Drug Development & Delivery

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

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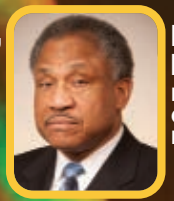
Controlled Release & Nanotechnologies: Recent Advances & Future Opportunities



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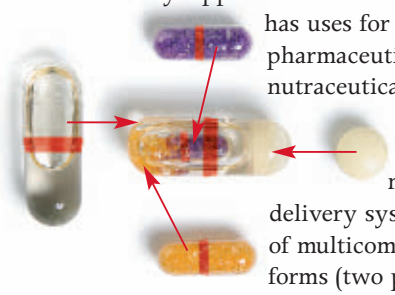
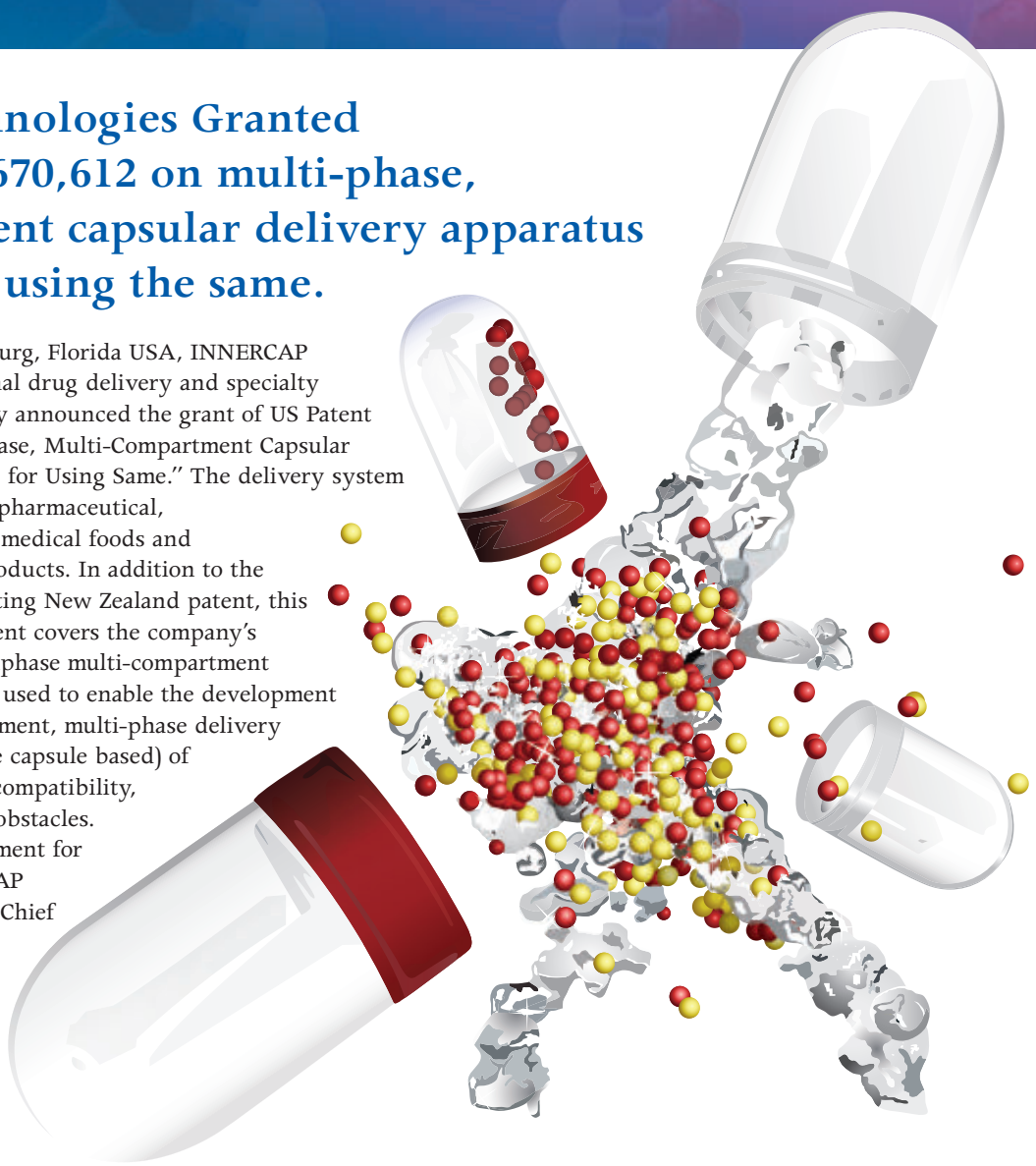
THE ADVANTAGES

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:

INNERCAP® TECHNOLOGIES, INC

United States Patent No. 7,670,612
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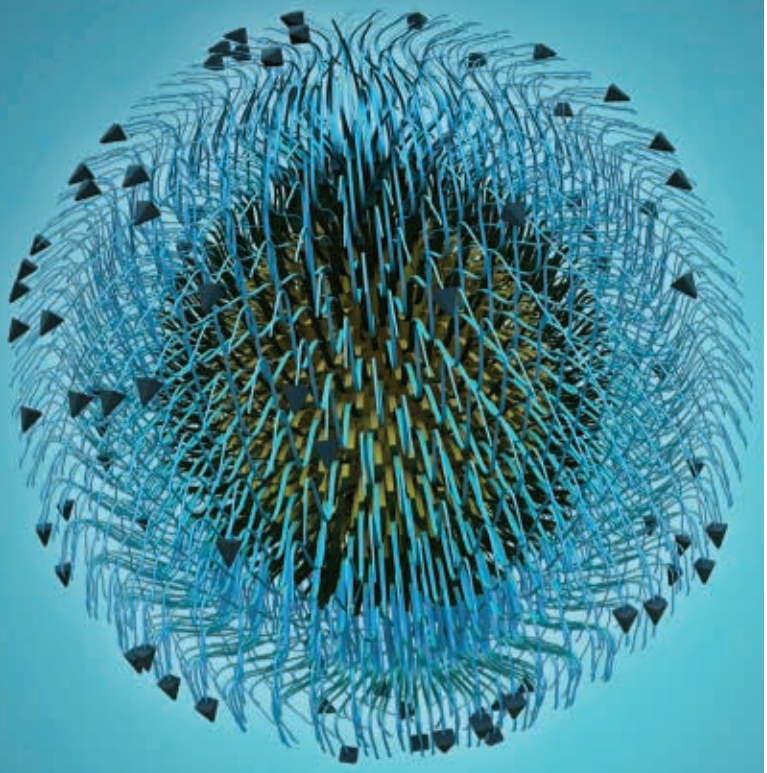

"The increasing demand for effective delivery of novel biopharmaceuticals is also driving the growth of the global top 10 drug delivery technologies market, with time-release technologies topping that list. As a whole, the global top 10 drug delivery technologies market is expected to grow from $43.8 billion in 2009 to $81.5 billion in 2015. More than 25% of the marketed drugs fail to provide expected commercial returns due to poor drug distribution and absorption levels within the body, therefore signifying the importance of drug delivery systems."

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TRANSDERMAL TRANSCENDENCE

That's the promise of Aveva Drug Delivery Systems, combining innovation and unparalleled industry experience to advance drug delivery and pioneer new frontiers in transdermal drug delivery for new chemical entities and life cycle management opportunities to enhance existing products.

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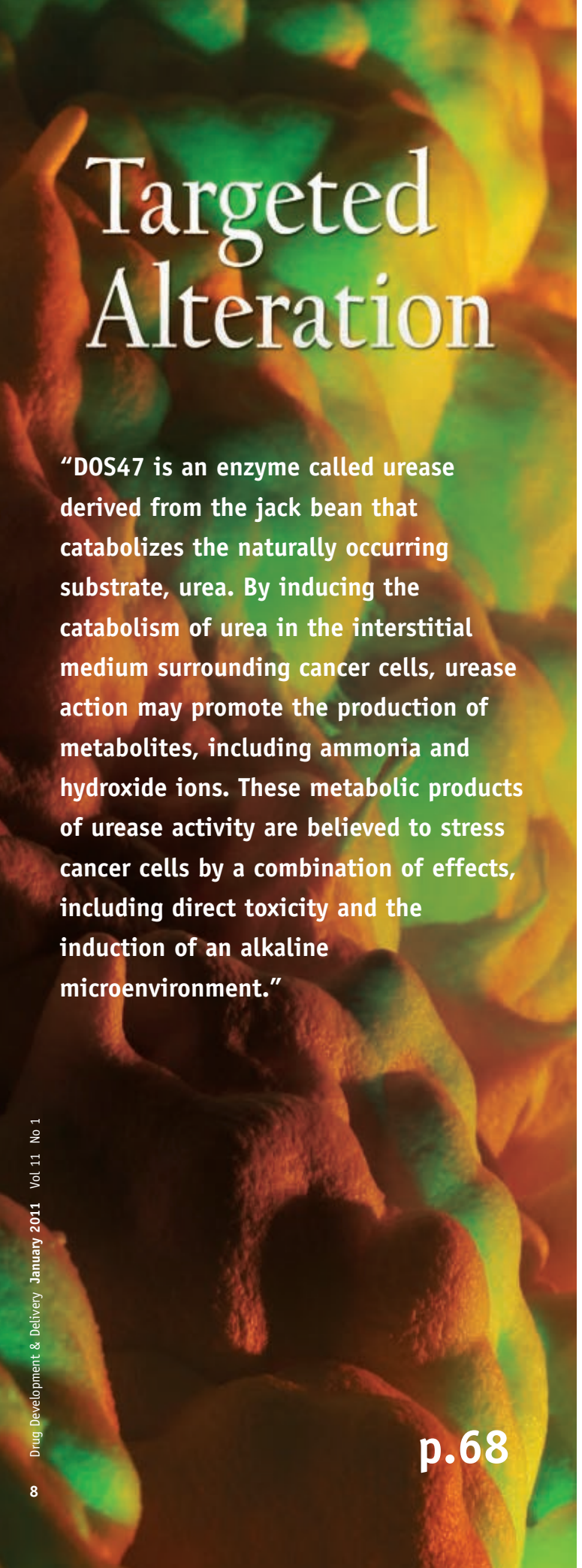

Targeted Alteration

"DOS47 is an enzyme called urease derived from the jack bean that catabolizes the naturally occurring substrate, urea. By inducing the catabolism of urea in the interstitial medium surrounding cancer cells, urease action may promote the production of metabolites, including ammonia and hydroxide ions. These metabolic products of urease activity are believed to stress cancer cells by a combination of effects, including direct toxicity and the induction of an alkaline microenvironment."

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Letter *from the* publisher

Ralph Vitaro
Publisher & CEO

Our Valued Readers

Welcome to our 10th anniversary! It is a milestone for any business, and we thank all of the advertisers, authors, EAB members, and subscribers for their support.

You may have noticed a slight change to our cover masthead this month. It is subtle, yet noteworthy.

To better reflect the editorial content and focus of the publication, this issue commemorates the addition of development to our title. So we welcome you to our 11th year serving the pharmaceutical industry by introducing you to our new name - ***Drug Development & Delivery.***

The new title now fully encapsulates all of the terms associated with the science and related business practices of drug development in the specialty pharma, biotech, and drug delivery arenas. As the only magazine completely devoted to drug development, each issue will continue to focus on developing a drug from post discovery to approval, including drug delivery, formulation development, combination products, devices, outsourcing & contract services, collaborations, pipeline strategies, and life cycle management.

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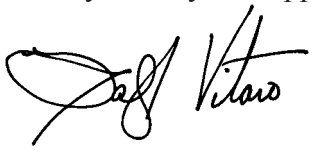

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Market News and Trends

Cephalon & Mesoblast Sign Landmark Stem Cell Therapy Agreement

Cephalon, Inc. and Mesoblast Limited recently announced they have entered into a strategic alliance to develop and commercialize novel adult Mesenchymal Precursor Stem Cell (MPC) therapeutics for degenerative conditions of the cardiovascular and central nervous systems. These conditions include congestive heart failure, acute myocardial infarction, Parkinson's disease, and Alzheimer's disease. The alliance also extends to products for augmenting hematopoietic stem cell transplantation in cancer patients.

Under the terms of the development and commercialization agreement between the companies, in exchange for exclusive world-wide rights to commercialize specific products based on Mesoblast's proprietary adult stem cell technology platform, Cephalon will make an up-front payment to Mesoblast totaling $130 million ($30 million upon Mesoblast shareholder approval) and regulatory milestone payments of up to $1.7 billion. Mesoblast will be responsible for the conduct and expenses of certain Phase IIa clinical trials and commercial supply of the products. Cephalon will be responsible for the conduct and expenses of all Phase IIb and III clinical trials and subsequent commercialization of the products. Mesoblast will retain all manufacturing rights and will share significantly in the net product sales.

In addition, under the terms of a stock purchase agreement and a subscription deed, Cephalon will make an equity investment to purchase a 19.99% stake in Mesoblast at $4.35 per share, totaling approximately US$220 million. This price represents a 45% premium to the last 30 days' volume weighted average price for Mesoblast shares. Cephalon has entered into a stand-still agreement to limit its investment to 19.99% of Mesoblast common stock for the next 12 months, with a right to maintain its equity stake on a top up basis, subject to the Australian Securities Exchange rules. Cephalon Chief Operating Officer J. Kevin Buchi will join the Mesoblast Board of Directors, effective immediately.

"This global licensing agreement positions Cephalon as a leader in regenerative medicine while further strengthening our late stage pipeline with another innovative biologic platform," said Mr. Buchi. "Mesoblast has done an outstanding job of developing Phase II clinical data in congestive heart failure and hematopoietic stem cell transplants, plus preclinical data in acute myocardial infarction. We are excited to have the opportunity to develop potentially the world's first stem cell therapy for indications that could serve millions of patients globally."

"Cephalon's demonstrated strength in late-stage product development and commercialization, and proven expertise in developing products for neurological diseases make Cephalon an ideal strategic partner for Mesoblast," added Mesoblast Chief Executive Professor Silviu Itescu. "We are therefore very pleased to partner with Cephalon in one of the largest biotechnology transactions of the past 12 months, and the largest ever in the regenerative medicine sector. We look forward to working with the Cephalon team to commercialize and deliver these products to physicians and the patients who will ultimately benefit from an arsenal of new innovative approaches for degenerative diseases."

Mesoblast will separately and with its own resources continue to develop, manufacture, and commercialize the rest of its suite of adult stem cell products for bone and cartilage applications, diabetes, eye diseases, and inflammatory and immunological conditions.

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Market News and Trends

3M DDS Signs Licensing Agreement With Spirig Pharma AG

3M Drug Delivery Systems recently announced it has signed an exclusive licensing agreement with Spirig Pharma AG, a Swiss manufacturer of dermatological and dermocosmetic products. Spirig Pharma AG will utilize one of 3M's immune response modifier (IRM) molecules to further its development of treatment for sun damaged skin. Spirig is known internationally for brands like its Daylong actinica, a medical device for the prevention of certain forms of non-melanoma skin cancer in at-risk patients, and Excipial moisturizer.

"The molecule offers potential for treating patients who suffer from a variety of dermatologic conditions. 3M is very proud of the many IRMs we have been developing for a variety of uses," said Mark Tomai, PhD, Vaccine Business Development Director for 3M Drug Delivery Systems.

In addition, 3M has IRMs available for license in the areas of cancer, asthma/allergy, and as vaccine adjuvants.

"3M is pleased to align with a leading European dermatology company to further develop our IRMs. In addition to its Swiss headquarters, Spirig's seven subsidiary locations, mainly in the EU, give us even more international reach," added Jim Vaughan, Vice President and General Manager of 3M Drug Delivery Systems Division.

"We are excited to expand our franchise of dermatology offerings in the prevention and treatment of sun damage-related skin conditions," said Dr. Silvio Inderbitzin, CEO of Spirig Pharma AG. "With 3M's IRM molecule, we can enhance our portfolio with the help of an experienced partner in drug delivery technologies."

3M Drug Delivery Systems partners with pharmaceutical and biotech companies to develop pharmaceuticals using 3M's inhalation or transdermal drug delivery technologies. 3M offers a full range of feasibility, development, and manufacturing capabilities combined with regulatory guidance to help bring products to market. In-house resources, including toxicology, regulatory expertise, quality assurance, operations, and marketed product support, are available for each step of the development and commercialization process.

Elan Pays Transition Therapeutics $9 Million in Amended Deal for Phase II Candidate

Transition Therapeutics Inc. recently announced the company and Elan Corporation, plc have mutually agreed to modify their collaboration agreement for the development and commercialization of ELND005. Under the terms of the modification, in lieu of a contractually required Phase III milestone payment, Transition will receive from Elan a payment of $9 million at the time of signing and will be eligible to receive an $11 million payment upon the commencement of the next ELND005 clinical trial. Transition also will be eligible to receive up to an aggregate of $93 million in additional regulatory and commercial launch-related milestone payments plus tiered royalties ranging from 8% to 15% based on net sales of ELND005 should the drug receive the necessary regulatory approvals for commercialization.

As the agreement is now a royalty arrangement, Transition will no longer fund the development or commercialization of ELND005 and will relinquish its 30% ownership of ELND005 to Elan.

Based on studies in preclinical models of Alzheimer's disease, ELND005 is believed to inhibit the aggregation (clumping) of amyloid-beta proteins in the brain, thereby neutralizing the toxic effects of these aggregates on nerve cell membranes (synapses). The toxic effects of amyloid-beta proteins include inhibition of nerve cell function and eventually death of nerve cells (neurons), resulting in memory loss and ultimately the dementia that is characteristic of Alzheimer's disease (AD). The safety and pharmacokinetics of ELND005 were evaluated in a total of 9 Phase I studies in 161 healthy volunteers, including healthy elderly subjects. ELND005 has also been evaluated in a completed Phase II study in mild-to-moderate Alzheimer's patients and an open-label extension of this Phase II study is currently ongoing.

ELND005 received fast-track designation from the US FDA in 2007 for treatment of AD. Fast-track designation can facilitate development and may expedite regulatory review of drugs that the FDA recognizes as potentially addressing an unmet medical need for serious or life-threatening conditions.

Transition is a biopharmaceutical company developing novel therapeutics for disease indications with large markets. Transition's lead product is ELND005 (AZD-103) for the treatment of AD, and Transition also has an emerging pipeline of innovative preclinical and clinical drug candidates. The other drugs in the pipeline address anti-inflammatory and metabolic indications.

