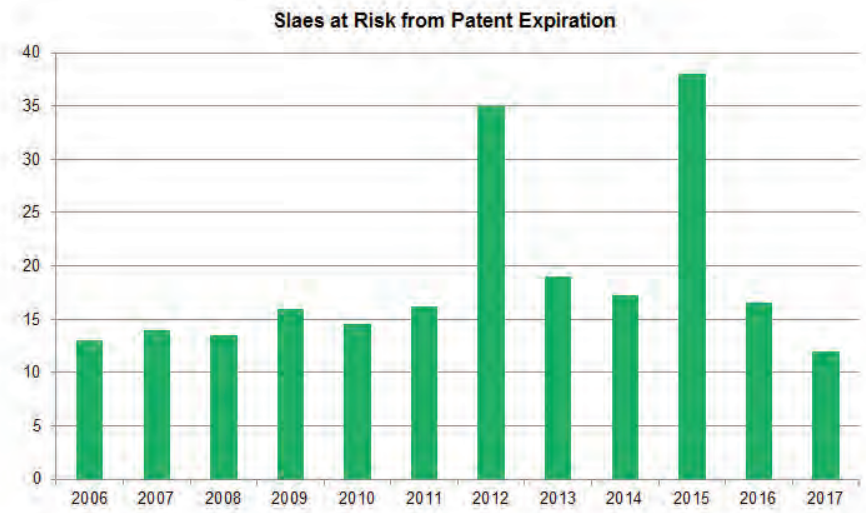
In the past 10 years, the level of externalization by large pharmaceutical and biopharmaceutical sponsors has increased from 15% to 20% to 40% to 60% across clinical development services. This is primarily driven by increasing cost pressure following the patent cliff to supplement capacity and expertise required to fuel innovation into their R&D operations.

Clinical development in general involves a large number of distinctive services. Some services are highly human skill oriented (eg, clinical monitoring, biostatistics, CDM, investigation, etc), while some require high-end equipment and processes as enablers (eg, sample archiving, central lab, etc). At the same time, some services like site management, patient recruitment, etc demand intense networking in the industry to ensure global-scale clinical trial operations.

Today, external vendors like full-service CROs, and functional service providers like SMOs, PROs, AROs, and niche vendors are playing an integral part in bridging this gap of innovation with cost efficiencies and operational flexibility, across clinical development operations for large pharmaceutical and biopharmaceutical sponsors.

In the drug discovery and development (D&D) value chain, the clinical development category is one of the critical operations in terms of spend (cost of operation), time, and innovation. At present, more than 50% of the clinical development operation for global sponsors is being managed by these external vendors.[1-4]

FIGURE 2

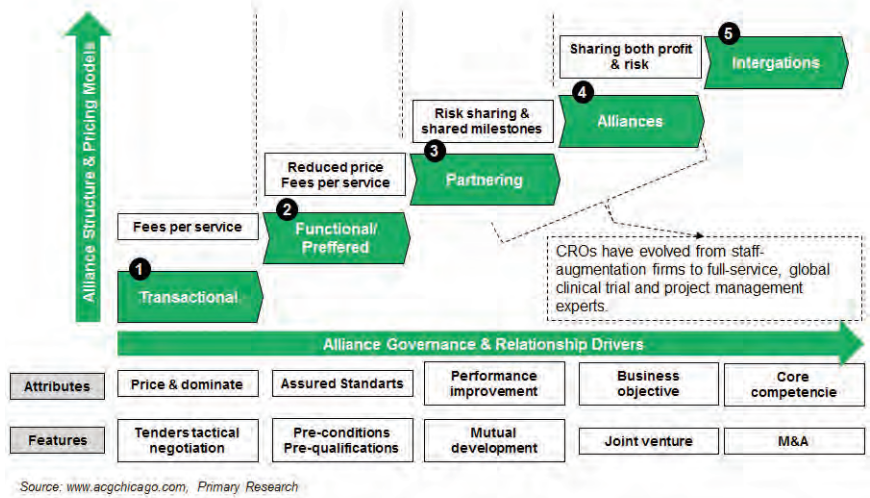


Risk due to the current and expected patent expiration.

ALLIANCE STRUCTURE: TRANSITION FROM COST-FOCUSED TO VALUE-FOCUSED PARTNERSHIP

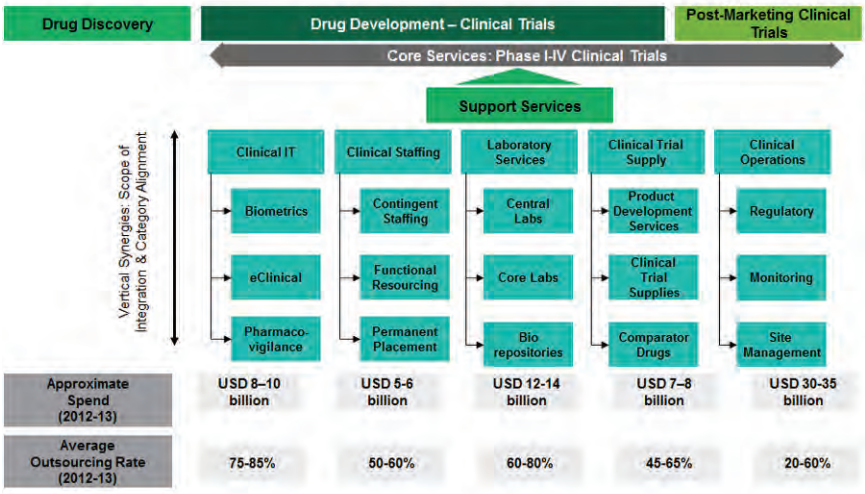
With time, the client-vendor relationship has undergone restructuring from ad-hoc contracts to preferred relationships on both sides for global alliances mainly focused on the regional or disease-specific clinical development requirements of the sponsor. As the vendors, especially functional and full-service CROs, are increasing their array of competencies to bridge the innovation gap; sponsors are placing increased emphasis on managing alliances with preferred vendors that provide competitive advantage with greater scale and efficiency. Figure 3 illustrates the pharma-CRO alliance structure and transition from a cost-focused to value-focused partnership.

