# Drug Development & Delivery

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OUR CAPABILITIES JUST WENT FROM

# BROAD TO BROADER

FROM SEMI-SOLIDS TO LIQUIDS TO SOLIDS

FROM NON-STERILE TO STERILE

FROM CONCEPT TO COMMERCIALIZATION

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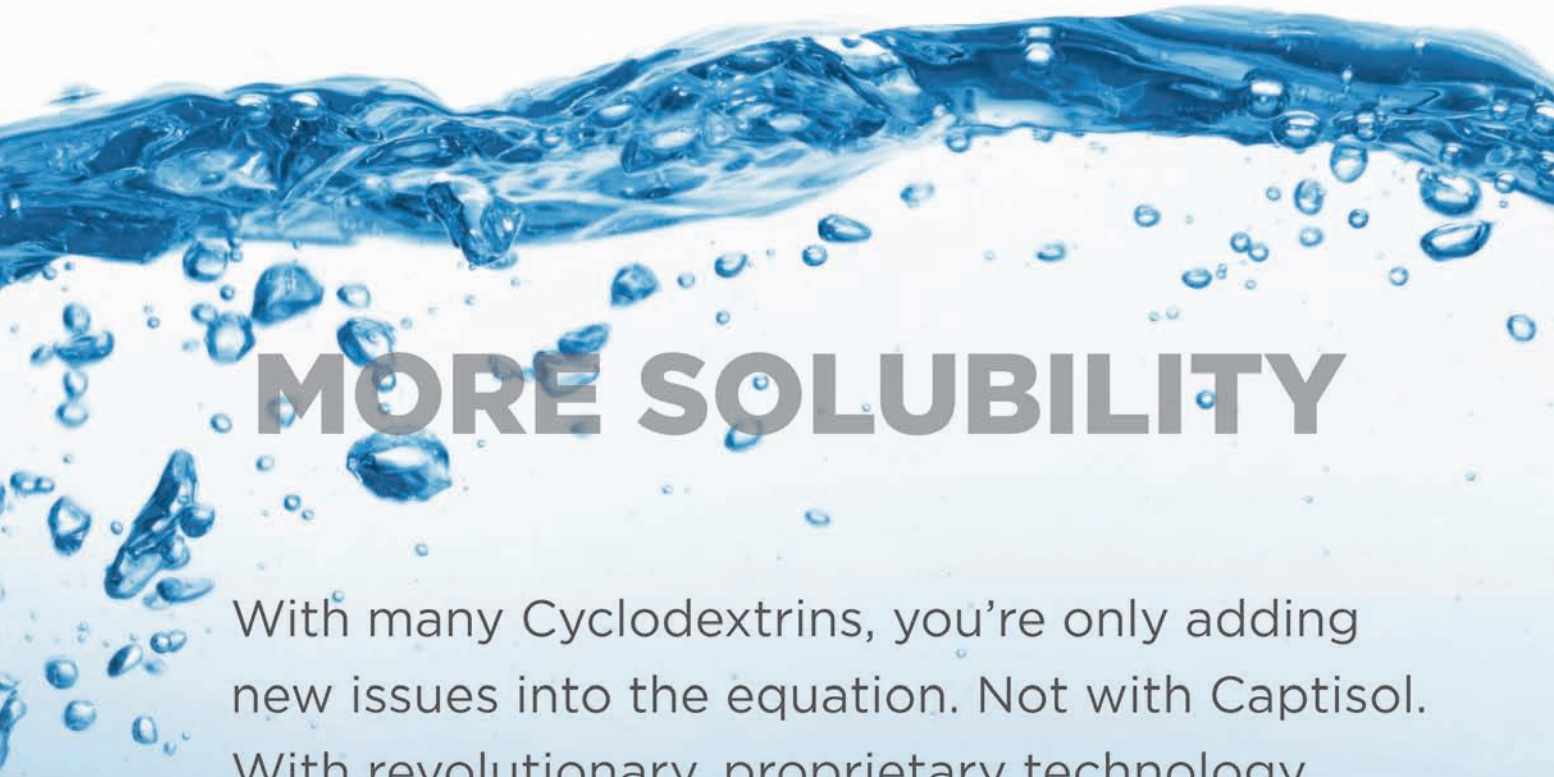

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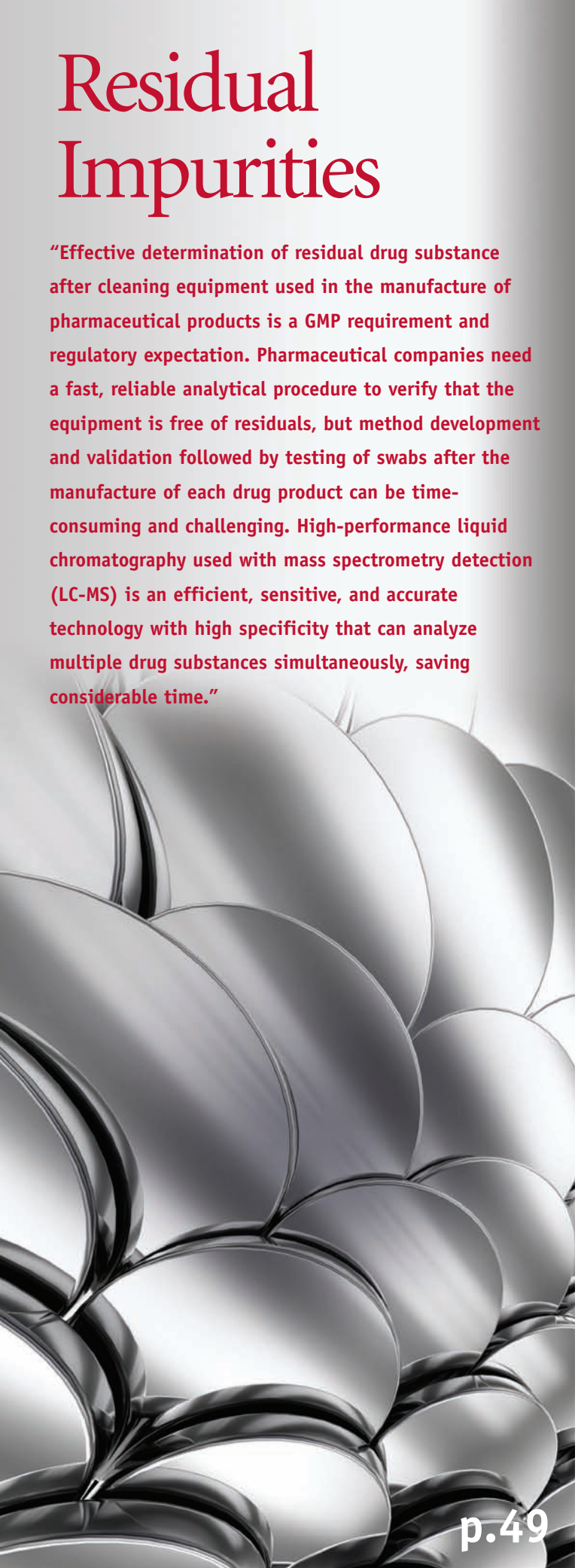
**"Effective determination of residual drug substance after cleaning equipment used in the manufacture of pharmaceutical products is a GMP requirement and regulatory expectation. Pharmaceutical companies need a fast, reliable analytical procedure to verify that the equipment is free of residuals, but method development and validation followed by testing of swabs after the manufacture of each drug product can be time-consuming and challenging. High-performance liquid chromatography used with mass spectrometry detection (LC-MS) is an efficient, sensitive, and accurate technology with high specificity that can analyze multiple drug substances simultaneously, saving considerable time."**



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# RBCC & Therakine Initiate Phase II of Revolutionary Delivery Technology

Rainbow Coral Corp. and its joint venture partner, Therakine, Ltd., recently announced they have reached a major new milestone in the development of a revolutionary new drug delivery technology. The companies reached terms to initiate Phase II of research and analysis on a new injectable, sustained-release technology poised to vastly improve patients' use of a crucial drug in the fight against drug and alcohol dependence.

Naltrexone is a prescription opioid receptor antagonist used primarily in the management of alcohol and opioid dependence. Phase I of the joint venture's research established excellent compatibility between the drug and Therakine's hydrophobic injection matrix as well as a highly promising release profile. Phase II will focus on micronization of the technology as well as extension of its sustained-release time.

RBCC has big plans for the breakthrough technology in 2014. If Phase II of research goes as well as Phase I did, the joint venture could soon supply the only intramuscular, programmable release of Naltrexone available anywhere in the $142.5-billion drug delivery industry.

"We believe this sustained-release tech is going to forever change the way addiction is treated around the globe," said new RBCC CEO Kimberly Palmer. "We're already in talks with Therakine about potentially acquiring an exclusive, international distribution license for this product. We're expecting next year to be tremendously fruitful for our company and our investors."

RBCC's biotech division, Rainbow BioSciences, is working with partners such as Therakine to capitalize on the incredible growth of the global drug delivery market by delivering new medical and research technology innovations in order to compete alongside companies such as Bristol Myers Squibb Co., Biogen Idec Inc., Abbott Laboratories, and Valeant Pharmaceuticals International. Rainbow Biosciences, LLC, is a wholly owned subsidiary of Rainbow Coral Corp. The company continually seeks out new partnerships with biotechnology developers to deliver profitable new medical technologies and innovations.

# Antitope Enters Research Agreement With Annexon

Antitope Ltd recently announced it has entered a research agreement with Annexon to generate novel antibody therapeutics for the treatment of neurodegenerative diseases.

Under the terms of the agreement, Annexon will provide antibodies against specific components of the complement system, and Antitope will use its Composite Human Antibody technology to generate a series of fully humanized antibodies devoid of T cell epitopes and with a consequent low risk of clinical immunogenicity. Annexon will screen the Composite Human Antibodies provided by Antitope and select a lead antibody to take forward into further preclinical and clinical studies. Annexon's most advanced program is for an orphan autoimmune neurological indication. The antibodies are expected to halt the progression of disease and allow the body to repair.

"This further agreement for Antitope's Composite Human Antibody technology provides another opportunity for our technology to produce a better biopharmaceutical for the treatment of patients who despite years of research are still not receiving adequate treatment for their disease," said Matt Baker, CSO of the PolyTherics group.

"We are very pleased to be working with Antitope to generate a fully humanized antibody against our novel target so that we can move it forward into advanced preclinical and clinical development for various neurodegenerative diseases," added Arnon Rosenthal, Co-founder and Chairman of Annexon.

Antitope Limited is a subsidiary of PolyTherics Limited, a group which focuses on providing services and technologies to enable the development of better biopharmaceuticals. Antitope undertakes immunogenicity testing of antibodies and other proteins, engineering of antibodies and proteins to reduce their immunogenicity, and development of manufacturing cell lines.

Annexon's mission is to develop a new class of drugs to inhibit the complement system and halt the progression of multiple neurodegenerative disorders, including Alzheimer's disease, glaucoma, Parkinson's disease, spinal muscular atrophy, stroke, traumatic brain injury, multiple sclerosis, neuromyelitis optica, and peripheral nervous system diseases including Guillain-Barre syndrome and myasthenia gravis.

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# Peptineo Inks Exclusive Option for Drug Delivery Technologies

Peptineo recently announced the company has inked an exclusive option for a broad set of nanotechnology patents in the area of drug delivery from Lawrence Berkeley National Laboratory. Under this agreement, Peptineo will work to commercialize drug delivery technologies developed in the laboratories of Dr. Carolyn Bertozzi and Dr. Jean M.J. Fréchet.

"Securing an option agreement with LBL marks a significant event in the evolution of Peptineo and will enhance ongoing research efforts within the company," noted Dr. Sheldon Keith Jordan, CEO.

"To us, Dr. Bertozzi's and Dr. Fréchet's collective body of research represent the highest standard of scientific expertise and will afford Peptineo multiple opportunities to address unmet drug delivery challenges in many therapeutic areas,"said Dr. Jordan.

While it is often useful to release therapeutic agents under mildly acidic conditions, few existing materials developed for drug delivery are both acid-sensitive and biodegradable/bioerodible. To address this gap, Jean Fréchet and a team of scientists have developed a new class of polymers that can encapsulate proteins, DNA/RNA-based materials, and other bioactive agents for vaccines, drug delivery, and gene therapy.

A key feature for this class of polymers is that they can be employed in any application that necessitates materials with precise control over the release of encapsulated cargoes. In the human body, these polymers will be able to quickly release their payloads or be eroded over time -breaking down into neutral byproducts that can be safely eliminated. Materials made from the polymers can be engineered to degrade at specific rates, ranging from a day to many months at physiological pH, depending on the formulation used.

Additionally, these same materials will allow for greater variation in the type of encapsulated therapeutic materials, targeted cell types, and drug-release kinetics than are currently available - including microencapsulation materials like poly-(lactide-co glycolic acid) (PLGA).

With regard to research efforts led by Carolyn Bertozzi, she and her colleagues have developed a method for creating high-purity, nano-sized polymer particles that display specific biological ligands on their surfaces. The resultant nanoparticles are hollow, spherical, polymerized liposomes that bind to biological targets and can be used as an inhibitor or be used for delivering a drug loaded in its interior. This technology forms the basis for a new class of materials that have great therapeutic potential. Briefly, the material starts out as a membrane in the spherical form of a liposome that is self-assembled from individual monomers. Monomers that bind to pathogens (such as influenza virus) or bind to disease sites in-vivo (inflamed tissue) are incorporated into the self-assembling mixture - thereby providing critical in vivo targeting capabilities. Finally, a quick and efficient polymerization by light gives a solid shell to the resultant nanoparticle.

# Unilife Announces Clinical Supply Agreement With Novartis

Unilife recently announced an agreement with Novartis to supply clinical products from one of its platforms of injectable drug delivery systems for use with one of Novartis' targeted early stage pipeline drugs.

Under this agreement, Unilife will supply Novartis with a customized delivery device, consisting of syringe, needle, tubing, controller, and pump, to enable administration of a novel investigational Novartis drug into a targeted organ in clinical trials. Unilife has granted Novartis an option for exclusivity under this agreement.

The program to supply customized products for clinical use with Novartis drug candidates is the next phase in a development collaboration between the parties that was commenced in 2011, and continues to progress successfully. Under this agreement, Unilife will generate revenue on the basis of the clinical product supplies and activities involved in clinical development.

"I am pleased with our success to date in being an effective collaborator with Novartis," said Mr. Alan Shortall, Chief Executive of Unilife. "This is another example of Unilife addressing the unmet needs of pharmaceutical companies to deliver advanced drugs in their pipelines. I am excited to supply Novartis with a differentiated game-changing device that provides alternative options for drug delivery."

# Adocia Signs Exclusive Nanotechnology License

Adocia recently announced the signature of an exclusive license agreement with the CNRS, the University Bordeaux I, the Institut Polytechnique de Bordeaux and Aquitaine Science Transfert (SATT Aquitaine). This agreement grants Adocia the development and commercialization rights over an international patent application protecting a nanotechnology for drug delivery in the field of healthcare. The cash position of the company is not significantly impacted by this acquisition, for which financial terms remain confidential.

Adocia has taken this opportunity to develop a new technology for oncology whilst pursuing as scheduled the clinical studies plan on its three insulin products and on its product for chronic wound healing. Its scientific expertise in drug delivery will be crucial for rapid industrial development.

The new technology, called DriveIn was developed by Professor Sebastien Lecommandoux and his team at the Laboratoire de Chimie des Polymeres Organiques (LCPO, UMR5629 CNRS - Universite de Bordeaux I – Institut polytechnique de Bordeaux). It is remarkably efficient in carrying active molecules and delivering them within solid tumors. This work has been published in multiple peer-reviewed journals.

Adocia will adopt a dual strategy for the development of this technology. It intends to develop proprietary products based on doxorubicin and docetaxel, two of the most used anti-tumoral treatments, which could greatly benefit from an enhanced intra-cellular delivery. Adocia will also propose the DriveIn technology to pharmaceutical companies to optimize the efficacy of their own proprietary molecules.

Research is ongoing to develop new treatments in oncology, but also to improve the performance of commercial products while limiting their side effects. Today, one of the main challenges is to more efficiently target the molecules toward solid tumors, so as to concentrate them on cancer cells and limit the damage to healthy tissues.

The innovation in DriveIn consists in its using nanoparticles that have a surface completely made of hyaluronan, a biopolymer naturally present in the human body, known to interact with the CD44 cell receptor. This receptor is overexpressed in a large number of solid tumors, thus allowing DriveIn nanoparticles to efficiently reach and penetrate cancer cells. This is known to be a limitation of current therapies.

# Monoclonal Antibodies Market for Colorectal Cancer to Witness Moderate Growth, as Late-Stage Pipeline Remains Weak

The market value for monoclonal antibodies (mAbs) in colorectal cancer treatment will experience a moderate increase from $3.7 billion in 2012 to $5.2 billion by 2019, at a Compound Annual Growth Rate (CAGR) of 5%, according to a new report from business intelligence provider GBI Research.

The company's latest report, Monoclonal Antibodies Market in Colorectal Cancer to 2019 - Favorable Pricing Policy in the US and Rising Prevalence in Europe and Japan Ensures Market Growth, states that this moderate growth is due to the slow rise of the prevalent population and weakness of the late-stage pipeline. Currently, there is only one mAb product in Phase III development for the treatment of colorectal cancer, named IMC-1121B.

Dominic Trewartha, Analyst for GBI Research, says "The efficacy of this drug has not yet been proven in large-scale, placebo-controlled Phase III trials, which creates an element of uncertainty in terms of the outcome of these products. As such, this weak late-stage pipeline is not expected to drive market growth to a significant extent during the forecast period."

The current metastatic colorectal cancer market is dominated by three mAbs - Avastin, Erbitux, and Vectibix - which are far more efficacious than the targeted small molecule therapies also marketed for this setting. Therefore, GBI Research believes there is a strong opportunity for the entry of new mAbs into the market, as long as they prove superior efficacy when compared to Avastin.

Mr. Trewartha says, "A product that can attain first-line status in the treatment of colorectal cancer, or even second-line status by displacing Erbitux and Vectibix, would have access to a considerable patient population and be able to generate a substantial amount of revenue. "Furthermore, there are currently no approved mAbs in the early stage setting for colorectal cancer, reflecting an additional opportunity for the development of new products."

The report provides in-depth analysis of three mAbs marketed for colorectal cancer, including analysis of their safety, efficacy, treatment patterns, and strengths/weaknesses. It also gives a comprehensive review of the pipeline for colorectal cancer therapies, including individual analysis of a number of late-stage pipeline drugs that are likely to enter the market during the forecast period. This report was built using data and information sourced from proprietary databases, primary and secondary research, and in-house analysis conducted by GBI Research's team of industry experts.

# Lightlake Therapeutics Joint Clinical Trial With NIDA Shows Nasal Delivery of Naloxone for Opioid Overdose to be Promising

Lightlake Therapeutics Inc. recently announced the initial findings of its clinical trial with the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health, supports Lightlake's intranasal delivery of naloxone as a promising innovative treatment for opioid overdose.

Initial data from the study shows that Lightlake's naloxone nasal spray potentially can be delivered into the blood stream at least as quickly as the injection process currently used by hospitals, first responders, and others treating opioid overdoses.

Naloxone is a medicine currently available through injection that can rapidly reverse the overdose of prescription and illicit opioids. Lightlake, in partnership with NIDA, commenced a 2-week clinical trial on September 23, 2013, designed to evaluate Lightlake's intranasal naloxone application.

"Opioid addiction has reached epidemic levels and is affecting families across the socio-economic spectrum, and our goal of creating an easier to use, more accessible form of naloxone is closer to becoming a reality," said Dr. Roger Crystal, CEO of Lightlake. "With the initial goal of submitting an NDA in 2014, we will meet with the FDA to discuss the results from this study. The data will also allow us to apply our novel method to a wide range of various addictions that are currently affecting millions of people on a daily basis."

"Given our collaboration with NIDA and current understanding of the regulatory pathway with respect to our prospective opioid overdose reversal product, we anticipate incurring relatively low costs to reach an NDA submission with the FDA," added Kevin Pollack, CFO of Lightlake. "Upon the prospective approval and launch of our product, we expect significant market demand given the growing opioid addiction epidemic and the multiple substantial advantages of our intranasal delivery of naloxone over the current injectable delivery of naloxone."

Lightlake Therapeutics Inc., a London-based biopharmaceutical company, is using its expertise in opioid antagonists to build a platform of innovative solutions to common addictions and related disorders. The company holds patents covering the use of intranasal naloxone to treat Binge Eating Disorder (BED) as well as patents covering addiction to drugs including cocaine, amphetamine, and MDMA.

# Kytosan USA Looks to Become Market Leader for Domestic Chitosan

Under an exclusive patent licensing agreement from its parent, KYTOSAN USA will produce and market high-quality industrial-grade chitosan, a specialty chemical made from discarded crustacean waste. Chitosan is used in the manufacture of an extraordinarily broad range of products.

Domestically, demand for consistently high-quality chitosan is considerable. It is used in food, pharmaceutical, cosmetic, water purification, industrial, and agricultural products. New uses for the specialty chemical are being discovered and developed at a rapid pace. The parent company is in the vanguard of chitosan-based product development.