Ligand Pharmaceuticals Earns $1 Million Up-Front Payment From Pfizer

Ligand Pharmaceuticals Incorporated recently announced its partner Pfizer, Inc. has granted a sublicense to a multinational pharmaceutical company for Tanaproget, also known as NSP-989. As a result, Ligand will receive an up-front payment of $1 million from Pfizer. Ligand is entitled to clinical and regulatory milestone payments from Pfizer as Tanaproget advances through the development process, as well as tiered royalties on net sales.

Tanaproget is a tissue-selective, non-steroidal contraceptive progesterone receptor agonist that has the potential for an improved side-effect profile over current steroid-containing contraceptives. The sublicensee is now responsible for the worldwide development, registration, and commercialization of Tanaproget.

"We are pleased with Pfizer's decision to enable further progression of Tanaproget through this sublicense agreement. Tanaproget is an example of the significant progress made in the field of women's health, providing an additional oral contraceptive option for women using both prescription and non-prescription methods of contraception," said John L. Higgins, President and Chief Executive Officer of Ligand Pharmaceuticals. "Our collaborative relationship with Pfizer continues to be very productive, and this sublicense adds another promising program to Ligand's large portfolio of assets."

Ligand discovers and develops novel drugs that address critical unmet medical needs of patients for a broad spectrum of diseases, including hepatitis, muscle wasting, Alzheimer's disease, dyslipidemia, diabetes, anemia, COPD, asthma, rheumatoid arthritis, and osteoporosis. Ligand's proprietary drug discovery and development programs are based on advanced cell-based assays, tissue-specific receptor ligand interactions and gene-expression tools. Ligand has assembled one of the largest portfolio of assets, including commercial therapies, developed in partnership with pharmaceutical companies. Ligand has established multiple alliances with the world's leading pharmaceutical companies, including GlaxoSmithKline, Merck, Pfizer, Bristol-Myers Squibb, and AstraZeneca, and more than 30 programs in various stages of development.

Market News and Trends

Novo Nordisk & Emisphere Announce License Agreement to Develop Oral Formulation of Insulin for $57.5 Million

Emisphere Technologies, Inc. and Novo Nordisk A/S recently announced they have entered into an exclusive development and license agreement to develop and commercialize oral formulations of Novo Nordisk's insulins, which have the potential of treating diabetes, using Emisphere's Eligen Technology. This is the second license agreement between the two companies. The first agreement for the development of oral formulations of GLP-1 receptor agonists was signed in June 2008 with a potential drug currently in a Phase I clinical trial.

The insulin agreement includes 57.5 million in potential product development and sales milestone payments to Emisphere, of which $5 million dollars will be payable upon signing, as well as royalties on sales. Further financial details of the agreement were not made public.

"This is an encouraging agreement on a promising technology for oral administration of proteins. We are delighted to continue working with Emisphere and their Eligen Technology. It fits very well with Novo Nordisk's strategy within diabetes research," said Peter Kurtzhals, Senior Vice President, Diabetes Research Unit at Novo Nordisk.

This extended partnership with Novo Nordisk is important for Emisphere for several reasons, added Michael V. Novinski, President and Chief Executive Officer of Emisphere. "To date, our collaboration with Novo Nordisk has been very productive, and this agreement has the potential to offer significant new solutions to millions of people with diabetes worldwide. Finally, it also serves to further validate our Eligen Technology."

Emisphere's broad-based drug delivery technology platform, known as the Eligen Technology, uses proprietary, synthetic chemical compounds, known as Emisphere delivery agents, sometimes called carriers. Emisphere's Eligen Technology makes it possible to deliver a therapeutic molecule without altering its chemical form or biological integrity.

Itamar Medical & Roche Sign Agreement For EndoPAT Devices in Preclinical Drug Development

Itamar Medical, a leader in non-invasive vascular health diagnostics, recently announced that an agreement has been signed with Roche by which Itamar will develop an EndoPAT device designated for use with animal models, enabling preclinical studies examining the efficacy of various compounds in the early stage of drug development essential for later stage development in humans. Itamar's EndoPAT device is a non-invasive technology designed to diagnose and monitor endothelial dysfunction, which constitutes an early stage of cardiovascular diseases in humans.

"Following on from our work with Roche in clinical studies, we are pleased to further our collaboration that will reinforce our strategy of EndoPAT playing a major role in developing personalized medicine and companion diagnostics," said Dr. Dov Rubin, Itamar Medical's President and CEO.

"EndoPAT offers the only non-invasive, FDA-cleared technology for detecting endothelial dysfunction that is easily applied and totally operator independent in humans," added Dr. Koby Sheffy, Itamar Medical's CTO and Senior Vice President. "This advanced development positions the EndoPAT to be the technology of choice to assess endothelial dysfunction in cardiovascular drugs development from the early animal model through the different clinical phase trials in humans."

Itamar Medical Ltd. is a publicly traded medical technology company utilizing PAT (Peripheral Arterial Tone) signal technology and applications. The PAT signal is a non-invasive "window" to both the cardiovascular and autonomic nervous systems. Itamar Medical is the developer of EndoPAT, which diagnoses endothelial dysfunction, an important state in the development and progress of atherosclerosis affecting both early and late stages of the disease. EndoPAT has now been deployed by over 10 pharmaceutical companies, many of which are among the Fortune 100, in nearly 20 large-scale drug development studies, and has been proven to shorten the time and reduce the cost of drug development.

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REFORMULATING SUCCESS

Pharma's Innovation Crisis: How Can Our Industry Save Itself?

Part 6 of a 6-part series on business models & best practices for navigating the new normal.

By: Derek Hennecke, President & CEO Xcelience LLC

Healthcare reform threatens to tighten margins, the rate of innovation is at a standstill, and patent revenues are falling off a cliff. The Generic Pharmaceutical Association reports that in 2009, 74% of all prescriptions were filled with generics. For every dollar lost to patent expirations by 2012, the large cap companies will recoup on average just 26 cents, according to Steve Paul, Bernard Munos, et al in *Nature* magazine's *How to Improve R&D Productivity* in the March 2010 issue.

All this is set against a backdrop of R&D costs escalating at a rate of increase of 13.5% per year. On our current trajectory, Mr. Paul et al foresee a looming potential "pharmaceutical ice age." I have noticed my office seems a little cooler of late. We need innovation, lots of it, and now. How is Big Pharma meeting this climactic challenge?

MERGER MANIA

The primary strategy at the moment, as any *Wall Street Journal* reader will tell you, appears to be mergers. Roche and Genentech, Merck and Schering Plough, Pfizer and King – the rush to buy innovation through mergers is on. Big Pharma is eager to produce a fertile coupling. Yet the birth rate of innovation continues to decline. Why?

This surge in M&A activity may be part of the problem, not the solution. Recently, I had the opportunity to speak with Bernard Munos, contributing author to the aforementioned article. He presents a persuasive argument that the surge of M&A activity in the past 12 years correlates to 95% of the *shortfall* in NME production of the industry. Of course there could be some compounding factors that fold into each other, so maybe it is not as correlated as it sounds. Nevertheless, let's look at his research.

Using a Poisson model to test the relationship between M&A activity and new molecular entity (NME) output, Mr. Munos, in an article titled *Lessons From 60 Years of Pharmaceutical Innovation* in the December 2009 issue of *Nature*, compared the Poisson parameter of companies before and after their mergers to see how much value was created. In analyzing 30 deals, they found that NME output only increases if small companies merge. For large companies, mergers are innovation neutral. They reduce some costs, but also add bureaucracy.

In fact, his research shows that large companies' share of NMEs has slipped from 75% in the


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early 1980s, to currently less than 50%. While the chances are low that any one of the 4,300 small pharma companies will produce an NME, the truth is that as a whole, the little guys produce slightly more NMEs, and they do it while cumulatively spending less than half the $65 billion spent by Big Pharma. Interesting. So what exactly should our industry be doing?

IF NOT MERGERS, THEN WHAT?

To improve the quality and quantity of drugs brought to market, there is no magic bullet; no way of sidestepping the obvious solution. We simply have to reduce the cost of R&D. We can do that in a number of ways. The previously mentioned Mr. Paul et al examine them in detail, but in a nutshell they include the following:

Partnerships: The industry needs more partnerships. Not mergers – co-operation. We need to leverage the small players by allowing them to feel the benefits of larger size through networking. Think about this from many angles: molecule-based risk-sharing partnerships, joint ventures, and use of functional-based services like toxicology and clinical development to reduce the cost of purchasing equipment and stage-specific expertise. A Morgan Stanley report quoted in the *Wall Street Journal* (Big Pharma is Winning War on Drugs, October 15) claims greater use of outsourcing could triple returns in investment. Being in the CRO business myself, I see companies realize these kinds of savings every day. We need partnerships like the Chemistry Playbook™, which can take a single molecule to clinical formulation through several companies in one streamlined process. These and more yet-unthought-of process innovations will enable the industry to do more with less money and less time.

Reducing Cycle Time: This is about improving processes. It's about prioritizing, looking for opportunities for parallel development, reducing inefficiencies, streamlining bureaucracy, and maybe concepts like Six Sigma to reduce time and save money.

Better Triage: Right now, Mr. Paul posits that the Phase II and Phase III attrition rates are unacceptably high (66% and 30%, respectively). In the *Nature* article, the authors propose an interesting "quick win, fast fail" paradigm that introduces a proof-of-concept stage right after preclinical development. Any drug that successfully passes through this gate has a higher probability of success. In fact, Mr. Paul claims the combination of better target validation and proof-of-concept would increase the Phase II success rates by as much as 50% and reduce the cost per NME by 30%. Any and all savings from this triage should then be reinvested in what they call the "R&D sweet spot," right before first-in-human doses. The goal is to increase the number of drugs entering the pipeline and weed the good from the bad earlier.

THE LARGE MOLECULE DISAPPOINTMENT

I have to add here something that I noticed in looking over the research. There is a significant difference as well in the R&D costs for small versus large molecules. Lately, much emphasis has been put on new biological entities (NBEs) – arguably at the expense of new chemical entities (NCEs). A lot of government and non-government attention has been focused on them. I wonder if this is justified.

The common wisdom is that NBEs are less expensive to develop. On the surface, that appears true, however slight the difference. The estimated cost per approved new molecule is $1.241 billion for an NBE and $1.318 billion for an NCE, according to Mr. De Masi.

The majority of the costs, however, are in the molecules that don't make it to launch. The preclinical costs for an NBE are twice that for a small molecule, at $615 million versus $376 million, using De Masi's numbers. That just makes sense – it costs more to develop a sterile drug than an oral one. But the fact that these costs are loaded at the front end of the pipeline exaggerates these costs: the probability of an NBE going from preclinical to Phase I is 100% and from Phase I to Phase II is 83.7% versus 71% for small molecules. Add to this the sheer length of the process – 19.5 months for an NBE versus 12.3 for an NCE – and the costs keep piling up. From a triage perspective, this is not a good thing. The earlier you find out that a molecule isn't viable, the less money wasted.

Once through the preclinical phase, biological drugs probably do have a slightly higher probability of making it to launch. The figure I hear quoted most often is 11% for biologicals versus 7% for chemicals, but this may be one of those oft-quoted numbers that have no actual basis in fact. Mr. Munos questioned the number and asked me to look for a primary source for it. I couldn't find one. If you have one, send it along please.

Maybe the popularity of NBEs is historical. When we decoded the human genome more than a decade ago, we were supposed to see an explosion of NBEs over and above that of NCEs. This significant potential drew vast amounts of research money.

What difference did this make to the rate of NBE approvals? Apparently none. Since 1997, the rate of creation of NBEs has been relatively constant, and in fact shows a marked decrease from 11 in 2004, to half that in 2007.

This non-performance trend on behalf of NBEs is particularly noteworthy in the realm of cancer treatment. Despite the large number of biopharmaceuticals reported to be in development for cancer indications, including recombinant

antibodies, none received approval in 2009. The same holds true if we look back over 2007 and 2008. On the other hand, 6 small molecules were approved for cancer treatments in 2009. This year, I counted 6 small molecules in one database, but according to the drugs@FDA website, only one NCE was approved as a cancer treatment so far this year. The score for large molecules? Zero.

I'm not arguing that chemical entities are the future – only that history led us to swing the pendulum very far in the direction of biological entities. Maybe time for us to consider restoring something closer to the previous balance, particularly given that chemical entities produce the majority of new drugs.

THE ORPHAN FOCUS – A WELL USED APPROACH

A further issue is not just the lack of drugs being approved – either NBE or NCE – but the lack of economic impact of those that do pass the bar. I don't believe many people will debate that few of these new products will achieve sales over $1 billion/year.

The FDA policy of encouraging the development of orphan drugs, however well-intentioned, may be having the effect of channeling resources into this area. Nearly all the newly approved products in 2009 are therapeutic advances for orphan indications. The economic impacts of these products may be limited in the beginning.

I say "in the beginning" because we all know that many companies use orphan indications as a gateway for market entry. They focus their initial licensing efforts in oncology on orphan indications to take advantage of government incentives and encouragement. In their first approved indication, 78% of the FDA-approved cancer drugs had orphan status, according to a Deloitte biotech database.

Millennium Pharmaceuticals did a brilliant job layering on to build a composite blockbuster with Velcade®, whose first US approval in 2003 was for a relapsed and/or refractory subset of patients with multiple myeloma, and is now moving into the treatment of lymphoma.

On the bright side, working on orphan indications might develop real IP for pharma companies as they gain an understanding of the mechanisms of rare diseases. Many rare diseases affect only one gene and help to point the way to more complicated polygenic common diseases.

A WHIFF OF CHANGE?

Despite all the hurdles to innovation I've just outlined, I'd be remiss if I didn't note differences in opinion. Worldwide R&D spending may be falling, but a BofA Merill Lynch report says that a drug in late-stage development now has a 1 in 3 chance of reaching the market versus 1 in 4 in 2007, and credits better targeted spending and more ruthless triage of early stage projects. Is this the beginnings of the change we want? While I'd love to believe this data, it does contradict other data, including the European Medicines Agency, which says that 50% of Phase III trials end up in failure, and 40% of the drugs submitted for approval do not get approved.

While I'd love to believe that we are on the road to improving the rate of innovation, my ears to the ground tell me we have a long way to go. We have all seen the shelving of early stage molecules in the past 3 years as resources have been shifted into later-stage candidates with more imminent pay-offs. Toxicology is not a pretty place to be as I write.

The gross underinvestment in preclinical candidates is going to have to change. The pipeline must be renewed, but this time with lower R&D costs brought about by more partnerships, better processes, and more triage. And there's no time to lose.

AUTHOR'S NOTE

A special thanks to Bernard Munos for sharing his views on the industry and its challenges. Connect with me on LinkedIn if you want any of the papers mentioned in this article. I would be glad to send them to you. ◆

BIOGRAPHY

Derek G. Hennecke, MBA
President & CEO
Xcelience

Derek G. Hennecke is a founding member of Xcelience and its current CEO and President. He has a long history of growing strong businesses around the world. He balances a scientific and business background with 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 strong growth. This growth was recognized in May 2008, when Mr. Hennecke was selected as a finalist for the coveted *2008 Ernst & Young Florida Entrepreneur of the Year* award, a nomination based on the demonstration of extraordinary success in the areas of innovation, financial performance, personal commitment to community, and the company's perpetual growth since its official formation. Mr. Hennecke was also recognized as a finalist for the *Ultimate CEO* awards by the Tampa Business Journal in 2008. This is in addition to Xcelience's nomination for *Small Business of the Year* by the Greater Tampa Bay Chamber of Commerce, also this year. Before founding Xcelience, Mr. Hennecke managed the same Tampa-based business while also overseeing a Seattle and a Montreal-based plant as Vice President and General Manager, Pharmaceutics and Biopharmaceuticals. Prior to that, he 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 radical turn-around in an anti-infectives plant that was originally slated for closure. He also 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 earned his BSc in Microbiology from the University of Alberta in Canada and his MBA from the Erasmus University in Rotterdam, The Netherlands.

Improved Bioavailability of Engineered Amorphous Nanostructured Compositions of Poorly Water-Soluble Drugs by Rapid-Freezing Particle Engineering Technology

By: Wei Yang, PhD; Donald E. Owens III, PhD; Jay I. Peters, MD; Robert O. Williams III, PhD

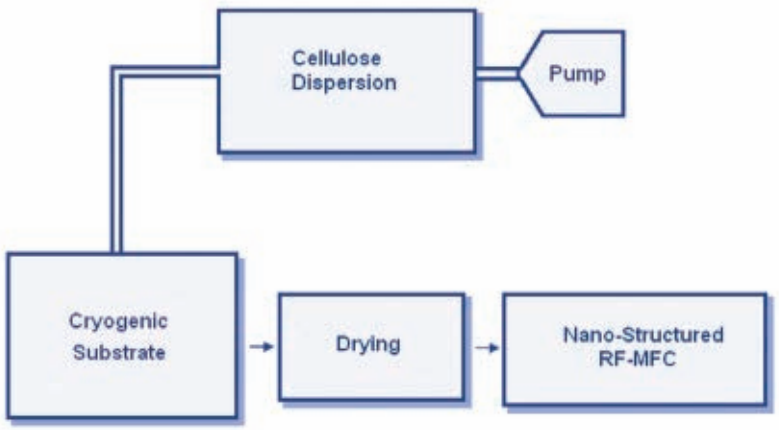
INTRODUCTION

The routine use of high-throughput screening and computational chemistry in modern drug discovery has resulted in a higher prevalence of lead compounds with increased molecular weight and lipophilicity, which often result in poor and highly variable bioavailability after administration.[1,2] Biopharmaceutical Classification System (BCS) Class II drugs (ie, poorly water-soluble/lipophilic drugs with high biomembrane permeability) comprise a large portion of these lead compounds, and their poor bioavailability is typically attributed to slow or very low rates of dissolution in biological media.[3] In practice, the use of these drugs directly, without the assistance of dissolution-enhancing processes or formulations, commonly results in sub-optimal therapeutic levels of drug in patients. Therefore, throughout the past decade, there has been a tremendous increase in of the number of new technologies and formulation strategies available to improve the dissolution properties of poorly water-soluble drugs.

Micronization and solubilization are the most commonly used means to increase dissolution rate to address the low bioavailability issues associated with poorly water-soluble drugs. According to the Noyes-Whitney equation, the reduction of particle size through micronization, which in turn increases surface area and thus the rate of dissolution, is one promising way to enhance drug dissolution rate.[4] However, this method does not increase or alter the equilibrium solubility of the micronized compound. Because of this limitation, micronization may not provide significant bioavailability enhancement for drugs with very low aqueous solubility.[5] Solubilzation techniques, on the other hand, (eg, salt formation, co-solvents, micellar solutions, and inclusion complexes with cyclodextrins) can increase the equilibrium solubility of poorly water-soluble drugs.[6-9] However, the large amount of excipients typically required to solubilize these drugs may potentially increase side effects, resulting in low patient compliance.

