Drug Development & Delivery

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Analytical Instruments: Addressing Pharma's Needs

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

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Lessons Learned

"Spin-offs can make shareholders very wealthy through arbitrage. Arbitrage is what made Warren Buffet the worldwide phenomena he is today. If you remove his arbitrage investments, Warren Buffet earned a formidable 27% on 202 investments between 1980 and 2003. But he earned 81% on just 59 investments, all of which were arbitrage investments. These raised his performance to 39% and left every other American investment institution cleaning his dust out of their teeth."

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Demands, Innovations & Savings

"There is a global demand for analytical instruments, and industry players are responding with product innovations. Despite the economic slowdown, end-user spending in the US analytical instrument market is expected to increase from $6.6 billion in 2011 to $ 7.3 billion by 2014."

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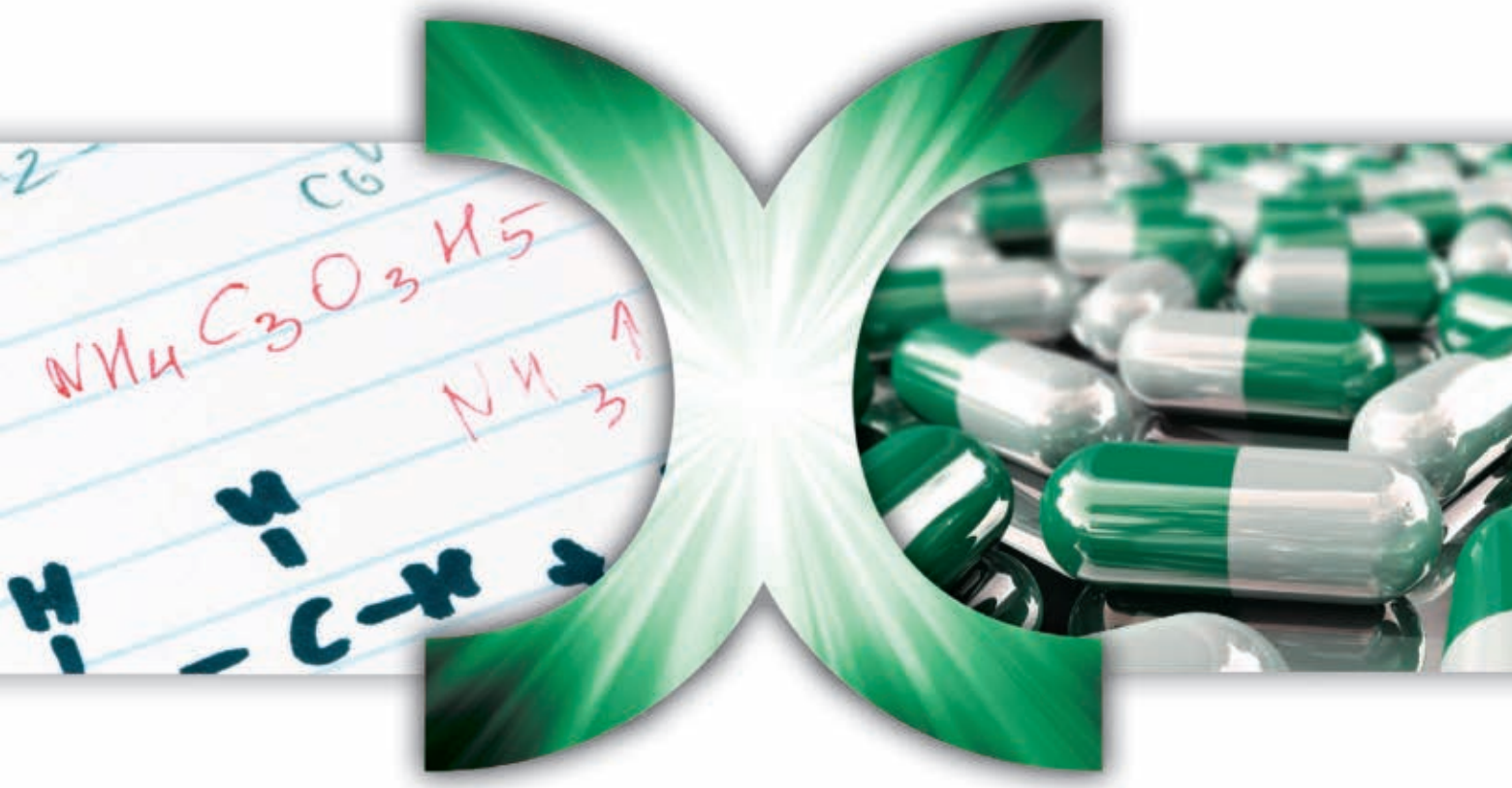

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Curis & Debiopharm Announce Initiation of Phase Ib Expansion Study

Curis, Inc. and Debiopharm Group recently announced that Debiopharm has begun treating patients in a Phase Ib clinical trial of Heat Shock Protein 90 (HSP90) inhibitor Debio 0932. Debiopharm recently successfully completed a Phase Ia dose escalation study with Debio 0932 and has indicated that it expects to initiate a combination Phase I/II study in non-small cell lung cancer patients in the second quarter of 2012.

"Our team has been very pleased with the development of Debio 0932, which has become an important molecule in Debiopharm's pipeline," said Rolland-Yves Mauvernay, President and Founder of Debiopharm Group. "We believe HSP90 represents an important molecular target in cancer therapy, and we are eager to advance this molecule in the Phase Ib clinical trial, as well in our planned Phase I/II studies, which we hope will yield important new data for the further development of Debio 0932."

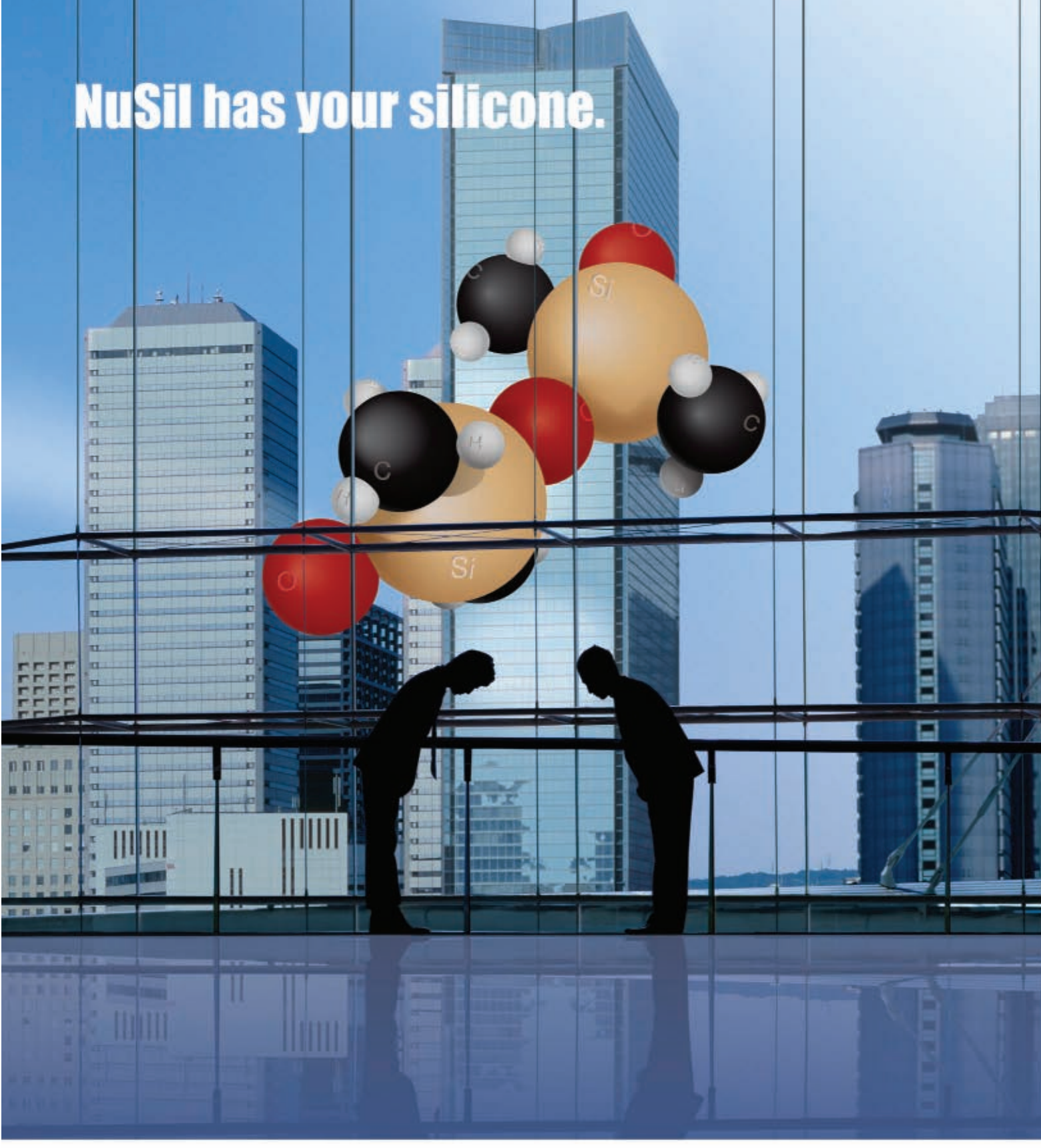
"We have been highly impressed with the depth of Debiopharm's development expertise and commitment to furthering Debio 0932 into additional clinical studies in 2012," added Dan Passeri, Curis President and CEO. "Importantly, we continue to be very pleased with the clinical results that have been observed to-date, and we look forward to reporting further progress on this molecule in the future."

Debiopharm initiated a Phase I clinical trial in April 2010 that was designed to evaluate the maximum tolerated dose and safety of Debio 0932. The first part of the study (Phase Ia), an open-label, multi-center dose escalation trial evaluating the safety and tolerability of escalating multiple dose levels of Debio 0932 given daily or every other day as a single agent by oral administration in patients suffering from advanced solid tumors, was recently completed.

Debio 0932 was generally well tolerated, with no evidence of ocular or liver toxicity, and showed promising signs of efficacy in patients with advanced solid tumors. The recommended dose, established at 1000 mg every day, will be tested in additional patients during the expansion phase (Phase Ib) of the ongoing Phase I study.

Debiopharm expects to treat approximately 30 patients as part of the Phase Ib expansion study. The objectives of this study will be to further assess the safety profile, pharmacokinetics, and pharmacodynamics of Debio 0932 at the recommended dose level and regimen, and to further assess anti-tumor activity in patients with advanced solid tumors, including patients with non-small cell lung cancer.

Debio 0932 is a novel heat shock protein 90 (HSP90) inhibitor with strong affinity for HSP90 alpha/beta, high oral bioavailability, and potent anti-proliferative activity against a broad range of cancer cell lines (with a mean IC50 of 220 nmol/L), including many non-small cell lung cancer (NSCLC) cell lines that are resistant to standard-of-care agents. Debio 0932 potently inhibits tumor growth in subcutaneous xenograft models of a number of solid and hematological malignancies, including models of NSCLC, which harbor mutations conferring acquired or primary erlotinib resistance. Furthermore, Debio 0932 is able to extend animal survival in models of brain metastasis due to its ability to cross the blood-brain barrier, and it enhances the activity of several standard-of-care agents in animal models of cancer.



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Catalent Pharma Solutions & NewMarket Sign Development Agreement

Catalent Pharma Solutions and NewMarket Pharmaceuticals LLC recently announced they have entered into an agreement to jointly formulate and develop a portfolio of products for treating production and companion animals using Catalent's proprietary, market-leading Zydis fast-dissolve technology and NewMarket's DSI platform (Direct Systemic Introduction, patent pending).

NewMarket Pharmaceuticals is currently developing five drugs that will combine Catalent's Zydis fast-dissolve and their own DSI technologies, initially including NSAIDs, beta agonists, proton pump inhibitors, and behavior modifiers across a variety of species, including horses, dogs, and cattle, with plans to expand the range in other classes. These new animal health products are expected to provide significant advantages over existing formulations currently used across a spectrum of indications for companion animals, equine, and production animals.

"These easy-to-use formulations could revolutionize the way we treat animals by providing for a simple, efficient, accurate method of treatment without the use of needles," said Mark Ridall, CEO of NewMarket Pharmaceuticals.

"This partnership with NewMarket Pharmaceuticals demonstrates not only our commitment to provide more products and better treatments to our customers, but also signifies the versatile benefits that our Zydis fast-dissolve technology continues to deliver," added Paul Jenkins, Global VP of Catalent's ODT business.

From drug and biologic development services to delivery technologies to supply solutions, Catalent Pharma Solutions has the deepest expertise, the broadest offerings, and the most unique technologies in the industry. With over 75 years of experience, Catalent helps customers get more molecules to market faster, enhance product performance, and provide superior, reliable manufacturing and packaging solutions.

NewMarket Pharmaceuticals was founded with the purpose of modernizing drug delivery systems for the treatment of animals. The company has identified a means by which established drugs that have proven safety and efficacy profiles, but exist in outdated or inefficient delivery systems, can be reformulated and administered to animals in a faster, safer, easier, and more accurate manner that has the potential to significantly expand the market for these drugs.

CHEMO & Particle Sciences Partner to Provide the Only Development-to-Commercialization Solution

Particle Sciences Inc. and CHEMO recently announced they have formed a partnership to offer complete contract product development and commercial manufacturing of hormone-eluting devices. Particle Sciences is a world leader in the formulation, testing, and scale-up drug/device combinations and has been working with CHEMO for several years on a number of hormone-based polymeric combination products.

"In our work with CHEMO and others, it became clear there was no complete solution for companies wishing to develop and commercialize hormone-based combination products," said Mark Mitchnick, CEO of Particle Sciences. "CHEMO is basic in many hormones, a well-respected global supplier, and has strong global marketing capabilities in WHC. Particle Sciences has the intellectual property, infrastructure, and development capabilities to rapidly get such products into the clinic. By combining our efforts, CHEMO and Particle Sciences now offer the only complete solution for combination product development. CHEMO has proven to be an excellent partner, and this is consistent with our business model of making sure our clients are positioned in the best possible competitive situation, in this case, by providing a rapid, cost-efficient path to commercialization."

Under the agreement, the two companies will leverage each other's strengths to provide a start-to-finish contract solution for those looking to develop and market hormone-eluting devices. Particle Sciences will execute the development work, establishing design, performance, scale-up parameters, analytic and QC methods, and producing clinical trial materials in their cGMP facility. CHEMO will assume production and fulfillment roles in mid-to-late clinical testing and through to commercialization. The companies are already successfully working on several products under this model with the first ones having already entered the clinic last year.

"Particle Sciences has a top-tier technical team and an excellent facility," said Lucas Sigman, CEO of Chemo's US subsidiary. "This relationship is yet another step in CHEMO's global technology-based expansion. As an API supplier and FDF manufacturer, bringing in hormone-based combination product capabilities is a natural step and one that we are very enthusiastic about."

Sandoz Buys Rights to Apricus Biosciences' Drug for $28 Million

Apricus Biosciences, Inc. recently announced its wholly owned subsidiary NexMed, Inc. has signed with Sandoz, a division of Novartis, an exclusive collaboration for Germany to market Apricus Bio's Vitaros drug for the treatment of erectile dysfunction. Pursuant to the collaboration, Sandoz will pay Apricus Bio up to EURO21 million - divided into a fixed up-front payment and specific regulatory and commercial milestones - as well as, double digit royalties on net sales. Total up-front and milestone payments represent approximately $28 million based on today's exchange rate.

"We are very excited about this major European collaboration with such an important international pharmaceutical company as Sandoz," said Bassam Damaj, Chairman, President, and CEO of Apricus Bio commented. "We are happy to work again with Novartis through their division Sandoz, and we look forward to expanding the reach of our Vitaros product for erectile dysfunction in Germany. This is yet another important milestone in our strategy to make Vitaros available worldwide and the successful continuation of the execution of our commercialization strategy of Vitaros."

The ED market in Europe is presently dominated by oral PDE5 treatments. However, there is still a need for new, safe, and effective treatments, especially for those patients who cannot or do not respond well to oral medication. Vitaros differs from oral PDE5 drugs like Viagra, Cialis, and Levitra in two ways. First, it is applied directly to the penis as a cream, instead of as a pill that is absorbed systemically. The topical application helps to reduce side effects and enables men who cannot take, or do not do well with the existing drugs, to have a patient-friendly alternative.

Second, Vitaros operates by a different biochemical mechanism than oral ED medications and causes erections to occur in a more localized fashion and more quickly when compared to oral treatments. Vitaros contains a previously known compound, with the chemical name alprostadil. When absorbed through the skin, alprostadil, a vasodilator, directly boosts blood flow, thereby causing an erection. Clinical studies have shown that Vitaros works on average in approximately 15 minutes, compared to a reported onset time of 30 minutes or more for oral medications indicated for the treatment of ED. The side effects reported were localized and transient.

Alprostadil is currently marketed as an injectable drug. Apricus Bio incorporated alprostadil with its NexACT delivery technology, resulting in a rapid and efficient topical delivery of the drug into the penis. In clinical studies, Vitaros worked in patients suffering from mild-to-severe ED, including men who did not respond to Viagra.

DARA BioSciences Signs Exclusive Agreement With Uman Pharma

DARA BioSciences, Inc. recently announced it entered into an exclusive US agreement with Uman Pharma Inc. for commercial rights to gemcitabine, DARA's second newly licensed anticancer agent. In 2010, gemcitabine generated branded (GEMZAR-Eli Lilly) sales of $780 million, according to IMS data. It went off patent in 2011 in the US, and a year earlier in Europe. The drug is widely prescribed as first-line therapy for ovarian, breast, lung, and pancreatic cancers.

"The exclusive agreement with Uman Pharma for rights to commercialize this chemotherapeutic drug in the US leverages DARA's existing cancer drug development program, provides DARA with an additional commercial opportunity, and further establishes a platform for adding other cancer and cancer-support products through ongoing licensing efforts We believe there is considerable upside potential in the generic, sterile injectable cytotoxic therapies market," said David J. Drutz, MD, DARA's President and CEO.

Last month, DARA acquired exclusive US rights to market Soltamox (licensed from Rosemont Pharmaceuticals Ltd.), the only oral liquid formulation of tamoxifen for breast cancer patients who have difficulty swallowing tablet formulations or simply prefer a liquid form of the widely prescribed hormone blocking therapy. DARA is targeting strategic oncology therapies and supportive care products as part of its strategic direction in the cancer market.

By partnering with Uman, a fully integrated pharmaceutical company, DARA has aligned itself with a company that has the expertise and capability to provide cGMP-produced products for worldwide markets. DARA and Uman are working to identify future partnership opportunities for additional sterile injectable products in the oncology market. Uman plans to file an ANDA for gemcitabine with the US FDA later this year.

Bend Research Signs License Agreement With Eli Lilly & Company

Bend Research Inc., a leading independent drug formulation development and manufacturing company, recently announced it has entered into a licensing agreement with Eli Lilly and Company. Under the terms of the agreement, Bend Research will make its proprietary spray-dried dispersion (SDD) technology available to Lilly. This technology, which improves the bioavailability of compounds with low aqueous solubility, has been applied successfully to hundreds of compounds at various stages of development, from preclinical studies to Phase III clinical trials. Lilly formulators and scientists will also have broad access to Bend Research's portfolio of other drug delivery technologies.

In addition, as part of an already existing agreement with Lilly, Bend Research will continue to provide formulation, development, analytical, engineering, and manufacturing services to Lilly to support its preclinical and clinical development programs.

"This expansion in our relationship with Lilly is a great milestone for us," said Rod Ray, Chief Executive Officer of Bend Research. "Our teams work well together and have a shared commitment to bring the best new medicines to caregivers and patients. We believe this collaboration will add significant value to Lilly's research efforts and help them advance their compounds more quickly and efficiently."

Bend Research provides formulation and dosage-form support, assists in process development and optimization, manufactures clinical-trial quantities of drug candidates in its cGMP facilities, and advances promising drug candidates from conception through commercialization. Bend Research is a leader in novel formulations, including SDDs and hot-melt extrusions, and controlled-release, inhalation, and biotherapeutics technologies.

Daiichi Sankyo Seeks to Acquire Three Indian Pharma Firms

Daiichi Sankyo, which in 2008 acquired Ranbaxy, is in takeover talks with at least three mid-sized Indian pharmaceutical companies. Daiichi Sankyo has appointed IMS Consulting Services for the talks and is seeking companies with an annual turnover of Rs300-500 crore that have drugs for treating diabetes, rheumatology, and women's healthcare.

Tokyo-based Daiichi made its last acquisition in April 2011, when it spent $935 million to purchase Berkeley, California-based cancer drug firm Plexxikon in order to step up its presence in the oncology market. However, its biggest acquisition to date is the 2008 purchase of a majority stake in generic drug company Ranbaxy Laboratories, for around $4.6 billion.

Formed through the 2006 merger between Daiichi and Sankyo pharmaceutical companies, Daiichi Sankyo expanded its generic drug business by establishing Daiichi Sankyo Espha Co in 2010.

Alize Pharma Licenses ASPAREC Therapy for ALL to EUSA Pharma

Alize Pharma II, recently announced the signing of a licensing agreement with EUSA Pharma for ASPAREC, a new L-asparaginase product currently in Phase I clinical development for the treatment of acute lymphoblastic leukemia (ALL).

Pursuant to the agreement, EUSA Pharma will be responsible for the development and worldwide commercialization of ASPAREC. In return, Alize Pharma has received an up-front payment and will be entitled to additional regulatory milestone payments and royalties on sales. The companies have not disclosed further financial information.

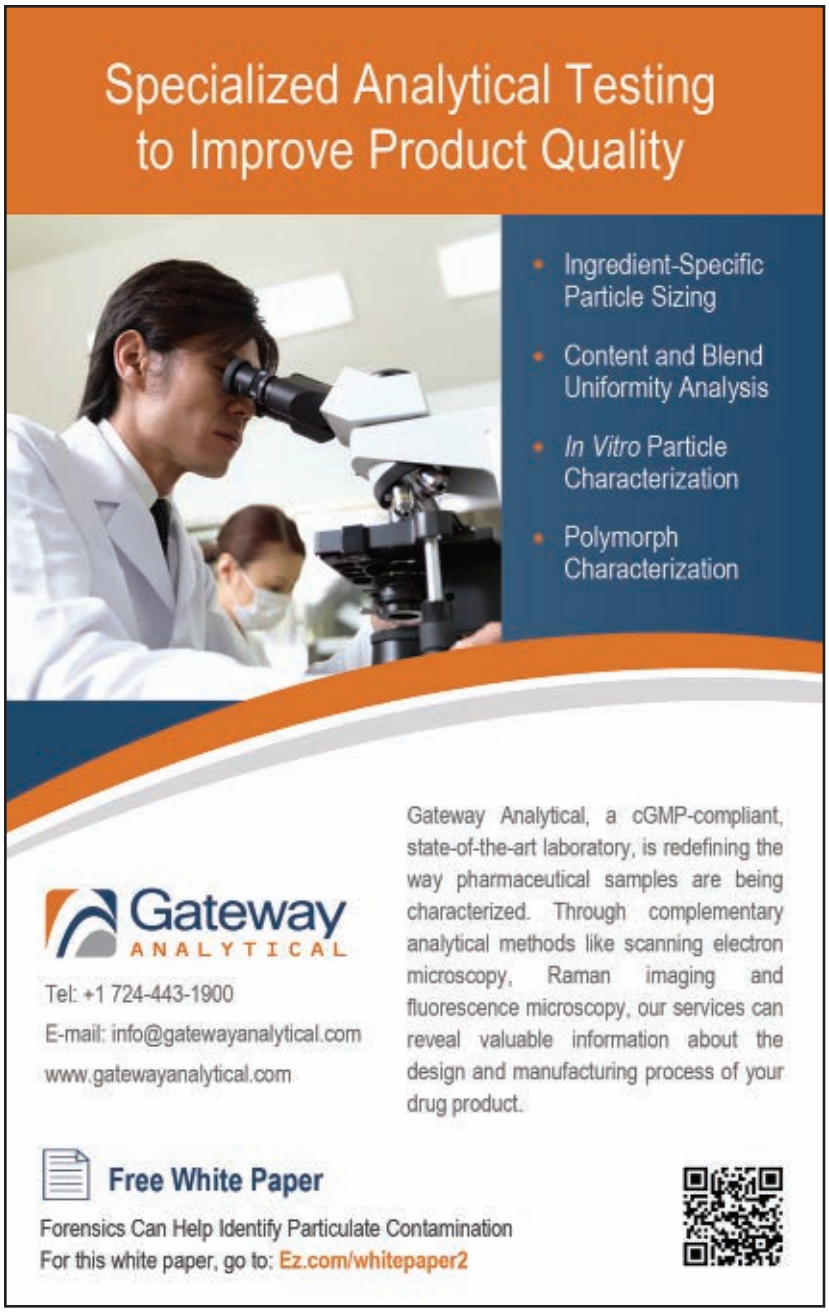
ASPAREC is Alize Pharma's PEGylated recombinant L-asparaginase derived from Erwinia chrysanthemi. It is being developed as a treatment for ALL in patients with hypersensitivity to E. coli-derived L-asparaginase. Preclinical data indicate that ASPAREC is both longer acting and less immunogenic than the currently available Erwinia chrysanthemi-derived L-asparaginase product.