FIGURE 3



Alliance structure and transition from cost-focused to value-focused partnership.

FIGURE 4



Possible synergies and scope of integration across functionalities/categories

CURRENT SUPPLY MARKET FOR CLINICAL DEVELOPMENT SERVICES & ITS CHALLENGES

In the past 2 years, the supply market for clinical development has witnessed a great deal of consolidation, especially from the global full-service CRO front. The acquisitions and collaborations among six large well-known CROs in the outsourcing world and recent IPO for the largest CRO show that investors still find the CRO market to be attractive, especially in the US, for future investments. Other examples include privatization and consolidation of mid-size CROs.

By providing a complete portfolio of drug development services from discovery through commercialization, under a multi-functional strategic alliance relationship, global full-service CROs are expected to take on much of the operating risk and provide most of the execution and project management resources. Also, the globalization of clinical trials and the ever-increasing dependency of sponsors have raised new operational challenges for full-service CROs, such as their declining productivity, while the spending associated with clinical trials is increasing:

- The productivity across the CRO industry has dropped more than 70% over the past decade[5,6]
- In the CRO industry, overall spending was about $11.5 billion in 2010 and is estimated to exceed $20 billion by 2017[7]

Inefficiencies across high-spend categories and pressure for global capacity expansion include:

- Over capacity in certain preclinical areas has reached 20% to25%. For example, toxicology services in particular have seen significant facility closures and price discounting
- Even the cost of conducting clinical trials in emerging countries is increasing more rapidly compared to developed regions like the US and EU. For example, the average annual increase in cost per patient in Phase II-III: LA = 17%, Eastern EU = 12%, Asia = 11%, Western EU = 9%, and US = 6%)
- The overhead rates are one of the major issues for many CROs managing clinical studies. About 25% to 30% in some categories and

TABLE 1

Vertical Scope of Integration			
Clinical Development Functionalities	**Categories**	**Current Vendor Base**	**Future Scope of Integration**
Clinical IT Services	Biometrics Services & Pharmacovigilance (PV)	Global ITEs & CROs with dedicated functional focus	Specialized eClinical providers like Medidata, BioClinica, etc can forward integrate to provide biometric services. Backward integration for global ITEs & CROs may not be a viable option.
	eClinical	Specialized eClinical & IT platform providers	
Laboratory Services	Central Lab & Biorepositories Services	Global Central Labs & CROs with dedicated functional focus	Global CROs like Covance, Quintiles Parexel, etc. who currently have dedicated functional focus for Central Lab and Biorepository services, may integrate one or more services under core labs. It is difficult for the Core Lab vendors to extend their service offerings into capital intensive and complex categories like Central Lab or Biorepositories.
	Core Lab Services	Specialized ECG or Spirometry or Imaging vendors & Functional Core Lab vendors	
Horizontal Scope of Integration			
Clinical Development Categories		**Current Vendor Base**	**Future Scope of Integration**
Clinical Data Management & PV Services		Global ITEs & CROs with dedicated functional focus	The increasing prevalence of virtual/ risk-based monitoring provides 40% to 50% scope of integration to global pharmaceutical and biotechnology sponsors across services like clinical trial monitoring and clinical data management.
Monitoring Services		CROs & Clinical Staffing	

An example on how to accesses the synergies and scope of integration across functionalities and categories of clinical development services.

in countries like the UK, it may be up to 30% to 40%

- Medical innovation, financial consideration, and study-specific complexities as well as stringent regulations like standard of care (SoC) for patients/subjects coverage are some of the major challenges associated with globalization of clinical trials.

SUBCONTRACTING RISK WITH FULL-PACKAGE ALLIANCE DEALS

Due to the resource crunch in the global clinical trial market, global full-service CROs are compelled to subcontract some of their operations (services not aligned to their core expertise) to organizations who have functional and local expertise for such services as clinical trial call centers, patient recruitment, clinical supply management, clinical staffing, etc mainly to ensure patient enrollment, avoid fixed costs, and mitigating operational challenges in emerging markets like China, Africa, Latin America, and Southeast Asia.

Subcontracting a clinical trial by a CRO may fragment the clinical trial-related assignment further and can lead to a lack of comprehension about the entire trial process (ie, lack of supply chain visibility). Recently, global regulatory authorities like FDA, EMA have raised concerns about the violation of global regulatory and quality compliances (like GCP/cGCP, GMP, GDP, SoC, etc.,) due to subcontracting in the Pharmaceutical industry.

FIGURE 5

Clinical Trial Monitoring Services	Medical Expertise	Technology Expertise	Integration Scope
Monitoring compliance with protocol and regulations			
Verify subject eligibility and informed consent			Yes
Ensure reporting of adverse events			
Review and verify data			
Management of study site related problems			
Study site preparation for FDA inspections			
Site qualification, initiation, monitoring and closeout			Yes
Ongoing site management & communication			
Recruitment planning and tracking, troubleshooting, staff training and motivation			
Flow of data between CRAs and Data Management/Biostatistics department			Yes

Clinical Data Management Services	Medical Expertise	Technology Expertise	Integration Scope
CRF/eCRF designing			Yes
Data management plan			Yes
Data base design & set-up			Yes
Import/Export set-up			
Dictionary set-up			
CRF tracking set-up			Yes
Data entry, loading, review			
Clinical data coding			
Document management			
SAE reconciliation			
QC, database audit			
Adverse events			
Evaluation of medical data			
Periodic review & QC			
Closure of interim, final database			Yes
Database lock			
Analysis & reporting			Yes

High Medium Low

Integration scope shows color coding for services. Services with similar color has the highest scope for integration.