One potential solution to the issues

FIGURE 1



Schematic Diagram of Rapid-Freezing Process (reproduced with permission from reference 14)

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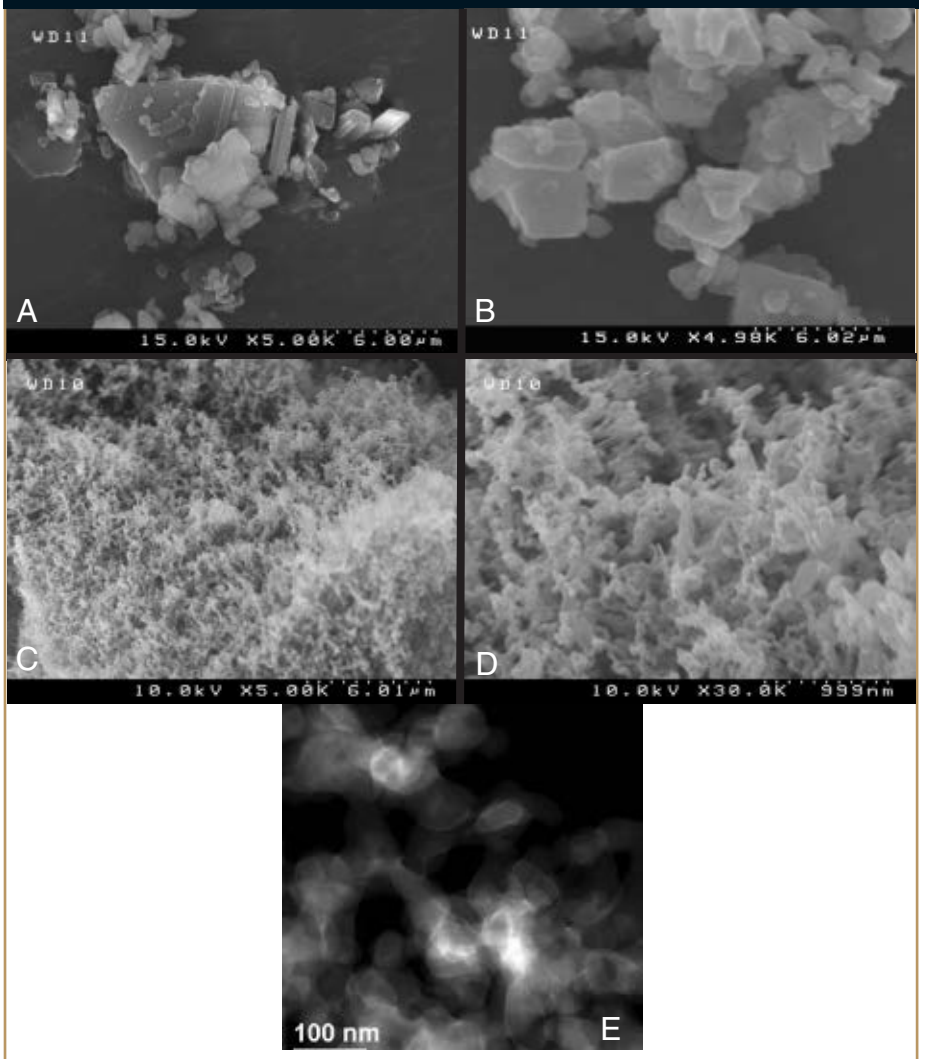
related to micronization and solubilization is the use of drug nanoparticles. Drug nanoparticles in the 100-nm and below size range not only dissolve more quickly, due to their increased surface area, but also to a greater extent (ie, higher equilibrium solubility) than simply micronized drug particles. This phenomena is due to the changes in dissolution kinetics and solubility that begin to occur as particle size is decreased to the nanometer scale and is described by for in the Ostwald-Freundlich equation.[10] Therefore, the production of drug-loaded nanoparticles and nanosuspensions has been shown to be a promising approach to overcome the poor bioavailabilities typically seen with poorly-water soluble drugs.[5]

In addition to preparing nanoparticle forms of poorly water-soluble drugs, studies have shown that polymorphs and amorphous forms of poorly water-soluble drugs can also increase dissolution rate and solubility due to the higher thermodynamic chemical potential of these states when compared to the crystalline state.[11,12] Delivery of amorphous drug forms can produce supersaturated solutions in aqueous biological fluids that increase systemic absorption and localized drug concentration at the site of administration.[13] Recent experimental studies have shown that supersaturation levels of 5 or less are typically achieved for micron-sized amorphous particles, despite theoretical calculations that would predict a much higher level of supersaturation, primarily due to the tendency of amorphous microparticles to recrystallize in the solid state before reaching complete dissolution.[11] However, significantly higher supersaturation levels approaching 100 were successfully achieved using amorphous nanoparticles.[14]

Therefore, the creation of amorphous nanoparticles of poorly water-soluble drugs, which can achieve high levels of supersaturation and improved rates of dissolution, is an ideal solution for achieving enhanced bioavailability and ultimately therapeutic effectiveness with BCS Class II drugs.

FIGURE 2 A-E

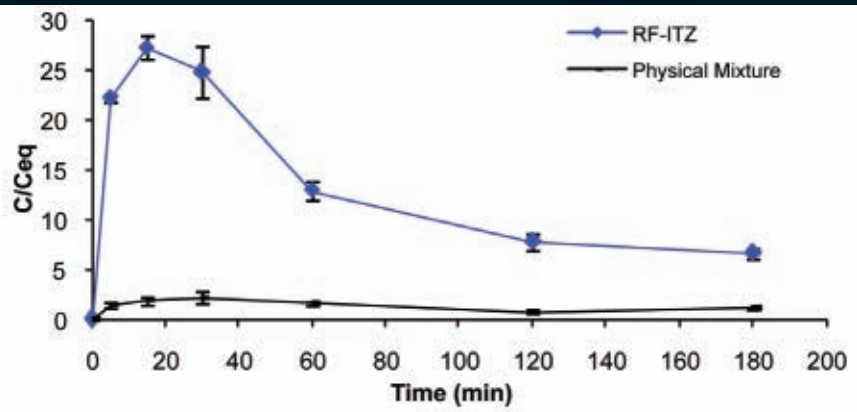


Scanning electron microscopy (SEM) images of (a) bulk ITZ at a magnification of 5000x, (b) physical mixture of ITZ:mannitol:lecithin = 1:0.5:0.2 at a magnification of 5000x, (c) URF-ITZ (RF-processed ITZ:mannitol:lecithin = 1:0.5:0.2) at a magnification of 5000x, (d) URF-ITZ at a magnification of 30000x, (e) scanning transmission electron microscopy (STEM) image of URF-ITZ at nano-scale. (reproduced with permission from reference 20).

RAPID-FREEZING PARTICLE ENGINEERING TECHNOLOGY

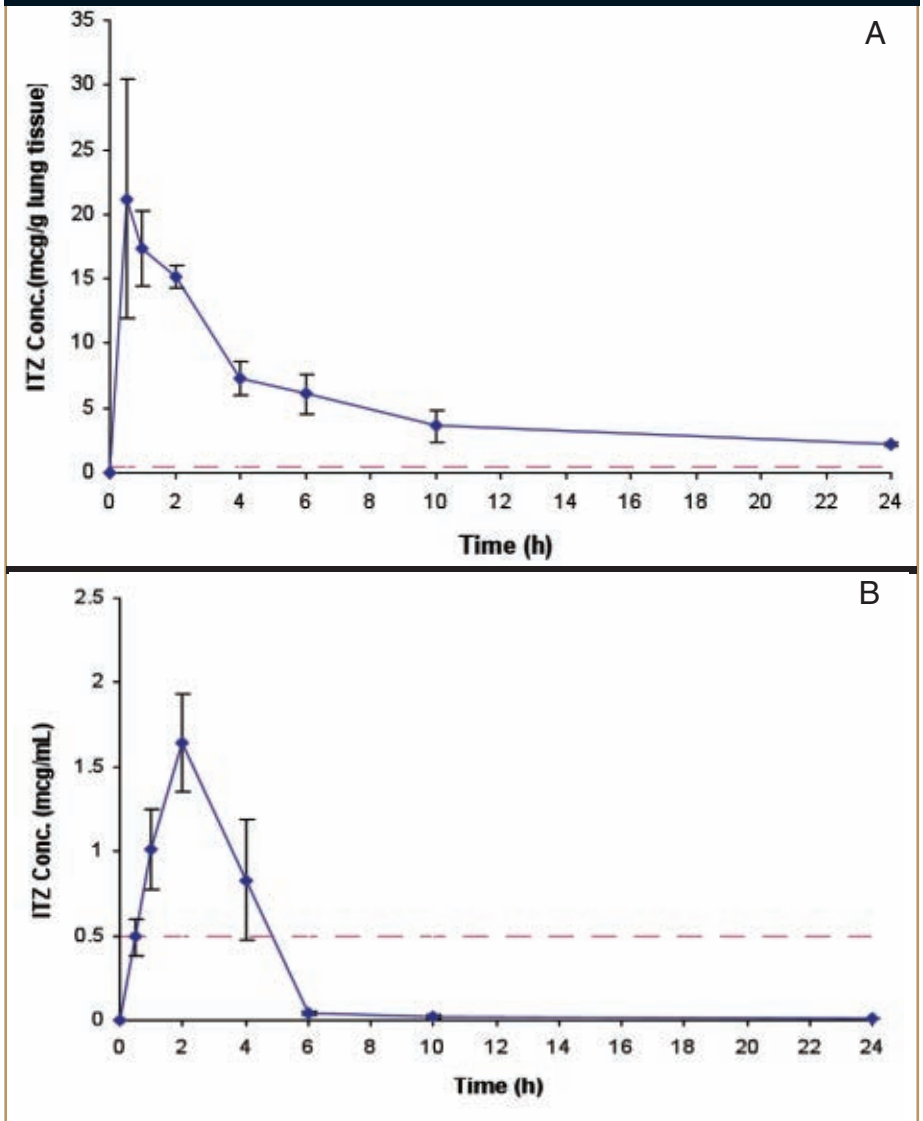
Rapid-freezing (RF), or Ultra Rapid Freezing (URF) as it is sometimes referred to, is a cryogenic particle engineering technology that has been successfully utilized to produce amorphous nanostructured particles using a wide variety of compounds, including BCS Class II drugs. The RF process, schematically illustrated in Figure 1, begins with the preparation of a solution of drug with or without added excipient(s), which is applied onto the surface of a continuously refreshed cryogenic substrate of desired thermal conductivity to form thin frozen pellets that freeze in the 0.05 to 1 second range.[15] After collection of the frozen pellets, solvents are removed via sublimation, and a highly

FIGURE 3



Dissolution profiles of URF-ITZ (RF-processed ITZ:mannitol:lecithin = 1:0.5:0.2) and physical mixture (ITZ:mannitol:lecithin = 1:0.5:0.2) in simulated lung Fluid (pH 7.4) at supersaturation conditions (eg, 100 times equilibrium solubility of crystalline ITZ was added) using 100-mL vessels and small paddle apparatus at 100 rpm and 37°C. (reproduced with permission from reference 20).

FIGURE 4 A&B



(a) Lung deposition and (b) serum concentration of ITZ in male outbred ICR mice after inhalation of nebulized URF-ITZ (ITZ:mannitol:lecithin = 1:0.5:0.2, weight ratio) colloidal dispersion by single-dose administration (equivalence of 100 mg of ITZ nebulized over a 10-min period). Dashed line:ITZ level (0.5 microg/g of lung tissue, or /mL of serum) was required to be therapeutic effective. Data are presented as mean ± SD.

porous nanostructured aggregate network of amorphous drug powder with high surface area is left behind. This unique structure is clearly evident when RF-processed materials are examined using scanning electron microscopy as shown in Figure 2.

The RF process is able to create both solid dispersion and solid solution nanoparticles composed of drug domains within a polymer/excipient matrix due to rapid freezing or vitrification of dissolved drug in the presence of excipient(s), which exist as disordered free molecules in the solution. Solid dispersions are systems in which drug particles are homogeneously distributed throughout a solid matrix. A solid solution results when the drug is molecularly dispersed throughout a solid matrix, in which the particle size of the drug has been reduced to its absolute minimum without any crystalline drug domains.[16] Due to the lack of any long range molecular order or structure, both solid dispersions and solid solutions created using the RF process result in an amorphous state. Due to their amorphous nature, both solid dispersions and solid solutions of poorly water-soluble drugs have greatly enhanced dissolution rates and high supersaturation levels, which lead to significantly improved bioavailability.

In addition to enhanced dissolution and supersaturation, the RF process also allows for the production of drug formulations with high drug loading, typically greater than 60%, with a wide variety of excipients, including FDA-approved and generally regarded as safe (GRAS) biodegradable and biocompatible materials, which are required for certain dosage forms. Compared to the conventional dosage forms, the lower amount of excipient and drug required in RF-processed compositions can result in increased patient compliance, safety, and

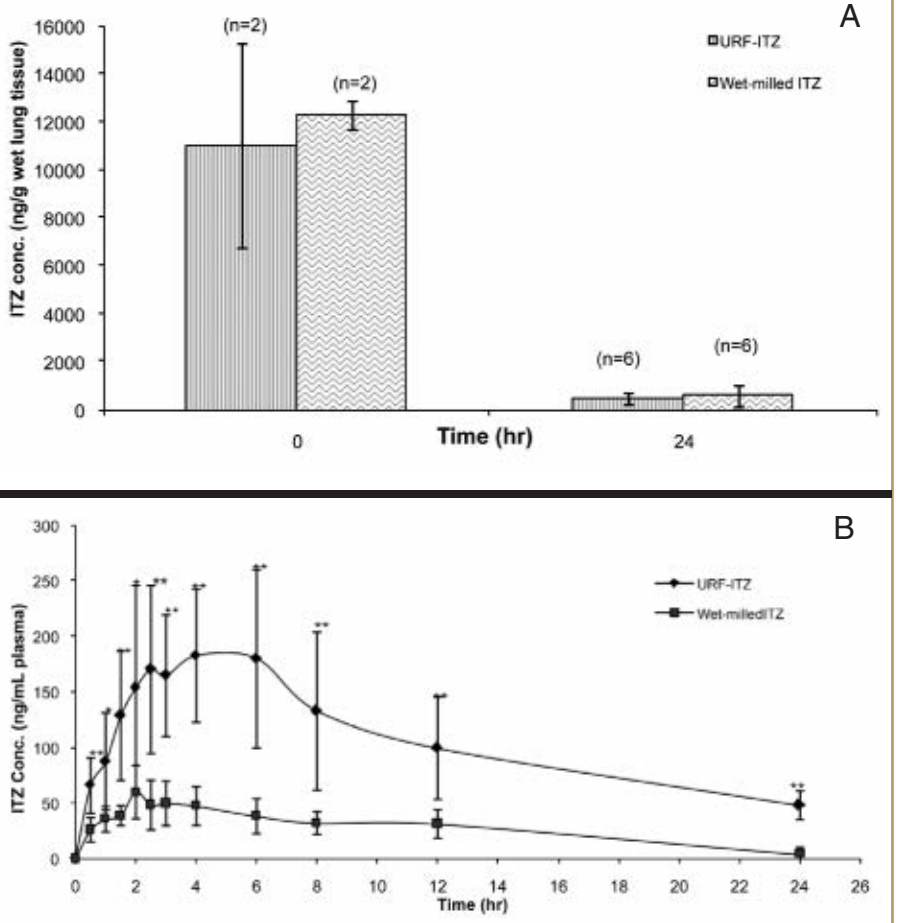
therapeutic efficacy for poorly water-soluble drugs. Furthermore, the RF process operates at a low temperature, eliminating the potential for thermal degradation of drug that occurs quite often in other high-energy particle engineering processes. In addition, the RF process is readily scalable due to the relative simplicity of equipment, low cost, short processing intervals, and continuous nature of the process.

PULMONARY DELIVERY OF RF-PROCESSED POORLY WATER-SOLUBLE DRUGS

Pulmonary delivery has become an increasingly attractive route of administration for poorly water-soluble drugs because of several advantages of this non-invasive administration route: (1) potential for high systemic absorption with an enormous absorptive surface area of averagely 100 m^2, very thin diffusion path to the blood stream, and rich vasculature that facilitate rapid delivery of large dose of drug from lung alveoli; (2) targeted local lung action with reduced systemic side effects compared to other administration routes; and (3) relatively low metabolic activity and avoidance of hepatic first-pass metabolism.[17]

Despite the unique advantages of pulmonary delivery, unlike other administration routes, only particles with an aerodynamic diameter of less than 5 microns (optimal range of 1 to 3 microns) are suitable for deep lung delivery. Particle size distribution and morphology of the drug-loaded particles have pronounced effects on drug deposition in the respiratory tract, dissolution in the lung lining fluid, clearance of drug from the lungs, and consequently bioavailability and therapeutic effects.[18] RF-processed drug-loaded nanoparticles have the potential to address these issues and achieve high bioavailability when used for pulmonary delivery of therapeutics. These benefits were clearly illustrated in a recent study using RF-process Itraconazole.