"This agreement between Alize Pharma and EUSA Pharma, a worldwide leader in the development and marketing of L-asparaginase products, is excellent news for us, for our investors, and for ALL patients," said Alize Pharma's President and Founder, Thierry Abribat. "It validates our medical approach, emphasizes our drug development capabilities, and fits well with our business strategy, which is to establish partnerships with the pharmaceutical industry early in the development of our programs in order to secure both near-term and long-term revenue streams."

"We are delighted to reach this agreement with Alize Pharma. ASPAREC fits perfectly with EUSA's specialty focus on oncology and orphan diseases and builds on our established portfolio in the field of acute lymphoblastic leukemia," added Bryan Morton, President and CEO of EUSA Pharma. "This agreement follows the approval last year of EUSA's first internally developed product and further underlines the company's strategic transition into a fully fledged development as well as commercialization organization."

Alize Pharma is a group of companies specialized in the development of innovative biopharmaceutical drugs, proteins, and peptides for the treatment of metabolic diseases and cancer. Its management is made up of a team of drug development experts and a board of directors offering wide international experience.

EUSA Pharma is a rapidly growing transatlantic specialty pharmaceutical company focused on oncology, oncology supportive care, and critical care products. The company has an established commercial infrastructure in the US, a pan-European presence, and a wider distribution network in numerous additional territories.



Comparitive Analysis

A Spate of Spin-Offs

Part 1 of a 6-part series on lessons learned from other industries.

By: Derek Hennecke, President & CEO Xcelience LLC

Breaking up is hard to do, unless you happen to be a major conglomeration. Last year, Expedia spun off Trip Advisor, ConocoPhillips announced it would let go of its refineries, Kraft said it's looking to dump snack foods, and McGraw-Hill pledged to split off educational books.

There may be Sixty Ways to leave your Large Organization, but only two are common. Getting sold is one. When the parent organization sells a unit or division, it collects proceeds that it can use to pay off debt, buy back stock, re-invest in equipment or technology, or acquire new companies.

But none of the break-ups I just listed involved sales. They are spin-offs. A spin-off is different from selling a division or unit. In a spin-off, no money is exchanged. The parent company and the smaller company just shake hands and go their separate ways. Sound like a bum deal for the parent organization? It depends on your objective. Parent organizations are made up of shareholders, and spin-offs can make shareholders a lot of money. For one thing, shareholders don't pay taxes on a spin-off, unlike a sale of a division. This is one of the reasons they're so popular today.

The year 2011 produced a bumper crop of spin-offs. As of December 2011, there were 76 completed spin-offs last year, up from 50 in 2010, according to Dealogic. In addition, the value of the deals was bigger, reaching $115.9 billion in completed spin-offs,

which was more than double the previous year.

Spin-offs can make shareholders very wealthy through arbitrage. Arbitrage is what made Warren Buffet the worldwide phenomena he is today. If you remove his arbitrage investments, Warren Buffet earned a formidable 27% on 202 investments between 1980 and 2003. But he earned 81% on just 59 investments, all of which were arbitrage investments. These raised his performance to 39% and left every other American investment institution cleaning his dust out of their teeth.

What is arbitrage? Arbitrage is a trading strategy. When a large conglomerate holds within it a smaller, money-making jewel, the value of the little company is often suppressed by the weight of the more mediocre-performing companies in the group. The parent can decide to unlock the smaller company's value by selling it off. When it does, the new company's true sparkle often doesn't become apparent to public investors until it trades on its own. Then it takes off.

Using one of Buffet's examples, here's how it can work. When Dun & Bradstreet announced the spin-off of Moody's in 2000, Buffet saw a diamond in the rough. He increased his position in Dun & Bradstreet to 24 million shares. On the day of the spin-off, his shares transformed and he owned 24 million shares in Dun & Bradstreet and 12 million in Moody's; all valued at $21/share. The Moody's shares rocketed out of the gate. He gradually sold off his Dun &Bradstreet shares, but he hung on to his Moody's stock, which split 2 for 1 in 2005. When he finally sold in 2010, he earned a pre-split equivalent of $60/share. This is arbitrage at its finest.

Not all spin-offs are diamonds in the rough, however. Sometimes companies are spun off not to unlock their hidden value, but to reduce the parent company's debt. The parent organization may even load the offspring up with debt before cutting it loose, in the hope of improving the larger organization's balance sheet. To understand the motivations behind a spin-off, you have to dig a little deeper.

These things are important to understand as the wave of spin-offs buffets our own industry. Abbott, Pfizer, and Covidien (itself a spin-off of Tyco) are all contemplating divestures.

Spin-offs are certainly not new to our industry: think Merck and Medco; Eli Lilly and Guidant; Abbott Labs and Hospira; and Bristol-Myers Squibb and both Zimmer and Mead Johnson. Sometimes they're good for both parent and offspring, sometimes not.

In our industry, spin-offs are particularly vulnerable because they lay another level of uncertainty onto the already fickle fortunes of all who rely on the drug development pipeline. Let's take a closer look at three industry spinoffs.

THE ABBOTT SPINOFF: DIAMOND IN THE ROUGH OR LUMP OF COAL?

Abbott Laboratories has announced it will spin its research-based pharma services off. The new publicly traded company will offer the market a portfolio of existing medications, such as Humira and Synthroid, along with a pipeline of some 20 compounds in Phase II or III development to treat immunology, chronic kidney disease, hepatitis C, oncology, and neuroscience. Based on 2011 estimates, the operation should have nearly $18 billion in sales.

The parent company will be free to focus on "diversified medical products," including branded generics outside the US; nutritionals, lab diagnostics, and medical devices. Abbott expects these will be high-growth products in more than 130 countries and represent about 40% of sales in emerging markets. The company predicts $22 billion in sales this year based on 2011 estimates.

Is this spin-off a hidden gem or a lump of coal? It's difficult to divine the spin-off's future finances because few investment institutions follow the economics of individual businesses hidden within the larger company.

But here's where I would start. As Deep Throat said, "follow the money." When a conglomeration spins off a beloved asset, company executives will tend to follow the company with the more promising prospects. Management knows where the value is.

On this note, I find it interesting that Abbott CEO Miles White will remain Chairman and CEO of the parent company. Richard Gonzalez, currently Executive VP of Global Pharmaceuticals, will be Chairman and CEO of the pharma spin-off.

THE PFIZER CORPORATE WEIGHT LOSS PROGRAM: CAN YOU LOSE TOO MUCH?

After years of gorging on major acquisitions like Warner-Lambert, Pharmacia, and Wyeth, Pfizer is now considering a new prescription for losing weight. Having already sold Capsugel to private equity company KKR for $2.4 billion last year, the drugmaker is said to be considering the spin-off or sale of all four non-pharma units, including nutritionals, consumer health, and animal health.

Being too big can be a bureaucratic nightmare, but as Pfizer well knows, slimming down is not necessarily without side effects either, particularly in the volatile and often unpredictable drug development business. While focusing on pharma may sound strategically coherent, it's the non-pharma side of the business that provides bread and butter in those years when the drug development pipeline fails to produce according to expectations. Pfizer of all companies should know this, having suffered a great deal from the whims of formulation's fortunes in the past decade, despite its current promising late-stage pipeline.

From a credit perspective, it's risky for pharma companies to sell off assets of either kind, pharma or non-pharma, unless the cash generated is being used to repay debt, or the businesses being sold are underperforming or taking too much management attention, according to Michael Levesque, a Senior VP at Moody's Investor Service. But reducing non-pharma assets means Pfizer is tipping the scale toward its pharma assets with their inherently higher patent risk, R&D risk, and litigation threats.

Bristol-Myers Squibb did the same thing, according to Levesque. Throughout the past 3 years, Bristol-Myers sold its medical-imaging unit, the ConvaTec medical devices business, and then sold and split-off its Mead-Johnson nutritionals business.

The medical-imaging unit was in fact a weak link, struggling under the weight of a key patent expiration, but ConvaTec and Mead-Johnson were solid, dependable income generators. As a result, come 2010, Bristol-Myers found that its top five brand-name meds represented 68% of sales. From a credit perspective, that's a lot of pills in just one bottle.

Granted, Bristol-Myers hung onto its A2 credit rating, but no thanks to the divestures. The management saved the company's rating by reducing debt through a bond tender offer and making smaller purchases to diversify. Lady luck may have played a role too as the pipeline

SIDEBAR

State of the Industry: Waiting for Lift Off

The general consensus seems to be that 2012 will be a lot like 2011 for the industry, but it won't feel as hard. The industry spent 2011 in the airport waiting lounge, hopeful but uncertain, waiting for the plane. Unfortunately, 2012 will be spent on the runway taxiing, but at least we know we're going to get somewhere. If you've brought your iPad or your laptop, you'll be fine. In 2013, that's when we'll see lift off: lots of small molecules will rendezvous with a recession-shrunk CRO industry, and demand in our industry will explode. I like to look to venture capital for the pulse of the industry, and Bruce Booth of Atlas Venture, a firm that funds emerging life science companies, posted a balanced but optimistic outlook for the industry in 2012 in his January blog of Life Sci VC. On the plus side, he referred to the great momentum generated by lots of deals with great multiples in 2011, including B-raf at Plexxikon, PI3Kd at Calistoga, LPA at Amira, dual PI3K/mTor at Intellikine, oncolytic viruses at BioVex, and Astofase Alfa at Enobia. He expects this trend to accelerate in 2012. Mr. Booth notes that venture capital flows into the life sciences were up 8% in 2011 over 2010, which he says bodes well for the availability of capital in the coming year. But what I find most exciting is the deal flow of 2011, when nearly 100 new biotech start-ups were seed or first round financed in the US; more than were created in 2009 and 2010 combined. He describes this volume as, “as good as it's ever been,” and expects more of the same ahead. Countering these and other positives for 2012, Mr. Booth notes a lack of excitement around early stage biotech IPOs. Lots of seeds are great, but not if they have no fertile soil to fund them. For big pharma, this is great news. Their pickings just got better. For biotech, it's mixed news; on the one hand, the chances of getting that Big Deal from Big Pharma just went from dim to dimmer. On the other, Big Pharma pays Big Money, as witnessed by the $2 billion Bristol Meyers just paid for Inhibitex. Deals like this will go a long way toward encouraging venture capital to invest in promising preclinical programs and not feel the need to carry them all the way to launch. Finally, call me a pessimist, but it comes as no surprise that government isn't showing any signs of making our lives easier soon; at least not as far as regulatory approval or reimbursement is concerned. FDA uncertainty has made many companies put obesity and diabetes on the back burner. Booth and others have said that the ALTITUDE failure of aliskerin can only mean even bigger pre-approval studies are around the corner. All of these factors will drag on us even as we prepare for blue skies ahead.

delivered above expectations.

It's companies like Johnson & Johnson that banks tend to favor, with its diversified, three-legged approach - drugs, devices, and consumer health items. The consumer health items have proven a rather crooked leg of late, but the matter seems to be straightening out now.

The banks are likely to be nervous about Pfizer's spin-offs from a risk perspective. They might be happy if the divestures raised cash that was used to pay down debt. Unfortunately, unlike the sale of Capsugel, the spin-offs will not raise any proceeds for the company to use to pay down debt. Not that Pfizer would have done so anyway; at least some of the money from the sale of Capsugel went directly to increase incremental stock buybacks. Not what the banks wanted to hear.

COVIDIEN: A CHIP OFF THE OLD SPLINTER

While diversified companies are more stable and less risky, let's be clear: the union of divisions is a marriage of convenience. If one of the divisions is consistently dragging on the other, it has to end. So it is with the unhappy alliance of pharma and medical devices in Covidien.

"The pharma division has been a drag on the company's top-line growth rate," says Joanne Weunsch, an Analyst with BMO Capital Markets, in the Bloomberg report. A spin-off "should provide a relief to the overhang and questions that have dogged this division."

Covidien, itself a splinter of the massive Tyco conglomerate, tried and failed to find a buyer for its pharma division, leaving a spin-off as its only remaining means of divesture, according to a Bloomberg report dated December 15. The new company, valued at $2 billion after the spin-off, will be quite a big baby to birth. It is one of the world's largest producers of bulk acetaminophen, the largest supplier of opioid pain medications in the US, and one of the country's top ten generic pharmaceutical manufacturers.

Still, the break-up is probably worth doing. CEO Jose Almeida says the pharma division has distinctly different business models, sales channels, customers, capital requirements, and talent bases. This is no small surprise; medical devices and pharma are vastly different businesses.

The $9.6-billion medical devices business (an after spin-off estimate) will be able to re-invest its profits and expand and grow this burgeoning area. But the pharma company will also be better able to focus and compete in the growing pain management area.

All the evidence, however, suggests a tough road ahead for the new pharma spin-off. The failed attempt to sell the company, and the fact that the management chose a new leader from outside the company both suggest that this company is anything but a diamond in the rough. The company's future will depend on its ability to secure new capital to invest in new products and refill the pipeline. It could be years before the company stands on solid ground again.

WHAT WOULD BUFFET DO?

So how is Warren Buffet playing the Abbott, Pfizer, and Covidien spin-offs? Unfortunately, he isn't. As of December 21, Mr. Buffet was not invested in any of the three, though interestingly, he does have holdings in the three-legged J&J, as well as Sanofi Aventis and Glaxo.

Buffet says he prefers buying biotech as a basket because drug approvals and patents are too difficult to predict. This is the joy of being an investor rather than a manager: he can mix and match his investments to optimize diversification by trading in and out of his portfolio at the click of a button. ◆

BIOGRAPHY

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

Bioabsorbable Cardiac Matrix: A Novel, Injectable Device That Supports the Damaged Heart After AMI, Preventing Cardiac Remodeling & Congestive Heart Failure

By: Daniel Tassé

In the United States alone each year, about 1 million people suffer a heart attack - technically, acute myocardial infarction (AMI) - in which a blocked coronary artery prevents blood from reaching portions of the heart muscle, starving it of oxygen and resulting in ischemic injury and infarction, or tissue death. About 25% to 30% of these individuals will suffer severe AMI, causing structural alteration to the heart and putting them at increased risk for developing congestive heart failure (CHF), in which the heart can no longer adequately pump blood to support the body's organs and tissues. CHF is a disabling disease that erodes a person's ability to function independently, greatly compromises quality of life, and ultimately is fatal. Moreover, CHF has an economic impact. The American Heart Association estimates that in 2008, the direct and indirect costs of CHF totaled $20 billion to $30 billion, about half of which is attributable to AMI. Currently, no FDA-approved treatments are available to prevent alterations to the heart and the subsequent development of CHF following severe AMI.

Ikaria, Inc., a critical care company focused on developing and commercializing innovative therapies for critically ill patients, is conducting a pivotal trial, to be used for registration in the EU, on a novel device called bioabsorbable cardiac matrix, or BCM. BCM, formerly known as IK-5001, is an aqueous liquid polymer mixture of sodium alginate and calcium gluconate, administered via injection directly into the coronary artery, intended to prevent the steps leading to heart failure in patients who recently have had a severe AMI. When administered, BCM is designed to undergo a chemical and physical transformation to form an extracellular gel-like matrix that functions as a mechanical scaffold to provide support to the damaged heart muscle as it heals, thereby minimizing the changes in cardiac structure and function that can lead to CHF. Following several weeks, the matrix gradually dissipates and is naturally excreted by the kidneys as elevated calcium levels in the heart following AMI return to normal.

SIGNIFICANT MEDICAL NEED

The heart muscle typically sustains substantial damage as a result of oxygen deprivation during the acute injury of severe AMI. Even if a person who has experienced severe AMI is fortunate enough to arrive at a hospital in time for an interventional cardiologist to open

FIGURE 1

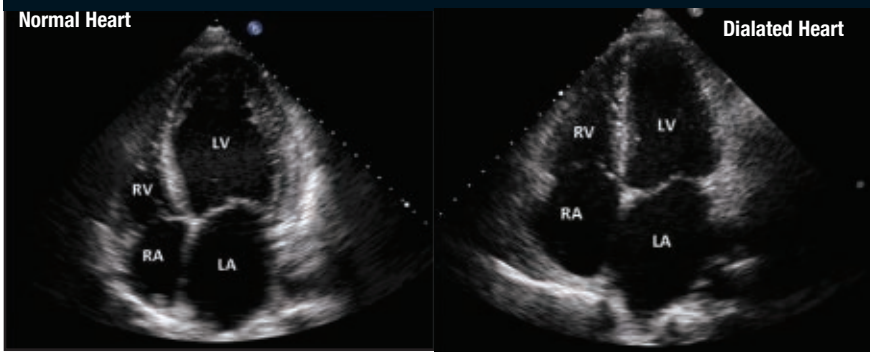


Photo courtesy of Dr. Pamela Douglas, Duke University Medical Center

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the clogged artery and insert a stent to restore and maintain blood flow to the heart muscle, (s)he still faces significant risks. The ischemic damage to the myocardium can result in scar tissue formation and cause the heart muscle to stretch and thin, compromising its ability to contract with the same force with which it did before the injury. To compensate, undamaged portions of the heart work harder, resulting in ventricle enlargement, more thinning of the heart's walls, and increasingly ineffective muscle tissue. The phenomenon reflecting the changes in structure and function of the cardiac musculature is called cardiac remodeling.

Imaging studies can document this remodeling within a few weeks of severe AMI (Figure 1). Advances achieved throughout the past 2 to 3 decades in cardiac reperfusion following severe AMI have made it possible for many more people to survive what previously would have been fatal cardiac events. In fact, survival is quite high in even the most significant of cardiac events, such as transmural MIs or acute ST-segment elevation myocardial infarction (STEMI), in which the damage extends full thickness from the inside to the outside of the myocardium. However, as a consequence of cardiac remodeling, the heart becomes progressively weaker and less effective in its ability to eject blood. Remodeling will continue to worsen as the functioning portions of the heart try to do the work of a normal, healthy heart muscle, thereby causing further remodeling. Therefore, some patients, despite surviving severe AMI, will die of CHF within a few years.

PROOF OF PRINCIPLE

Preclinical and safety studies suggest that BCM strengthens the injured portion of the heart, functioning as a temporary matrix that minimizes cardiac remodeling. It is intended to prevent, rather than treat, remodeling, thereby minimizing a patient's risk of developing life-threatening CHF. A pilot safety study in 27 STEMI patients, completed in 2008, demonstrated a 2-mL volume of BCM to be safe, well tolerated, and feasible.

In fact, preclinical studies in multiple animal models demonstrated that when BCM is injected into the reopened coronary artery, it flows into the damaged heart muscle and forms a protective matrix that provides physical support and enhances the mechanical strength of the myocardium post severe AMI. As the heart muscle repairs itself, the matrix prevents cardiac wall thinning and loss of muscle tone, which is characteristic of cardiac remodeling, thereby preserving cardiac function. When the infarcted area has healed, BCM gradually breaks down and is excreted.

The main component of BCM in its liquid form is a highly purified and stabilized form of alginate, the anionic polysaccharide present in purified brown algae. Alginate commonly is used as bone filler in orthopedic procedures and as an ingredient in various food products. It is safe and well accepted for consumption and internal administration.

At some time following balloon angioplasty and stent insertion to open the coronary artery following severe AMI, an interventional cardiologist would inject a bolus of 4 mL of BCM, an aqueous mixture of sodium alginate and calcium gluconate, directly into the injured coronary artery. The injection takes no more than 60 seconds.

Its mechanism of action is quite simple. BCM assembles as a matrix in the presence of elevated calcium levels as a function of basic calcium chemistry, targeting the site of the injury. Increased concentrations of calcium are present in the damaged heart muscle following AMI, providing a rich source of calcium to bind with the alginate. Therefore, the sugars that compose the polysaccharide chains of alginate react with calcium within the infracted tissue, resulting in cross-linking of the chains and the formation of a gel-like matrix. When the calcium concentration declines as the heart muscle heals - typically about 6 to 8 weeks following severe AMI - the matrix disassembles, eliminating the need for a separate procedure to remove the temporary matrix. Specifically, the gel-like matrix reverts to its liquid form, and is excreted by the kidneys.

PATH TO MARKET

In January 2012, Ikaria launched its global development program for BCM, announcing the beginning of CE marking process with a clinical trial in Australia, which will be followed by patient enrollment in the United States, Europe, and other countries. Results from this trial will be used to support a CE marking application in Europe. *A Placebo-*

Controlled, Multi-center, Randomized, Double-Blind Trial to Evaluate the Safety and Effectiveness of IK-5001 for the Prevention of Remodeling of the Ventricle and Congestive Heart Failure after Acute Myocardial Infarction, or PRESERVATION I, is evaluating 4 mL of the device delivered during a second procedure performed 2 to 5 days following the initial reperfusion procedure following the severe AMI. The goal is to enrich the study population with patients at the highest risk for cardiac remodeling and follow them for 6 months. Based on the outcome of this trial, the development program for the device will evolve into a larger trial involving 1,000 to 1,200 patients and will follow essentially the same protocol, but would be expected to have a minimum 12-month follow-up period based on discussion with the FDA.

The ultimate endpoint for assessing the efficacy of the treatment will be evidence that the treated patients neither develop nor die of CHF. However, gathering survival data would require 5 to 10 years of follow up. Therefore, and in light of the significant unmet medical need, the FDA's Center for Devices and Radiological Health (CDRH), has accepted the design of the development program that will assess the following endpoints:

- an anatomical endpoint of cardiac remodeling using imaging procedures to measure the heart chamber sizes and ejection fraction to gauge the extent of ventricular distention compared to control subjects;
- a functional endpoint based on a determination of how far a patient can walk in 6 minutes; and
- a quality-of-life assessment using the Kansas City Heart Questionnaire, which has been calibrated and validated to evaluate early signs of heart failure and is designed to provide an objective view of how a patient feels.

Thought leadership, project management, and site management for PRESERVATION I is being led by Duke Clinical Research Institute (DCRI) as the global development program's Academic Research Organization. Ikaria licensed exclusive worldwide rights to develop and commercialize BCM from BioLine Rx in 2009. ◆

BIOGRAPHY

Daniel Tassé is Ikaria's Chairman and Chief Executive Officer. Prior to joining Ikaria in 2008, Mr. Tassé served as General Manager of the Pharmaceuticals and Technologies Business Unit of Baxter International, a division that was created by integrating the company's Anesthesia & Critical Care, Hospital I.V. Drug, and BioPharma Solutions Business Units. Earlier in his career, Mr. Tassé held a number of senior management positions at GlaxoSmithKline, including Vice President and Regional Director for Australasia. Mr. Tassé is a member of the Healthcare Leadership Council and of the Board of Directors of the Roundtable on Critical Care Policy. He also is a member of the Board of Directors and Health Section Governing Board of the Biotechnology Industry Organization (BIO), where he participates on its bioethics, regulatory environment, and reimbursement committees, and is a member of the Board of Directors of the Pharmaceutical Research and Manufacturers Association of America (PhRMA), where he participates on its rare disease and emerging company committees. He earned his BSc in Biochemistry from the University of Montreal. Under his leadership, Ikaria is developing innovative therapies and has become a leader in the critical care space.