Note: maturity in vendor base and increasing adoption of technological platforms are expected to promote integration by 40-50% for services across clinical trial monitoring (risk-based/virtual monitoring) and clinical data management.

FUTURE SOURCING OPTIONS FOR CLINICAL DEVELOPMENT SERVICES

Identifying Synergies for Functional Integration & Leveraging Core Competency

Most of the global pharmaceutical and biopharmaceutical sponsors are considering the core competency assessment of their external vendors as one of the critical first steps in developing an effective outsourcing strategy. A maturing vendor base and increasing adoption of technological platforms is expected to provide operational synergies and scope of integration across specific clinical development service categories. Figure 4 illustrates possible synergies and scope of integration across functionalities and categories.

Key Sourcing Considerations

In order to optimize and leverage the these synergies across the clinical development functionalities and categories, global pharmaceutical and biopharmaceutical sponsors need to analyze their current internal category scope and subsequently streamline their sourcing practices by rationalizing their current vendor base (Table 1):

- Internal Category Alignment (Vertical Scope of Integration): Analyzing and redefining current category scope of operations and rationalizing it by evaluating the level of integrations with other categories of functionality

- Vendor Base Rationalization (Horizontal Scope of Integration): Assessing the core competencies of the current vendor base through robust KPIs across each category/function, and evaluating the scope of integrated sourcing approach to leverage the synergy across functionalities

Figure 5 illustrates horizontal scope of integration with an example of core competency mapping for vendors evaluation across CDM and monitoring category services.

SUMMARY

To ensure a successful externalization execution path while mitigating these challenges, global pharmaceutical and biopharmaceutical sponsors should continuously evaluate and restructure the way they engage with these external vendors by identifying the synergies, understanding the sourcing best practices, analyzing the governance or alliance scale-up risks, and devising the risk mitigation strategy over the lifetime of these contracts.

In near future, the clinical development service market is expected to witness further rationalization, which should distinguish the current supply base into core service providers (Phase I-IV clinical trials) and single or multiple functional support service providers (clinical data management, central laboratory, clinical staffing or in-sourcing, patient recruitment, etc) for clinical trial operations across therapeutic areas and geographic scope.

With the maturity of the supply market driven by these rationalizations, global pharmaceutical and biopharmaceutical sponsors should proactively revive their current category sourcing strategy by undertaking an internal category alignment and vendor base rationalization. This would enable them to bridge the gap of innovation and enhance future productivity by optimizing their externalization process for clinical development services. ◆

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BIOGRAPHY

Kamaljit Behera is a Team Lead with Beroe Inc., a global provider of customized procurement services specializing in sourcing, supply chain visibility, financial risk analysis and environmental impact to Fortune 500 organizations. Kamaljit specializes in tracking various sourcing categories for Pharmaceutical and Biopharmaceutical companies and has 3 years of expertise in undertaking cost-benefit analysis, supply market analysis, innovation-value analysis, sourcing best practices, and spend analysis. He has worked on multiple projects for many Fortune 500 clients involving categories such as Central and Core Laboratory, Animal Sourcing, Clinical Staffing, Clinical Trial Site Management, Patient Recruitment, and Post Marketing Services Categories. Kamaljit earned his degree in Master of Business Administration from the Christ University- Bangalore.

METAL-COORDINATED PHARMACEUTICALS

Reducing Inter-Subject Variability With Metal-Coordinated Pharmaceuticals: A Case Study With Furosemide

By: John D. Price, PhD, Thomas Piccariello, PhD and Scott Palmer, MD

ABSTRACT

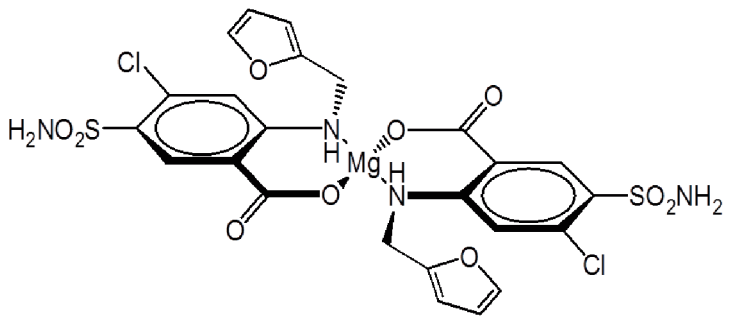
Oral furosemide, a loop diuretic commonly used to treat congestive heart failure and other fluid overload states, is poorly and variably absorbed, with bioavailability ranging from 11% to 90%.[1] This variability can lead to unintended underdosing, re-dosing, and overdosing in both stable and deteriorating patients. Synthonics has used its metal coordination chemistry to create a novel coordination complex of furosemide and magnesium that is absorbed more efficiently and consistently than furosemide itself.