FIGURE 5 A&B

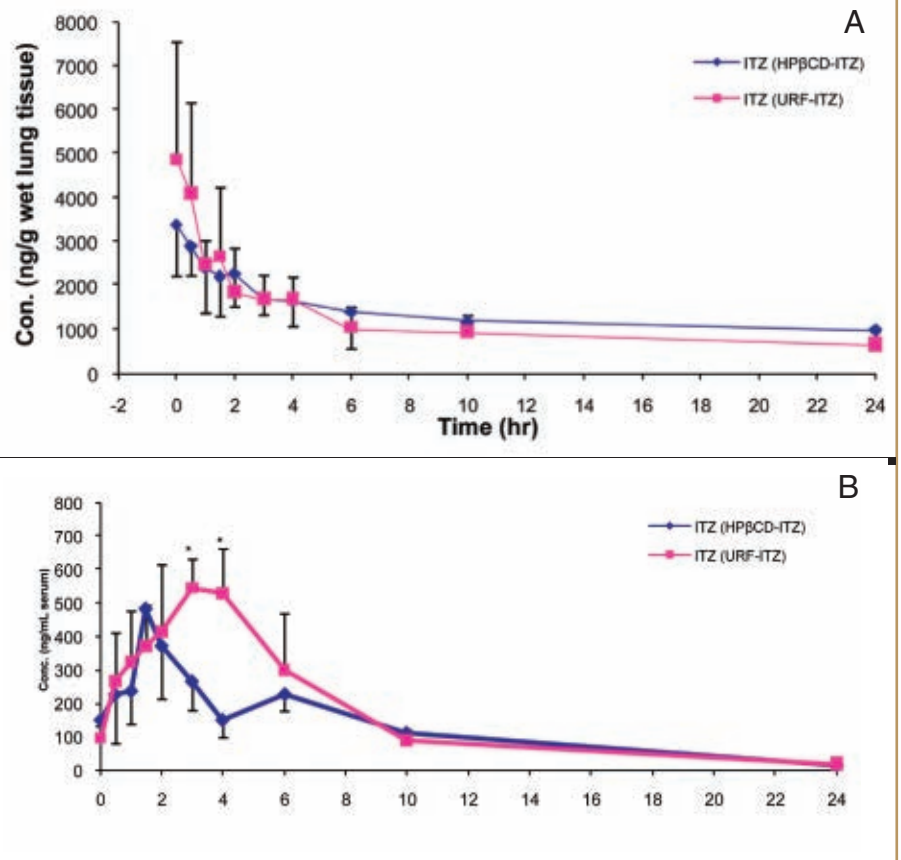


(a) Lung deposition of ITZ in rats at 0 and 24 hrs post inhalation, (b) plasma concentration of ITZ in rats after a single-dose nebulized aqueous Wet-milled ITZ colloidal dispersion (ITZ/mannitol/lecithin = 1:0.5:0.2, weight ratio) and URF-ITZ colloidal dispersion (ITZ/mannitol/lecithin = 1:0.5:0.2, weight ratio). Data are presented as mean ± SD. (reproduced with permission from reference 21).

Itraconazole (ITZ) is an antifungal drug with an extremely low aqueous solubility of approximately 1 ng/mL at neutral pH and about 4 micrograms/mL at pH 1.[19] Currently marketed ITZ products have been reported as having low and erratic oral absorption, making them therapeutically ineffective, especially for the treatment of invasive fungal infections in immuno-compromised patients with the lungs as primary port of entry for the pathogens. Therefore, a novel amorphous nanostructured ITZ composition for pulmonary delivery was prepared using the RF process, and is referred to herein as URF-ITZ (ITZ:mannitol:lecithin = 1:0.5:0.2, weight ratio).[20]

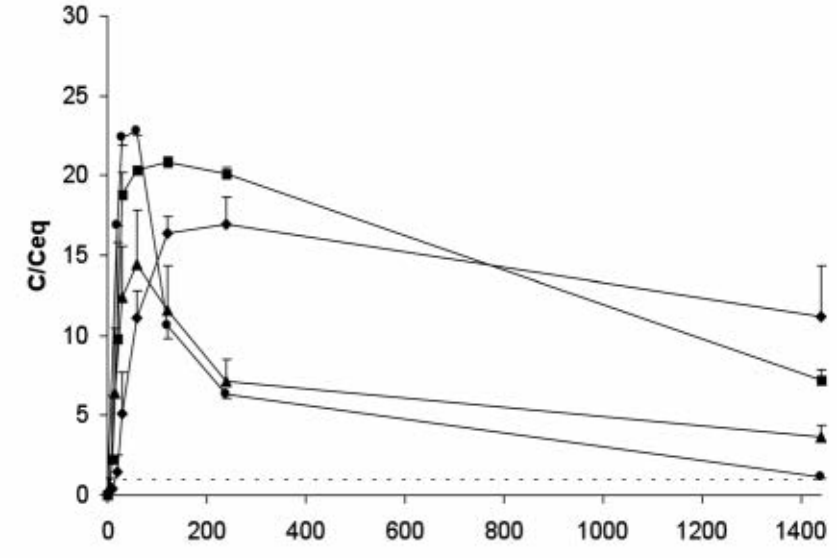
When dispersed in purified water, the URF-ITZ had a mean particle size of 230 nm and a supersaturation level of up to 27 times the aqueous equilibrium solubility of crystalline ITZ, as shown in Figure 3. Nebulized aerosols of the URF-ITZ colloidal dispersion demonstrated optimal aerodynamic properties for deep lung delivery. The in vivo bioavailability study on a murine model demonstrated that inhalation

FIGURE 6 A&B



Concentration-time profile of ITZ in (a) mice lung, (b) mice serum after inhalation of nebulized aerosols of HP CD-ITZ solution (ITZ:HP CD = 5.3:150, weight ratio) and URF-ITZ (ITZ:mannitol:lecithin = 1:0.5:0.2, weight ratio) colloidal dispersion (equivalent to 5.3 mg/mL of ITZ) in a whole-body exposure dosing apparatus. Data are presented as mean ± SD (n = 6) at each time point. *p < 0.05. (reproduced with permission from reference 22).

FIGURE 7



Supersaturated dissolution of tacrolimus in acidic dissolution medium: URF-SDS (▪), URF-PVA:P407 (▲), URF-P407 (●), PRO capsule powder (♦), tacrolimus equilibrium solubility (- - -). (reproduced with permission from reference 25).

of nebulized URF-ITZ aqueous colloidal dispersion containing 100 mg ITZ equivalence produced significantly high drug deposition in lung and systemic absorption, as shown in Figure 4. Generally, ITZ trough levels greater than 0.5 micrograms/mL in blood, or 0.5 micrograms/g in lung tissue are required for inhibition of Aspergillus sp. infection. ITZ deposition in lung was well above the effective inhibition drug level for the entire 24-hour observation period. In systemic circulation, effective therapeutic levels of ITZ can be maintained for about 5 hours after a single-dose inhalation, suggesting the effective therapy and proving the concept of pulmonary delivery of poorly water-soluble drug to achieve high lung local drug deposition and systemic bioavailability. The significantly improved bioavailability of the RF-processed ITZ was mainly attributed to the amorphous nature, smaller nano-scaled particle size, and the presence of lecithin, which is biocompatible to lung and acts as a permeation enhancer to facilitate ITZ permeation through the lung epithelium.

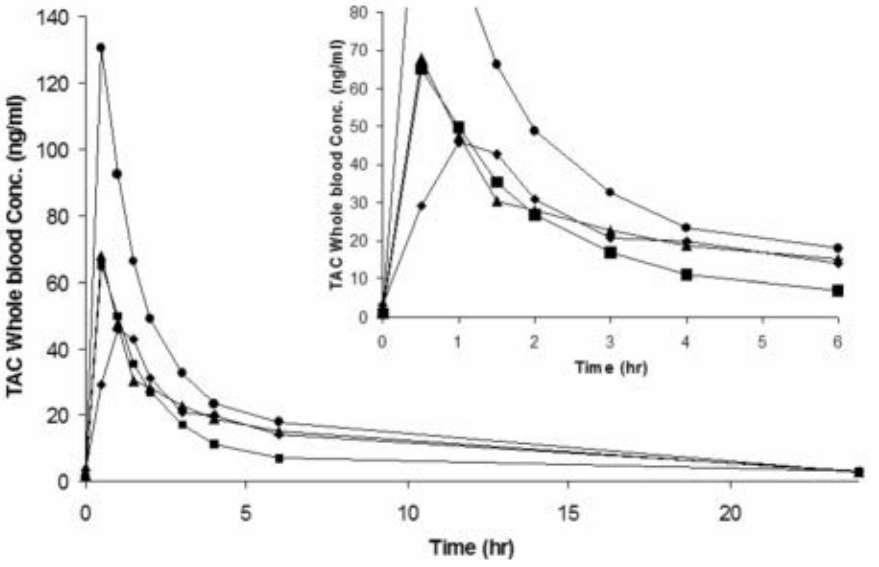
A subsequent study was designed to assess the impact of amorphous versus crystalline nanoparticulates of a poorly water-soluble drug on in vivo bioavailability following pulmonary delivery.[21] Crystalline nanoparticles of ITZ were made using a wet milling process (referred to as Wet-milled ITZ) to compare with the amorphous nanostructured aggregates of URF-ITZ. Dissolution tests revealed that the extent of supersaturation was 4.7 times higher for URF-ITZ versus Wet-milled ITZ, though their dissolution rates were similar. The aerodynamic performances of both aqueous colloidal dispersions were comparable and suitable for deep lung delivery. A single-dose 24-hour pharmacokinetic study was

conducted on a rat model following inhalation of the nebulized colloidal dispersions (equivalent to 20 mg ITZ/mL in 5 mL) of the crystalline and amorphous nanoparticles of ITZ. Despite similar lung depositions following inhalation of both compositions, in systemic circulation, URF-ITZ dosing group achieved 3.6 times higher C_{max} and 3.8 times of AUC^{0-24} values than those of the Wet-milled ITZ group, as seen from Figure 5. It is hypothesized that the supersaturation in the lung fluid that is produced by inhalation of amorphous nanoparticles of the poorly water-soluble drug led to higher systemic absorption and thereby enhanced bioavailability, relative to the nanocrystalline counterpart.

Furthermore, it was hypothesized that inhalation of an effectively solubilized form of poorly-water soluble drug could lead to faster absorption through the lung mucosal epithelium as compared to the nanoparticulate form, which requires a drug dissolution process prior to absorption. In the same series of studies, the pharmacokinetic profiles of inhaled aerosols of nebulized URF-ITZ aqueous colloidal dispersion and solubilized ITZ in cyclodextrin solution (equivalent to 5.3 mg ITZ/mL in 5 mL) were also investigated.22 Single doses of the nebulized aerosols in mice produced similar ITZ depositions in lung and pharmacokinetic profiles. The solubilized ITZ in cyclodextrin solution demonstrated faster systemic absorption of ITZ across lung epithelium, but overall less drug was absorbed ($AUC_{0-\infty}$ value was 67%) relative to URF-ITZ, as shown in Figure 6. The fast absorption of solubilized ITZ across the lung mucosal surface may be due in part to the elimination of the phase-to-phase transition. However, due to the increased flexibility in dosing regimen and loading of the URF-ITZ colloidal dispersion; these systems would be preferred over solubilization of poorly water-soluble drugs using cyclodextrin for pulmonary delivery because of the uncertain stability, limited drug loading, and lack of regulatory approval for the delivery of cyclodextrin to the lung.

In addition to the aforementioned example of amorphous ITZ nanoparticles, RF particle engineering has been successfully demonstrated on a wide variety of additional poorly water-soluble drugs for pulmonary delivery. One recent study using tacrolimus (a poorly water-soluble immuno-suppressant often used for organ transplantation), demonstrated high lung local concentration and systemic absorption of an RF-processed tacrolimus formulation after pulmonary delivery in a rodent model.[23]

FIGURE 8

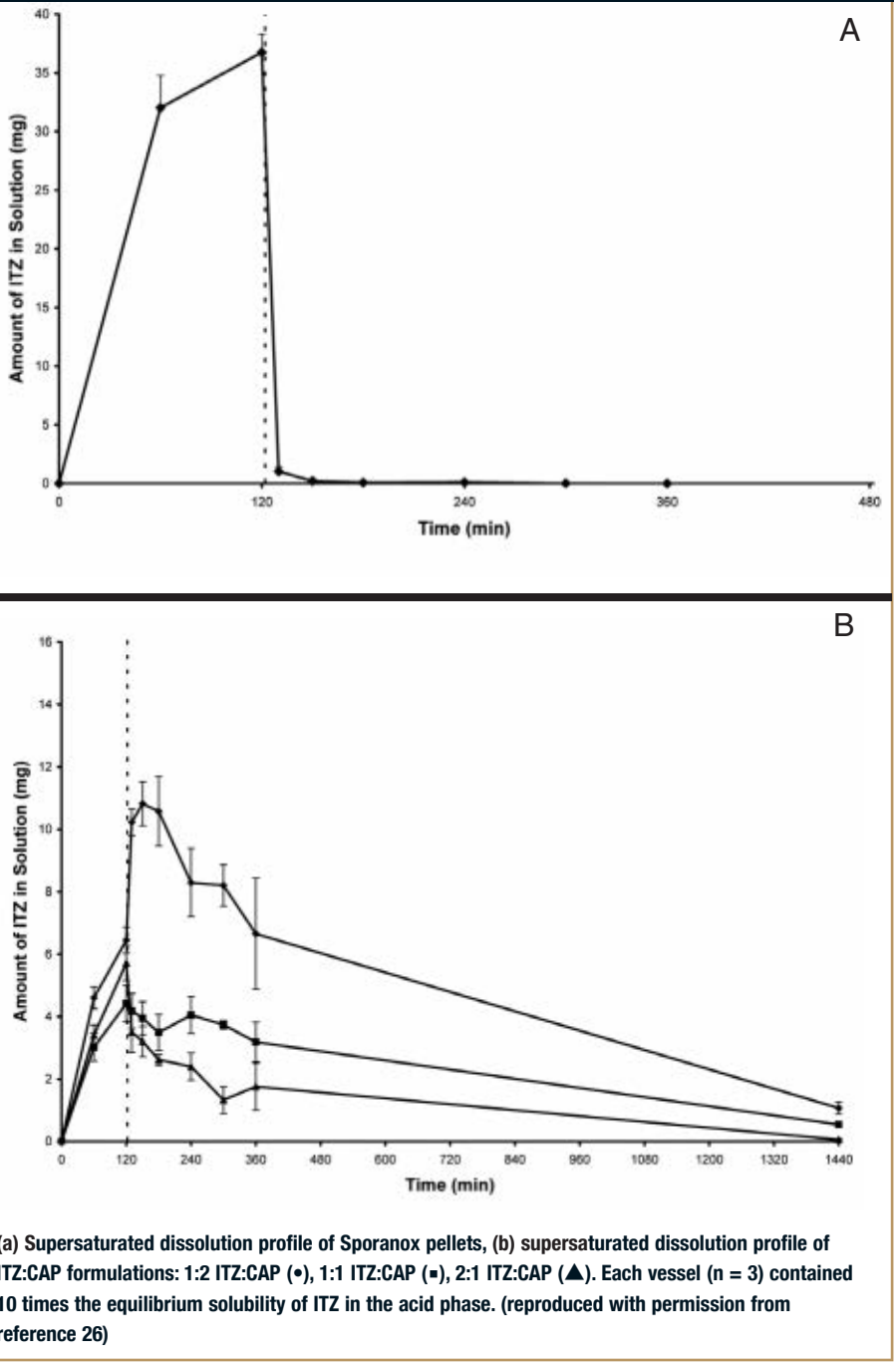


Mean whole blood absorption levels of TAC compositions produced using the URF process compared to the commercially available tacrolimus product. Powders were given an gelatin capsule containing 1.5 mg equivalent TAC (5 mg/kg) dosed via oral gavage to a rat model: URF-SDS (▪), URF-PVA:P407 (▲), URF-P407 (●), PRO (♦). (reproduced with permission from reference 25)

ORAL DELIVERY OF RF-PROCESSED POORLY WATER-SOLUBLE DRUGS

BCS class II poorly water-soluble drugs, when delivered orally, have been shown to exhibit a direct relationship between bioavailability and the dissolution rate of the drug product. Specifically, increased dissolution rate typically results in an increase in oral bioavailability.[24] However, it was also discovered that in order to greatly enhance the bioavailability of poorly water-soluble drugs, stabilizers were needed to ensure that once supersaturation is achieved, it can be maintained for a longer period of time at the site of absorption. Decreasing levels of solubilized drug due to recrystallization can result in incomplete absorption and highly variable bioavailability. Therefore, the use of the RF process to prepare amorphous forms of poorly water-soluble compounds for oral delivery is ideal because it allows for the

FIGURE 9 A&B



(a) Supersaturated dissolution profile of Sporanox pellets, (b) supersaturated dissolution profile of ITZ:CAP formulations: 1:2 ITZ:CAP (•), 1:1 ITZ:CAP (▪), 2:1 ITZ:CAP (▲). Each vessel (n = 3) contained 10 times the equilibrium solubility of ITZ in the acid phase. (reproduced with permission from reference 26)

incorporation of a wide variety of stabilizing excipient materials at relatively low but effective concentrations to ensure enhanced absorption and bioavailability are achieved.

The versatility of the RF process and the amorphous nanostructured drug powders produced using this method allows for the preparation of a variety of final dosage forms that can be delivered by various administration routes, including oral, pulmonary, parenteral, and topical among others. Of these, the oral delivery route is the most commonly used, and the benefits of the RF process for oral delivery are clearly illustrated in the following study, which utilized RF-processed tacrolimus.

Solid dispersions containing tacrolimus (TAC) and various stabilizers for oral delivery were prepared using the RF process.[25] All prepared TAC compositions demonstrated increased dissolution rates and supersaturation with the highest supersaturation level reaching approximately 22 times the equilibrium solubility of crystalline TAC in acidic medium, as shown in Figure 7. The in vivo oral bioavailability of these TAC compositions was then examined using a rat model, and the results of this study (Figure 8) clearly indicate that the best performing RF-processed composition was able to achieve a greater than 150% increase in AUC compared to Prograf®, the marketed oral tacrolimus product. Additionally, all RF-processed TAC compositions examined in this study demonstrated faster absorption relative to the Prograf® control.

In addition to tacrolimus, engineered solid dispersions of ITZ containing enteric polymers intended for oral administration were also produced using the RF process.[26] In vitro dissolution performance using a pH-change method showed that all RF-processed enteric ITZ compositions provided significantly lower levels of supersaturation in acidic media and greater extents of supersaturation in neutral media compared to the commercial product Sporanox® solid dispersion formulation. Among all the enteric ITZ compositions, the one containing cellulose acetate phthalate (CAP) as a carrier showed the substantially greatest degree of supersaturation and ability to stabilize ITZ in the supersaturated state as shown in Figure 9, and was selected for in vivo testing in a rat model. When compared to the Sporanox® dose at the same strength, a greater than 200% increase in oral bioavailability was observed (Figure 10), indicating the utility of RF particle engineering technology for improving the oral bioavailability of poorly water-soluble drugs.