Characterization of Recombinant Albumin as an Effective Multifunctional Excipient to Enhance Drug Stability

By: Mark Perkins, PhD

The correct choice of excipient in the formulation of a new or redeveloped drug product is critical for the success of any formulation program. Novozymes' recombinant human serum albumins (rAlbumins) offer drug manufacturers a powerful formulation solution by providing a quality product based on comprehensive understanding of both its physical and functional properties. These characteristics allow faster development of safe and stable formulations of even challenging drug candidates.

A multifunctional excipient, rAlbumin acts to stabilize the drug product by reducing aggregation, oxidation, and surface adsorption. Particularly valuable for liquid formulations, rAlbumin can significantly decrease the attrition rate in formulation development and provides increased freedom to choose the best candidate for further development.

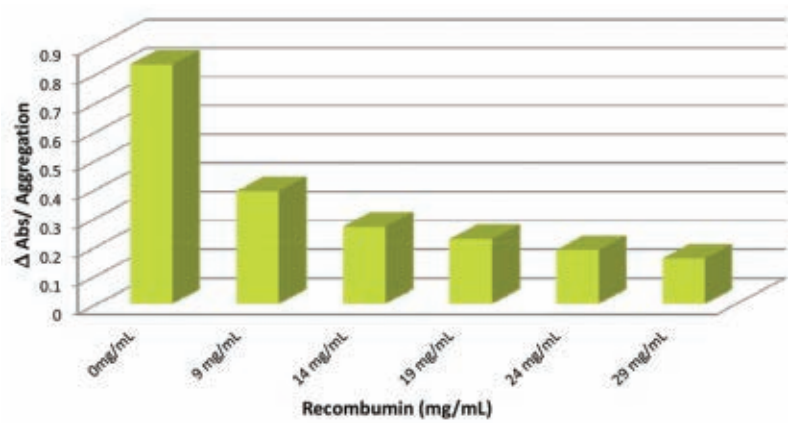
CHALLENGES IN DRUG FORMULATION

Industry recognition of the importance of excipients in the manufacture, delivery, and performance of a stable pharmaceutical drug product has seen excipient choice increasingly defined early in the development process. Formulation of challenging candidates from the classes of complex small molecules (such as water-insoluble anti-ancer drugs), difficult-to-stabilize antibodies, proteins (such as high-potency, low-dose drugs), and poorly soluble or surface-binding peptides may not be achieved with conventional stabilizing excipients, such as sugars, amino acids, and detergents (SADs).

As an alternative, human serum albumin (HSA) is a useful excipient in drug formulations. The most abundant protein in human plasma, HSA has limited immunogenicity, making it an ideal excipient candidate. Furthermore, given albumin's stability in solution, there is significant potential to stabilize therapeutic proteins in liquid formulations over extended periods. Traditionally sourced from human serum, the increasing regulatory concerns over the use of animal-derived material in the manufacture of human therapeutics has brought about the need for a safer and more consistent albumin product.

To address these issues, Novozymes has developed a range of recombinant human albumins (rAlbumins) specifically for the pharmaceutical industry. Manufactured in an animal-free process to the highest quality standards, Novozymes' rAlbumins act as multifunctional excipients. Their use reduces the requirement for multiple excipients, such as SADs, and delivers a safe and consistent product that enhances the stability and performance of the customer's drug

FIGURE 1



Measurement of protein aggregation by absorbance. In this example, protein aggregation of a malarial antigen was reduced in the presence of Recombumin following freeze-thawing.

product. This following demonstrates the functional properties of rAlbumin as an effective excipient in three areas commonly affecting product stability: (1) aggregation; (2) oxidation; and (3) nonspecific adsorption. It also provides a comparison of the physiochemical properties of a range of commercially available albumins through detailed product analysis.

SIMPLIFYING THE FORMULATION PROCESS

The development of novel treatments is placing time and cost pressures on the drug manufacturer, and, with no guarantee of success, drug companies are finding better ways of formulating both new and existing drug products.

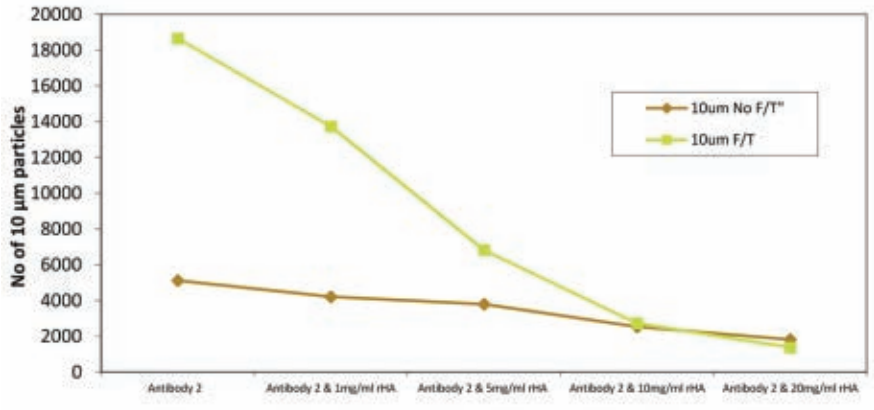
During preformulation stages, critical evaluation of both the physical and functional characteristics of each excipient is required to determine their desirable properties. Excipient characterization is also vital for predicting potential interactions between drug and excipient that may impact on the safety and efficacy of the final product.[1] However, excipient properties often vary if the excipients are obtained from multiple vendors and sources. Excipient variability also occurs with respect to vendor product quality standards, reliability of supply, and regulatory and technical support.

Characterization of each excipient can be time-consuming and costly, delaying the registration process and prolonging time to market. Incorporating a well-characterized multifunctional excipient, such as albumin, into the formulation strategy reduces issues with variability in quality, provides a level of control from lot-to-lot and supplier-to-supplier, and reduces the time involved in formulation optimization.

An acceptable drug formulation must be safe to administer, must be physically, chemically, and biologically stable, and must have low immunogenicity and a suitable shelf-life. Albumin has no endogenous activity, a naturally long half-life, and, as an effective carrier of numerous ligands, offers numerous functional benefits during formulation development.

In addition, Novozymes' rAlbumins have unprecedented technical and regulatory support. Manufactured to cGMP quality standards in large-scale facilities, USP-NF compliant, and supported by a strongly documented safety package and drug master file, they reduce registration and regulatory issues. By including rAlbumin in the formulation strategy, drug manufacturers can reduce development timelines, getting the final product to market sooner.

FIGURE 2



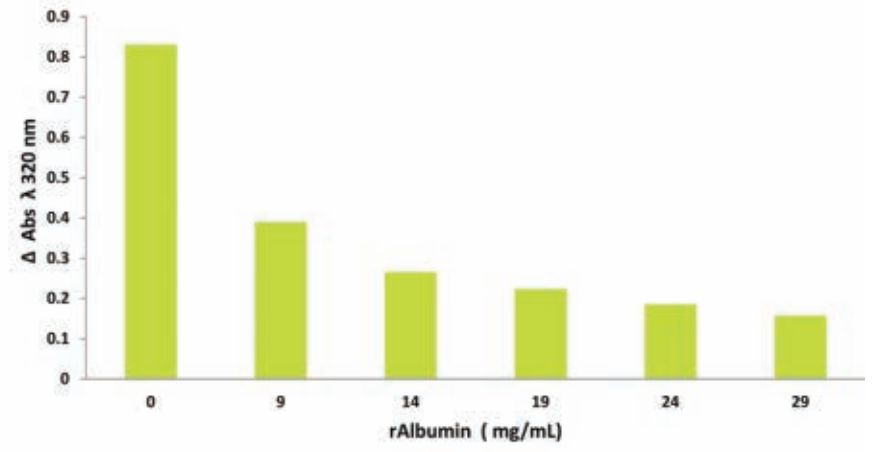
Measurement of particle formation. Particle formation of IgG4 (1 mg/ml) was measured in the presence of varying concentration of Recombumin following freeze-thawing.

IMPROVED PRODUCT STABILITY

Protection Against Aggregation During Freeze-Thaw

Unwanted aggregation of the therapeutic protein or vaccine product is common during manufacture and storage. With the ability of aggregates to form in both liquid and solid states, aggregation is a major concern impacting on product recovery, delivery, and

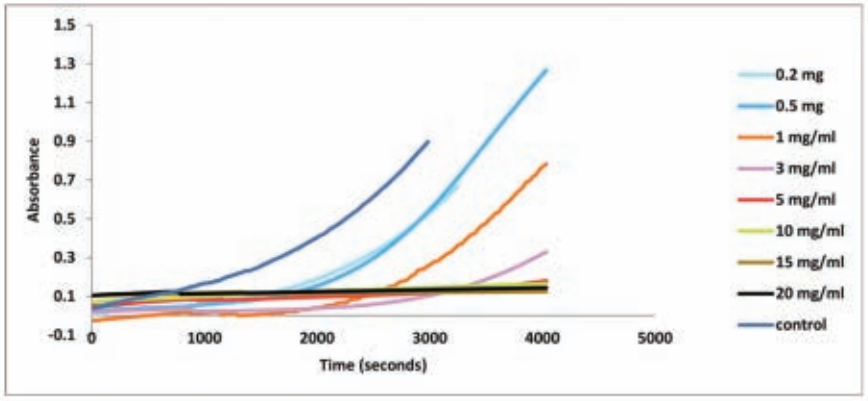
FIGURE 3



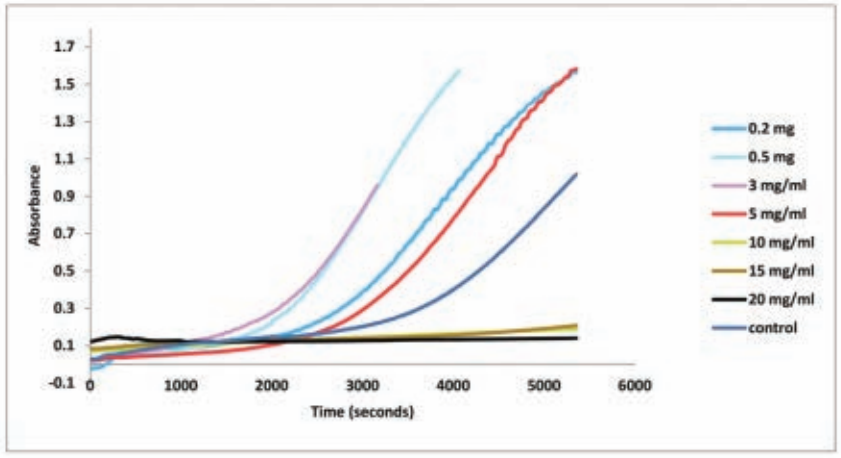
Suppression of MSP-2 protein aggregation in the presence of rAlbumin. rAlbumin suppressed aggregation of the MSP-2 protein (3.5 mg/ml) in a concentration-dependent manner following a single freeze-thaw cycle.

FIGURE 4A,B,C

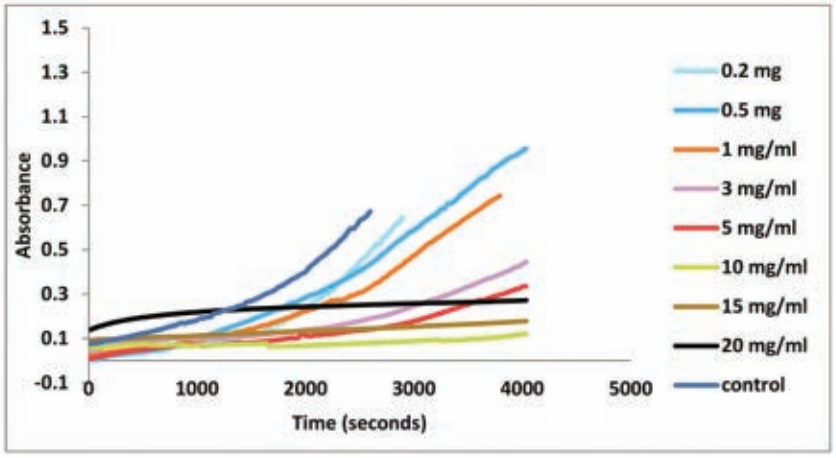
A



B



C



A range of Recombumin concentrations was tested with three different antibodies and exposed to elevated temperatures for a maximum time of 2 hours. Agilent UV absorbance at 350 nm was used to measure turbidity. The maximum temperature difference between the peltier unit and cell during temperature ramp was ~3°C to 4°C. Length of lag time before an increase in A350 nm is indicative of the colloidal stability of the system.

immunogenicity. As a result, minimizing aggregation is a primary goal for many drug development scientists.[2]

Bulk freeze-thaw is a stress which protein drug substances can be exposed to during the manufacturing process to enhance operational flexibility while maintaining product stability. However, exposure of the protein during the freeze-thaw process to low temperature, altered concentration of solutes; and pH changes can result in changes in the conformation of the protein molecule, leading to the formation of aggregates and visible and subvisible particles.[3]

Novozymes' rAlbumins are effective stabilizers against protein aggregation during the freeze-thaw process. As an example, a malarial antigen protein, merozoite surface protein 2 (MSP-2) (4 mg/ml), subjected to freeze-thaw cycles in the presence of varying concentrations of Recombumin® was shown to be protected from degradation, thereby reducing aggregation (Figure 1).

In a separate study, a fully humanized IgG4 antibody (1 mg/ml) with varying concentrations of Recombumin was subjected to five controlled freeze-thaw cycles (-40°C to 20°C). Subvisible particles at 10 micrometers were analyzed using an HIAC 8012 liquid particle counting system.

The addition of rAlbumin was shown to protect against particle formation in a concentration-dependent manner. Recombumin at 10 mg/ml was sufficient to eliminate 10-micrometer particle formation caused by freeze-thaw stress (Figure 2).

Other excipients used to reduce aggregation in protein formulation, such as polyethylene glycol (PEG), polysorbate 80, and glycine, were compared to Novozymes' rAlbumins in respect of their ability to stabilize the malarial antigen protein. Again, Recombumin was shown to be effective in stabilizing the protein, resulting in reduced aggregation (Figure 3).

Protection Against Aggregation During Transport & Storage

After final formulation, fill, and finish, the final drug product can be subjected to further stresses during transport and storage. Particularly in the case of liquid formulations, these stresses, such as temperature variation and agitation, can induce protein aggregation, increasing particle formation.

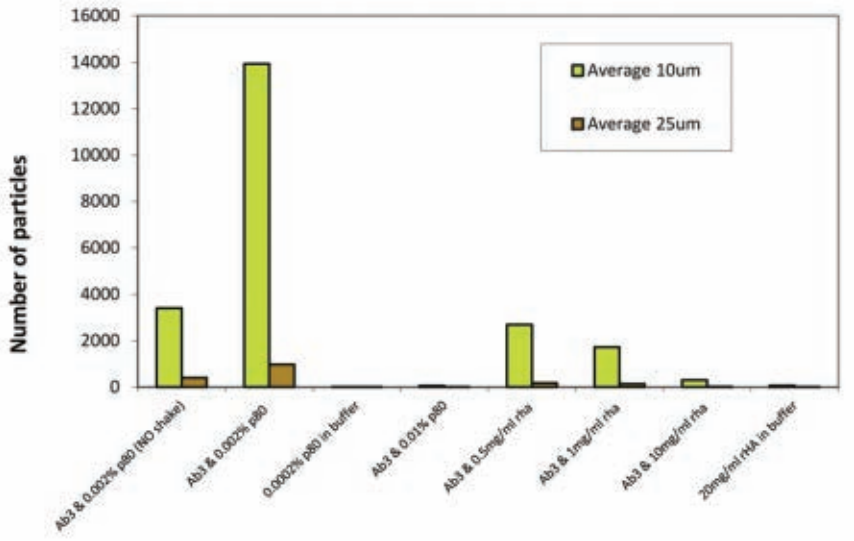
To examine the ability of rAlbumins to stabilize IgG and reduce particle formation due to temperature variation, colloidal stability was assessed. Turbidity changes in solution after exposure to elevated temperature were measured for three separate IgGs in the presence of a range of rAlbumin concentrations (Figure 4a, 4b & 4c).

The results demonstrated that the lag time increased compared to the control formulation in the presence of rAlbumin in a concentration-dependent manner, suggesting that the presence of rAlbumin had a protective effect against aggregation at elevated temperatures.

To further examine the ability of rAlbumin to stabilize a drug product during transportation, a fully humanized antibody (Ab3) at 50 mg/ml was subjected to vigorous shaking (600 rpm) in the presence of a range of rAlbumin concentrations and the level of particle formation analyzed. Novozymes' Recombumin formulation contains a small amount of polysorbate 80, so a control sample containing 0.002% polysorbate 80, and no Recombumin was included in the experiment. Comparison with a concentration of polysorbate 80 typically used in antibody formulations (0.01%) was also included.

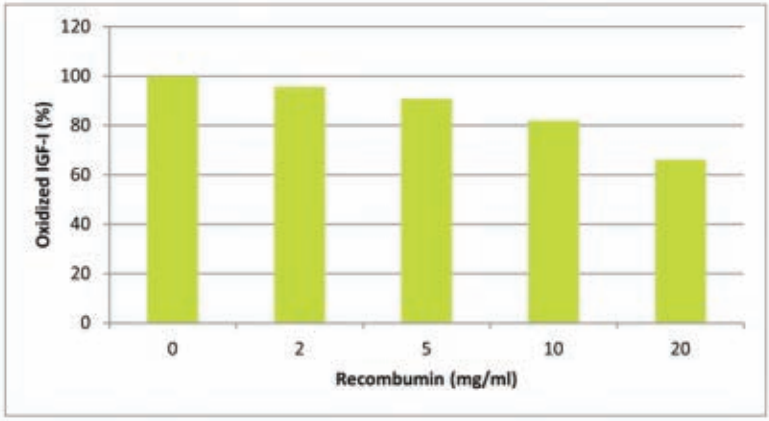
The results indicated that vigorous agitation caused a greater than four-fold increase in the number of 10-micrometer particles in the formulation containing Ab3 plus 0.002% polysorbate 80 compared to the unshaken control. The addition of rAlbumin protected against 10-micrometer particle formation during vigorous agitation in a

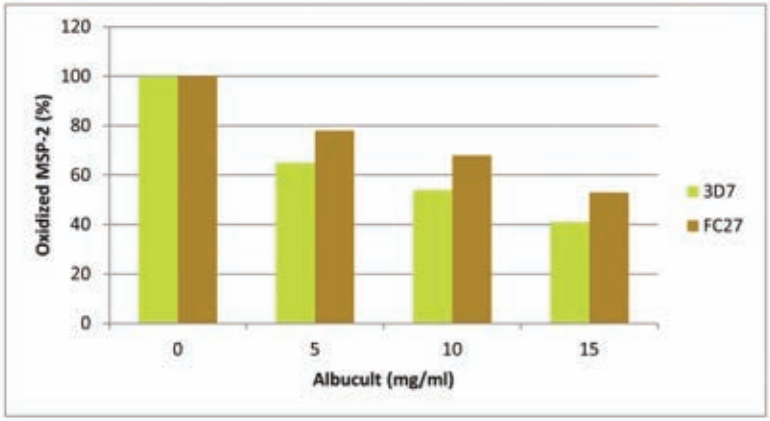
FIGURE 5



An IgG1 antibody (50 mg/ml) was subjected to vigorous shaking (600 rpm) in the presence of Recombumin (0.5 mg/ml, 1 mg/ml, 10 mg/ml, and 20 mg/ml) and the level of 10-micrometer and 25-micrometer particles analyzed by HIAC 8012 liquid particle counting system.

FIGURE 6





Measurement of oxidized protein in the presence of rAlbumin. IGF-I (20 µg/ml) or MSP-2 protein was added to samples containing a range of rAlbumin concentrations followed by H2O2 to a final concentration of 0.0005%. The reaction was terminated with catalase and the degree of oxidation analyzed by reverse-phase HPLC. Percentage oxidation of for each protein was calculated against the main protein peak for all samples.

concentration dependent-manner. rAlbumin (20 mg/ml) provided comparable protection in this formulation to 0.01% polysorbate 80 (Figure 5).

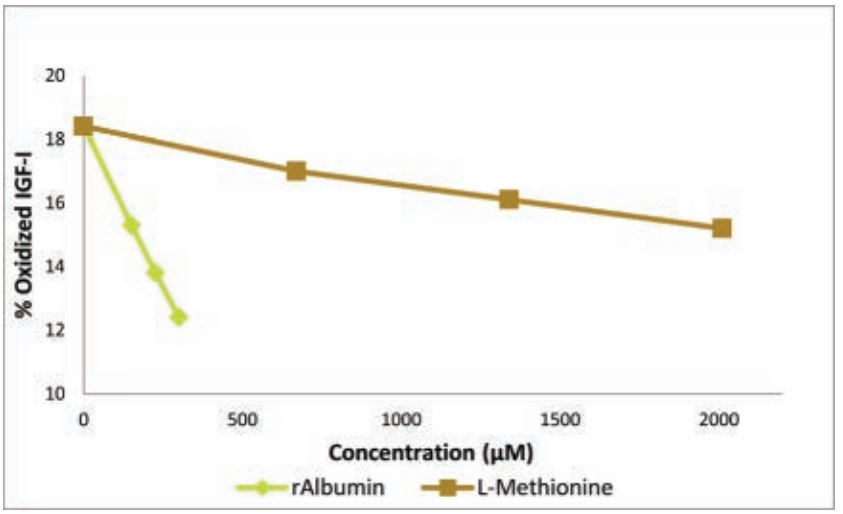
Protection Against Oxidation

Formulation excipients are also often used to stabilize the protein against oxidation, another mechanism by which protein degradation can occur. Both the excipients and the active drug product may be vulnerable to oxidation. Excipients containing reactive aldehyde, alcohol, and phenolic groups are particularly susceptible, while it is the methionine and cysteine residues on protein surfaces that can be vulnerable to oxidation. Induced by normal process operations, such as air and light exposure, and heavy metal ions, modification of the protein product by oxidation can lead to inactivation or unwanted activation of the drug, altered binding affinities, increased susceptibility to aggregation, proteolysis, and altered immunogenicity. Moreover, the guidelines of the US FDA suggest that oxidation must be controlled in the product formulation of therapeutic proteins.[4]

Oxidative degradation reactions can be complex. Free radical formation through normal process operations interacts further with oxygen to form peroxy radicals. These radicals can then interact with the oxidizable drug substance and break down to produce more free radicals, which can then be involved in further reactions. Detergents, such as Triton and polysorbate 80, widely used in biochemical formulations, are known to be susceptible to oxidative degradation during storage, with the formation of unwanted peroxides.[5] Novozymes' rAlbumins act as a potent antioxidant, primarily due to the free-thiol at position Cys 34 and its surface methionine residues, with HSA-SH acting as a potential scavenger for reactive oxygen species (ROS).

