Drug Development® & Delivery

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

Corey J. Bloom, PhD
Amorphous Dispersions & Other Tools for Drug Discovery Formulation Support

Pamela Palmer, MD, PhD
Sufentanil NanoTab® Technology: Revolutionizing Patient-Controlled Analgesia

Cindy H. Dubin
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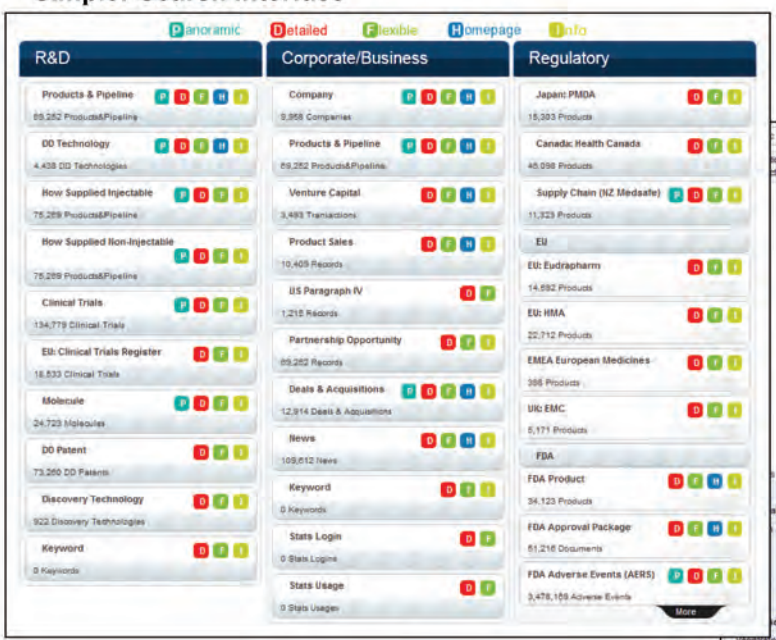

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Biogen's Injectable Drug Significantly Cuts Relapse Rate

Biogen Idec recently announced the positive, full first-year results from its 2-year pivotal Phase III ADVANCE study of PLEGRIDY (peginterferon beta-1a), the company's investigational candidate for relapsing-remitting multiple sclerosis (RRMS) dosed once every 2 weeks or every 4 weeks. These data, recently presented at the American Academy of Neurology's 65th Annual Meeting, indicate that PLEGRIDY significantly reduced multiple sclerosis (MS) disease activity, including relapses, disability progression, and brain lesions, compared to placebo at 1 year.

"These full first-year results provide a more complete picture of PLEGRIDY and its positive effects on the reduction of relapse, disability progression, and lesion development," said Peter Calabresi, MD, Director, the Johns Hopkins Multiple Sclerosis Center. "These data suggest that, if approved, PLEGRIDY may offer the benefit of a less- frequent dosing schedule, which would be a meaningful advance for people living with MS."

STUDY RESULTS FOR TWO-WEEK DOSING ARM AT YEAR 1

Primary Endpoint

- PLEGRIDY met the primary endpoint of reducing annualized relapse rate (ARR) at 1 year by 36% compared to placebo (p=0.0007).

Secondary Endpoints

- PLEGRIDY reduced the proportion of patients who relapsed by 39% compared to placebo (p=0.0003).
- PLEGRIDY reduced the number of new or newly enlarging T2-hyperintense lesions on brain MRI scans by 67% compared to placebo (p<0.0001).
- PLEGRIDY also demonstrated significant positive effects on disability progression by reducing the risk of 12-week confirmed disability progression, as measured by the Expanded Disability Status Scale (EDSS), by 38% compared to placebo (p=0.0383).

Additional Results

- PLEGRIDY significantly reduced the number of gadolinium-enhancing (Gd+) lesions by 86% compared to placebo (p<0.0001).
- The incidence of PLEGRIDY neutralizing antibodies was less than 1%.
- PLEGRIDY dosed once every 4 weeks was also shown to be effective, and met the primary and secondary endpoints in the ADVANCE trial. PLEGRIDY dosed once every 2 weeks resulted in a numerically greater treatment effect across these relapse and the aforementioned MRI endpoints.

"In the first year of the ADVANCE trial, PLEGRIDY demonstrated strong efficacy. We saw a marked reduction in relapse rate and this was supported by MRI results. If approved, PLEGRIDY will make an important therapeutic option in the injectable treatment segment", said Gilmore O'Neill, Vice President, Global Neurology Late Stage Clinical Development at Biogen Idec. "In addition to these encouraging therapeutic results, PLEGRIDY may reduce the treatment burden for patients by reducing the number of subcutaneous injections."

PLEGRIDY showed favorable safety and tolerability profiles in ADVANCE. The overall incidence of serious adverse events (SAEs) and adverse events (AEs) was similar among the PLEGRIDY and placebo groups. The most common SAE was infections, which was balanced across all treatment groups (=1% per group). The most commonly reported AEs with PLEGRIDY treatment were redness at the injection site and influenza-like illness.

PLEGRIDY is a new molecular entity in which interferon beta-1a is pegylated to extend its half-life and prolong its exposure in the body, enabling study of a less-frequent dosing schedule. PLEGRIDY is a member of the interferon class of treatments and, if approved, would be a new addition to this class, which is often used as a first-line treatment for MS.

After completing 2 years in the ADVANCE study, patients have the option of enrolling in an open-label extension study called ATTAIN and will be followed for up to 4 years.

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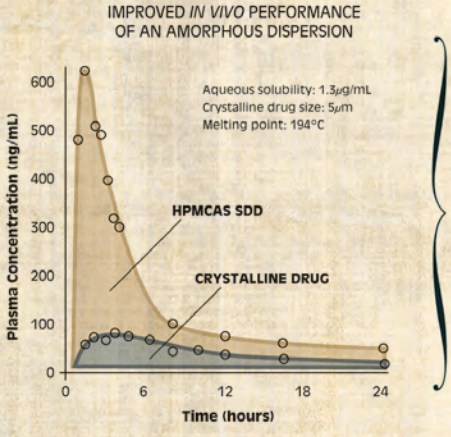

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Cerecor Acquires Rights to COMT Inhibitors

Cerecor Inc. recently announced it has acquired exclusive, worldwide rights to develop, register, and commercialize agents that inhibit catechol-O-methyltransferase inhibitors (COMT inhibitors), previously discovered and owned by Merck, known as MSD outside the US and Canada.

COMT is an enzyme that breaks down dopamine, a neurotransmitter that plays a key role in higher brain functions, such as motivation, cognition, and emotion. Drugs that inhibit COMT have been used to treat patients with Parkinson's disease; however, they have poor brain penetration and limited safety and tolerability. COMT inhibition also has broad potential applicability in other CNS diseases, such as addictive behaviors and schizophrenia, by specifically increasing dopamine levels in areas of the brain affected by these conditions. While the development of schizophrenia drugs to date has focused on reducing psychosis, improvement in functional outcome has been largely unattainable because current drugs do not have clinically significant impact on the "negative symptoms" and cognitive impairment of the disease. Drugs that inhibit COMT improve working memory and other measures of cognitive function in animals and in clinical studies (normal subjects and in schizophrenics).

"Merck has developed an innovative COMT platform that has addressed the toxicity associated with existing COMT drugs. By accessing this platform, Cerecor broadens its cognition pipeline, which also includes DAAO inhibitors. This enhances our leadership in neuropsychiatric drug development," said Dr. Reza Mazhari, Cerecor's VP of Drug Discovery and Development.

Under the terms of the agreement, Cerecor will evaluate more than 2,000 molecules and select lead candidates for clinical development. Consideration includes milestone payments and royalties consistent with other preclinical licenses in neuroscience. Cerecor anticipates completing the technology transfer activities in 2013.

"Adding COMT inhibitors to our drug development portfolio enhances our mission. Cerecor continues to focus on targets or technologies that have demonstrated human proof of concept, and for which biomarkers could be used to steer early clinical development. We are delighted that Merck has chosen Cerecor to help realize the value of such an innovative body of work as contained within their COMT patent portfolio," added Dr. Blake Paterson, Cerecor's Co-founder and CEO.

"Cerecor's approach to the development of safe and effective therapies, combined with its experienced management team, makes them an ideally suited to help advance this platform targeted for the treatment of CNS diseases," said Dr. Richard Hargreaves, Vice President, Worldwide Head of Basic Research, Neuroscience, Merck Research Laboratories.

Cook Pharmica Receives Additional Approval From US FDA

Cook Pharmica, which develops and manufactures pharmaceutical and biopharmaceutical products on a contract basis, recently received more good news from the US FDA. The company earned another commercial approval from the FDA and did so with the FDA waiving the otherwise required pre-approval inspection.

“We are grateful for the confidence shown in our facilities by the waiving of the inspection and are especially pleased that the quick approval will allow this drug to make it to patients in need. We will continue to work with the FDA to ensure that future clients experience the same efficient approval process,” said Tedd Green, President of Cook Pharmica.

The approval of this drug product will help fill a void for patients in need, which resulted from a known, national drug shortage of a product currently listed on the FDA’s Drug Shortage Index. Added Green, “We will continue to seek productive ways to support the biopharmaceutical industry, the FDA, and ultimately patients by using our contract manufacturing assets to help increase the supply of sterile injectable products in shortage.” Fifteen million vials and 70 million syringes can be filled each year by the state-of-the-art manufacturing lines at the technologically advanced facility.

Cook Pharmica is an integrated contract development and manufacturing organization providing the pharmaceutical and biopharmaceutical industries with drug substance manufacturing from mammalian cell culture; analytical and formulation development; parenteral manufacturing in vials and prefilled syringes; lyophilization; and secondary packaging.

OXiGENE Announces Patent Issuance for Novel Anticancer Class of Agents

OXiGENE, Inc. recently announced the US Patent and Trademark Office issued US Patent No. 8,397,859, covering certain benzosuberene-based compounds, including the analogues referred to as KGP18 and KGP156 that are currently in preclinical development. The patent also covers methods of using those compounds to inhibit tubulin polymerization, to reduce blood flow to a tumor, or to restrain, slow, stop, or reverse progression of a tumor.

These compounds are the product of OXiGENE's ongoing collaboration with Kevin G. Pinney, PhD, and Mary Lynn Trawick, PhD, at Baylor University to identify inhibitors of tubulin polymerization as vascular targeting agents and as back-up compounds to OXiGENE's combretastatin A-4P (ZYBRESTAT) and OXi4503.

Recently, the focus of this collaboration has centered on the development of novel antiproliferative agents (benzosuberenes) and anti-invasive molecules (cathepsin L inhibitors). OXiGENE has an exclusive license to the worldwide rights to all of the compounds that result from this collaboration.

"The issuance of the patent covering benzosuberenes is an important achievement for OXiGENE that enhances the value of our anticancer portfolio for potential pharmaceutical partners and investors," said Peter J. Langecker, MD, PhD, OXiGENE's Chief Executive Officer. "We believe that this exciting new class of compounds has the potential to enhance treatment options for oncologists and patients with cancer. This work also demonstrates the continued productivity of our collaboration with Baylor University."

"This benzosuberene series of molecules are among the most potent antiproliferative agents identified to date in our laboratories, and we believe this exceptional potency coupled with their antivascular activity make these compounds potentially well-suited for selective delivery strategies, including their use as payloads for antibody-directed therapy," said Dr. Pinney, Professor of Chemistry at Baylor University.

Benzosuberenes have highly potent anti-proliferative activity via inhibition of tubulin assembly at the colchicine binding site. Lead compounds include KGP18 and KGP156, which are potent small-molecule tubulin depolymerizing agents displaying sub-nanomolar (in the case of KGP18) antiproliferative activity in vitro against a number of human cancer cell lines. These compounds have also been shown to disrupt capillary-like networks of endothelial cells in vitro and induce reductions in tumor blood flow in human tumor xenografts in mice.

PerkinElmer Introduces Novel Non-Invasive Near-Infrared Imaging Agent

PerkinElmer recently introduced The GFR-Vivo 680 imaging agent, the first fluorescent agent that allows researchers to measure glomerular filtration rate (GFR) non-invasively, in vivo in animals. GFR-Vivo 680, in combination with Fluorescence Molecular Tomography (FMT) imaging, provides a non-invasive approach to generate consistent GFR measurements in animal models of kidney disease, dysfunction, and drug toxicity.

GFR is the leading standard for measuring kidney function and is used to determine progression of kidney disease as well as drug-induced kidney toxicity. This agent allows researchers to get an accurate read out of GFR in vivo without the need for blood or urine sampling or labor intensive microplate assays. This fluorescent imaging agent is well-suited for researchers studying in vivo toxicology or drug safety assessment.

The GFR-Vivo 680 was launched at this year's Society of Toxicology's 52nd Annual Meeting and ToxExpo in a presentation titled, Novel Near Infrared Agent for Non-Invasive Imaging and Quantification of Glomerular Filtration Rate in Mice. PerkinElmer also plans to feature the new imaging agent at booth No. 1424 at the American Association for Cancer Research (AACR) Annual Meeting from April 6-10.

Enanta Pharmaceuticals Raises $56-Million in IPO

Enanta Pharmaceuticals, Inc. recently announced the pricing of its initial public offering of 4,000,000 shares of its common stock at a price to the public of $14.00 per share. The shares of Enanta's common stock will trade on the NASDAQ Global Select Market under the symbol ENTA beginning on March 21, 2013. All of the shares of common stock are being offered by Enanta. In addition, Enanta has granted the underwriters a 30-day option to purchase up to an additional 600,000 shares of common stock to cover over-allotments, if any. The offering is expected to close on March 26, 2013, subject to customary closing conditions.

Enanta Pharmaceuticals is a research and development-focused biotechnology company that uses its robust chemistry-driven approach and drug discovery capabilities to create small molecule drugs in the infectious disease field. Enanta is discovering and developing novel inhibitors designed for use against the hepatitis C virus (HCV). These inhibitors include members of the direct acting antiviral (DAA) inhibitor classes - protease (partnered with AbbVie), NS5A (partnered with Novartis) and nucleotide polymerase - as well as a host-targeted antiviral (HTA) inhibitor class targeted against cyclophilin.

Additionally, Enanta has created a new class of antibiotics, called Bicyclolides, for the treatment of multi-drug resistant bacteria, with a current focus on developing an intravenous and oral treatment for hospital and community MRSA (methicillin-resistant Staphylococcus aureus) infections.

INNERCAP Granted Patent for Multi-Phase, Multi-Compartment Capsular Delivery Apparatus

INNERCAP Technologies, Inc., a combination drug delivery system company, recently announced the grant of US Patent No. 8,361,497 B2 titled Multi-Phase, Multi-Compartment Capsular Delivery Apparatus. The delivery system has uses for biopharmaceutical, pharmaceutical, medical foods, and nutraceutical products. In addition to the existing US, Canadian, Australian, and New Zealand patents, this patent covers the company's multi-phase, multi-compartment delivery system used to enable the development of multi-compartment, multi-phase delivery forms of combination products that have compatibility, formulation, or targeted delivery requirements.

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

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

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

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

Management Insight

Listening to the Voice of Inexperience

By: Derek Hennecke, CEO & President, Xcelience

Part 3 of a 6-part series offering an overview of this year's six best business books with insights into what they can teach the Pharma industry.

It's May 1940, and the German offensive has begun. Britain follows a path of appeasement. The Chamberlain government has collapsed, and all of Britain turns to one man: Lord Halifax. Lord Halifax is the man the system has created for this moment. A 20-year veteran of the House of Commons and Secretary of War under Chamberlain, he is on the forefront of the movement to appease the Nazis. He was bred to be prime minister.

But Halifax turns the position down. An astute politician, he realizes that whatever peace treaty is negotiated will be a ticking time bomb. Better to step into the shadows for a while, and swoop in to clean up later. His unexpected sidestep leaves the nation rudderless, and another man is hastily rushed in from the political hinterland. This man is everything Halifax is not. An advocate of confrontation, a political outsider, Winston Churchill is a risky choice for a nation on the brink of war.

The rest is, as they say, history. Churchill was exactly the right man for that moment, and became one of the greatest wartime leaders ever.

Now the year is 1860, and America is a handful of quibbling states barely held together. The southern states move toward secession, but the Republicans don't take the threat seriously. Even if they do leave, most surmise, they'll be back. Just let them go.

Three men vie for the Republican nomination, and Abraham Lincoln, a man with little political experience beyond two losses in the senatorial races, is no one's first choice. But he is everyone's second choice, and when the three top contenders fail to produce a victory, he takes the nomination. The Democratic convention can't even produce a candidate, so a political neophyte sweeps into power. Lincoln does what the Washington insiders would never have dreamed of: he refuses to give up the Union stronghold of Fort Sumter, SC, without a fight. Devising a strategy that forces the South to fire the first shot, he unites the North behind him. Abraham Lincoln became one of the greatest wartime leaders ever.

Sometimes, the best leader for the job is the one with the least experience, writes assistant Harvard professor Gautam Mukunda in, *Indispensable: When Leaders Really Matter.* There are two kinds of leaders, according to Mukunda: filtered and unfiltered. A filtered leader is one whose career was built on the inside, following the political or corporate ladder. An unfiltered leader comes from outside and happens into the job, often by chance or circumstance. Looking at historian rankings of the best presidents for the past 60 years, Mukunda found that the experienced contenders rarely outperformed their less-experienced counterparts. In fact, Mukunda found the inexperienced men were by far the most effective - though, he goes on to explain, they could also be the least effective.

Most lists of the five greatest presidents include Washington (unfiltered), Jefferson (filtered), Lincoln (unfiltered), T. Roosevelt (unfiltered), and F. Roosevelt (unfiltered). All of these men brought outside experience inside the White House and made extraordinary decisions because of their perspective. All, that is, with the exception of Jefferson, who was brought up for the top job, and whom Mukunda argues did not truly earn his spot among such distinguished company, since the Louisiana Purchase that brought him fame was an exchange that any President in his place would have accomplished. All the other great Presidents were men who did NOT do what the insiders thought should be done.

Political and corporate insiders - men like Jefferson - are highly interchangeable, says Mukunda. They are very often good, but very rarely great. These filtered leaders rule with competence, steady the ship, avoid risk, and chart a safe and secure course.

But who wants safe and secure? Don't we all yearn for breakout leaders? Bring on Bill Gates and Mark Zuckerburg. Let's make history! We want Charles Coffin, the man behind what General Electric is today - a man who incidentally came from the shoe business. We want Sam Walton, a military man until he opened his first variety store. Such men are unfettered by the norms of industry thinking and as a result, do things differently.

The pharmaceutical industry, I have often argued, is ripe for radical change. We can't go on orienting an entire industry on the search for a blockbuster drug. The cost of development is too high, the success rate too low, and the run time too short since the advent of generics. We need leaders. **Where is the Steve Jobs of the pharma world?**

Not so fast, Mukunda would caution. Unfiltered leaders are at least as likely to blaze trails as they are to reduce the entire forest to ashes. Examples of unfiltered leaders gone wrong litter the world stage - think Hitler and Lenin - but the shelf-life of unfiltered business leaders is much shorter, so most just flicker out and vanish.

Still, they're there if you look for them. Pfizer's Jeff Kindler may be such an example. A Harvard law grad and litigator who later became general counsel at McDonald's, Kindler was known as an aggressive, combative fighter. He cleaned house at McDonald's, and his success caught the eye of Pfizer, which offered him general counsel of their 330-strong legal team and the promise of better things to come. This was Pfizer's heyday, when its stock was made of helium, multiplying in value tenfold in a decade. The press

bestowed the company with accolades like "best managed" and "most admired."

Kindler accepted the post, and despite his newness to the industry, quickly outmaneuvered his rivals to take the top job in 2006. He promised to energize and modernize the company.

Instead, he oversaw a 35% decline in share value. While it would be unfair to blame him for the failure of the two blockbuster candidates that Pfizer was pinning its future on, his flip-flopping style did little to improve a bad situation. He closed six R&D facilities and halted research in 10 disease areas, while at the same time setting a goal of launching four new internally developed drugs a year by 2010. Desperate to shrink the company, Kindler laid off 20% of the US sales force, then grew the company exponentially with the purchase of pharma giant Wyeth. He split research into two, creating a separate unit for biological drugs and built an expensive new facility in San Francisco, then reversed the decision 30 months later.

Bruce Roth, the scientist known as the father of Lipitor, said, "When every 18 months you throw the organization up in the air and are shifting therapeutic areas or closing sites, you have this period of turmoil when everybody in the organization is paralyzed. You need some continuity to do science." Ironically, Roth lost his job when Kindler closed Roth's site in Ann Arbor, and is now VP of Chemistry at Genentech.

Today, Pfizer is run by the steadier hand of Ian Read, a company insider and filtered leader who has a Chemical Engineering degree and began his Pfizer career in 1978.

Unfiltered leaders are high risk, high reward. Most of the time, what we really need, Mukunda argues, are the industry insiders - the Tim Cook's and the Neville Chamberlains. Such men, formed and shaped by their own industries, will tend to make the same decisions regardless of which one of them you put on top. And that's fine, most of the time. After all, the man who led Pfizer through the glory years of Lipitor and Viagra was an industry man if ever there was one. William Campbell Steere, Jr. rose up the ranks after starting in the company as a drug salesman in 1959. And there was never more of an inside man than George Merck, the man who's largely credited with making Merck what it is today. Merck took over his father's company as just one more link in chain of chemists and pharmacists that stretched back three centuries.

Mukunda's thinking can be generalized to leadership throughout the organization, not just in the top spot. We, as scientific companies should be especially open to unfiltered thinking, despite the risks, because innovation often finds its inspiration off the well worn path.

Angiogenisis research owes its genesis to an unfiltered thinker named Judah Folkman.

Folkman was a surgeon who was drafted by the navy and asked to look into the possibility of developing whole blood substitutes that could be used in transfusions. To test potential substitutes, he needed access to tissues that would grow outside the body, and he chose cancer cells. During his research he noticed something odd. The tumors that fed on the blood substitutes he and his partner developed stopped growing at 1 mm in diameter. When transplanted back into living animals, however, the cells resumed reproduction. Folkman deduced that cancer cells needed the circulatory system to grow. He theorized that the cancers expressed an unidentified factor that caused capillaries to grow toward them, and that the tumors might be stopped from growing by supressing that factor.