CONCLUSION

With the increasing number of poorly water-soluble compounds appearing in developmental pipelines, the associated issues of low solubility and poor bioavailability are quickly becoming an industry wide issue, and a means to improve the dissolution properties of these compounds is of vital importance. Using RF particle engineering to make amorphous nanoparticulate formulations of poorly water-soluble drugs is an attractive and promising approach to overcome these issues by providing drug formulations with higher dissolution rates and the ability to supersaturate, which will subsequently result in enhanced bioavailability. RF technology provides the flexibility to choose various excipients and solvents in drug formulations to tailor the properties of RF-processed drug compositions, accommodating the requirements of various dosage forms for optimal delivery of poorly water-soluble drugs.

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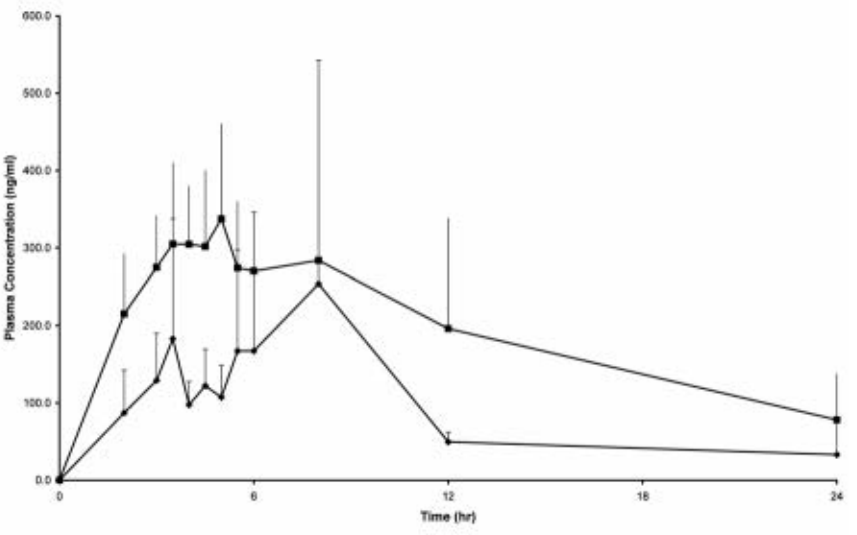
FIGURE 10



In vivo plasma profile of ITZ in rats after oral gavage at a dose of 15 mg ITZ/kg of body weight per rat (n= 6). Sporanox pellets (◆), 1:2 ITZ:CAP (■). (reproduced with permission from reference 26).

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BIOGRAPHIES

Dr. Wei Yang is a Senior Research Scientist with Enavail, LLC in Austin, TX. She earned her PhD in Pharmaceutics from The University of Texas at Austin. Her primary research interests involve formulation and particle engineering technologies to improve bioavailability of poorly water-soluble drugs. Dr. Yang has authored several publications and co-invented patents involving the use of cryogenic technologies for drug delivery.

Dr. Donald E. Owens III serves as Director of Operations for Enavail in Austin, TX. Prior to Enavail, Dr. Owens worked at ExxonMobil and Proctor & Gamble primarily in R&D, product development and manufacturing scale-up roles. He holds a B.S. in Chemical Engineering from Purdue University and a PhD in Chemical Engineering from the University of Texas at Austin.

Dr. Jay Peters is Professor of Medicine and Chief of Pulmonary and Critical Care at the University of Texas Health Sciences Center - San Antonio. He chairs the Airways Disorder Network for the American College of Chest Physicians and is a member of the Cochrane International Airways Committee. Dr. Peters earned his medical degree and training in Pulmonary, Critical Care, and Infectious Diseases at Baylor College of Medicine, Houston, Texas.

Dr. Robert O. (Bill) Williams III is the Johnson & Johnson Centennial Professor of Pharmaceutics, College of Pharmacy, University of Texas at Austin. He earned his BS in Biology from Texas A&M University, and a BS in Pharmacy and PhD in Pharmaceutics, both from the University of Texas at Austin. He has published over 225 articles, abstracts, and book chapters in pharmaceutical technology and drug delivery. Dr. Williams was elected a Fellow of the American Association of Pharmaceutical Scientists in 2006.

On The Rise

Drug Development Companies You Should Know About

By: Cindy H. Dubin, Contributor

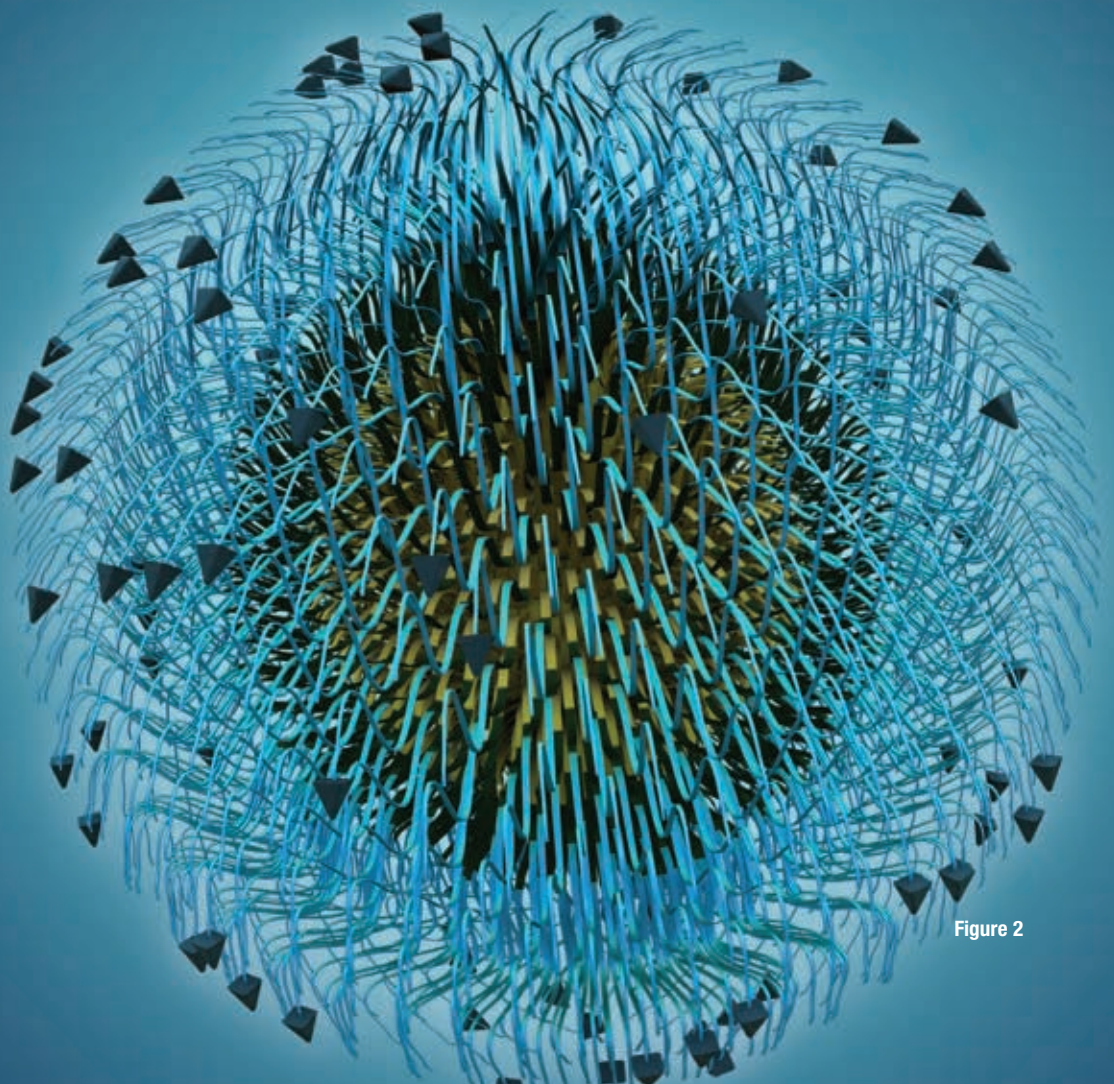

Figure 2

Recent patent expiries for blockbuster drugs and potential patent losses are causing major pharmaceutical companies to reposition and reformulate drugs. And according to GBI Research, this has resulted in significant growth in the drug delivery sector, which is expected to become a $199 billion market by 2016, up from $101 billion in 2009.

The increasing demand for effective delivery of novel biopharmaceuticals is also driving the growth of the global top 10 drug delivery technologies market, with time-release technologies topping that list. As a whole, the global top 10 drug delivery technologies market is expected to grow from $43.8 billion in 2009 to $81.5 billion in 2015, states a new report from MarketResearch.com. More than 25% of the marketed drugs fail to provide expected commercial returns due to poor drug distribution and absorption levels within the body, therefore signifying the importance of drug delivery systems. Rapid enhancements in drug discovery technologies have lead to significant developments in proteomics and genomics, resulting in a greater demand, and thus impact, on the drug delivery technology market. Unconventional modes of drug delivery, such as pulmonary, nasal, and transdermal, are also gaining popularity, especially for chronic disease conditions, such as diabetes, hypertension, CNS, and cancer.

Drug Development & Delivery magazine recently spoke with the corporate leaders of several drug development and delivery companies that are brining innovative delivery methods to the market. These technologies have several attributes in common: ease of use, better dosing, and improved quality of life for patients.

AGERE PHARMACEUTICALS, INC.–USING PHYSICAL CHEMISTRY TO IMPROVE SOLUBILITY

New chemical entities (NCEs) in modern discovery libraries and development programs have an ever-increasing number of non-conventional physical and chemical properties. Up to 70% of discovery compounds and 40% of pipeline candidates are insoluble in water. These promising molecules present unique formulation and development challenges. Agere Pharmaceuticals, Inc. of Bend, OR, (Figure 1) was established to tackle these challenges and provide solutions for developing poorly soluble compounds.

Agere's science-based approach to formulation selection and development is based in physical chemistry mechanistic principles, integration of unique analytical measurements with predictive computational modeling, and execution of high-quality manufacturing, explains Agere's Dan Smithey, PhD, Co-Founder and Chief Scientific Officer.

"Agere's technologies rationally design and select solubilization formulations for poorly soluble APIs based on physical chemistry mechanisms of the delivery systems and the compound's physical-chemical properties," he says.

Agere's approach can be applied to any therapeutic area or biological target. Through proprietary analysis of a molecule's physical-chemical properties, an appropriate technology is selected, and formulation prototypes are screened *in vitro* to accurately measure critical-to-performance drug species (eg, free drug, excipient-drug colloids or nanoparticles, and miceller drug) concentrations and their individual dissolution rates in biorelevant media. This approach leads to the optimum drug delivery technology, the preferred excipients within that technology, the proper process methodology, and the final dosage form.

For example, for solid dispersions, it is often difficult to select the preferred polymer and API loading to ensure maximum oral absorption and simultaneous physical and chemical stability. Because there are numerous polymeric excipients that can be used, and a large number of potential API loadings, it is highly desirable to use a rational approach toward formulation selection.

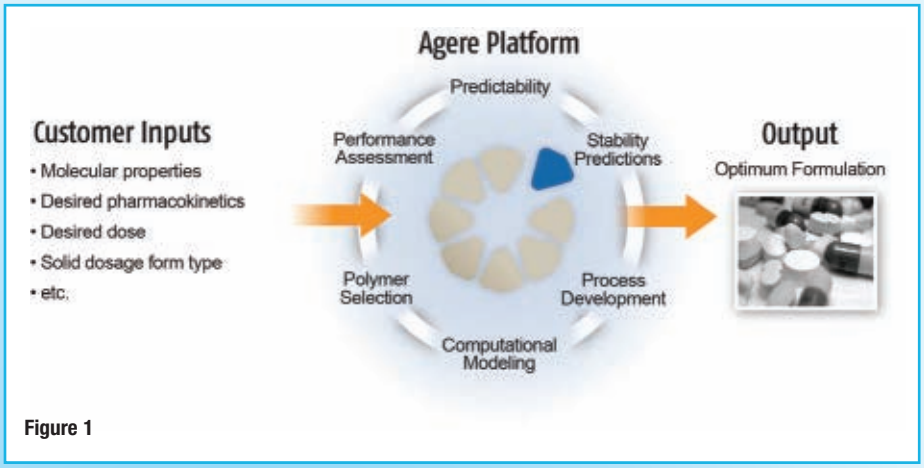

Figure 1

"Agere's technology can identify the optimum formulation composition rapidly with as little as a few hundred mgA, and within 1 to 2 weeks. In addition, Agere's customers can access the technology using a simple fee-for-service approach, without licensing constraints," says Dr. Smithey.

In early 2010, Agere launched several fee-for-service technologies to greatly de-risk and accelerate the progression of promising, but solubility-limited, compounds within all therapeutic classes. This includes Agere's Solid Dispersion Platform™, ParaSol™, OraLead™, and SoluForm™ technologies that comprise a complete portfolio to advance delivery of challenging APIs.

Agere's Solid Dispersion Platform enables accurate design and rapid selection of preferred formulations using solid dispersion technologies that will enhance oral bioavailability of poorly soluble compounds. Specifically, based on compound properties, Agere scientists design and select the preferred formulation technology, excipient type, drug loading, and dosage form for virtually any poorly soluble compound. Similarly, ParaSol is a recently launched technology to optimally develop parenteral formulations for insoluble APIs. OraLead is a discovery-enabling technology facilitating lead selection of discovery compounds that will be most enhanced using solubilization technology.

This greatly relieves solubility constraints during lead optimization of promising NCEs, says Dr. Smithey. In addition, Agere has a rapid experimental and computational platform for prediction of physical and chemical stability of amorphous formulations. To date, Agere's technologies have been applied to more than 100 compounds and have helped advance low-soluble compounds beyond *in vivo* studies (ie, PK, dose escalation, efficacy, and toxicity) and into the clinic.

Agere recently moved into a new facility and has embarked on the implementation of cGMP analytical services and manufacturing of solid dispersions via spray drying to produce Phase I and II clinical trial material (CTM).

"This extends our solubilization formulation services to meet the demand of our customers who want to work with Agere beyond the design stages of formulation development for BCS II, III, and IV compounds," explains Dr. Smithey.

Agere will soon finalize the installation of cGMP manufacturing of solid dispersions using both spray-drying and melt-extrusion processes. In addition, Agere will have cGMP manufacturing capability for solid dosage forms, specifically tablets and capsules, throughout the next year. Future technology launches at Agere include a GI-permeability-enhancement technique that does not alter the physiological environment. Proof-of-concept of this technology is planned in animal models in 2011. Finally, Agere plans to initiate several excipient collaborations and drug discovery co-development programs throughout the next several years.

INTEZYNE, INC.–TREATING CANCER BETTER

Drug delivery remains a challenge in the management of cancer. Approximately 12.5 million new cases of cancer are being

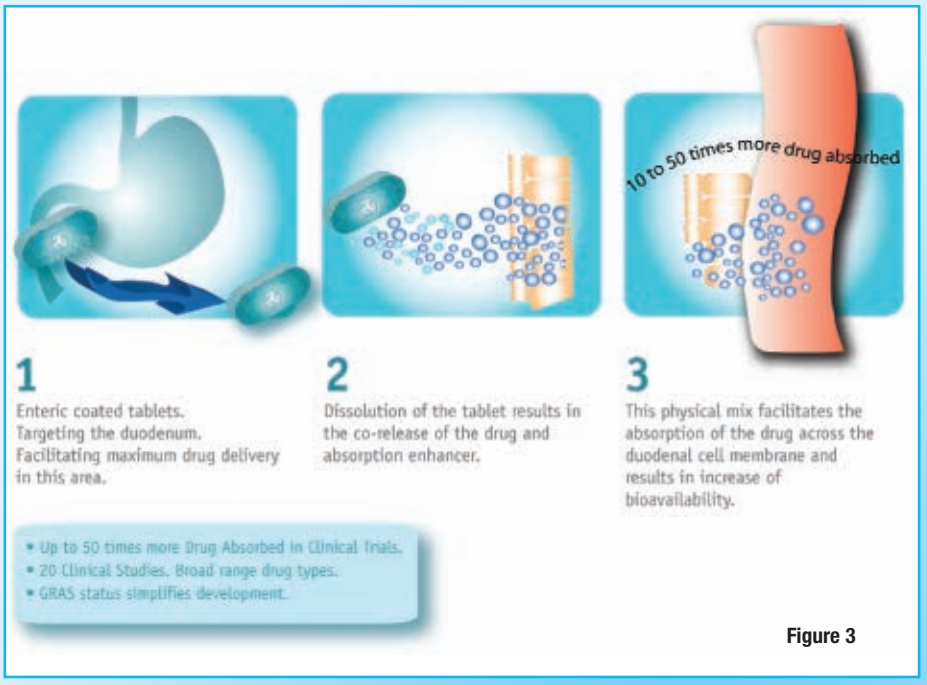

Figure 3

diagnosed worldwide each year, and considerable research is in progress for drug discovery for cancer. The focus is on a targeted cancer therapy that delivers drug directly to tumor tissues and prevents damage to healthy surrounding tissues.

Intezyne, Inc. in Tampa Bay, FL, has made its primary mission is to treat cancer better by creating safer and more efficacious treatments.

"The potency of cancer drugs often is handicapped by non-specific delivery outside of the tumor site, requiring higher dosing and resulting in severe toxicities," says Intezyne CEO Habib Skaff, PhD. "Our drug delivery platform, the IVECT™ Method, is designed to overcome these hurdles, securely and stably encapsulating active therapeutic in proprietary, polymeric, nanoparticle micelles (Figure 2). The micelles minimize exposure to healthy tissues and shield the contents from the body's natural defenses."

Intezyne's IVECT Method is based on a multi-disciplinary approach, integrating polymer physics and materials science with organic chemistry, polymer chemistry, biochemistry, and biology. The IVECT Method has four distinct hallmarks: stability, solubility, versatility, and tunability. Enhanced stability increases circulation time in the bloodstream and the amount of drug that reaches the tumor. Solubility is afforded through the micelles themselves, and this is key, according Dr. Skaff, because there are many drugs that previously could not be administered because of their low solubility. From a versatility perspective, the technology has been shown to deliver many classes of compounds with diverse applications in oncology, as well as other disease areas. Tunability is enabled by attaching cell targeting groups, which can anchor IVECT micelles to tumor tissue. A proprietary cross-linking technology can provide a triggered release mechanism to actively dispense the drug payload at the tumor site.

"Using the IVECT Method, our researchers encapsulate a therapeutic agent within a PEGylated micelle consisting of proprietary tri-block copolymers, versus standard diblock polymers," explains Dr. Skaff. "The middle, cross-linking block of each copolymer stabilizes the size of the micelle to 60 to 100 nm. It also increases the ability to keep the drug in the bloodstream, in some cases over 1000% longer than current modalities. This affords more passes at the tumor and up to 10 times greater accumulation of therapeutic within the disease tissue. In contrast, diblock polymers have much reduced stability and therefore are cleared much more quickly from the bloodstream."