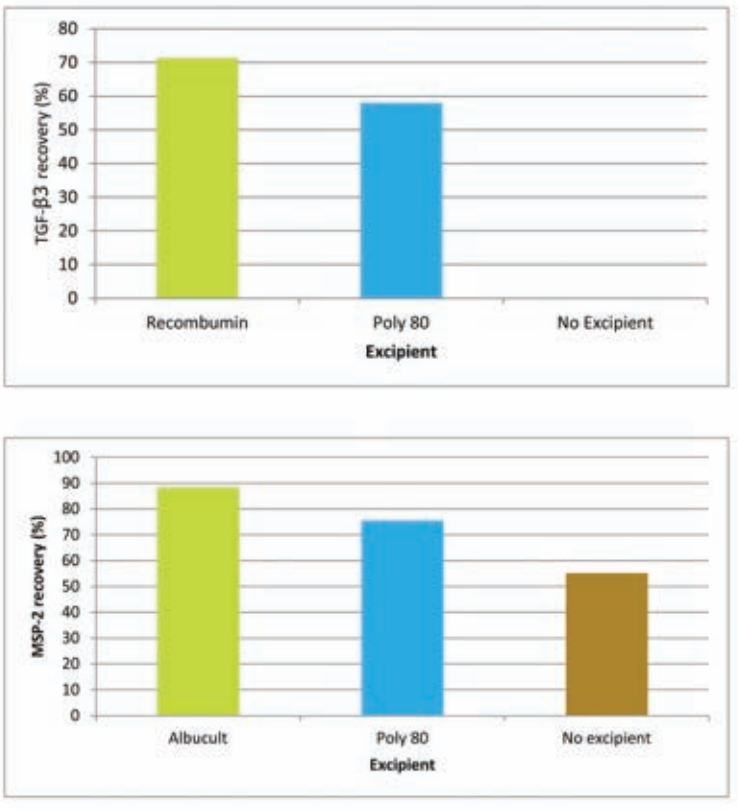
In an experimental model, pharmaceutically relevant concentrations of insulin-like growth factor-I (IGF-I), known to be susceptible to oxidation during storage, and two malarial antigen protein MSP-2 allelic variants, were exposed to trace amounts of the oxidizing agent hydrogen peroxide (H_2O_2) in the presence of a range of rAlbumin concentrations. In all examples tested,

FIGURE 7



H2O2 induced oxidation of IGF-I (20 µg/ml) in the presence of increasing concentrations of Recombumin or L-methionine.

FIGURE 8



Measurement of protein recovery in the presence of excipient. In this experiment, TGF-β3 (0.5 µg/ml) or MSP-2 (5 µg/ml) was added to a glass container in a buffer solution containing either rAlbumin (0.1 mg/ml), polysorbate 80 (0.1 mg/ml), or no excipient. Each sample was mixed, centrifuged, then transferred to HPLC vials for analysis via reverse-phase HPLC. Percentage recoveries of each protein were calculated against reference standard.

Novozymes' rAlbumin was shown to effectively reduce protein oxidation, thereby enhancing the stability of the protein product (Figure 6).

The ability of rAlbumin to act as an antioxidant following exposure to hydrogen peroxide was also compared to the commonly used antioxidant L-methionine. The results showed rAlbumin to be a potent antioxidant when compared with L-methionine following exposure to H_2O_2. rAlbumin provided almost complete protection against the formation of oxidized species at the top concentration and proved effective at molar concentrations approximately 13 times lower than that of L-methionine (Figure 7).

Reduces Nonspecific Binding to Surfaces

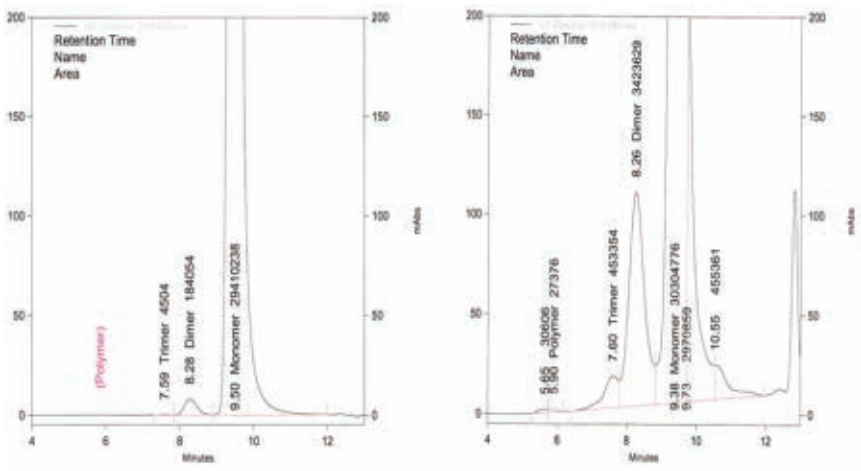
Instability of pharmaceutical drug products can also occur due to nonspecific adsorption to surfaces, altering the concentration of the drug in the administered dose and potentially altering the pharmacokinetics and efficacy of the drug. In addition, binding of the protein to surfaces can result in conformational changes, leading to aggregation and loss of product.[6]

Blocking agents are often used in formulation to limit nonspecific adsorption of protein drug products. Albumin acts to prevent protein adsorption due to its high interfacial activity, binding to both hydrophobic and hydrophilic surfaces.[7] To demonstrate an additional functional benefit of Novozymes' rAlbumin as an effective blocking agent, the recovery of TGF-β3, an active ingredient used in scarless wound healing, or the malarial antigen protein (MSP-2) was measured after exposure to glass containers in the presence of rAlbumin. This experiment confirmed that Novozymes' rAlbumin could be applied to formulation strategies to significantly reduce product loss to manufacturing and storage surfaces (Figure 8).

FIGURE 9

Commercial albumins all diluted 10% (w/v).

FIGURE 10



SE-HPLC a) Recombumin, b) recombinant human albumin (rice). In this experiment Novozymes Recombumin, manufactured in Saccharomyces, was compared directly to recombinant human albumin manufactured in rice using SE-HPLC.

QUALITY ATTRIBUTES OF ALBUMIN

As described earlier, excipients are critical components in drug formulation for stability and performance. However, physical and chemical interactions between the drug and excipient as well as excipient impurities and the drug can lead to loss of efficacy and safety. Each excipient must therefore be well-characterized and manufactured to the highest quality standards to deliver a safe and consistent product.[8,9]

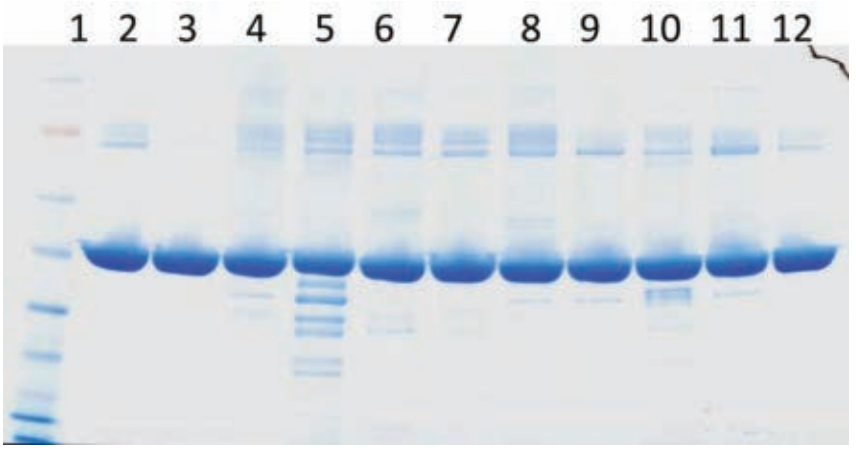
Characterization of the physical and chemical properties of excipients helps to build quality into the product. The continued implementation of Quality by Design (QbD) concepts across all stages of the pharma industry has meant a more systematic approach to achieving quality and characterizing acceptable variation in the formulation process. A comprehensive understanding of excipient properties and functionality is critical at preformulation stages if a drug candidate is to progress.

The challenge for drug manufacturers is to source well-characterized excipients with limited variability in commercial quantities and of a reliable quality standard. To demonstrate the physiochemical variability of albumin between vendors and sources, Recombumin and albucult® were compared to other commercially available albumins. Specifically, a selection of analytical tests typically applied to rAlbumin was performed on alternate albumin products to assess variability.

Visual Inspection

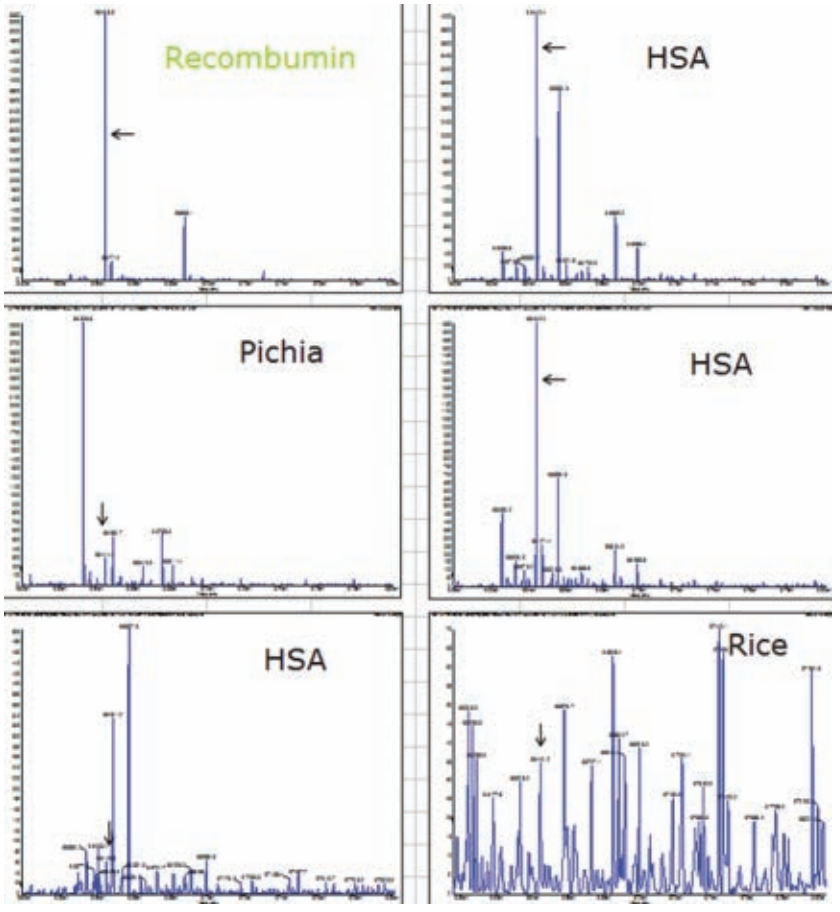
Visual inspection is often one of the first analytical tests performed to examine product color and clarity. Both these characteristics provide the drug manufacturer with their first impression of product quality and purity and can greatly influence their decision as to which product they will move forward with. The albumins tested were from various vendors and derived from both recombinant sources, such as rice, *Pichia*, and *Saccharomyces*, and serum extraction. As seen in Figure 9, there was good clarity for all the albumins tested, but significant color variability was observed, with Novozymes' rAlbumins found to be the least pigmented.

FIGURE 11



SDS-PAGE non-reducing. In this experiment, Recombumin (lane 1) and Albucult (lane 2) were compared both recombinant and serum derived albumins SDS-PAGE.

FIGURE 12



ES-MS of separately sourced albumins. In this experiment, ES-MS for Recombumin was compared to both recombinant (pichia and rice) and serum-derived albumins (intact albumin indicated with arrow).

Excipient Purity

To examine product variability and purity, three analytical techniques - size exclusion chromatography (SE-HPLC), SDS-PAGE, and electro-spray mass spectrometry (ES-MS) - were applied to a range of commercially available albumins.

In all three tests performed, Novozymes' rAlbumins were found to be the most homogeneous products. SE-HPLC showed that Novozymes' rAlbumins had more than 97% monomer, compared to the most heterogeneous sample tested, which had only 80% monomer (Figure 10). Confirmation of the homogeneity and purity of Novozymes rAlbumins' compared to other albumin sources was also obtained from the SDS-PAGE results (Figure 11) and ES-MS (Figure 12).

The examples demonstrated the vast variability between vendors and sources of albumin as a commercial excipient. Choosing a well-characterized albumin that is of high quality is therefore essential for inclusion of the excipient in successful formulation activities.

THE SOLUTION

Pharmaceutical manufacturers may find that conventional excipients, such as SADs, do not always provide an adequate formulation solution, particularly in the stabilization of

complex small molecules, proteins, and peptides. In addition, variability in the functional and physical properties of excipients, as well as in quality and technical and regulatory support between vendors and sources, means that excipient choice must be carefully considered. Novozymes has taken a broad approach to excipient performance through extensive understanding of its rAlbumins' functional and physiochemical properties, stability, pharmacokinetic attributes, and regulatory compliance.

Extensive studies have shown Novozymes' rAlbumins to be effective multifunctional excipients in enhancing protein drug stability through protection against aggregation, oxidation, and non-specific adsorption. Detailed analysis of the physiochemical properties of its recombinant albumin products provides a better understanding of how rAlbumin can contribute to the successful manufacture and functionality of the final drug product, especially for difficult-to-formulate products. By working directly with the drug manufacturer, Novozymes delivers safe, consistent, and well-characterized recombinant albumins that allow efficient development of stable formulations for rapid initiation of clinical evaluation of a drug product.

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BIOGRAPHY

Dr. Mark Perkins is a Formulation Chemist with a PhD in Pharmaceutical Sciences from the University of Nottingham. He joined Novozymes Biopharma in 2010 as a customer solution specialist. Within this role, he works with partners who are evaluating Novozymes recombinant albumin products and associated technologies in the areas of biopharmaceutical formulation and half-life extension. Prior to this position, Dr. Perkins worked as a Materials Specialist at an inhaled drug development company and as a Project Manager within an analytical consultancy.

PERSONALIZED MEDICINE

Technology Trends in the Pharmaceutical & Biopharmaceutical Industry

By: Cecilia E. Van Cauwenberghe, Senior Research Analyst, Life Sciences & Biotech, Technical Insights, Frost & Sullivan

INTRODUCTION

The development of novel therapies in medicine has been triggered mostly by the need to find the right treatment for the right patient at the right time. While there are several externalities that drive the demand for novel solutions in the healthcare industry, the most important factors are outlined below.

MARKET DRIVERS

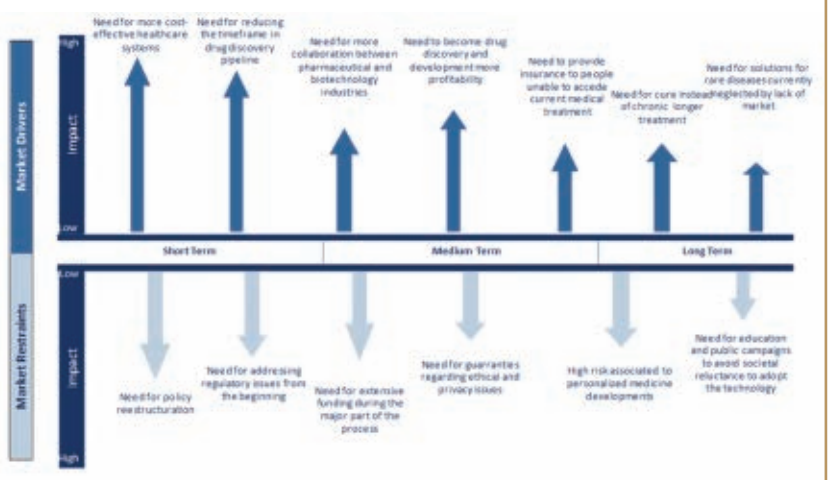
From the point of view of the market, the new concept in the pharma industry is seen to be driven basically by two factors: the continuously increasing cost of healthcare around the world (significantly in the US) and the climbing cost and timeline of the drug discovery pipeline.

A growing sense of urgency to provide insurance to people unable to afford current medical treatment and make healthcare more cost effective has arisen from current US healthcare reform. In addressing this concern, focus has been on achieving better diagnostic tests at the molecular level to bestow more effective therapies to a reduced pool of patients, which is considered to be the potential resource to reduce both costs and time.

Furthermore, the current drug discovery and development value chain has become inefficient over time in providing good and rapid solutions, at a time when the cost to develop new drugs is continuously climbing. An in-depth understanding of the involved process is important in being able to introduce an activity-based costing system to drive the impact of technology toward reducing the cost of activities conventionally considered to be mandatory in the process of drug discovery and development. Pharmaceutical and biotechnology companies are re-evaluating their approach to drug discovery and development, focused on the improvement of productivity, as well as the reduction of R&D costs.

It is important to highlight the results of this scenario as attractive for small and medium enterprises (SMEs), which have found a variety of opportunities from these facts. More complex technological, economic, regulatory, and societal forces surrounding personalized medicine need to be considered to leverage this technology adoption.

FIGURE 1



Market Drivers & Restraints of a Novel Approach to Medicine (Source: Frost & Sullivan)

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TECHNOLOGY DRIVERS

A broad spectrum of science fields drive the development of prospective medicine. Nevertheless, principal promoters, that is, genomics and proteomics, will be cited in the following paragraphs in accordance with their corresponding biomarkers, in order to depict the technology drivers' landscape in a more precise way.

The initiation of genomics from the Human Genome Project (HGP), which has enabled the sequencing of the entire human genome, has set the course of personalized medicine. From this point, while representing the core of this discipline, pharmacogenomics is focused on understanding the inherited differences in drug metabolism and response. By these means, both treatment response and patient disease can be correlated with genetic variations. The characterization of individuals' genetic variations represents a direct link toward a more personalized approach to medicine. Such variations are generally associated with single nucleotide polymorphisms (SNPs), which denote an essential tool to predict genetic sensitivity to specific drug compounds, as well as to establish certain predisposition facing a given disease. Under this concept, SNPs can be seen as biomarkers, which have the function of localizing specific genes in DNA sequences. The development of genomic biomarkers, that is, biological molecules that serve to declare the physiologic state as disease progress, involves the utilization of whole genome microarrays.

Proteomics play one of the most relevant roles in enabling future technologies to develop personalized medicine. Indeed, proteome provides a better description of the disease process by involving dynamic characteristics. From the protein expression analyses, various factors can be derived in addition to the temporal and functional regulation of the gene expression, being the most frequent mRNAs differential splicing and post-translational modifications (PTMs). Similarly, protein expression can be used as a fundamental biomarker. Drawbacks used to appear in dealing with very small quantities, which has promoted the development of novel technologies that enable selectivity and specificity. Protein arrays in the form of large-scale functional chips, antibodies, or reverse protein arrays constitute some instances of such developments.

On the other hand, nanotechnology approaches to a variety of life sciences applications, including protein measurements in the range of miles per drop of blood, are also considered as a technology driver. Moreover, computational and mathematical tools that are suitable to work with large volumes of information, as well as serve to perform high-level complexity modeling and simulation of biological systems, should account as a parallel technology driver, including all of their branches in computer science, mathematics, physics, electronics, bioengineering, etc.

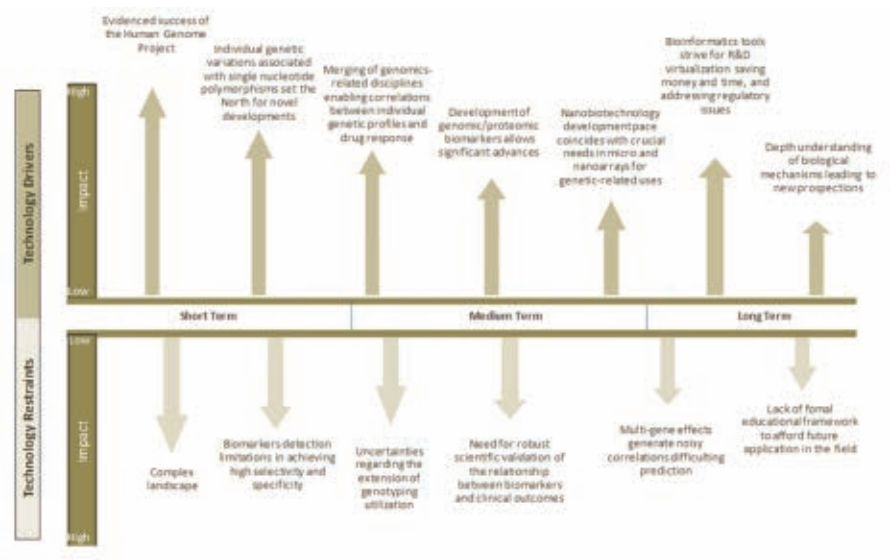
MARKET RESTRAINTS

The main barriers regarding novel approaches to the pharmaceutical industry, from the point of view of the market, rely on the uncertainty and privacy issues with relation to insurance coverage and reimbursement. For instance, although the concept of personalized medicine is set on the base of a cost-effective approach, the development of those technologies that enable this discipline to become reality need extensive funding, and the risk associated is expected to be high.

TECHNOLOGY RESTRAINTS

The response to a drug comprises a complex phenotype, encoded by a large number of genes, as well as many environmental factors, so that a gradient of response involving the different players should be expected. Furthermore, biomarker detection becomes difficult with diseases that evidence a higher complexity. Novel technologies that enable biomarkers' selectivity and specificity constitute technological aspects of continuous concern. According to such limitations in biomarkers' sensitivity and specificity of many genomic tests, their use for screening large populations to detect conditions with low prevalence could result in a large number of false positives. Therefore, it is expected that physicians, according to their re-education regarding these issues, perform an appropriate clinical evaluation of these tests in order to avoid a misunderstanding in the use of the

FIGURE 2



Technology Drivers & Restraints of a Novel Approach to Medicine (Source: Frost & Sullivan)

personalized medicine approaches that obstruct their flowering.

MARKET CHALLENGES

The processes involving genetic and clinical validation require the appropriate insurance coverage and reimbursement that compensate the increased cost of technology development. Reimbursements based on commodity pricing, which constitute the current trend, causes results that are inadequate for post-genomic technology. In accomplishing this goal, extensive clinical studies will be required. Indeed, the number and complexity, as well as the cost of validation studies, reach those resulting from a therapeutic approach, including clinical trials. These statements reveal the necessity for an appropriate insurance coverage and reimbursement, so that a large number of products and differentiation technologies can reach the market.

On the other hand, this revolution in life sciences and medicine technology clusters involves the discussion of decisive factors to strive for the clinical utility and validity of the developments, over which suitable decisions can be made promoting the product development and reimbursement opportunities.

TECHNOLOGY CHALLENGES

A personalized medicine approach involves the extensive use of molecular biomarkers, on the base of genomics and proteomics fields, in attempting to match the best treatment and regime, including the appropriate standard therapy selection, with the genetic characteristics of the patient. The critical issue is given by the robust validation of the relationship between biomarkers and clinical outcomes. The methodology involved in such a process will certainly spend some time and many corrections based on continuous learning approaches that will emerge.

Cancer research has been the former line of work focused on the correlation of genetic variations in single genes or protein markers, which are expressed by tumoral cell lines. Naturally, a major complexity is evidenced in dealing with multi-gene effects. A deeper understanding of interactions among different variations is challenging, but is needed in order to rightly establish a correlation that allows for its use to predict disease susceptibility, disorder progression, drug response, and recurrence probability.

REGULATORY CHALLENGES

The most important points regarding regulatory issues is taking into consideration their evolution along time, as well as the role of conventional players in these new scenarios. In accomplishing these commitments, a new regulatory process addressing the needs for appraisal of individuals' genetic profiles should be also unmet, in order to be able to successfully correlate clinical studies for their predictive use.

The approval process for technological approaches to personalized medicine, including diagnostic tests, exhibits a similar treatment as that of pharmaceuticals and biotech products. Broadly speaking, the US FDA establishes two categories for diagnostic tests. Such categories are constituted by in vitro diagnostic tests (IVDs) and in vitro diagnostic multivariate index assays (IVDMIAs). Both studies are supervised by the FDA, along with the US Center for Medicare and Medicaid Services (CMS), a branch of the US Department of Health and Human Services. CMS is the federal agency that administers the Medicare program and monitors the Medicaid programs offered by each state.

The methodology utilized by the FDA in regulating IVDs and IVDMIAs is similar to those used for Class III medical devices. Class III devices are those commonly known as support human life devices, so that their evaluation results at this stage are extremely important. This mechanism of regulation is based on the substantial equivalence of the new test to an existing, so that a premarket approval (PMA) is taken into consideration. Such a process constitutes the most rigorous brand of device marketing application according to FDA statements, and indicates that the applicant must receive FDA approval, guaranteeing safety and effectiveness of the device under the appropriately valid scientific evidence, corresponding to its PMA submission prior to marketing the device.

ETHICAL CHALLENGES

The standard of medical records in the next decade will be individual genomes, so that any strategy concerning ethical issues should take this into consideration, protecting the information and in turn avoiding any obstacle for the arising technology.