This was the mid 1960s, and the filtered thinking within the oncology world was virtually entirely focused on the hunt for chemicals to kill cancer cells. Blood vessel research was unheard of, and he found almost no support for it within the oncology community. Folkman begged for money for most of his career, but the men and women he had to look for funding and to publish his papers were conventional researchers. After countless refusals, when he finally received a small grant from the National Institutes of Health, he mistakenly received a document with the handwritten note, "This is the limit. We do not want Folkman to build an empire," scribbled in the margins.

As this negative sentiment from cancer researchers built, he was eventually forced to give up his coveted position as Chief of Surgery at Boston Children's Hospital. His colleagues there deemed his research "irrelevant" to the job of surgeon.

Without a secure source of funding, in 1974, Folkman was forced to look for new sources. In 1974, he created the first partnership between a corporation and a university for biomedical research. His resources now secure, the personal campaign against him continued. His innovative new funding agreement led a science magazine to investigate him. At the height of the animosity, when Folkman rose to speak at a conference for experimental biologists, a hundred audience members stood and walked out.

Folkman fought on long past the endurance of most people, and mankind today owes him a debt. His out-of-the-box thinking led to one role of the Ras gene, which is part of the Ras-Mek-Erk pathway that supports tumor growth, and a decade later, Folkman's thinking is widely accepted and central to the treatment of a growing number of diseases, including blindness caused by macular degeneration and the use of interferon to heal

hemagiomas. His research is credited with the development of angiostatin, endostatin, vasculostatin, caplostatin, and lodamin. Genentech's Lucentis and Avastin are both FDA-approved angiogenesis inhibitors based on Dr. Folkman's hypothesis, and there are more than 50 angiogenesis inhibitors in clinical trials.

All this, from a man with no formal background in oncology, who came up with the idea and had it thoroughly and vehemently rejected by the oncology insiders. Folkman's story is also recounted in another book *The Emperor of All Maladies: a Biography of Cancer* by Siddhartha Mukherjee. This is a real feel-good book for those of us in the industry, highlighting not how far we have to go to cure cancer, but how much we have already accomplished. Just the history of the butchery surrounding mastectomies will be enough to keep us all working late nights. And the introductions of new oncology medicines throughout the book point to the value of chemistry over surgery.

So here's the upshot: the filtered leader can be counted on to do a reasonable job, with reasonable consistency. The unfiltered leader is a high-risk proposition, but when that bet pays off, the course of history changes.

How can you apply Mukunda's reasoning to your own organization? I can only tell you how this book has influenced me. I want both types of leaders in my organization. Mostly, I want filtered leaders. But I also appreciate the perspective of someone who comes from outside the industry, particularly in my management team. Our new CFO is not from the industry, and his questions and insights have been eye-opening. The problem is, unfiltered leaders are harder to fit in most areas of the organization. For one thing, headhunters always try to give me the most filtered possible candidate. They see it as their mission to give me someone with experience doing exactly what I need them to do, which is the definition of a filtered candidate. Many times, that's great. I don't really want resumes from leaders in microbiology when I'm looking to fill an analytical chemistry position. I credit the system with finding me a new clinical packaging BD who will greatly enrich that side of the business with her wealth of industry experience.

If I want a less-filtered candidate, I have to search a little harder. Start-ups are often run by unfiltered leaders, because these businesses are high risk, and it can be hard to find comfortably well-paid and experienced executives to get off the couch and get into the dirt. Consultants can also provide a splash of outside perspective from time to time.

But I can also do something Mukunda doesn't talk about, and that's to create a culture that's open to new ideas. I want to run the kind of company that, should a Sam Walton or Mark Zuckerberg get hired here, he would feel comfortable staying. I want an inside culture that leaves all the windows open and lets the outside in.

I'm still probably going to put the filtered leaders at the helm most of the time, but I'll also work to create access to different perspectives; and to make sure that the voice of inexperience isn't silenced by the organization's natural filtration process. Then, when 1940 looms or 1861 approaches, I hope to God that I can recognize it for what it is, and let the unfiltered leader deliver. ◆

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 2007, 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.

Next generation HPMC capsules greatly expand pharmaceutical uses

by Dominique Cadé, PhD

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.

Figure 1

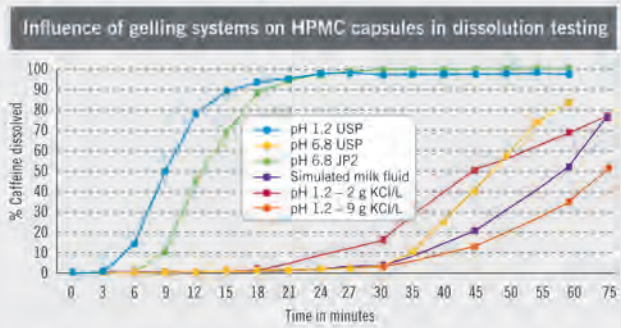
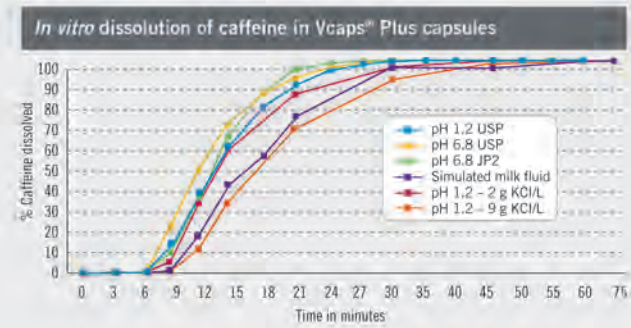


Figure 2



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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Vcaps® Plus

For more information about Vcaps® Plus capsules visit VcapsPlus.com.

CAPSUGEL®

IntelliCap: An Intelligent, Electronic Capsule for Oral Drug Delivery & Development

By: Jeff Shimizu and Christoph Wanke, PhD

Characterization of drug absorption in vivo throughout the gastrointestinal (GI) tract is essential for successful oral modified-release product development. This can be challenging, costly, and time-consuming. Medimetrics has developed an electronic drug delivery and monitoring device, the IntelliCap system. By accurately controlling and targeting drug delivery along with simultaneous measurement of pH and transit, detailed in vivo data are captured quickly to effectively guide a modified-release development project. Future applications of electronic smart pill systems promise to open new perspectives for personalized therapies and disease management.

INTRODUCTION

The oral route of administration is by far the most preferred drug delivery route. Whenever possible, an oral dosage form is developed and deployed. Further, to improve patient convenience and compliance, once-daily administered formulations are preferred. For compounds with short half-lives, this has led to the development of extended- or modified-release products. The toolbox for oral modified-release development continues to be refined and improved but does suffer from several limitations. Development can be painstaking and prone to failure. There is a strong need for a quick and simple way to precisely and reliably control the delivery of the compound within the GI tract to determine whether a compound is a valid candidate for further modified-release development.

A technology force that exerts influence on almost every area is the use of electronics for control and for integration of data from multiple sources. This has long led researchers to envision creation of an electronic drug delivery pill. With the advancement of electronic and mechanical technologies along with an impetus to bring new approaches into the world of drug development, the time is right for electronic oral drug delivery. A recent report from Market & Markets analyzed the Smart Pills technology market, in which a smart pill is defined as an ingestible capsule with miniaturized micro-electronics.[1] The report cites a fast-emerging cross-platform technology market growing from $442 million in 2012 to an estimated $965 million by 2017. Within that market, the emergence and rapid growth in drug delivery and monitoring devices is anticipated.

Medimetrics is a pioneer in electronic oral drug delivery. The company has created and applies its IntelliCap® technology, the world's first intelligent oral drug delivery and monitoring capsule.[2] The IntelliCap system combines controlled drug release, patient monitoring, and real-time wireless communication. This combination of elements is applied to create a crucial tool for the development of oral modified- release products. The flexibility and ease of use allows for rapid in vivo evaluation of a drug when delivered at precise rates and locations within the GI tract. Obtaining this information early in the development process saves time and money, and allows resources to be effectively allocated to candidates that show the greatest probability of success.[3] Today, the IntelliCap system is used as an effective tool within drug research and development. In the future, the advantages of electronic drug delivery will be exploited in therapeutic applications in which precise delivery, personalized behavior,

FIGURE 1

Photograph of the IntelliCap Capsule Showing Modular Construction With a Drug Reservoir & an Electronics Body

patient monitoring, and integration into a connected healthcare system promises to enable innovative and effective therapeutic options to treat disease and improve outcomes.

THE INTELLICAP SYSTEM

Medimetrics has developed the IntelliCap system, a unique R&D tool for the targeted delivery of drugs within the GI tract. The IntelliCap technology provides a fast, cost-effective, and convenient means for the controlled release of drugs to specific sites in the GI tract. In addition, quantitative data such as GI residence times, temperature, and local pH are measured and recorded during the process. In the form of a capsule, the IntelliCap incorporates a microprocessor, battery, pH sensor, temperature sensor, RF wireless transceiver, fluid pump, and drug reservoir. A photograph of the capsule is shown in Figure 1. The photograph illustrates the construction of the capsule in two main subunits: the electronics body and the drug reservoir. With this modular design, the drug comes into contact only with the reservoir, which is made from inert polymer materials. To enable the capsule to release drug with flexible profiles over time, the drug payload is in the form of a liquid (solution, suspension, or gel).

The IntelliCap capsule communicates via a wireless transceiver to an external control unit worn by the test subject. IntelliCap technology features real-time wireless data recording, plus wireless remote control of dose delivery, giving researchers the ability to monitor the capsule's progress through the GI tract and direct the delivery profile "on the fly." The capsule measures pH and temperature nominally every 10 seconds and reports the data immediately for display on a control station computer.

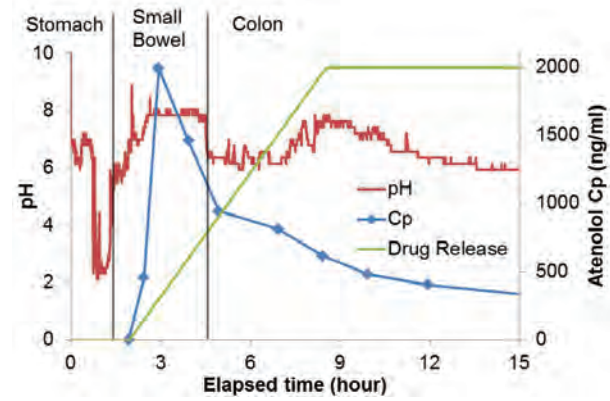
Measurement of individual, local GI pH environment is essential to fully understand drug absorption and pharmacokinetics. First, the pH environment into which the drug formulation is released can have a strong influence on the solubility of the compound. Second, the pH profile reveals location of the capsule within the GI tract. There is typically a sharp rise in pH as the capsule passes from the acidic environment of the stomach into the neutral environment of the duodenum. Subsequently, there is a fall in pH as the capsule passes from the small bowel into the colon. These landmarks are used for example by the SmartPill system to measure and diagnose motility disorders.[4,5] In an IntelliCap study, these landmarks are used to determine location of the capsule in order to control delivery to a targeted region and later on, to determine individual GI transit times to calculate local drug absorption in a pharmacokinetic (PK) study.[6]

APPLICATIONS IN DRUG DEVELOPMENT

Development of oral controlled-release products is often challenging, prone to errors and delays. Modeling or preclinical testing does not fully predict behavior in vivo. To accurately understand the in vivo properties of a compound and rationalize its development efficiently, the absorption of the product throughout the entire GI tract must be well characterized. A traditional way to determine this is to develop one or several extended-release formulations and test them in the clinic. This takes time and resources, eventually jeopardizing clinical development timelines and marketing application. In early stages of drug development, the question is often whether the compound is a good candidate for a modified-release formulation and thus worth the investment for such a development route. This creates a "chicken or egg" problem. In addition, modified-release technology is tuned toward the time constants and physiological properties of the human GI tract and therefore cannot easily be applied to preclinical models like dog for example.

The IntelliCap system can be used to quickly design and complete a study in either a preclinical (animal model) or clinical setting. The drug-release profile is fully programmable and may be adapted to the individual GI transit properties in different species. The following example illustrates such a scenario. A study was performed in five beagle dogs with a reference arm in which a known compound, atenolol, is targeted for release into the small bowel and colon.[7] Start of release is manually triggered after the capsule passes

FIGURE 2



Sample Data for Zero-Order Release of Atenolol in Dog

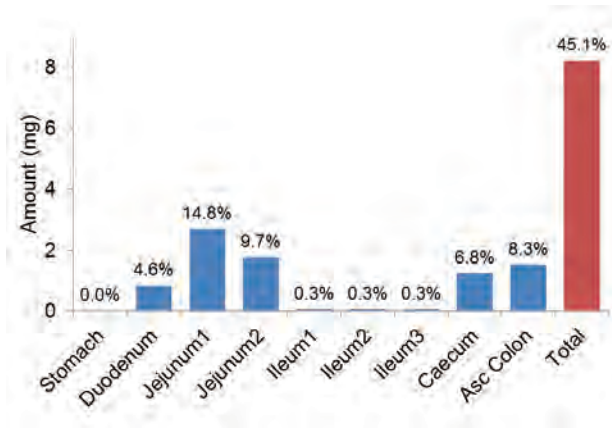
TABLE 1

PK Parameter (Unit)	Treatment	N	Geometric Mean	Geometric Mean Ratio (Test/Reference)[a]	90% CI for Geometric Mean Ratio
AUCinf (ng*hr/mL)	Test	14	414	1.03	(85, 123)
	Reference	14	401		
AUClast (ng*hr/mL)	Test	14	405	1.02	(87, 123)
	Reference	14	396		
Cmax (ng/mL)	Test	14	28.8	0.78	(62, 99)
	Reference	14	36.7		

a: Test: IntelliCap; Reference: Mylan ER capsule

Human bioequivalence data for the test, diltiazem solution dispensed from the IntelliCap capsule, and the reference formulation (Diltiazem HCl ER 60 mg, Mylan).

FIGURE 3



Compartmental Analysis of Absorption of Atenolol in Dog

into the small bowel. The release profile chosen is a zero-order linear release over 6.5 hours ensuring compound delivery both into the small bowel as well as into the colon. The average transit in the small bowel of a beagle dog is about 2 hours. An example of the captured pH and PK data for a representative subject is shown in Figure 2. The pH data provides information as to location of the capsule in the stomach, small bowel, and colon. These individual transit times are used during the analysis of the PK data. Results for the compartmental absorption while accounting for individual transit with modeling software (GastroPlus, Simulations Plus) are shown in Figure 3. This example shows moderate colonic absorption, consistent with published results. Notice how absorption throughout the entire GI tract was studied with a single administration. This strategy allows for rapid assessment and characterization of local compound absorption properties that are hardly achievable by other means. This principle can be as well applied in clinical development. Adding an IntelliCap arm in a first-in-man study provides an early proof-of-concept for modified-release feasibility and initial data for further clinical development.

As a drug candidate advances toward modified-release formulation development, it is critically important to quickly evaluate how the drug-release profile translates into in vivo PK properties. Typically, one or more formulations are created and then tested in a clinical study. If results are unsatisfactory, the process must be repeated or the project is abandoned. The programmable nature of the IntelliCap capsule allows the release profile to be explored, altered, and adapted quickly to determine up-front (ie, before committing resources for solid dosage form development) the optimal release profile. This rapid formulation prototyping approach is illustrated in the following example. A first-order, 24-hour drug-release profile is programmed in the IntelliCap capsule mimicking the in vitro dissolution profile of a commercial extended-release product (Diltiazem HCl ER 60 mg, Mylan). The programmable nature of the IntelliCap system allowed the profile to be reproduced and verified in vitro within days. The reference commercial extended-release formulation and IntelliCap were then clinically evaluated in a small number of healthy volunteers (pilot bioequivalence study).[8] Bioequivalence data between the test and reference formulations are shown in Table 1. Sample data from a representative subject for IntelliCap delivery is shown in Figure 4. The study illustrates how an arbitrary release profile can be quickly generated and tested in man and how the IntelliCap system allows for the rapid evaluation of the optimal release profile before committing time and resources to formulation development.

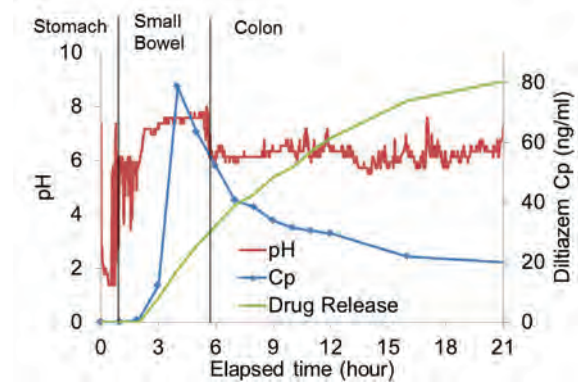
FUTURE APPLICATIONS FOR ELECTRONIC DRUG DELIVERY

As electronics and wireless devices continue their relentless push into ever more areas of our lives, so too shall we see the emergence and growth of smart electronic pills. A smart drug delivery pill promises to bring unique capabilities to treat disease and manage care. The combination of drug delivery, monitoring, and communication will enable a range of applications bringing oral drug therapies from uncontrolled bioactive deposition to accurate site-specific personalized drug delivery and disease management.

Targeted topical drug delivery has many potential advantages for the treatment of locally active disease of the gut, such as inflammatory bowel disease (IBD), intestinal cancers, and irritable bowel syndrome (IBS). Topical delivery only to the region of involvement may reduce toxicity from systemic exposure and limit the formation of antibodies for biologics therapies. Region of involvement can vary from patient to patient and within a patient over time. The programmable nature of an electronic pill allows the target site and dose to be personalized. Localized and controlled delivery has applications beyond diseases of the gut. Delivery of peptides or other large molecules may be combined with delivery enhancers and location targeting to achieve effective oral delivery. Oral vaccines for example may be protected from the degrading environment of the upper GI tract and delivered to the ileum, where they are presented to antigen sampling cells.

In addition to site-specific drug delivery, the electronic pill may also incorporate biomarker sensors and reporting of measurement

FIGURE 4



Sample Data for a 24-hour Extended-Release Profile of Diltiazem in Man

and actions from within the gut. Sensor measurements may be transmitted wirelessly, and data integrated automatically into the patient's health record for reporting, diagnostics, and management of long-term treatment. The microbiota environment and balance of the gut is increasingly recognized as critical to overall health.[9] Monitoring, managing, and treating gut health may become a key part to healthy living, and the electronic pill can play an important role.

CONCLUSION

Electronic smart pills represent an emerging area with great potential for growth. Already established in the diagnostic area, the next move is into monitoring and drug delivery. Drug delivery from a swallowed electronic device brings several advantages and opportunities. Medimetrics is a pioneering entrant into this segment, and its IntelliCap system is an approved measuring and drug delivery device available today. The first application is in drug delivery studies in which controlled targeted delivery along with measurements of individual transit and pH enable quick and accurate data of in vivo properties for a drug in development. This is particularly valuable for modified-release development and for compounds in which local enteric delivery is central to the product target profile. Looking forward, the electronic smart drug delivery pill enables a range of novel therapies and transforms the conventional, swallowed pill to a key building block of a future personalized and interconnected healthcare environment. ◆

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BIOGRAPHIES

Jeff Shimizu is a pioneer of the IntelliCap drug delivery system, Co-founder and CTO of Medimetrics. He has a background in physics and optics. Prior to Medimetrics, Mr. Shimizu had been with Philips Research for over 20 years in systems research and development. Research into medical devices led to the development of IntelliCap, an electronic drug delivery capsule. Medimetrics was formed to bring this technology to the market.

Dr. Christoph Wanke is Clinical Program Leader at Medimetrics. With over 15 years of experience in pharmaceutical industry, he is responsible for the preclinical and clinical development of the IntelliCap system and customer services. Dr. Wanke earned his PhD from the Swiss Federal Institute of Technology in Zurich.

A Real Eye-Opener: Advances in Hyaluronic Acid for Ophthalmology

By: Hans Ole Klingenberg

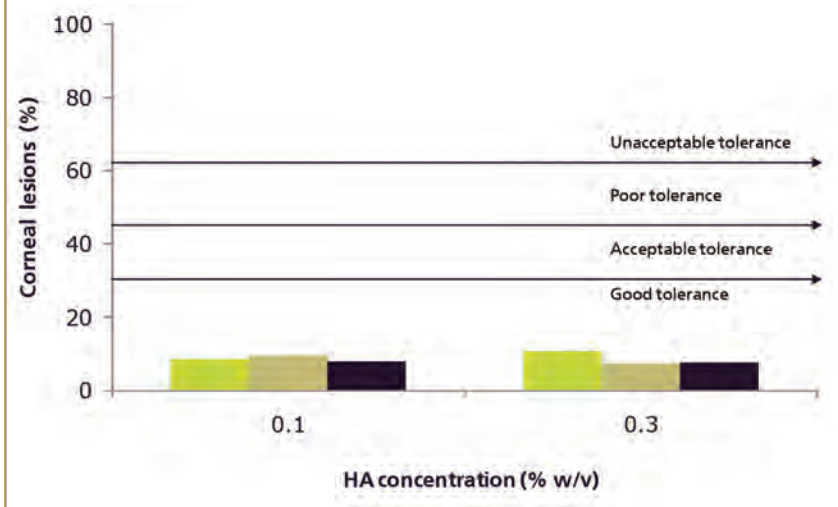
The complexity of medical conditions related to the anatomy, function, and diseases of the eye can vary from eye dryness, which can be treated with lubricating eye drops, to pathological opacification of the eye, which requires cataract surgery and the use of viscoelastic devices during the removal of the natural lens of the eye. Whether it is to enhance the hydration and lubrication of corneal surfaces, promote physiological wound healing, or extend the residence time of topically applied drugs in the eye, the benefits of incorporating hyaluronic acid (HA) in ophthalmic formulations are now well documented.[1-3]

Research into ophthalmic drug delivery has recently oriented itself toward sophisticated solutions, such as implantable devices. In addition to offering a better control of drug-release kinetics, these solutions give the possibility of more specific and targeted delivery. As the delicate structure of the eye requires pure and safe components, preferably biodegradable and/or bioresorbable, HA provides a range of advantages owing to its exceptional water-binding, viscoelastic, and biological properties, offering many benefits for the development of novel ophthalmic solutions.