According to Global Industry Analysts, Inc., an independent market research firm, worldwide demand for chitosan will exceed $21 billion by 2015. Presently, US buyers must import chitosan, because there are no major domestic producers of the chemical. Problematically, the quality of the imported chemical is unreliable, inconsistent, and, too often, poor. With its exclusive patent to efficiently produce consistently high-quality chitosan, KYTOSAN® USA is poised to become the leading domestic producer and will control the market for consistently high-quality chitosan.

Annually, the company will produce approximately 2,000 metric tons of chitosan at its plant facility in Opelousas, LA. Quantities mentioned in letters of intent to purchase chitosan from the company exceed the current planned production capacity. Expansion is inevitable. A Front End Engineering Design for establishing a pilot product line and three full production lines has been completed. Environmental studies have also been completed and permits to begin construction are being secured.

KYTOSAN USA, in collaboration with its parent, intends to develop production capabilities for manufacturing even higher grades of chitosan. These higher grades are in demand by the medical/pharmaceutical industries and command prices that allow for substantially higher profit margins than the high profit margin industrial-grade chitosan that will be produced initially. To emphasize the environmentally friendly nature of its enterprise, all KYTOSAN® Brand chitosan products will be marketed exploiting the company logo and motto.

# Management Insight

## Six Reasons Why the Affordable Care Act May Be a Bad-Tasting Medicine That Could Heal Our Industry

By: Derek Hennecke, CEO & President, Xcelience LLC

Like it or hate it, the *Affordable Care Act* so far has been a difficult pill to swallow. First, there was the government shutdown. Then there was the ongoing debacle of the opening of the healthcare.gov website. We are extending healthcare coverage to as many as 34 million currently uninsured Americans. There are so many variables in play in this massive 2409-page social experiment that I don't believe anyone can possibly predict the outcome.

As the makers of the medicines, we have a major interest in the outcome of this experiment. When the *Affordable Care Act* was first proposed, it came on the heels of a weak drug pipeline with numerous impending patent expirys. Many saw the reforms as a double punch to the industry. But pharma is recovering now (see sidebar), and many of our worst fears about the *Affordable Care Act* seem to have been sidestepped.

Whether you love the *Affordable Care Act* or abhor it, the fact is, there are billions of dollars of government money in

play. Some industries are going to benefit from that. It's looking more and more like the pharma industry could be one of them. The following will discuss six reasons why the *Affordable Care Act* may be a bad-tasting medicine that could heal our battered industry.

## 1. MORE PHARMA CONSUMERS

This is the obvious and glaring benefit for the industry. The government estimates 34 million more Americans will have healthcare coverage. True, many of these will be young, healthy individuals, but just using the insurance effect - a well-known economic phenomena in which people consume more simply because something is cheaper - the pharmaceutical industry expects a 3% ($10 billion) boost from increased consumption, according to *Pharmalot*.

## 2. NO MORE DONUT HOLE

When the Medicare prescription drug program was created in 2003, it included a gap in coverage that has become known as the donut hole. Patients were covered up to an expenditure of $2930 (in 2012). After that, they had to pay 100% of prescriptions up to the catastrophic ceiling of $6630, whereupon full coverage kicked in again. From a healthcare point of view, this never made any sense; it was quite simply a means of reducing costs so we could afford the entire program. Still, the effect was that those individuals most in need of prescription help lost it and were forced in some cases to choose between their meds and their groceries for months at a time. Today, the gap has begun to fill in. Under a deal to help fund the *Affordable Care Act*, the pharma industry will discount drug costs in the donut hole by 50%. I am not sure how long this deal will last, but overall, it will still be profitable for Pharma given that drugs costs are typically less than 10% of the cost of goods. The disappearance of the infamous Medicare donut hole could lead to a further $7 to $8 billion lift, says *Pharmalot*.

## 3. FINANCIAL INCENTIVES FOR ORPHAN DRUGS

John Crowley was a financial researcher with two young children who were dying of Pompe disease, a rare inherited disorder that affects the child's ability to walk, talk clearly, and even breathe. A typical orphan disease, there was no cure and no financial motive for researchers to develop one because the disease affects fewer than 10,000 people worldwide.

So Mr. Crowley borrowed $100,000 on his home and 401(k) plan, started a biotech company, and when the company found an enzyme that showed promise, he raised $27 million in venture capital. Thinking he needed the muscle of a major drug company to get the drug through production and testing, he sold his company to Genzyme for $137 million. Genzyme harnessed a government incentive for orphan drug development to fund the research. Then the true drama began, when a shortage of the drug, conflict of interest questions, and Genzyme's internal protocols conflicted with Mr. Crowley's own goal - and he couldn't get the drugs to his kids.

Now a major motion picture starring Brendan Fraser as the father and Harrison Ford as the lead researcher, the movie *Extraordinary Measures* has brought the challenges of incentivizing the development of orphan drugs into the public spotlight.

Under the new reforms, there will be much stronger financial incentives for the development of orphan drugs for rare childhood diseases. In return for targeting these small, unprofitable markets, cooperating pharmaceutical manufacturers will earn vouchers for faster FDA approvals of other, more profitable drugs. Don't underestimate this incentive - a voucher that cuts a drug's FDA review time from 10 months to 6 months could earn a company more than $500 million in additional sales on patent-protected medications, Congress estimates. Even better, the vouchers will have a market value because they can be sold to other companies.

## 4. AN INSURANCE SYSTEM THAT ENCOURAGES MORE PRESCRIPTION DRUG OPTIONS

A proposed rule by the US Department of Health and Human Services (HHS) would require essential health benefits in each state exchange to offer more than one prescription drug in each drug class. The HHS fears that by offering only one drug in each class, there is too much risk of a shortage of that particular medication. Insurers would be required to offer one drug per category or class, or as many as determined by the Essential Health Benefits Benchmark, whichever is greater. This proposal, which is expected to take effect this year, would effectively increase the market for prescription drugs.

## 5. NO COMPETITIVE IMPORTS

The amendment that would have allowed pharmaceutical imports from specified countries like Canada has been quashed, at least for the moment. The effect of such a move would have been

massive. The Congressional Budget Office (CBO) estimates that allowing these imports would save the government $20 billion over 10 years; a cost that would be multiplied in its negative effect on the industry when you consider non-governmental purchases. Given that government represents about 36% of total pharmaceutical expenditures, the Center for Medicare and Medicaid Services estimates actual loss to the industry would have been in the range of $5 to $6 billion/year.

## 6. PHARMA GETS TO PAY FOR COPAYS

In November, it was determined that pharma companies would be allowed to cover the cost of the copays on brand name drugs for people who get coverage under the exchanges.

This had been a sticking point. Before this change, under Federal law, drug makers were not allowed to assist in paying for copays for Medicare or Medicaid. This essentially gave drug consumers no option but to choose the (subsidized) generic alternative. The non-generic drug in many cases is very substantially - if not astronomically - more expensive. The exchanges, as it turns out, are excluded from this arrangement because the insurance offered under the exchanges is not a federal health care program. Now drug companies have a chance to make non-generic drugs competitive in the exchanges.

Why is paying for the copays by pharma a good thing for us? Again, it's because of the insurance effect. More people will use the exchanges if their costs are reduced, and the volume of sales will increase overall.

## WINNERS & LOSERS

While our industry as a whole may be well positioned to benefit from the new reforms, not every company will benefit equally. Billions of dollars are in play, and the smart pharma companies are positioning themselves to capture more of those government dollars. The winning ideas are:

- Sending out armies of sales reps last year, to ensure that their products were well positioned. These companies know that the influx will be greatest in the areas with the largest currently uninsured populations, particularly the South, where 20% are uninsured (compared to 11% in the North East and 12% in the Mid West).

- Stepping up comparative effectiveness testing now. The products that come out ahead will not necessarily be the ones with just the most compelling evidence, but those with the largest onslaught of evidence. Smart companies began undertaking these time-consuming studies in 2013, so they could dominate the marketplace in 2014.

- Helping harried doctors, not getting in their way. Practitioners are going to be busier than ever with 10 to 20% more patients than last year. The last thing they need is to squeeze in another pharma rep visit. Smart reps got their two cents in last year, before the crowds could hit the waiting room. They made an effort to get in and out fast, to ensure that doctors saw them as partners in improving efficiency. One of the things they can do for doctors is to help them understand the repercussions of the

### SIDEBAR

**Cheaper, Faster Drug Development**

After years of prodding by patients, investors, and politicians, the FDA has successfully opened the spigot on the drug development pipeline. In fiscal 2012, the FDA fast-tracked more than half of the drugs under its prevue using expedited reviews, according to *Pharmalot*. The median time for drug approval has plummeted from 19 months in 1993, to under 10 months in 2011. Not surprisingly, the cost of bringing a drug to market has also been declining. The number of new drugs approved per $1 billion of R&D spending is at its highest level in a decade, according to analysis from Mark Schoenebaum at ISI Group, as reported in *The Wall Street Journal*. All this is fantastic news for the industry and patients alike, and the Obama Administration continues to press for even further shortening of FDA timelines. But the number of patients tested in the expedited method is already nearly one fifth of the standard number. There's probably not a lot more to trim here, for the sake of speed. More importantly, if we want to keep the fast-track system, pharma companies need to take post market studies very seriously. Post-marketing studies are designed to make up for any potential shortcomings in scientific rigor before approval. Yet a study by *JAMA Internal Medicine* examined 20 molecules approved with the expedited system in 2008 and found that 4 years after approvals, as few as 40% of those commitments have been met. Faster and cheaper is good for the industry, and good for patients whose only hope may be an experimental drug. But if our industry doesn't stay on top of post-market studies, it may only take a single law suit to slam the breaks on the entire fast-track system.

*Affordable Care Act* on brands and consumers. Smart companies have already educated their reps.

## WILL THE AFFORDABLE CARE ACT SUCCEED?

Even with these six positive outcomes, there is significant cause for concern going forward. Clay Shirky, a widely read writer and professor of internet technologies, blogs persuasively that any new initiative taken on by a government is in effect a new business, and most start-ups fail. Failure, Shirky concludes, is the most likely option. And yet the *Affordable Care Act* has no out if this system doesn't work.

Failure is even more likely if you consider the people charged with creating it. Most of these people have spent their lives in government, and hence are least likely to have the background to understand what it takes to get such a fragile new entity off the ground. The most important requirement for any new business is to start small and grow incrementally. Government initiatives can accomplish this; President Kennedy's efforts to put a man on the moon are a perfect example: It took 10 years and our first step was to circle the earth with a monkey. If what Shirk predicts is true, the failure of the healthcare.gov website may in fact be just an example of what is to come.

## PHARMA NEEDS IT TO WORK

We're too far into the *Affordable Care Act* script to start over. The country is committed. If the *Affordable Care Act* rolls out according to plan, our industry stands to benefit. But if it fails, expect the government to come to our doorstep for a bailout.

If the healthcare marketplace fails to enroll enough young, healthy Americans, the cost of the new system will skyrocket. As soon as there is pressure to reduce costs, the pharma industry will be in the crosshairs again. Even if this experiment does somehow succeed in reducing overall healthcare costs, the government will be at our door when it's time to deal with the structural budget deficit, as healthcare is one of our nation's largest expenses. Proposals to allow imports, to reduce patent lengths, and others will inevitably resurface. Really, the question isn't whether or not the government will come to us to reduce costs, it's whether it will ring the bell or arrive with a battering ram.

President Obama's about face regarding his promise not to drop existing health insurance plans isn't helping matters. The *Affordable Care Act* needs all these dropped patients to move over to the new exchange and pick up coverage there. But why should they? They could just pay the ridiculously low individual penalty. In 2014, individuals who don't obtain health coverage will be subject to a paltry fine of $95 for an individual or 1% of family income, whichever is greater. In 2015, things will tighten up a bit when the fine increases to $325 per adult, or 2% of family income, whichever is greater. Still, the penalty only applies if the individual is getting an income tax refund. If there's no refund, there's no penalty whatsoever.

I am a Canadian, but I have chosen to build a CRO in the United States because the lower taxes and free market structure of the pharmaceutical industry here has created an environment that is more favorable to research than any other country. In the near-term future, I see blue skies. But I'd feel a lot better if I knew what weather tomorrow might bring. ◆

## 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.

# The Second Quadrant

## A New Year for Solubility Enhancement

By: Marshall Crew, PhD, President & CEO, Agere Pharmaceuticals, Inc.

As we launch into 2014, I'd like to review and update some of the data that summarizes the important challenges we face, but also cover the significant progress we've made. Last year, contributing authors to the column gave insights into what's driving the increase in insoluble compounds, and what excipient and solubilization technology providers are doing to innovate toward their clients' success. Their participation itself represents a growing need for collaboration, and a willingness to work together to achieve a common goal.

### THE NUMBERS & TRENDS

2013 has proven to follow the FDA-approval trend from the past 10 years. The FDA's Center for Drug Evaluation and Research (CDER) reported 26 NME approvals as of December 16, 2013, five fewer than the same time in 2012, and well below the 2012 year-end total of 39. With the 10-year average number of yearly approved NMEs in the range of 26 compounds, one might be inclined to ponder a silver lining.

A deeper dive into the data shows that there are promising trends and that the past significant investments may well pay off in the next several years. Data from the Pharmaceutical Research and Manufacturers of America (PhRMA) show that the investment in research and development over the past 20 years has been a steady 17% of the total pharmaceutical sales (PhRMA 2013 Profile). This is a significant increase relative to the 1980s when only 9% of sales was invested. So if there has been such an increase in spending, what indication do we have that there is an improvement in productivity? This can be found in the global pipeline when during that period we have seen more than a doubling of the number of compounds in clinical stage development (Figure 1) compiled from PhRMA industry reports. If one takes into account that the average time for a compound to navigate through the pipeline is on the order of 10 years, it is not hard to imagine that these investments will take time to manifest in terms of approved drugs. All things being equal and given that the clinical pipeline has grown significantly, there is good reason to believe that we will see a corresponding increase in approvals over the next few years.

While the pipeline appears to be growing in strength, there are other trends that are at play that cannot be ignored. The nature of the compounds moving through development and entering the market place is changing, and in particular, there are numerous reports of how early phase compounds are increasingly insoluble. Estimates of the percentage of insoluble NMEs in development today (in preclinical through Phase II clinical trials) vary broadly, and have been stated at 40%, 70%, and even 90%.[1-3] Regardless of the exact percentage, with over 10,000 NMEs in the combined preclinical and clinical development stages, the number of solubility-challenged compounds is extremely large.


However, one need not look only at the early phase compounds to see these trends. An Agere analysis of the approved compounds from the past 30 years shows the same trends. In Figure 2,

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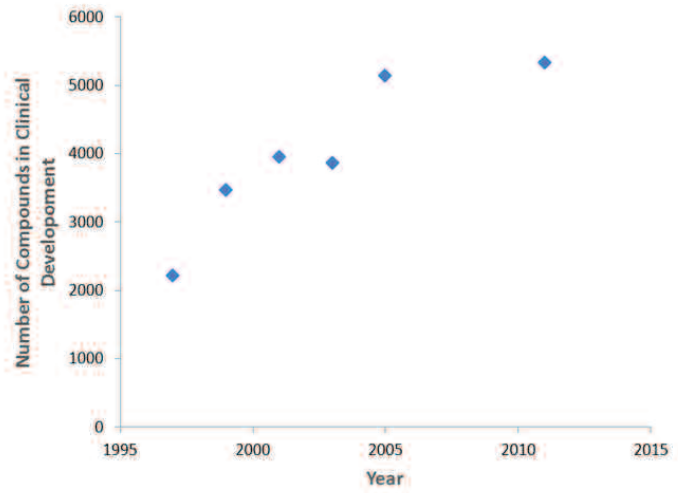
the average of the logP and log(solubility - mg/mL) of all approved compounds in a given year is plotted against the year in which they are approved.[4] As the graph clearly demonstrates, there has been a continuous rise in the lipophilicity and a corresponding decrease in the solubility of approved drugs. In fact, the average solubility of all approved drugs in 2012 was more than 10X less than those drugs approved in 1983.

In The Second Quadrant (Drug Development & Delivery, May 2013), I reported on an analysis conducted at Agere to map the solubility space of more than 1,300 marketed drugs from the past 30-plus years. We visualized this space by plotting the number of compounds with a given solubility and logP as a function of those two variables. Figure 3 compares the individual compounds approved in 2012 with this solubility space. As can be seen, the compounds of today are clearly on the edge of the averaged solubility space with a strong trend to higher logP and lower solubility.

Various reasons exist for the trend toward lower solubility and higher lipophilicity, many of them touched on by contributing authors to The Second Quadrant in 2013. Examples include the fact that diseases being addressed today are much more complex than those in the past; the nature of the binding pockets in modern drug targets favoring compounds with lower solubility; and modern methods for designing, synthesizing, and optimizing chemical libraries that have led to new chemistries with low aqueous solubility.

## FIGURE 1



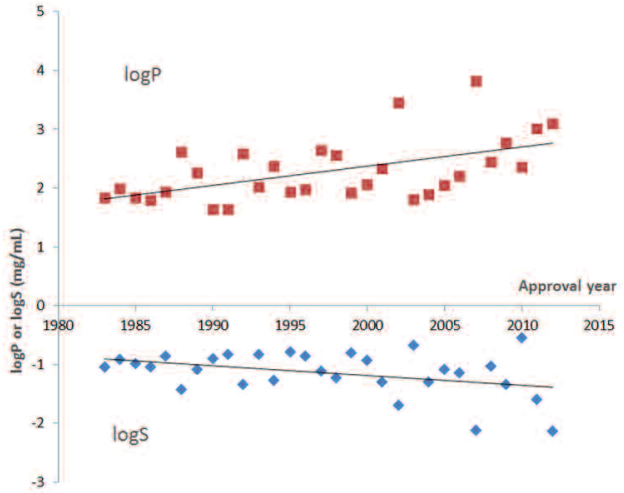

**The Number of Compounds in Clinical Development 1997-2011**

## SIGNS OF SUCCESS

With the trends showing a clear need, platforms for delivering poorly soluble molecules continue to be a strong need in the industry. We learned about many advances in The Second Quadrant series in 2013, and evidence of these contributions manifests in a growing list of drugs that have been approved that have leveraged a broad array of solubilization technologies. More than 40 drug products have benefitted from amorphous solid dispersions, supercritical fluid processing, SMEDDS, nanocrystals, cyclodextrins, and lipid technologies (the list can be found at http://www.agerepharma.com/collaboration/resources). This represents a small overall component of the overall number of approved compounds, but on the flip side of the coin, it also demonstrates that significant progress has been made throughout the past 15 years in the adoption of solubilization platforms.

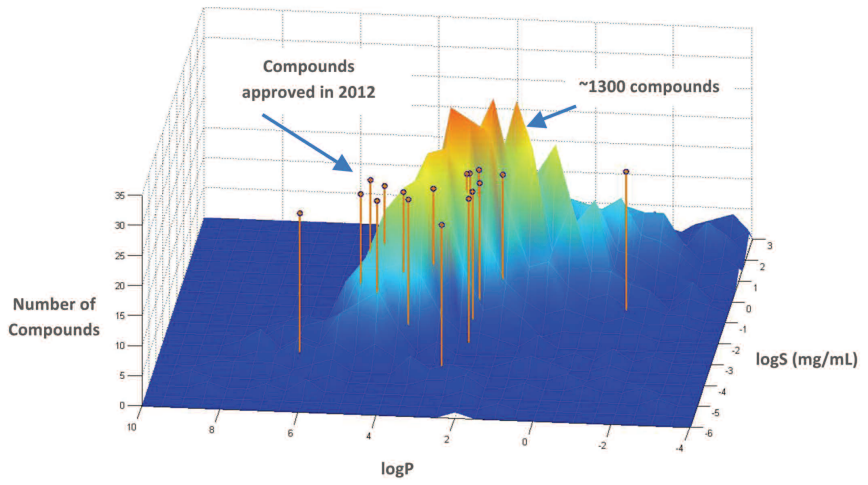
Adoption of new drug delivery technology is not purely composed of the

## FIGURE 2




**The Rise in Lipophilicity & Decline in Solubility of Approved Drugs**

## FIGURE 3




**Compounds Physical Property Landscape: Compounds Approved in 2012 Noted**

precedence set by approved drugs. Any vital industry experiencing an underlying shift in a key component of its products must also be seeing advances scientific knowledge and innovation. The pharmaceutical industry is certainly no exception. To gain more quantitative insight into how the scientific knowledge has expanded, Agere analyzed the number of journal citations that reference "solid dispersions." This study found that literature citations referencing solid dispersions grew from 8 in 1980 to more than 1,400 per year 30 years later. This growth in the literature demonstrates that the collective knowledge base of the industry is expanding exponentially.

A consequence of a broader and deeper scientific understanding of the issues surrounding delivery of poorly soluble molecules is greater adoption of the platforms required for successful products. Arguably, one measure of the successful translation of scientific knowledge into products is patents. Patents (applications and granted) have grown in a similar exponential pattern to the literature. As an example, the number of patents referencing solid dispersions has grown from 2 in 1977 to an estimated 668 for 2013.[5]

In summary, there are a number of indicators that show the pharmaceutical industry is making good progress to increasing the number of marketed drugs. As compounds in the global pipeline evolve to lower solubility, drug delivery is playing an increasingly important role in the successful development of drug products. Finally, given that these trends are 30 years in the making, it appears safe to say that solubilization is not a fad but rather firmly here to stay.