The Genetic Information Non-Discrimination Act (GINA) enacted in 2008 by the US Congress was designed to proscribe the inadequate utilization of the individual genetic information in health insurance and employment. Nevertheless, several further improvements can be performed regarding security and privacy issues. Among them, new measures to protect database security and controls on data use are necessary, as well as procedures for encryption, password protection, audits, and access codes for each transaction at interoperable electronic databases shared by clinicians and clinical researchers.

Also, an accurate correlation between individual genetic information and its clinical studies, including drug response and organism behavior, should be achieved avoiding any compromise regarding the privacy of the patient, which undoubtedly represents a critical point.

EDUCATION CHALLENGES

Physicians and patients need education concerning the right use of the associated technologies striving for a personalized approach to medicine, as well as a clever interpretation of data outcomes from genetic tests.

Furthermore, physicians need to learn more about these advances from a point of view significantly different to traditional faculty. Personalized medicine needs to be introduced to physicians at formative stages, enabling a more comprehensive map of opportunities for patients facing a novel treatment.

INTELLECTUAL PROPERTY CHALLENGES

The advent of a variety of technologies regarding personalized medicine brings about certain complexity in getting traditional patent protection. Citing the example of the US Patent and Trademark Office (USPTO), the intellectual protection for certain types of personalized medicine approaches, including genetic diagnostics, has been reported as a crucial challenge nowadays.

At this concern, the critical point relies on the measurements of the amplification of a single gene as part of some personalized medicine diagnostics approaches, attempting to generate a score associated with drug response or disease severity by using predictive modeling algorithms. The underlying difficulty evidenced in obtaining effective patent protection for this type of diagnostics process takes place from the possibility to explore various combinations of biomarkers developing equivalent predictive models.

This prospect of conflict leads to an uncomforted position for the patent applicant. Broadly speaking, the situation indicates that, for a simple combination of a few of the total genes, if the predictive power results are appropriate, a patent for a single combination of such genes, null all possibility of patent protection.

FINAL COMMENTS

Although the main competitive behavior around the pharmaceutical industry is based on technology differentiation and cost-based strategies, the rules governing the course of the industry are based on a complex understanding of the principal actors' interaction. On that note, some valuable insights can be obtained from such an analysis regarding competitive issues, technical strategy, and market strengths.

It is remarkable that particular industries, including pharmaceutical and biotechnology, are significantly influenced by economies of scale, so that big actors are implicated in the final market perception. Therefore, leadership and differentiation are directly related to the first movement attempting to get a competitive position. In that sense, the categorical strategy consists of leaving competitors unarmed to face the shifting circumstances.

Naturally, in the industries driving personalized medicine, competitive strategy is crucial, being difficult for a company to generate competitive advantage within this cluster of innovative and competent industry actors. Indeed, in recent years, as the top pharmaceutical firms have merged and grown, they have become more diversified in terms of therapeutic focus.

Therefore, the trend consists of the concentration on niche areas, having smaller end-markets, and comprising specialist physicians and interdisciplinary research teams. This approach provides companies with more competitive strategies to effectively exploit their capabilities, allowing them to offer advantages other than simply money when negotiating new deals. With this focus, the main challenge consists of choosing the right areas to focus on and thus move toward new opportunity scenarios. ◆

BIOGRAPHY

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TRANSDERMAL DIFFUSION

In Vitro Diffusion Studies in Transdermal Research: A Synthetic Membrane Model in Place of Human Skin

By: Vivek Joshi, PhD, David Brewster, and Peter Colonero

INTRODUCTION

Delivery of drugs via a transdermal route can offer a number of advantages over delivery via oral or intravenous routes, including the avoidance of first-pass metabolism and possible gastrointestinal tract difficulties, a more controlled release of the drug, and improved patient compliance. Limitations of transdermal delivery include the risk of irritation and sensitization.

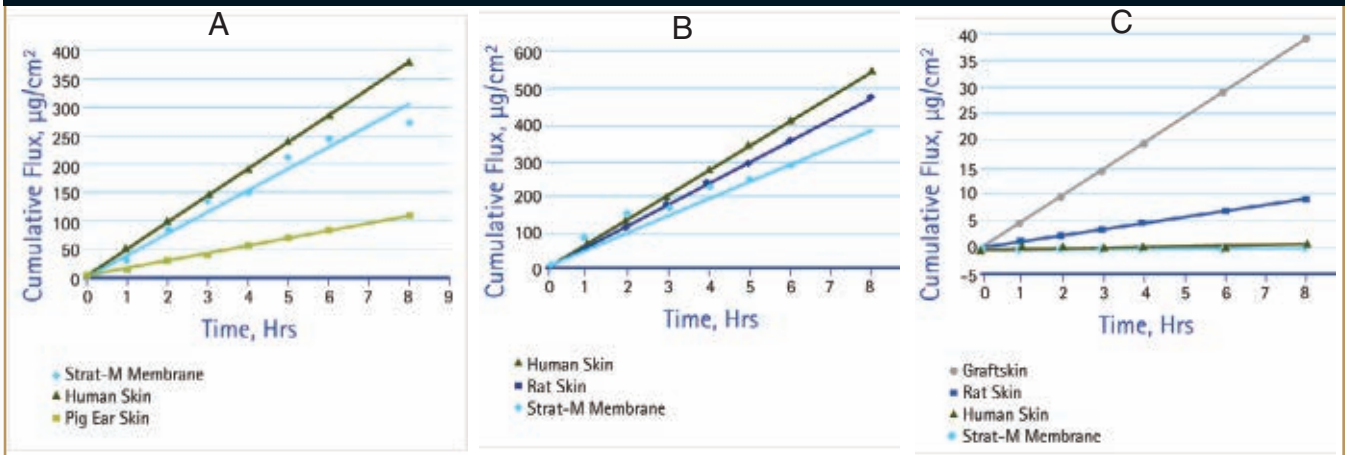
During development of transdermal drugs, assessment of percutaneous adsorption of the active pharmaceutical ingredient is critical. These studies are typically conducted using human cadaver skin or animal models. Unfortunately, a number of drawbacks to these models exist. Human cadaver skin can show high variability; intra-lot skin variability can be as high 22% to 37% whereas inter-lot variability can be as high as 50%.[1]

A recent publication describes this high inter-lot variability of human skin for a number of compounds, including benzoic acid, testosterone, and caffeine.[2] Diffusion through human skin is also dependent on the site from which the skin is removed (arms, legs, or trunk), and diffusion is also affected by the age, race, and sex of the donor.[3]

Of the various animal skin models currently used for transdermal diffusion studies, pig skin is considered closest to human skin and provides closer correlation to human skin.[4] Rat, mouse, and mini pig skin are also used as surrogate models for human skin diffusion. While the availability of pig skin is typically not problematic, the availability and cost of these other models can be a challenge.

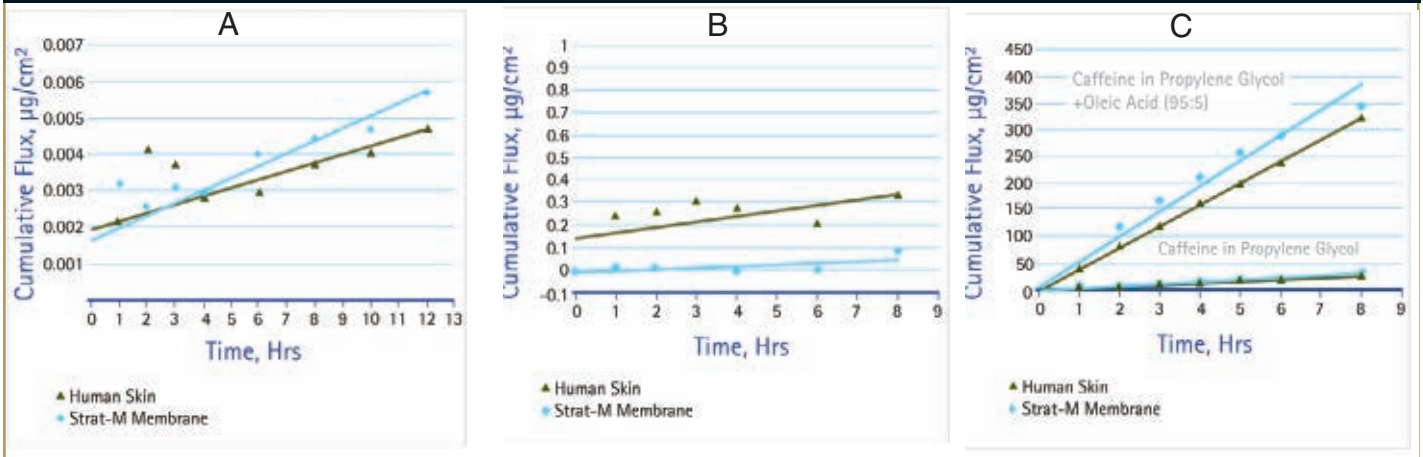
The following presents data on the applicability of a synthetic membrane (Strat-M™) for in vitro transdermal diffusion studies in place of human or animal skin as a model. The advantages

FIGURE 1A,B&C



Diffusion of aspirin (A), nicotine (B), and hydrocortisone (C) through the synthetic membrane and comparison with various skin models used for in vitro diffusion studies.

FIGURE 2A,B&C



Three types of formulations were used for diffusion across the synthetic membrane and human cadaver skin.

and disadvantages of various models typically used in diffusion studies are also discussed.

The Strat-M synthetic membrane is an ultrafiltration membrane composed of polyether sulfone. Multiple layers of the membrane create a morphology similar to human skin. Membrane layers are increasingly more porous and open and also increasingly larger in thickness. The membrane includes a top layer supported by a porous substructure bound to a non-woven fabric support. Both human skin and the membrane display a layered structure with a very tight top layer.

In the studies described further, the porous membrane was treated with synthetic lipid chemicals. Skin contains various lipids, such as phospholipids and ceramides, which impart hydrophobic character to skin. As such, the stratum membrane was treated with synthetic lipid materials to mimic the presence of lipids in human skin.

EXPERIMENTAL METHOD

The treated Strat-M membrane was used in permeation studies. Saturated solutions of various compounds (active pharmaceutical ingredients, cosmetic ingredients, and insecticides) were prepared in water or propylene glycol and used in diffusion studies. Diffusion studies were carried out using a vertical Franz cell arrangement. The formulation under study was added to the donor chamber. The receptor chamber was filled with receptor solution (for example, phosphate buffered saline, pH 7.4) and was maintained under constant stirring. Temperature of receptor solution was typically maintained at 37°C. Synthetic membrane, human skin, or any other biological skin model was mounted between donor and receptor chamber, and samples were collected from receptor chamber at various time points, which helped determine the flux of the compound through the membrane

Phosphate buffered saline (pH 7.4) was used as a receiver solution. Permeation studies were carried out over 24 hrs; 500-microliter samples were collected at 0, 1, 2, 3, 4, 5, 6, 8, 10, 24, and 26 hrs. The receiver chamber was replenished with fresh buffer each time sample was withdrawn.

Samples were analyzed by HPLC for quantitation of the analyte of interest. All experiments were carried out with n=6. Experimental data were compared against literature data available on human and animal skin as well as living skin equivalents whenever available.

Hydrocortisone cream (1%), a proprietary sunscreen formulation and a solution of caffeine in propylene glycol and oleic acid were used to study effect of formulations on diffusion characteristics of the membrane. These data were compared against diffusion through human cadaver skin. Physico-chemical properties of some of the compounds tested are shown in Table 1.

RESULTS

In this study, the membrane treated with synthetic lipid chemicals offered a much closer correlation to human skin than the untreated membrane. Preliminary data for various compounds covering a broad range of hydrophobicity (Log P values from -0.13 to +4.05) shows very close correlation of transport characteristics of the treated membrane and human skin. Figure 1 shows the diffusion of aspirin, nicotine, and hydrocortisone through the synthetic membrane in comparison to various skin models used for in vitro diffusion studies. Data reveal the difficulty in correlating animal skin diffusion to human skin.

In many cases, the correlation between treated membrane and human skin is much

TABLE 1

Name	Mol. Wt.	Log P	Log S	pKa	Log D
Caffeine	194.2	-0.131	-1.25	0.63	-0.13
Nicotine	162.23	0.72	-0.24	8	0.02
Acetyl Salicylic Acid (Aspirin)	180.2	1.19	-2.09	3.48	-1.89
Hydrocortisone	362.4	1.462		12.48	1.42
Benzoic Acid	122.12	1.96		4.2	-0.4

Physico-chemical properties of some of the compounds tested.

better than the commonly used skin models (rat, pig, and Graftskin™ LSE™) in in vitro testing of transdermal formulations.

Data for diffusion of caffeine from propylene glycol versus a mixture of propylene glycol and oleic acid shows that the permeability characteristics of the membrane are modulated by presence of an enhancer in a formulation as is the case with human skin (Figure 2). Similar diffusion behavior was observed for each of the formulations with skin and the synthetic membrane.

The shelf life of the synthetic membrane was also evaluated. Very high lot-to-lot reproducibility and shelf life was achieved with the membrane as opposed to human or animal skin (data not shown).

CONCLUSION

Data indicate that the Strat-M synthetic membrane provides much better correlation to human skin in terms of diffusion characteristics for a wide range of compounds and formulations. Addition of an enhancer to a formulation led to higher diffusion of analyte under study similar to human cadaver skin. The synthetic membrane can therefore be used in compound screening as well as formulation screening when working with various transdermal formulations. Similar to skin, effect of enhancer was observed as indicated by increased diffusion through the membrane

Results indicate the synthetic membrane can be successfully used in place of human or animal skin for in vitro diffusion studies to provide meaningful and reproducible information about permeation characteristics of the compound. For compounds with a wide range of physico-chemical properties (Log P and Mol. Wt.) skin-like diffusion characteristics were obtained using the synthetic membrane. ◆

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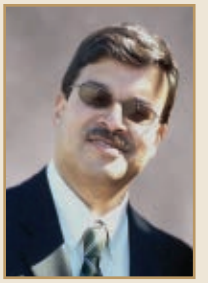

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Special Feature

Analytical Instruments: Global Demands, Innovations & Cost-Savings

By: Cindy H. Dubin, Contributor

There is a global demand for analytical instruments, and industry players are responding with product innovations. Despite the economic slowdown, end-user spending in the US analytical instrument market is expected to increase from $6.6 billion in 2011 to $ 7.3 billion by 2014.[1]

The pharma industry is one of the largest sectors sustaining the analytical instrument market, particularly due in part to pharma's analytical technology (PAT) initiative. Instruments here include process gas chromatographs, process spectrophotometers, process gas analyzers, and process liquid analyzers. Such equipment is enhancing throughput and accuracy and reducing delays in reporting.[2]

Drug Development & Delivery recently asked some analytical instrument providers to describe their most recent analytical instrument offerings to the pharma market, and how they are making these products not only easier to use for faster data analysis, but also how they have developed the systems to be less expensive to meet tighter pharma budgets.

Participants include Terry Adams, Life Science Business Unit Manager, Shimadzu; Tim Freeman, Managing Director, Freeman Technology; Royal Hanson, Chairman, CEO, Hanson Research Corporation; Ian Jardine, Chief Technology Officer, Thermo Fisher Scientific; Dr. Richard Ladd, Senior Director, Pharmaceutical and Life Sciences Marketing, Waters; Richard A. Larsen, PhD, Spectroscopy Product Manager, Jasco; Ciaran C. Murphy, Head of Product Management, Malvern Instruments Ltd; and Geofrey Wyatt, President, Wyatt Technology Corp.

Q: How much of an impact is pharma having on the analytical instrument market?

Mr. Adams: Despite some volatility, the pharmaceutical market, especially if encompassing biopharmaceuticals and CROs, remains a major market that demands attention. R&D continues to be a major focus as there continues to be a need to develop better, more efficient drugs that are targeted to larger percentages of the population. In concert with this, there is a strong need for safer, higher quality pharmaceuticals, so the manufacturing aspect of the market will continue to be a strong player as well. Key to success here is to have a strong global network as many companies will choose to consolidate efforts around the world, thus a global supplier is a must.

Mr. Murphy: From our estimates, pharmaceutical, which includes both small and large complex molecules, would account for about 25% of analytical instrument activity. Timelines for drug development can be between 10 to 15 years, while costs can be from $500 million to $1.2 billion. Investment in analytical instrumentation that can reduce costs and timelines to market typically offers a high ROI. In drug discovery, pharma is a highly sophisticated and demanding user of the latest technology, wherever it brings information and insight. Further along the pharma process into formulation, development, and manufacture, the pharmaceutical industry's use of analytical technology is growing as the industry increasingly focuses on efficient production.

Dr. Ladd: By the nature of the industry, pharmaceutical/life science represents the most innovative segment of the markets we serve. In fact, it is typically the pharmaceutical scientists who are pushing for more sensitive and more efficient advanced technology to meet their analytical needs for a wider array of both regulated and non-regulated applications.

Mr. Freeman: First, pharma is an innovative industry with a significant R&D spend that still relies heavily on bringing new products to market. Analytical information drives that innovative cycle. Second, it's an industry facing new challenges on the manufacturing front with increasing pressure toward greater process efficiency. Understanding how the process works and how to engineer it effectively is essential for competitive manufacture, post-patent expiry, and here too, it is analytical data that provide the necessary knowledge.

Dr. Larsen: Pharma has a significant impact on the analytical instruments market, both positively and negatively. When pharma R&D is increasing, heavy investment in analytical instrumentation is more likely, writing off that investment more quickly than other consumers and constantly purchasing "the latest and greatest." However, when pharma companies consolidate or reduce research efforts or production, there is a corresponding impact on analytical equipment purchases as they do not purchase new equipment, but instead keep and maintain older instruments as long as possible.

Q: According to BCC Research, the global market for process analytical technology (chromatographs, spectrophotometer, analyzers, etc) was valued at nearly $195 million in 2010 and is expected to increase to $279 million in 2015.[3] Can you explain why these instruments have become more critical to R&D scientists in boosting process throughput and efficiency?

Mr. Jardine: Instruments continue to get easier to use and to provide even more accurate information than ever before. For example, drug metabolism or impurity analysis by LCMS/MS can not only identify components, but can quantitate them at the same time, lessening the need for separate quan runs and improving productivity. Anytime more accurate information is provided, this usually reduces the requirement for repeat runs or analysis with orthogonal systems.

Mr. Murphy: Process analytical technology is typically associated with in- and on-line instrumentation that provides real-time process monitoring. Increasingly within the pharmaceutical sector, there is a drive toward QbD (Quality by Design), which is ensuring that variable parameters in the process arena are understood and controlled to achieve consistent quality. What this typically drives in R&D is running a pilot unit under the exact conditions you want to investigate, and also delivers the ability to reliably and efficiently identify cause and effect, thereby accelerating development. Proving technology in R&D so that it can transfer with the process through to commercial operation is also important.

Mr. Freeman: PAT means different things to different audiences. To me, it means analytical technology that measures or controls properties that are critical for efficient manufacture and/or to define product quality. The pharmaceutical industry is currently seeking to transition from empirical batch manufacturing to knowledge-led manufacture, potentially with continuous processing, to access greater efficiency.

Dr. Ladd: A key advancement in chromatography process analytical technology was the analytical speed of sub-2 micron column particle separations. This enabled scientists to realize the potential of using this new-found throughput combined with superior analytical results for process analysis to complement chromatographic data and knowledge sharing from discovery and early development laboratories. In doing so, companies can standardize analytical methods from R&D to product commercialization, boosting productivity.

Q: Whether selling your products to an analytical lab or an in-house pharma lab, what are these customers demanding of analytical instruments?

Mr. Hanson: Faster, better, cheaper! As an analytical instrument designer and manufacturer, this is the mantra I see across the board. We service and support R&D and QC labs throughout the worldwide pharmaceutical industry. We typically see labs requiring increased productivity and throughput, with tight schedules and heavy workloads.

Dr. Larsen: All users are requesting that instrumentation be more compact and less expensive. They also require the software interface be easy to use, more streamlined, and with greater intelligence so that minimal training is required to obtain meaningful data and dedicated technicians are not required to operate the instruments.

Mr. Wyatt: Customers demand the instruments do more, are automated, require less human intervention, and cost the same as previous-generation instruments. While hitting all of these metrics is sometimes like changing the laws of physics (it can't be done), automation is a large theme in whatever analytical instrumentation gets developed.

Mr. Murphy: A critical requirement for pharmaceutical customers - whether in house labs, CROs or CMOs - is the ability to provide complete validation support, which includes lifecycle documentation and 21CFR Part 11 compliance. In addition, flexible instrumentation that efficiently delivers the information to drive development is really important. In many instances, our customers are looking for analytical instruments that reliably provide useful information, for all users, across multiple applications. Quick, easy, highly automated analysis is now essential in areas such as laser diffraction particle sizing because the technique enjoys such widespread use.

Mr. Adams: Key concerns/demands we hear focus on the quality, stability, and robustness of the instruments. In effect, these qualities are tied together. Customers want assurances they are making solid investments that can be relied upon. Many laboratories are running instruments continuously, so purchasing high-quality instruments that won't break down while delivering reliable, precise data is essential. Other demands include easier-to-use software as well as strong post-purchase technical service and support. While many customers are looking for breakout technologies, the reality is that practical, robust instruments are in demand.

Dr. Ladd: The range of laboratory analytical needs is as general and specific as the focus of the organizations that depend on those labs for answers. There is always an interest in higher sensitivity, higher performing technologies to address challenging problems, especially in the early discovery phase of a molecule's lifecycle. There is a need to broaden the use or access of liquid chromatography and mass spectrometry through improved and simpler user interfaces. We are also seeing interest in our fit-for-purpose systems, where instruments, chemistries, and software are designed to address specific applications.

Q: What new products have you introduced to speed up or address issues facing R&D scientists?

Mr. Freeman: Our philosophy is to add new powder testing capability to the instrument as we become convinced of a need. Currently, we believe the shear, bulk, and dynamic test capabilities of our FT4 Powder Rheometer cover the vast majority of test applications, so our recent focus has been to refine the software to deliver a better user experience. Our new FT4 Powder Rheometer version 5 software delivers a clean, clear, and intuitive graphical interface with enhanced display of real-time test information. It provides step-by step guidance to assist new users in selecting and running tests while still allowing experienced users the freedom to develop and run bespoke methodologies.

Dr. Larsen: Jasco designs various analytical instruments and accessories in the spectroscopy and chromatography fields to obtain better sensitivity in less time. We have provided simpler user interfaces so that analyses can be obtained as rapidly as possible. These developments reduce the amount of time spent on obtaining analytical data, allowing greater time for interpretation of the data by management.

Mr. Murphy: Our newest product is the Mastersizer 3000 laser diffraction particle size analyzer. It delivers high performance across the broadest of measurement ranges from 10 nm to 3500 microns, and a number of features enhance measurement flexibility and lighten the analytical load. Of significant value to the pharmaceutical industry is a new dispersion unit that extends the benefits of dry measurement to even fragile and cohesive powders. This development cuts measurement times and reduces the environmental impact of analysis. The instrument software, with embedded support, assists at every stage of measurement so that all users can make reliable measurements.

Mr. Wyatt: Our DynaPro Plate Reader and our Mobius zeta potential instrument are both examples of products we have introduced to help scientists make more measurements with less human intervention. Traditionally, dynamic light scattering measurements have been made using single quartz cuvettes. A scientist was required to fill the cuvette, insert it into the instrument, make a measurement, remove the cuvette, empty the sample, clean the cuvette, and then introduce another sample and repeat the entire process. Obviously, this is a tedious procedure - at best. Our Plate Reader was designed so a scientist could introduce anywhere from 1 to 1,536 samples onto a standard well plate, insert the well plate into the DynaPro, and walk away for however many hours - or days - it took to complete the measurements. Similarly, our Mobius instrument enables the automation of measurements that were formerly labor-intensive, individual operations.

Dr. Ladd: We collaborate very closely with our customers to understand their needs and how that might drive our future portfolio. We know that because R&D areas within pharmaceutical organizations have been hardest hit with budget and resource cuts and LC/MS is moving out of the realm of expert users and into the hands of non-experts. Waters' UPLC retains the core operating principles of traditional HPLC. Pairing UPLC with mass spectrometry performance and versatility, engineered simplicity yields pertinent MS information from fewer experiments in the simplest manner possible, allowing every scientist to convert data into critical business and organizational knowledge in less time.