INTRODUCTION

Metal coordination entails attaching a minute quantity of a pharmaceutically acceptable metal, such as zinc, bismuth, or magnesium, to an active pharmaceutical agent to create a new and more effective molecule. By varying the metals and adjuvants used, metal coordination can affect a range of pharmacokinetic changes. For example, magnesium can improve a poorly absorbed drug's solubility in water while maintaining the solubility in lipid bilayers necessary to permit its efficient passage from the digestive tract to the bloodstream and the target cell, while bismuth can impart bioadhesive properties to drugs that require controlled and extended release.

Although metal coordination can be used to impart a wide range of qualities to a diverse mix of drugs, this article focuses on its use to reduce the variability of absorption of furosemide. Furosemide is among the most commonly prescribed drugs for the management of congestive heart failure, hypertension, and other edematous states.[2] Loop diuretics, such as furosemide, block the Na-K-Cl cotransporters in the ascending limb of the loop of Henle, which increases urinary sodium chloride and water excretion and induces a negative fluid balance in treated patients.[3] They tend to have a relatively short duration of action and are typically utilized in more severe cases of fluid retention and congestive

FIGURE 1



Structure of magnesium furosemide coordination complex, $Mg(fur)_2$

TABLE 1

Compound	EtOAc	THF	Water
Furosemide	6.60	186.24	0.08
Mg-Fur Salt	61.10	94.84	12.00
Mg-Fur Complex	150.97	306.00	39.66

Comparative solubility data (mg/mL)

TABLE 2

Compound	pK_a	Log $D_{7.4}$
Furosemide	3.40	-1.7
$Mg(Fur)_2$	3.59	-0.86

Potentiometric Log D and pKa values of furosemide and $Mg(fur)_2$

heart failure, and in chronic edematous states associated with renal insufficiency or hepatic dysfunction.[4]

Although furosemide remains the current standard of care for most patients, its erratic bioavailability can affect patients' responses to daily furosemide dosing and can complicate the clinical management of patients receiving it in acute and chronic settings.[5] Over time, the variability in absorption can lead to unintended under-dosing, re-dosing, and overdosing in both stable and deteriorating patients with inadvertent reflex-activation of the renin-angiotensin-aldosterone system, exacerbation of electrolyte imbalances, aggravation of diuretic resistance, and worsening fluid retention. Reducing the variability of furosemide's absorption could significantly reduce the incidence of adverse effects and improve the clinical management of patients.

Synthonics has used its proprietary metal coordination chemistry to create a patent-protected magnesium-furosemide complex ($Mg(fur)_2$, (Figure 1)) that enhances furosemide's dissolution properties and improves its absorption.[6]

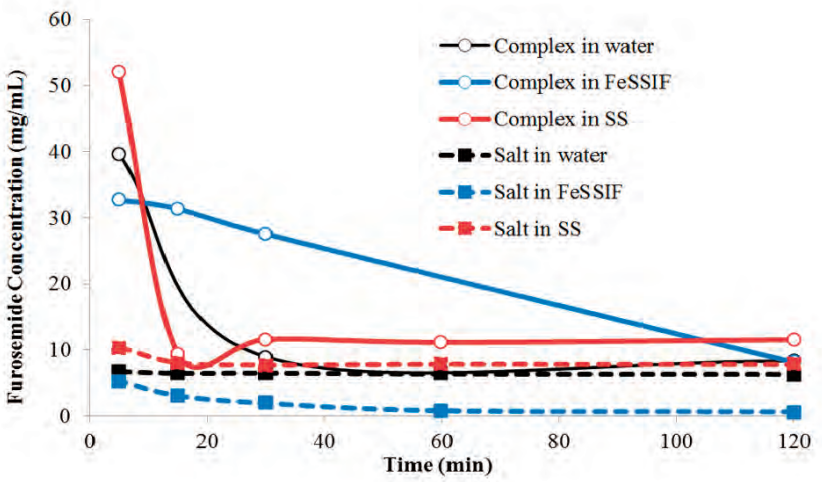
RESULTS

In vitro solubility and partition coefficient studies demonstrate the altered physicochemical properties of $Mg(fur)_2$. The data in Table 1 show that complexing furosemide to magnesium increases its range of solubility (ie, amphiphilic properties). Of particular note are $Mg(fur)_2$'s water solubility relative to magnesium furosemide salt and organic solvent solubility relative to furosemide.

In addition to increased solubility, $Mg(fur)_2$ demonstrates more lipophilicity (greater log D) than fursosemide (Table 2). While enhancing lipophilicity through the reaction of a carboxylate with a metal ion might seem counter-intuitive, it is entirely consistent with the formation of a metal coordination compound with properties distinct from its metal salt. Thus, these data suggest a degree of covalency between the drug and the metal.

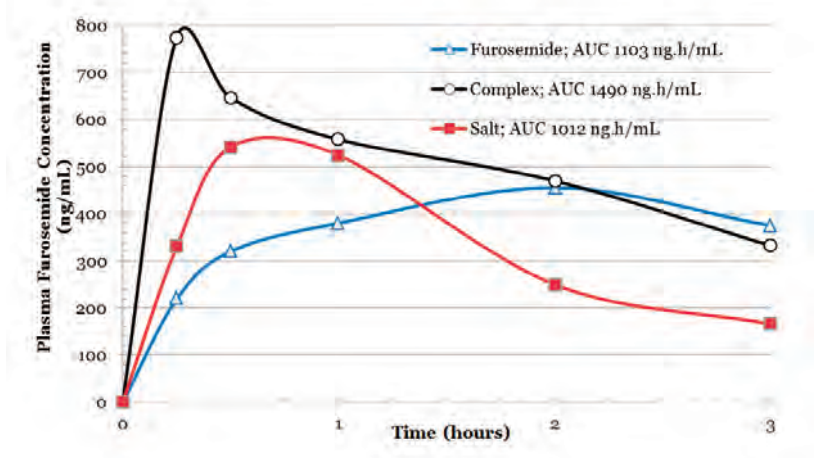
$Mg(fur)_2$ dissolved much more rapidly in