THE ROLE OF HA IN THE EYE

HA is a naturally occurring polysaccharide with distinct physicochemical properties that underlie its use as a viscoelastic tool and drug delivery solution in ophthalmology applications. Within ophthalmology, HA was initially developed as an intraocular viscoelastic that was primarily used in cataract and other intraocular surgeries to protect the cornea post-procedure. Today, HA is widely used in many applications, including penetrating keratoplasty, trabeculectomy, retinal reattachment, and trauma surgery, as well as a treatment to relieve the symptoms of dry eye disease.

FIGURE 1



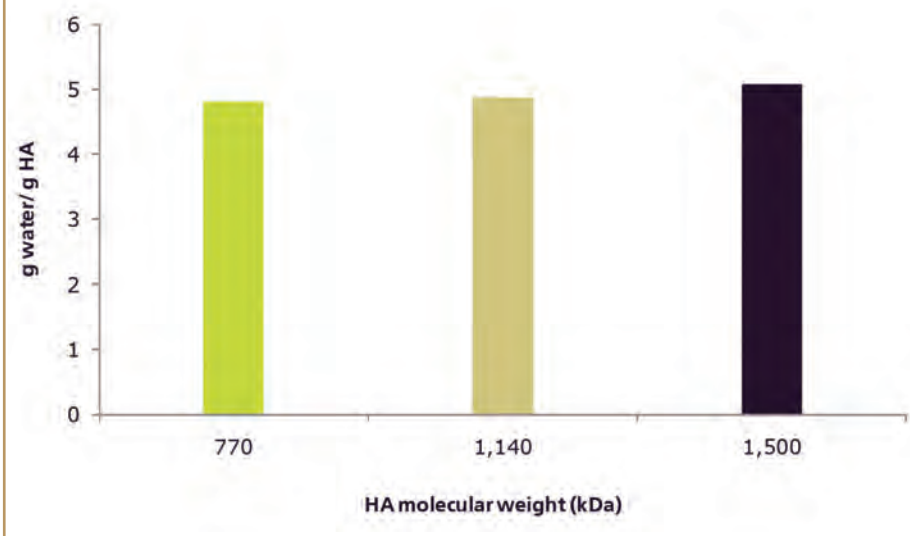
Percentage of corneal lesions as a function of HA molecular weight and concentration according to confocal laser scanning ophthalmoscopy.

In the eye, HA is mainly found in the vitreous body, which is the transparent, colorless, gelatinous mass filling the space between the lens of the eye and the retina lining the back of the eye. HA's function in the vitreous body essentially relates to providing shape, volume, and structure to an environment mostly composed of water (98% to 99%), as well as a small amount of solutes, such as salts, sugars, vitrosin, collagen, and other proteins. The use of HA in ophthalmic treatments is explained by its moisturization properties and its ability to extend drug-retention time and promote tissue healing. As a result, HA is a natural choice when evaluating possible excipients for drug formulations or ophthalmic devices.

REGULATORY CONCERNS FOR MANUFACTURERS

The popularity of animal-free ingredients is continuously growing, with regulatory authorities beginning to enforce tighter quality controls on products used in ophthalmic applications to improve safety and minimize risk to patients. Traditional commercial sources of HA are primarily derived from either rooster comb extraction or various attenuated strains of *Streptococcus* bacteria. However, these sources can potentially result in contamination risks from animal-derived proteins, viruses, or endotoxins. Moreover, both extracted HA and microbial-derived HA are purified using harsh organic solvents, which pose further health issues to patients.

FIGURE 2



Mass ratio of bound unfreezable water to HA as a function of molecular weight.

In response to industry demand for safer sources of HA with a higher degree of purity, recent years have seen the emergence of biotechnological sources that eliminate the associated concerns and deliver increased safety and consistency, presenting new opportunities for ophthalmology applications both intraocular and topically.

BACILLUS-DERIVED HA™

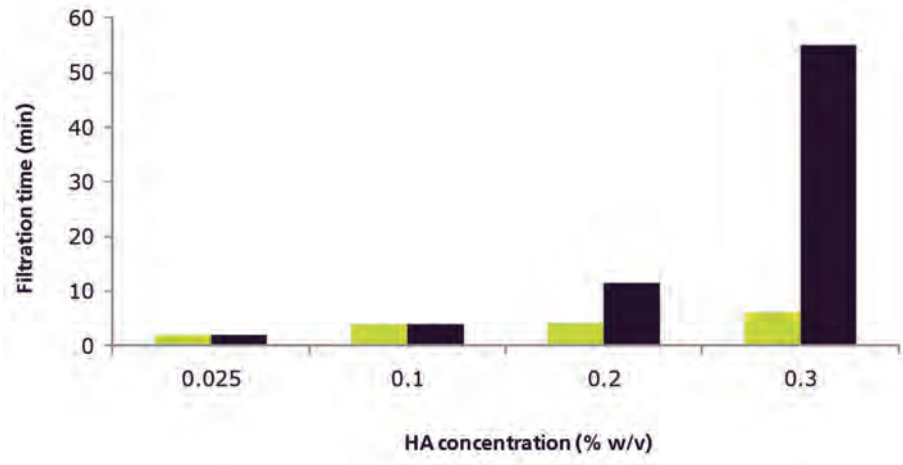
A *Bacillus*-derived fermentation process for the production of HA has been developed to overcome the manufacturing and safety challenges associated with animal-derived sources. *Bacillus subtilis* is a non-pathogenic host whose products are Generally Recognized as Safe (GRAS) by the FDA. The process uses minimal medium, no animal-derived raw materials, and a water-based technique, which removes the use of organic solvents at any stage during the manufacturing process. The resulting HA is characterized by low amounts of nucleic acids, proteins, bacterial endotoxins, exotoxins, and microbial contamination, which reduces hypersensitivity reactions. Using biotechnology to produce HA not only increases safety, it allows for the manufacture of ophthalmic-grade HA polymers of various chain lengths and molecular weights. This, in turn, enables the production of ophthalmic solutions in varying viscosities.

The controlled *Bacillus*-derived production process affords a HA material with a wide-range of unique benefits. The findings of a recent study demonstrate the advantages of its use in ophthalmic formulation.

CORNEAL TOLERANCE OF HA

The corneal tolerance of HAs of different origins and molecular weights was evaluated by estimating the level of corneal

FIGURE 3



Filtration time as a function of HA molecular weight and concentration.

lesions (epithelial cell loss), following repeated applications of three HA-containing formulations onto the cornea (Figure 1). All HA samples, irrespective of their source, molecular weight, or concentration, induced a percentage of corneal lesions lower than 10%, which demonstrates good corneal tolerance. These findings also highlight the safety and biocompatibility of HA for ophthalmology applications.

WATER-BINDING CAPACITY

The water-binding capacity of HAs from various sources and chain lengths was assessed by measuring the amount of HA-bound unfreezable water using differential scanning calorimetry (Figure 2). Overall, HA's water-binding capacity did not depend on molecular weight because the different HAs tested bound equally large amounts of water in the range 4 to 5 g/g HA. As a result of its water-retentive properties, *Bacillus*-derived HA has the potential to enhance moisturization of the ocular surface, while contributing to the stabilization of the precorneal tear film.

VISCOSITY

The performance of eye drops and artificial tears is related to their rheological properties and primarily depends on the nature, molecular weight, and concentration of the viscosifying agents employed. The non-Newtonian and shear-thinning properties of HA solutions make HA a viscosity enhancer of choice. Indeed, HA contributes to the uniform distribution of ophthalmic solutions on the surface of the eye while decreasing their drainage rate. This results in improved lubrication and function. However, highly viscous HA-based preparations can lead to increased blinking frequency, transient blurry vision, and ocular discomfort. Solutions incorporating *Bacillus*-derived HA possess well-defined rheological properties and feature optimal viscosity profiles for increased comfort and efficacy.

FILTRATION

The filtration times of a *Bacillus*-derived HA solution and a solution derived from *Streptococcus* are presented in Figure 3. Up to a polymer concentration of 0.1% (w/v), HA molecular weight did not have an influence on the filtration time. However, at 0.2% and 0.3%, the filtration time of the higher-molecular-weight *Streptococcus* HA solution was three and seven times longer respectively than that of the *Bacillus* HA solution. At 0.3%, the *Bacillus* HA solution was filtered in less than 10 minutes against nearly 1 hour for the *Streptococcus* HA. The short filtration time of *Bacillus*-derived HA makes it easy to handle and helps reduce the manufacturing time of preparations sterilized by filtration.

HEAT STABILITY

Studies have shown that *Bacillus* HA remains stable during the heat sterilization of ophthalmic solutions. After treatment at 121°C for 16 minutes, *Bacillus* HA was shown to retain 82% of its initial molecular weight against 60% for a *Streptococcus*-derived HA of the same starting chain length. This enhanced stability upon heating is most likely related to the purity of *Bacillus* HA. As a result, formulations containing this source of HA can be heat-sterilized under standard conditions without compromising final product viscosity.

DRUG DELIVERY

As a result of its viscosity-enhancing properties, HA can be used as an efficient carrier for ophthalmic therapeutics. In this respect, *Bacillus* HA presents good compatibility with a variety of drugs such as ciprofloxacin, diclofenac, and dexamethasone. Increased lacrimation and tear turnover following the application of ocular formulations most often lead to short precorneal residence time and, as a result, poor drug bioavailability. According to gamma scintigraphy, the precorneal residence time of *Bacillus*-derived HA is similar to that of *Streptococcus*-derived HA of higher molecular weight at the same concentration. Furthermore, the incorporation of HA in drug-containing ophthalmic solutions can increase drug retention in the tear fluid, along with drug contact time with the ocular surface, consequently improving drug bioavailability. The underlying mechanisms for drug retention are believed to be largely related to viscosity, bioadhesion (mucoadhesion), and physical attachment.

The *Bacillus*-derived fermentation process offers a source of HA with a reproducible molecular weight and narrow size distribution. In addition, the HA offers improved processability due to the porosity and reduced size of it spray-dried particles and can dissolve much faster than HAs manufactured with an organic solvent-based process. This reduces processing time at large scale while contributing significant savings on manufacturing costs. A high degree of purity of the material also permits sterilization by autoclaving without significant loss of product properties.

SUMMARY

The use of HA in ophthalmic treatments is continuously growing due to its ability to extend drug-retention time and promote effective tissue healing. *Bacillus*-derived HA offers new opportunities for ophthalmic applications by providing a safe and biocompatible source that can streamline manufacturing processes, while offering convenient application and increased patient comfort and compliance. The latest technology ensures high levels of safety, consistency, and stability, conferring numerous benefits to both manufacturers and patients. ◆

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BIOGRAPHY

Hans Ole Klingenberg is Director for the Global Marketing group in Novozymes Biopharma. Hans Ole has been with the company for more than 10 years and has held various positions in the area of corporate business development, with a focus on establishing new business entities for Novozymes in the biopharmaceutical industry. Since 2007, he has been working in Novozymes' Biopharma business with a focus on marketing, and is commercially responsible for the establishment of the company's Hyaluronic Acid business franchise. Mr. Klingenberg is a graduate of Copenhagen University with a Bachelor's in Chemistry and Master's in Economics. He is based in Denmark.

Amorphous Dispersions & Other Tools for Drug Discovery Formulation Support

By: Corey J. Bloom, PhD, and David K. Lyon, PhD

ABSTRACT

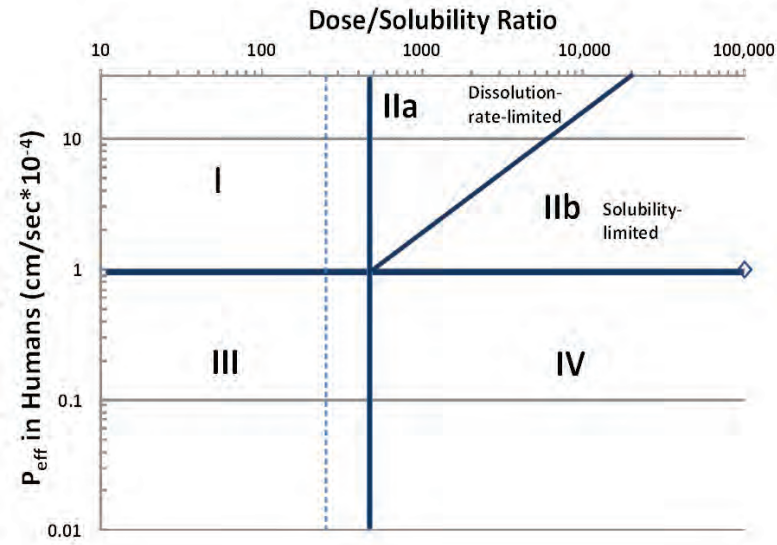
Low-solubility compounds are commonly encountered in the drug discovery process. It is widely estimated that more than half of the promising small molecules identified in current drug discovery programs exhibit low solubility. Molecules with low permeability and rapid metabolism also plague discovery programs. Each of these shortcomings poses challenges for oral absorption, which must be addressed because of the prevalence of new compounds that fall into these categories.

This paper describes broadly applicable formulation approaches and biomodeling tools that have been successfully used to improve the solubility and in vivo performance of low-solubility compounds. The approaches, including spray-dried drug/polymer dispersions and drug/polymer nanoparticles, are ideally suited for use early in the drug development process from discovery through formulation and toxicology screening. In addition, the approaches are readily scalable, facilitating progression of compounds through commercial manufacture. Combined with the judicious use of biomodeling tools, these approaches can result in efficient selection of compounds and formulations for advancement.

INTRODUCTION

To categorize the types of drug molecules encountered during drug discovery, two systems are useful: the commonly cited biopharmaceutical classification system (BCS) and the more recent developability classification system (DCS), both of which categorize drug molecules based on solubility, dose, and permeability.[1] Figure 1 is a representation of the DCS model.

FIGURE 1



DCS Classifications, Plotting Effective Permeability (P_{eff}) vs Function of Dose/Solubility Ratio (Adapted from Butler and Dressman, 2010)

Class II compounds, which exhibit low solubility and high permeability, are of particular interest because they are common in discovery programs and can often be delivered orally with the help of solubilization technologies. The DCS system provides a further distinction between compounds in Class IIa, which can be successfully delivered via an increase in dissolution rate (ie, reduced particle size), and those in Class IIb, which require solubilization.

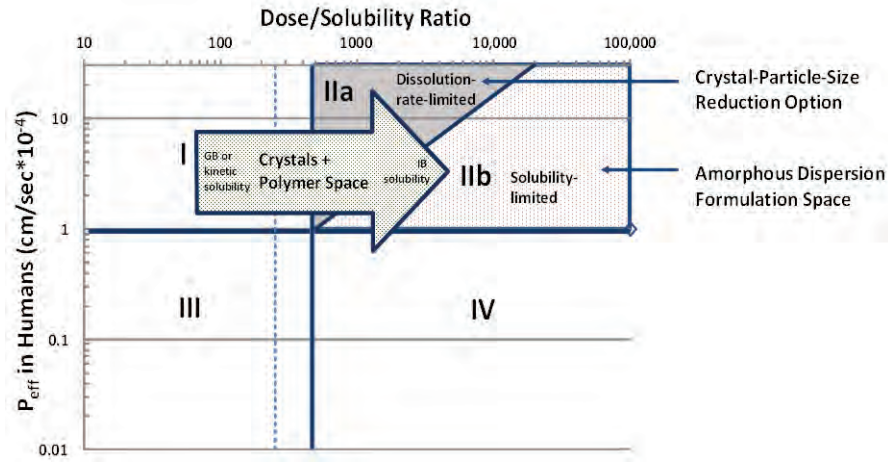
Numerous formulation options exist to deliver low-solubility compounds in discovery and early development programs. Common formulations include amorphous dispersions, attrition-milled crystalline drug (nanocrystals), high-energy salt forms, self-emulsifying drug delivery systems (SEDDS), and vehicles based on polyethylene glycol (PEG) and solvents.

Among these approaches, amorphous dispersions stand out because they are broadly applicable, are scalable from milligram to metric ton scale, and offer a direct path to solid dosage form development using well tolerated and precedented excipients. Properly formulated dispersions provide improved solubility and absorption due to increased dissolution rate, higher inherent solubility, and sustained supersaturation in intestinal fluid.

Figure 2 is a modified version of the DCS map shown in Figure 1, showing the approximate space for drugs that can be enabled by amorphous dispersions and nanocrystals at typical doses. Note that the large space for dispersions overlaps with the nanocrystal space, indicating the breadth of applicability for dispersions. As shown by the large green arrow, some compounds can be delivered as salts or other high-solubility crystalline forms, dosed along with crystallization-inhibiting polymers.

Further, we provide information on these solubilization approaches, as well as information on a biomodeling tool that is used to refine formulation selection further during early stage development.

FIGURE 2



DCS Map Overlaid With Solubilization Technology Approaches, Showing the Overlap Between the Space for Amorphous Dispersions & Crystal Size Reduction (GB = Gastric Buffer, IB = Intestinal Buffer)

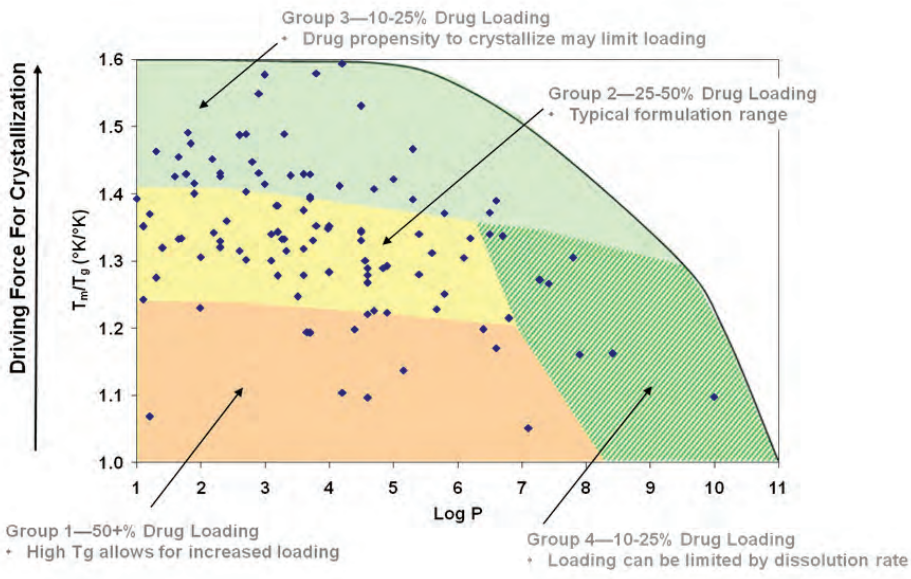
FORMULATION APPROACHES FOR DELIVERING LOW-SOLUBILITY COMPOUNDS

Two main formulation approaches have been particularly effective at delivering DCS Class IIa and IIb compounds: amorphous drug/polymer dispersions–produced by spray-drying and hot-melt extrusion (HME)–and drug/polymer nanoparticles.

FIGURE 3

Custom-Built Bend Research Small-Scale Spray-Dryer Suitable for Milligram Drug Quantities

FIGURE 4



Simplified Map of Drug Chemical Space Use to Guide Formulation of HPMCAS-Based SDDs (Adapted from Friesen et al, 2009)[2]

Amorphous Drug Dispersions

Amorphous drug/polymer dispersions are well suited for the oral delivery of low-solubility compounds and for formulation screening in discovery and early development. Tuning the composition of the dispersion by polymer selection, drug loading and, in some cases, the addition of surfactants, produces dispersions with excellent dissolution performance and physical stability for a broad range of low-solubility compounds.

Dispersions are most commonly manufactured by two processes: spray-drying and HME. The HME process can have significant cost advantages at large scale for drugs and formulations that are amenable to the high-temperature processing. However, HME is not suitable for drugs and polymers that cannot withstand exposure to high temperatures and is difficult to use at small scales. In contrast, spray-drying is particularly flexible with respect to scale and formulation.

Spray-dried dispersions (SDDs) can be readily manufactured at the milligram scale needed to formulate compounds in discovery and early development programs and is readily scalable up to the metric ton capacity. At Bend Research, we use custom-built, small-scale spray-dryers (Figure 3) to manufacture SDDs at high yield using as little as 5 mg of drug. Small-scale commercial spray-dryers are also available.

Because of this small-scale manufacturing capability, SDDs are well suited to screening formulations for compounds and providing supplies for initial pharmacokinetic (PK) or toxicology studies early in drug discovery. In early drug discovery, when the supply of active pharmaceutical ingredient (API) is limited and time and cost are critical, milligram-scale SDDs can be manufactured using standardized low-drug-loading formulations for rapid in vitro and in vivo testing. If the SDD technology is selected for advancement, compounds can be rapidly evaluated for efficacy and toxicology at an early stage, leaving formulation optimization until after the lead compound has been selected. With knowledge of some basic drug properties, such as solubility profile, Log P, melting point, and glass-transition temperature, SDD formulation development can be rationally directed to focus screening on a minimal number of formulations.

At Bend Research, we have found the enteric polymer hydroxypropyl methyl-cellulose acetate succinate (HPMCAS) to be particularly well suited to SDD formulations for many low-solubility compounds. This polymer, which is also sold under the trade names hypromellose acetate succinate and AQOAT (Shin-Etsu Chemical Co. Ltd.) and Affinisol™ (The Dow Chemical Company), is available in three grades: HPMCAS-L, HPMCAS-M, and HPMCAS-H.

Figure 4 shows a formulation map that was developed at Bend Research based on

the formulation of hundreds of low-solubility compounds as HPMCAS SDDs using various drug loadings and HPMCAS grades. The map allows the formulator to screen a limited set of drug loadings (ie, drug/polymer ratios) that are likely to produce physically stable SDDs with the desired performance.