## NEXT ISSUE

In 2013, we gained insights from the perspectives of many companies that collaborate as part of the emerging supply chain on which pharmaceutical companies depend for overcoming poor solubility. Throughout the next few issues, we'll explore drugs have benefited from solubilization platforms. We hope to learn from the challenges faced, how technologies were selected, and key issues that came up and were overcome. If your company has had an experience in successfully delivering poorly soluble compounds that you would like to share, please contact me to be included. Other companies facing similar challenges and CROs supporting clients would benefit from your insights about what worked, what is still needed to simplify the process, and what could be done differently going forward. ◆

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4. Experimental data was used when publically available. All other values were estimated via calculation. All peptide and protein therapeutics were excluded.
5. Drug Bank, Agere Analysis.



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# Engineering the Perfect Click for Drug Delivery Devices

By: Chris Hurlstone

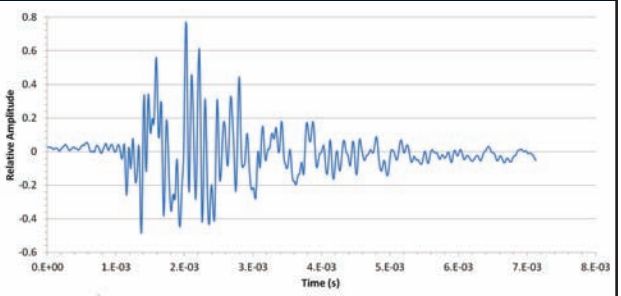
If you were to tell some people that one of the most frustrating aspects of the development of a drug delivery device would be the little clicks that it makes as part of its operation, they would probably think you had lost your sense of priority. Yet time and time again, the engineering of the click becomes a real and serious issue. Device developers know this - whether human factors experts or industrial designers, mechanical engineers, or risk analysis teams - yet this aspect of device design, like many others, is frequently not given the attention it deserves. So why is a click so important?

For many drug delivery devices, including inhalers but particularly pen and autoinjectors, the feedback users receive from a device during the sequence of use can be critical in helping them achieve effective and complete delivery of their medication. Designers will endeavour to make device use as intuitive as possible, but the products that we are considering are used by people from all walks of life, of all ages and physical condition, so intuitiveness is not always easy to achieve. Hence, feedback from the device can help give the user confidence that they are carrying out the steps required correctly, especially when these steps are part of the instructions for use and, if appropriate, patient training.

FIGURE 1


Clickhaler®, SureClick® & ClikSTAR® Devices

FIGURE 2




Raw Acoustic Waveform

## WAIT FOR THE CLICK...

Take the Asmabec® Clickhaler® for example, a dry powder inhaler for asthma treatment. The IFU instructs the user to "press the dosing button down firmly once until it clicks, then release." Or the Aranesp® SureClick® autoinjector IFU, which references first and second clicks, with the instruction to "Wait until the second click before lifting the injector from the injection site." And then there is the ClikSTAR® Lantus® for injection of insulin - "screw in the insulin cartridge holder until it clicks into place…" Or, as a final example, the Advair® Diskus® - the current world best seller - which has three basic instruction steps: "Open, Click, Inhale." All these instruction steps are critical to achieving successful delivery of a full dose, and all are dependent on the user hearing and correctly interpreting the click.

## THE CLUE IS IN THE NAMES...

So clicks are vitally important for users, and yet we see time and again they are not good enough. Engineers and designers face

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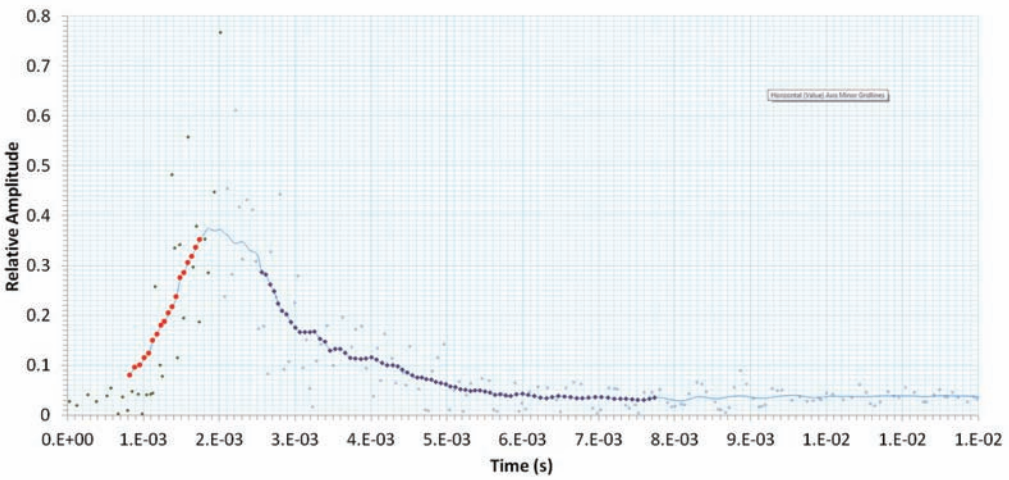
this issue frequently, and there is a wealth of evidence from user research - formative and summative - that highlights not only the criticality of these audible cues and how they combine with other aspects of interaction design to influence user behavior, but also what happens when clicks are not right. Subtle variations can mean the difference between success and failure when self-administering vital medication, and as there won't always be a second chance, the user must be certain that they have received the medication they need. Yet clicks are different to other critical characteristics of device performance, such as actuation forces or dose volumes, in that they are not so easy to define and describe. We know what we want when we hear it - and we know what we don't want as well - but how can we describe clicks accurately? Maybe we should start with defining what a good click "looks" like?

**FIGURE 3**




**Smoothed Acoustic Waveform**

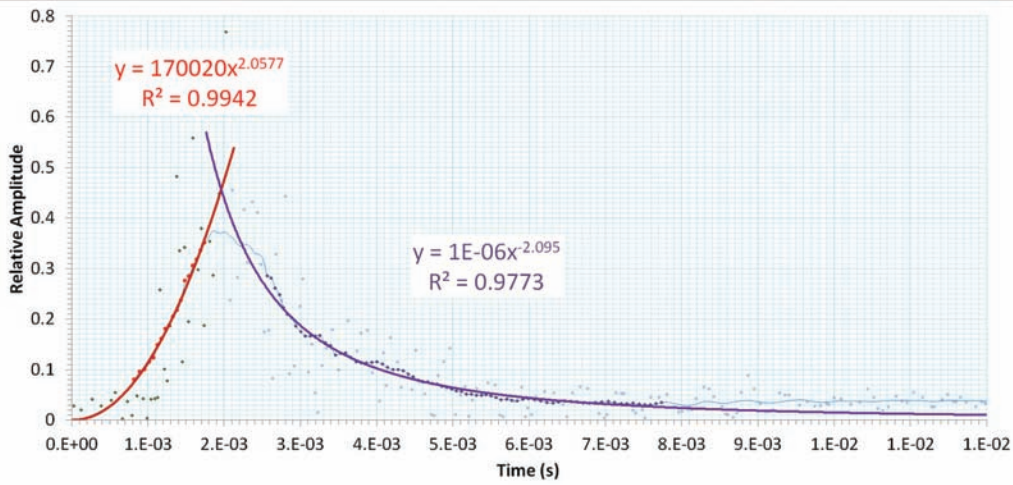
## VISUALIZING THE PERFECT CLICK

It is one thing to recognize the importance of a device performance characteristic, but quite another to know how to engineer it; to know how to develop, optimize, and verify a characteristic so that we get what we need, when we need it, every time.

We can (usually) describe quite easily, in subjective terms, what we want from the click that a device has to make. For example, we can say that it needs to be clear, distinct, gentle, or that it needs to give an indication of quality, robustness, or re-assurance. And it certainly mustn't be scary or alarming. We know what we mean and it is certainly a good idea to think in these terms to begin with. But to really get into the detail, we need to establish a more objective set of descriptors that allow us to define good and bad clicks.

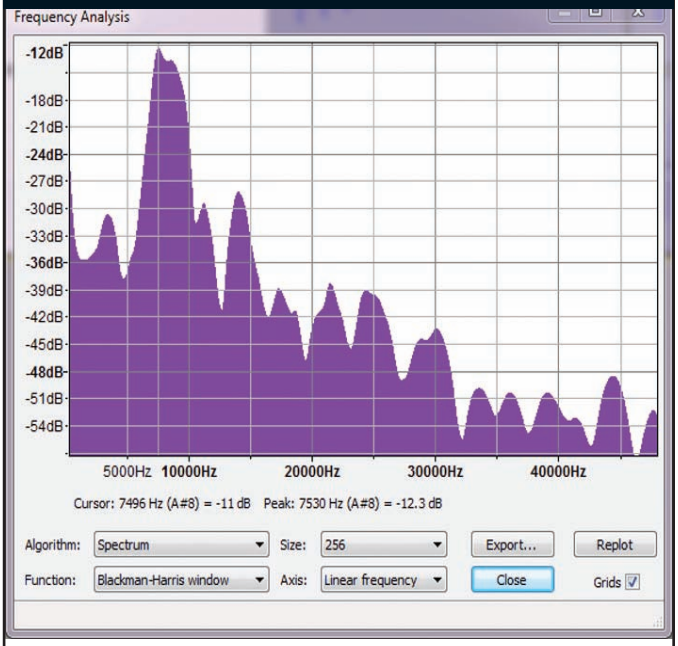
A good - and fairly obvious - starting point is to look at a click's acoustic waveform. This is the best way to characterise a sound, after all, and that is primarily what a click is. With high-quality recording equipment and software, it is relatively straightforward to obtain a high-resolution acoustic signal, in terms of amplitude versus time. But care must be taken when recording the sounds, especially if you wish to exclude external (consequential) sounds such as reverberation. If you want to isolate the click fully from all external

**FIGURE 4**




**Smoothed Acoustic Waveform With Power Regression Functions**

FIGURE 5




**Frequency Spectrum**

sounds, then a sound-proof anechoic chamber will be necessary. Bear in mind though, that a click heard in a chamber is not how the user will hear it. Similar consideration needs to be given to the way you hold the device, as quite often the caseworks will act as soundboards.

Once you have obtained the acoustic waveform (Figure 2, which shows a typical waveform for a device click), you can then apply a range of smoothing and clipping algorithms to give an amplitude envelope that can be characterized for each of the click's two main stages - attack and decay - as shown in Figures 3 and 4. This approach is a little different to applying a standard ADSR (Attack, Decay, Sustain, and Release) envelope as might be done in other acoustic analyses. However, clicks are by their nature very short acoustic events, and if we can reduce the level of detail while retaining the level of characterization needed to work effectively, that is generally a good thing.

Once completed, the characterization of the acoustic waveform will result in a set of parameters that can be used to describe each click in a simplified but more manageable way. This opens up opportunities for specifying (and hence also verifying) clicks, for comparing different clicks in order to improve or optimize them, or for comparing the consistency of the same click, perhaps under different conditions, such as hot or cold temperatures.

As well as looking at the amplitude waveform of the sound, it is also possible to use Fast Fourier Transform analysis to obtain a spectrum of sound frequencies that make up the click. Off-the-shelf software packages can carry out this analysis very quickly and effectively (Figure 5 shows a screen capture from the Audacity software package, which is one possible tool). As for the amplitude waveform, these outputs can then be clipped and smoothed as appropriate to give a more readily applicable tool when seeking to characterise the click's acoustic signature.

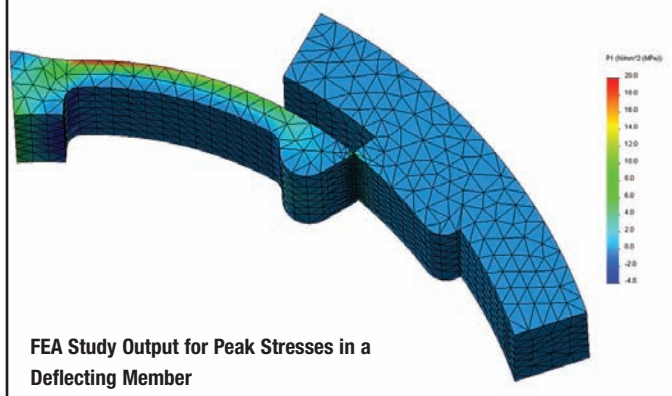
How much detail is required when capturing and analysing the sound characteristics of the device will vary on a case-by-case basis. The point here is to show that, through careful application of reasonably accessible tools and methodologies, important acoustic device characteristics can be readily described, analysed, and understood.

## WHAT INFLUENCES CLICK CHARACTERISTICS?

When considering click characteristics, the first thing to determine is what is actually making the click, which might not be what you think. A typical click will involve a deflecting member with a relatively sharp tipped form somewhere on its length; this rides over a step or falls off an edge, which causes it to snap back. In some embodiments, the substantial part of the click will be generated by this deflected member returning quickly and striking a surface, but in many cases, it is the action of the tip falling off the edge - so that the member accelerates through the air - which generates the sound energy. This is further combined, to differing degrees, with vibration of the edge feature itself (and any features that support it) as these are also likely to vibrate to some extent due to the rapid removal of the reaction force.

Because sound is a very low-energy phenomenon, it only takes small variations in system properties, such as feature stiffness, inertia, additional system vibrations (for example a rattle), or damping, to result in very different sounds. Hence, material properties (modulus, density) feature design, joint characteristics (if

FIGURE 6



**FEA Study Output for Peak Stresses in a Deflecting Member**

the click features are part of an assembly), and how the device is held or secured can all influence the characteristic. When developing a set of click features, all of these elements need to be considered, just as when investigating an unwanted click in an existing system. In the latter case, it may also be worth using high-speed video - possibly synchronized with acoustic measurements - to establish exactly what is happening at the instant of the click. Things may not be what they seem…

## HOW REPEATABLE WILL THE CLICK BE?

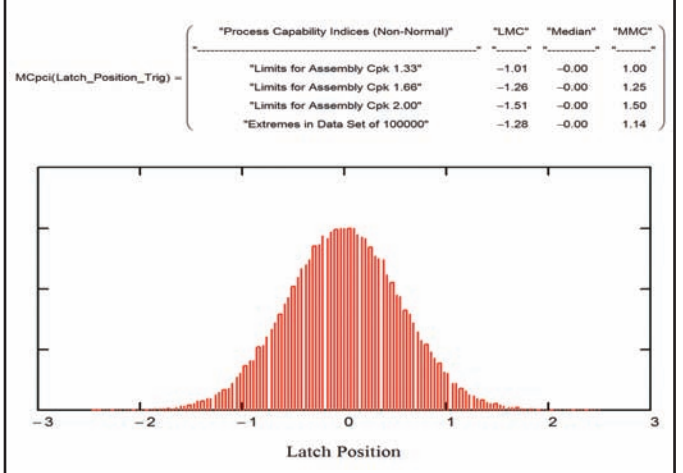
Any variation in the design parameters that influence the system properties previously described will clearly result in a variation in the click that we hear. Some parameters will be relatively constant once the design specification is finalized, but others can also vary through the lifecycle of device use.

The impact of temperature on material - and hence feature stiffness - needs to be considered, and material selection will clearly be a driving factor. Material suppliers DuPont™, for example, provides information on which of its polymer grades might be most appropriate for a particular application, and provide an interesting case study on their Delrin® 100ST super tough grade used within the automotive industry. It is selected for a combination of properties, including toughness and flex fatigue at temperature extremes in order to ensure the required auditory safety signal (in other words, the click) is achieved on replacement of a fuel filler cap.

This automotive example may be an extreme case in terms of possible temperature of use (the material is approved for use from -40°C to +80°C), but it is easy to envisage scenarios in which the environment of use of a medical device, though not as extreme, is either difficult to control (for example, the emergency use inhaler or injector) or different to the conditions anticipated by the designer (such as a device used straight after removal from a fridge, where it is stored due to the nature of the drug formulation). Also, the nominal form and stiffness of the key features may not remain constant throughout device life; permanent strain may arise from over-stressing, fatigue (due to repeated use or play by the user), or creep, which can occur if the design allows the main click features to be left in a deflected, stressed position for significant periods of time.

Engineering analysis can be of assistance here and, for these examples, finite element analysis is an effective way to develop system understanding. For example, changes in material modulus arising from temperature changes allow assessment of the impact on contact forces (which relate to click energy), while a review of peak

**FIGURE 7**




**Tolerance Analysis for Click Timing**

strains and stresses (see Figure 6 for an example of an FEA study) across the range of anticipated deflections will inform review of susceptibility of the design to permanent deformation or creep.

Another aspect of variation inherent to a design is the manufacturing tolerance that can be achieved, and tolerance analysis is an indispensable tool for assessing these potential effects. We all remember that the contact force for a deflected member (of the kind shown in Figure 6) varies with the cube of the section thickness, but understanding the combined impact of all likely variations - including tolerances on diameters, ovality, or concentricity - is less intuitive though readily achievable with a bit of basic MathCAD.

## GOOD CLICKS - A QUESTION OF TIMING

Where tolerance analysis can also prove invaluable is in the prediction of variation in the timing of a click. Going right back to the use of clicks as a reference point in an IFU or PIL, if we are asking the patient to react to the generation of a click from a device, we need to be sure the click happens at the right time. This can be critical if the click is linked to mechanisms that may influence dose cutting or dose delivery, engagement/release of safety features, or successful location/retention of a key element of the device. For such critical features of a design, it is usually necessary to build in a safety factor so that, allowing for system variations, the click will always happen before or after (depending on the case in question) the critical device state is achieved. Tolerance analysis then allows the design engineer to assess what happens at the other end of the system variance - how early or late - the click might occur, and what the implication might be. Figure 7 shows a very basic tolerance stack

that illustrates potential angular misalignment in the timing of two diametrically opposite clicks which, in theory, should happen at the same time, but in practice will probably not.

By building up a tolerance analysis in a mathematical package, such as MathCAD, rather than in a spreadsheet, it is comparatively straightforward to introduce more complex functions and inter-relationships. This allows us to take into account complex trigonometry or system dynamics, such as spring and frictional forces, and hence achieve a much more comprehensive picture of a system and its sensitivities and variations. Through use of statistical methods, such as Monte Carlo analyses, and input data, including desired and/or achieved process capabilities, a full picture of the timing of a click relative to other key mechanism functions can be derived for a range of manufactured devices - real or virtual.

## CHOOSE YOUR WEAPONS....

This article has outlined a range of tools and techniques for objectively describing many of the characteristics of a highly subjective, but often important and overlooked, device performance requirement - the click. Not all of this analysis is needed every time a click is required or desired, but being aware of these options and how they can be applied during the development process (not during design verification and validation) puts the designer in a stronger position. Device testing - from prototypes to pilot devices, in the lab and in the hands of users - is of course another key part of developing an effective click, but to rely solely on testing without building an understanding of how the click is working risks delays, through poorly guided design iteration, and potential compromise on performance.

Yet, to reiterate what was said in the introduction, compromise may simply not be an option. The need to engineer designs that pose a minimum risk of use-error is one of the hot issues in medical device development at the moment - a key focus of the US and European regulatory bodies whose approval for product launch is required. All aspects of user-device interaction can be critical to success in this regard, including the humble click, and more and more people in the industry are recognizing and learning this, sometimes the hard way. And the hard way can be very hard indeed. ◆

## BIOGRAPHY

**Chris Hurlstone** is currently the Director of Engineering for Team Consulting, directing the company's engineering expertise and working with the heads of development groups to ensure Team delivers consistently world-class consultancy services and robust, reliable, user-focused, and commercially successful device solutions. He is still very much hands-on, especially in areas such as risk management, technical audit, design verification, industrialization, and technical trouble-shooting. Mr. Hurlstone has more than 15 years of experience with Team, developing technologies and devices for healthcare markets. He has successfully brought products to market in technical lead and project management roles, including inhalers, injectors, and an award-winning ophthalmoscope, and in the process, has worked extensively with global suppliers of manufacturing and technical expertise. A named inventor on numerous patents, he has a strong track record in delivering innovative and robust solutions to many of Team's international clients. Mr. Hurlstone graduated from the University of Cambridge with a degree in Mechanical Engineering and a post-graduate diploma in Design, Manufacture, and Management.

# A new HPMC capsule for optimum formulation of pharmaceutical dosage forms

by Dominique Cadé, PhD

Eliminating gelling systems solves the variability of performance

True pH and ionic media independence in dissolution

Stability at a wide range of temperatures

Moisture sensitive compounds can now be effectively encapsulated

## A powerful alternative for pharmaceutical dosage forms

Polymer choices in pharmaceutical dosage forms have always been a balancing act between performance and development time, and historically has been shaped by the interactions of gelatin. The first generation of HPMC capsules, which relied on a secondary gelling agent, were recognized by formulators as having issues with dissolution performance and product stability. Fortunately, new scientific discoveries in polymers and capsule manufacturing have resulted in the creation of the next generation of HPMC capsules – one that offers better performance and reduced development time compared to gelatin and first-generation HPMC capsules.

Capsugel, the market leader in research and development in this area, is now offering these second-generation HPMC capsules under the trade name, Vcaps® Plus capsules.