FIGURE 2



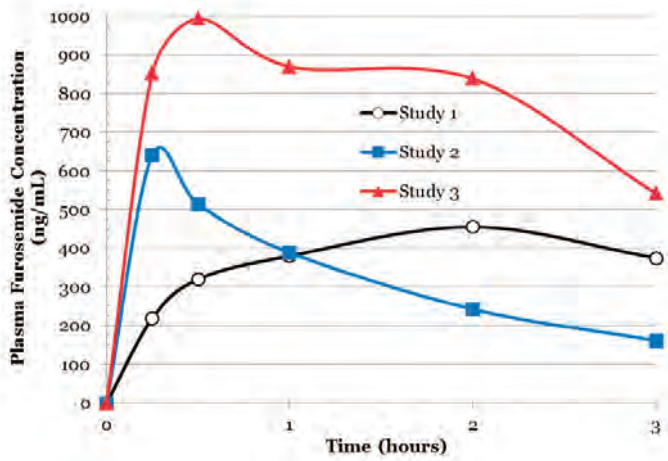
Comparison of the magnesium furosemide complex and salt dissolving in various buffer systems.

FIGURE 3



Plasma profile after treatment with furosemide, complex and salt in rats.

FIGURE 4



Three plasma profile studies of furosemide in a rat model.

aqueous systems than did the magnesium furosemide salt. The magnesium furosemide salt had a solubility in the range of 5 to 10 mg/mL initially and remained in that range in water and simulated saliva (SS). In the fed state simulated intestinal fluid (FeSSIF), the concentrations of furosemide dropped from 5.3 to 0.6 mg/mL over 1 to 2 hours, possibly due to conversion of the salt form to furosemide and magnesium oxide. These solubility profiles contrast with that of $Mg(fur)_2$, which rapidly dissolved (initial concentrations in the range of 32 to 52 mg/mL) and slowly converted to the salt (Figure 2).

Standard in vivo pharmacokinetic studies involving single oral doses of $Mg(fur)_2$ and furosemide in a set of male Spargue-Dawley rats show the impact of $Mg(fur)_2$'s physicochemical properties on the absorption of orally administered furosemide. As shown below, $Mg(fur)_2$ was more rapidly and consistently absorbed relative to furosemide. This figure illustrates the plasma furosemide concentration versus time curves (plasma profiles) when rats (n = 5) were dosed with equimolar amounts (2 mg/kg furosemide) of standard furosemide, the magnesium furosemide salt, and $Mg(fur)_2$.

$Mg(fur)_2$'s enhanced and consistent absorption profile reflects the stability of the complex in the aqueous systems encountered between oral administration and initial interaction with the gastrointestinal epithelium. If hydrolysis of the complex had converted a significant amount to the salt, the plasma profiles would be more similar. Figures 4 and 5 show the plasma profiles of furosemide and the complex over three separate rat studies. In addition to the clear difference in the average C_{max} of furosemide compared to the complex, the curves also indicate differences in inter-subject variability between furosemide and $Mg(fur)_2$.

Although these data indicate that $Mg(fur)_2$ is sufficiently stable in solution and in the GI tract, the precise kinetics of dissociation between magnesium and furosemide in the complex milieu of plasma and the GI tract are difficult to determine. Caco-2 studies and parallel artificial membrane permeability assay studies reveal no significant increase in permeability of $Mg(fur)_2$ relative to furosemide and no meaningful change to the efflux mechanism. This may indicate that cell membrane components themselves cause dissociation of the magnesium furosemide coordination complex following administration.

Application of the Hartley test to the ratio of σ_2 values in Table 3 indicates that the reductions in the variances were statistically significant at each time point with a confidence level of at least 95%.

Subsequent rat studies compared inter-subject variability between $Mg(fur)_2$ and furosemide. Furosemide (~10 mg/kg) and

TABLE 3

	Furosemide (N=20)			Magnesium(furosemide)$_2$ (N=20)		
Hours	**Mean**	**SD**	**σ^2**	**Mean**	**SD**	**σ^2**
0	0	0	0	0	0	0
0.25	587.9	532.6	283,638	676.5	313.0	97,982
0.5	585.7	427.8	182,990	676.8	259.0	67,080
1	506.9	344.6	118,752	558.9	189.9	36,076
2	444.6	402.2	161,753	411.8	197.6	39,044
3	309.9	248.5	61,768	232.0	106.1	11,255

Data from studies 1-3, N=20

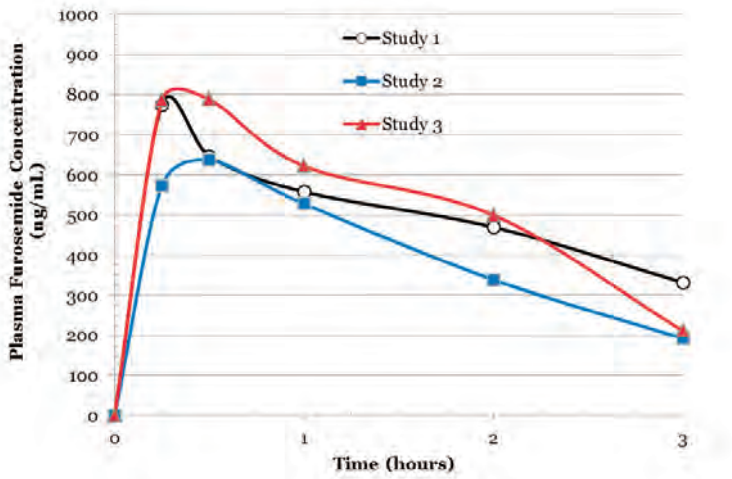
$Mg(fur)_2$ (~7 mg/kg) were fed to rats by oral gavage and blood samples were taken at the expected t_{max} for each test material and at a later time, t_{res}, and the ratio of the variances between the two test materials at the two time points was calculated. The use of over 30 rats for each test compound assured statistically significant ratios. Based on earlier studies, t_{max} was estimated to be 90 minutes for furosemide and 20 minutes for $Mg(fur)_2$. The t_{res} values of 150 minutes for furosemide and 50 minutes for $Mg(fur)_2$ were based on expected blood levels of about half C_{max}.