A number of other commercially available polymers are also available for use in SDDs, including hydroxypropyl methylcellulose (also known as hypromellose) (HPMC), poly(vinylpyrrolidone-co-vinyl acetate) (PVP-VA), polyvinylpyrrolidone (PVP), cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), poly(methacylic acid-co-methyl methacrylate) (Eudragit® L).

During screening, formulations are evaluated for dissolution performance and physical and chemical stability. For discovery support, dissolution performance is paramount, with stability and manufacturing constraints becoming more important as the compound and formulation progress through development.

Regardless of the ultimate formulation chosen, SDDs can be used as a broadly applicable tool for pharmacophore screening, lead selection, and toxicology testing. And, given the ready scalability of the spray-drying process, formulations can be tested with the confidence that they can be advanced to the clinic and the market. In some cases, particularly for compounds with low melting points, an HME process can be developed for use at large scales that may offer better process efficiency as the compound and formulation move through the development process.

Amorphous Drug/Polymer Nanoparticles

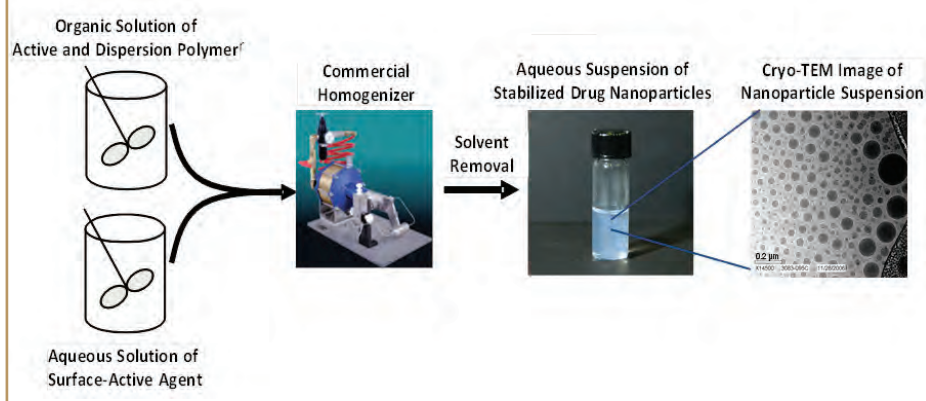
Amorphous drug/polymer nanoparticles are another formulation well suited for use in discovery and early development, providing many of the same performance benefits as amorphous dispersions. Like SDDs, drug/polymer nanoparticles improve absorption by increasing dissolution rate and providing increased solubility relative to crystalline drug.

Aqueous suspensions of drug/polymer nanoparticles can be prepared at the milligram scale by two approaches: emulsion-based (using solvents that are not miscible with water) and precipitation-based (using solvents that are miscible with water). An overview of the emulsion process and a typical suspension image are shown in Figure 5.

Nanoparticle formulations can be used for oral solubilization and, in many cases, provide similar or superior performance to that of SDDs. However, nanoparticles offer an additional advantage: nanoparticle suspensions are a natural tool for alternative delivery routes (eg, parenteral delivery).

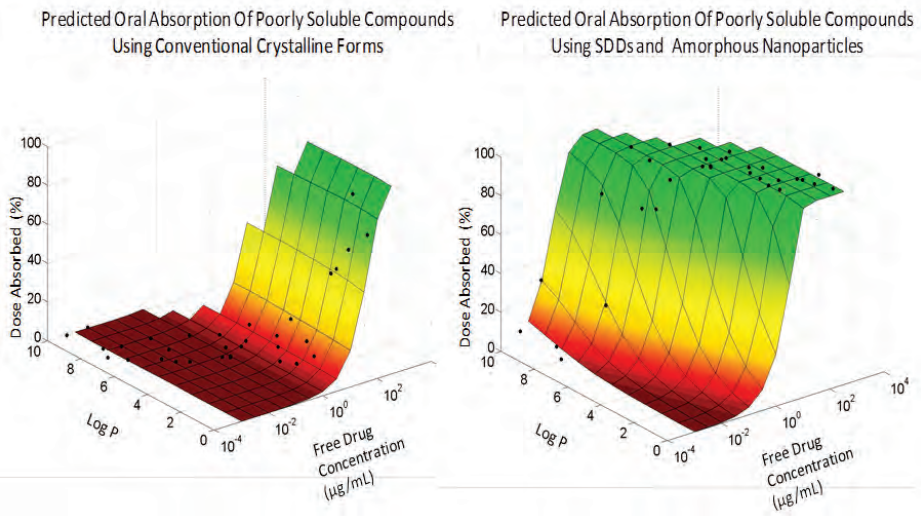
Together with our partners, Bend Research has used amorphous drug/polymer nanoparticle suspensions to test discovery compounds using various parenteral routes, including subcutaneous and intravenous delivery. This formulation approach can provide improved exposure and toleration relative to solution-based parenteral formulations that require high concentrations of organic solvents and

FIGURE 5



Overview of the Small-Scale Emulsion Process for Nanoparticle Manufacturing, Showing a Picture of an Example Suspension & Transmission Electron Microscopy (TEM) Image of a Frozen Suspension Sample (0.2-micrometer Scale Bar)

FIGURE 6



Example Guidance Surfaces for Bulk Crystalline Drug (a) and SDDs and Nanoparticles (b) Using the Bend Research Oral-Absorption Biomodel. Assumptions in this analysis include permeability as a function of Log P, constant animal model, fasted state, dose of 10 mg/kg, and constant particle size (dissolution rate) for crystalline and SDD formulations. Dots are example historical compounds observed at Bend Research. Example compounds "move" on the free-drug axis based on the increase in solubility for an amorphous form relative to crystalline drug.

surfactants. Often, the ultimate goal of these programs is to develop an oral medication, but the parenteral route is used in animal models as a way to screen core pharmacophores and early lead compounds for efficacy and gross toxicology readouts. If a compound is selected for advancement using drug/polymer nanoparticles, the project team can have confidence there are several options for full development of amorphous dispersions for solubilization.

PHYSIOLOGICALLY RELEVANT BIOMODELING

In combination with the aforementioned formulation approaches, predictive biomodeling offers another useful tool in discovery and early development. Biomodels can be used to predict drug absorption based on basic physicochemical and structural properties (eg, Log P, solubility) and some key assumptions or additional measurements (eg, permeability, metabolic stability). Using these predictions, compounds can be grouped into classes with more precision than allowed by the basic guidelines of the BCS or DCS systems. Predictive biomodels also enable prediction of whether and to what extent solubilization technologies will enable oral delivery of a given molecule or set of compounds.

While commercial software packages are available for PK biomodeling, Bend Research has developed a physicologically relevant compartmental biomodel for predicting the oral absorption of drugs. Figure 6 shows example "guidance surfaces" based on a compilation of absorption predictions from the Bend Research biomodel. In this approach, the absorption of hypothetical compounds is predicted for bulk crystalline drug and SDD formulations. To create the broadly applicable guidance surfaces, a number of assumptions are made regarding selected parameters, including permeability (assumed to be a function of Log P), dose (assumed to be constant at 10 mg/kg for this comparison), feeding state (fasted for this comparison), and dissolution rate.

By making these generalized assumptions, the user can probe the surface to determine the expectations for success in delivering a broad array of compounds using these two approaches. Obviously, more specific predictions can be made for individual compounds based on known or assumed values of key parameters, such as permeability or particular dose levels, and feeding state.

Several conclusions can be drawn based on these guidance surfaces. For example, more-soluble compounds are obviously better absorbed with all else being equal. However, it is less obvious that in concert with solubilization by SDDs, at some ranges of solubility, a more liphophilic (generally more permeable) molecule may be delivered much more successfully than a more hydrophilic molecule with the same solubility. Said another way, if a tradeoff in properties must

be made, a compound that has poor solubility due to high lipophilicity but has good permeability is preferable to a compound that has poor solubility due to high melting point but has lower permeability. The solubility of the more permeable lipophilic molecule can be increased using an amorphous dispersion to provide acceptable absorption. This sort of guidance is less obvious and can be useful when confronted with a number of potential leads that all suffer from low solubility, or when seeking to alter the physicochemical properties of a pharmacophore through chemical modifications.

These guidance-surface biomodeling outputs, in addition to others, can also be used to identify compounds that have low probabilities of successful delivery with any technology at the required dose. Thus, inefficient use of resources can be avoided, along with unnecessary selection of alternate compounds or direction of compounds for additional chemical modification rather than further formulation attempts.

Biomodeling can also be used to help identify challenges outside of solubility, such as permeability and metabolism. When compounds and formulations should provide acceptable absorption based on in vitro performance and modeling, but in vivo exposure is much lower than expected, issues with metabolism or permeability should be strongly suspected and explored before further formulation efforts are made to improve solubility.

SUMMARY

Low-solubility compounds are routinely encountered in the drug discovery process. Many of these compounds can be successfully advanced using a variety of solubilization technologies. Amorphous dispersions are ideally suited for oral delivery of a broad range of low-solubility molecules and well suited for manufacture from the milligram to metric ton scale. Judicious use of additional tools, including predictive biomodeling, can assist in efficient selection of compounds and formulations for advancement. ◆

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BIOGRAPHIES

Dr. Corey J. Bloom is the Director of Formulation Science at Bend Research Inc. His responsibilities include developing pharmaceutical formulations to improve stability and bioavailability for oral and targeted drug delivery, assessing dosage forms and formulations, and developing biological models. He earned his BS in Chemistry from Gustavus Adolphus College and his PhD in Analytical/Materials Chemistry from Colorado State University.

Dr. David K. Lyon is Senior Vice President at Bend Research Inc., where he leads efforts in scientific excellence and global business development. His expertise includes solubilization of pharmaceuticals, nanotechnology-based drug delivery, and controlled-release formulations. Dr. Lyon joined Bend Research in 1991, and he earned his BS in Chemistry from Western Washington University and his PhD in Inorganic/Organometallic Chemistry from the University of Oregon.

Impurities Detection in Pharmaceuticals

By: Kevin P. Menard, PhD

INTRODUCTION

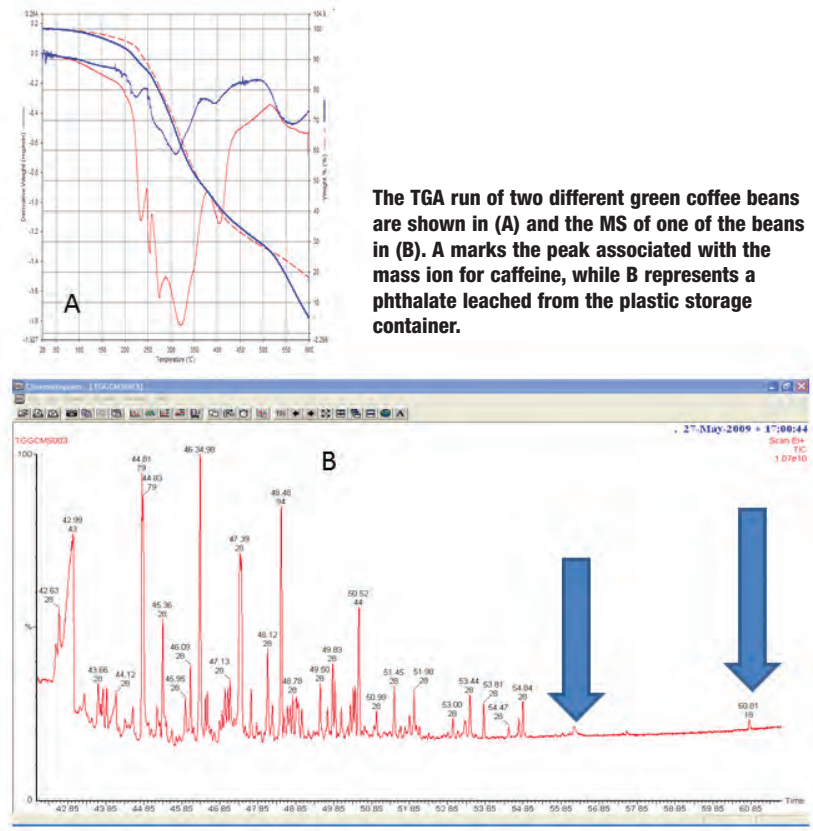
As regulations on pharmaceuticals develop lower limits as for impurities, detection methods must become more sensitive and selective. Increasingly, it is important to detect the impurities not only in the active ingredient but in the final formulation. Thermal methods, FTIR, and GC/MS, are all used in this. For inorganics like traces of heavy metals, ICP-MS is an important tool. In this article, we focus on the detection of residual solvents from processing and small levels of contaminates leached from containers.

RESIDUAL SOLVENT DETECTION BY EGA

Thermogravimetric analysis (TGA) is a commonly used technique in pharmaceutical research and quality labs to investigate residual solvents in formulations. Pharmaceutical samples often show weight losses associated with the loss of solvent/water, de-solvation, or decomposition of the sample. This information is then used to assess the purity and stability of the material and its suitability for use. The TGA gives a quantitative measure of mass lost from the sample, but it does not provide information on the nature of the products that are lost from the sample often required for complete characterization.

Several techniques exist to address this and are collectively known as Evolved Gas Analysis. The most common is the combination of a TGA with FTIR, referred to as TG-IR. An example would be a Pyris 1 TGA coupled to a Frontier FTIR running on Timebase software, which allows importation of the TGA data into the IR software. This technique allows one to determine what materials come off of the sample at which temperature within

FIGURE 1



The TGA run of two different green coffee beans are shown in (A) and the MS of one of the beans in (B). A marks the peak associated with the mass ion for caffeine, while B represents a phthalate leached from the plastic storage container.

the limits of IR's sensitivity and to map it as a function of temperature. One also has to deal with confounding affects and overlapping peaks. More sensitivity and resolution can be obtained by moving to a TG-MS system. Replacing the FTIR with a mass spectrometer (MS) allows for both increased sensitivity and improved resolution.

COUPLING TGA TO GC/MS

Even more resolution can be obtained by coupling a gas chromatograph-mass spectrometer (GC/MS) like the Clarus SQ 8 to a TGA. While this technique allows us to bring the full power of GC/MS to identify evolved materials, it requires collection of the gases. Several techniques exist to do this, including trapping material on a column, gas collection loops, and use of Swafer technology. The downside is that we lose the temperature or time relationship to what was coming off the TGA. As the time/temperature evolution of the compound can help determine if it is a contaminant or if it results from the degradation of a compound, this can be a problem. However, this is offset by the ability to detect very small amounts of material, making it suitable for measuring leachable compounds like plasticizers and other low level containments. These can then be identified using the extensive libraries for GC/MS. An example is shown in Figure 1.

Recently, PerkinElmer® has addressed this problem by the introduction of a combined TGA to FTIR to GC/MS system using its TL-9000 transfer line. In this approach, the sample is heated in the TGA to first evolve solvents and then burn the constituents to volatile compounds. The gas is transferred to the FTIR and allows for the tracking of the time or temperature dependence of a material's evolution in the TGA. Sequentially, the gas of interest is then collected and run through the GC/MS for complete identification. This allows detections of impurities to very low levels (Figure 2). Applications include the detection of low levels of plasticizers leached from storage containers, trace levels of contaminates remaining from processing, and degradation products from exposure to higher temperature or UV radiation.

FIGURE 2

TG-IR-GC/MS system allows one to combine TGA, FTIR, and GC/MS data to characterize the offgas from the TGA.

SUMMARY

Hyphenated techniques allow detection of residual solvents, leachables, and low level contaminates in pharmaceuticals, excipients, as well as other biomedical materials. Combined systems allow for the maximized performance of each to obtain the best data and to determine low levels on impurities. ◆

BIOGRAPHY

Dr. Kevin P. Menard earned his PhD in Chemistry from Wesleyan University and his MBA from Texas Woman's University. He has worked in a variety of industries before coming to PerkinElmer, where he is the Global Business Manager for Thermal Analysis. He has over 150 publications and 14 patents to his credit.

Special Report

Outsourcing Formulation Development and Manufacturing: An Early Approach Saves Time and Money

By: Cindy H. Dubin, Contributor

The global pharma outsourcing market will likely climb from about $85 billion in 2011 to as much as $150 billion by 2015, states JZMed, Inc., a market research company. Key components of the outsourcing market are formulation development and manufacturing. Demand for outsourced manufacturing will increase from drug developers of all sizes. A new report, *Pharmaceutical Contract Manufacturing: World Market Outlook 2012-2022*, predicts that the world market for pharmaceutical contract manufacturing was worth $47.6 billion in 2012, and the overall market will grow with a compound annual growth rate (CAGR) of over 6% through 2016.

In 2011, active pharmaceutical ingredient (API) manufacturing services formed the largest market sector, accounting for more than two-thirds of revenues. APIs will account for the majority of revenues throughout the coming years. Increased demand for generic drugs will drive revenue growth for emerging-market contract manufacturing organizations, highly potent API manufacturing will drive growth in the US, increased outsourcing of finished dosage manufacturing will also stimulate developed-market growth. Development of biologics will increase demand for injectable dosage manufacturing services, including fill-finish and lyophilization, the report also notes.

With regard to formulation development, an October 2012 survey (commissioned by Capsugel and conducted by an independent market research company) revealed that 82% of the respondents believe innovative dosage form technologies are required to meet the needs of today's pharmaceutical research and development challenges. Yet, the development of suitable drug formulations and delivery systems remains a major challenge and there is an increasing need for outsourcing to fill the knowledge gap. More than half (58%) of the companies indicated that they outsource dosage form development. Poorly soluble compounds represent a very high proportion of the industry's development pipeline. Yet survey respondents cited only moderate expertise on specific technologies related to poorly soluble compounds, specifically lipid drug delivery technologies. Half (50%) reported plans to specifically outsource lipid drug delivery technologies for poorly soluble compounds.

In this annual *Drug Development & Delivery* report, leading manufacturing and formulation development providers reveal why it is important to partner with a contractor early in the process to avert risk and save time and money in getting a drug through the development pipeline.

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Outsourcing of development services continues to be in high demand, and formulation and development services addressing bioavailability have experienced strong growth over the last several years. Agere Pharmaceuticals, Inc. has experienced that growth first hand. Its CRO/CMO services span formulation design and development through cGMP analytical and clinical final dosage forms. All services are customized on a per-compound basis and delivered as fee-for-service. Its global client base includes virtual and small- and mid-sized companies as well as big pharma.

One trend that Casey Jones, VP of Corporate Development at Agere has identified is the realization that a different approach is needed to improve the predictability of outcomes. "Far too many compounds are failing: We estimate that today nearly 30% of NDEs attrite from Phase I clinical trials due to solubility issues. This trend is getting worse, and requires a new way to look at analyzing and formulating drugs for bioavailability," she says.

To address the issue of greater predictability, Agere is developing and integrating a suite of computation tools that perform more accurate and agnostic polymer selection, predict in vivo performance, and model shelf life. "We have been working on this for years, and in early 2013, we introduced a model-free method of measuring phase diagrams for solid amorphous dispersions."

Another trend that Jones sees is that solid and liquid dispersions have become more popular for enhanced solubilization, and there is an increase in suppliers of excipients and the types of excipients that target this segment. In response to its clients' requests, Agere expanded its cGMP operations to include Phase IIb manufacturing. And, it added regulatory guidance services in 2012 to leverage Agere's expertise in solubilization.

"Most of our customers are seeking a full service pre-clinical formulation development carried through to cGMP into mid-stage clinical trials," says Ms. Jones. A one-stop-shop makes our clients lives easier by limiting the number of contractors they have to manage."

In addition, she says pharma expects service providers to have the level of quality and expertise they'd want in an internal group. This includes a strong team of scientists and technologists, robust quality systems, effective project management, streamlined technology transfer and overall transparency.

"As big pharma continues cut overhead by sending formulation development and dosage form manufacturing to CMO's, it's more critical now than ever before for service providers to obtain preferred provider status." This status isn't easy to come by, as clients are becoming more demanding about some of the characteristics vendors must have.

"As the outsourcing market is growing, no doubt it will attract even more CROs, increasing the competitive nature of the business," says Ms. Jones. "Differentiating the quality of services provided -- including better predictability to reduce downstream risk -- will become even more essential. Innovative use of technology, science and expertise to efficiently deliver customized and optimized services will become a must-have."

ALKERMES—CONTRACT PHARMA SERVICES DEVELOPMENT AND COMMERCIAL CAPABILITIES

There is an increase in the number of highly potent compounds coming through development – approximately 25% of drugs currently in development are classified as highly potent. This number is expected to grow by a CAGR of 8.4% to 2015.

To address this growing area, Alkermes Contract Pharma Services has increased its expertise in the manufacture of highly potent compounds. "We are currently tech-transferring a highly potent compound into commercial manufacture for a large pharmaceutical company," says Fidelma Callanan, Senior Director, Marketing &

Commercial Development at Alkermes Contract Pharma Services.

She says there has also been increasing interest in compounds that are poorly water soluble and require bioavailability enhancement and in the commercial manufacture of poorly water-soluble compounds using its NanoCrystal® technology. "It is one of the very few solubility enhancement technologies that has been successfully scaled to commercial level and is the technology behind five commercially available poorly water-soluble compounds on the market–Emend® Merck; Invega® Sustenna® Janssen; Rapamune® Pfizer; Megace ES® Par Pharmaceuticals; and TriCor® Abbott," she says.

Alkermes plc was formed following the merger of Alkermes Inc and Elan Drug Technologies in September 2011. The contract pharma services part of the business provides late-stage development, tech transfer, and manufacturing services to third parties, with a focus on solid oral dosage forms – particularly in controlled release formulations, poorly water-soluble compounds, and high-potency manufacturing. In the US, Alkermes has a dedicated sterile fill/finish facility as well as a controlled substance manufacturing facility.

Whether it's to address highly potent drugs or issues of solubility, Ms. Callanan says it is strategically sound to pursue outsourcing services to fulfill specific tasks, solve problems, and improve efficiency and productivity. One of the growing trends is the outsourcing of late-stage scale-up and commercial manufacturing activities, evidenced by the fact that in the last three years, more than 100 manufacturing facilities owned by pharmaceutical companies closed their doors for business in the US alone. "The value of partnering with a contract partner can very positively impact a pharma company's bottom line by alleviating capacity constraints, reducing capital spending and improving supply chain predictability," she says. "Building a solid relationship based on experience and expertise, with an enthusiasm to successfully execute on a project, backed up with a positive quality record with key regulatory agencies, has the power to turn a third-party arrangement into a long-term, strategic, win-win partnership for all parties concerned."