By overcoming the challenge of stabilizing micelles, other technology attributes can come into play. Cell-targeting groups attached to the water-soluble block of Intezyne's tri-block help localize the micelle within a targeted disease tissue, such as a tumor. Once inside the target tissue, the relative decrease in the pH triggers the cross-links to release the drug within the micelle. The copolymers are then excreted by the body.

In the past year, Intezyne has made substantial progress validating its IVECT Method in preclinical *in vivo* models. Based on this progress, the company is within 12 months of going into the clinic. Its most advanced product candidate is IT-141, containing SN38, the active metabolite of irinotecan. IT-141 has entered preclinical *in vivo* toxicology studies and is expected to commence clinical testing for the treatment of metastatic colorectal cancer by Q3 2011.

"Our strategy is to advance this program ourselves, achieve Phase I results by mid-2012, and then partner this product candidate," says Dr. Skaff. "We also expect to bring into clinical testing next year a second product candidate, IT-143, which delivers daunorubicin, whose indication will either be in osteosarcoma or renal cell carcinoma."

The IVECT Method has proven to be extraordinarily versatile, able to deliver many classes of small molecules, in addition to nucleic acids, oligopeptides, and diagnostic imaging agents. In the next three years, Dr. Skaff says he expects Intezyne to expand beyond oncology to include inflammatory disease. Inflamed tissues would allow targeting in ways similar to tumor tissues.

As a result of Intezyne's research and its ability to rapidly develop and test new formulations, Dr. Skaff says there is growing interest from potential partners.

"In the more immediate term, we are seeking an additional round of financing, which we hope to complete sometime in 2011 and expect to announce our first, top-line clinical results in an oncology application by mid-2012."

MERRION–TURNING INJECTABLE CHALLENGES INTO ORAL SOLUTIONS

Bone metastases occur in more than 1.5 million patients with cancer worldwide and are most commonly associated with cancers of the prostate, lung, and breast, with incidence rates

as high as 75% of patients with metastatic disease. Despite the availability of current treatments, a significant proportion of these patients still experience bone complications or are not candidates for existing treatment.

Merrion Pharmaceuticals, Ireland, is offering hope to these patients with its lead product, Orazol™, a weekly tablet bisphosphonate (zoledronic acid) compound for the treatment of early-stage breast cancer and metastatic bone disease. To date, the oral drug delivery market holds the biggest presence in the overall drug delivery market, with 52% of the market share. It is expected to reach $92 billion by 2016, according to GBI Research.

Following consultation with the FDA in November 2010, Merrion is preparing for its Phase III study for Orazol. If successful, the Phase III study will permit a new drug application for Orazol to be made under the FDA's 505(b)(2) abbreviated approval procedure using a single Phase III study. The study will compare Orazol against a placebo as an adjuvant breast cancer treatment with a primary endpoint of Disease Free Survival of patients with breast cancer.

"If approved, this drug would provide a new treatment, which could improve prognosis, in combination with existing treatments, for early-stage breast cancer patients," says John Lynch, CEO of Merrion. "Subject to a licensing partner and FDA approval, Phase III trials for Orazol would commence in 2011. It is estimated (Edison Research) that Orazol could be on the market by 2016."

Orazol Phase II results showed several benefits over the current infusion therapy. Orazol tablet taken weekly had equal efficacy after 1 week compared with the monthly infusion. Orazol had faster and greater magnitude of bone pain relief with no acute phase reaction side effect compared to 50% APR with the infusion, explains Mr. Lynch.

Orazol will be delivered using Merrion's patented GIPET® drug delivery technology (Figure 3), which allows the oral dosing of drugs previously only available in intravenous form. GIPET uses specifically designed oral formulations of patented absorption enhancers that activate micelle formation, facilitating transport of drug and substantially increased absorption, with good reproducibility and a strong safety profile.

"The absorption enhancers we use are of GRAS/food additive nature, and their strong safety profile minimizes development risk," explains Mr. Lynch.

GIPET enteric-coated tablets target the duodenum, facilitating maximum drug delivery in this area. The dissolution of the tablet results in the co-release of the drug and absorption enhancer. This physical mix facilitates the absorption of the drug across the duodenal cell membrane and results in increased bioavailability.

In a database comprising more than 40 compounds that have poor permeability, GIPET has shown the ability to improve absorption by as much as 200 times, achieving excellent intersubject reproducibility, indicates Mr. Lynch. This database covers a range of compounds with varying physio-chemical properties and molecular weights, including small molecules as well as biopharmaceutical peptides and proteins.

Merrion's technology is endorsed through collaborations with pharmaceutical companies, such as Novo Nordisk and Ferring Pharmaceuticals. Novo Nordisk initiated a Phase I trial for orally administered GLP-1 analogue in April 2010, formulated using Merrion's GIPET technology. This was in addition to an oral insulin Phase I that commenced in November 2009. In September 2010, Novo Nordisk also announced that an oral basal insulin would be in a Phase I trial within 6 to 9 months.

"Novo Nordisk has had considerable success this year with its injectable GLP-1 product Victoza, which has significantly beaten analyst sales predictions since launch," says Mr. Lynch. "This has heightened interest in developing an oral version. Novo Nordisk describes oral insulin developed using Merrion's GIPET technology as a potential game-changer in the diabetes field."

Just within the past couple of months, Merrion announced two additional oral drug delivery feasibility and option agreements. The first agreement with Rebel Pharmaceuticals will evaluate the ability of GIPET to enhance and substantially improve the clinical profile of two undisclosed compounds. Upon successful completion of the feasibility agreement, Merrion and Rebel Pharmaceuticals will enter into license agreements, the financial terms, including milestones and royalties, have already been agreed. Rebel Pharmaceuticals is a speciality pharmaceutical company focused on enhancing approved drugs using proven and patented drug delivery technologies.

The second agreement is with a Big Pharma company to evaluate GIPET to boost the bioavailability of three compounds, which have a range of molecular weights. Following the feasibility studies, the company will have the option to enter into a licensing agreement for Merrion's GIPET technology.

"These agreements are further validation of the broad applicability of GIPET and the high level of interest in using the power of

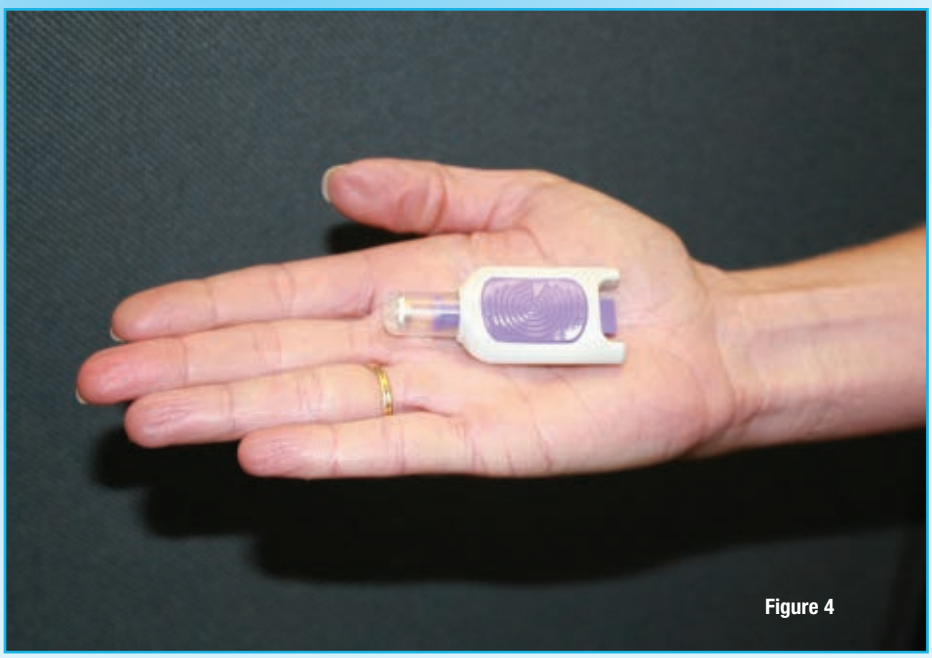

Figure 4

GIPET in the pharmaceutical industry," says Mr. Lynch.

Merrion has a state-of-the-art pharmaceutical production and laboratory space in Dublin, and in July 2010, the facility was licensed under the EU Clinical Directive for investigational medicinal products by the Irish Medicines Board. The 30,000-sq-ft facility will allow Merrion to progress several products through the stages of development simultaneously.

"This was an important milestone for Merrion as it allows us to manufacture for clinical trials and enables us to expand the number of products we can develop for ourselves and partners, all the while maintaining our track record of high-quality standards in rapidly developing and manufacturing products based on our GIPET technology, concludes Mr. Lynch."

MYSTIC PHARMACEUTICALS–PRESERVATIVE-FREE & PRECISE OPHTHALMIC & NASAL DELIVERY

Ophthalmic drug delivery systems have been difficult to develop primarily because the eye has natural protective barriers, and is particularly sensitive to devices, implants, and compounds that deliver drugs to the eye. For nearly 100 years, the accepted form of front-of-the-eye delivery has been eye-drops, which constitutes 95% of all drugs administered to the eye. Within the past decade, there have been a limited number of new technologies developed for front-of-the-eye delivery. The single-use, blow-fill-seal vial was perhaps the most compelling development that occurred nearly 20 years ago. The primary benefit of the unit-dose vial was to provide aseptic packaging–a key factor needed to address the rising demand for preservative-free ophthalmic products. Limited advances have also been made in preservative-free pump drop ophthalmic delivery systems; however, none of this class of delivery systems has been used as yet for prescription ophthalmic products in the US.

A critical shortfall of all these devices was the lack of precision control over delivered dose volume and delivered dose consistency. The fundamental physics of fluid dynamics of these devices renders them incapable of dispensing doses of less than approximately 40 microliters with a variability of ± 20 microliters when used by the average consumer. The human eye will carry a maximum dose volume of 7 to 12 microliters of drug before it overflows out of the eye and is absorbed into the body via the nasolacrimal duct. Excessive dose delivery has historically been an insurmountable limitation of the traditional ophthalmic delivery system paradigm for pharma manufacturers and lies at the root of a number of undesirable side effects that span inconvenience, increased systemic absorption, reduced efficacy, waste, and higher costs for both consumers and manufacturers, explains Timothy Sullivan, President and CEO of Mystic Pharmaceuticals, Inc., an Austin, TX-based specialty pharma company.

Mystic has developed the VersiDoser™ Delivery Platform (Figure 4), a liquid unit-dose drug delivery technology platform for both ophthalmic and intranasal applications. All VersiDoser delivery systems enable simplified self-administration, reliable consistent dose control, and efficient packaging and delivery of pharmaceuticals, biopharmaceuticals, and biologics, which reduces the waste and cost for the consumer and the manufacturer.

The VersiDoser Platform uses an aseptic Form-Fill-Seal manufacturing process to package liquid drugs in a proprietary unit-dose blister, which can be configured to dispense precise dose volumes ranging from 15 to 500 microliters. Blisters are produced from USP class, multi-layered foil laminates that provide barrier properties against water, vapor, oxygen, and light transmission. Each Unit Dose Blister incorporates a VJet™ nozzle that is optimized for the specific drug contained in the system. The VJet precisely controls dose volume and key characteristics of the dispensed spray geometry (droplet or particle size, particle distribution, spray angle, and velocity).

Mystic's Nautilus Delivery System completed a Phase Ib clinical trial for Age Related Macular Degeneration in late 2009. Both the drug compound and the delivery system successfully met the clinical endpoints, says Mr. Sullivan, enabling patients ranging in ages from 55 to 87 to easily self-administer a precise dose of a preservative-free drug formulation throughout the duration of the trial. Patient acceptance of Mystic's novel ophthalmic delivery system was exceptional, with 87% of the participants expressing a preference for the Mystic delivery system over traditional eye drop delivery bottles. VersiDoser Opthalmic Delivery Systems are available in multi-dose disposable and reloadable configurations.

Mystic's VersiDoser Intranasal Delivery Platform is designed for precise self-administration of drugs or biologics systemically into the body via the nasal route.

Figure 5

According to Greystone Research Associates, self-administration devices will have a significant impact on the future of drug delivery because they safely and reliably satisfy treatment protocols and compliance goals. These VersiDoser delivery systems eliminate the need for priming with enhanced safety features that prevent inadvertent dispensing and a "safety lock" that eliminates the risk of abuse once the device has been used.

The VersiDoser Delivery Platform is clinical ready. Mystic operates a pilot cGMP manufacturing facility with the capability to manufacture clinical supplies for preclinical and Phase I–Phase III clinical trials.

Also under development by Mystic is the VRx2™ Delivery Platform, capable of automatically reconstituting thermo-stabilized powdered drugs, biologics, and vaccines at the time of administration, which allows for improved product stability and reduces the requirement for cold chain management. The VRx2 platform includes ophthalmic, as well as intranasal and oral reconstitution delivery systems.

Key to Mystic's success is collaborations with Big Pharma, biotech, and specialty pharma manufacturers to provide advanced ophthalmic and nasal delivery solutions, says Mr. Sullivan.

Mystic licenses its technology to pharma and biotech manufacturers, provides co-development services for product integration and clinical and commercial supply services. Mr. Sullivan anticipates significant expanded use of the VersiDoser Delivery Platform to late-stage clinical trials in 2011 with partners, and commercial availability by 2013.

PANTEC BIOSOLUTIONS AG–REACHING DIFFICULT SKIN LAYERS

The market for drugs delivered transdermally was valued at $5.6 billion in 2009, with the majority of these sales being accrued by products using first-generation patch technologies, according to a new report from Advances in the Transdermal Drug Delivery Market: *Market Size, Leading Players, Therapeutic Focus & Innovative Technologies*. Innovative technologies that deliver drugs with a broader spectrum of characteristics are poised to revolutionize the transdermal drug delivery market and drive significant growth.

One company finding its way in this market is Pantec Biosolutions, AG, out of Liechtenstein. Its P.L.E.A.S.E. (Precise Laser Epidermal System) laser-assisted transdermal delivery platform enables delivery of large-molecular weight compounds, such as proteins, through the skin.

"Transdermal delivery is a less-invasive means of drug delivery and is, in most cases, more efficient," says Dr. Christof Böhler, CEO of Pantec.

While most large molecules and proteins cannot pass unassisted through the skin, the P.L.E.A.S.E. platform consists of a hand-held laser device that is used to create tiny micropores on a small area of the skin before applying the drug patch or ointment. In this way, the microporated skin allows the transfer of very large molecules that would otherwise have to be administered by injection.

"The transdermal route of administration is favorable over injections and, on a case-by-case basis, also over oral or other modes of delivery because the first-pass effect is avoided," says Dr. Böhler. "In addition, P.L.E.A.S.E. allows precise drug permeation into difficult-to-reach tissue areas, where injections are not feasible or not possible to use."

Pantec's technology rests on a breakthrough in the size and ease of use of the laser unit. Er:YAG solid-state lasers are widely used in medical practices, but they are large, slow, high-maintenance devices that use a lamp pump that requires extensive cooling and servicing, explains Dr. Böhler. P.L.E.A.S.E. uses a diode pump and a hand-held laser, opening the way for home- or private-based therapies (Figure 5).

The Er:YAG laser ablates biological tissue, such as skin, by evaporating water in microseconds. These water molecules leave the tissue at ultrasonic speed, thereby ablating the entire tissue in the area of the laser spot size. The result of this cold ablation process is a clearly cut micropore with no coagulation on the pore bottom and walls. This process of microporation results in the creation of multiple precise and controlled micropores into the outer layers of the skin. Once created, these micropores allow macromolecules to permeate across the skin, making it a very powerful technology for the permeation of large amounts of even the largest protein drug molecules.

The fast, controlled, and precise delivery makes P.L.E.A.S.E. an ideal method for delivering accurate doses of drugs and vaccines. Another area of application is infertility treatment. According to Dr. Böhler, current delivery of various fertility hormones is not adequately managed through periodic injections. Pantec selected infertility hormone treatment to validate the technology, with the goal of replacing around 50 or more injections in the long protocol stimulation cycle.

Pantec currently has two infertility hormones in Phase II clinical development: IVF001 is a triptorelin patch used for pituitary down regulation of infertility patients before controlled follicle stimulation, while IVF002 is a follicle-stimulating hormone patch used for controlled stimulation of follicles in egg cell donors or infertility patients.

"Phase I data in IVF001 showed that it had an excellent pharmacokinetic profile, allowing us to actually reduce both the dose and size of the patch, making it as user friendly as possible," says Dr. Böhler.

IVF002 showed therapeutically relevant blood concentrations of FSH in a Phase I study, and preliminary results of a first exploratory Phase IIa study shows follicle growth in egg cell donors form the combination of P.L.E.A.S.E. and the FSH patch. Pantec will keep its focus on infertility hormone treatment and will be looking for partners for co-development and commercialization in the US, South America, and Asia in the next few years.

Simultaneously, Pantec plans to commercialize a P.L.E.A.S.E. product solution for dermatologists in the form of P.L.E.A.S.E. Professional, a CE-marked table-top version to treat certain dermatological conditions from non-melanoma skin cancers to aesthetic dermatology. P.L.E.A.S.E. Professional will be marketed first in Europe before FDA registration is sought in the coming years.

SOLID FORM SELECTION

A Fit-for-Purpose Strategy Toward Solid Form Screening & Selection

By: Pingyun Chen, PhD, and David Igo, PhD

INTRODUCTION

Solid form screening and selection is one of the most critical activities for successful development of small-molecule drug candidates.[1-5] It provides an opportunity for chemists and formulators to modify the physico-chemical properties and overcome development challenges of an API. The most notable situation is the use of salt formation to improve the solubility and bioavailability of poorly soluble acidic or basic drugs. Identification of a developable crystalline form during candidate selection can facilitate isolation and purification of the API, ensuring the supply of drug substance with consistent and desired physical properties, simplifying development of formulations that support preclinical and clinical studies, and accelerating commercialization.