The variability in the furosemide group was so large that t_{max} may have been anytime between about 90 minutes and 150 minutes. The consistency in the earlier animal studies with $Mg(fur)_2$ indicated a t_{max} close to the predicted 20 minutes.

An χ^2 test revealed that the standard deviation of absorption at the estimated t_{max} for $Mg(fur)_2$ is approximately 2.4 times less than that of furosemide. Assuming that the reduction in variability at t_{max} persists throughout the drug's absorption phase and extrapolating the results to humans, a patient taking a 40-mg pill could expect to absorb between 4 and 36 mg of furosemide (ie, 11% to 90% of the active agent), while one taking $Mg(fur)_2$ could expect to absorb between 17 and 30 mg of furosemide (ie, 54% to 95% of the active agent).

The inter-subject variability of the furosemide dosed animals and the $Mg(fur)_2$ dosed animals can be graphically represented by plotting the number of subjects against a range of plasma concentrations of furosemide at the estimated time of t_{max}. Figure 6 illustrates a normal distribution of absorption of furosemide at the estimated tmax in the population of animals dosed with $Mg(fur)_2$ and a disparate and sporadically distributed absorption of furosemide at the estimated t_{max} in the furosemide dosed animal population, which indicates the significant reduction in inter-subject variability with $Mg(fur)_2$.

FIGURE 5

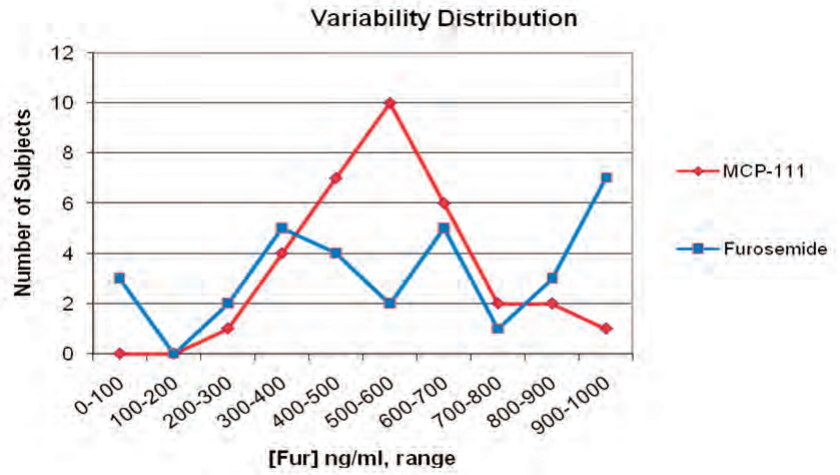


Three plasma profile studies of the $Mg(fur)_2$ in a rat model. At each time point in the combined studies 1-3, the standard deviation (SD) and variances (σ^2) of the furosemide plasma concentration values from the rats fed $Mg(fur)_2$ were consistently lower than those from the rats administered furosemide.

DISCUSSION

There are several possible mechanisms responsible for transport of furosemide across the brush border membrane in the gastrointestinal tract. Whereas passive diffusion is reported to be furosemide's principal mechanism of absorption, there is evidence for active transport mechanisms particularly associated with efflux, such as the p-glycoprotein system.[7,8]

FIGURE 6



Normalized C_{max} distribution in an animal model: $Mg(fur)_2$ versus furosemide.

TABLE 4

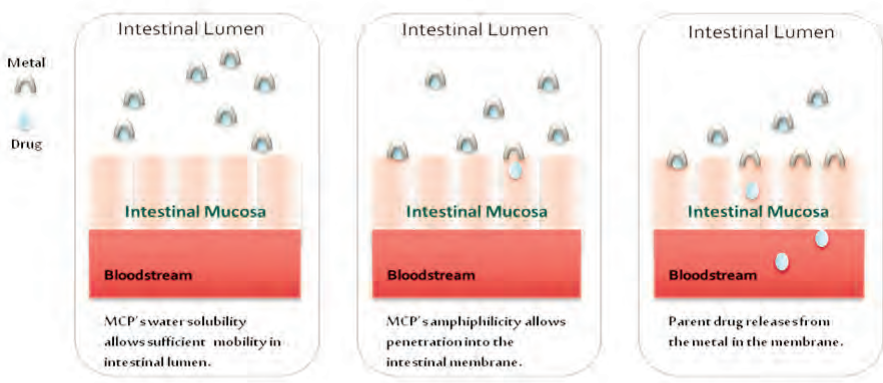
	Furosemide	ng/mL	$Mg(fur)_2$	ng/mL
	90 Minutes	150 Minutes	20 Minutes	50 Minutes
Mean	718	730	560	468
SD	365	460	185	145
σ^2	133,364	212,146	34,486	21,121