ALMAC PHARMA SERVICES—DEVELOPMENT TO COMMERCIALIZATION

With its clients facing increased pressure to bring clinical candidates through their pipeline, faster, more efficiently and at a lower cost, Almac Pharma Services opened a non-GMP development facility to offer flexibility and speed when assessing the feasibility of technical concepts and formulations, creating a streamlined progression from development to clinic to scale-up to commercialization.

"The formulation development facility is supported by additional GMP analytical laboratories," explains John McQuaid, Vice President, Technical Operations. "Having established ourselves as a development partner of choice, this expansion was quite simply due to increased client demand. With regard to formulation development, I expect a continuation of the trends of more potent drugs requiring high containment and also development of drugs that have bioavailabilty challenges."

Formulation development and manufacturing activities are supported by analytical development and testing activities, so the technical strength and scale of the analytical discipline is an important consideration. Almac has more than 200 analytical personnel dedicated to formulation development and manufacturing services. There are also chemical development and clinical packaging and distribution operations. "This offers tangible savings in cost and time in the supply chain for clinical materials, and also reduces risks associated with unnecessarily transporting in-process materials," says Mr. McQuaid.

Over the last few years, he says that within solid oral dose development in early-stage development, there has been an increasing trend towards API in capsule "If the attributes of the API are suitable, API in capsule can be good choice as it uses less material."

There is also an increase in developing both highly potent compounds and compounds with challenging oral bioavailability attributes. The increased demand for potent handling capabilities resulted in Almac investing in bespoke, containment solutions within its development facilities.

Almac Pharma Services is an FDA- and EU-approved outsourcing partner to the global pharmaceutical and biotechnology industries with more than 30 years' experience in the development and manufacture of solid oral dosage products. Scientists develop clinical candidates into optimum formulations, and manufacture drug products for all phases of clinical trial supply and through to commercialization—all at a single location. Its customer base is global and includes academic institutions, small virtual companies, biotech companies, mid pharma, and big pharma.

APTUIT—AN EARLY START TO FORMULATION IS LESS RISKY

Aptuit LLC provides early- to mid-phase development services for small, mid to big pharma as well as fully virtual drug development companies. In the past year, Aptuit has invested substantial resources in expanding some key manufacturing technologies. For poorly soluble compounds, the company has optimized a wet bead milling (WBM) technology to support toxicology studies with "simple" solid and liquid formulations containing nanosized API, which can guarantee an increased API exposure in animals without using organic vehicles, explains Roberto Bartolini, Formulation Development Group Leader, Chemistry, Manufacturing & Control, The Aptuit Center for Drug Discovery & Development – Verona, Italy. "We have already extensively studied and developed our WBM platform technology for the development of tablet or capsules to support clinical studies in humans."

Using its foundation competencies in characterization of DPI (dry powder inhaler) and blending mechanisms, Aptuit offers formulation development and GMP manufacturing of DPI from early clinical phase to late phase. "We are able to offer our early-phase approach to DPI formulation development using both low and high shear blending capabilities and semi-industrial microdose capsule filling technology," says Mr. Bartolini.

He continues: "With regard to solid dosage development, there is an increasing demand to shorten the time to the start of the clinical study, saving money and reducing the API demand. Instead of producing a fully formulated drug product, simple formulations (API in capsule, simple blend or granule in capsule) can be prepared and assessed for stability and *in vitro* performance." Mr. Bartolini says that preparation of this simple "fit for purpose" formulation requires a clear understanding of the biopharmaceutical profile of the API with its complete physico-chemical characterization and the evaluation of the risk associated with the possible inadequate performance. "A contractor with specialized expertise, capabilities and proprietary technology in the early development phases can make such outsourcing quicker, cost effective and less risky."

And with the growth of the biologics market, Aptuit has expanded its Glasgow, UK, sterile fill/finish capability to enable automatic filling of vials within a restricted access barrier system. "This has substantially increased our batch sizes for GMP sterile filling and lyophilization of both small molecules and biologics," he explains.

Outsourcing early formulation development and manufacturing should be considered the cornerstone of a successful project strategy, says Mr. Bartolini. "It is not only a matter of accelerating the development or reducing the costs, but being able to access expertise to design the most efficient drug delivery platform. This reduces risks and provides all the required scientific knowledge to safely move into the next project phase."

BEND RESEARCH—SOLVING SOLUBILITY ISSUES

A current trend in the pharmaceutical industry is the advancement of increasing numbers of compounds that have low

solubility. It is estimated that more than half of all new chemical entities have poor bioavailability. To overcome this growing challenge, Bend Research offers solutions such as spray-dried and hot-melt-extruded amorphous dispersions.

Bend Research has capabilities to support the advancement of drug candidates from discovery through commercialization. These include formulation and dosage-form support, process development and optimization, and cGMP manufacturing. With a client base ranging from big pharma to virtual biotechnology companies, Bend Research also serves the non-profit, academic and generic sectors, as well as non-pharma companies with projects that use its expertise in materials science, process development, and applied mathematics.

In the past year, the company has significantly expanded its facility footprint to enhance its Phase 1 to Phase 3 development and clinical spray-drying, and hot-melt extrusion, as well as adding commercial manufacturing offerings. In the spring of 2012, a new facility was validated that expanded GMP capabilities to include the spray-drying of high-potency compounds and biotherapeutics. Further expansion is expected to continue throughout this year.

Bend Research finds that its clients' discovery organizations are producing an increasing quantity of poorly bioavailable compounds. Thus, Bend Research is aiming in two directions–supporting existing bioavailability-enhancing technology platforms and developing next-generation technologies–according to David Lyon, PhD, Senior Vice President, Research, at Bend Research.

"With fewer molecules in the pipeline, it is crucial for us to provide innovative formulation development and dosage form solutions to our clients. This will ensure a higher chance of success for their drugs," Dr. Lyon said.

Additionally, Bend Research has been granted certification of compliance with European Union GMP regulations. This certification was granted in January 2013, after an extensive audit of operations that was requested by Bend Research. "This means that investigational drug products we make for our clients can be used in clinical studies in the EU and all of the many countries that recognize the EU authority," says Dr. Lyon.

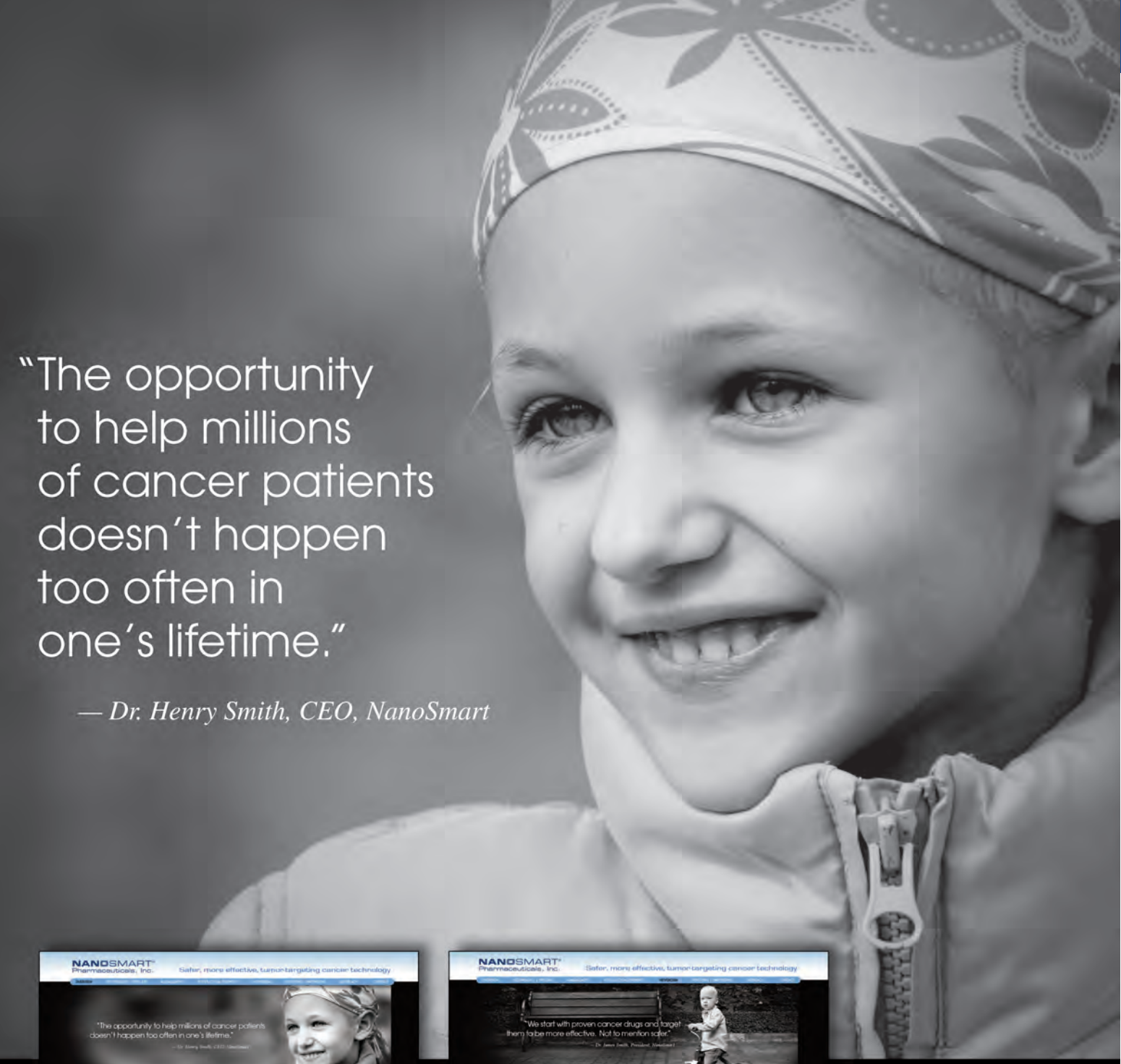
CMIC CMO USA CORP.—MINDFUL OF MULTIPARTICULATE AND MODIFIED-RELEASE DELIVERY

CMIC CMO USA Corporation is a member of the CMIC Group, a pharmaceutical focused company with facilities in 6 countries and more than 4,500 employees worldwide. Its FDA-registered facility is located in Central New Jersey. With a focus on formulation and process development, GMP commercial manufacturing, analytical and quality assurance of NDA and ANDA solid-dosage products, the company's clients include big pharma, generic pharma, specialty pharma and excipient suppliers.

Currently, Jeffrey Dopf, Director of Business Development for CMIC, says the company is seeing high interest in multiparticulate and modified-release delivery to support life cycle management projects and to improve patient compliance. To that end, CMIC has completed the construction and validation of 3 new development and GMP clinical supply suites. "These suites are designed for flexibility and quick initiation of development and feasibility batches," he says.

CMIC's Freund-Vector Granurex® GXR technology in New Jersey is a one-pot system for granulation, spheronization, drug layering, and spray coating. "This equipment allows us to produce eloquent beads for multiparticulate systems and a robust layering process for tight assay and dissolution specifications," he says.

The company is also vigilant in its understanding of the current FDA requirements. According to Mr. Dopf, the agency continues to be concerned with dose dumping of controlled release products. "Our extensive experience with the development of controlled release products and with coating systems helps us



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meet the challenges of dose dumping."

The FDA is also looking for a greater understanding of the design space for a formulation and process. CMIC scientists' experience and expertise with a focus on oral solid dosage contributes to a greater understanding of the most common formulation and process failures and typical root causes, explains Mr. Dopf. "We have the ability to improve productivity with our initial Quality by Design (QbD) programs and through formulation and process optimization."

DR. REDDY'S— PREFORMULATION AND FORMULATION DEVELOPMENT

The pharmaceutical development process is a complex and dynamic area, requiring detailed knowledge of API characterization, formulation, process, analytical development, sound experimental design, and regulatory requirements. Given the breadth and depth of expertise necessary to successfully develop a pharmaceutical product, many companies opt to outsource formulation activities. Some may not have development capabilities in-house, may have expertise limited to a specific area, or may have certain knowledge or capability gaps that influence the need for outsourcing. Others may be seeking novel technology, intellectual property, or unique capabilities offered by an outsource provider. Cost constraints, tight timelines, lack of staffing, competing priorities, or the need to allocate resources for other strategic purposes may also drive a decision to outsource. And, as the landscape of the pharmaceutical market evolves with mergers and acquisitions, the need to outsource may be critical as organizations are disrupted and integration activities are implemented.

Dr. Reddy's Custom Pharmaceutical Services division (CPS) is serving the pharmaceutical, generic, and biotech space with two R&D centers for preformulation and formulation development studies of NCEs and generic drug products, as well as 8 formulation manufacturing units. Preformulation services are designed to evaluate the basic properties of drug substances for developing drug products in both the solution phase and solid state.

The current trends in the formulation and manufacturing market include the development of various dosage forms over the entire spectrum of development such as preclinical studies and clinical studies up to registration batch for one compound. Design of Experiments (DoE) and Quality by Design (QbD) during scale-up stages have now become mandatory by a few regulatory agencies and customers are further emphasizing the need for a vendor to have this expertise.

"We have offered the following services within the past year: Our own in-house resource for DoE, data analysis and QbD, technical expertise in developing conventional solid oral dosage forms, delivery of drugs with modified release profile, combination product with multiple incompatible actives, combination product with sequential release, gastro retentive dosage forms, taste masking, and stabilization," says Praveen Raheja, Formulation Technology Manager.

Over the next 5 to 10 years, the pharmaceutical industry will see generic competition as more blockbusters come off patent, and the emergence of biosimilars. "More and more, clients are looking for true one-stop-shop service providers who have experience and expertise starting from preformulation development through to technology transfer for commercial manufacturing. It has been observed that as more providers, including companies from emerging markets, begin to offer formulation outsourcing services, the emphasis on quality and regulatory compliance, scientific expertise, specialized service, and program management takes higher priority," says Mr. Raheja.

Additionally, the other areas that will emerge over the next decade include development of biologics at higher concentration, special drug delivery systems like pre-filled syringes, and lyophilized formulations. "A larger piece of formulation outsourcing will go to the large and financially strong CDMOs with integrated services as well as to a few

smaller companies that offer specialized technologies.

"There is an increasing trend to reduce complexity in pharmaceutical supply chains. For big pharmaceutical companies, it is becoming more important to concentrate their sourcing at fewer CDMOs with the right capabilities and reduce supply chain and project management challenges. Both trends make it more difficult to select the right CDMO partner," says Mr. Raheja.

EI INC.—AN EMPHASIS ON QBD

According to John F. Lang, PhD, PE, Associate Director of R&D Technical Services at Ei Inc., pharma clients are becoming increasingly aware of the relationship between the desired attributes of a product and process conditions. "To simply achieve the desired attributes of a product with little or no awareness of the underlying scientific basis for those attributes can lead to a lack of process robustness as well as scale-up and product stability problems," he says. "Once the relationship between the product attributes and process conditions is understood, the process can be adjusted to improve the product. If you add to this the increasing regulatory expectations (especially Quality by Design), the trend for greater scientific understanding of products seems inevitable."

The areas that are receiving the most attention are identification of process parameters that affect the critical quality attributes of the product, chemical interactions between the components of a formulation that affect stability, API characterization (especially particle size and polymorphic state), efficient HPLC methods for assaying multiple active ingredients, and scale-up methodology.

Ei, a Pharmaceutical SolutionWorks™, develops and manufactures topical Rx, OTC, and cosmetic skin care and animal health products for customers ranging from big pharma to virtual start-ups. Ei recently constructed a 165,000-square-foot development and manufacturing facility outside of Charlotte, NC. Ei's facilities are cGMP compliant and have been audited by FDA and EMA. Services include API characterization, formula development, technology transfer, method development, packaging development, ICH stability, process scale-up, clinical and commercial manufacturing, filling, and regulatory filing assistance.

Dr. Lang says that big pharma has been slow to adopt QbD approaches to product development, which he says lead to a clear understanding of the design space of a product. "The design space, which is obtained by experimentation, describes the process ranges within which a product can be reliably manufactured with achievement of all of the desired product attributes," he explains. "Our clients report a warm reception at FDA for product development conducted with a QbD approach. When one considers the importance of speed to market, faster regulatory approval easily pays for the added cost of QbD development."

In addition to rapid formulation and process development and cost-effective manufacturing services, efficient analytical method development services are becoming increasingly important. This is especially true when there are multiple active ingredients, each with several known impurities. The active ingredients in a liquid formulation are more prone to degradation than those in solid dosage forms. In addition, FDA is placing increasing emphasis on tracking impurities not listed in compendial sources. In the drug product, each active must be assayed and each degradant impurity tracked. "Because not all impurities are degradants, an understanding of the chemical degradation pathways is important to limit the number of impurities whose quantitation must be validated in the analytical method. Given this complexity, analytical development can easily delay projects unless a well-organized team is in place," says Dr. Lang.

In light of this, during the analytical development phase of a project, Ei places early emphasis on the application of

chemical reasoning and limited experimentation to distinguish between process and degradant impurities of the APIs present in a drug product. While this is occurring, literature and manufacturers' methods are evaluated as a starting basis for testing the drug product. Careful attention is given to strategy, especially whether multiple methods for each API or a single method for all APIs should be attempted. If the right calls are made, the development time can be significantly shortened.

Looking ahead, Dr. Lang sees three areas where outsourced formulation development and manufacturing relationships can be improved. First, he sees a greater need for the integration of other disciplines, especially chemistry and chemical engineering, into the formulation and process development of topicals. An understanding of the chemical interactions in a product leads to more effective products and more stable ones, he says. It also greatly simplifies the analytical development process. "Chemical engineering plays a role in understanding API characteristics, the internal structure of the product (such as droplet size), and the development of scale-up methodology, and is essential for QbD development."

Second, there is increasing demand for more detailed pharmaceutical development reports and carefully designed manufacturing documents for both bulk and filling operations. "Given the complexity of many manufacturing processes, the associated documents must be sufficiently detailed to avoid errors during manufacturing, which can be very costly to a drug development program," says Dr. Lang.

Finally, agility is very important in the contract process development and manufacturing space. "Several of our clients have other business partners and some have divided the development process among multiple suppliers. This leads to a situation where plans can readily change and communication is vital. It has become somewhat clichéd to say that forming partnerships with clients is important, but the fact remains that effective partnerships are essential to a smooth development process when multiple parties are involved. This requires regular communication among all parties to ensure plans are unfolding in the same direction."

MPI RESEARCH—A PRE-CLINICAL CRO

MPI Research is a preclinical and early clinical CRO that provides discovery, surgery, safety evaluation, bioanalytical, and analytical services. As a CRO in the preclinical market place, its expertise lies in the production of many different types of formulations for various types of dose administration routes. Compound types range from traditional small molecules, oligonucleotides through to protein therapeutics while dosing vehicles range from simple solutions to complex feeds, gels, and creams. Preparation of preclinical dosing formulations is typically completed based on instructions provided by the sponsors, however, modifications to the instructions may be required to accommodate batch size, available equipment, chemical and physical instability, and homogeneity considerations.

In the CRO preclinical arena, where a large number of compounds are being formulated every day for many different studies for many different sponsors, eliminating the potential for cross contamination is paramount. "Our approach has been to use a state-of-the-art laboratory space incorporating designated clean ('in') and dirty ('out') anterooms, containment hoods, and extensive cleaning validation studies along with secondary containment of bulk test article and formulated material," explains Amy Smith, Director of Laboratory Sciences. Laboratory space has been designated for vehicle preparations to eliminate the possibility that a test article is ever introduced into the control material. "Specific cleaning and verification procedures are in place to ensure containment of the test article and to minimize the introduction of any contamination."

MPI formulation experts work with analytical scientists to ensure timely

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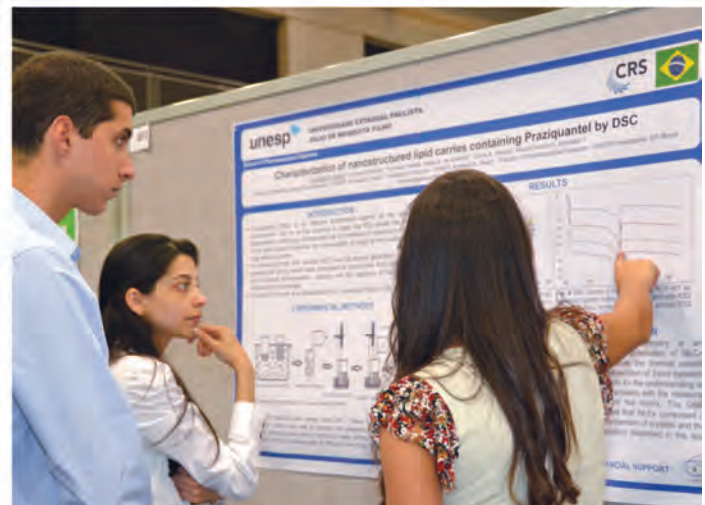


response to any observed anomalies in the formulation. Some examples of anomalies include, but are not limited to, observation of out-of-specification results, chemical and physical instability, adsorption of the dosing material in the dosing delivery system, and incompatibility of the test article with the vehicle for the specified dosing route.

In the preclinical CRO market, flexibility, rapid response time, and a broad range of scientific experience and quality are essential to ensuring a successful study. Electronic chain-of-custody is maintained from preparation of the formulated material through dosing and subsequent disposal. Flexibility is required in order to accommodate both the large volume and different complexity of test materials and vehicles. This includes preparation equipment, storage conditions, and preparation techniques.

"A CRO that understands the principles and practice of formulation development–that can deliver the experimental results in a timely manner to both the consultant and the client–will be well positioned for success in the market place," says Ms. Smith.