In a number of studies, Vcaps Plus capsules have been shown to deliver optimized compound stability and predictable *in vitro* dissolution while also helping to eliminate the complexity in formulation development. Known globally for their reliable and predictable performance, Vcaps Plus capsules are well suited for over-the-counter (OTC) or off-patent products as well as for new chemical entities (NCEs).

## True pH and ionic media independent performance

Traditionally, HPMC capsules were created using secondary gelling agents and ionic gel promoters, which have been found to interact with dissolution media and delay compound release from the capsule. The activity of the gelling agent kappa-carrageenan, for example, is enhanced by potassium and calcium cations contained in many foods. The extent of the resulting delay in dissolution time was shown in an *in vitro* test in which caffeine-filled traditional HPMC capsules were dissolved in a number of dissolution media. In the simulated normal acidic environment of the stomach (pH 1.2 USP), 90% of the caffeine was dissolved within approximately 15 minutes (Figure 1). Adding 2 g/L of potassium chloride (KCl) to this medium resulted in no dissolution after 15 minutes and a caffeine dissolution between 70% and 80% after more than one hour. Increasing the KCl content to 9 g/L delayed caffeine release even further, with a dissolution rate of just over 10% in 45 minutes. Results with simulated milk fluid were equally disappointing. Similar delays in dissolution times were observed and attributed to carrageenan in an independent study (Ku et al., 2011). Of course, such long delays in capsule dissolution are unacceptable particularly for rapid-relief products.

Capsugel addressed this situation by developing a proprietary new thermal gelation manufacturing process for Vcaps Plus capsules that eliminates the need for gelling systems all together and provides true pH and ionic media independence in disintegration. *In vitro* tests showed that these second-generation HPMC capsules had similar rates of dissolution at pH levels of 1.2 and 6.8 and with simulated milk fluid, achieving a nearly complete dissolution of the caffeine contents within approximately 30 minutes (Figure 2). Even adding 2 g/L or 9 g/L of KCl to the dissolution medium did not affect the performance of Vcaps Plus capsules, with dissolution of over 90% within 30 minutes, even under the most disadvantageous condition.

These findings were supported by an independent study that compared the dissolution performance of traditional and second-generation HPMC capsules

(Ku et al., 2011), and underscores the superior performance of Vcaps Plus capsules.

## Ideally suited for moisture sensitive compounds

While gelatin capsules have been effectively used for over a hundred years, due to their excellent flexibility and highly desirable dissolution properties, they are not typically the polymer choice for moisture sensitive compounds. Vcaps Plus capsules on the other hand have a three-fold lower moisture content than gelatin capsules and are less hygroscopic. That equates to fewer broken capsules due to brittleness and less of a chance of drug degradation compared to gelatin capsules.

## Improved stability at high and low temperatures

Capsugel in-house studies and an independent study conducted at Wyeth (Ku et al., 2010) have demonstrated the superior stability of Vcaps Plus capsules. An exposure of up to one week to temperatures ranging from 4°C to minus 18°C did not change the appearance or performance of unfilled Vcaps Plus capsules in closed high-density polyethylene (HDPE) bottles.

The same stability was found with empty Vcaps Plus capsules in fully-filled glass bottles that were heated for 24 hours to temperatures ranging from 40°C to 60°C.

In long-term storage condition studies, including a 6-month storage at 40°C and 75% relative humidity and 2 years at either 25°C and 65% relative humidity or 30°C and 70% relative humidity, Vcaps Plus capsules disintegration and dissolution characteristics remained unchanged.

The wider temperature capabilities of Vcaps Plus capsules make them the perfect choice for longer term storage and when used in progressively unpredictable home environments.

## Superior machinability

Traditional and second-generation HPMC capsule attributes have been compared on many common high-speed capsule filling machines (Ku et al., 2010). With respect to filling and rejection rates, Vcaps Plus capsules performed much like gelatin capsules and were superior to traditional HPMC products. In addition, Vcaps Plus capsules can be adapted for use with liquid compounds.

## Wide regulatory and industry acceptance

Vcaps Plus capsules are manufactured in certified ISO 9001 facilities and in accordance with IPEC's (International Pharmaceutical Excipient Council) Good Manufacturing Practice (GMP) Guide for Bulk Pharmaceutical Excipients. They are acceptable for use in pharmaceutical and dietary supplement oral dosage applications in major markets of the US, Canada, EU, Japan, and Australia. In addition, Vcaps Plus capsules are certified Kosher Ko and Halal by IFANCA, and are approved for vegetarians by the Vegetarian Society.

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**Secondary gelling systems create variability while Vcaps Plus capsules, without gelling agents, provide ionic and pH independence in dissolution.**

**Figure 1**

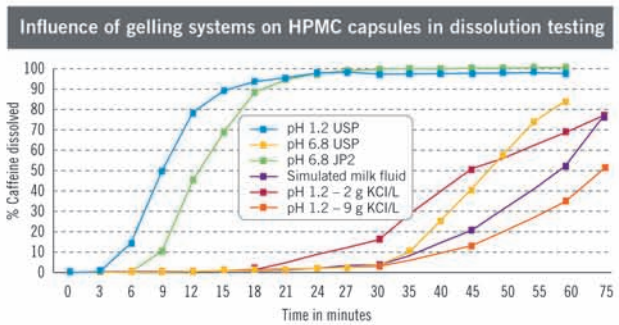
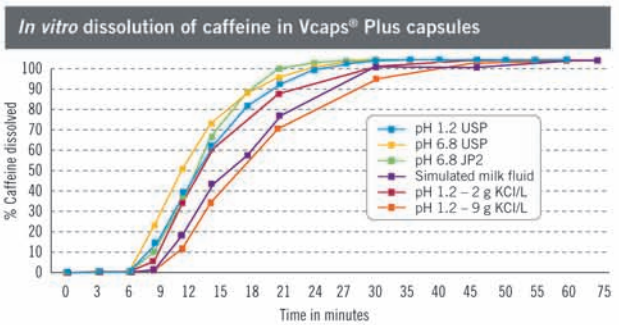



**Figure 2**

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# Roundtable Discussion

## Reformulating Opioids to Deter Abuse

By: Cindy H. Dubin, Contributor

Pain is a significant public health problem in the United States. It is estimated that over 100 million people in the U.S. live with chronic pain.[1] Prescription opioid analgesics are the mainstay of pharmacologic management of pain. They are administered through various routes and are available in many dosage forms. In the past two decades, the use of opioid therapy for the treatment of pain has dramatically increased. Simultaneously, opioid prescription abuse and overdose has markedly increased.[2,3] From 1997 to 2007, the milligram-per-person use of prescription opioids in the U.S. increased from 74 to 369 mg, an increase of 402%.[2] In addition, in 2000, retail pharmacies dispensed 174 million prescriptions for opioids; by 2009, 257 million prescriptions were dispensed, an increase of 48%.[4] National surveys show that opioid misuse has increased dramatically over the past decade and that opioid medications have surpassed cocaine and heroin as the leading drugs of abuse.[5,6]

Due to the emerging issues of opioid misuse and abuse, the FDA issued a new Risk Evaluation and Mitigation Strategy (REMS) for

extended-release (ER) and long-acting (LA) opioids in July 2012. The REMS program stems from the national prescription drug abuse plan that was announced by the Obama administration in 2011. According to U.S. Pharmacist.com,[7] REMS is a risk management plan that exceeds standard drug prescribing information; the FDA selected the ER and LA formulations of opioids because of the inherent risks of using these drugs. These formulations contain greater amounts of drug compared to the short-acting formulations, thus making those medications more dangerous in situations of abuse and misuse. The program focuses on educating providers and patients on the safe use of ER and LA opioids while ensuring that patients who require treatment with opioids have access to them. Manufacturers are responsible for creating educational programs and materials for all Drug Enforcement Administration (DEA)–registered prescribers.

In an effort to further safety precautions with the use of ER/LA opioid analgesics, the FDA has imposed safety labeling changes and postmarket study requirements. The labeling changes will include an updated indication emphasizing the use of ER/LA opioids in patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment is inadequate.[8]

In this exclusive *Drug Development & Delivery* magazine roundtable discussion, several Specialty Pharmaceutical company executives were asked to share their thoughts about FDA's labeling requirements, describe their company's formulation technologies, and explain their vision for where they think the opioid market is headed. Participants are: Ted Andrew, Product Manager-Rx Softgel, Catalent Pharma Solutions; Nasrat A. Hakim, President & Chief Executive Officer, Elite Pharmaceuticals Inc.; Bob Radie, President and CEO, Egalet Ltd.; and Anthony Soscia, President, Atlantic Pharmaceuticals.

**Q: The FDA "limitation of use" labeling language suggests that extended-release opioid-containing products should only be used when other alternatives have not been successful. Do you think that this may eventually drive physicians to further prescribe immediate-release opioids and non-opioids as an alternative for chronic analgesic therapy?**

**Mr. Soscia:** The labeling changes for ER/LA opioids were primarily intended to address the Physicians for Responsible Opioid Prescribing ("PROP") Citizen's petition filed in July 2012, which requested changes to the approved labeling of all Extended-Release/Long-Acting (ER/LA) opioid analgesics, quantity, and day limits, and that ER/LA dosing be limited when prescribed for non-cancer pain. The current language deletes the reference to moderate pain and adds the requirement that the prescriber has explored other treatment options. This change is intended to encourage prescribing decisions based on an individualized assessment, which is necessary for any patient on ER/LA opioids.

I do not believe it is FDA's intention to push prescriptions one way or the other but there may be a prescribing shift to immediate-release (IR) opioids and non-opioid treatments as there are certain patients taking ER/LA therapy who may be better served by IR opioids or non-opioid therapy. In addition, there are several side effect trends being observed with the chronic use of opioids in certain populations. These include hyperalgesia and alterations in hormonal production such as testosterone. In certain cases, an acute, immediate-release product may be more appropriate. The FDA will most likely be following these trends very closely.

**Mr. Andrew:** The FDA has taken a proactive approach to addressing the growing epidemic of prescription drug abuse by narrowing the scope of extended-release labeling to a second level therapy, only after immediate-release, faster-acting opioids and non-opioid treatments are exhausted or not applicable.

The "limitation of use" labeling is an effective step that will, at a minimum, serve to educate the patient and physician, which in turn, can foster a more substantive dialog about the risks and other treatment options available. However, ultimately, this is a physician-patient decision so I do not feel like the movement to more immediate-release prescriptions at the expense of extended release will be significant.

**Mr. Hakim:** I do not believe the "limitation of use" labeling language will drive physicians to switch from extended-release opioids to immediate-release opioids. I believe the vast majority of physicians already understand both the benefits and shortcomings of extended-release and

immediate-release opioids and prescribing will continue to be driven by what is best for the patient. Given all considerations, I believe extended-release opioids will continue to be the primary choice for chronic pain.

**Q: There are several types of technologies being evaluated for abuse deterrence i.e. physical, aversive, antagonist, and pro-drug. How do technologies in the same class differentiate themselves from other technologies and from generics that may pursue competitors' technologies?**

**Mr. Andrew:** As the public and regulatory pressure for effective abuse-deterrent opioids increase, the technology available continues to expand. The abuse market continues to develop to address new trends in abuse. This creates an environment where an effective abuse-deterrent technology will need to continually evolve and/or be multi-level to be effective in the longer term.

While different abuse-deterrence technologies have strengths and weaknesses, a successful approach needs to balance therapeutic effectiveness, level of abuse deterrence, and cost considerations. For example, while incorporating an aversion or antagonist adds complexity to the formulation to prevent abuse, it could potentially impact patients taking the medicine as directed. Physical deterrence is another method that has shown some initial promise making it more difficult to abuse, however, can be readily abused by adding manipulation steps.

**Mr. Hakim:** Key factors that will differentiate these products include safety, which includes product attributes such as robustness and stability. For example, within the antagonist category, there was an abuse-deterrent product pulled from the market due to stability issues. Companies developing new products will want to avoid such issues.

Intellectual property is also a differentiator. The area of opioid abuse resistance has the interest of many companies and this has led to a large number of patents for abuse-resistant technologies. To be successful, companies will not only have to develop a product to address the market and regulatory needs, but the product will need to have patent protection. Any company introducing a new abuse-resistant product can expect to be challenged in the courts by competitors.

Finally, with regard to epidemiological data, the FDA would like to see a number of years of epidemiological data to determine what technologies work and, given time, this data will differentiate technologies and products.

**Mr. Soscia:** Differentiation within and between classes is an important question with regard to establishing the market longevity of the branded products containing abuse-deterrent technologies. The abuse-deterrent product's market life is a key metric to observe meaningful changes in abuse-deterrence before generic penetration. It remains to be seen how the FDA is going to allow generic competition to technologies in the same class. Questions include issues of abuse-deterrent matching or equivalence on the category and tier abuse deterrent labeling. What constitutes abuse-deterrence equivalence? Will a generic have to match an innovator product with Phase 4 studies that may be included on the innovator label?

Other questions and issues arise relative to incremental increases in abuse-deterrence in the same category. For instance, if a new technology exhibits statistically significant improvements in drug extraction resistance or in nasal liking compared to a currently marketed abuse-deterrent platform, will the FDA grant the new entry a branded status and remove the former abuse-deterrent product? How about other classes of drugs that are known to exhibit safety issues if accidentally or intentionally abused? Can those be reformulated and will the FDA force or agree to removal of the reference listed drug? This is certainly only the beginning of myriad of questions that will evolve in this space. The FDA labeling changes should encourage current and future development of these products but not be used in a way to stifle long-term competition or more advanced technologies.

**Q: Describe your abuse-deterrent formulation technology and how it works to deter abuse yet maintain patient effectiveness.**

**Mr. Soscia:** Our patented abuse-deterrent drug delivery technology is called SMART/Script™ (SMART/Simple, controllable, resistant, insoluble, physical trap). The Atlantic technology is unique amongst physical technologies in that when a moderate amount of physical force, such as that incurred by chewing or grinding with a coffee mill, is applied to the product, the drug contained is sequestered and reduced


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from dose dumping. This decrease in release may be permanent depending on the circumstances. When taken intact however, the drug will release as intended. The sequestering action does not require an external solvent to activate (a.k.a. gelling agents). It can be applied to both immediate- and sustained-release drug candidates whereas most platforms take either an immediate-release or sustained-release abuse-deterrent approach.

**Mr. Hakim:** Elite's proprietary abuse-deterrence technology uses an antagonist approach and is a multi-particulate formulation in a capsule. It uses a two-bead system consisting of the opioid agonist and the opioid antagonist, naltrexone. Both bead populations are the same size, shape, weight, density, etc., so the bead population cannot be differentiated between the two. When our product is taken as intended, the opioid will release and the opioid antagonist will pass through the body unreleased, giving the patient the desired therapeutic effect. If the product is tampered with, the naltrexone will preferentially bind to the same receptors in the brain that the opioid would target, rendering the opioid useless.

**Mr. Radie:** Egalet has created two drug delivery systems, each with abuse-deterrent features and the ability to control the release profile of the active pharmaceutical ingredient. Our one-component system is used to produce tablets, such as Egalet-001, that consist of a hard matrix that is difficult to crush, grind or dissolve and that also controls the release of the API. The matrix, which contains the API as well as inactive agents, erodes over time in the GI tract, releasing the API.

Our two-component system is used to produce tablets, such as Egalet-002, that consist of a matrix similar to the matrix that is a part of our one-component system, but that is surrounded by a water-impermeable, non-eroding, hard shell made of polylactic acid that creates a cylinder, with the API-containing matrix exposed at both ends. The shell serves to limit the portion of the matrix's surface area that is exposed to the GI tract, which allows us to tailor the release rate of the API and makes it even more difficult to crush or grind the tablet, thereby enhancing its abuse-deterrent properties. We use an injection molding technology to create the matrix and shell.

**Mr. Andrew:** Catalent OptiGel Lock™ technology incorporates multi-level abuse deterrence in a softgel dose form. First, because it is in a softgel form, it cannot be ground, grated or blended to create micro particles for both inhalation and further diversion. Second, numerous formulations can potentially be developed that may reduce the syringeability and render the remaining API unavailable for misuse. In addition, the same technology serves as a barrier to heat and solvent extraction and concentration of the formulated opioid.

**Q: How does your technology satisfy the FDA's proposed abuse-deterrent labeling requirements and still promote patient safety?**

**Mr. Radie:** Using our proprietary technology platform, we have developed a pipeline of clinical-stage, opioid-based product candidates in tablet form that are specifically designed to deter abuse by physical and chemical manipulation while also providing the ability to tailor the release of the API. In addition to our planned clinical trials for Egalet-001 and Egalet-002, we are currently conducting abuse-deterrence studies with both product candidates in accordance with the FDA draft guidance, with the goal of obtaining abuse-deterrent claims in our product labels.

We believe that our systems offer several advantages. For example, with regard to abuse deterrence, abusers often seek to accelerate the absorption of opioids into the bloodstream by crushing in order to swallow, snort or smoke, or dissolving in order to inject the drug. Tablets produced using our systems have physical and chemical barriers intended to deter these common methods of abuse.

Additionally, we can tailor the release. In our tablets, the API is integrated into the matrix, which makes it difficult for abusers to extract quickly. However, when the tablet is exposed to GI fluids, the matrix erodes, thereby releasing the API. Using our technology, we can change the amount and composition of the polymer used to create the matrix formulation and can vary the surface area of the matrix exposed to the GI tract. By varying the matrix composition and

surface area, we can control the rate of erosion of the matrix and the rate of release of the API, which allows us to develop products with immediate-release, extended-release, and sustained-release profiles.

**Mr. Soscia:** A product formulated with SMART/Script™ will satisfy the pre-marketing Tiers and Categories in the recently released FDA guideline regarding abuse-deterrent labeling. If the Smart/Script product is taken as directed, the drug will release in the same manner as the currently marketed products.

**Mr. Hakim:** Our formulations, when intact and taken as intended, provide the delivery of the drug in the same manner as the current extended-release formulations. The products will have the same safety and efficacy profile as current products on the market. If the drug is crushed, then our technology will release an antagonist, which will reduce the euphoria level achievable through whichever route of administration the abuser might want to use.

**Q: What do you see as the pros and cons of immediate-release vs. extended-release opioid formulations as they relate to abuse deterrence?**

**Mr. Hakim:** The objective of the industry is to create abuse-resistant technologies that are effective for both immediate-release and extended-release products. The technologies that work for each type of product may be different or maybe not, but the key is simply that they are effective. If the industry can achieve that, then the choice of using IR or ER will be driven by the patient needs and not by any external factors. This is where I believe the market is heading.

**Mr. Andrew:** Immediate-release products tend to be over prescribed for acute pain and give a more euphoric feeling compared to extended-release products. Thus, there is a view that immediate-release formulations may more readily lead to addiction.

While extended-release products potentially offer pain management with a lower potential for addiction, the danger occurs when these products are manipulated through crushing or extraction to convert to an immediate-release form. Having a higher concentration of active ingredient than the immediate-release version, the risk of overdose is greater.

Abuse-deterrence technology, in order to be effective, should be applicable across formulations. While the mechanism of abuse can vary, the overall top line methods should be addressed: oral (dose dumping with alcohol), nasal (crushing), injection (extraction), rectal, and smoking.

**Mr. Soscia:** I believe abuse-deterrent formulations need to be applied to the entire category otherwise you just push abuse to another non-abuse deterrent product (i.e. the pushing down on one side of a balloon to see the other side rise). That theory has been borne out with the reformulation and removal of the previously marketed form of OxyContin. While the epidemiological data is still being collected and analyzed, there was an early observed shift in abuse from the newly reformulated "hardened" OxyContin to other molecules, primarily to immediate release oxycodone products. Empirically this makes sense, as abuse would be driven to the molecule that can be most easily acquired and manipulated. Currently, the number of prescriptions in the U.S. dispensed for immediate-release opioid greatly outnumbers those for extended or long-acting formulations and I believe that trend will continue. In addition, as a 30mg IR oxycodone contains the same amount of API as an ER 30mg oxycodone product there should be a matching abuse-deterrent immediate-release dosage form to compliment the latter. The majority of abuse-deterrent technologies are focused on the extended-release market while the immediate-release market has very few technologies. I believe it is possible to re-brand the generic immediate-release space using Atlantic's technology and further focus on branded products such as an immediate-release, single-ingredient hydrocodone. This product in particular is a priority due to the hepatoxicity, ototoxicity and high abuse rates of hydrcodone:acetaminophen IR combinations.

**Q: Is there anything you'd like to add or comment on that is not discussed above?**

**Mr. Hakim:** The barriers to abuse are very different between physical versus pharmacological approaches. While no approach is perfect, we believe the barrier to prevent abuse is higher with the pharmacological approach. In other words,

the difficulty in using either crushing or extraction to convert the opioid product into an abusable form is greater with a pharmacological approach, and we believe prescribers will understand this as more products become available. ◆

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# LYOPHILIZATION
## PACKAGING

# Packaging Freeze-Dried Substances - There Are Options

**By:** Thomas Otto

### INTRODUCTION

Many biotechnologically manufactured substances are not sufficiently stable in aqueous solutions. Because of this, liquid formulations are quite difficult or in some cases, merely impossible to preserve for longer periods of time. One solution, however, is freeze-drying, by which water is extracted from the substance in solution under vacuum and low temperatures. But before being administered to the patient, the drugs must be reconstituted. This freeze-drying, or lyophilizing, offers drug manufacturers a range of options for packaging, such as sterile WFI syringes and dual chamber systems.