Data from the N=30 rat study

The amino acid transport system relies on a sodium gradient when transporting β-amino acids, such as furosemide. This sodium gradient causes the pH of the luminal side of the brush border membranes to be 5.5 to 6.9 If furosemide absorption depends, at least in part, on the sodium gradient, then the low pH microenvironment at the luminal surface of the intestines will reduce the solubility of furosemide, thereby limiting its availability for passive or active absorption.[10] $Mg(fur)_2$ is much more soluble than furosemide at this lower pH, and its dissociation rate is unlikely to be a factor during transport through the microenvironment. It seems plausible, if not likely, that the rate-limiting step for the absorption of furosemide is its movement through the low pH external surface layer lining the gastrointestinal epithelial cells. In addition, $Mg(fur)_2$'s enhanced solubility and greater log D reveals an enhancement in the amphiphilic properties of furosemide. Amphiphilicity has been linked to improved bioavailability and enhanced penetration through the water/bilayer interface leading to improved adsorption at the gastrointestinal epithelia (Figure 7).[12,13] The concomitant increase in solubility and enhanced amphiphilicity could translate into an overall improved bioavailability and faster onset of action. Figure 8 shows a three-dimensional plot of effective permeability (P_{eff}), solubility (Dn), and relative bioavailability (BA) based on a well-known mathematical model.[14]

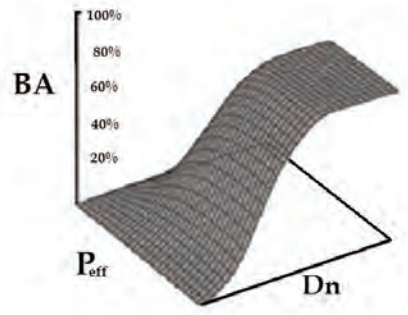
Key factors that influence the bioavailability of orally administered drugs include solubility and permeability. A significant component to a drug's effective permeability is its availability for adsorption at the water/bilayer interface of the epithelial membrane. Therefore, for the purpose of this discussion, the relative P_{eff} of $Mg(fur)_2$ depends on its adsorption efficiency to the epithelial cell layer.

FIGURE 7



Metal coordination enhances the solubility of the reference drug, which allows mobility in the intestinal lumen and increases a drug's lipophilicity. Ultimately, the reference drug exits the basal side of the membrane.

FIGURE 8



Three-dimensional plot of effective permeability (P_{eff}), solubility (Dn), and relative bioavailability (BA) based on a well-known mathematical model.

The plot in Figure 8 shows that at values of P_{eff} and Dn along the steep slopes of the curve, changes in either factor or secondary effects, such as stress, edematous conditions, stomach contents, or gastric emptying, can cause a significant change in bioavailability. However, at the values of P_{eff} and Dn represented by the plateau of the three-dimensional curve, changes in these factors cause little change in bioavailability. Thus, one can minimize the variability in a subject drug's bioavailability by maximizing that drug's absorption availability and solubility. Metal coordination chemistry provides the amphiphilic properties necessary to optimize both the absorption availability and therefore P_{eff} and solubility, which is critical to maintaining bioavailability on the plateau of the three-dimensional curve.

Factors other than gastrointestinal epithelial permeability and solubility impact the inter-subject variability of furosemide (and

other drugs for that matter). Still, the amphiphilic properties and enhanced dissolution of furosemide imparted through the application of metal coordination chemistry should result in a significant improvement in inter-subject variability. ◆

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7. Note that although the mean concentrations for the $Mg(fur)_2$ group were lower than those of the furosemide group due to differences in dosage size, as a percentage of the administered dose, the mean concentrations for the $Mg(fur)_2$ group exceeded those for the furosemide group.
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BIOGRAPHIES

Dr. John D. Price is Vice President of Research and Development at Synthonics, Inc., where he is working on the design of new metal-coordinated pharmaceuticals, and on expanding this discovery platform into additional areas of drug delivery, including mucoadhesive bismuth coordination complexes for the controlled release of oral pharmaceuticals. Prior to joining Synthonics, Dr. Price worked in the fields of coordination and inorganic polymer chemistry as they relate to pharmaceutical development. As Director of Medicinal Chemistry at Allomed Pharmaceuticals, he led efforts investigating metal-coordinated insulin mediators as therapeutics for treating diabetes and Alzheimer's disease. As Director of Research at Magnox, Inc. he helped develop several Super Paramagnetic Iron Oxide Nanomaterials. Dr. Price earned his BS in Chemical Engineering from Washington University in St. Louis and his PhD in Chemistry from Iowa State University. Over the course of his career, he has worked at the interface of several chemical disciplines, combining physical organic chemistry, synthetic biology, pharmacology, and metal coordination chemistry. He has publications and patents in all of these areas.

Dr. Thomas Piccariello is a Co-founder of Synthonics and currently serves as its President and Chief Science Officer. His current research is focused on the impact metal coordination has on pharmacokinetics and pharmacodynamics. Prior to founding Synthonics, Dr. Piccariello was Vice President of Polypeptide Drug Development at New River Pharmaceuticals and was the lead inventor on the Carrierwave technology. In that capacity, Dr. Piccariello oversaw the R&D efforts, including the set up of a cGMP CTM production facility. He has also been involved in the start-up of Insmed Pharmaceuticals. Dr. Piccariello founded (and later sold) Synthons, a CRO, and Chermetic, a contract manufacturing company. He earned his BS in Biology and his PhD in Chemistry from Virginia Polytechnic Institute and State University (Virginia Tech). Over the course of his career, he has worked in areas that involve synthetic chemistry, metallurgy, electrochemistry, plant enzymology, chemical manufacturing, pharmacology, and metal-coordination chemistry. Dr. Piccariello has over 100 patents and patent applications to his credit, most of which deal with novel drug delivery technologies.