PFIZER CENTRESOURCE—SOLID ORAL DOSE COLLABORATION

Cancer is a leading cause of death worldwide, and the development of more effective, efficient and targeted cancer treatments is critical and urgent. High potency active pharmaceutical ingredients (APIs) have characteristics that allow the selective targeting of cancer cells, blocking their growth while causing less harm to normal cells. With new classes of high potency APIs being developed, often better tolerated by patients and available in oral dosage forms, this area has become one of the fastest growing segments in the global pharmaceutical industry.

The very thing that makes these APIs so effective – their potency – adds layers of complexity to development and manufacturing processes. Thus, many companies are choosing to outsource the development of these compounds for both strategic and economic reasons in the race to get new therapeutics approved and on the market. "We have seen demand across the realm of high potent solid oral dose products from development services through clinical and commercial supply," says Cristin Grove, Director, Contract Manufacturing, Pfizer CentreSource (PCS).

Over the past two years, PCS has been focusing our marketing towards high containment solid oral dose collaborations. "We partner with our customers to provide formulation development, process optimization, analytical services and clinical supplies for compounds in Phase I/II through commercial," says Ms. Grove.

PCS is a separate operating unit within Pfizer Inc., with capabilities and experience in active pharmaceutical ingredient (API) and dosage form manufacturing. PCS manufactures steroid APIs and antibiotics; supplies GMP custom fermentation services; manufactures and packages finished dosage forms; provides product development, process development, and advanced manufacturing for high potency oral solid drug product; and offers therapeutic bioprocessing development and manufacturing across microbial and fermentation platforms.

RESEARCHDX—THE NEW CDO BUSINESS MODEL

The Contract Diagnostics Organization (CDO) is a new business model, which allows diagnostic, biotechnology and pharmaceutical companies to outsource to a single partner offering integrated services within one organization. The CDO has become an increasing presence in the world of personalized medicine. It is in this space that ResearchDx is forging a path. Biopharmaceutical companies need diagnostics partners that can easily and readily adjust to meet new or unexpected challenges during the development process. According to Philip D. Cotter, PhD, FACMG, FFSc(RCPA), Principal, ResearchDx, the traditional CRO cannot meet all the demands of developing

companion diagnostics.

"The growth of personalized medicine and the likely demand for therapeutic companion diagnostic co-development will further drive the trend to outsourcing of the diagnostics component," says Dr. Cotter. "IVD diagnostics and manufacturing are all going to be important factors in helping address the overall health of humans. With that being said, providing more targeted therapeutics, not just in Oncology but across the board, will become essential to meeting the above challenges we are confronted with in medicine."

ResearchDx helps biopharmaceutical companies accelerate, develop, and manufacture companion diagnostic products. Managing the entire diagnostic development process – from initial assay concept and discovery all the way through clinical research to regulatory approval, manufacturing services include reagents, sample collection kits, custom diagnostic kits, and product manufacturing.

Dr. Cotter says that in the CRO market space, there are few companies whom can provide integrated services for the entire diagnostic development process. Many pharma companies partner with multiple service providers and in the end lose ground on their time-sensitive drug or device. By comparison, ResearchDx offers GMP/GLP manufacturing together with all other aspects of companion diagnostics development to eliminate the multiple vendors/labs issues that may arise for the customer.

With global markets growing and expanding, the folks at ResearchDx are paying close attention to the US market, focusing on a growing population, unmet medical needs, and changes in health insurance policies. For ResearchDx clients—the biopharma industry—this has meant expanding in multiple international sites while maintaining a domestic presence. "This puts us at the the forefront of personalized medicine," he says.

SUZHOU PHARMA SERVICES—A CDMO WITH MULTINATIONAL EXPERIENCE

The outsourcing market grows more competitive every year, with new and expanded entries seeking to capitalize on the rapidly expanding outsourcing trend in the global pharmaceutical industry. In the past, the decision to outsource manufacturing was primarily based on the need to acquire a new skill or to compensate for a lack of in-house, internal capacity. However, over the last decade or so, the decision to outsource has been strategically embraced as a way for pharmaceutical companies to: reduce costs, lower drug development risks, adapt to shifting manufacturing requirements, gain access to manufacturing expertise, and reduce drug commercialization development times.

Cost control is one of the main reasons that pharmaceutical companies are increasingly turning to CDMOs for manufacturing help. The need for pharmaceutical companies to assiduously control costs has been caused by impending "patent cliffs" resulting from recent blockbuster drug patent expiry, increased regulatory scrutiny and decreased new drug approvals, and genericization and downward pricing pressures on branded prescription drugs. The challenge for contract development and manufacturing organizations (CDMOs) will be to offer high quality services with both experienced, well educated personnel and modern, highly compliant facilities, while maintaining their own need to control costs.

Suzhou Pharma Services is a new division of Amerigen Pharmaceuticals, the parent company that specializes in generic development and manufacturing from the site in Suzhou, China. Suzhou Pharma Services is a US-based CDMO that specializes in solid oral dosage forms with operations from its FDA-inspected and Chinese SFDA-licensed cGMP finished dose manufacturing facility in Suzhou.

"We serve as a reliable manufacturing partner to support entrance into the growing Chinese market as well as act as a CRO to the numerous multi-national and local Chinese pharmaceutical companies," says Oliver W. Mueller, President, Suzhou Pharma Services and Marc Finn, Sr.

Director Business Development, Suzhou Pharma Services, Amerigen Pharmaceuticals. "We are seeing significant potential in the Chinese market segment whereby large multi-national companies who are currently invested in China with new R&D facilities are also seeking drug discovery, clinical and R&D services to support efforts for late-phase clinical and manufacturing for the local Chinese markets. We also see a better acceptance and understanding of outsourcing services to China by our US customers who are currently in China for early formulation and drug discovery phases and seeking to expand on those services to include dosage form development and manufacturing and take further advantage of the Chinese cost model."

Mr. Mueller adds that regardless of which region of the world your facility is located, global pharma demands the same high quality standards expected by government authorities in the western world.

UPM PHARMACEUTICALS, INC.—SAVING TIME AND MONEY

A predominant trend in the formulation development and manufacturing market is for clients to choose a development partner with the capability to provide cradle to commercial support for their molecule. With compressed project timelines, and R&D dollars at a premium, it becomes very difficult for organizations to move a molecule from one CDMO to another. Transfers have to take place, methods have to be validated, and communication needs to be robust among separate organizations. This can become quite laborious and time consuming, not to mention very expensive.

UPM is working to save its clients time and money. As a drug development and contract manufacturer serving the pharmaceutical and biotechnology industries, UPM's development and manufacturing capabilities are predominately geared towards solid oral dosage forms. Development capabilities include immediate- and controlled-release tablet and capsule formulations, highly insoluble compounds, oral disintegrating tablets, matrix and coating formulations, and wet and dry granulations.

UPM has added 50% more manufacturing space, 3 new R&D labs, high-potency containment, and humidity controlled manufacturing space. Specific capabilities include Brevi-Batch®, a development capability to handle 100-gram batch sizes, low solubility solutions, and has a preformulation area with TGA, DSC, and laser detection equipment. Manufacturing processes include granulations, extrusion/spheronization, and roller compactions. UPM has automated tableting, encapsulation, overencapsulation, coating, weight sorting, and packaging.

UPM is equally adroit in simple API in capsule manufacturing. "One trend we see is with API capsule projects; we now see capsule quantities in the mid-five figures for Phase II and even Phase III studies supplied with the dosage form," explains Frank Sorce MBA, Director, Business Development/Marketing, UPM Pharmaceuticals. UPM has constructed an API in a capsule dedicated manufacturing area to accommodate 24/7 manufacturing, with controls available for light, potency, and humidity.

A daunting trend that Mr. Sorce sees is the percentage of poorly soluble compounds in the development stage; between 50% and 65%. For poorly soluble compounds, UPM has invested in equipment for particle size reduction (micronization and nano-sizing) as well as processing such as liquid fill into hard gelatin capsules, spray drying, and hot melt extrusion. "Difficulty in formulating poorly soluble drugs will continue to challenge pharmaceutical scientists," he says. ◆

DRUG DEVELOPMENT Executive

Solubilization: Accessing Broader Chemistries by Integrating Fundamental Science With Automation for Greater Predictability

Marshall Crew
President & CEO
Agere Pharmaceuticals, Inc.

Increasingly, drug targets are found to require molecular design elements that reduce the solubility of the drug candidate below historically acceptable limits. The industry as a whole can benefit significantly by further embracing drug delivery technology for poorly soluble compounds, thereby accessing new chemical space. However, to be effectively applied to a broad spectrum of compounds, advances in formulation technology are needed. Driven by this growing need for improving the oral bioavailability of BCS II-IV compounds through solubilization technologies, Agere Pharmaceuticals is creating a new approach to meet the challenge. Borrowing from other industries dealing with similar complexities, Agere has focused on learning best practices and is beginning to apply similar techniques to overcome bottlenecks and accelerate growth. One analogous business segment is electronic design automation that supports the semiconductor industry. Electronic design automation emerged in the 1960s out of the necessity to automate integrated circuit design and prototype and analyze functionality, performance, and manufacturability in software before manufacturing. Drug Development & Delivery recently spoke with Marshall Crew, President and CEO of Agere, to discuss how the company is taking a different approach that leverages expertise, but relies heavily on the principles of physical chemistry to enable automation.

"Finally, assuming the average net present value of a compound on the market is approximately $300M, this would translate to $135B in today's dollars - roughly expanding the accessible market by 35%. Given recent predictions of revenue erosion in the pharmaceutical industry through 2014, being able to expand the market with solubilization technologies seems to be an opportunity well worth pursuing."

Q: Can you provide our readers with an overview of the role you see solubility playing in the pharmaceutical industry?

A: Well, to begin, it's important to summarize the trends we are all aware of and the direction we are going. According to the PhRMA 2012 Profile, R&D spending is continuing to increase for their member companies and was in the range of $50B in 2010 and 2011, representing a jump of more than 9% over 2009, and yet NCE (new chemical entity) approval rates don't reflect that level of investment. That same study shows what we have seen throughout the past many years - that for every 5,000 to 10,000 compounds that begin drug discovery, only 1 receives FDA approval. While there is increasing demand for new drugs, the industry has reached a bottleneck, and in fact, some forecasts show global pharmaceutical revenues shrinking by more than $200B between 2009 and 2014.

Q: As you stated, we're all aware the number of NCEs entering the market has been slowly declining over the past 15 years, and costs are increasing. What are your thoughts on this issue?

A: It motivates looking into the root causes for the decline. We all know that this is a very complex issue with numerous economic and technical factors contributing to clinical failures; drug metabolism and pharmacokinetics, efficacy, toxicity, and clinical safety being the broad categories. But a different cut through the data reveals that more than 40% of failures are due to the inability to overcome solubility issues. Some companies report even larger percentages.

Q: What do you believe are the reasons for this trend in low-soluble compounds?

A: The reasons are varied. For example, the diseases we are addressing today are much more complex than those in the past. There is much discussion in the literature as to the nature of the binding pockets in modern drug targets. This topic is controversial, but many believe that carefully engineered hydrophobicity is required to achieve the desired potency and selectivity. This, coupled with modern methods for designing, synthesizing, and optimizing chemical libraries has led to a large increase in the number of compounds with low aqueous solubility. It's unfortunate, but many of these potentially promising compounds attrite very early on in development due to the perception that they will have poor pharmacokinetic properties.

Q: It seems like a lot of missed opportunities. What is being done to address discarded compounds with low solubility?

A: While technologies for delivery of poorly soluble compounds have been in development for more than 50 years, the pharmaceutical industry has only just begun to fully embrace them in the past decade or so. Notably, amorphous solid dispersions are now broadly utilized in clinical development, and a number of commercial drug products they enable are now on the market. A recent example is Vertex's product Incivek®.
However, in relative terms, we have only

just begun to explore the potential for solubilization to expand the accessible chemical space for drug discovery. Significant advances in our understanding of the technology are still required. If the technology were to be further developed and fully exploited, the potential impact on the pharmaceutical industry could be significant.

Q: It's exciting to hear about this potential. Can you expand on your thoughts about the impact solubilization can have on the pharmaceutical industry?

A: An analysis we have conducted at Agere shows there is a significant, unrealized market opportunity. Using a database containing data on 1,308 marketed drugs, we analyzed compound solubility and logP (water-octanol partition coefficient) and found that the (log normal) distribution is centered on a solubility of 100 micrograms/mL and logP of approximately 2.2. This distribution of compounds represented a market in 2011 of nearly $400B. If we were to shift this distribution to slightly higher logP and lower solubility, say, a solubility of 10 micrograms/mL and logP of ~4 (easily accomplished with current technology), and assume a similar density of compounds compared to historical records, we estimate that 450 new, yet-to-be-discovered compounds could be enabled on the market using solubilization.

Finally, assuming the average net present value of a compound on the market is approximately $300M, this opportunity represents $135B in today's dollars - roughly expanding the accessible market by 35%. Given recent predictions of revenue erosion in the pharmaceutical industry through 2014, being able to expand the market with solubilization technologies seems to be an opportunity well worth pursuing.

Q: This is a significant impact. What will it take for the industry to further adopt this technology and explore this opportunity?

A: As discussed previously, there have been significant advances in the scientific understanding of solubilization. However, in order for the technology to have broad acceptance and not be thought of as "enhanced delivery," an underlying foundation needs to evolve to make it a more predictable science. There are far too many uncertainties in the development process that are currently addressed with empiricism, an approach that can inhibit disruptive change and innovation. This is why Agere is dedicated to advancing the knowledge of the fundamental science of solubilization, which will enable a more automated and predictable process for drug formulation and development. This approach is similar to that used in other industries such as in electronic design automation.

Q: Most of our readers may not know about electronic design automation. Can you provide a brief overview?

A: The first integrated circuits were demonstrated in the late 1950s. At that time, they consisted of fewer than 10 transistors, and it was possible to design those using very manual approaches. But by the next decade, it became apparent that automation was needed to handle the rapidly increasing complexity. Design tools started

appearing and these enabled designs to be captured digitally to accelerate the drafting process, and also to constrain the designs to conform to requirements such as angles required for manufacturing. But the act of encoding designs also enabled the use of computational programs to simulate and analyze integrated circuit designs for functionality, performance and manufacturabilty. Today, integrated circuit complexity can exceed 7 billion transistors, and it would be impossible and prohibitively expensive to design today's electronics without being able to create and test virtual prototypes before manufacturing. Given the similar complexity and the cost of modern medicines, it seems that we now have an analogous situation in pharmaceuticals.

Q: Can you provide an overview of what it means to add automation to solubilization?

A: We encapsulate expertise using scientific and engineering fundamentals to develop rigorous models and then automate as much of the design and optimization process as possible. Part of being able to automate is to also have more standardized inputs and outputs for each stage. The ultimate goal is to achieve a solubilization platform to improve the predictability of formulation efforts on behalf of our clients. This approach promises to reduce cost and development time, and to greatly minimize down-stream risk. Assembling a comprehensive, modern platform is not going to be an easy task, as it requires going back to the fundamentals of physical chemistry and then building on that foundation. But we are making progress, and Agere has the vision, expertise and capabilities to get there.

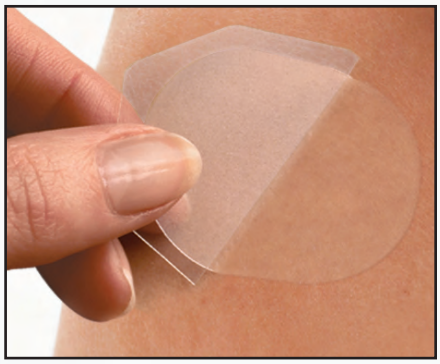
Q: Are you able to tell our readers about some of the advances you are referring to?

A: We have started to put some of the pieces in place. I have conveyed what a challenge the industry faces in moving the solubilization technology forward. So, while we have made significant progress, there's a long way to go. On the way to a comprehensive and integrated system, there are two main categories Agere is paying attention to. One has to do with standardization of inputs and outputs, which enables both automation and more effective technology transfer. The other area relates directly to technical and scientific innovations leading to better predictions.

Examples include phase diagrams that allow Agere to predict the key physical properties of a solubilized drug form. Related to the phase diagram analysis, we have developed technology to predict physical stability and enable selection of packaging configurations. Agere has also developed a free drug assay that enables better selection of excipients and prediction of in vivo performance. We think of each of these as similar to links in a chain. Right now they enhance the analysis and results for each specific targeted task. When ultimately connected with the other technologies we are developing, the entire solubilization process will be streamlined and much more accurate. ◆

Technology & Services Showcase

Transdermal Drug Delivery



With more than 30 years of transdermal experience, 3M Drug Delivery Systems (3MDDS) excels at integrating adhesive, drug, and components into a single, simple system that provides superior product stability and optimal system performance throughout the duration of the wear period. 3M DDS serves as a contract manufacturer to pharmaceutical companies that market transdermal products, and helps companies develop and adapt their drugs for transdermal delivery. The company delivers core advantages to help ensure technical success, including expertise in customizing solutions to fit drug formulation needs, access to material and process technology expertise, regulatory and toxicology support, streamlined pathway through development, and contract pharma manufacturing services. For more information, visit 3M DDS at **www.3M.com/TDD-Systems.**

Drug Development Services

AAIPHARMA®

Your Results Become Our Reputation®

Analytical Testing • Drug Development • Manufacturing Services

AAIPharma Services Corp. is a highly experienced provider of drug development, manufacturing, and analytical services that supports all phases of drug development. Our extensive expertise and wide array of capabilities include analytical development, formulation development, microbiology, oral solid dose and parenteral manufacturing (clinical and commercial), pharmaceutical packaging, stability storage, and analytical testing services. We are focused on providing the absolute best service and have a reputation for solving the toughest development problems - Your Results Become our Reputation®. To request a quote or learn more, contact AAIPharma at (800) 575-4224 or visit **www.aaipharma.com.**

CRO/CMO

Agere Pharmaceuticals offers clients cGMP services, solid dosage forms produced under cGMP, and formulation design and development services for enhanced bioavailability. cGMP services include clinical trial materials, cGMP analytical, regulatory guidance, and IND/IMPD regulatory document support. All services are offered on a fee-for-service basis. For more information please contact Sheri' DuMond of Agere Pharmaceuticals at (541) 639-8397 or visit **www.agerepharma.com**.

Licensing & Capabilities

Aveva has a number of products for license from its development pipeline along with a full complement of R&D capabilities to produce transdermal drug delivery systems that fortify pipelines and maximize product life cycles. Aveva Drug Delivery Systems is one of the world's largest manufacturers of, and a pioneer in, transdermal drug delivery systems with a rich history of providing pharmaceutical partners with fully integrated, controlled-release transdermal products that fulfill unmet market needs. Products for licensing include Sufentanil, Fentanyl, Clonidine, and Nicotine. For more information, contact Robert Bloder, VP of Business Development, at (954) 624-1374 or visit **www.avevadds.com**.

Technology & Services *Showcase*

Development & Manufacturing

BEND RESEARCH
WE MAKE MEDICINES WORK

Bend Research is a leading independent scientific development and manufacturing company with more than 35 years of experience in the development of pharmaceutical delivery systems. To achieve its mission of improving health through the advancement of its clients' best new medicines, the company uses a multidisciplinary problem-solving approach grounded in science and engineering fundamentals to address the most difficult challenges. As a leader in novel drug delivery technologies and formulations, Bend Research provides expertise in solubilization technologies, such as spray-dried dispersions and hot-melt extrusion formulations, as well as biotherapeutic, controlled-release, inhalation, and nanoparticle technologies. Capabilities include formulation science, process development and engineering, dosage-form development, cGMP manufacturing, and analytical services for the advancement of drug candidates from early discovery to commercialization. Bend Research also pioneers, advances, and commercializes new technologies. For more information, contact Phoenix Barringer of Bend Research at (800) 706-8655 or Phoenix.Barringer@BendResearch.com or visit **www.BendResearch.com**.

Gum Base Supplier

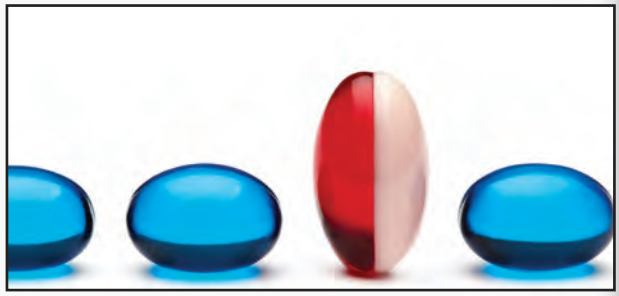
Health in Gum by CAFOSA
www.healthingum.com

Cafosa, part of the Wrigley/Mars group of companies leading the chewing gum market, is the world's leading Gum Base supplier for confectionery, nutraceutical, and pharmaceutical applications. Gum Base is the main ingredient used to produce chewing gum, a combination of polymers, resins, and softeners plus an inorganic filler that gives different textures and chewing properties to chewing gum depending on its composition. Cafosa has developed an innovative concept for the pharmaceutical industry: Health in Gum is an excipient, a directly compressible powder gum containing a mix of Gum Base and polyols to which you can add your API, so you can create medicated chewing gum by adding your APIs to Health in Gum powder. Health in Gum offers an innovative drug delivery system for your products. There is no need for specific chewing gum production equipment. For more information visit Cafosa at **www.healthingum.com**.

HPMC Capsules

Capsugel's Vcaps Plus HPMC (hypromellose) capsules are non-animal capsules with low-moisture content that also meet global pharmaceutical standards. A proprietary capsule-manufacturing process eliminates the need for gelling agents and delivers gelatin-like consistent disintegration and dissolution properties. The unique performance characteristics of Vcaps Plus HPMC capsules expand the range of applications for two-piece capsules. The proven properties of Vcaps Plus capsules make them an excellent alternative to gelatin or traditional HPMC capsules for optimizing delivery, performance, and stability of over-the-counter, New Chemical Entities, and off-patent products, as well as reduce development timelines. For more information, contact Capsugel at (888) 783-6361 or visit **www.capsugel.com**.