High-throughput screening technologies having automated sample preparation and integrated analyses have been developed and utilized throughout the past decade to support the discovery and evaluation of different solid forms using a limited amount of drug substance and short cycle time.[6,7] These technologies enable the solid form studies to be applied at earlier stages, eg, when comparing pharmacokinetics (PK) of solid doses of multiple compounds during lead optimization.[2]

Solid form selection is particularly critical for poorly soluble compounds that exhibit solubility and dissolution rate-limited absorption and for formulations in which the drug concentration is close to its equilibrium solubility.[1-3,8] Not only will a more soluble solid form be required to improve the bioavailability and enable the preclinical and clinical studies using simple formulations, a change in solid form later in the development cycle often requires bridging PK and repeating toxicological studies, resulting in increased cost and potential delays.[3-5,8]

The following will highlight the key considerations throughout the solid form selection process and provide a practical framework for developing an appropriate strategy to meet specific technical needs and ensure a successful and cost-effective progression of drug candidates through various development milestones to commercialization.

PHARMACEUTICAL IMPACT OF SOLID FORMS

The best way to define an appropriate solid form selection strategy is by examining its impact on key drug properties and development activities, including the API purification and isolation process, API physico-chemical properties, formulation strategy to support the preclinical studies, clinical trials, and commercialization.

API Isolation & Purification - Crystallization is the most valuable and widely used technique to isolate and purify products from reaction mixtures on a large scale. It is therefore essential to identify a suitable crystalline form of an API to ensure it can be manufactured on a large commercial scale even if a crystalline form is not required for formulation and other drug development activities.

Ideally, a single crystalline form of an API can be identified and used for purification, all development activities, and commercialization. In some cases, however, it may be advantageous to have two crystallization steps using different crystalline forms, eg, crystalline parent for impurity rejection and a salt for preclinical studies and formulations. This approach minimizes the risk of an impurity profile change if a different form or salt is required later in development.

If a suitable crystalline form has not been obtained for a drug candidate, crystallization and salt screening should be considered to support process development and scale-up activities. For compounds that are difficult to crystallize due to a high degree of rotational freedom, conformational flexibility, and imbalanced H-bonding donors and acceptors, salt formation and co-crystals with structurally complementary counter-ions or co-crystal formers can be an effective means of promoting crystallization and improving

physical properties, such as melting point and hygroscopicity. Key considerations of a suitable crystal form for isolation and purification include the following:

- Chemical stability in process solvents at elevated temperature
- Acceptable yield and impurity rejection
- Form control (eg, a single polymorph)
- Acceptable morphology and bulk density
- Thermal stability at drying temperature (ideally a non-solvated/non-hydrated form having a melting point of > 100°C).

API Physicochemical Properties - Solid forms can have a significant influence on many physical properties, including melting point, solubility, stability, hygroscopicity, and bulk density. In fact, most screening and selection processes primarily focus on improving physical properties to enhance the drug-handling characteristics, absorption, and delivery options.[9] In most cases, more soluble salts are pursued to enhance fast release and absorption of poorly soluble acidic and basic drugs.[1-3]

Two key preformulation activities include drug substance characterization and measurement of its solubility and chemical stability at different pH values. Use of crystalline drug substance for solubility studies is important because amorphous solids are typically 10 to 1000 times more soluble.[2] The pH solubility and stability data are used to: 1) calculate pK_a value(s) and determine the feasibility of salt formation, 2) assess whether drug absorption will be limited by solubility and dissolution rate using the Biopharmaceutical Classification System (BCS), 3) identify chemical instability that may be improved via solid form selection, and 4) develop formulation strategies.[3,10]

If salt formation is feasible for a poorly soluble compound, a salt screening should be conducted to find a more soluble crystalline salt, which is preferred over bio-enhanced formulations using amorphous solids, meta-stable polymorphs, solid dispersions, and lipid-based formulations. A soluble salt with adequate solubility and stability will help reduce PK variations (dose-to-dose, inter-subject, and inter-species), increase exposure and toxicological coverage, and enable simple formulations, such as powder in bottle (PiB), powder in capsule (PiC), and suspensions to be used in preclinical and clinical studies.

Salt screening for poorly soluble compounds should be focused on the discovery of more soluble salts, eg, structurally small, hydrophilic counter-ions, such as acetate, methanesulfonate, and citrate. It is important to recognize that salt solubility may not be a reliable surrogate for bioavailability, and PK studies may be required to select the best salt (vide infra). Polymorph screening studies of the selected salt should also be completed to ensure the selection of the most stable polymorph prior to 28-day GLP toxicological or first time in human (FTIH) studies.

Solid form selection also offers an opportunity to improve chemical stability of drug substances and compatibility with excipients. Because of lower molecular mobility and hygroscopicity, crystalline solids typically have much better physical and chemical stability compared to amorphous solids.

Formulation Strategy & Drug Delivery - Solid form selection should also take into consideration the route of administration, dose, dosage form, and release profile that are required to support preclinical and clinical studies and the target commercial formulation. For example, a soluble salt is typically preferred for oral delivery of a poorly soluble drug, while its uncharged parent may be required for topical

TABLE 1

Stage	Key Development Objectives	Solid Form Studies
Discovery (Lead to Candidate Selection)	• A crystalline form for isolation & purification (anhydrates, hydrates, solvates) • A suitable form with adequate solubility & stability to support PK and tox studies	• Drug substance characterization • Crystallization, salt if feasible based on pK_a, co-crystal screening for unionizable or intractable compounds.
Early Development (DRF, GLP/28-day toxicology, FTIH, Phase IIa)	• A developable crystalline form to support all development activities to the desired milestone. • Assess polymorphism, form relationship and select the most stable polymorph. • Risk assessment and mitigation plan if a more stable form is encountered or new salt is required.	• Crystal-form/polymorph screening • Competitive ripening and solubility studies at different temperatures • Revisit salt screening and selection as needed
Late Development (Phase IIb, Phase III, Launch)	• The final form to support the pivotal study through product launch • Final API crystallization process • Commercial formulation • Drug product manufacturing	• Comprehensive crystal-form/polymorph screening • Process robustness (solvents, temperatures, handling attributes) • Form control in API and drug product manufacturing (seeding studies, wet-granulation, particle-size reduction).
Life-Cycle Management (New indications & formulations, generic)	• Comprehensive solid form knowledge • Patent all important solid forms • Optimal form for new API manufacturing, new indications and formulations.	• Comprehensive salt and co-crystal screening

Typical Solid Form Studies at Different Development Stages

applications for which transdermal permeability is more critical than solubility.

Different dosage forms may require different physico-chemical properties and frequently different solid forms. For oral solid dosage forms, the key considerations include solid-state stability, sufficient solubility and dissolution rate, compatibility with excipients, bulk density, and compressibility. However, it is important to recognize that higher aqueous solubility of a salt does not necessarily mean higher bioavailability because of the precipitation events that can occur in vivo. In these cases, excipients and surfactants that inhibit the nucleation and crystallization should be included in formulation. For inhaled powder formulations, chemical and physical compatibility with excipients and device components, hygroscopicity, and milling are particularly important.

Solution formulations are commonly used to support toxicological studies, parental formulation, intranasal, and pulmonary delivery. In these cases, solubility and chemical stability in the formulation vehicle will be the most critical factor in solid form selection. Natural pH of the salt solution should also be considered carefully as it may be outside the acceptable pH range. Solution formulations also require knowledge of form space to ensure the drug concentration is below the equilibrium solubility of the most stable form in the formulation.[8] The requirements for suspension formulations are similar to those for solutions except that the solid form must be stable and remain suspended during dosing.

SOLID FORM SCREENING & SELECTION STRATEGIES

As discussed previously, solid form requirements vary with the drug candidate, development strategy, and over the course of drug development and product life-cycle. Table 1 highlights how solid form studies are typically aligned to achieve specific development objectives at different stages of development. The main focus of the studies at earlier stages is identifying a suitable crystalline form to support isolation and purification of an API and to provide drug substance with adequate solubility and stability for preclinical and clinical studies. As the drug development progresses to later stages, additional studies are conducted to assess and discharge the solid form risks during API and drug product manufacturing processes, to expand solid form knowledge, and to maximize the development opportunities via the selection of the optimal solid form for new indications/formulations.

CONCLUSION

Solid form of an API can have a profound impact on physical properties and nearly all drug development activities. The process outlined in this discussion takes into consideration the fundamental physico-chemical properties of a drug molecule, the impact of different solid forms on API purification, physical properties, and formulation strategies. It can be used to develop an appropriate selection strategy to ensure a rapid and successful progression of small molecule drug candidates.

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BIOGRAPHIES

Dr. Pingyun (PY) Chen is currently Manager of Optiform™ Technologies at Catalent Pharma Solutions. He earned his PhD from the University of North Carolina at Chapel Hill in 1989, joined Nicolet Instrument Corporation as FT-IR/Raman Product Specialist in 1998, and began his pharmaceutical career at GlaxoWellcome in 1999. After spending 1 year as Principal Research Scientist in the Crystallization Process Laboratory at Eli Lilly in 2004, he returned to Chemical Development at GlaxoSmithKline to provide global salt and polymorph screening and selection support of drug candidates from discovery through commercialization. Dr. Chen has given multiple presentations at national meetings, coauthored a book chapter on the application of vibrational spectroscopy in pharmaceutical development, and named a co-inventor on multiple patents. Dr. Chen's research interests include solid form screening strategy and technologies, material characterization, crystallization process development, drug absorption, and delivery.

Dr. David Igo earned his PhD from the University of Cincinnati, where he studied the structural behavior of inorganic/polymeric electrochemical sensors using extended X-ray absorption fine-structure (EXAF) spectro-electrochemistry under the direction of William R. Heineman and Richard C. Elder. Dr. Igo began his industrial career with Glaxo Inc. in 1991 (now GlaxoSmithKline; GSK), where he supported various aspects of drug development, including preformulation, product development, chemical development, materials characterization, and technology development. In his nearly 2-decade tenure at GSK, he co-invented a variety of high-throughput technologies utilized in solid-state screening along with a range of unique crystalline salts and solid-state forms of GSK compounds. He is currently Director of Optiform™ Technologies at Catalent Pharma Solutions. Optiform Technologies combines novel automation tools and solid-state workflows to support the discovery and evaluation of crystalline forms, salts, and co-crystals.

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ORAL DELIVERY

Controlled Release & Nanotechnologies: Recent Advances & Future Opportunities

By: Gary Liversidge, PhD

INTRODUCTION

Controlled-release and nanoparticle-based technologies are two of the main market drivers within the drug delivery sector. The following will discuss recent advances in both and outlines the potential opportunities for their separate and indeed combined utilization by the pharmaceutical industry over the coming years.

RECENT ADVANCES – CONTROLLED RELEASE

Controlled-release technologies have continued to create the largest market demand due in no small part to the fact that oral drug delivery remains the preferred route of drug administration by physicians and patients alike. At present, there are more than 1,400 controlled-release products on the market.[1] Oral drug delivery implies versatility, ease of administration, and very often, improved patient compliance. The cost of non-compliance alone in the US, according to a recent New England Healthcare Institute report, is estimated to cost as much as $290 billion, or 13% of total annual healthcare expenditure.[2]

Generally, controlled-release medicines can be categorized into the following two groups based on actions:

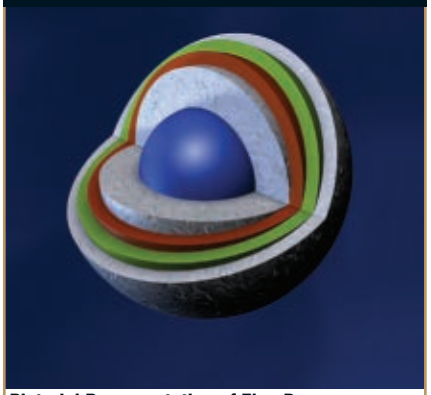
1. Extended-release formulations deliver a portion of the total dose shortly after ingestion and the remainder over an extended timeframe. For example, Avinza® is a once-daily, rapid-onset, extended-release morphine product developed by Elan Drug Technologies and marketed by King Pharmaceuticals Inc. in the US.
2. Delayed-release systems that provide steady dosing after passage through the stomach, such as with Bayer Healthcare's Safety Coated Bayer Aspirin product.

Two of the most widely commercialized controlled-release technologies are the OROS® technology developed by J&J's Alza, and the SODAS® technology developed by Elan Drug Technologies (Figure 1). Other successfully commercialized technologies include SkyePharma's Geomatrix®, Eurand's Diffucaps®, and Flamel's Micropump® systems.

Since the development of the aforementioned technologies, both they and others have evolved to address specific therapeutic needs, such as in the treatment of pain and hypertension. A number of companies are engaged in the development of pulsatile-release systems in which drug is released in pulses, separated by defined time intervals. Ritalin® LA and Focalin XR®, both used to treat Attention Deficit Hyperactivity Disorder (ADHD), mimic the twice-daily dosing of a conventional immediate-release tablet. These once-daily pulsed profiles offer the patient efficacy throughout the day, negating the need for children to take a second dose during school hours. Ritalin® LA and Focalin XR® both utilize Elan's SODAS® technology.

Orally disintegrating tablet (ODT) technology is an important delivery system for drugs that treat medical conditions vulnerable to a sudden onset of symptoms. Such conditions include allergies, nausea, migraine headaches, and schizophrenia. Among the available ODT technologies are Catalent Pharma Solutions' Zydis®, CIMA Labs' (Cephalon) Durasolv® and Orasolv®, and SPI Pharma's Pharmafreeze™ systems. Catalent's Zydis® technology has been the most commercially successful, has numerous

FIGURE 1



Pictorial Representation of Elan Drug Technologies' SODAS® Technology
Based on the production of controlled release beads, the SODAS® technology is characterized by its inherent flexibility, enabling the production of customized dosage forms that respond directly to individual drug candidate needs.

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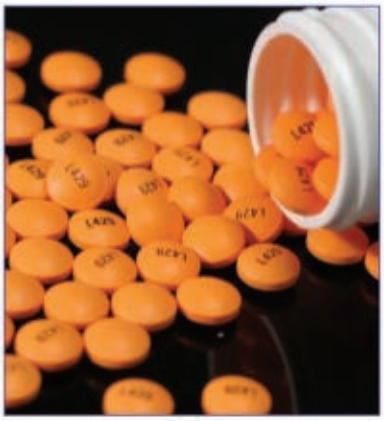

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products launched through licensees, and includes Eli Lilly's Zyprexa®, which is one of the most prescribed drugs that have been adapted to ODT delivery.

FUTURE CHALLENGES & OPPORTUNITIES – CONTROLLED RELEASE

While oral drug delivery is still the most active area in terms of deals being signed, the pharma market has evolved significantly throughout the past number of years to embrace a variety of goals beyond traditional extended/controlled-release solutions. Significant research effort is being dedicated to such areas as mini-tablet delivery, overcoming both alcohol dose dumping and opioid abuse issues, as well as targeted delivery.

Mini-Tablets in One System for Greater Flexibility

The launch of new drugs that incorporate a number of different mini-tablets provides a very flexible oral dosage option. Each one can be formulated individually and designed to release drug at different sites so that higher dose loading is possible within the gastro-intestinal tract. It is also possible to incorporate mini-tablets of different sizes so that high drug loading is possible. The Trilipix® fenofibrate product launched by Abbott in January 2009 is composed of a number of mini-tablets. Another technology using a similar approach is the PRODAS® delivery system from Elan Drug Technologies.[3]

Abuse-Resistant Delivery Systems

Opioids are the mainstay of pain management with $10 billion in sales for long- and short-acting opioids in the US with continued growth in the market. However, issues of abuse, misuse, and diversion have gained growing regulatory and public attention in recent years. A record 36 million Americans have abused prescription drugs at least once in their lifetime, a US government study found.[4] Though clinical, regulatory, and commercial issues have proved to be significant, the opportunity to develop abuse-resistant opioids is large. At present, there are a number of initiatives to minimize the risk associated with abuse of drugs, in particular strong pain medications. Pain Therapeutics was considered the front runner with its abuse-resistant formulation of oxycodone, which was formulated with DURECT's sustained-release gel-cap ORADUR® technology. In December 2008, Pain Therapeutics received a complete response letter from the US FDA for its NDA (submitted in June 2008) for REMOXY®.[5] Based on its review, the FDA has determined the NDA would not be approved in its present form. It is now expected that REMOXY® will be re-filed with the FDA at the end of 2010/early 2011. Embeda®, which involves a combination technology comprising morphine and the antagonist naltrexone, has received approval by the FDA but is subject to a REMS program that does not allow it to use an abuse-resistant claim on its label.

TABLE 1

Product/Licensee	Technology Developer	Launch Year
Rapamune®/Pfizer	Elan Drug Technologies	2001
Emend®/Merck	Elan Drug Technologies	2003
TriCor® 145/Abbott Fournier	Elan Drug Technologies	2004
Megace® ES/Par Pharmaceuticals	Elan Drug Technologies	2005
Abraxane®/Abraxis BioScience	Abraxis	2005
Triglide™/Sciele Pharma	SkyePharma	2005
INVEGA® SUSTENNA®/Janssen	Elan Drug Technologies	2009

Nanosized Products Launched in the US (Source: Elan Drug Technologies)

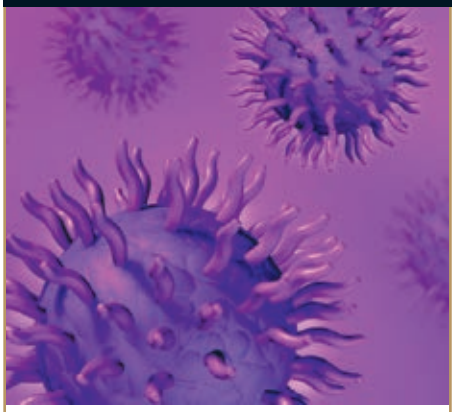
Alcohol Dose Dumping Strategies

Another challenge for the controlled-release market is that of alcohol dose dumping. In 2005, Palladone® capsules were withdrawn from the market in the US and Canada due to dose dumping when co-ingested with alcohol. Work to resolve this problem is being addressed by a significant number of companies, including Flamel with its Trigger-Lock® Micropump technology. The Trigger-lock® formulation of an opioid analgesic is being studied in two clinical trials. Egalet's key technology is an oral drug delivery system of capsules comprising a coat and a drug-release matrix. The drug is distributed throughout the drug-release matrix and is released over time as the coat and matrix are eroded within the gastro-intestinal tract. Egalet's technology claims to be abuse resistant (neither crushable nor injectable-receptive to fast extraction) and does not experience alcohol-induced dumping. Other technologies designed to avoid/reduce alcohol dose dumping include DURECT's SABER™ technology, SOLIQS' Meltrex® technology, and Banner's Versatrol™ controlled-release softgel technology.