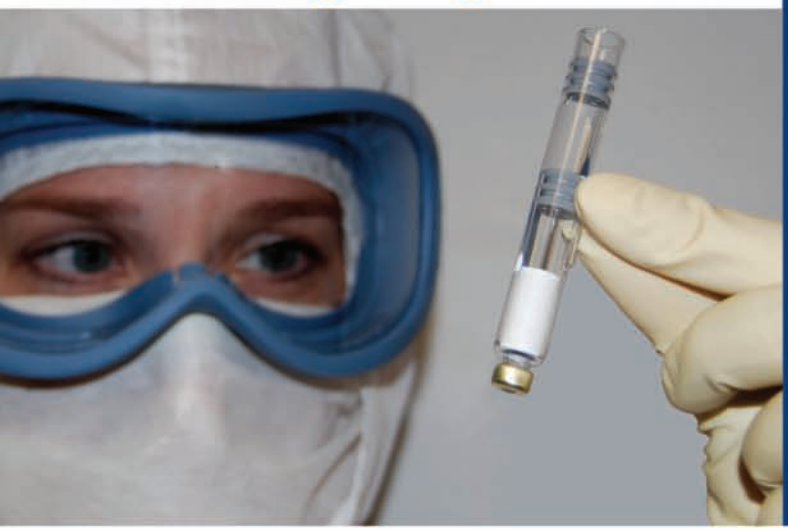
Freeze-dried substances are driving growth on the market for injectables. Almost one-third of all FDA approvals in the past few years for parenteralia were for lyophilized drugs. Based on current market research, the number of approvals in this segment could rise to 50% in the near future. One reason for this increase in demand is the emergence of new complex molecular substances that are often produced through biotechnological processes. By their very nature, however, they are extremely sensitive to environmental influences and often cannot be stabilized in aqueous formulations for long periods of time. For drug manufacturers, an alternative is to protect the product through lyophilization. This approach allows for a longer shelf-life without impacting the effectiveness of the drug. Freeze-drying also offers additional advantages, such as exact dosing and substance use even with the smallest filling volumes.

With lyophilization, the formulation must be carefully established to enable efficiency. Special excipients and auxiliary substances are needed to attain the quality desired. These substances include buffer salts, bulking agents, stabilizers, and tensides, all of which can help to increase the stability of the complex molecular structure and the resistance to the stress of the freezing process. The composition of the solution to be freeze-dried, based on its thermal properties, dictates the freeze-drying process in terms of temperature and pressure. The lower these temperatures are, the longer the freeze-drying cycle will have to be to allow drying without collapse or meltback, which would compromise the product

**FIGURE 1**

**Lyophilized vial**

# Prefilled Cartridge & Syringes



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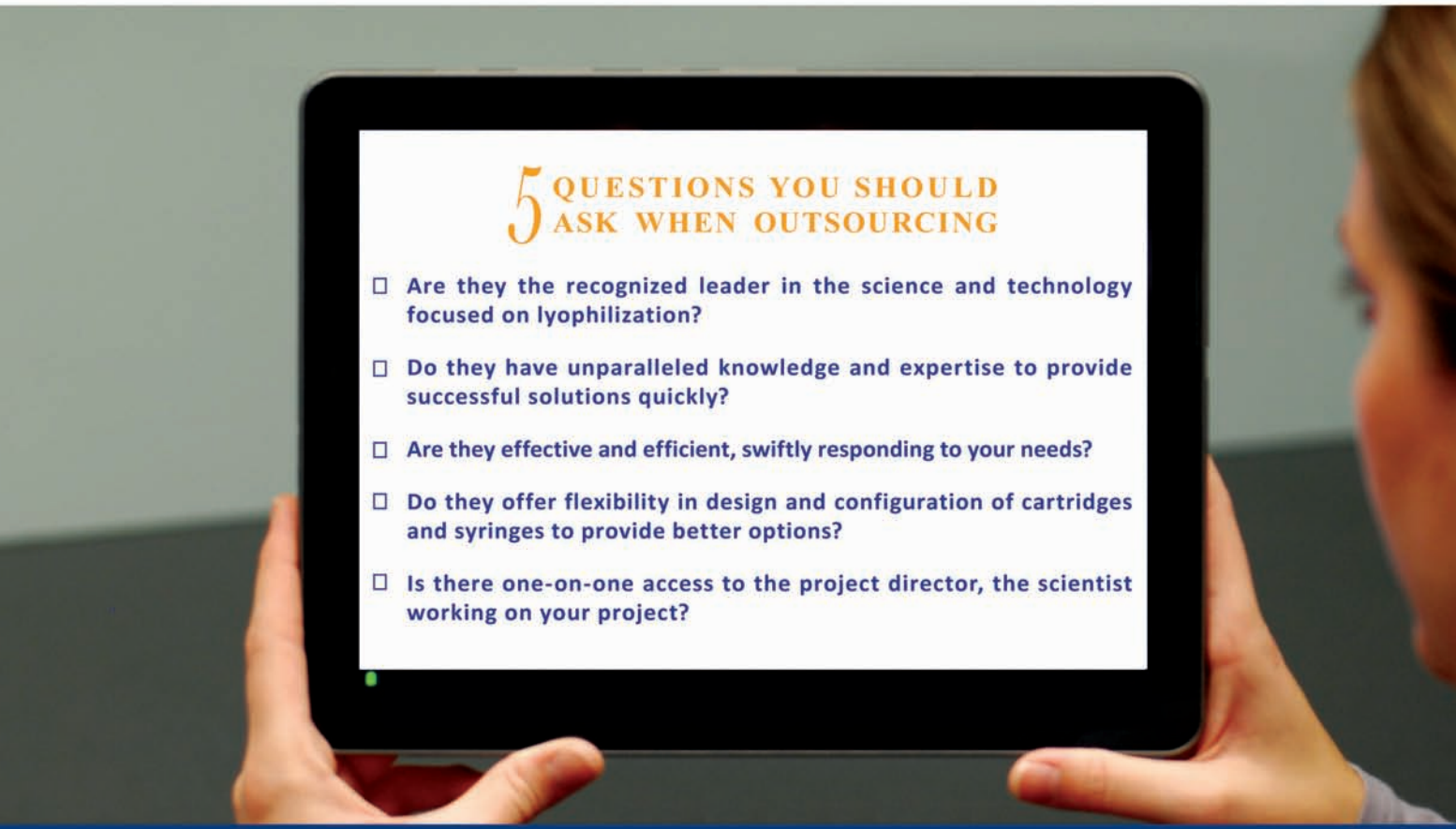


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quality.

The physical packaging can also influence the process. For example, the heat conductivity of the material and the distance between the substance and the cooling plate can determine how much heat is transferred and thus, affect the lyophilization process. Preparing for commercial processes therefore requires exact calibration of formulation and packaging in order to optimize costs. As for the product's desirability and uptake once it reaches the market, this is best determined by how well the substance can be reconstituted prior to administration. Therefore, when choosing a delivery system, packaging know-how and experience with lyophilization are essential.

## MAKING THE RIGHT CHOICE

Companies that manufacture lyophilized substances have a range of packaging solutions on the market from which to choose. And, each system has its own processing requirements, offering its own set of possibilities for efficiency. These options include:

- vials
- dual-chamber syringes
- dual-chamber cartridges

**Vials**

Vials are well established in the industry and offer a good packaging system for lyophilization. The vial can contain anywhere from 0.1 ml to 200 ml, and is useful for single or multiple doses. The packaging assembly itself is also relatively simple, consisting only of a glass body and a stopper (secured by a crimp cap), which limits the risk of incompatibilities. Because of the large inner diameter, they also have a fairly large product surface in relation to their filling volume, facilitating heat transfer and rapid sublimation during drying. To ensure the desired dosage, however, a certain amount of overfill is needed, which increases the loss of API.

**Dual-chamber syringes**

Dual-chamber syringes are one of the more innovative packaging forms for lyophilized substances and are particularly good for single doses and filling volumes ranging from 0.1 ml to 5 ml. This "all-in-one" option places the lyophilized substance and the solvent in the same system. Their assembly, however, is a lot more complex than vials, consisting of a glass body separated into two chambers by a central stopper. Additionally, an end-stopper, plunger, and a closure are also needed. The syringe body and components must also be siliconized in order to obtain suitable break loose and glide forces. Due to the smaller diameter, the geometry of the frozen matrix during drying offers more resistance, which can result in longer drying times. Another factor contributing to the longer cycle is the fact that the substance is lyophilized on the middle stopper, which is a few centimeters away from the cooling plate. The overfill amount is far less because the substance is actually inside the injection system. This leads to less loss of API.

**Dual-chamber cartridges**

Dual-chamber cartridges are yet another development of dual-chamber syringes, providing fill volumes of 0.1 ml to max 1 ml for single and multiple doses. They have both the advantages and disadvantages of dual-chamber syringes as it pertains to structure. The closure is different, however, and consists of an injection membrane for needles. The dual-chamber cartridge is ideal for use in pen systems and simple drug delivery. There are special cartridge closures available that can be sealed in the lyophilizer, thus creating a nitrogen atmosphere over the product, which helps maintain the low residual moisture. Final assembly of the system also requires

FIGURE 2

**Dual-chamber syringe Vetter Lyo-Ject® (diluent & lyophilized product)**

FIGURE 3

**Dual-chamber cartridge V-LK® (diluent & lyophilized product)**

careful calibration with the pen system. The specifications and tolerances for the outside measurements and break loose and glide forces have to be taken into consideration.

## ANSWERING DIFFERENT NEEDS

In addition to the specifications and the requirements of the processes, the market environment and the needs of the users must also be examined. Ultimately, the systems influence the way medications can be administered and the skills the users may actually possess. Therefore, manufacturers must be aware of two fundamental issues:

1. What is the product's competitive environment?
2. Who are its users?

It is intuitive that drug manufacturers always check the market to determine if similar products exist on the market already. Furthermore, the delivery form and application system to be used must also be defined. Yet another important question is where will the drug be administered and by whom? Are these users professional caregivers in a clinical surrounding, or non-professionals like the patients or their family members? Answering these questions will provide valuable information for choosing which system to use.

## VIALS: THE INDUSTRY STANDARD

The industry standard for lyophilized products is the vial. The majority of pharmaceutical and biotech companies with a lyophilized product initially develop in vials. The main reasons for this are the development process and the regulatory requirements are generally well known. Development in a vial is a less-complex process and this can reduce the overall risks in clinical phases. Because of these factors, time-to-market can be reduced in turn increasing the length of patent protection.

However, only experienced users should use vials with lyophilized substances due to the fact that reconstitution requires several steps. The first includes a syringe being used to draw up the solvent and inject it into the vial. The dissolved substance can then be drawn into a second syringe and administered. And, because the dose must be exact, experience with injection systems is vital. This complexity, however, will limit the market for this product primarily to healthcare professionals.

## INCREASING SCOPE

To help with the administration process of the drug, particularly among the patients and their family members, drug companies have come up with systems that assist them in addressing this target group. For example, vials can be upgraded by adding an adapter with a luer lock connection. Thanks to this connecting system, cannulas are not needed when reconstituting the substance, thus they are only needed for the injection process. This considerably reduces needle stick injuries, and particularly among unpracticed users.

Another option for simplifying the handling of vials with lyophilized drugs is prefilled syringes with sterile water for injection (sWFI). These syringes can be filled with the precise amount of solvent needed to obtain the right dose. The process can be made even easier by connecting the sWFI syringe with the vial containing the lyophilized substance using a luer lock system. Combined, sWFI and adapters are an effective way to react to the needs of unpracticed users, and represent yet another

effective option to meet the challenge of up-and-coming competitive products on the market.

## SOLVING SWFI CHALLENGES

Lyophilized drugs in vials complemented with sWFI syringes can be differentiated from other freeze-dried drugs in a vial through greater user-friendliness. A sWFI syringe avoids unnecessary components and application steps. And, they minimize the effort and the risk of making dosing mistakes. But development and manufacturing of these solutions is quite challenging. Contract development and manufacturing organizations (CDMOs) can provide special sWFI programs that simplify the process and offer solutions, such as freeing up the company from doing any manufacturing. Contract fillers often offer standard solutions that are flexible and often, economical.

The systems are usually accompanied with stability data and approval documents. For example, validation and stability data are provided that comply with USP, Ph Eur, PH J, and ICH guidelines. This service is particularly useful to manufacturers because they do not have to generate their own stability data, reducing both development times and time-to-market. Service providers can also take care of the annual renewal of the stability data. Standard services also apply to filling volumes, ranging anywhere from 0.5 ml and 3 ml. This is because all preliminary work has been clarified in bracketing concepts that cover the smallest to the largest volumes. The solution includes process capability of the needed formats, validation of the terminal sterilization and filling processes, as well as documentation of the stability data.

These varying forms of solutions give drug manufacturers greater flexibility, for example, allowing them to adjust dosing during the development process. With a standard program, contract fillers also have the option of offering high-quality packaging for the sWFI at optimized costs. Service providers can also help keep costs in check by offering stability data for up to 5 years. And because sWFI syringes can be filled in large batches, costs can be optimized. Thus, standardized sWFI programs give drug manufacturers an efficient way to provide lyophilized drugs in a vial with an additional user-friendly aid system.

**FIGURE 4**

**Sterile water for injection syringe**

## DEALING WITH THE COMPETITION

There is another market trend currently taking shape that is compelling pharmaceutical and biotech companies to deal with growing competition. In fact, a number of market research institutes have already established forecasts in this regard, including IMS Health who suggests in their study, The Global Use of Medicines: Outlook Through 2016, that throughout the next 3 years, approximately one-third of all new molecular entities will be in the “follower therapies” category. Meanwhile, the share of generics will gradually increase to 35% of the total market. Clearly, companies will have to prepare for these developments as early in the process as possible if they are to remain competitive.

Again, service providers are in a position to provide support, especially if they have experience in product lifecycle management and packaging. Dual-chamber systems, either syringes or cartridges, provide an opportunity in a more competitive market environment,

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allowing a product to differentiate itself from those that are lyophilized and packaged in vials. Dual-chamber systems can also meet the challenge of competition from drugs available in liquid formulations. As a syringe or a cartridge, they allow reconstitution inside the packaging because the substance itself is in one of the chambers while the solvent remains in the other. The two are only combined just prior to administration, which allows for immediate injection of the exact dose all within a few easy steps. The simple handling of these all-in-one solutions also lowers the dangers of needle stick injuries. Non-professionals can safely use the injections themselves without stress. Dual-chamber syringes can also be equipped with special safety needles for even higher safety. For drugs with multiple dosing, dual-chamber cartridges can be inserted into pen systems, which allows for simplified administration. These are especially suited to medications for children and older patients, affording drug manufacturers access to different market segments.

## LONG-TERM SUCCESS BY STEPS

The various packaging options for freeze-dried substances have another advantage, ie, they offer possibilities for lifecycle product management that goes beyond an expense search for a stable, liquid formulation, and can be adapted to the drug's particular competitive situation. In a market without competition, an innovative drug can start out in a vial. If a competitive product then appears on the horizon, attention can shift to the user perspective. Solutions like the aforementioned adapters and sWFI syringes allow for added value. One economical solution in particular is the standardized sWFI program. If the market demands other standalone features, the drug can then be moved to a dual-chamber system. Dual-chamber cartridges combined with pens offer a high level of user-friendliness and can support market success in the long-term.

We can see that a specialized CDMO can provide efficient solutions to the many challenges surrounding lyophilized substances. But it should be ascertained that they have packaging, manufacturing, and lyophilization expertise. Such a partnership will give pharmaceutical and biotech companies a product that differentiates itself from the competition on the market via simple and safe handling. These products will also be prepared for changes in the market because the companies will be able to design the right strategies early on. In spite of stringent technical demands, drug manufacturers will find that lyophilization can offer many opportunities to meet the challenges of the changing market. ◆

## BIOGRAPHY

**Thomas Otto** has been a Managing Director of Vetter Pharma-Fertigung GmbH & Co. KG since December 2002. He joined the company as a Project Engineer in 1990 after graduating from the Technical College in Stuttgart with an Engineering degree in Packaging Technology and Print Processing. From 1995 to 1999, he managed the Department of Packaging Materials Development. From 2000 to 2002, he directed the Department of Research & Development as Vice President.

# Developing & Validating an Efficient Method to Determine Residuals of Hormone Products by LC-MS After Cleaning of Equipment

**By:** Geoff Carr, PhD

## INTRODUCTION

Effective determination of residual drug substance after cleaning equipment used in the manufacture of pharmaceutical products is a GMP requirement and regulatory expectation. Pharmaceutical companies need a fast, reliable analytical procedure to verify that the equipment is free of residuals, but method development and validation followed by testing of swabs after the manufacture of each drug product can be time-consuming and challenging.

High-performance liquid chromatography used with mass spectrometry detection (LC-MS) is an efficient, sensitive, and accurate technology with high specificity that can analyze multiple drug substances simultaneously, saving considerable time. This article describes the benefits of LC-MS and presents an effective method developed and validated by Patheon Inc. using this technology to determine the potential residual amount of eight active ingredients used in oral contraceptive tablets after cleaning equipment used in their manufacture.

## CHALLENGES IN METHOD DEVELOPMENT

Oral contraceptive (OC) tablets are usually manufactured with combinations of active ingredients in the same tablet with extremely low dosage strengths. Developing an appropriate cleaning verification method requires detecting and quantitating the hormones at an extremely low concentration. The ideal analytical procedure for cleaning verification of equipment used in the manufacture of oral contraceptive tablets and other drug substances is a method that is rapid, accurate, sensitive, specific, linear within a reasonable working concentration range, and robust to minor testing condition changes. To meet these requirements, Patheon chose LC-MS, an analytical procedure that can simultaneously determine the potential residual carryover from multiple drug products.

## ADVANTAGES OF LC-MS

LC-MS is a desirable technique due to the sensitive and highly specific nature of MS compared to other chromatographic detectors, and its ability to handle complex mixtures efficiently. MS, a primary tool for identifying residual impurities, consists of ionizing chemical compounds to generate charged molecules or molecule fragments that are selected for measurement on the basis of their mass-to-charge ratios.

LC-MS provides sensitivity at low concentrations and demands less critical chromatographic separations of components, requires a short analytical run time, and can be applied to a wide range of pharmaceutical APIs. Instead of having to develop a series of methods for multiple drugs, fast scanning speeds allow a high degree of multiplexing, enabling many compounds to be analyzed in a single run. LC-MS technology,

however, does require considerable technical expertise and specialist training.

## METHOD DEVELOPMENT

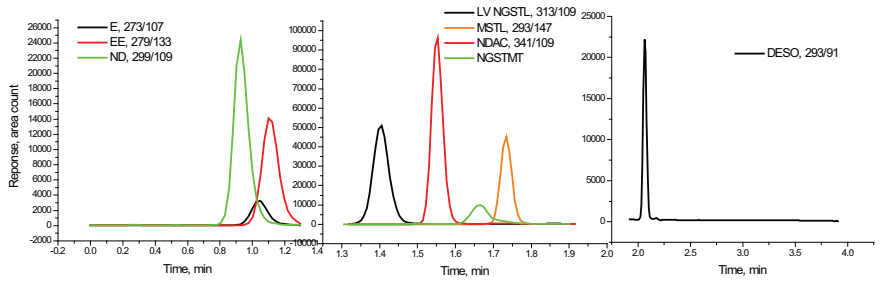
Patheon developed an analytical procedure using LC-MS to simultaneously determine the residual carryover in samples collected after equipment cleaning from eight commonly used hormones in oral contraceptive tablets: desogestrel, estradiol, ethinyl estradiol (EE), norethindrone, norethindrone acetate, norgestrel (levo-norgestrel), mestranol, and norgestimate. Sample and standard concentrations are driven by carryover limits dictated by the surface area of the equipment and the dosage.

Cleaning residual limits (CRLs) for each hormone from a swab applied to a 100-cm$^2$ area and extracted into 10 mL of solvent ranged from 0.006 to 0.08 µg/mL for EE, and from 0.03 to 1.0 µg/mL for other hormones. Quantitation limits were significantly lower than the required CRLs, and the final working standard concentration was arbitrarily set up at 0.05 µg/mL for all hormones.

### Standard Preparation

Five mg each of the hormone reference standards were dissolved and diluted to volume with methanol. These solutions were further diluted with 40% methanol to provide a final concentration for each hormone of approximately 0.05 µg/mL.

**FIGURE 1**




**LC-MS Chromatogram From a Standard Solution Containing All Eight OC Hormones**

### Sample Preparation

The sample for the recovery test was prepared by simulating residuals from the equipment surface and spiking 0.5-mL standard solution at 1 µg/mL for each hormone onto a stainless steel coupon. Using swabs pretreated with 70% isopropyl alcohol, the chemists swabbed the surface, collecting residual samples. The swabs were then transferred into 20-mL scintillation vials, and the analytes extracted with 10.0-mL 40% methanol with sonication for 10 minutes.

## ANALYSIS

The hormone compounds were separated on an LC column with a 4-minute gradient program, and detected by mass-to-charge ratio using multiple reaction monitoring (MRM). As the residual APIs can be ionized, Patheon used MS due to its selectivity and sensitivity. The method was evaluated for potential interferences, limit of detection, and limit of quantitation and tested to ensure acceptable levels of precision, accuracy, and linearity. Quantitation was performed by external standardization using peak areas.