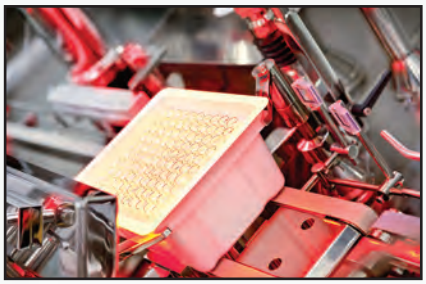
Softgel Technology



Catalent RP Scherer softgel boasts more than 75 years of development expertise and manufacturing experience. RP Scherer improves solubility and optimizes performance in all of its capsules. RP Scherer is supported by a global infrastructure of cGMP, FDA, and EMA. RP Scherer Softgel technology improves solubility, increases bioavailability, and offers valuable product differentiation of different shapes colors and sizes. This technology also helps bring compounds to market faster using a proven dosage form and helps reduce regulatory risk. RP Scherer capabilities continue to expand. In Q1 2013, Catalent announced two major joint ventures in China significantly expanding it RP Scherer softgel innovations, proven operational excellence, and regulatory compliance in the Asia Pacific region. To learn more about Catalent's global RP Scherer Softgel technology capabilities, call (877) 587-1835 or visit **www.catalent.com/index.php/offerings/softgel/softgel-tech**.

Technology & Services *Showcase*

Integrated CDMO



Cook Pharmica is an integrated contract development and manufacturing organization providing the pharmaceutical and biopharmaceutical industries with drug substance manufacturing from mammalian cell culture; analytical and formulation development; parenteral manufacturing in vials and prefilled syringes; lyophilization; and secondary packaging. The small-scale train has capacity up to 250 L, featuring disposable technologies. Our large-scale train houses one 600-L and two 2,500-L stainless steel bioreactors, and disposable seed tanks up to 100 L. Cook Pharmica's parenteral drug product manufacturing has the capacity to aseptically fill product in vials or syringes for clinical or commercial supply. The current manufacturing lines are fully automated within barrier isolators. The high-speed syringe filling line can fill 600 units/minute, while the vial line can fill at a rate of 150 units/minute. For more information, contact our Business Development team at busdev@cookpharmica.com or visit Cook Pharmica at **www.cookpharmica.com**.

Development & Manufacturing

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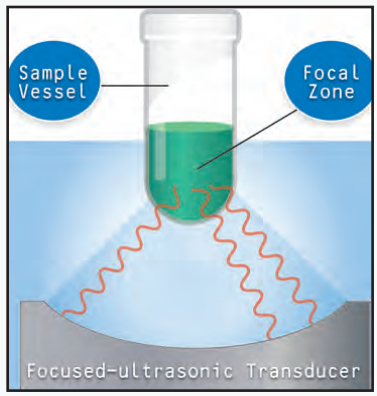
Faster to First-In-Human



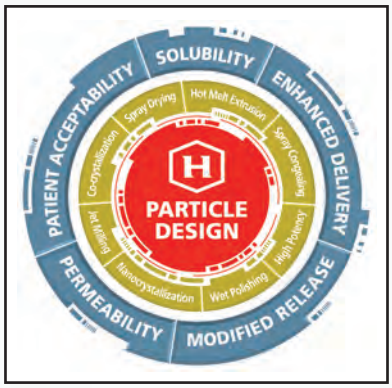
Accelerate the pace to First-In-Human (FIH) testing with an easy, scalable, and reproducible method to manufacture nanoparticles, nanoemulsions, nanosuspensions, and liposomes. Covaris Adaptive Focused Acoustics (AFA™) has the capability to produce a "Best in Class" particle size in a non-contact, self-contained vessel with 100% material recovery. AFA can allow an early stage compound to move forward into development that might have otherwise been dropped due to limited material availability. Covaris AFA is the method of choice to manufacture lipid-based nanoparticles for drug delivery. Liposomes are produced without the use of solvents and at low temperature, allowing for easy liposome formulation without degrading delicate molecules such as biologics. For more information, contact Covaris at (781) 932-3959 or visit **www.covarisinc.com**.

Hot Melt Extrusion

Foster Delivery Science has over 20 years of experience in melt extrusion for life science applications. Our cGMP facility is equipped with state-of-the-art melt extrusion equipment to support pharmaceutical clients. We offer complete services throughout the product life cycle, including Formulation (Material Selection), Feasibility (Small Batch Production), Process Development (Non-GMP Process Definition), GMP Trials (Clinical Supply), Scale-Up (Maximization of Throughput),Validation (Process & Test Methods), and Production (Implement Manufacturing Protocols). Foster's inventory of downstream processing equipment is available to manufacture traditional and customized dosage forms, including Tablets & Tablet Coating, Pellets & Spheres for Capsules, Pellets & Micro Pellets, Films (Transdermal & Transmucosal), Fibers & Monofilaments, Intra Uterine Devices, Implants, and Customized Dosage Forms. For more information, contact Brittany Palmer of Foster Delivery Science at (860) 630-4525 or **bpalmer@fostercomp.com**.

Technology & Services Showcase

Manufacturer & API Specialist



Hovione is a global company with over 50 years of experience in Active Pharmaceutical Ingredient and Drug Product Intermediate development and compliant manufacture. With four FDA-inspected sites in the US, China, Ireland, and Portugal, the company focuses on the most demanding customers in the most regulated markets. Hovione offers integrated API, particle design, formulation development, and manufacturing. In the inhalation area, Hovione is the only independent company offering such a broad range of services. For more information, contact Isabel Pina of Hovione at 351 21 982 9362 or ipina@hovione.com or visit **www.hovione.com**.

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Manufactured specifically for the biopharmaceutical and medical device markets, Novozymes Biopharma's animal-free, recombinant human albumins (rAlbumins) are applicable in formulation, drug delivery, and medical device coating. Proven to stabilize proteins by preventing aggregation, oxidation, or adsorption of the active drug, Novozymes' rAlbumins are pure, high-quality ingredients that can help customers deliver safer products to the market faster. Recombumin® Alpha is supplied as an ingredient for the manufacture of pharmaceutical drugs, medical devices, and advanced cell therapy products. Approved for use in the manufacture of human therapeutics, Recombumin® Prime is the world's first commercially available, GMP-manufactured, animal-free rAlbumin developed for drug and vaccine manufacturing. Novozymes' rAlbumins are manufactured to regulatory standards to deliver a secure supply of batch-to-batch consistency and increased efficiency for customers looking for a compliant albumin alternative. For more information on Novozymes' rAlbumins, visit **www.biopharma.novozymes.com**.

Knowledge Management

PharmaCircle is an innovative knowledge management company specializing in the drug delivery, pharmaceutical, and biotechnology fields, with a current client base ranging from start-up life science companies to world leaders in Big Pharma. Clients choose PharmaCircle's services and content for its comprehensive technical (pipeline, products, molecule, and technology) and business (deals, acquisitions, royalty, licensing, drug revenues, market information, etc) related information and analysis, which are ideal for all segments of small and large companies. PharmaCircle helps facilitate product life cycle management (LCM), partnering, licensing, and competitive intelligence efforts as well as supplements internal efforts and costs at a fraction of the cost if performed internally. For more information, contact PharmaCircle at (920) 850-3056 or visit **www.pharmacircle.com**.

INNOVATION AWARDS

Drug Delivery Award Winners Move Innovation Needle; Formulation Takes Center Stage

By: Marc Dresner

This past February, three companies were honored by their industry peers with prestigious awards for breakthrough drug delivery innovation at the Institute for International Research's 17th annual Drug Delivery Partnerships (DDP) conference.

The awards recognize companies that have demonstrated exemplary, forward-thinking leadership in the field and/or which have developed technologies that will likely propel the industry in promising new directions. Nominations are open to and come from the industry. Voting was conducted at the 2013 DDP conference.

Before reviewing DDP's 4th annual *Drug Delivery Innovation Award* winners' respective achievements, I would be remiss if I did not reference the news reported the same month that researchers at Methodist Hospital Research Institute have discovered a way to sneak nanoparticles targeting specific cell types – cancerous ones – past the immune system by coating them in white blood cell membranes.

Their accomplishment got me thinking about how innovation is currently perceived and gauged in drug delivery. Where have we set the bar? Clearly, we may expect to see more biologic solutions, micro-targeting to improve outcomes and minimize adverse events, and therapeutic approaches tailored to the disease stage, the demographic and, ultimately, the individual. All made possible by delivery technology. And as you'll see, the winner of this year's Drug Delivery *On The Rise Company Award* for Innovation, NanoSmart Pharmaceuticals, is doing remarkable work in precisely these areas.

There is also no doubt that delivery instruments and modalities are advancing at a stellar pace. Indeed, an industry expert recently remarked to me that drug delivery is becoming very "Star Treky" – microneedles, nano-implantables, ultrasound leveraged for transdermal delivery… Science fiction is becoming drug delivery fact!

All of this is incredibly exciting, of course. But talk of innovation is frequently steeped in hyperbole, and more often than not, the most elegant, innovative solutions may be found in formulation, which may not always receive the attention it deserves amidst all of the breathless headlines about sexy devices and such.

So I was personally gratified when attendees at this year's Drug Delivery Partnerships conference awarded two top honors to companies whose strides were based on formulary feats. The first, Pearl

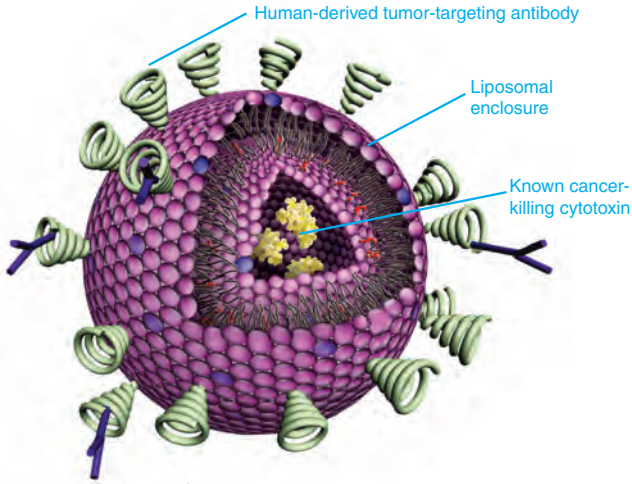
FIGURE 1A&B

Therapeutics – winner of DDP's Technology Innovation category – specializes in an area that is near and dear to me personally: Treatment of respiratory afflictions like COPD, a category of lung disease. Surprisingly few people are familiar with the acronym, despite the fact that it claims so many lives. My dad suffered from it before lung cancer ultimately took him.

Pearl's achievement is outlined in detail below, but the crux of the honor is based on Pearl's ingenious co-suspension formulation platform. The implications for people who suffer from chronic respiratory conditions are not insignificant.

Our other formulary hero, Unigene, has

FIGURE 2



NanoSmart's Tumor-Targeting Immunoliposome.
A phospholipid bilayer (liposome) encapsulates an anti-cancer agent (FDA-approved drug) and is coated with NanoSmart's patented antibodies. The drug formulation is administered intravenously and travels in the blood to the tumor sites. Once the immunoliposomes reach areas of necrosis within and around tumors, they bind there and slowly release the anti-cancer agent, eliminating the tumor while protecting healthy cells.

essentially turned what traditionally required an injection into an oral delivery. Consider the healthcare cost savings and probable compliance improvements their work will achieve. More importantly, when we think globally, the potential advantages of migrating from an injection that must be administered by a professional to a pill in emerging markets, in particular, are astounding.

In summary, all three of the 2013 *Drug Delivery Innovation Award* winners' accomplishments exemplify not only the increasingly critical role delivery systems are playing in health science progress, but also the tremendous level of sophistication being brought to bear in the field of drug delivery today. Without further ado, here they are!

TECHNOLOGY INNOVATION

Winner: Pearl Therapeutics

This award celebrates game-changing technological innovation in drug delivery within the last year. Pearl Therapeutics' co-suspension formulation technology is the foundation of a broad portfolio of product candidates for globally prevalent respiratory diseases, such as COPD, asthma, and rhinosinusitis.

These candidates are all based on the simple and widely prescribed metered-dose inhaler (MDI) dosage form. MDIs have been used for the delivery of pulmonary medicines for more than five decades. But major therapies – particularly dual and triple combinations of well-known inhaled medicines – have proven difficult to develop in MDI format due to formulation challenges, such as inconsistent dosing, instability over time, and partial or variable delivery to the airways.

Pearl's co-suspension formulation platform overcomes these challenges via proprietary airway-compatible lipid-based porous particles, which keep drug crystals suspended in the propellant without the need for additional excipients (Figure 1). These co-suspensions are highly uniform and minimize drug crystal-crystal interaction throughout manufacturing, storage, and drug delivery. They are also stable over time and deliver consistent doses under a variety of storage or handling conditions.

As a result, Pearl can develop products over a broad dose range with major pharmacological classes of inhaled therapeutic agents, without the need to invest in complex devices. It is this novelty, versatility, and universal applicability of Pearl's formulation technology that sets Pearl apart, earning them this year's *Technology Innovation* award.

Pearl's technology innovation has demonstrated several benefits to the clinical development of inhaled medicines. The ease of co-suspension has allowed Pearl to manufacture and test nanogram-dose MDIs, enabling what is believed to be the first complete characterization of the dose-response curve of a potent bronchodilator, glycopyrrolate (GP).

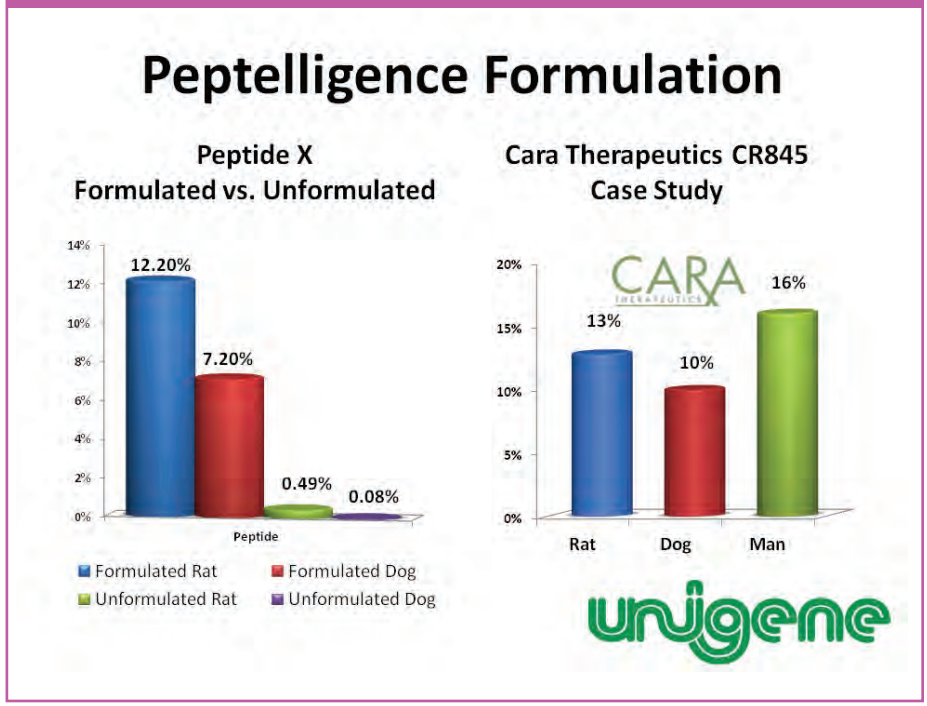
Pearl has conducted similar dose ranging with its lead product candidate, PT003, a dual combination of GP with another highly potent bronchodilator, formoterol fumarate. The dual co-suspension in PT003 has also generated unprecedented dose-ranging data, yielding both optimal and non-effective doses in

Phase II studies, increasing Pearl's confidence in the long-term clinical assessment to be conducted during Phase III. The co-suspension platform has allowed such predictable dose and formulation iteration that Pearl was able to complete 10 Phase I and II studies, and progress their combination bronchodilator, PT003, and its monotherapy components toward Phase III readiness in a remarkable five years from initiation of studies.

In another industry first, the dual co-suspension format was extended in vitro to a triple co-suspension, in which seven different formulations (three monotherapies, three dual subcomponent therapies, and the triple) yielded results that demonstrated formulation-independent delivery of each drug – a task virtually impossible to accomplish with the variety of inhalers currently available.

"The co-suspension platform has enabled Pearl to conduct clinical development at an unprecedented speed and with a sense of predictability that has eluded respiratory product development for decades," said Sarvajna Dwivedi, Pearl's Co-founder and Executive Vice President. "We believe the innovations Pearl scientists have made in respiratory drug delivery have set a new benchmark in the field of pulmonary product development, and will help bring many needed therapies to millions of patients suffering from chronic breathing problems." For more information, visit www.pearltherapeutics.com.

FIGURE 3



ON THE RISE COMPANY

Winner: NanoSmart Pharmaceuticals

This award celebrates industry newcomers, start-ups, and fresh entrants that demonstrate potential to introduce disruptive science in drug delivery. NanoSmart's patented platform drug delivery system (Figure 2) utilizes human-derived antinuclear antibodies that target areas of necrosis present in many different types of solid tumors and other diseases. Combining this tumor-targeting antibody with a lipid nanoparticle results in a drug delivery system that allows NanoSmart to rapidly and economically develop significantly enhanced versions of drugs that are already on the market. NanoSmart is optimizing its preliminary targeted nanoparticle formulations and is currently engaged in preclinical testing of its lead candidate drug products.

The tumor-targeting antibody can be incorporated into many different drug delivery formulations, including liposomes and lipid nanoparticles, creating the potential for a very broad therapeutic drug pipeline. The liposome or lipid nanoparticles protect normal healthy cells from the drugs' harmful side effects, enabling more of the drug to act on the tumor over longer periods of time, while NanoSmart's targeting antibody acts by anchoring the drugs directly at the tumor site.

Reformulating already-proven drugs into NanoSmart's drug delivery platform holds the promise of safer, more effective drugs that can target many different types of tumors. NanoSmart currently focuses on pediatric cancer indications. The company expects market entry of its first products will pave the way toward efficiently expanding its pipeline to other cancers and disease indications, while significantly

increasing the value of its core intellectual property. For more information, visit www.nanosmartpharma.com.

INDUSTRY ACHIEVEMENT

Winner: Unigene Laboratories

The *Drug Delivery Innovation Awards*' equivalent of the MPA's Oscar for Best Picture, this category recognizes the company that has shown best all-around achievement in the drug delivery space throughout the course of the year. It's worth noting that Unigene took last year's DDP Industry Achievement Award for its advancements in the oral delivery of peptides. And the company has had yet another transformational year.

To start, Unigene has solidified an additional seven sponsored oral formulation programs and one licensing agreement for their oral peptide delivery technology, Peptelligence. Adding to the list, Unigene's partner, Cara Therapeutics, announced that it has achieved 16% oral bioavailability in the Phase I trial of its lead peptide compound, CR-845, a kappa opioid receptor agonist.

Tarix Pharmaceuticals, another Unigene partner, announced that they were able to achieve oral bioavailability levels with TXA-127 that were equal to or greater than that achieved by the current subcutaneous formulation. Based on these results, Tarix has entered into a definitive license agreement for the use of Peptelligence.

Unigene also had an extremely positive year with its internal programs. In October, Unigene reported positive clinical data in its Phase II study of oral calcitonin for the prevention of postmenopausal osteoporosis.

"Unigene's Peptelligence technology continues to demonstrate its utility for the oral delivery of a wide variety of molecules," said Nozer Mehta, PhD, CSO, Unigene. "We have recently demonstrated that for smaller, derivatized peptides, the bioavailability can be equivalent to or superior than that achieved with subcutaneous injection. We have also recently demonstrated that Peptelligence can dramatically increase the bioavailability of small molecule drugs with poor solubility or permeability. These advances, as well as our successful clinical studies, further strengthen our position as the industry-leading technology for oral delivery, offering our partner companies a solution to their delivery problems for NCEs, or for expanding the therapeutic indications or life cycle of drugs with a patient-friendly technology that will increase physician and patient compliance." For more information, visit www.unigene.com. ◆

The 18th Annual Drug Delivery Partnerships conference will be held January 27-29, 2014, in Boca Raton, FL. For more information or to submit a nomination for the 2014 Drug Delivery Innovation Awards, please visit www.drugdeliverypartnerships.com or contact DDP's Program Director, Heather King, at HKing@iirusa.com.

BIOGRAPHY

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Therapeutic Focus

Sufentanil NanoTab® Technology: Revolutionizing Patient-Controlled Analgesia

By: Pamela P. Palmer, MD, PhD; Larry G. Hamel; and Badri Dasu, MS

Introduction

Despite advances during recent years, acute pain management, particularly in the hospital setting, remains a pressing challenge and a significant unmet medical need. Up to 75% of surgical patients report inadequate pain relief following surgery, and with more than 30 million inpatient surgical procedures performed annually in the US, millions of patients endure inadequately managed post-surgical pain each year.[1,2] Inadequate treatment of post-surgical pain can lead to decreased mobility, which increases the risks of other medical complications, including deep vein thrombosis.[3] Additionally, severe post-surgical pain is one of the two main predictors for the development of chronic post-surgical pain (CPSP) syndrome.