Mr. Adams: Two recent introductions are the LCMS-8030 triple quadrupole mass spectrometer and the Perfinity Workstation. LCMS-8030 combines LC performance with advanced mass spectrometry technologies to create fast detection. With polarity switching of 15 m/second, an ultrafast scan speed of 15,000 u/second, and 500 MRMs/second, the LCMS-8030 keeps pace with the chromatographic resolving power of our UHPLC systems. Perfinity exploits new separation technology to automate sample preparation. This platform integrates each step of the mass spec sample preparation process: affinity selection, buffer exchange, digestion, desalting, and reverse phase separation. Automated integration of these steps removes much of the error, time, and cost associated with mass spectral analyses of proteins. Protein digestions can now be performed in less than 4 minutes with high reproducibility.

Mr. Hanson: Our specialized focus is in the field of dissolution testing, which is an in vitro release rate test of pharmaceutical dosage forms. We have just introduced a new dissolution test platform including new testers with automated sampling, collection, and analysis. We designed these systems for maximum versatility and flexibility for the research and quality control scientist, such that one instrument platform may handle a multitude of varying analytical test protocols.

Mr. Jardine: Many products from faster more convenient sample preparation to high resolution/high mass accuracy mass spectrometry. For instruments, more easy-to-use and applications-focused software is in high demand. In sample preparation, we have added a new electronic pipette platform, pipette stand, and reloadable rack.

Q: How are you working with pharma/biopharma to help them take advantage of all that analytical instrumentation offers but still keep their costs down?

Mr. Murphy: Getting the most from an instrument relies on understanding its capabilities and how to exploit them to reach your goals. We have experts in all the technologies we deliver to help customers get the most from their instruments. In addition, we understand how our techniques can be applied in combination to leverage a more comprehensive information flow that maximizes the return on analytical spend. We are also conscious that our analytical instrumentation is used in critical areas within the pharmaceutical pipeline, including the production arena.

Mr. Freeman: I believe an important issue here is the level of support we offer and the quality of that support. For us, the focus has always been on how we can test powders so we can process them more efficiently. We have a dual focus: development of the most useful powder tester and the application of that tester to solve real-world problems. We're active in all the industries we serve to understand the problems they face, and we invest substantial research resources in-house to advance our understanding of powders. These activities elevate the level of support we provide to customers to help them optimize their use of the instrument and solve the problems they face.

Dr. Ladd: When it comes to a question of cost, we work with our customers to look at the larger picture of their organizational needs. We believe in working with our customers to understand their challenges to provide innovative, high-performing technology. So when we talk with our customers about costs, we demonstrate how our technologies support higher productivity, optimized laboratory operations, and the capability of making profound discoveries.

Mr. Adams: Shimadzu has a strong history of working with customers to provide applications-based solutions. One example is our work with Eisai, which has led to the development of online sample preparation LC systems designed to improve productivity by automating complicated sample preparation processes. This joint development with Eisai began in 1997 and has resulted in a number of systems, the most recent being one called Co-Sense for Impurities, which was developed partly in response to the recent guidelines for genotoxic impurities. By partnering with the thought leaders, identifying market needs, modifying our off-the-shelf versatile modules for HPLC, and providing customized software, we can create various workstations directed to solve problems in a very cost-efficient manner.

Mr. Hanson: Our instrument platforms are modular, such that different instrument components may be configured to achieve maximum productivity for any given test requirement and application. This means specific instrument components may be selected to achieve specific desired results, eliminating redundant investment. We also provide support and preventive

maintenance programs to our customers to keep our systems qualified and on-line, avoiding down time and resulting costs.

Dr. Larsen: Many users want dedicated analysis methods, so we are constantly trying to research these applications and provide them as standard methods for our instrumentation. In addition, we are always discussing customer requirements, so as we continue to develop new generations of analytical instruments, we can incorporate these suggestions and requirements into the newest analytical instruments we provide. By removing unnecessary components or capabilities, we can provide instruments with enhanced capabilities, but with lower investment and maintenance costs.

Q: What do you see as the trends for the future of the global analytical instruments market? Please explain.

Mr. Adams: Generally, the industry will remain strong and fairly stable but with periods of mergers and acquisitions as companies look to complement their product offerings with other established players. Specifically, there will be a continued push to develop faster, more robust instruments that can improve a laboratory's efficiency and productivity. Instrument manufacturers will also be pressed to make these instruments easier to use, more compact to conserve laboratory space, and more environmentally friendly.

Dr. Larsen: I believe the global instrument market will continue to increase, perhaps more gradually than before, due to the economic crises in many countries. As more countries become industrialized, they will require analytical instruments for production. Greater product requires that companies invest in analytical instruments to improve their production processes. Analytical instrumentation assures the producer that his products are optimized and will be purchased by the consumer.

Mr. Murphy: There is an ongoing trend toward continuous process analysis, a prime aim for many being the complete automation of control. Going forward, it seems inevitable this trend will continue and that more technologies will go on-line. Having said that, it's also clear customers will be looking to new instrumentation to deliver more information more efficiently. Ease of use is a major issue for lab throughput and as products become more sophisticated, instruments that provide new layers of insight are increasingly important.

Dr. Ladd: The notion of more capability in a single analytical platform seems to be a prevalent need as the industry becomes increasingly cost and resource conscious. A single LC or LC/MS platform is now often relied upon to be used for research or routine analyses. This is especially seen in the organizations that must support larger pharmaceutical companies nimbly and cost effectively, such as academic institutions and CROs. Thus, this puts more emphasis on pairing highly versatile informatics platforms and easily interchangeable components, such as MS ionization sources and multi-column managers, to easily perform a multitude of application-specific tasks and obtain high-quality, relevant answers.

Mr. Hanson: I see developing markets, such as Asia and Latin America, increasing their investment in the quality assurance of medicine, which is a growth area for our instrumentation. I also see a trend toward international harmonization of drug standards and testing, which contributes to the resilience of the global marketplace. Lastly, I see the pharmaceutical industry investing in new drugs and special dosage forms, which is an opportunity for companies such as ours to invest in new technologies to facilitate such research.

Mr. Wyatt: In the future, I believe there will be greater integration among worldwide operations of international pharma companies. At the moment, certain companies allow some choices for analytical techniques in different countries, but as companies try to exploit greater efficiencies, these choices will disappear and one monolithic "solution" will be imposed worldwide.

Q: Is there any topic not yet discussed that you would like to address here?

Mr. Adams: There is a trend for companies to outsource service to a single entity rather than each instrument to its specific manufacturer. The benefit of course is reduced cost and the savings associated with negotiation with a single entity. The downside, however, is that it is almost impossible for the third-party group to have enough knowledge to keep up with enhancements in manufacture as well as possible firmware and hardware upgrades. The loss of the connection and distance placed between the end user and

manufacturer as it relates to existing instrumentation is a concern. Moreover, because many of these companies have an alliance with an instrument manufacturer, there is some threat the service entity will be prejudiced in how they handle maintenance and repair. It is only natural they will tend to provide the best service to the instruments they are most familiar with.

Mr. Murphy: It is relatively easy to read the headlines within the traditional pharmaceutical sector and believe it is all doom and gloom. However, the sector is still growing at a good rate, and the global market is set to exceed $1 trillion by 2015. There is still large R&D investment going into the pharmaceutical sector; however, the characterization challenge is increasingly shifting from small to large complex molecules. As an analytical instrument provider, we look forward to working with and meeting the future challenges of the sector. ◆

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ODT TECHNOLOGY

Lyoc (Lyophilized Wafer): An Orally Disintegrating Tablet Technology

By: Suniket Fulzele, PhD; Derek Moe, PhD; and Ehab Hamed, PhD

INTRODUCTION

Drug Delivery is often challenged to provide new technologies that offer significant clinical and financial value in addition to research and innovation niche. The innovation designs may involve modifying formulation compositions and manufacturing technologies to achieve new product performance end points. Orally disintegrating tablets (ODTs) offer improved patient compliance as they enable oral administration without water or chewing. The US FDA defines an ODT as "a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue."[1] The 2008 FDA guidance recommends a disintegration time of 30 seconds or less based on US Pharmacopeia disintegration test method and maximum tablet weight of 500 mg. ODTs are preferred by multiple patients groups with swallowing difficulties, including geriatrics, pediatrics, dysphagic, and bed ridden. ODTs also offer potential for product line extension for first-to-market product and marketing differentiation for Over the Counter Products (OTCs).

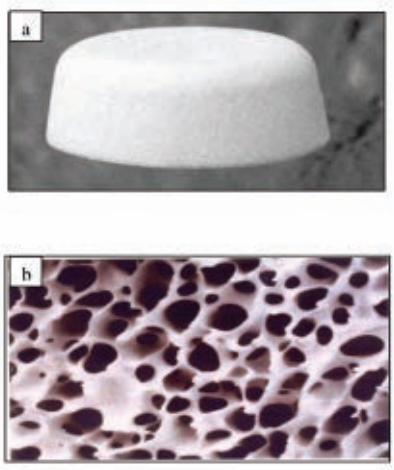
The ODT market is expected to exceed $13 billion by 2015, which is more than double its value in 2009.[2] The increase may be attributed to three main driving factors:

- Increased generic competition and the need for product differentiation.
- Expected increase in the number of prescription products switch to OTCs.
- The 2007 introduction of the European regulation on medicinal products for pediatrics.

This new regulation mandates that all newly developed products (including new indication, new route, and new dosage forms of existing molecules that are still IP protected) to have a pediatric formulation. The European medicinal agency's Committee for Medicinal Products for Human Use describe ODT as having "great promise for children."[3] The committee also acknowledges that taste will be a challenge for these ODTs because a limited quantity of flavor and/or sweetener will be allowed in these dosage forms, and the need for alternative taste-masking techniques like particle coating will be needed.[3]

Tablet compression and lyophilization remain the two most popular industrial approaches to manufacture ODTs. The compressed ODT involves conventional tableting with achieved rapid disintegration using super-disintegrants in combination with lower compression forces and/or the use of water-soluble excipients. Direct compression is often the technique of

FIGURE 1A&B



Lyoc Tablet (a) Porous Structure (b)

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choice. Some of the patented compressed ODT technologies include Flashtab, Advatab, Orasolv, Durasolv, Wowtab, and Ziplets. The lyophilized ODT employs the process of lyophilization in which solvent is removed from a frozen drug solution or suspension containing structure forming excipients. The lyophilization manufacturing process produces wafer with greater porosity, allowing for shorter disintegration times than compressed ODTs. The patented lyophilized ODT technologies include Zydis, Lyoc, and Quicksolv. The advantages and disadvantages of both (compressed and lyophilized ODTs) have been extensively reviewed in literature.[4-7] Other techniques to manufacture ODTs include spray drying, molding, thin films, melt granulation, extrusion, and sugar floss.[8] The following article reviews the lyophilized wafer technology, specifically Lyoc, that offered the world's first ODT, ODA Lyoc (sodium saccharinate and flamenol) in 1968.

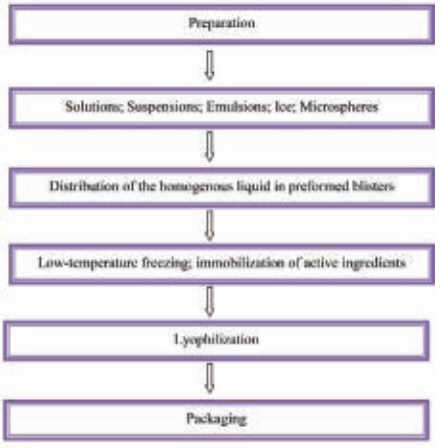
LYOC TECHNOLOGY

Lyoc technology is an oral solid porous dosage form that immediately dissolves in the mouth without the need for water (Figure 1). The technology is suitable for a variety of actives with different physicochemical properties and can be tailored to incorporate drug particles with different functional coatings, including taste-masked, extended-release, and modified-release coating. There are currently seven commercialized ODT products utilizing Lyoc technology, including Spasfon-lyoc (phloroglucinol), Para-lyoc (paracetamol), Proxa-lyoc (piroxicam), and Loperamide-lyoc (loperamide).

Lyoc utilizes a unique manufacturing process based on an innovative non-polluting, environment-friendly, freeze-drying technology that yields high purity and safe products as it operates in the absence of organic solvents. The typical Lyoc manufacturing steps (Figure 2) include:

- Preparation of a suspension, solution, or emulsion containing active ingredients.
- Distribution of this liquid homogenous preparation in preformed blisters (Figure 3).
- Very low temperature freezing (preferably below -40°C). At this stage, the active molecules are immobilized; their properties remain unaltered as the rate of chemical reactions is nearly nil at this low temperature.
- Sublimation or water elimination: this is typically carried out at low temperature and low pressure. Under particular conditions, the ice is directly converted into the vapor phase. The lyophilization step is depicted in Figure 4.
- The finished product is a porous solid capable of very rapid disintegration (Figure 1). The active ingredients remain in a dispersed state within the mass.
- Sealing the blister with top foil.

FIGURE 2



Lyoc Manufacturing Process

FIGURE 3

Lyoc-Filling Process

FIGURE 4

Lyophilization Step Involved in Lyoc Manufacturing

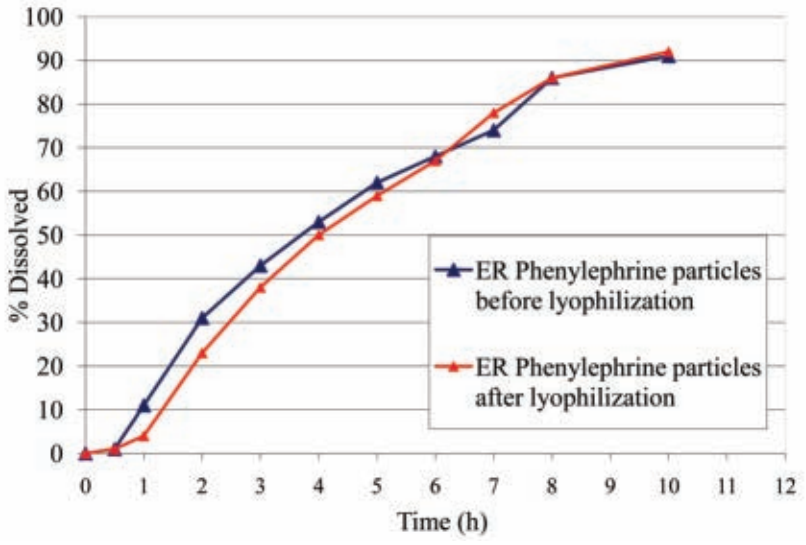
MANUFACTURING CHALLENGES FOR LYOPHILIZED ODTs

Two main challenges face the development of lyophilized ODTs; the rarity of industrial-scale manufacturer with the appropriate know-how and the difficulty in incorporating drug particles with functional coat into the product.

Manufacturing Know-How

To the authors' knowledge, there are currently only two companies that are approved to manufacture lyophilized wafers on industrial scale in Europe and US, Catalent Pharma Solutions and Cephalon. The uniqueness of the manufacturing process has limited the number of contract manufacturing organizations (CMOs) that offer the technology. With the expected increase in the number of ODT products, commercial incentives could lead to an increase in the number of CMOs that provide the technology. However, given the inherent complexity in the formulation design and manufacturing process development, a long learning curve is expected before any new company masters the manufacturing process development. Lyoc technology offered by Cephalon has been used to commercialize ODTs since the late 1960s. The manufacturing facility is approved by the EMEA and other regulatory authorities. The accumulated know-how has streamlined the development process to allow the fast production (three batches per day for each freeze dryer) of robust lyophilized wafers that can be packaged in push-through foils, a feature that is not affordable by many compressed tablets ODT technologies due to the production of soft tablets that are much more friable.

FIGURE 5



Dissolution Profiles of Extended-Release Phenylephrine HCl

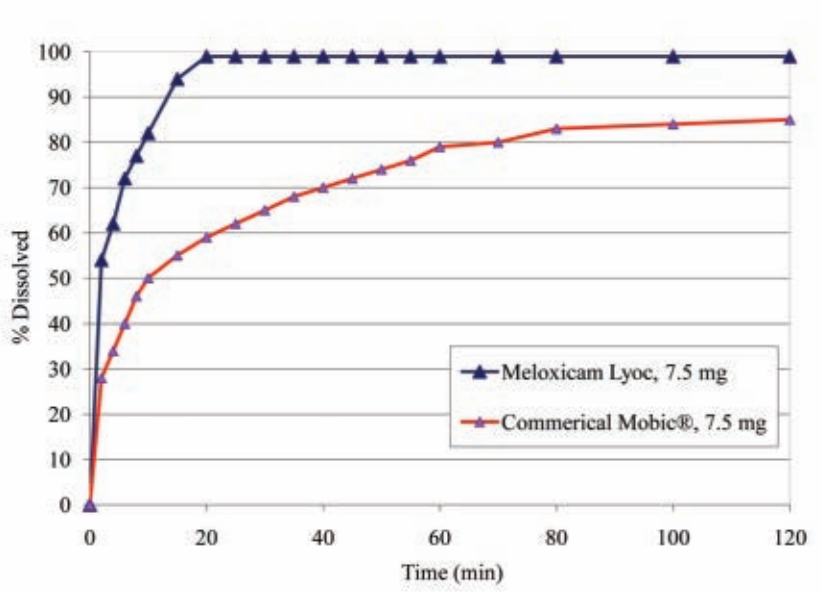
Incorporation of Drug Particles With Functional Coat

The difficulty in incorporating coated drug particles into a lyophilized wafer has limited the spread of the technology as a large percentage of orally administered drugs have bitter, unwanted taste, which may require particle coating for taste-masking. This difficulty also limited the use of lyophilized ODTs to provide extended-release or delayed-release features. The difficulty stems from the following two factors: (1) the need to reduce "drug leakage" from the coated drug particle during manufacturing, and (2) ensuring the drug suspension can sustain the freeze drying process and still yield a highly porous and robust dosage form.

Reducing Drug Leakage During Manufacturing

As previously described, the Lyoc manufacturing process includes suspending the drug particles in an aqueous system before dosing into preformed wells. During scale-up to manufacturing scale, the duration of time needed to prepare, dose the suspension into wells, and freeze is significantly longer than what is typically employed during prototype development. This could lead to failure during scale-up if the formulation component, particularly the taste-masked component and the solution used are not appropriately optimized. Batch-to-batch variability in suspension preparation and dosing time during routine commercial manufacturing must be factored in during prototype development. Therefore, one of the lyophilized ODTs critical quality attribute (CQA) that must be tested and confirmed during prototype development is the prevention of drug leakage in the manufacturing solution for an extended period of time (preferably at least 6 hours). The developed formulation must allow immediate drug release in the stomach, which is typically assessed through drug dissolution using pharmacopeia methods. The balance between these two CQAs (limited drug leakage and fast dissolution) can be achieved through the careful selection of the taste-masking agent(s) and the lyophilization solution's physical and chemical properties and the understanding of the manufacturing-scale limitations early during prototype development. Ionic strength, pH dependent solubility, osmotic pressure, viscosity, and coated drug particle size can be successfully optimized to protect the particles during production. Figure 5 shows the release profiles of extended-release phenylephrine HCl-coated beads before and after lyophilization. Extended-release drug particles offer a bigger challenge compared to taste-masked particles as even minor drug leakage during manufacturing could lead to the product failing the dissolution requirement. As seen in the figure, the developed Lyoc formulation was able to maintain the drug-release profile from the coated drug particles unchanged after exposing them to suspension in water, dosing, freezing, and drying as Lyoc.

FIGURE 6



Dissolution Profile of Miloxicam Lyoc

Ensuring the Drug Suspension Can Sustain the Manufacturing Process

During scale up, shorter freeze-drying cycles are mandated for obvious cost-reduction rationale. For all lyophilization processes, the drying steps are the longest and are typically the focus of process optimization to shorten the production cycle. To achieve this, drying processes are "pushed" to higher shelf/product temperature. The formulation must be designed to have high product collapse temperature (preferably above -5°C), which is achieved through the use of high level of bulking agents like mannitol and glycine. Mannitol is an obvious excipient of choice for any ODT owing to its slight sugary taste and cooling sensation that improves the palatability of the product. However, with the introduction of other excipients to minimize drug leakage from the coated particles, a decrease in product collapse temperature can be expected due to the formation of a glassy phase during freezing. For decades, Lyoc formulations have been successfully designed with the aforementioned balance in mind. The optimized Lyoc formulations are designed to sustain primary and secondary drying in less than 6 hours without melt back or collapse.

FUTURE TRENDS FOR LYOC

In addition to its application in manufacturing ODTs, Lyoc technology can also be used to prepare buccal wafers and improve drug solubility/bioavailability. Buccal wafers can be designed to offer oral disintegrating attributes for patient

compliance and/or product differentiation or it can be used to prepare the dosage forms for buccal delivery. For drug solubility/bioavailability enhancement, Lyoc technology can be used in conjunction with other formulation/excipients approach to enhance drug solubility. For example, the drug can be formulated into a microemulsion that can be converted into a "self-microemulsifying system" upon lyophilization. Figure 6 presents the dissolution profiles of a Lyoc meloxicam micro-emulsifying formulation compared to the marketed product Mobic®. Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) that is practically insoluble in water. The poor solubility is a limiting factor for gastrointestinal absorption and subsequent onset of action, which restricts the use of meloxicam for acute indications. As seen in the Figure 6, meloxicam Lyocs shortened the time needed to release more than 80% of the dose from 75 to 80 minutes for the commercial product to about 10 minutes. The fast meloxicam dissolution was maintained following prolonged storage.

SUMMARY

Lyoc offers innovative and wide-ranging possibilities to pharmaceutical formulation development. The technology has evolved to allow the incorporation of coated particles, which widens the technology application to include more efficient taste-masking, delayed-release, and extended-release dosage forms. Combining the pharmacological and therapeutic advantages aside from pharmaco-economics, Lyoc brings a strong differentiation to product lines. It allows optimizing new products, extending existing ranges, and even strengthening the patent protection of older products. ◆

ACKNOWLEDGEMENT

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BIOGRAPHIES

Dr. Suniket Fulzele is an experienced drug delivery and formulation development scientist. He joined CIMA Labs, a Cephalon Company, in 2010 and is involved in developing immediate- and modified-release oral solid dosage forms. Prior to this, Dr. Fulzele worked at Nektar Therapeutics and Aradigm Corporation. He earned his PhD in Pharmaceutics from Nagpur University, India, followed by post-doctoral research at Florida A&M University. He has published over 100 peer-reviewed research articles, abstracts, and patents.

Dr. Derek Moe is currently Vice President, Drug Delivery Technologies at CIMA Labs, a Cephalon Company. Dr. Moe came to CIMA in 2001 from the formulation group at Pfizer Global Research and Development in La Jolla, CA (previously Agouron). He began his career as a Formulator at Syntex, Inc. in Palo Alto, CA. Dr. Moe earned his PhD in Pharmaceutics from the University of Minnesota and his BA in Chemistry and Math from St. Olaf College.

Dr. Ehab Hamed started as a Formulation Scientist at CIMA Labs nearly 10 years ago and is currently the Director of the Formulations Department at CIMA. In this role, he is responsible for all internal and partnered new drug product formulation development, including prototype design, CTM manufacturing, process scale up to pilot and commercial scale, as well as commercial products transfer between sites. He also provides technical leadership role in IP strategy/litigation, technology/product valuation, and regulatory filings. He has numerous patent applications, book chapters, and published articles to his credit. He is a pharmacist by training and earned his PhD in Industrial Pharmacy from the University of Cincinnati.

DRUG DEVELOPMENT Executive

UNILIFE medical solutions

Alan Shortall
CEO

Unilife Corporation

"Market-leading, differentiated devices that can protect healthcare workers, enhance patient care, or improve therapy compliance can help a drug beat its competition. In addition, there are more than 30 biologics now approaching patent expiration with combined revenues of nearly $50 billion. Pharmaceutical companies recognize that the transition of these drugs to superior devices that are not accessible to biosimilar competitors can extend product lifecycles by protecting or retaining market share."