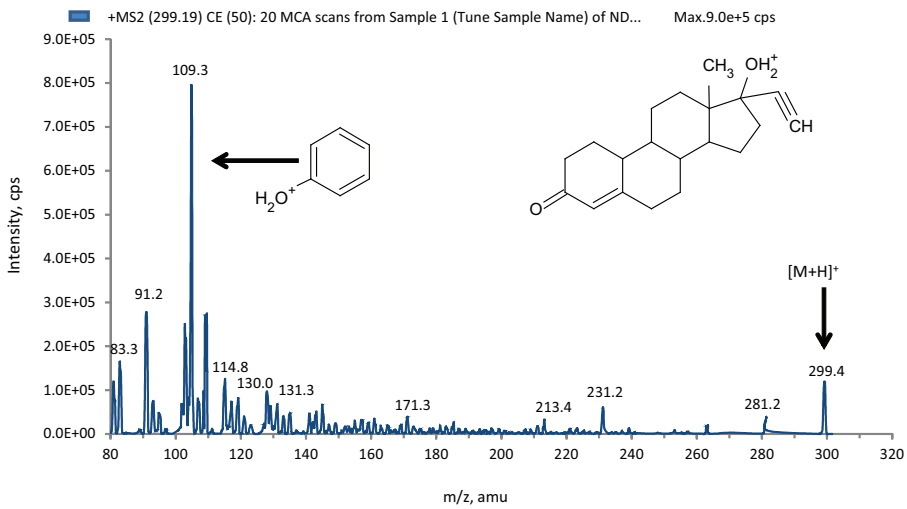
## RESULTS

A typical LC-MS chromatogram that depicts the separation of the 8 OC hormones is illustrated in Figure 1. Figure 2 depicts a typical mass spectrum of one of the hormones, norethindrone, that has been extracted from the chromatogram shown in Figure 1. Based on this mass spectrum, the fragment ion with m/z = 109.3 was used for quantitation for this component.

### Sensitivity

The quantitation limits (QLs) were evaluated by making serial dilutions of a standard solution with 40% methanol and injecting them onto an LC-MS system. All signal-to-noise ratios were far above the typical value of 10:1 per ICH Q2 guidance. The QL solution had concentrations much lower that the corresponding CRLs calculated for each hormone. Desogestrel showed the lowest signal to noise ratio of 69, at concentration of 0.0050 µg/mL. Six

## FIGURE 2




**Mass Spectrum of Norethindrone Taken From 0.86 Min Retention Time Peak in Figure 1.**

consecutive injections of the QL solution showed RSDs from 2% to 5%, lower than the 10% acceptance criterion. The data demonstrated that the method is sufficiently sensitive to determine all eight hormone residuals and the verified QLs are reliable and reproducible.

### Linearity

A series of dilutions of the eight hormone standard solutions was made and tested. Peak areas of the compounds were measured and plotted against corresponding concentrations using a linear regression analysis. The results demonstrated the peak area responses are linear ($r \geq 0.995$) within a concentration range of 0.005 to 0.2 µg/mL for all hormones.

### Solution Stability

The stabilities of the standard and sample solutions were determined by comparing concentrations after initial preparation and then after storage of solutions. The observed hormone concentrations, expressed as a percent of their corresponding initial values, were within 92% to 104% after 4 days. The data indicated the standard and sample solutions were stable up to 4 days at room temperature or under refrigeration.

### Recovery & Precision

A recovery from surface study was performed to assess the intra-assay method precision and potential recovery from the equipment surfaces. Stainless steel coupons were spiked with all eight hormones at 100% working standard level and swabbed. Six independent samples were prepared and tested, and the procedure was repeated by a second Patheon chemist using a different MS instrument and LC column.

The mean recovery of the hormone compounds was 71% to 93%. The RSDs for each recovery from the six samples for eight hormones were not more than 7%, and the differences in recovery between the studies performed by the two different chemists were within 6%. Recoveries for all hormones were satisfactory and analytical procedure showed adequate precision.

### Accuracy

Method accuracy was evaluated with triplicate sample preparations at three levels by placing pre-treated swabs in 20-mL scintillation vials. Ten mL aliquots of the hormone solutions at concentrations of approximately 0.035 µg/mL, 0.05 µg/mL, and 0.065 µg/mL were added into each scintillation vial and sonicated in the same way as the swab sample preparation. Solutions were tested by LC-MS for hormone recoveries. The mean recoveries ranged from 93% to 108% with RSDs from 1% to 6%, indicating the swabs create no significant interferences with this procedure and the method is accurate to determine the eight residual compounds.

### Specificity

Method specificity was evaluated by preparing and analyzing 10 mL of the following solutions with a pre-treated swab:

- An excipient solution containing all 19 excipients at the highest possible concentrations, based on the 28 formulations investigated, spiked with the hormones at 100% working standard level.

- A solution with all four detergents used in equipment cleaning, spiked with the eight hormones at 100% working standard level.
- Samples containing only blank swabs, blank placebo mixture, and blank detergents.

Results demonstrated the peak areas of each hormone compound from the excipient and detergent preparations spiked with the analytes were within 94% to 109% of their corresponding responses in the working standard solution. These results indicated the excipients and detergents had no impact on the hormone content. Also, no interferences were observed in the chromatograms of the swab blank, placebo blank, and detergent blank. Therefore, the method is specific for the eight hormones in the presence of the excipients, detergents, and swabs used.

### Robustness

The robustness of the method was evaluated by analyzing a working standard solution with a variation of formic acid content (±0.01%) in the mobile phase and detection mass (±0.1) in quadrupoles 1 and 3. For all hormones, the peak areas were within 96% to 102% of the peak areas obtained from the target condition. The method proved robust toward these minor changes.

## CONCLUSION

Pharmaceutical companies seeking an efficient, sensitive, reliable method to verify that equipment used in drug manufacture is free of residuals after cleaning can benefit from LC-MS, which can simultaneously determine multiple drug substances that can be ionized. The combined technology, which is applicable to a wide range of molecules, eliminates the need to fully resolve components as MS detection provides selectivity. Despite the lack of baseline separation, the method reliability is not compromised.

Patheon, a CDMO, developed and validated a method that was accurate, precise, specific, robust, and reliable to quantitate the eight hormone residuals collected after cleaning equipment used in the manufacture of OC drug products. As the use of this technology requires considerable expertise and sophisticated equipment, pharmaceutical companies typically rely on a contractor with the cutting-edge technology to achieve the greatest efficiency as well as accuracy in method development and validation.◆

## ACKNOWLEDGEMENTS

The author would like to gratefully acknowledge the valuable help provided by Heng Yao in the preparation of this article.

## BIOGRAPHY

**Dr. Geoff Carr** is a chemist with 36 years of experience in the pharmaceutical industry. He is Director, Analytical Development, Ontario at Patheon, former Head of Analytical Development at Chiroscience UK and Wyeth Research UK, and former Head of the British Pharmacopoeia Laboratory. Dr. Carr is a member of the US Pharmacopeia Expert Committee on General Chapters, Chemical Methods, and previous member of British and European Pharmacopoeia Committees.

DRUG DEVELOPMENT Executive

# EMD Millipore: Enhancing the Bioavailability of Active Pharmaceutical Ingredients

**Steffen Denzinger**
Head of Portfolio Development
**EMD Millipore**

**We offer ~400 different chemicals and 15 to 20 different technologies ranging from counter ions for salt screening or activated PEGs for conjugation of proteins. We also offer drug carriers, inclusion compounds, specific lipids for liposomal delivery, and specific highly functional binders that allow economic production of dosage forms using some physical measure like micronization or nanomilling.**

*Bioavailability - or ensuring that the right amount of drug gets to the right place in the body at the right time - has increasingly become a key factor to a therapeutic's success. Nearly 40% of drug candidates fail in clinical trials due to poor bioavailability properties, representing a significant loss of time and resources invested in drug development. Avoiding these failures can help control skyrocketing drug development costs and accelerate the development process, as well as boost pipeline productivity, secure return on investment, and enable more effective life-cycle management. EMD Millipore offers a comprehensive portfolio of products and technologies for enhancing drug bioavailability, including solutions for solubility enhancement, optimized release, and targeted drug delivery. Drug Development & Delivery recently interviewed Steffen Denzinger, Head of Portfolio Development at EMD Millipore, to discuss bioavailability challenges and how EMD Millipore's formulation portfolio and expertise are helping the pharmaceutical industry achieve maximum efficacy with active pharmaceutical ingredients.*

**Q: To what extent has bioavailability become more of a challenge for the pharmaceutical industry? Why?**

**A:** A basic definition of bioavailability is that the drug gets to the right place in the body at the right time. In the current, collective pharmaceutical pipeline, 90% of all new active pharmaceutical ingredients are either in BCS class II or IV, which means they are either poorly soluble or poorly soluble and have a bad permeability. As such, the initial challenge is to get enough of the drug substrate into solution, get the PK/PD profile, and target the active in the most suitable way, all in a formulation that ensures ease of use and patient compliance.

## Q: What are the most common causes of bioavailability problems that you have experienced? Has this evolved over the years?

**A:** Solubility of the API has become more and more of a challenge. In today's marketed drugs, about 40% of the actives are either BCS class II or IV. Establishing the correct PK/PD profile is more of a challenge today. Furthermore, many drugs have high efficacy but are not very targeted, a classical example being the chemotherapeutic agent cisplatin. Due to its toxicity to healthy cells, dosage and therapy cycles are difficult to adopt to give the best treatment to the patient. If such actives can be targeted in a way that only tumor cells are attacked, major advantages for therapy will be seen. Similarly, the structure of large biological molecules requires adopted strategies to address the same issues as described.

## Q: What is your process when a customer comes to EMD Millipore with a bioavailability challenge?

**A:** First, we need to know as much as possible about the properties of the active related to the bioavailability issue. This can be a challenge as customers may be quite reluctant to disclose the molecular structure - but information about BCS class, solubility, and molecular weight will most definitely be needed as well as information about the intended target.

A tablet will need different strategies than an intravenous injection, different again from a nasal delivery or a transdermal patch. There is never a one-size-fits-all approach. Depending on the challenge, the solution can be quite straightforward, such as trying either a specific counter ion in salt screening or use of a carrier system, or an inclusion compound to enhance the solubility.

But very often the problem is not straightforward as it may include more issues than just solubility. For example, after the solubility is addressed, stability issues can occur, so this may mean trying several options to find the most suitable. The key to quick success is most definitely information exchange. The more the customer and EMD Millipore work together as partners the better.

The advantage of a real partner is to not offer only one technology based on either a strength in a specific chemistry or a specific physical modification method. Rather, the range of options should be as broad as possible in order to find the optimal solution. For this, we have developed roughly 15 to 20 different technologies to address various bioavailability challenges.

## Q: With 400 products, how do you quickly assess what is the correct path?

**A:** We offer ~400 different chemicals and 15 to 20 different technologies ranging from counter ions for salt screening or activated PEGs for conjugation of proteins. We also offer drug carriers, inclusion compounds, specific lipids for liposomal delivery, and specific highly functional binders that allow economic production of dosage forms using some physical measure like micronization or nanomilling.

The time required to make an initial recommendation will strongly depend on the complexity of the issues the active is facing. The recommendation may come very quickly, or we may have to go to the lab and try different approaches, such as loading of new drug carrier systems, which will take somewhat longer.

## Q: What is the business model? Does EMD Millipore develop formulations to address bioavailability challenges or do you provide counsel only to the customer?

**A:** We provide counsel to our customers and applications services all the way through to developing the formulation. The need depends very much on the problem our customer is facing. For our new drug carrier systems, a crucial step is the loading of the API, so we offer development of the best loading procedure for our customers so that they can get the biggest benefit for this innovative solution. ◆

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**By:** Justin M. Wright, PhD, and Herve Soukiassian

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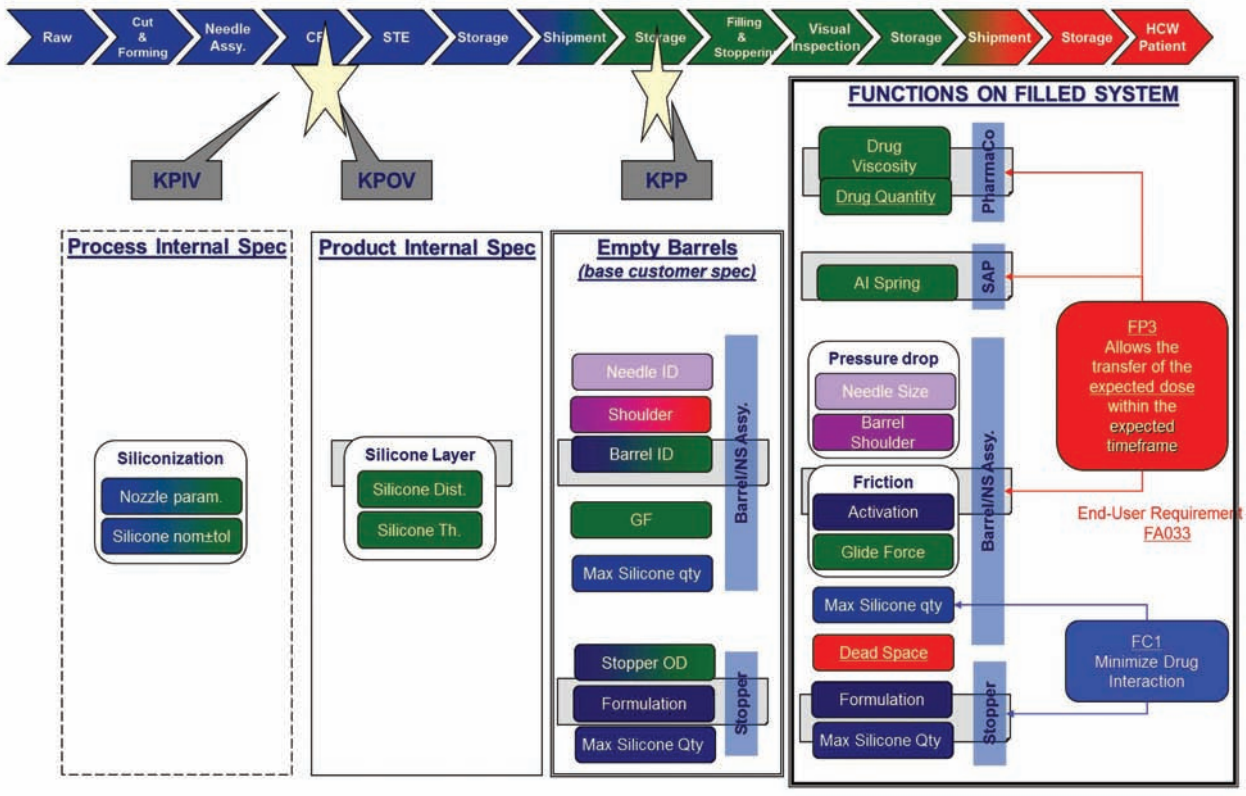
FIGURE 1




**Application of Functional Analysis**
**The BD process is represented starting on the left with the blue arrows, moving across to the pharmaceutical company processes in green, and finally to the end user: healthcare worker or patient. The boxes in the right-hand column show the functions filled by components of the drug delivery system.**

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  - **The Impact of Technology on Vaccine Manufacturing and the Downstream Impact on Human Health**, Rahul Singhvi, ScD, Senior Vice President/ COO, *Takeda Pharmaceuticals International, Inc.*
  - **Patient Access to Treatment: How Clinical and Cost Effectiveness of Drugs can be Ensured**, Mark B. McClellan, MD, Director Health Care Innovation and Value Initiative, *Brookings Institute (invited)*
- **Plenary Session Two: Science and Innovation**
  - **Innovative Science and Future Benefits for Patients**, David Shanahan, President, *Mary Crowley Research Center* and President, CEO and Founder, *Gradalis*
  - **Cell and Gene Therapy**, Wilfried Dalemans, PhD, CTO, *TiGenix*
- **Closing Plenary: Emerging Technologies and Marketing**
  - **Emerging Markets**, Martin VanTrieste, Senior Vice President, Quality, *Amgen, Inc.*
- Poster Presentations
- Networking Receptions & Events like the 8th Annual PDA Golf Tournament at the AT&T Canyons Golf Course and the PDA 8th Annual Walk/Run
- Post-Conference Workshop: **PDA Bioburden and Biofilm Workshop** on April 9-10
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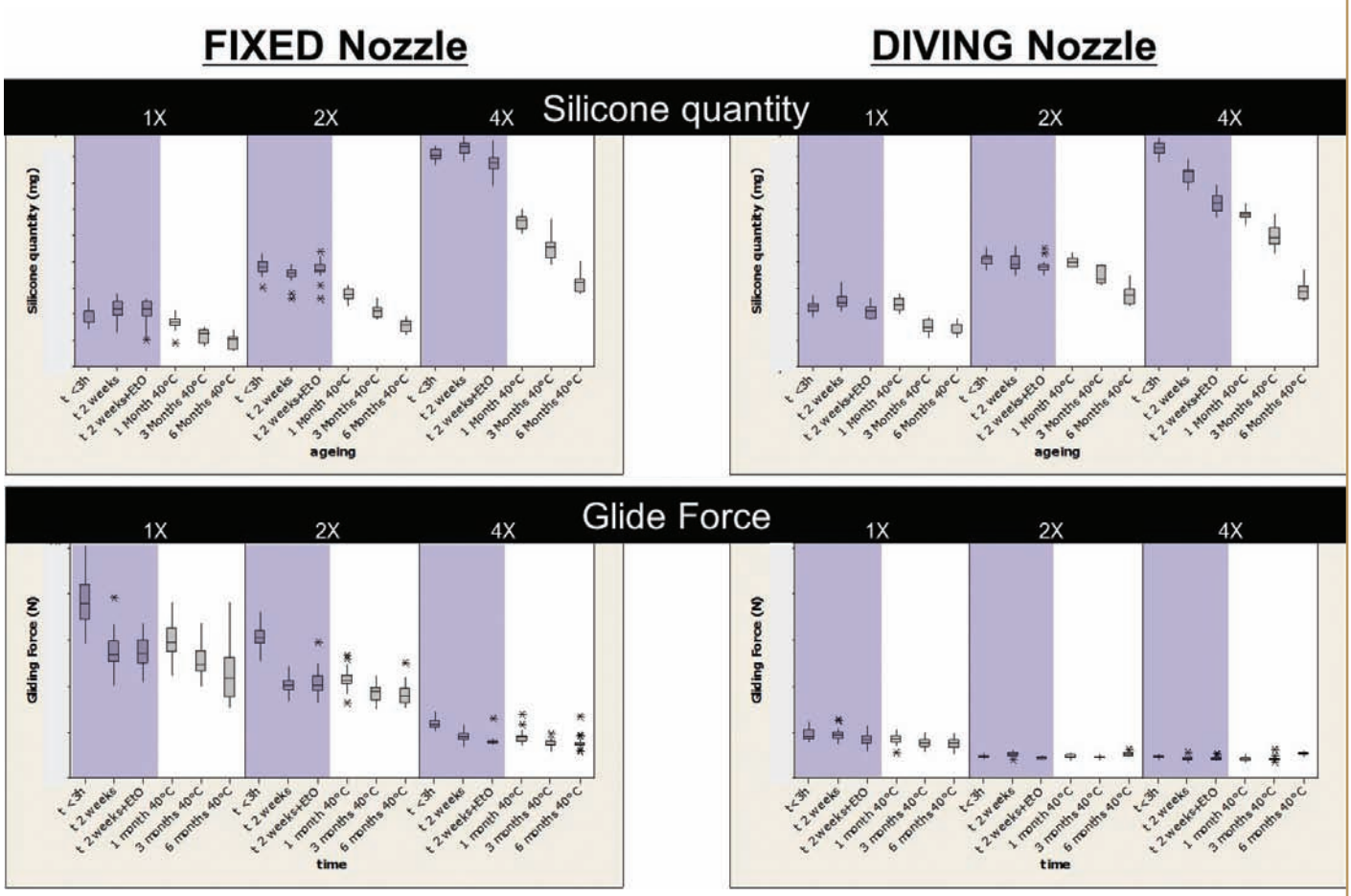
special thin-walled (STW) needle that allows comfortable injection of highly viscous biopharmaceuticals. BD Neopak™ glass PFS became available in June 2013 and is expected to reset the standard for quality and innovation in delivery of today's novel drug therapies.

BD's philosophy is the same today as it always has been: to be a total solutions provider for customers across all aspects of delivery for injectable drug products. BD understands that meeting customers' complex and evolving needs requires extensive consultation throughout the entire process from development through commercialization, and has built an organization and capabilities that deliver support at every step. Step 1 is forming a cross-functional project team mirroring a customer's own, facilitating interaction at every level and allowing BD to be an extension of each customer's organization. Step 2 is consulting early with customers to define their drug delivery needs and determine the optimally suited container and device solution. Step 3 is compatibility testing designed to mitigate risk proactively as it relates to drug product compatibilities and stability. Step 4 is moving toward routine implementation, delivering worldwide filing and regulatory expertise. Finally, step 5 is leveraging BD's established manufacturing capabilities, ensuring continuity and risk mitigation of supply.