Intravenous patient-controlled analgesia (IV PCA) is one of the most common methods currently utilized to help control post-surgical pain. IV PCA delivers a dose of pain medicine, typically morphine or hydromorphone, directly into the patient's vein via a programmable pump kept at the patient's bedside. When patients feel pain, they depress a button attached to the pump and receive a dose of medication. A lockout interval is programmed into the pump to reduce the chance of the patient overdosing. Numerous studies throughout the past few decades have demonstrated that allowing patients to control their own post-operative pain medication results in improved analgesic efficacy and patient satisfaction relative to nurse-administered analgesic medication.[5,6] Patient-controlled analgesia is an important aspect of post-operative pain management as evidenced by the millions of patients in the US each year utilizing IV PCA to manage their post-operative pain in the hospital setting.[7] Unfortunately, IV PCA technology is increasingly associated with significant safety concerns, including medication errors due to mis-programming of the pump, analgesic gaps due to issues with IV tubing, potential for infection due to the need for venous access, and adverse drug events due to the side effect profiles of the commonly used opioids.[8-11] According to published literature, IV PCA errors occur an estimated 407 times per 10,000 people treated in the US each year.[7] The most common and serious types of errors involve human factors, such as mis-programming the PCA pump or administering the wrong dose, which can lead to adverse events and even death.[8] In 2002, approximately 5% of operator errors reported to the US FDA resulted in patient deaths.[12]

Recently, the FDA has taken notice. In 2010 it evaluated a broad spectrum of

Figure 1.

infusion pumps across manufacturers and concluded that there are numerous issues with device design, manufacturing, and adverse event reporting. Approximately 56,000 adverse events relating to infusion pumps were reported to the FDA between 2005 and 2009, prompting 70 Class II infusion pump recalls (potential for temporary or reversible adverse effects) and 14 Class I infusion pump recalls (potential for serious injury or death).[13] These issues with infusion pumps have resulted in the issuance of draft guidance by the FDA.[14]

In addition to the complexity of the infusion pump, IV PCA safety concerns extend to the side effects associated with the drugs themselves. Published data on IV PCA side effect profiles show that approximately 50% of patients experience sedation, and oxygen desaturation has been shown to occur in approximately 10% of patients.[15,16] Morphine, still utilized in the majority of post-operative IV PCA cases, has active metabolites, which are eliminated by the kidney and can lead to unanticipated pharmacokinetic-pharmcodynamic effects, such as prolonged duration of action and untoward side effects in patients with decreased renal function.[17-19] Morphine can also produce somnolence, delirium, oxygen desaturation, and respiratory depression.[20] Hydromorphone use in IV PCA has increased recently but has also demonstrated excessive levels of somnolence. In a systematic review of adverse events for opioids used post-operatively, hydromorphone was associated with a 43% incidence of central nervous system (CNS) side effects, mainly sedation.[11] Excessive sedation in the post-operative setting can lead to respiratory depression and can slow post-operative rehabilitation and discharge from the hospital. Further, being tethered to an IV pole when using IV PCA reduces patient mobility, and along with IV-related complications, such as infections or analgesic gaps, can further delay discharge. Complications resulting in delayed discharge are costly; a 2009 study estimated that hospitals incur $1,657 in actual costs per day for inpatient surgical patients.[21]

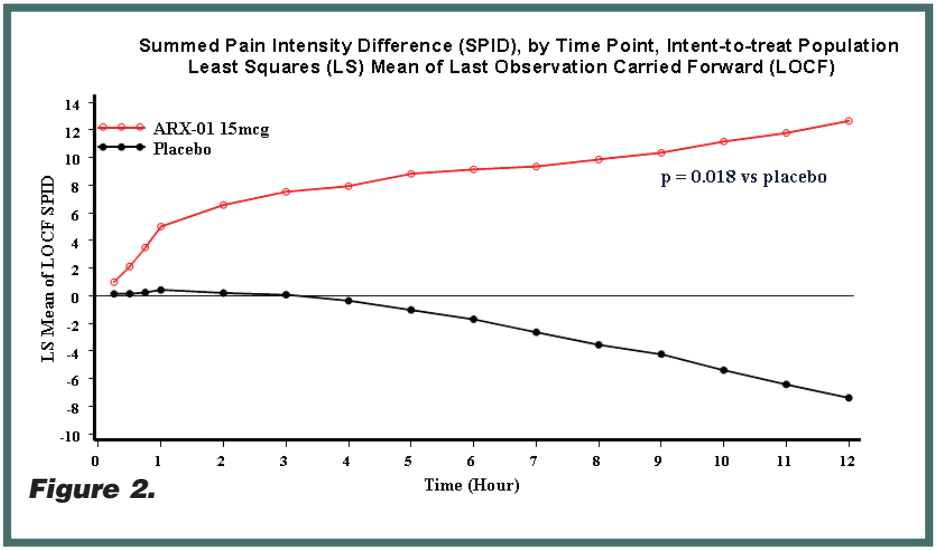

Figure 2.

To mediate these challenges, pain management practices have evolved to reduce the amount of opioid utilized to manage post-operative pain. Adjuvant pain management methods, such as regional anesthetic techniques (e.g., epidurals, spinals, nerve blocks) and non-opioid pain relievers (e.g., acetaminophen and anti-inflammatory drugs), can reduce opioid consumption post-operatively.[22] However, they can also create their own challenges, including increased complexity and additional cost of care, and the potential for additional side effects unique to each adjuvant must be taken into consideration.[23-28] Furthermore, most adjuvant analgesics lack the patient-controlled aspect of post-operative pain management, which has the potential to reduce patient satisfaction.

Patients, nurses, physicians, pharmacists, and hospital systems need a solution that can deliver the benefits of PCA in terms of patient pain relief for moderate to severe pain conditions and satisfaction while reducing both drug and device safety risks. Such a system would also represent an opportunity to reduce the overall complexity of pain management, and hence reduce the cost burden on the healthcare system. AcelRx Pharmaceuticals has developed the Sufentanil NanoTab PCA System to address these specific issues.

Opportunities for Innovation & Improvement – The Triumvirate of Safety

To enable the concept of PCA to reach its true potential for improving care and satisfaction, post-operative patients need effective, rapidly titratable pain relief combined with low risk for adverse events and medication errors. In order to achieve these goals, AcelRx looked at the three fundamental building blocks of PCA: drug, route of administration, and device. Of these, the first and most important consideration is the choice of pain medication.

Opioid	Therapeutic Index
Meperidine	5[1]
Methadone	12[1]
Morphine	71[1]
Hydromorphone	232[2]
Fentanyl	277[1]
Sufentanil	**26,716[1]**

1. Mather, 1995,"Opioids. A Pharmacologist's Delight", page 834
2. Kumar et al, Eur. J. Pharmacol. 597: 39, 2008 (ED_{50}) and Purdue Pharma MSDS, 2009 (LD_{50})

Table 1.

Sufentanil: An Underutilized Opioid

Sufentanil is an opioid that potentially offers multiple pharmacologic advantages over other opioid pain therapies commonly used to manage post-operative pain in the hospital setting. It is commonly understood that sufentanil is 5 to 10 times more potent than fentanyl and lacks active metabolites, thereby minimizing complex pharmacokinetics post-operatively.[29] What is less well known is sufentanil's high therapeutic index (Table 1). Therapeutic index is the ratio of the lethal dose to the effective dose of a drug, which is used as a measure of the relative safety of the drug for a particular treatment. Sufentanil's therapeutic index in preclinical models is approximately 80 times higher than fentanyl and 370 times higher than morphine. From a clinical perspective, published studies demonstrate that sufentanil produces a less-frequent incidence of respiratory depression relative to its analgesic effects compared to other opioids, including morphine, alfentanil, and fentanyl.[17, 30-34]

These pharmacological advantages of sufentanil have the potential to reduce the risk of medication-related side effects, improve patient safety, and provide enhanced pain control. Therefore, sufentanil appears to be an optimal opioid for post-operative PCA. Yet, despite sufentanil's established record of analgesic efficacy and safety, its use as a systemic analgesic has been limited due to its very short duration of action when delivered intravenously. Thus, AcelRx seeks to access sufentanil's potentially improved safety and pain-relieving capability via sublingual delivery to prolong its duration of action.

NanoTab® Technology: Tiny Tablet, Huge Advance

When evaluating the appropriate route of administration for PCA, it is important to consider several criteria. The route must allow patients to dose themselves even if they are unable to take oral medication, must provide a rapid and consistent onset of action, and must be amenable to repeat dosing. Ideally, the route of administration is non-invasive, patient-friendly, and does not restrict patient mobility.

Sufentanil NanoTabs are very small (3-mm diameter), bioadhesive tablets and are formulated to be non-irritating. When placed under the tongue, the Sufentanil NanoTab adheres quickly to the sublingual tissue and is largely undetectable by the patient. Because of its small size, the NanoTab generates very little salivary response - thereby minimizing reflex swallowing of saliva containing dissolved drug - and enables sufentanil to be delivered almost entirely through the sublingual transmucosal route.[35] Sufentanil NanoTabs display highly consistent pharmacokinetics due to this single, highly consistent route of drug uptake, which allows for safe repeat dosing in the post-operative setting.[35]

Due to sufentanil's pharmaceutical attributes, including degree of lipid solubility and ionization, uptake from the sublingual tissues is rapid, and therefore, onset of action is rapid as well - making sufentanil an ideal pain medication for post-operative patients experiencing significant pain.[35,36] In addition, when delivered sublingually, sufentanil avoids the first-pass metabolism and delayed onset of oral medications and avoids the high peak plasma levels and short duration of action of IV administration, enabling patients to dose themselves as necessary to titrate to an analgesic level and maintain a consistent level of pain relief.[35]

The non-invasive nature of the NanoTab is patient-friendly, and removes the opportunity for complications or analgesic gaps associated with IV delivery. Further, patients need not be tethered to an IV pole to manage their pain, enabling greater patient mobility.

In order to further enhance the benefit of NanoTab technology, the Sufentanil NanoTabs have been coupled with a novel PCA delivery system to allow the patient-controlled aspect of post-operative pain management.

The Sufentanil NanoTab PCA System: Delivering Rapid, Reliable Relief

The Sufentanil NanoTab PCA System (Figure 1) is a unique, preprogrammed, hand-held technology system designed to deliver all of the beneficial features of typical IV PCA while leveraging the potential benefits of sufentanil to address the need for rapid and reliable patient-controlled pain management in the hospital setting.

The Sufentanil NanoTab PCA System is preprogrammed with a fixed Sufentanil NanoTab dose of 15 mcg and a fixed 20-minute lockout interval between doses, eliminating the risk of pump programming errors, which are a potential source of patient harm with typical IV PCA technology. The patient wears a radio-frequency identification (RFID) thumb tag, which uniquely identifies that patient to the device and controls access to the medication. An RFID-controlled access card is used by healthcare professionals to set up and access administrative functions on the system. The system is designed to be simple to use for both patients and healthcare professionals, and tracks dosing history to assist in assessing appropriate use and enable enhanced drug reconciliation.

AcelRx completed human factors studies with nurses and a Phase II open-label device functionality study in patients to ensure the design and functionality of the system was easy to use and understand. In the nurse study, nurses were asked to complete a number of tasks and rate the ease of use with the system. After completing all tasks, the nurses gave the system an overall average Ease of Use rating of 4.73 and an overall average Ease of Learning rating of 4.57 using a 5-point scale (1=extremely difficult to 5=extremely easy). All thirty patients (100%) in the Phase II study reported in a questionnaire that they could "handle the system easily and the instructions were clear". Results from these studies demonstrated the Sufentanil NanoTab PCA System is easy to learn and use.[37-39]

Clinical Results to Date

Clinical data to date demonstrate the safety, efficacy, and clinical benefit of Sufentanil NanoTabs. Three Phase II studies of Sufentanil NanoTabs have reported positive clinical results. Two of the Phase II studies were multicenter, double-blind, randomized, placebo-controlled trials, one in patients undergoing elective unilateral knee replacement surgery and the other in patients undergoing major abdominal surgery. The final Phase II study was an open-label Phase II system functionality study of the hand-held component of the Sufentanil NanoTab PCA System in unilateral knee replacement surgery (Figure 2). The primary efficacy endpoint in these studies was the sum of the pain intensity differences at each evaluation time point compared to baseline over the 12-hour study duration (SPID-12). The group treated with Sufentanil NanoTabs 15 mcg showed a statistically significant reduction in pain intensity over the study period ($p < 0.02$ for knee surgery and $p < 0.001$ for abdominal surgery). These studies were conducted with no rescue opioids or adjuvant therapy, demonstrating that the majority of patients were able to effectively manage their post-surgical pain with Sufentanil NanoTabs alone.[40,41]

In these Phase II studies, the average time interval between doses was approximately 80 minutes.[38] This compares favorably to the much shorter redosing interval, which is typical for IV PCA (20 to 40 mins).[42,43] The longer redosing interval observed with Sufentanil NanoTabs not only allows patients to easily manage their pain, but allows for increased periods of mobility or sleep, which could have a positive effect on post-surgical recovery.

In all studies, Sufentanil NanoTabs were well tolerated. Patients dosed with Sufentanil NanoTabs exhibited a low incidence of sedation (3%) and oxygen desaturation (1%) at the 15 mcg dose.[37,40,41] The incidence of these critical adverse events is quite low when compared to a published meta-analysis of post-operative IV PCA-induced side effects, as mentioned earlier.[15,16]

Future Development and Milestones

Based on these positive results, and the unmet medical need for improved patient-controlled analgesia in the post-operative hospital setting, the Sufentanil NanoTab PCA System is currently undergoing Phase III testing. The Phase III program includes two randomized, double-blind, placebo-controlled studies and one open-label active comparator study. Placebo studies include both a major abdominal and a major orthopedic surgery study, while the active comparator study is a non-inferiority study with IV PCA morphine as the comparator in both of these post-surgical populations combined.

Meeting the needs of post-operative patients in pain, and meeting those needs in a safe, effective way, is an imperative for modern healthcare. The technology behind the Sufentanil NanoTab PCA System represents a significant departure from existing therapeutic options and delivery systems, and has the potential to both improve patient care and reduce health system burdens.

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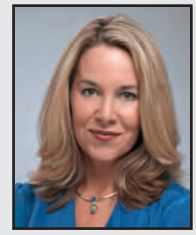

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Dr. Palmer has served as Chief Medical Officer and a Board member of AcelRx since she co-founded the company in July 2005. Dr. Palmer has been on faculty at the University of California, San Francisco since 1996 and is currently a Clinical Professor of Anesthesia and Perioperative Care. Dr. Palmer was Director of UCSF PainCARE-Center for Advanced Research and Education from 2005 to 2009, and was Medical Director of the UCSF Pain Management Center from 1999 to 2005. Dr. Palmer earned her MD from Stanford University and her PhD from the Stanford Department of Neuroscience.

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Executive Summary

Martin Driscoll
CEO
Asmacure, Ltée

Asmacure, Ltée: A New Mechanism for the Treatment for Asthma

Asthma is a chronic disease affecting 8% to 10% of the population. According to the 2010 *Global Strategy for Asthma Management & Prevention, Global Initiative for Asthma (GINA) 2010* report, asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment. Despite the widespread availability of today's treatment options, there is still a significant medical need as a large number of patients' exacerbations are uncontrolled. Many patients receive high doses of medication and therefore become less responsive to their treatment over time. Additionally, many patients require combination therapies to completely manage their asthma symptoms, but some patients are hestitant to take the required doses of these therapies because of the potential negative side effects. Many patients with asthma (approximately 50% in the US) experience only intermittent episodes of exacerbations of their disease. These patients have a "mild" form of the disease and can oftentimes be well-controlled with the intermittent or "as needed" use of an inhaled beta agonist or rescue inhaler. The *Guidelines for the Diagnosis and Management of Asthma*, released by the National Heart, Lung and Blood Institute's (NHLBI) *National Asthma Education and Prevention Program*, define mild asthma as a condition in which the patient has few clinical signs or symptoms of asthma, except for occasional episodes of coughing and wheezing no more than one to two times a week. Unfortunately, a growing population of people with asthma experience persistent, intermittent episodes of significant bronchoconstriction, which is defined by GINA as a "tightening of the muscles that surround the airways." Their disease is a more moderate or severe form. These patients typically require chronic or daily therapies for effective management of their disease. Asmacure Ltée is a biopharmaceutical company based in Québec (QC), Canada, focused on the development of nicotinic receptor agonists for the treatment of asthma and other inflammatory diseases. The company is currently developing a novel, new molecular entity for the treatment of asthma. Asmacure's compound was the first nicotinic receptor agonist in the clinic for this indication. *Specialty Pharma* recently interviewed Martin Driscoll, CEO of Asmacure, to discuss the company's unique, yet practical approach to treating asthma and its core symptoms.

Q: ***Why is there a need for more asthma treatments?***

A: Currently, the main treatments for the chronic management of asthma are fixed-dosed combinations of inhaled corticosteroids (ICS) and long-acting beta agonists (LABAs). These drugs work by providing the dual capabilities of reducing inflammation in the airways and producing bronchodilation in the person with asthma. This makes the airways less sensitive to asthma triggers and allows patients to have better control of their symptoms. Although these fixed-dose combination medications have been shown to be effective for many patients, the chronic

administration of inhaled corticosteroids has been associated with a number of potential negative effects, which can make patients hesitant to use them frequently. Moreover, many patients taking these fixed-dose combination products on a chronic basis often find the need for increasing doses over time and/or the addition of other therapeutic modalities for increased efficacy.

Q: ***What are the most common side effects of inhaled corticosteroids?***

A: The most common side effects of inhaled corticosteroids include oral candidiasis (also known as thrush), dysphonia, bronchospasm, poor growth in children, easy bruising, and decreased bone density. Patients taking higher doses of corticosteroids have an increased risk for these side effects. Asmacure's lead product, ASM-024, acts by a different mechanism than the current standard of care for the chronic maintenance treatment of asthma, which are fixed-dose combination medications. ASM-024 is a nicotinic acetylcholine receptor agonist for the treatment of asthma. Preclinical studies of ASM-024 have indicated the compound may provide the dual clinical capabilities of an anti-inflammatory and bronchodilator in a single entity compound. If these potential dual capabilities of ASM-024 are demonstrated safely and effectively in clinical trials and ultimately approved by regulatory authorities, ASM-024 could be the first treatment for asthma that combines the effects of an anti-inflammatory agent with bronchodilation in a single-entity compound and perhaps avoid the potential negative effects of the inhaled corticosteroids and long-acting beta agonists.

Q: ***How is Asmacure's lead product, ASM-024, expected to compare to other asthma treatments currently on the market?***

A: Asmacure's scientific approach of using nicotinic receptor agonists for the treatment of inflammatory diseases originated from the very early clinical observation that smokers have a lower incidence of several inflammatory respiratory diseases. Extensive research by Asmacure has demonstrated that activation at the nicotinic receptor sites has a marked inhibitory effect on lung inflammation.

Nicotinic receptor agonists have been seen to have anti-inflammatory properties and in some instances, smooth muscle-relaxing effects. Because inflammation and smooth muscle contraction in the airway are the two major components of asthma, nicotinic receptor agonists have the potential to offer asthma sufferers a unique new treatment modality for their disease.

Q: ***If ASM-024 has the anti-inflammatory properties of nicotine, does it have the addictive properties as well?***

A: Because nicotine is addictive and presents a very limited therapeutic potential, it has not been used in any existing asthma tretaments. However, ASM-024 has been specially designed not to cross the blood brain barrier; therefore, it has not been shown thus far to be associated with the same addictive properties as nicotine. ASM-024 contains dimethylphenylpiperazinium (DMPP), one of the numerous nicotinic agonists from natural and synthetic sources commercially available, which is not expected to cross the blood brain barrier and thus not expected to have addictive properties.

Q: ***Is there clinical data that suggests ASM-024 is safe and effective?***

A: ASM-024 has demonstrated activity in preclinical in vitro, ex vivo and in vivo models of inflammation and/or asthma, including in mice, dogs, and human cells and pulmonary tissue. In preclinical studies, ASM-024 demonstrated dual properties in a single entity for the treatment of asthma. The compound was shown to act both as an anti-inflammatory and a bronchodilator.

Utilizing a novel mechanism-of-action, ASM-024 has been tested to date in 99 healthy volunteers in two successful Phase I clinical studies. ASM-024 is currently undergoing

two proof-of-concept Phase II studies. These studies are being conducted in patients with both mild and moderate asthma to assess the anti-inflammatory, bronchodilating, and bronchoprotective properties of ASM-024 administered by inhalation. Phase II results are expected to be announced during the fourth quarter of 2011.

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

A: Currently, Symbicort® and Advair® are the major fixed-dose combination medications available in the US for the treatment of asthma. Both of these drugs combine a corticosteroid and long-acting bronchodilator into one inhaled medication to chronically manage the asthma patient's disease. ASM-024 was the first nicotinic receptor agonist to enter the clinic for study as a treatment for asthma. It has not been reported to date whether other nicotinic receptor agonists in development have demonstrated preclinically the dual capabilities of anti-inflammatory properties and bronchodilation.

Q: ***What would you say to people who are experiencing the symptoms of asthma and may not be happy with their current treatment?***

A: Those who currently have asthma, or who have friends or family with asthma, should keep themselves updated on new research developments in this area, such as ASM-024. Many new therapies are in clinical development and could one day provide better asthma relief with fewer adverse effects. Although there is currently no definite date for bringing ASM-024 to market, Asmacure is looking forward to advancing this compound further through clinical development as there are a large number of asthma patients with uncontrolled symptoms who may benefit from treatment modalities that are active at different targets.

Q: ***Can you tell us more about yourself and how you came to be the CEO of Asmacure?***

A: I have had the opportunity to work in the wonderful industry of pharmaceuticals for more than 30 years. My experience in the pharmaceutical industry has included senior roles in general management, commercial operations, and business development for both privately held and publicly traded life science companies.

Prior to being elected CEO of Asmacure, I was CEO and a Director of Javelin Pharmaceuticals, Inc., a publicly traded company focused on the development of acute care pain products, from March 2008 until July 2010, at which point I led the successful merger of the company with Hospira, Inc. Prior to my role with Javelin, I held senior managerial roles at Schering-Plough Corporation, ViroPharma, Inc., and Reliant Pharmaceuticals. During my tenure at Schering-Plough, I spent a significant amount of time as General Manager of Key Pharmaceuticals, the Schering unit responsible for all respiratory products marketed in the US.

Asmacure was founded in 2002 by Co-Founders Yvon Cormier, MD, an internationally recognized pulmonologist, and the company's current Chief Medical Officer and immunology and inflammation expert Evelyne Israël Assayag, MSc. I was appointed CEO of Asmacure in April 2011 to use my experience in the biopharmaceutical industry to advance the clinical development of the company's nicotinic receptor-based programs.

I'm delighted to have joined a unique development company with such novel proprietary technology that has the potential to meet significant unmet medical needs and enhance current clinical practice. The science that has been developed by the team at Asmacure is truly impressive. I look forward to closely working with the talented Asmacure team as we lead the company through this exciting time of development and growth. ■

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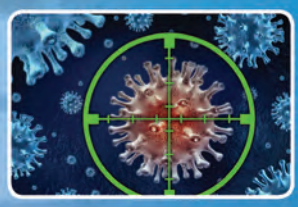

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