UNILIFE: DEVICE TECHNOLOGIES TO ENABLE COMMERCIAL SUCCESS

Unilife Corporation is a US-based developer and commercial supplier of a diversified portfolio of advanced drug delivery systems. The company serves pharmaceutical and biotechnology companies seeking access to innovative, differentiated devices that can enable and enhance the delivery of their injectable therapies. Proprietary technology platforms developed by Unilife in direct response to unmet market needs include: prefilled syringes with integrated safety features, drug reconstitution delivery systems, auto-injectors, subcutaneous patch systems for large-volume doses, and novel devices for targeted organ delivery. In January 2010, Drug Development & Delivery interviewed Unilife CEO, Alan Shortall, to discuss his company's unique business model, transformational approach to the market, and his thoughts on how to move forward. Just recently, we met with Mr. Shortall once again to discuss Unilife's unique evolution and steady progress throughout the past year and what lies ahead.

Q: Unilife started as a safety syringe specialist and has grown rapidly in the past few years. Can you describe what Unilife is now?

A: Unilife has developed a full range of prefilled and hypodermic safety syringes with our distinctive system of automatic, operator-controlled needle retraction. But Unilife is much more than a safety syringe company. By addressing the device innovation needs of pharmaceutical companies with speed, agility, and reliability, we have quickly expanded the size and scope of our business. Today, Unilife is a US-based developer and commercial supplier of advanced drug delivery systems. Our innovative, market-leading platform of device technologies can help to enable or enhance the commercial success of injectable drugs and vaccines, protect healthcare workers, and improve patient care. Combine this with our deep industry expertise, advanced operational capabilities, and entrepreneurial structure, and Unilife is a business that is perfectly aligned to address the unmet needs of pharmaceutical companies.

Q: Can you provide a brief update of Unilife's expanding product line?

A: We have developed one of the most complete and customer-focused portfolios of advanced drug

delivery systems on the market. At the leading edge of our highly innovative portfolio is the Unifill syringe, the world's first prefilled syringe with fully integrated safety features. Together with other Unifill products, such as the Unifill Select with attachable needles and the EZMix dual chamber syringe, we have an integrated platform of delivery systems that can accommodate the needs of virtually all prefilled drugs and vaccines. Additional market-leading technology platforms we have developed in direct response to the needs of our customers include our AutoInfusor range of subcutaneous pump infusion systems for the patient administration of large-volume drugs, highly compact auto-injectors with true end-of-dose indicators, and novel devices for targeted organ delivery.

Q: What do you consider to be the most significant unmet market needs for injectable drug delivery?

A: Biologics and other emerging injectable therapies are becoming more complex. They require innovative device solutions that can be developed or customized to address the specific needs of the customer, his or her drug, and the target patient. Off-the-shelf commodity components are no longer good enough. A large and growing number of these emerging therapies are so complex that they must be lyophilized for reconstitution at the point of delivery. Many are also being targeted for self-administration by patients at home. And those products that are used in healthcare facilities must comply with safety laws targeted at protecting healthcare workers from needlestick injuries. In addition, there are increasing levels of competition in many therapeutic classes between novel, generic, and biosimilar drugs. You put all these trends together, and there is a clear need for safer, simpler devices with best-in-class features that can improve therapy compliance and generate powerful brand differentiation for the drug product.

Q: How is Unilife positioned to address these unmet needs?

A: Unilife represents a compelling choice to pharmaceutical companies seeking innovative device solutions for the delivery of their injectable drugs and vaccines. Unlike incumbent manufacturers of me-too products, Unilife provides its pharmaceutical customers with a total system solution. We serve as a one-stop shop for device innovation. Our seamless array of services includes design, rapid prototyping, pilot production, commercial production, packaging, supply chain management, and bioanalytical testing. We also operate under an open architecture model, whereby we can develop or customize each of our products to ensure every customer receives the right device to deliver the right drug to the right patient. Unilife has a proven track-record for serving the unmet needs of our customers with flexibility and reliability, and we look forward to continuing on that trajectory.

Q: What are the key advantages of your lead product, the Unifill prefilled syringe?

A: The Unifill syringe is the world's first and only prefilled syringe with integrated safety features. Unlike conventional safety options that must be attached onto standard prefilled syringes after it's been filled with the drug, the Unifill syringe is the primary drug container. It has been designed for integration into fill-finish lines now used with equivalent standard prefilled syringes, and has USP class six compliant materials in the drug fluid path. This can streamline the fill-finish process, and reduce packaging, transport, and storage costs by as much as 70%. Because the Unifill syringe has automatic, operator-controlled needle

retraction features fully integrated within the glass barrel, it offers optimal protection from harm and is highly intuitive for use by both healthcare workers and patients. The Unifill syringe is a game-changer in the pharmaceutical market for prefilled syringes, and can be leveraged by our customers to optimize the lifecycles of their drugs and vaccines in competitive therapeutic markets. Initial production of the Unifill syringe has now commenced at our US facilities, with the device now available for supply to customers seeking to commence stability studies.

Q: Why did Unilife expand beyond the Unifill syringe and enter into other markets for drug delivery systems?

A: It has never been our strategy to be a one-product company. Our plan all along has been to use the Unifill syringe as a showcase for our unparalleled capacity for innovation and meeting project milestones. Throughout the past few years, our number one focus has been to complete the commercialization of the Unifill syringe. I am proud to say that this massive program was completed ahead of schedule. By doing what many thought was impossible with the Unifill syringe, we have received many other inquiries from pharmaceutical companies asking for our collaboration to solve some of their other needs for the delivery of their emerging therapies. Every one of our new technology platforms, including auto-injectors, drug reconstitution delivery systems, subcutaneous drug infusion systems, and organ delivery devices, has been developed in direct response to unmet customer needs.

Q: Can you tell us more about your new production facility in York, PA?

A: Our state-of-the-art facility and global headquarters enables us to serve both the current and future needs of our customers. It was designed by US pharmaceutical architects of choice to serve as an integrated center for device innovation. The $32-million 165,000-sq-ft first-stage of the facility was constructed fully on schedule in just over 1 year. It features 11 cleanrooms where environmental factors are tightly controlled, as well as bioanalytical and quality labs, a product development center, and an advanced warehouse. The facility is a key business enabler for our company. When pharmaceutical customers visit us, they quickly recognize that we have the operational capabilities, quality assurance systems, and expertise to serve as a long-term preferred partner.

Q: Why are devices playing such a big role in brand differentiation for drugs and vaccines?

A: There are more than 1,000 injectable drugs and vaccines now in development. It can cost more than $1 billion to bring these drugs to market, where they must often struggle to secure market share against incumbent competition. Market-leading, differentiated devices that can protect healthcare workers, enhance patient care, or improve therapy compliance can help a drug beat its competition. In addition, there are more than 30 biologics now approaching patent expiration with combined revenues of nearly $50 billion. Pharmaceutical companies recognize that the transition of these drugs to superior devices that are not accessible to biosimilar competitors can extend product lifecycles by protecting or retaining market share. Pharmaceutical companies with generic and biosimilar drugs have major competitive advantage if they have access to a device that is safer and simpler than the innovator product.

Q: Why are pharmaceutical companies partnering with you during the clinical development of pipeline drugs?

A: Unilife helps enable and enhance the commercial success of injectable drugs and vaccines during all stages of their clinical development and commercial lifecycles. When it comes to a pipeline drug, we will look to work in parallel with the customer to develop a device to address its specific molecular, formulation, packaging, and patient needs. This can help a drug secure regulatory approval and generate competitive brand differentiation upon its commercial launch. Furthermore, regulatory agencies, such as the FDA, review claims for the filing of the overall drug-device combination product. A device can therefore generate unique regulatory claims to support the filing of the combination product. A generic or biosimilar rival could be obstructed from submitting an ANDA if they could not find an alternative device with equivalent performance or operating principles. Unique devices can therefore help to obstruct the entry of generic or biosimilar competition, which could add significant value to the lifecycle of a brand name drug.

Q: One of the fastest-growing areas for injectable drug delivery is auto-injectors. As Unilife has just developed its first auto-injector, what makes yours different?

A: Traditional auto-injectors are very bulky because they need to conduct a number of steps, such as the insertion of the needle into the patient, the injection of the dose, and the withdrawal of the empty prefilled syringe into the chamber. And they have no true end-of-of dose indicator. This means patients might remove the device from the body before the full dose has been injected. This can reduce patient compliance with treatment. A standard rule for the industry is that the easier and safer it is to inject the drug, the more likely it is for physicians to prescribe that drug for use by the patient. For many auto-injectors, it is also very easy to get a needlestick injury if a finger was placed into the hole at the base of the device once the prefilled syringe has been withdrawn. Our range of auto-injectors are unlike anything else on the market because the leverage the design and safety features of the Unifill syringe. They are ultra-compact for easy handling and portable transport. The Unifill syringe also has an audible, tactile click to alert the patient to true end-of-dose. As soon as the patient hears the click, it can be removed from the body where he or she can view the retracted needle inside the window. This automatic needle retraction mechanism virtually eliminates the risk of a needlestick injury. In fact, the patient never sees the needle during the injection of the dose.

Q: What's in store for the future of Unilife?

A: We have received very strong levels of acceptance for the Unifill syringe from customers, healthcare workers, and patients. As a result, there are now many opportunities for the Unifill syringe that we are now advancing in our commercial pipeline. These include pipeline and approved drugs targeted for use across a number of therapeutic drug classes, and may in some cases also incorporate special access fees.

We also expect to enter into multiple agreements with pharmaceutical customers for the clinical development and industrialization of other products in our expanding device portfolio. Indeed, we expect to begin serving as a preferred partner for innovative device solutions to many customers who require our support in enabling or enhancing the commercial success of their injectable drugs and vaccines. ◆

Technology & Services Showcase

Contract Diagnostics

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Pharmaceutical Solutions

Catalent Pharma Solutions is a world leader in patented drug delivery technologies. For more than 70 years, we have developed and manufactured advanced drug delivery systems and partnered with nearly every major global pharmaceutical company. We continually work to advance the science of drug delivery and enhance the therapeutic and market performance of our customers' drugs. Our advanced drug delivery technologies bring new options to resolve the technical challenges development scientists face every day. These patented technologies can improve the odds of successful formulation by enhancing bioavailability, optimizing the rate of release, and targeting the site of absorption. Our technologies include softgel and Vegicaps® Soft capsules; Zydis® fast-dissolve dosage form; modified-release technologies; and a range of inhaled technologies, including MDIs, DPIs, nasal sprays, and solutions/suspensions for inhalation, nebulizers, and liquid inhalers. For more information, contact Catalent Pharma Solutions at (866) 720-3148 or visit **www.catalent.com**.

Albumin Fusion Technology

Novozymes' Albufuse®Flex technology has been developed to tailor the pharmacokinetic profile of target proteins and peptides for flexible use. The new technology is based on the interaction between albumin and the neonatal Fc receptor (FcRn) to extend circulatory half-life. Building on Novozymes' Albufuse platform, AlbufuseFlex has been modified to increase receptor binding and thus should deliver a corresponding increase in the pharmacokinetics of fused or conjugated therapeutics. AlbufuseFlex technology illustrates an exciting new era in drug delivery, offering the potential to increase half-life according to specific medical needs. This should allow delivery of novel drugs with extended circulatory time, reducing frequency of injection and increasing patient compliance. Novozymes' AlbufuseFlex technology has one published patent application and two patent applications awaiting publication. Albufuse® is a registered trademark of Novozymes. For more information on Novozymes' AlbufuseFlex technology, visit **www.biopharma.novozymes.com**.

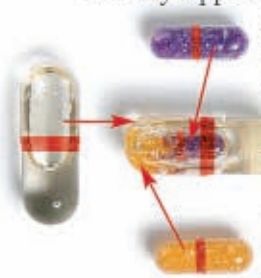
Biopharmaceutical CDMO

Cook Pharmica is a biopharmaceutical contract development and manufacturing organization (CDMO) with process development, clinical and bulk drug substance manufacturing, formulation development, clinical and commercial parenteral drug product manufacturing (including liquid and lyophilized vials, prefilled syringes, and secondary packaging), and an array of supported services all at a single facility in Bloomington, IN. Founded in 2004, Cook Pharmica is a division of Cook Medical, the world's largest privately held medical manufacturing company. For more information, contact Cook Pharmica at (877) 312-2665 or visit **www.cookpharmica.com**.

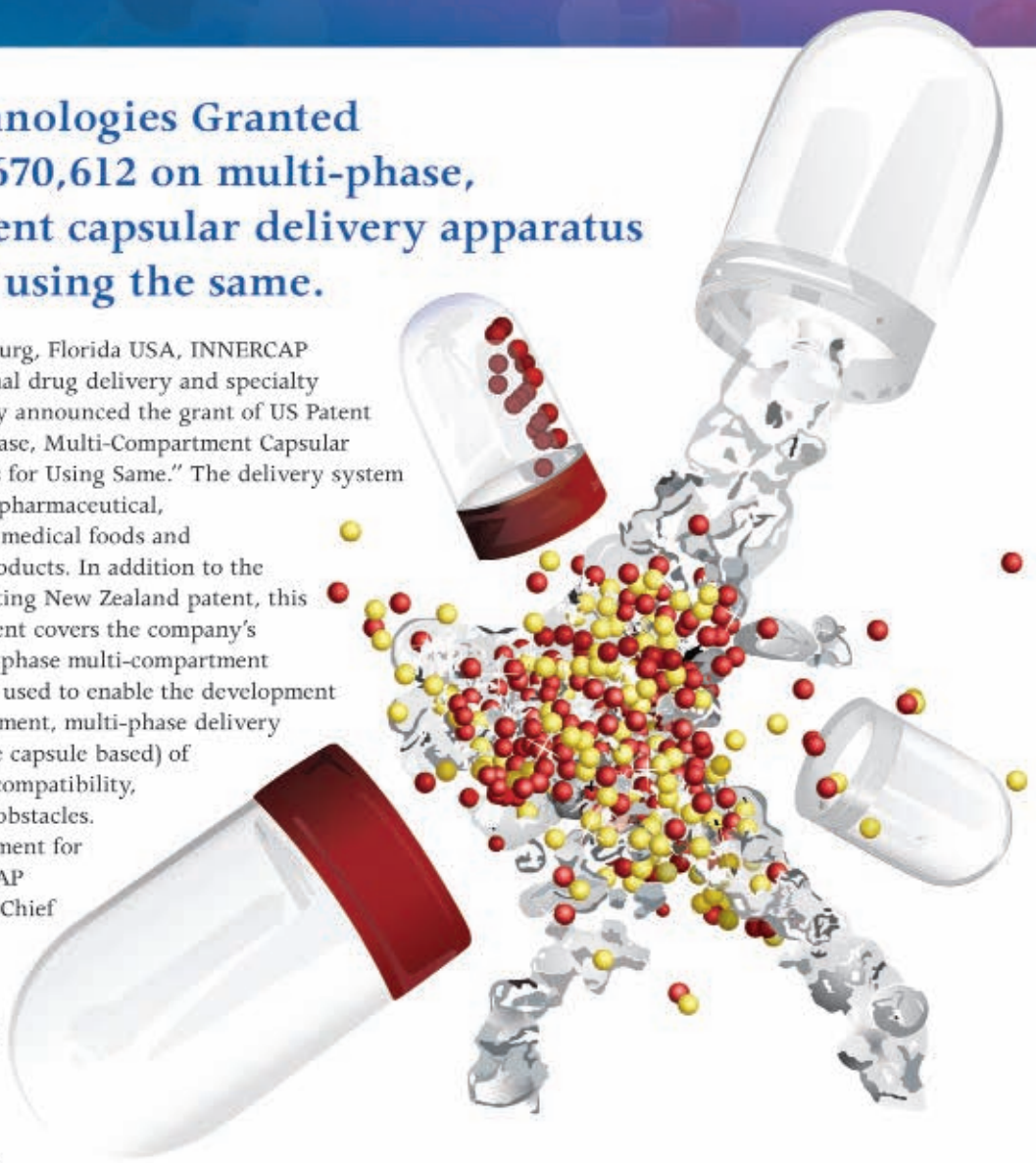
THE ADVANTAGES

OF MULTI-PHASE, MULTI-COMPARTMENT CAPSULES ARE CLEAR

INNERCAP® Technologies Granted US Patent No. 7,670,612 on multi-phase, multi-compartment capsular delivery apparatus and methods for using the same.



March 23, 2010, Saint Petersburg, Florida USA, INNERCAP Technologies, Inc., an international drug delivery and specialty pharmaceutical company, recently announced the grant of US Patent No. 7,670,612 entitled "Multi-Phase, Multi-Compartment Capsular Delivery Apparatus and Methods for Using Same." The delivery system has uses for bio-pharmaceutical, pharmaceutical, medical foods and nutraceutical products. In addition to the existing New Zealand patent, this patent covers the company's multiphase multi-compartment delivery system used to enable the development of multicompartment, multi-phase delivery forms (two piece capsule based) of combination products that have compatibility, formulation or targeted delivery obstacles.



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

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 normally 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 (www.ddkpatent.com) based in New York City.

For more information contact us at the telephone number and email address below:

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Therapeutic Advances in Non-Small Cell Lung Cancer: Targeting Activating & Resistant Forms of EGFR & ALK

By: William C. Shakespeare, PhD, Vice President, Drug Discovery, ARIAD Pharmaceuticals, Inc.

Introduction

Lung cancer is the leading cause of cancer-related mortality in both men and women with approximately 220,000 new cases being diagnosed in the US alone in 2011. Of these, approximately 75% are non-small cell lung cancers (NSCLC), which can be further subdivided based on histology, including squamous cell carcinomas, large cell lung carcinomas, and adenocarcinomas. Throughout the past decade, further subcategorization has led to the realization that NSCLCs are also very heterogeneous at the molecular level, harboring "driver" mutations in distinct genes that disrupt normal signaling and lead to the uncontrolled growth and proliferation of tumor cells (Figure 1). The molecular understanding and subsequent targeting of these subsets has completely revolutionized disease treatment, further supporting the "oncogene addiction" hypothesis - that many tumors have an Achilles heel, and hence can be uniquely targeted with specific small molecule inhibitors and antibodies.[1] Of the many defined subsets, activating mutations in the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) genes may be the most well-defined, and in both cases, small molecule inhibitors targeting each have been approved by the FDA. The following is a brief review of both targets, including approved agents, mechanisms of resistance, and next-generation agents in development, many designed specifically to target disease-resistant mutations.

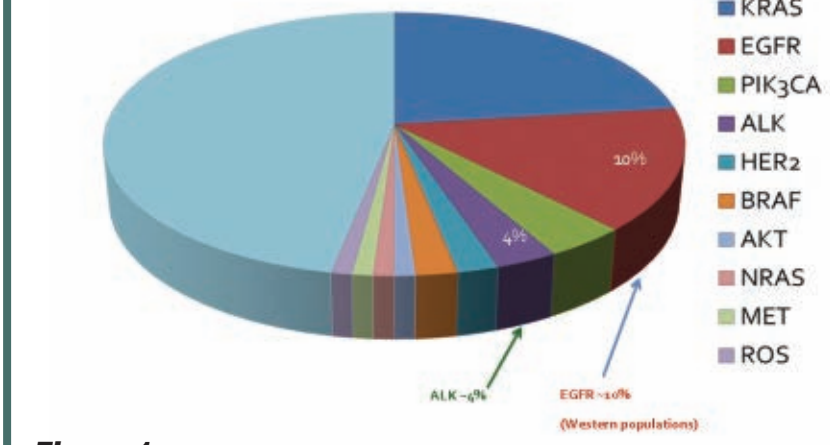

Figure 1.
Genetically Defined Subsets of NSCLC

Mutant EGFR & NSCLC

EGFR is a member of the ERB-family of receptor tyrosine kinases whose ligand-induced homo- and hetero-dimerization leads to intracellular signal transduction controlling key cellular functions, including growth and cell survival.[2] Early targeting of wild-type EGFR for cancer treatment was based on

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observations that gene amplification leading to receptor overexpression was observed in multiple human tumors. This led to a body of preclinical data demonstrating small molecule efficacy in multiple mouse tumor models, including NSCLC.[2,3] Based on these early experiments, gefitinib and erlotinib, two small molecule tyrosine kinase inhibitors designed to target wild type EGFR, were advanced into clinical trials in unselected NSCLC patients who had failed prior therapies. Although overall response rates in these early trials were underwhelming, confirmatory trials identified unique clinical characteristics in those responders, including tumor histology (adenocarcinoma), gender (female), ethnicity (East Asian), and never or light smokers.[4,5] In 2004, several landmark papers identified the existence of somatic mutations in the EGFR gene whose presence correlated well with patient sensitivity to both erlotinib and gefitinib and with those aforementioned clinical characteristics.[6-8] In 2009, results from the IPASS trial unequivocally validated the predictive nature of EGFR mutations to gefitinib.[9] In a subgroup analysis of 261 previously untreated NSCLC patients harboring activating mutations in EGFR and randomized versus carboplatin-paclitaxel, significantly longer progression-free survival (PFS) (9.5 versus 6.3 months) and response rates (71.2% versus 47.3%) were attained. Moreover, the IPASS trial demonstrated that patients without EGFR mutations were insensitive to gefitinib and fared better with standard platinum-based chemotherapy.

The most common activating EGFR mutations observed in NSCLC patients are a substitution of arginine for leucine at position 858 (L858R) in the activation loop (A-loop) adjacent to the highly conserved DFG motif, and a deletion mutation (del E746_A750) adjacent to the glycine rich P-loop. Both occur in equal proportions in approximately 10% of all NSCLC patients.[10] Both mutations render the protein devoid of normal autoinhibitory mechanisms promoting constitutive activity and aberrant EGFR-signaling in the absence of any external ligand. Downstream signaling effects of activating mutations (principally anti-apoptotic) render NSCLC cells highly dependent on functional EGFR for survival and such "addiction" makes them uniquely sensitive to erlotinib and gefitinib inhibition.[11] Interestingly, both mutant versions of the protein bind gefitinib and erlotinib more tightly than native EGFR while simultaneously reducing their affinity for ATP.[12]

Despite what are now the obvious clinical successes in treating patients harboring activating EGFR mutations with small molecule inhibitors, responses are not durable, and all patients ultimately develop resistance to both drugs. The most common mechanism of resistance is a mutation at the gatekeeper position, T790M, which is observed in roughly 50% of all gefitinib/erlotinib-resistant patients.[12,13] In contrast to the analogous BCR-ABL gatekeeper mutation, T315I, which impedes effective drug binding, the presence of T790M has almost no effect on gefitinib binding, but rather restores ATP affinity, increasing binding site competition and rendering both compounds clinically ineffective against this drug-resistant mutant.[12]

Although few reversible EGFR-T790M inhibitors have been reported, multiple compounds targeting the active site cysteine, C797, have been described.[3] These "irreversible" inhibitors form a covalent bond to the protein via C797 permanently

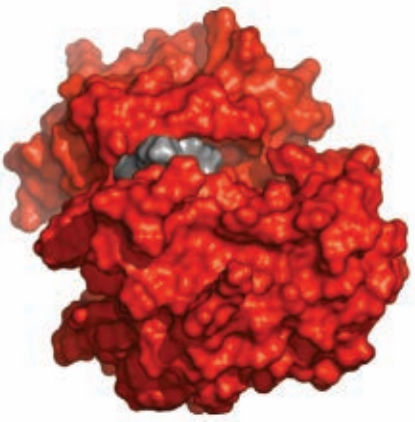

Figure 2.
Model of AP26113 Binding to ALK

inactivating the enzyme. Notable amongst the reported inhibitors are neratinib, canertinib, pelitinib, PF0029904 (all from Pfizer), and afatinib (BIBW-2992, Boehringer Ingelheim). Although many of these inhibitors are active preclinically in EGFR-T790M-driven models both in vitro and in vivo, to date, no second-generation irreversible inhibitors have demonstrated clinically significant, single agent, improvements in patients harboring the T790M-resistant mutation. All designed to target the T790M mutation, most second-generation irreversible inhibitors simultaneously inhibit native EGFR at lower concentrations, potentially promoting toxicity at circulating plasma levels well below what may be required for clinical efficacy in this patient population.[3] Native EGFR is the "natural" receptor, expressed throughout the body but at particularly high levels in both the skin and gastrointestinal (GI) tract. Inhibition, therefore, can lead to clinically observed skin and GI toxicity with non-selective agents. More recently, an irreversible inhibitor with T790M selectivity relative to WT EGFR was reported, but its development status remains unclear.[15] In short, there remains a real unmet medical need for compounds selectively targeting the

EGFR-T790M gatekeeper mutation in resistant NSCLC patients.