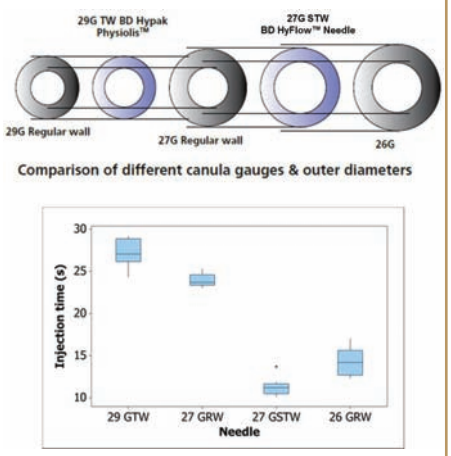
Three key stakeholders in the biotech space help drive BD's culture of innovation: patients and healthcare workers looking to improve compliance and comfort through fewer, simpler, and more comfortable injections; regulatory agencies looking at drug safety, drug/container interactions, and whether combined systems meet requirements of combination product guidelines and human factor design; and pharmaceutical companies, where targeted therapies for cancer and chronic diseases are driving development of biologic drugs - which tend to have larger molecular weight active components at high concentrations and to have specific requirements due to their high viscosity. A final consideration is total cost of ownership. BD has a long history of working closely with

**FIGURE 2**




**Fixed nozzle versus diving nozzle technology and effect on glide force. Note on the left how the highest (4X) quantity of silicone is required with the fixed nozzle to deliver optimal glide force, whereas optimal glide force is delivered consistently at any silicone quantity applied using the diving nozzle (right).**

## FIGURE 3




**BD Hypak™ Physiolis™ (second from left) and BD HyFlow™ Needle (fourth from left) use innovative needle technology to facilitate injection of viscous drugs. Patient experience is optimized with BD HyFlow through shorter injection times (bottom graph). (BDPS-0002)**

pharmaceutical companies to ensure continuity of supply and minimal waste, keeping costs in line with customer needs and expectations.

## BD NEOPAK™ GLASS PREFILLABLE SYRINGE

The BD Neopak PFS represents a step change in syringe technology, taking lessons learned from experience with the BD Hypak syringe and adding cutting-edge technology in manufacturing, design, and durability. BD Neopak syringe comes from a new, fully indexed manufacturing process with less intrinsic variability that delivers parts per million process control.

With all PFS, treating the patient and the patient's well-being must be top of mind. The most important function of the syringe is delivering the expected dose to the target tissue within the expected time frame. The delivery system must protect the drug and maintain its safety and efficacy and must be produced at commercial scale once the drug is developed and marketing approval is received. Therefore, a key consideration is compatibility with the filling, inspection, and assembly processes at the pharmaceutical company or a contract manufacturing organization, including meeting quality standards and delivering the quantity required to meet market demands. Figure 1 illustrates how BD applied this functional analytical approach to development of the BD Neopak glass PFS. The takeaway is that the BD process started with the "end use" of the PFS in the patient's hands and worked backward to identify the elements needed to supply that function and maximize the chances that the full system would work together smoothly once the drug was inside. In doing so, BD is changing standards for glass PFS through technology and innovation in functionality, dimensions, strength, and needle technology.

## REDUCING VARIABILITY AND DEFECTS

BD Neopak glass PFS is built using a unique manufacturing infrastructure that employs 2 parallel forming modules (versus 8 to 10 for BD Hypak syringe) to feed the single needle-assembly machine. This reduces intrinsic variability, enhances the ability to trace each unit to its source, and accelerates manufacturing timing. This infrastructure also uses a new process to ensure product quality by avoiding glass-to-glass contact, unnecessary inner contact with the syringe, and other novel techniques that convey multiple benefits (Table 1). The result is a process engineered to eliminate potential causes of defects and reduce variability.

Glass strength is a basic feature of glass syringes and of increasing concern to regulatory agencies, as illustrated by an increase in recalls and Warning Letters regarding glass-related issues. Glass is a non-crystalline solid that exhibits brittle behavior and is prone to fracturing in use or during manufacture. Factors contributing to fracture risk are the density or probability of encountering defects in the glass, the energy applied, and the initial state of internal constraint. BD's strategies to mitigate glass breakage include reducing the occurrence of glass defects at all points from manufacture to delivery to the patient; reducing the energy applied, for example, by choosing a small round flange or secondary packaging that better protects the PFS; and increasing the level of compression strength at the material surface.

The manufacturing process for BD Neopak syringe addresses these issues through a Quality-by-Design approach. Compared with BD Hypak for Biotech syringe, BD Neopak syringe has three times greater crush resistance, which facilitates auto-injector compatibility and minimizes risk of breakage.

## TABLE 1

| What | Expected Benefit |
|---|---|
| No glass to glass contact | >> Elimination of a major cause of cosmetic defect |
| No inner contact with syringe | >> Elimination of potential source of inner contamination |
| Over-pressurized environment | >> Reduction of cause of external contamination |
| Syringe conveyed tip up | >> Reduction of cause of internal contamination |
| Vertical cutting | >> *Improved cut quality…* |
| *… elimination of glass cutting at forming* | >> Elimination of glass particles |
| *Gas flow control* | >> Reducing variability at forming |
| 100% controls | >> Ensure 6σ quality |

**Novel Components of BD Neopak™ Syringe Manufacturing Process & Expected Benefits**

## IMPROVING DOSE ACCURACY

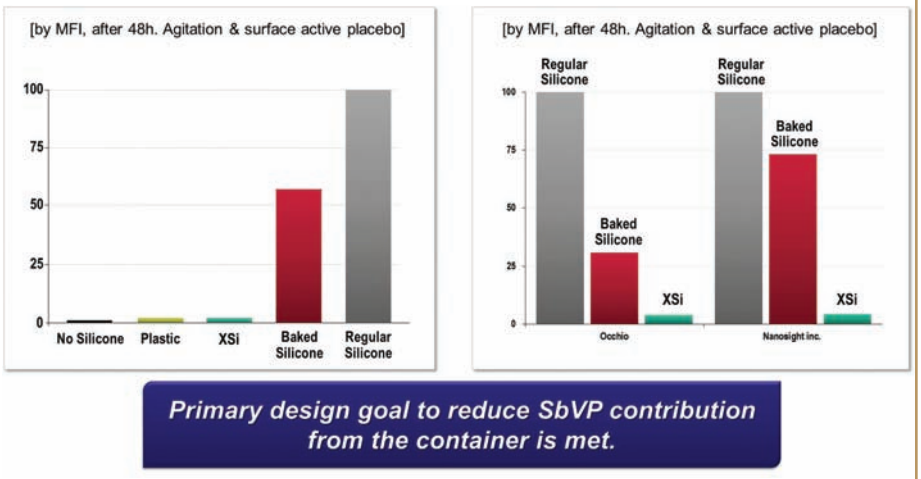
Another example is dimensional precision of the PFS, which is important not only in the context of drug administration but also during the manufacturing process. BD has chosen to improve the tolerances of the glass cane to reduce variability for filling height requirements. This also provides benefit by design in terms of dimensional variability at the forming stage. BD has put the "dead space" - which affects overfill and dose accuracy - under control. The result is more accurate dosing with less need for overfilling the syringe.

## IMPROVING FUNCTIONALITY

Glass syringes are coated internally with a layer of silicone to facilitate movement of the plunger during injection. Traditionally, silicone is applied using a fixed nozzle located outside the cylinder. BD developed a coating technology using a "diving-nozzle" that is inserted into the cylinder and pulled out as the silicone is sprayed, delivering a uniform coating throughout the inner surface. A BD study showed that at a typical manufacturing setting (0.4 mg), the diving nozzle produced a more consistent coating than the fixed nozzle, which left some gaps in silicone coating near the tip of the cylinder. The practical effect of this is evident when friction in terms of glide force is examined. A greater quantity of silicone is needed to optimize glide force using the fixed nozzle process. In contrast, the diving nozzle process delivers optimized glide force consistently at all quantities (Figure 2). With the BD Neopak syringe, the diving nozzle is used along with the lowest amount of silicone, delivering minimal friction to ensure functionality for the end user while reducing the risk of drug-silicone interaction.

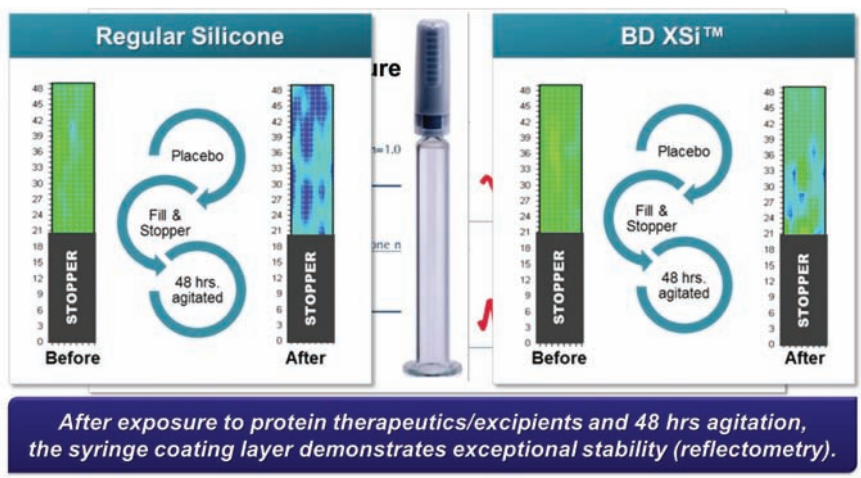
Needle technology also affects functionality. Today's biotech drugs are large, complex molecules, formulated at high concentrations that lead to highly viscous drug products. A larger needle diameter can facilitate delivery of these highly viscous drug products, but also can negatively affect the patient's experience. At BD, innovation in needle technology has made available two needles specially designed to address these issues: BD Hypak™ Physiolis™ needle and BD HyFlow needle. The BD Hypak Physiolis needle combines a 29-gauge, 0.5-inch, 5-bevel thin-walled needle and a novel Rigid Needle Shield, using BD260 elastomer that helps to preserve needle point integrity. This needle is clinically proven to improve patient experience through a 40% decrease in pain perception and a 70% decrease in penetration force. BD HyFlow is a STW 27-gauge needle that enables self-injection of viscous drugs using a lower penetration force than 26-gauge needles. By allowing a wider inner diameter

**FIGURE 4**



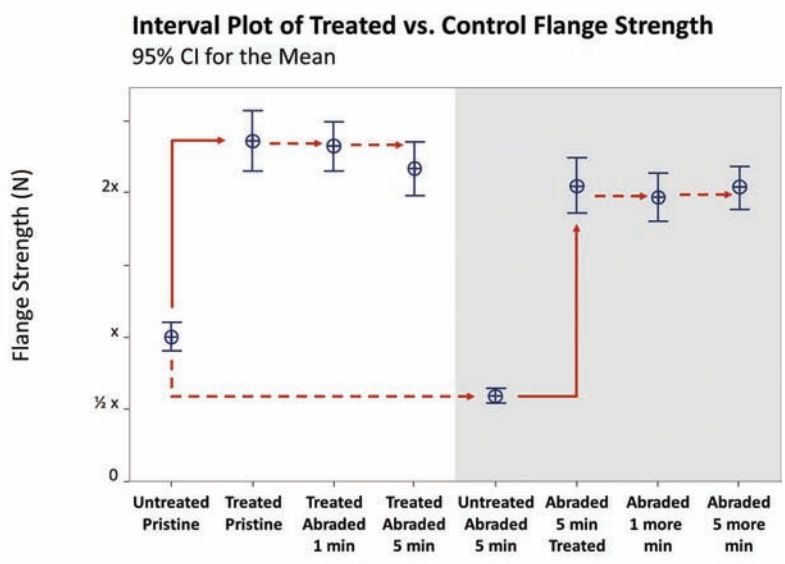

**(Left) SbVP per mL with different syringe types after 48 hours of agitation: note that XSi™ coating is similar to uncoated glass and plastic syringes in the number of SbVPs produced. (Right) Submicron particles with various silicone coatings. Again, XSi coating is associated with a very low percentage compared with other silicone coatings.**

**FIGURE 5**




**Note how the regular silicone coating on the left is perturbed after 48 hours versus the stability of the BD XSi™ coating shown on the right.**

## FIGURE 6




**Force strength needed to induce flange failure in syringes created without chemical glass strengthening (A0 and B0) and with chemical glass strengthening. Much higher force is required to induce failure in the strengthened glass, even with up to 5 minutes of glass-to-glass contact as shown in the right-hand panel.**

to facilitate drug delivery inside a smaller outer-diameter needle (Figure 3), injection times using BD HyFlow needle are 50% shorter versus standard 27-gauge needles and 10% shorter versus 26-gauge needles.

To summarize, BD Neopak glass PFS have been designed from the ground up to meet the requirements of pharmaceutical companies, regulatory agencies, and the patients or healthcare workers who will be using these products. Through innovative design and manufacturing processes, the BD Neopak syringe provides a drug delivery system with improved strength, accuracy, and function.

## REDUCING SUBVISABLE PARTICLES (SBVPS): BD XSI™ COATING

Although silicone is a necessary component of modern glass PFS, concerns have arisen about the potential for SbVPs of silicone to leach off from the syringe's inner wall and become mixed with the drug product. This presents the challenge of maintaining syringe and auto-injector functionality while simultaneously minimizing or eliminating SbVPs. BD approached this challenge through developing an understanding of silicone oil's role in development of SbVPs and then investigating ways to reduce or even eliminate the contribution of the container to SbVPs in the drug product. The result is a cross-linked, inert silicone coating, called BD XSi™ coating for syringes. BD XSi coating consists of a polydimethylsiloxane (PDMS) layer using Dow Corning 360 silicone oil, which introduces no new chemistry or chemical substances, and limited new regulatory issues. The cross-linked PDMS builds an immobilized, hydrophobic layer between the glass and the drug product that is theoretically inert to proteins. What this means in practice is that BD XSi syringes deliver SbVP levels barely distinguishable from glass containers with no silicone coating at all (Figure 4). These findings have been confirmed in studies with therapeutic monoclonal antibodies, supporting the low SbVP potential of BD XSi technology.

Another factor is the integrity of the surface coating as it relates to the syringe, measured by filling syringes that have different coatings with a surface-active placebo and agitating them for 48 hours. After the filling is drained, the coating is examined using refractometry. A normal silicone oil coating will show substantial perturbation following this test, but BD XSi coating remains essentially intact after 48 hours of agitation (Figure 5). This finding contributes to BD's confidence that upon storage or shipping, BD XSi-coated syringes or auto-injectors will remain stable, with very little disturbance to the coating or development of SbVPs.

## IMPROVING GLASS STRENGTH & DURABILITY

In assessing marketplace needs to address, BD returned to the glass used in making syringes and auto-injectors, and how techniques to strengthen glass could improve issues of breakage, system integration, time to market, and total cost of ownership. After reviewing various glass-strengthening technologies, a decision was made to pursue ion-exchange technology, as it is an established technique that met BD's standards for cost and regulatory thresholds.

Ion exchange technology improves glass strength and durability. The technology involves immersing a glass syringe in a molten bath of neat potassium nitrate. On an atomic level, larger potassium atoms and smaller sodium atoms exchange at the surface of the glass, resulting in the installation of a

compressive layer at the surface. The result is a much higher performing glass syringe than has been seen in the past.

The flange test and the crush test, both standard in industry, are used to measure glass syringe strength. In the flange test, the syringe is held by the flange within a fixture while a probe is advanced through the syringe's internal space until the flange breaks. In the crush test, the syringe barrel is placed on a V-block with the flange hanging on the edge; a cylindrical pin pushes on the outer diameter of the syringe until it fails. Figure 6 shows results of a flange strength test for glass syringes created without and with the ion-exchange process.

In using this technology, BD is challenging the industry notion that strength deterioration is progressive and irreversible. In fact, with these technologies in place, it appears deterioration can be prevented and, even in containers that have undergone tremendous processing, reverse the defects and "install" strength.

This translates to a patient benefit in increased durability of their injection systems. In a drop test done by ISO methods with 10 strengthened syringes placed in a commercially available auto-injector, all 10 samples remained intact after 100 drops - whereas standard syringes in the same auto-injector broke after a range of 8 to 81 drops. The results of the strengthened syringe drop tests were confirmed by X-ray to ensure no breaks were missed. An interesting side note is that all 10 samples of non-strengthened syringes in BD Physioject™, an auto-injector optimally designed to protect the PFS, also survived for 100 drops, demonstrating the importance of whole-system design to the robustness of a drug delivery system.

The strengthened glass has been subjected to mechanical and chemical testing to determine whether other features of the product were affected by the ion-exchange process. In a large-scale feasibility study, more than 70,000 syringes were tested against a control standard syringe over 6 months and in various conditions. No changes were seen in silicone behavior or migration, glide force, closure integrity, or other crucial factors, providing strong evidence and confidence that ion-exchange strengthened glass is a viable solution for the market.

## SUMMARY

In summary, BD has made significant development and commercial manufacturing investments in glass PFS container technology for the biotech industry with three key areas of focus: reducing overall variability, reducing SbVPs, and increasing glass strength and durability performance. The BD Neopak glass PFS is a culmination of these efforts that should reset glass PFS quality performance levels in manufacturing operations and in the marketplace. The BD Neopak syringe manufacturing process minimizes variability and delivers part-per-million quality control, meaning that instead of a certificate of conformance, customers receive a certificate of analysis. With the methodologies of Quality-by-Design and the way BD has thoughtfully approached these challenges, there is a possibility of achieving zero preventable defects across a number of syringe attributes. ◆

## BIOGRAPHIES

**Dr. Justin M. Wright** is currently Director, Pharmaceutical Development, BD Medical-Pharmaceutical Systems. He earned his PhD in Bio-Organic Chemistry from Clemson University and spent 2 years as a research fellow at Harvard Medical School. He then joined Merck & Company, where he spent 7 years in roles of increasing responsibility across new product development, product commercialization, and franchise management. In early 2007, Dr. Wright joined BD Medical - Pharmaceutical Systems, where he currently serves as BD's primary technical interface for the Biotech, Vaccine, and Pharmaceutical industries in developing and commercializing complex and sensitive drug products in drug delivery systems and platforms. In recent years, he has served as an expert witness in numerous forums, including the National Acadamies of Sciences (IOM), National Vaccine Program Office, and Biomedical Advanced Research Development Authority (BARDA), where he provided expert testimony for the US National Vaccine Plan and the National Pandemic Plan. His current research interests include developing novel approaches and scientific strategies for assessing drug product performance in drug delivery systems and defining clinical models for micro and macro drug administration. Dr. Wright is a member of the AAPS, PDA, and ACS. He is the author of more than 25 patents and publications.

**Herve Soukiassian** is the Biotech cluster core leader at BD Medical – Pharmaceutical Systems and manages a worldwide cross-functional team focused on serving the needs of the Biotech industry. Prior to joining BD 6 years ago, he was a member of the Board of Directors at ActiCM, a start-up company spin-off from the Commissariat à l'Energie Atomique (CEA) specialized in Optical CMM, where he led the portable devices product line for 4 years. During his former 13 years with Hewlett Packard, he gained experience and developed expertise in the field of process engineering - learning and applying key concepts of Total Quality Control, Design for Manufacturing & Assembly, Just in Time, Single Minute Exchange of Die, Theory of Constraint - in the field of product development - mainly in relation with Far East OEMs - and supply chain during the HP-Compaq merger.