Dr. Scott Palmer, M.D., is Chairman of the Scientific Advisory Board and a member of the Board of Directors of Synthonics, Inc. He's a board-certified internist and an Assistant Professor in Department of Internal Medicine at Rush University Medical Center in Chicago. Dr. Palmer did his internship, residency and chief residency at Rush Presbyterian - St. Luke's Hospital in Chicago and has been designated a top doctor by numerous regional and national publications. Dr. Palmer is a member of the American College of Physicians and is also a Medical Team Physician of the Chicago Bulls and the Chicago White Sox. Dr. Palmer's research interests include pharmaceutical management of autistic spectrum disorders, cancer. He is a graduate of the University of Michigan and Rush Medical College and has an active clinical practice.

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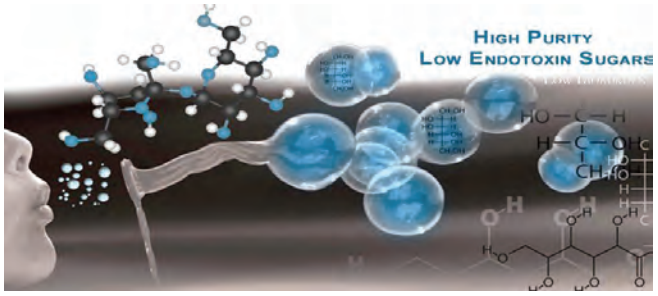

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If You Are Not At Risk of Losing Your Job, Then You Are Probably Not Doing It Right!

By: John A. Bermingham

I don't get it. If I'm at risk of losing my job then that means I am doing my job correctly? Well yes. Too many companies today, and the people that run them, have developed a negative culture on responsible risk. I say responsible risk because I am not talking about taking a high risk flyer into the unknown, I'm talking about conducting your due diligence on an idea, discussing the idea with the appropriate people, and then making a decision to take responsible risk and go forward with it. A company with a management culture that takes punitive measures against a person who takes a responsible risk and it fails is a company that is headed for problems.

Where would the world be if Sony had not taken the risk for a small portable audio cassette player using mini headphones that would be called the Walkman? Or when the entire world played 33 and 1/3 RPM vinyl records for music had Sony not taken the risk on a new format called compact disk? Or how about when everyone was using 5 and 1/4-inch or 8-inch floppy disks had Sony not introduced the 3 and 1/2-inch plastic jacketed floppy disk and disk drive?

If you are a person who is overly cautious or someone who is afraid to take any kind of responsible risk, then you are exposing yourself to a potential termination. Last month, I wrote about the Compensation Paradox and the Cost to Company (CTC) of an employee to his or her company. In that article, I wrote about what a person's perceived value is by his or her manager.

If you are a person who stays quietly out of the way and never exposes himself or herself to any type of responsible risk decision, then your perceived value is not in any way close to the perceived value of a person who is always looking for the next great idea and trying new ideas that have passed the responsible risk test.

Responsible risk takers are never 100% successful. Some ideas flop. But some ideas don't flop and go on to create tremendous value for the company. That's why if you are not at risk of losing your job, then you are not doing your job correctly. You're not taking any responsible risk, and thus you're not creating value.

AT&T in its original form, although a monopoly prior to its break up in 1984, was still one of the world's leading technology companies through Bell Labs. They developed the transistor, the cell phone, the laser, the CCD, and a multitude of other technology developments resulting in seven Nobel Prizes. I left Sony to join AT&T as a Group Vice President because of AT&T's technology leadership.

So where is the former AT&T now? It isn't anywhere. It was broken up into three pieces by its Chairman and CEO, Bob Allen, in 1995. Eventually, AT&T was acquired by Southwestern Bell, Lucent by Alcatel in France, and NCR Corporation became its own company in a much smaller footprint.

One of the reasons that AT&T was broken up was because it was failing. It was failing because it had a risk adverse company culture. One of my responsibilities as a Group Vice President was to assess new consumer products technologies being developed at Bell Labs and to determine if these technologies could be developed into actual businesses. I was like a kid in a candy store. I had the best job at AT&T. Or not.

Every time I found a new technology at Bell Labs that I believed strongly could be developed into a real business, I made a formal business plan presentation to AT&T senior management. And every time I made a presentation, these dinosaurs found reasons not to take a responsible risk and develop the technology platform into a business.

Over the past 10 years, I have watched company after company introduce new products and technologies that we had at AT&T 20 years ago. But because AT&T was so risk adverse, it never took advantage of its great potential as technology developers and innovators and never developed businesses around them. Don't let yourself become a personal AT&T and fail because you will not take responsible risk. Be more like a Sony. Take responsible risk and you will be doing your job correctly! ◆

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BIOGRAPHY

John A. Bermingham
Executive VP & COO
1st Light Energy & Conservation Lighting, Inc.

John A. Bermingham is currently the Executive Vice President & COO of 1st Light Energy & Conservation Lighting, Inc. He was previously Co-President and COO of AgraTech, a biotech enterprise. Previous to that, he was President & CEO of Cord Crafts, LLC, a leading manufacturer and marketer of permanent botanicals. More previously, he was President & CEO of Alco Consumer Products, Inc., Lang Holdings, Inc., and President, Chairman, and CEO of Ampad, all of which he turn around and successfully sold. With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona, Corporation, and Rolodex Corporation as well as turning around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group, and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served 3 years in the US 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 graduated from the Harvard University Graduate School of Business Advanced Management Program.

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