ALK Translocations & NSCLC

Anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase in the insulin receptor superfamily, was first identified as a nucleophosmin (NPM) chromosomal rearrangement (NPM-ALK fusion gene) in anaplastic large cell lymphoma (ALCL) and subsequently in other tumor types including diffuse large-cell lymphoma (DLCL) and inflammatory myofibroblastic tumors (IMT).[16,17] Additionally, echinoderm microtubule-associated protein-like-ALK (EML4-ALK) has more recently been identified in 3% to 7% of NSCLCs.[18] In all cases, the ALK fusion partner (eg, NPM or EML4) induces a ligand-independent conformational change resulting in constitutive kinase activation and aberrant and continuous downstream signaling. Preclinical studies with small molecule inhibitors demonstrate that ALK inhibition induces apoptosis and tumor regression in multiple ALK-driven models, highlighting, similar to activating mutations EGFR, a discrete Achilles heel, and identifying ALK translocations as "driver" mutations further underscoring their potential as viable therapeutic targets.[17]

Crizotinib (PF-02341066), a small molecule TKI originally designed to target cMet and subsequently identified to be a potent ALK inhibitor, was the first compound evaluated clinically for activity in ALK-positive NSCLC patients.[19] After screening approximately 1500 NSCLC patients, 82 (5.5%) were identified as ALK-positive by fluorescence in situ hybridization (FISH) and enrolled in the trial.[20] Encouragingly, at the mean treatment duration of 6.4 months, the overall response rate was 57%, and the estimated probability of 6-month progression-free survival was 72%. In a companion publication to the Phase I study, crizotinib also demonstrated activity in an IMT patient driven by a separate ALK translocation.[21] Together, these data provide clinical validation for ALK as a target and further highlight the value of early genotyping in effective clinical trial design and in streamlining the drug discovery process. On the basis of a larger Phase III registration trial comparing crizotinib to single-agent chemotherapy in advanced NSCLC patients harboring the ALK gene, crizotinib was recently granted accelerated approval by the FDA. What makes this story so remarkable is the relatively short time from target gene identification (EML4-ALK, 2007) to regulatory approval (2011), the span of approximately 4 years. While the process was certainly accelerated by the presence of the candidate molecule (crizotinib) in an alternate clinical trial (cMet), it is nonetheless still extraordinary and a likely increasing paradigm for many targeted agents now in clinical development.

Unfortunately, as with other targeted therapies involving "driver" mutations, such as BCR-ABL and EGFR (previously discussed), acquired resistance in crizotinib-treated patients have now been reported leading to eventual relapse.[22] To date, three single-point kinase domain mutations in ALK have been reported. Two were reported in tumor cells identified from a single NSCLC patient, including L1196M at the "gatekeeper" position, and C1156Y just preceding the C-alpha helix.[22] Similar to the gatekeeper mutations in BCR-ABL (T315I) and EGFR (T790M), the site most frequently mutated in acquired resistance to TKI treatment, the EML4-ALK L1196M mutation precludes effective compound-binding substantially reducing potency and leading to patient relapse at clinically achievable crizotinib plasma levels. Although C1156Y does not contact crizotinib directly, it presumably destabilizes the crizotinib-ALK binding conformation leading to reduced potency. More recently, mutation at F1174L in an IMT patient harboring the RANBP2-ALK translocation was reported.[23] Coincidentally, mutation at this position (in full length ALK) has been detected in neuroblastomas and is reported to be transforming.[24] Similar to the C1156Y mutation, L1174 does not make direct inhibitor contact but likely shifts the ALK conformational equilibrium away from that required for optimal crizotinib binding.

Several compounds have recently been reported to have activity against crizotinib-resistant mutations, including TAE684 (Novartis), X-396 (Xcovery), and CH5424802 (Chugai). TAE684, an ALK inhibitor based on the pyrimidine template, was shown in two independent mutagenesis studies to maintain substantial activity against a wide range of crizotinib mutations, including L1196M.[25-27] Similarly, X-396, an aminopyridizane-based ALK inhibitor that shares common structural features with crizotinib was reported to be active against both L1196M and C1156Y.[28] Lastly, CH5424802, a structurally unique ALK inhibitor derived from a screening lead, was also reported to have activity in multiple preclinical models, including oral in vivo efficacy in EML4-ALK 1196M-driven tumors.[29] Of the three inhibitors, only CH5424802 has advanced into clinical trials (Japan) but no data highlighting clinical activity has been reported.

AP26113 Clinical Trials

ARIAD Pharmaceuticals, a biopharmaceutical company based in Cambridge, MA, has been targeting mutant ALK and EGFR for the treatment of NSCLCs, and recently initiated a Phase I/II clinical trial of AP26113 (Figure 2), an investigational dual ALK/EGFR inhibitor (NSCLC, NCT01449461, www.clinicaltrials.gov). Similar to the crizotinib clinical trial structure, the Phase I component will probe initial safety, tolerability, pharmacokinetic profile, and the recommended dose, while the Phase II component will probe preliminary anti-tumor activity through four genetically defined cohorts including:

- ALK+ NSCLC patients with no prior ALK inhibitor therapy;
- ALK+ NSCLC patients resistant to one ALK inhibitor;
- EGFR+ NSCLC patients resistant to at least one prior EGFR inhibitor; and
- Patients with other ALK+ expressing cancers or other known targets of AP26113

AP26113 is unique in that it targets both ALK and EGFR and so has the potential to be two drugs in one. In preclinical models, in addition to being at least ten-fold more potent against the native form of ALK, AP26113 is active against crizotinib-resistant mutations both in vitro and in vivo.[30] Additionally, AP26113 is active against both activating and resistant mutants of EGFR while sparing the native form of the protein.[31] This is in contrast to the aforementioned irreversible inhibitors, which while potent against T790M, simultaneously inhibit the native form of the protein, which may contribute to their observed clinical toxicity. Importantly, oral doses that are efficacious in mice against activated and T790M EGFR are similar to those active against native and crizotinib-resistant ALK mutants, suggesting that AP26113 has the potential to address both clinical needs. Polypharmacology through multitargeted kinase inhibition is not unique to AP26113, but simultaneously targeting two well-defined and important subsets of NSCLC make this investigational agent appealing, and it is believed that expedited development based on this profile should be feasible.

Summary

The approval of crizotinib, and its companion diagnostic (Abbott), for the identification and treatment of NSCLC patients harboring activating ALK mutations is the most recent example of an evolving paradigm of biomarker-driven, targeted therapy, for cancer treatment. Together, with the identification of activating EGFR mutations, almost 15% of all NSCLC patients are thus candidates for treatment with targeted agents based on the identification of one of these two molecular abnormalities. Coupled with the recent approval of vemurafenib for mutationally driven melanoma and imatinib for CML, the exemplar of targeted therapies, the era of personalized medicine in cancer is quickly becoming a reality. Unfortunately, treatment of patients with these "driver" mutations can lead to acquired resistance and so the development of newer, more potent agents will remain an important goal. ■

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Contract Manufacturing

Early is Better: Navigating the Contract Manufacturing Process

By: Eric Resnick, Vice President of Research & Development, Engineering, West Delivery Systems

Introduction

Determining appropriate container closure and delivery systems for a drug product is a complex process. For pharmaceutical manufacturers, the new focus on enhanced requirements and regulatory compliance may mean that in-house research and development efforts are not the most effective or cost-conscious approach to determine a drug product's proper packaging. As a result, many pharmaceutical manufacturers are partnering with companies that focus primarily on packaging and drug delivery solutions in the early stages of a product's lifecycle. Such partnerships can help to ensure that high quality is built into a product's packaging from the earliest stages of drug development. Engaging packaging manufacturers early in the process helps to ensure compliance and patient safety and enhance the overall patient experience.

The Need for Early Partnerships

Pharmaceutical companies are challenged to meet expanding requirements for safety with delivery devices and systems that are compatible with and safe for new drug products. By working with an experienced partner early in the development process, drug manufacturers can create a unique and integrated packaging and delivery system that is at once easy to use and compliant for the end user while ensuring the integrity of the drug product.

Figure 1.
West utilized human factors testing when developing its ConfiDose® auto-injector system. The result was a simple, three-step process that provides users with visual, audible, and tactile features that aid with injection.

There are several reasons the relationship should start early. First is to ensure that packaging is right for the drug product. How the product is going to be delivered should be determined based on the clinical application. This will help the pharmaceutical manufacturer to understand what type of primary packaging is needed, and how that packaging will fit with the delivery system. Ideally, the same material should be used for containment from research through commercialization.

The selection of the ultimate delivery format also should be made early in the development process to ensure timely market introduction. This will enable the selection or development of the most effective combination of container and device, and ensure that appropriate regulatory approvals have been taken into consideration. Working closely together, pharmaceutical and packaging manufacturers can look for ways to differentiate a product through the packaging and delivery systems.

Novel Materials Help Alleviate Packaging Concerns

To make the most of a partnership with a packaging manufacturer, pharmaceutical companies should seek out those who can provide unique container-closure systems that are consistent throughout drug development, clinical trials, and commercialization. Traditional container closure systems are typically made of glass. Because the desired properties for container closure systems include strength, transparency, stability, impermeability, and resistance to chemical attack, glass has long been the material of choice. However, recent recalls caused by glass breakage, delamination, and particulate have alerted the pharmaceutical industry to the risks associated with glass containers.

Figure 2.
The Daikyo Crystal Zenith® 1-mL insert needle syringe can be used within West's ConfiDose® auto-injector system. The combination helps to reduce the risks associated with glass syringes, including breakage and particulate contamination.

Pharmaceutical manufacturers, with the help of delivery systems companies such as West, are introducing new materials for prefillable syringes, including break-resistant cyclic olefin polymers, such as Daikyo Crystal Zenith®, and unique designs that allow for easier and safer injection. These systems are not only manufactured from a novel plastic material that reduces the risk of breakage, but the dimensional tolerances, quality standards, and freedom from materials such as silicone oil, tungsten, or adhesives help to ensure the systems provide the combined benefits of a plastic with the features necessary to contain a sensitive pharmaceutical.

With such materials, companies can create new, easy-to-use, and safe devices and systems without having to conform to the traditional container closure systems, such as glass vials or prefillable syringes. Unique devices can help differentiate a product in a crowded market, and may help with patient compliance.

As packaging manufacturers assume more responsibility for compliance, they must work alongside pharmaceutical manufacturers to apply cGMP to all aspects of manufacturing. Packaging manufacturers often see themselves as filling a void in the device lifecycle. By offering services that appeal to drug companies, for reasons such as capacity, cost, and capabilities, contract manufacturers are positioned to play increasingly significant roles in the development of new devices. They have been evolving through physical expansion, by adding services, and developing and adopting new technologies. Packaging manufacturers who are invested in quality and regulatory systems, in addition to expanding manufacturing capabilities, are available to provide both basic and advanced manufacturing services for more sophisticated delivery devices.

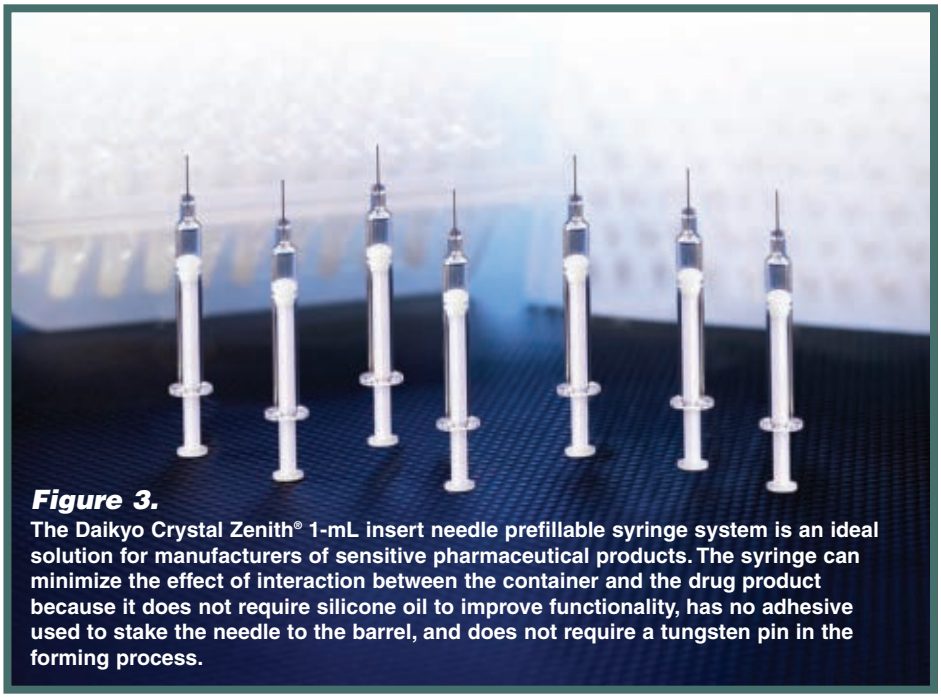

Figure 3.
The Daikyo Crystal Zenith® 1-mL insert needle prefillable syringe system is an ideal solution for manufacturers of sensitive pharmaceutical products. The syringe can minimize the effect of interaction between the container and the drug product because it does not require silicone oil to improve functionality, has no adhesive used to stake the needle to the barrel, and does not require a tungsten pin in the forming process.

Judging Success: Human Factors Testing

Perhaps the most important factor in the success of a drug product is the relationship between the design of the delivery system and the end-user. Human factors testing is incorporated to develop a deeper view of the emotional needs and desires of the intended user, and provides perspective on features and visual cues. It can help the manufacturer understand the nuances between where a device is used (clinic, doctor's office, or patient's home) and who is using it (doctor, patient, or care giver). Such an analysis begins with patient interviews to determine issues with current systems and needs for future designs. Often, simple factors are important, including the size of the device, how easy it is to hold, and where the activation button will be placed. Visual, audible, and tactile features also may help end users comply with drug delivery instructions.

After this initial interview, prototypes are created and tested by end-users. All considerations should be noted and prototypes redesigned to ensure that the basic form and feel of the delivery system is acceptable to the patient. Additional testing, which may include more formal training through written instructions for use or verbal instruction, will assist in fine-tuning the system and ensure that the device performs as intended.

By working with a packaging manufacturer who has intimate knowledge of the regulatory and quality requirements of the medical field, pharmaceutical manufacturers will increase their ability to create an innovative, novel device that establishes the drug product as a leader in the market. Differentiation through delivery system technology, as well as advice from a partner with experience and understanding of the drug packaging industry and end-user needs, will benefit patients, aid in compliance, and may also help pharmaceutical manufacturers move products to market faster. ■

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Eric Resnick is Vice President of Research & Development, Engineering, West Delivery Systems. He joined the Tech Group (a West company) in 2001 as Program Manager - Healthcare and Product Development, and assumed his current role in 2010. Under Mr. Resnick's leadership, Tech Group engineering transitioned successfully into a drug delivery device developer and integrator of complex manufacturing systems for contract and proprietary products. Mr. Resnick is a certified Six Sigma Black Belt with a BS in Plastics Engineering from the University of Lowell and an MBA from the University of Phoenix.

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The Presentation: Part I, Getting Ready

By: John A. Bermingham

When you are looking to raise investment dollars, be it seed capital, venture capital, or a private equity investment, the presentation is where the rubber meets the road. You and your presentation will determine whether your company will receive funding. As I once said in a previous article, the investor has read your business plan and has enough interest in your company to want to meet with you. So the mindset you now have to have is that the investor is now looking closely at the jockey (you) and not the horse (business). Investors want to know if they can work with you, they have a comfort level, and believe you can make the company and their investment successful.they knew the difference before accepting a penny!

THE BASICS

Your PowerPoint Presentation should emphasize the key elements of your business in a concise and focused manner. The presentation should be10 to 12 slides (15 slides maximum) and last for 20 to 30 minutes. In addition, make certain you have bound printed copies of the presentation to hand out to each person as well as an Executive Summary. Your slides should be straight-forward, not have special effects like little sparkles with each slide change, be in bullet-point form without lengthy narratives, and be the outline for you to verbally fill in the details. Rehearse your presentation several times so you are smooth in your delivery and to stay within your timeframe. Below is a general description of 10 slides that can be adapted to almost any industry. You would be surprised how common sense it seems, yet many times, this is not the case….you know what I am talking about investors!

THE SLIDES

1. Introduction – Tell investors what the company does, and when you founded it.

2. Overview – Tell investors what you are going to tell them at this time because later on, you will tell them what you want to tell them, and then at the end, you will tell them what you told them. Make this quick, don't dwell.

3. Market Opportunity – Explain what the opportunity is, why your business model will take advantage of the opportunity, and when highlighting these points, sell the sizzle without droning on about each point.

4. Products or Services – Explain what the product or service is, the development stage it is in, and don't get into technical terms or buzz words. You will lose the listener if you do this.

5. Management – Explain who the management is, what they will be responsible for, and include pertinent biographical information.

6 .Financial Performance – Identify your fiscal year, show actual numbers going back 2 years, and add a 2-year forecast to this, or, if you are not in business yet, show a 5-year pro forma but do not exaggerate the growth curve. Be conservative.

7. Sales & Marketing Plan – Indicate your channels of distribution and customer targets, show market size statistics and their sources, show the uniqueness of your marketing plan, and identify competitors and what your competitive advantages are.

8. R&D Plan – If you are not ready for market, show your R&D plan. If you are ready for market, show your go-forward R&D plan.

9. Strategic Partners or Relationships – Do not exaggerate anything. If you are in discussions, say that you are in discussions. Don't say that you have a relationship when you do not have one or are just at the beginning stage of discussions.

10. Funding Requirements – Show exactly what funding you need and what it will be used for. Be very detailed. Don't be generic or at a high level. Instead, drill down into the minutiae.

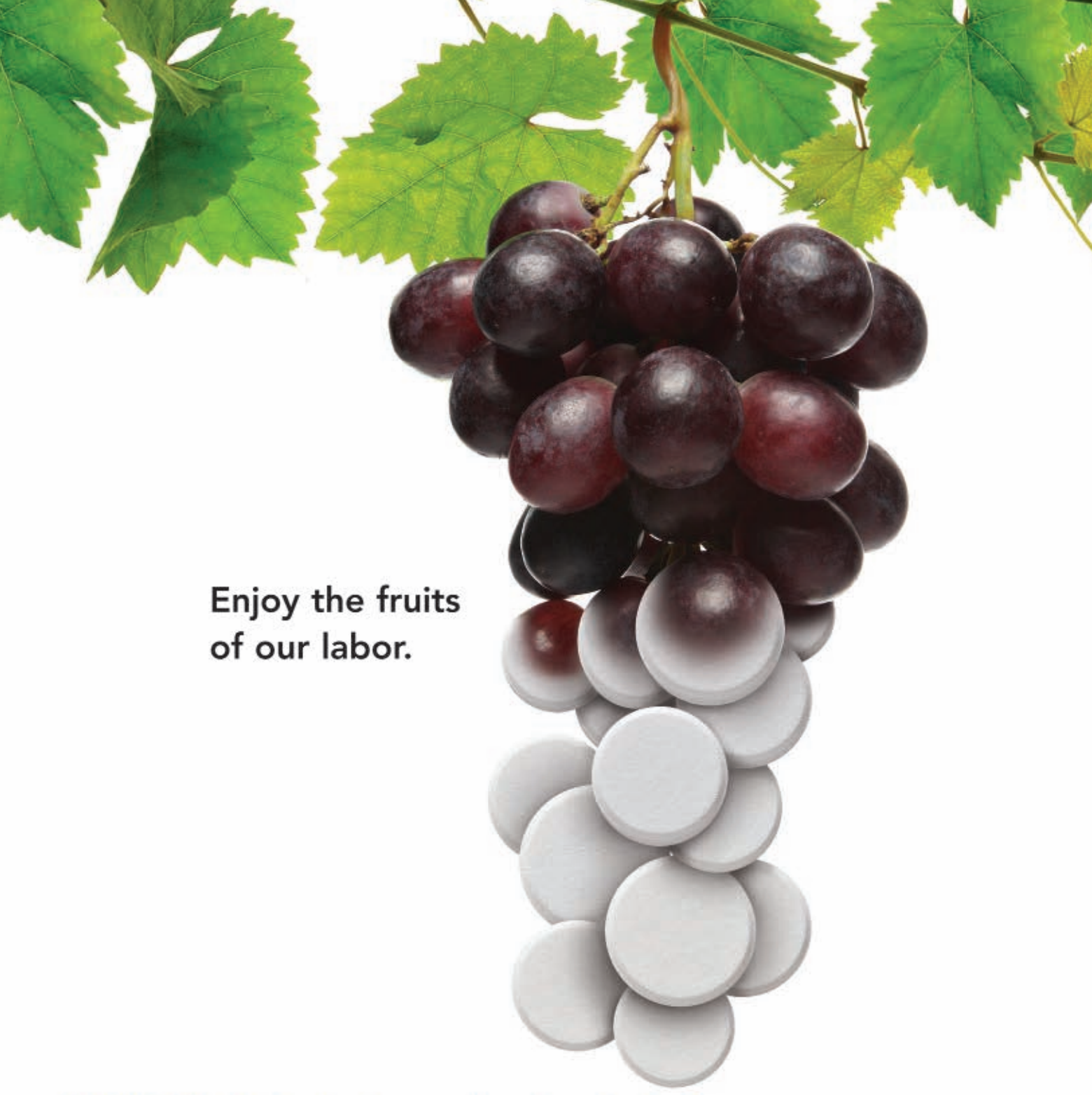
11. Summary – Summarize what you have presented.

12. Contact Information – Show the full corporate name of the company, address, phone and fax numbers, e-mail addresses of key people, website address, outside counsel, bank, and auditors.

Next issue, we will discuss the dos, don'ts, whys, and wherefores of making the presentation. ◆

BIOGRAPHY

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



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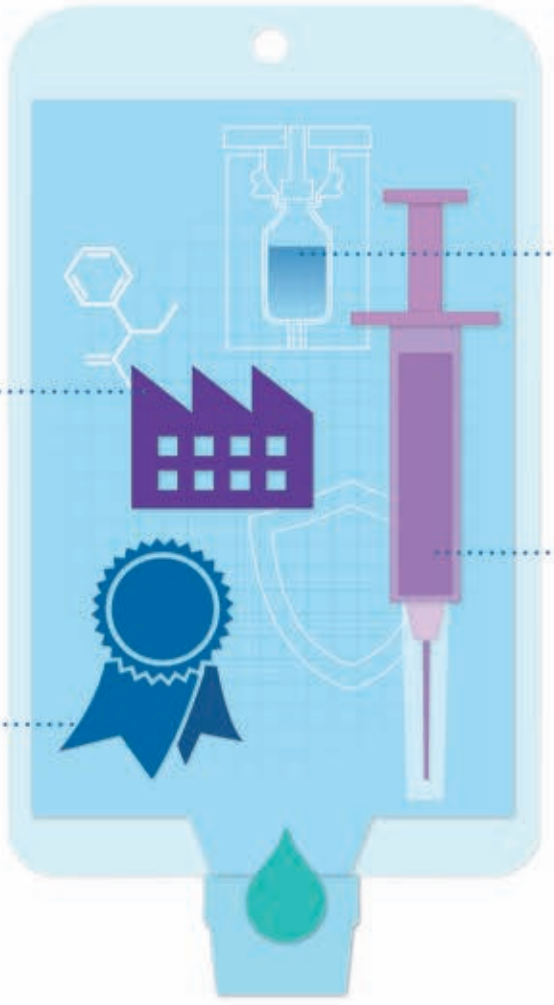

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