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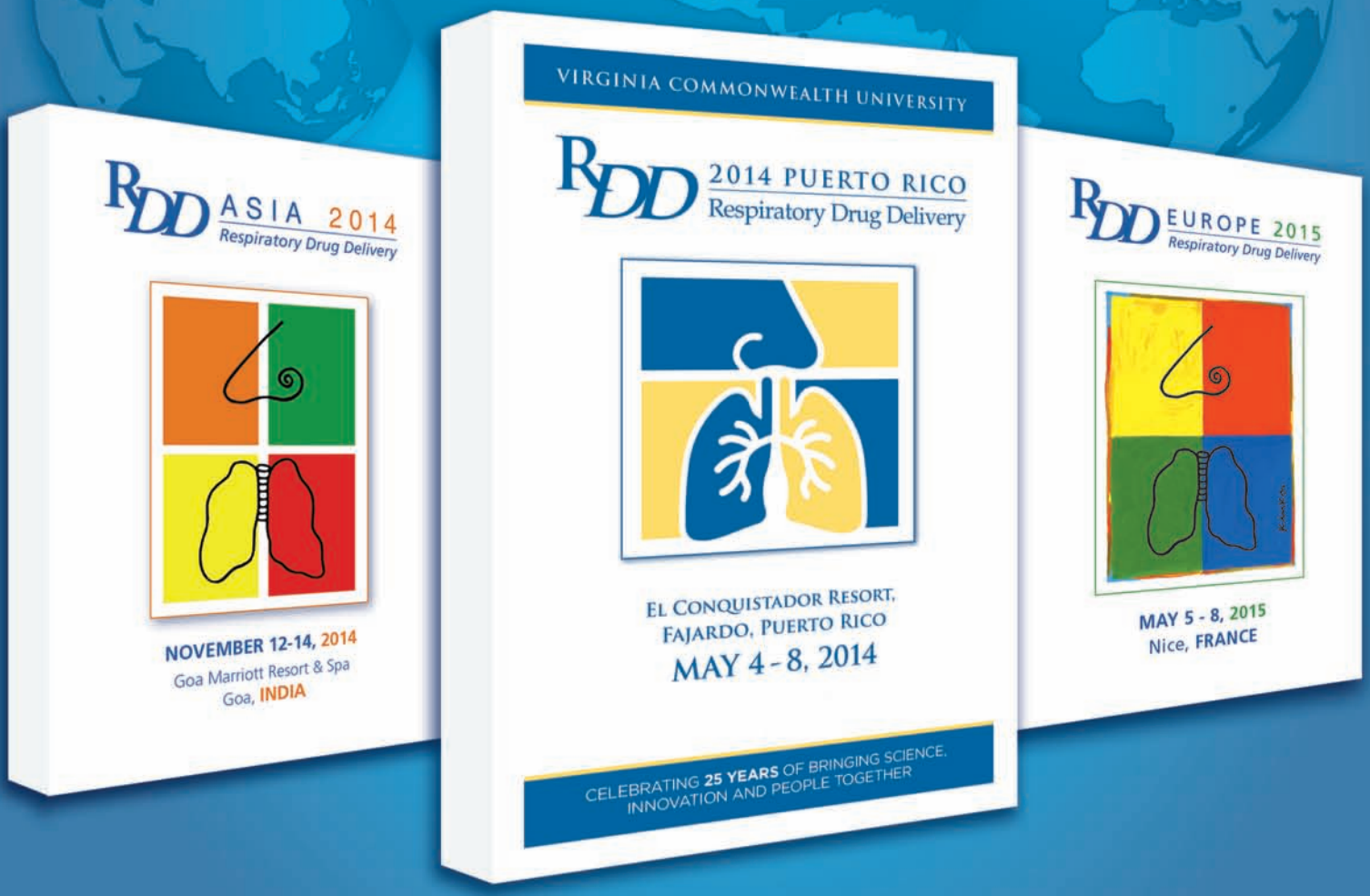


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# BATTELLE: INNOVATION IN DRUG DELIVERY THROUGH INTEGRATED SCIENCE & ENGINEERING

**Amy Heintz, PhD**
Senior Research Scientist
**Battelle**

**"Battelle brings together teams that have the vital technical depth and breadth, as well as industry viewpoint. Not many organizations would think to put chemical engineers, industrial designers, biochemists, device engineers, fluidics modelers, and business people on a drug delivery device development team. In this way, we provide new, fresh ideas to solve problems from the industry, customer, and end-user perspectives."**

*Battelle has been solving the problems that matter most for more than 80 years. At major technology centers and national laboratories around the world, Battelle conducts research and development, designs and manufactures products, and delivers critical services for government and commercial customers. Headquartered in Columbus, Ohio, since its founding in 1929, Battelle serves the national security, energy, health, and environment industries. Historically, Battelle has been a leader in working with customers to find elegant and innovative ways to deliver drugs. Amy Heintz, PhD, Senior Research Scientist at Battelle, recently spoke with Drug Development & Delivery about the company's relationship with customers and the importance of integrating device design, formulation, and human factors in the development of safe and efficient drug delivery solutions.*

### Q: Can you provide some background on Battelle?

**A:** Battelle is a global research and development organization founded by the will of industrialist Gordon Battelle in 1929. Following his vision that science and research can solve problems in business and society, Battelle takes an independent, innovative approach to solving problems for health and analytics, consumer and industrial, national security, and energy and environmental industries. The company conducts research and development, designs and manufactures products, and delivers critical services for commercial and government customers.

### Q: Battelle works with other companies to innovate medical devices, including drug delivery methods. How do those relationships work?

**A:** Battelle's relationships are firmly centered on our customers' needs. Many clients come to us for end-to-end development of a product while others reach out at a particular point in the development cycle. For example, Battelle may start with market research, concept generation, and technical assessment and work through the development process to a final result. Alternately, we may perform failure analysis or usability testing on a finished product. Our customers rely on the broad range of problem-solving capabilities we offer and Battelle's strict confidentiality to protect our relationships.

## Q: How has drug delivery changed throughout the years for Battelle?

**A:** There have been a few important factors that have changed drug delivery throughout the years. One change has been in the policy governing drug delivery devices, which emphasizes the importance of usability. Previously, usability was looked at from a marketing perspective; patients and users selected one brand over another based on personal preferences. The FDA now requires companies to demonstrate that patients can use their combination drug delivery devices safely and effectively to self-administer their therapies. Battelle applies the art and science of human factors to usability, combining behavioral and cognitive psychology perspectives with industrial design and contextual research to develop devices that fulfill the safe and effective interaction requirement.

Drugs and diseases have also changed, which influences how we approach drug delivery methods. In recent years, drugs have moved from a small molecule format to larger protein molecules. These protein drugs, because of their composition, degrade by many delivery methods, such as oral. The result is that drugs need a device - such as an injector or infusion pump - for delivery. At the same time, the preference is to provide devices that can help patients receive dosing at home or a doctor's office rather than in a clinic. Additionally, many of the diseases that are being treated are autoimmune disorders in which patients may have limited dexterity or strength, further complicating the device due to the human factors compliance issues.

## Q: What are some of the biggest challenges in developing drug delivery methods?

**A:** Drug delivery has been one-size-fits-all for many years. Drugs are born in a primary container. Most often, bioavailability studies, pharmacokinetics, and stability are done before the device is selected. The result is that delivery is not always taken into consideration during the drug development cycle, and that puts a lot of constraint on device innovation. Transitioning protein formulations to devices requires addressing challenges associated with delivering highly concentrated, high molecular weight molecules in a manner that is easy, reliable, and minimizes risk to the patient while not damaging the protein.

## Q: How is Battelle uniquely qualified and able to address those challenges?

**A:** It's as simple and as complicated as putting the right team together. Battelle is uniquely qualified to tackle challenges because worldwide we have 22,000 proven problem solvers. It's more than just solving a given challenge; it's about taking a systems approach to devising the best solution when all factors are considered. Battelle brings together teams that have the vital technical depth and breadth, as well as industry viewpoint. Not many organizations would think to put chemical engineers, industrial designers, biochemists, device engineers, fluidics modelers, and business people on a drug delivery device development team. In this way, we provide new, fresh ideas to solve problems from the industry, customer, and end-user perspectives.

## Q: Are there any ground-breaking projects or advancements Battelle is working on now that you can discuss?

**A:** Right now, we are working on human centric interface designs for device users who have limited dexterity and strength. We've performed usability research to identify cognitive and physical risks and linked design features with usability considerations. With another company, we are working on a device that provides instantaneous and consistent subcutaneous delivery, including delivery of high-viscosity protein formulations. Finally, we have translated methods of flow used in the oil and gas industry to an early syringe concept that will minimize drag and interfacial stress on the protein to enable delivery of high-viscosity formulations by syringe.

## Q: What do you see as the trends for drug delivery in the future?

**A:** Battelle is tracking several trends, with particular focus on large molecule therapeutics and "smart" solutions to disease treatment. In the near-term, we know that protein drugs will continue to grow in importance, moving beyond single-dose injectables to larger volumes delivered via wearable injectors and to multiple-dose, controlled-release depot injections. These delivery systems are emerging now and require continued advances to device design.

Closed loop sensing and delivery technologies are also moving closer to reality. The benefits of such technologies are obvious, but the accuracy required for these devices to be effective has so far fallen short of what is required for most applications, like the artificial pancreas.

Another trend to watch is advanced formulations to enhance large molecule stability or enable new routes of delivery. Proteins can be combined with polymers or a colloidal dosage form like microemulsions, nanoparticles, and liposomes. Colloidal formulations offer many new opportunities for protein drugs, as well as for traditional small molecules drugs, due to their unique size, shapes, and characteristics. For example, these systems are being explored to help deliver therapeutics through challenging biological barriers, such as blood-brain barrier and ocular routes.

A grand challenge for drug delivery is to combine advanced formulations with molecular recognition elements and sensing-response elements to create molecules that can, for example, seek-and-destroy cancer cells at a very early stage. Development of such "smart drugs" has been, and remains, a long-term objective.◆

# Data Management

## Taking Regulated Content to the Cloud

**By:** Martin Magazzolo, Global Practice Director, Software Solutions Group, CSC Life Sciences

### Introduction

The cloud presents a strong alternative to costly internal solutions when managing content for R&D, allowing companies to shift their focus to innovation. Expensive infrastructure purchases and bespoke software developments are becoming less common in the business world today. Instead, companies across all industries are adopting or considering hosted as-a-service, or cloud, offerings in many parts of the business. An IDC report shows 80% of firms expect 50% of their internal environment will be transferred to cloud-like capabilities in the next few years.[1] In response, many service providers have updated their offerings, and the same IDC survey shows about 80% of new software offerings will be available as cloud services by 2014.

As a rule, the life sciences industry has been slower to adopt new technology trends than less-highly-regulated industries have, yet the majority of life sciences companies are showing strong interest in cloud solutions - at least in some parts of the business. Cloud or as a service is now more commonly used in such areas as back office functions, HR, finance, customer relationship marketing; and more recently, some of the large pharma companies have embraced the cloud for managing their supply chains.[2]

That shift away from internally driven solutions to off-premise hosting of many aspects of the business comes as companies seek to focus more on the differentiators (meaning, the development of products and of a company's intellectual property) rather than on the storage and management of content.

### The Cloud in R&D

There are several well-known issues that are forcing the life sciences industry to rethink its approach to managing its data and content, including a more tightly regulated landscape and declining pipeline productivity, which in turn is forcing companies to reduce operational costs and outsource more functional aspects of the business. These factors require companies to be able to access their content from wherever it resides in the business quickly and easily, and make good use of that content.

With this in mind, pharma companies are showing greater interest in adopting as-a-service solutions for submission-relevant content and the trial-master-file content in clinical trials, according to a survey by Gens and Associates.

Traditionally, that content was considered to reside within the regulatory domain. In reality, however, it gets used and reused throughout an organization for multiple purposes, including for websites, in sales and marketing material and by

manufacturing facilities.

Furthermore, much of such content consists of information that needs to be shared among and viewed by not only those within the organization but also by external partners, from ones in academia to ones in biotech to contract research organizations, and so on.

The fact is that R&D today is more than ever a collaborative effort, and those external partners are now critical to the process of discovering and developing new products. Therefore, the ways information gets gathered, stored, and shared must be considered carefully. Bespoke internal platforms can make information sharing difficult, placing additional burden on busy R&D professionals to extract information from a local system in order to share it with partners. Instead, a cloud or a content-as-a-service solution makes information accessible through a common, Internet-based platform.

Accessing content through the cloud also removes the problem of using inconsistent or inaccurate information elsewhere in a company. For example, if reps make unsupported claims or talk about off-label indications when they shouldn't, the company could face heavy fines. This is undoubtedly a content management issue and demonstrates the importance of ensuring information about a product remains consistent. It means that what a rep tells a physician about a product must adhere to clinical studies and regulatory submissions.

## Cost Pressures

The industry is under greater pressure to take cost out of the business and to improve efficiency. In such an environment, the development and maintenance of tailored electronic content management (ECM) solutions are unsustainable. From a cost point of view, such solutions involve not only internal server and storage facilities but also ongoing licenses and employment of the necessary staff for maintaining and updating the technology.

Many of those costs are averted by using cloud platforms. To begin with, all of the security considerations, infrastructure, and storage requirements are shared, which spreads the cost among users. Moreover, rather than being an internal solution that is developed to cope with peak demand and that therefore remains a constant cost, content as a service lets companies pay only for what they require.

Cloud solutions also significantly reduce time to delivery. Rather than the months-long wait for a solution to be developed and put in place, the standardized nature of cloud solutions (developed for use by multiple companies using a standard application) means a project can be up and running within days. This creates a double benefit in that it not only reduces the time it takes to start up but also the likelihood the solution will have become obsolete by the time it gets implemented, a danger with bespoke internal solutions. And from the point of view of delivering products, not having to spend time on infrastructure provision allows the focus to be solely on innovation within each R&D portfolio.

For the data-rich life sciences industry, the cloud has the potential to expedite the management of data from when it is created, stored and used for reports or analysis. This allows companies to gain greater insight into where the data lie, how these are being used and how that impacts decision-making.

The escalating significance of emerging markets on the pharma bottom line creates another incentive for cloud adoption. This is particularly true from a regulatory point of view. Few emerging markets use the electronic Common Technical Document (eCTD) format, which means companies looking to submit products for marketing applications in countries such as Brazil, China or India, cannot simply take the processes and practices they use in Europe and the US into those markets. Instead, regulatory departments must prepare submissions for those countries and liaise with affiliates and, very often, external country regulatory experts to manage a submission. This increases the burden on already busy

regulatory departments. On the other hand, regulatory solutions supplied through the cloud can be built to meet the requirements of all agencies and submission types, and will also be more cost-effective since, as stated earlier, companies can simply purchase the capacity they need.

## Cloud Doubts

Though the cloud has much to recommend it as a platform, companies have some reservations, most notably around security. There remains the fear that putting content in the cloud would put that information at risk and thereby give others access to invaluable intellectual property. Certainly, there are cases when some cloud providers have not provided as secure a platform as promised, and companies are right to be vigilant.

Those issues can be resolved, however, with secure transmissions that partition data from other customers that are using the same cloud platform. Indeed, such cloud solutions are typically more secure than internal solutions are. Unfortunately, internal leaks that expose passwords and data happen more frequently than companies admit.

Performance remains the other major barrier to adoption. Companies want to know they can get the same level of control (and therefore the same level of performance) if they go to an external provider that delivers content management as a service.

In an informal survey conducted by CSC among a group of clients, a further issue that was raised was that of interface interoperability with other systems. Given the complex environments in which R&D takes place, in which systems and processes are tightly coupled across a heterogeneous environment, these are considerations that any cloud provider (and indeed cloud adopter) must consider carefully. However, cloud technology has evolved significantly, and today's application programming interfaces are standardized, so accessing and sharing information or indeed allowing systems to interface with one another is less complex than in the past.

Companies are also a little wary of data lock-in, whereby a contract with a vendor makes it difficult to get data back should they wish to change to a different solution or a different vendor. Companies do need to ensure (1) that what they are agreeing to is the purchase of a unit of capacity over a short and renewable fixed term and (2) that the applications and volumes of data that get placed on that capacity are specifically agreed to. Ultimately, the client should always remain the owner of the data and always be able to move that data should it wish to.

Doubts over the use of cloud also vary according to region. Survey results from Gens and Associates indicate that for companies that are headquartered in Europe or the US, security is the primary concern, whereas Japan-based companies are most concerned about reduced functionality or capability.

## Reluctance to Change

Throughout the past 20 years, large pharma companies have invested heavily in tailored internal platforms, not simply in terms of a financial cost, but also the processes and people involved. Understandably, some staff, or even departments, within a large company will be disinclined to adopt a new way of thinking and operating.

Moreover, a change from an internal platform to as a service would entail changes to the way companies operate their IT function in that they would need to prepare for consumer service rather than providing internally designed solutions, and that takes a change in mindset.

Reticence over as-a-service also stems from unwillingness (in part born from concerns over security and confidentiality) to cede control over the location of data to a third party. Historically, these concerns are understandable and highly relevant since R&D departments understand full well the consequences of data loss, both from a commercial and regulatory perspective.

For the highly regulated life sciences industry, validation remains a cause for concern with regard to changing the status

quo and adopting a cloud-based platform. Pharma companies need to know that their application suppliers have provided certified minimum specifications for the infrastructure required to support their application in the application's intended use. Companies then build hardware configurations that meet or exceed the specification required, and any changes or updates are managed through a change-control process to maintain qualification of the environment and validation of the system. With the cloud, however, it could potentially be difficult to qualify the hardware because companies don't know which hardware applications are going to be used.

This issue, in particular, underscores the importance of knowing that the supplier meets the tightly specified and controlled standards required.

## Moving to the Cloud

The role of the regulatory function has changed significantly in recent years, and today, regulatory operations have become a standardized function, meaning it is not in companies' interests to invest in costly bespoke systems. This allows the regulatory department to focus on its true job, which is to secure and maintain market access.

Companies want (and should expect) their providers to offer best practices on how to deliver data and content management in the cloud. Companies want to be able to easily access and share information while knowing that their sensitive intellectual property remains secure and that they are in compliance with regulations. And they're seeking more integration with other solutions, both internal and external, without having to worry about systems and software upgrades.

The cloud or content as a service is one way to effectively drive additional value and reduced costs to the business. While as a service won't necessarily be the answer to every aspect of the business, companies need to ascertain whether it is in their interests to develop or maintain infrastructure internally, both economically and for competitive advantage. As the focus shifts away from managing everything internally toward collaboration and partnership in the search for improved productivity and reduced costs, the advantages of cloud to manage data and content become more discernible. ■

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**Martin Magazzolo**

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Martin (Marty) Magazzolo, Global Practice Director, Software Solutions Group, with CSC Life Sciences, has more than 20 years of experience in the field of information technology, with 18 of those having been spent in the life sciences. He has a deep understanding of the needs of pharmaceutical companies across technology, services, and sales. His expertise in the areas of electronic collaboration and enterprise content management enables him to respond to the requirements of ECM customers across product development, support and global services and solutions. His expertise extends to managing and supporting the full life-cycle of application development, from analysis, design, development and implementation.

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# Product Versus Service Businesses

By: John A. Bermingham

This past November, I joined 1st Light Energy as its Chief Operating Officer, and my wife and I relocated to Northern California. 1st Light Energy is a solar and conservation lighting business that installs solar arrays and highly efficient lighting on residential homes and commercial buildings.

Obviously, this was a time of major change for us, and I quickly came to realize that I was also going through an additional change. I was now going to run a service business for the first time after having led products businesses my entire career. I quickly began to see the differences in these two types of businesses as service businesses are very different from product businesses.

In a products business, you are selling tangible items over and over to your customers. Customers can come to you either in a brick and mortar store and walk out with the product in their hands, or they can go on the internet and have it delivered.

I found that in a service business, you are the product. And you are not just selling a service; you are selling trust and confidence in yourself and the service that you provide. The product in this case is also a promised result made by you to the customer, and the make or break in this situation is whether or not you deliver quality results in the timeframe specified.

This new business appeared to me as being much more personal in nature. I was used to selling a feature benefit set on a product or product line. In the service business, I was selling me and then the capability of our company. It is imperative that you gain your customers' trust and convince them that you will deliver on your promise.

I also found that marketing is also quite different when comparing product to service businesses. Marketing in a product business centers around the 4 Ps of product, price, place, and promotion. In a service business, marketing centers around three additional Ps of people, process, and physical evidence. So you have to consider all 7 Ps in service business marketing.

There are two basic types of marketing, push and pull. Push marketing is pushing your products or services on to people. Pull marketing is attempting to draw people to your products or services. I believe that the service business is more of a push business. In 2012, before I joined 1st Light, the company had spent substantial marketing dollars on pull marketing. They advertised on radio, in print, and spent most of their marketing dollars on a huge direct mail campaign. They did not achieve what they had anticipated for their expenditure.

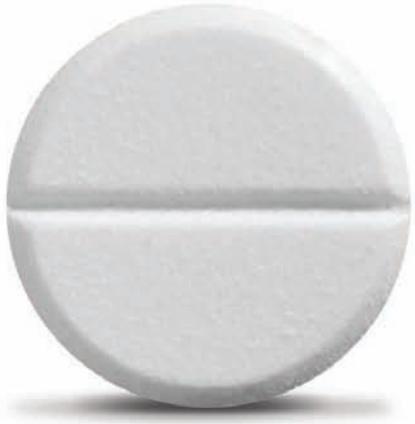
I realized, after joining the company that we really needed to spend our marketing dollars on a push marketing strategy. We hired a sales force that would go door to door and push the idea of solar energy and the tremendous cost savings it provided, not to mention its green energy capability. We also directly marketed to commercial building owners. The results are that we tripled our residential solar business in 1 year, and the commercial business is growing rapidly.

So there are distinct differences between product businesses and service businesses, and I am still learning. I am also learning that there are similarities between the two business types, but that is for another discussion. ◆

## Biography

**John A. Bermingham**
**Chief Operating Officer**
**1st Light Energy & Conservation Lighting**

John A. Bermingham is currently the COO of 1st Light Energy & Conservation Lighting. He was previously Co-President and COO of AgraTech, a biotech enterprise focused on chitosan, a biomaterial processed from crustacean shells (shrimp, crawfish, crab, etc), as well as President & CEO of Cord Crafts, LLC, a leading manufacturer and marketer of permanent botanicals. Prior to Cord Crafts, he was President & CEO of Alco Consumer Products, Inc., an importer of house ware, home goods, pet, and safety products under the Alco brand name and through licenses from the ASPCA and Red Cross. He successfully turned around the company in 60 days and sold Alco to a strategic buyer. Mr. Bermingham was previously the President & CEO of Lang Holdings, Inc. (an innovative leader in the social sentiment and home décor industries) and President, Chairman, and CEO of Ampad (a leading manufacturer and distributor of office products). With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona Corporation, and Rolodex Corporation. He turned around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served 3 years in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes, earned his BA in Business Administration from Saint Leo University, and completed the Harvard University Graduate School of Business Advanced Management Program.



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