Other Drug Delivery Research

Other approaches that also have significant potential include the targeting of drug directly to the colon and the stomach.[6,7] Colonic drug delivery has attracted interest primarily for local delivery in diseases of the colon, such as Crohn's disease, ulcerative colitis, and colorectal cancer. Furthermore, it has been proposed that the colon is a better site than the small intestine to promote oral macromolecule uptake. The colon is also typically a site of drug absorption from extended-release preparations in which a substantial portion of the drug is delivered to the colon. One approach is XenoPort's proprietary Transported Prodrug™ technology, which utilizes the body's natural mechanisms for actively transporting nutrients through cellular barriers to gain efficient absorption into the bloodstream. XenoPort's approach typically relies on a drug's ability to diffuse passively through the intestinal wall to enter the bloodstream and reach the targeted tissue. Its most advanced project is currently in Phase III clinical trials. Other approaches being investigated include Alizyme's Colal delivery system (also in Phase III) and Cosmo's MMX technology, which is in Phase II.

FIGURE 2



Schematic Representation of Elan Drug Technologies' NanoCrystal® Technology
NanoCrystal® technology is a manufacturing and formulation approach designed to increase the specific surface area of active pharmaceutical ingredients with poor water solubility.

RECENT ADVANCES - NANOTECHNOLOGY

While a number of other delivery systems are being developed, such as gastro-retentitive delivery and transmucosals, the successful development and commercialization of nanoparticle-based drug delivery systems has proven to be one of the most significant achievements in the field of pharmaceutics throughout the last decade. Advances in nanotechnology provide one of the most significant opportunities for growth in oral delivery, by addressing the poor water solubility issues associated with an estimated 40% of drugs leaving the clinic. There is no universally accepted definition of the terms nanoparticle or nanoparticulate, just as there is no universally accepted definition of nanotechnology. In the physics disciplines, a definition of nanotechnology as relating to things having at least one dimension less than 100 nm is often applied. A less-rigid approach is to consider nanotechnology as relating to the nanometer-scale materials and structures that exhibit novel properties or phenomena as a result of their smaller size. In a pharmaceutical context, nanosizing can refer to materials of 1,000 nm or in some cases, more than 1,000 nm in size.

Nanosizing

A number of methods are available to produce drug nanoparticles, involving top-down processes, based upon attrition, or bottom-up processes, based upon molecular deposition. Examples of the latter include spray-freezing into liquid (SFL), rapid expansion from a liquefied-gas solution (RESS), and gas antisolvent recrystallization (GAS). RESS and GAS represent two approaches in development based upon supercritical fluid technology.[8] RESS is used for compounds that are soluble in supercritical fluids. The resulting solution is subjected to a rapid reduction in pressure and/or a rapid elevation in temperature, causing the solute to emerge from solution. Under optimal conditions, submicron particles can be generated. The GAS process is used for compounds that are not soluble in supercritical fluids. The compound is first dissolved in an organic solvent and then re-crystallized by admixing with the supercritical fluid. More recently, Microfluidics has employed impinging-jet crystallization technology to produce crystalline nanoparticles.[9]

The alternate and more established path for generating drug nanoparticles entails top-down processes. Large drug particles (typically > 5 microns in diameter) are subjected to high-pressure homogenization or high-energy wet milling in a fluid phase consisting essentially of water, yielding drug particles in the nanometer size range.[10] Key to the success of both processes is the inclusion of surface modifiers in the fluid phase. The surface modifiers prevent aggregation and/or Ostwald ripening of the nanoparticles during and after processing. Surface modifiers are chosen from the list of pharmaceutically acceptable substances and typically possess surface active properties capable of wetting the large drug particles and providing steric and/or ionic stabilization to the resulting nanometer-size drug particles. Some of the most commonly used stabilizers include povidones, phospholipids, polysorbates, poloxamers, cellulosics, and anionic surfactants, eg, SLS and DOSS.

The high-pressure homogenization/microfluidization approach has been championed in recent years by NanoPure, Baxter Healthcare's NanoEdge Technology, SkyePharma's IDD solubilization technology, and Microfluidics.[11-14] For high-energy wet milling, Elan Drug Technologies' NanoCrystal® technology is a recognized leader with its nanotechnology approach for poorly water-soluble compounds (Figure 2).[15]

Several commercially viable nanotechnology-based products have been launched throughout the past 10 years. Table 1 provides a list of nano-sized products that have been commercialized in the US.

To date, five licensed products incorporate Elan Drug Technologies' NanoCrystal® technology, with annual in-market sales of over $1.9 billion. EDT's commercialized products using NanoCrystal® technology include:

- Rapamune®: An immunosuppressant, Wyeth's (now Pfizer) Rapamune® received marketing approval from the FDA in 2000. Rapamune® was previously available only as an oral solution in bottles or sachets. The oral solution requires refrigeration storage and must be mixed with water or orange juice before administration. The development of a NanoCrystal® formulation of sirolimus enabled the

TABLE 2

Year	Reformulations	NCEs	Total
2002	55	17	72
2003	49	21	70
2004	69	31	100
2005	64	18	82
2006	77	18	95
2007	50	16	66
Total	**364**	**121**	**485**

FDA Approvals 2002-2007 (Source: www.fda.gov)

preparation of a solid dose form.

- Emend®: The product was approved by the FDA in March 2003 and was launched by Merck in April 2003. Emend® is a capsule containing 80 mg or 125 mg of aprepitant formulated as NanoCrystal® drug particles. Emend® was developed as an NCE in a NanoCrystal® formulation.

- TriCor® 145: The product was launched in December 2004 by Abbott in the US following FDA approval. The new formulation of TriCor® incorporating NanoCrystal® technology provides the benefits of a lower dose, simplified, flexible dosing regime and allows for administration with or without food. The old formulation had to be taken with food.

- Megace® ES: Approved in July 2005 by the FDA, Megace® ES uses the NanoCrystal® technology to improve the rate of dissolution, increase the rate of absorption, and improve the bioavailability of the original Megace® Oral Suspension.

- INVEGA® SUSTENNA®: The product was approved by the FDA in July 2009 and is marketed by Janssen in the US. This once-monthly extended-release injection was the first injectable product launched using the NanoCrystal® technology. Major benefits include monthly dosing using a small bore small-volume needle, and negating the need for a power injector, which can all help to improve compliance for schizophrenic patients.

For marketed products, nano-sizing is also a means to present an old drug in a new drug delivery platform that offers new benefits and improved performance. Reviewing the number of FDA approvals throughout the past years, NCEs have accounted for only 25% of all products approved, with the majority of approvals being re-formulations or combinations of previously approved products (Table 2).

FUTURE CHALLENGES & OPPORTUNITIES - NANOTECHNOLOGY

The nanotechnology drug delivery market is expected to grow at a CAGR of 21.7% for the period 2009 to 2014, reaching almost $16 billion by 2014, according to a recent Business Insights report.[16] Formulating poorly water-soluble molecules using the various aforementioned nano-sizing approaches has the potential to add tremendous value throughout the drug development cycle. These formulations can now be administered not just orally but by multiple routes. Further development of parenteral nano-based products is being addressed. Parenteral nanotechnology products with high drug payloads have significant potential. A recent example is Janssen's one-month IM depot product, INVEGA® SUSTENNA® indicated for the treatment of schizophrenia. And because the formulations are well-tolerated and provide maximal exposure for a poorly water-soluble compound, they may prove to be an invaluable tool for toxicokinetic studies. As development programs move into preclinical and clinical testing, the formulation used in discovery can be refined and/or post-processed to meet the requirements of the emerging target product profile.

A COMBINATION APPROACH

Combining nanotechnology with controlled-release technologies may provide significant benefits for certain drug candidates. If a drug presents itself as poorly water soluble, the application of nanotechnology could reduce particle size, improve dissolution rate, and enhance oral bioavailability. Applying then a controlled-release technology might offer the additional benefits of modified- or controlled-release properties and allow the drug to be presented as a tablet/capsule. By incorporating both technologies, the final dosage form could display the characteristics of a number of different conventional dosage forms: immediate-release, delayed-release, or modified-release. It is clear that the drug delivery sector remains a vibrant source of technology-based product solutions with significant potential in the coming years.

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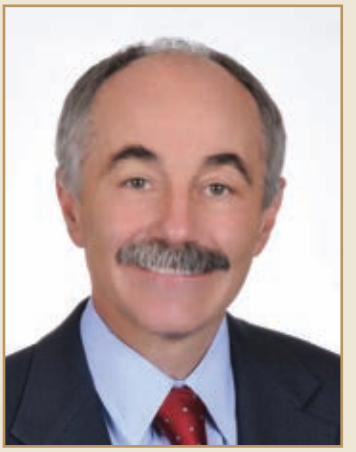

Dr. Gary Liversidge was appointed Chief Technology Officer in October 2008. For more than 20 years, Dr. Liversidge has been at the forefront of developing the NanoCrystal® technology and related technologies at EDT. Since Elan's acquisition of the technology in 1998, Dr. Liversidge has served in a number of critical scientific and managerial positions related to the strategic advancement of EDT's technologies, products, and relationships.

Advances in Interferon Delivery Methods: A Historical Perspective

By: Jaleel M. Shujath, MBA

ABSTRACT

In 1937, G.M. Findlay and F.O. MacCallum described the phenomenon of viral interference, whereby the infection of an animal by a virus protected it against infection by another virus. Later, Alick Isaacs and Jean Lindenmann (in 1957) found an agent of viral interference [naming it Interferon (IFN)], a protein released by cells exposed to a virus, that enabled other cells to resist viral infection. Independently, Y. Nagano and Y. Kojima (1958) reported similar findings. Since that time, additional IFN family members have been identified, and the clinical use of IFN proteins has been the object of intense research. Despite this, the path from their initial identification to subsequent incorporation in treatment regimens for numerous diseases has not been without setbacks. In recent years, attempts have focused on refining and honing the delivery of IFN proteins to prolong their half-lives in vivo and limit unwanted side effects while simultaneously maximizing their therapeutic benefits. In order to achieve these goals, further development of delivery methods to extend systemic circulation time, or ideally, to target IFN delivery only to local sites of tumor outgrowth or viral infection, will be required. This review will provide an overview of some of the advances in IFN delivery methods to date.

INTRODUCTION

Interferons (IFNs) are water-soluble cytokine molecules that are classified as either Type I, Type II, or Type III. Human Type I IFNs include IFN-α, IFN-β, IFN-ε, IFN-κ, IFN-ω, and IFN-ν. All these proteins bind to and signal through the heterodimeric surface receptor IFN-αR1/IFN-αR2. The sole member of the Type II family is IFN-γ, which signals through IFN-γR1/IFN-γR2. Type III interferons have only recently been discovered and include IFN-λ1 (IL-29), IFN-λ2 (IL-28A), and IFN-λ3 (IL-28B). The Type III interferons signal through a heterodimeric surface receptor IL-28R/IL-10R. Type I IFNs play a major role in innate immunity, where they inhibit the amplification and spread of viruses during infection, whereas the major role of IFN-γ is the activation and development of adaptive immune responses. This review will focus primarily upon the delivery and use of Type I IFNs.

As shown in Figure 1, although IFN was originally discovered in 1957, it was almost two decades before purification of IFNs to homogeneity was achieved. Even prior to purification of these proteins, speculation about their potential use as therapeutics had begun. Immediately following identification of the coding sequence for human IFN-α2a, it was expressed in *E. coli*, purified using monoclonal antibodies, and immediately applied to both basic research projects and clinical trials. Within days of purification, paperwork was filed with the FDA, and with an unprecedented turn around time, IFN was approved for use in a clinical trial 90 days later.[1]

Initially approved for treatment of hairy cell leukemia, the application of IFN has expanded to include hepatitis B and C viruses, malignant melanoma, follicular lymphoma, and Kaposi sarcoma[1]. IFN-β is the major treatment available for symptoms of multiple sclerosis, and IFN-γ is approved for chronic granulomatous disease. Due to the fact that IFNs are not absorbed through the gastrointestinal tract, they are typically administered by intramuscular or subcutaneous injections.[2]

PKS OF UNMODIFIED TYPE I IFNS

Due to the low molecular weights of IFNs, they are susceptible to rapid renal clearance and protease degradation. The route of administration can alter the effective half-lives of IFN proteins, as renal catabolism of IFN has been shown to occur more rapidly following intravenous infusion or injection than subcutaneous or intramuscular injection.[3]

The short half-lives of IFN proteins post-administration has been a major

obstacle for their therapeutic use. Peak serum concentrations of conventional IFN-α are reached within 4 to 12 hours after injection and are undetectable in serum by 24 hours.[2] This fact has necessitated repeated, long-term dosing to achieve desired clinical responses. However, numerous debilitating side effects are associated with IFN use, and these also peak at approximately 8 hours post injection, coincident with increased plasma levels of the drug.[1] The short half-lives of unmodified IFNs gives rise to undesirable fluctuations in IFN serum levels, characterized by "peak and valley" patterns that follow each injection. This leads to repeated spikes in IFN levels that are associated with the repetitive onset of adverse side effects. At the same time, rapid clearance leads to days in which no detectable IFN is present in the serum, thereby allowing viral replication or tumor growth to proceed unchecked. These deficiencies limited the clinical utility of unmodified IFN administration, and triggered intense research efforts to develop both enhanced IFN proteins with better pharmacokinetic (PK) profiles and improved IFN delivery techniques.

MODIFICATIONS TO IFN PROTEINS

Improved PKs With Pegylated IFNs

In attempts to improve the PK profile of IFN proteins, development of an enhanced IFN molecule with a covalently attached polyethylene glycol (PEG) moiety was undertaken. PEGylation lends greater molecular weight and bulk to IFN proteins, thereby shielding them from degradation. However, steric hindrance caused by the addition of PEG moieties can interfere with bioactivity of the core molecule, a factor that must be taken into consideration during drug development.

There are currently two PEGylated interferons on the market. Peginterferon-α2a (brand name Pegasys) is composed of 40 kD branched repeating ethylene oxide monomers attached to IFN-α2a.[4] Peginteferon-α2b (brand name PEG-Intron) is a linear 12 kD moiety attached to the IFN-α2b molecule.[5] The PKs for each form differ, with peginterferon-α2a exhibiting peak plasma concentrations of 72 to 96 hours, a restricted V_D, systemic clearance 100 times lower than conventional, and a mean elimination half-life of 80 hours. The PK profile of peginterferon-α2b consists of similar absorption and distribution rates to that of conventional interferon, systemic clearance 10 times lower than the conventional form, and a mean elimination half-life of 40 hours.[2,5] The improved PKs of PEGylated IFNs translate into several clinical advantages for patients, including less-frequent injection schedules and significantly increased, sustained virologic response rates. Currently, PEGylated IFNs are in clinical trials for the treatment of hepatitis B and C infections (Table I).

Chimeric IFN Molecules

Although PEGylation has resulted in improved clinical efficacy of IFN therapeutics, many different approaches have been and are being attempted to modify IFN proteins via conjugation to other molecules. Albumin is the most abundant serum protein, and it exhibits a relatively stable profile in circulation, with a half-life of nearly 20 days. A conjugate of Albumin-IFN-α2b was introduced in 2002 and was found to have a 10- to 20-fold increase in serum half-life, as compared to unmodified IFN.[2] Early reports indicated that the Albumin-IFN-α2b conjugate was well-tolerated in hepatitis C virus (HCV) patients and led to reductions in viral RNA loads when administered on a bi-weekly schedule.[6] Thus, this appears to be a promising therapeutic strategy for IFN

FIGURE 1

Timeline of IFN therapeutic developments

1957:	Isaacs and Lindeman discover IFN
1978:	Leukocyte IFN purified for further study
1980:	Biologically active recombinant E. coli IFN produced
1980-82:	Mutliple IFNα family members identified
1986:	Hepatitis C virus (HCV) therapy with IFN – ribavarin combination
1996:	Avonex (IFN-β1) approved for treatment of MS
1997:	Introduction of the wholly synthetic IFN alfacon1 (SQ injections)
2000:	Implantation of IFN in synthetic matrices for sustained release
2002:	IFN-albumin fusion protein introduced; successful entrapment of IFNα-2a in synthetic microspheres
2002-06:	PEGylated IFNs developed for use
2005:	IFN liposomes show sustained release profiles
2007:	IFN-α2b arabinogalactan-protein (AGP) chimeric proteins introduced
2010:	anti-CD20/ IFN conjugate reported for use against B cell lymphoma

administration.

IFNs are also being explored as therapeutics for a variety of cancers. Rituximab is an anti-CD20 monoclonal antibody used for treatment of B cell lymphomas, such as non-Hodgkin's lymphoma and chronic lymphocytic leukemia. This antibody exclusively targets B cells due to their surface expression of the CD20 protein. Recently, conjugation of IFN-α to anti-CD20/Rituximab has been explored as a means to specifically target pathologic B cells for destruction, while also increasing the anti-tumorigenic properties of IFN-α by delivering the molecule directly to tumor cells. Fusion proteins consisting of 1-4 IFN-α molecules bound to humanized anti-CD20 were found to inhibit lymphoma cell proliferation in vitro and reduce lymphoma tumor burdens in vivo in preclinical murine models.[7,8] Although the biologic activity of IFN-α was reduced slightly in vitro, the conjugate was shown to have in vivo efficacy against Rituximab-insensitive tumors, suggesting that sufficient IFN-α activity was retained to provide biologic activity in vivo.

Additional IFN Conjugation Strategies

Many other modifications have been undertaken in an attempt to enhance the PK profile and clinical utility of IFN therapeutics. These include altering single amino acids within IFN-α to make it less susceptible to protein degradation, and producing arabinogalactan-protein (AGP)/IFN chimeras that have an increased half-lives in circulation.[9] Other modifications have sought to target IFN delivery to the liver for treatment of HCV infection. To accomplish this, researchers conjugated IFN-α to pullulan, a linear non-ionic polysaccharide that accumulates in the liver at high concentrations. Chemical conjugation of IFN and pullulan is an efficient reaction, resulting in 70% to 90% of IFN binding to this polysaccharide. Steric hindrance is a problem with IFN-α/pullulan conjugates, however, in that 60% to 90% of biologic activity can be lost compared to the unmodified IFN protein.[10,11] Despite this, promising results have been obtained in HCV models, perhaps due to a 121-fold increase in IFN accumulation in the liver at 24 hours post-administration in mice.[11] Therefore, conjugation can both increase the PK profile of IFN therapeutics and target IFN delivery to the necessary site of action, which could translate into lower dosing requirements and diminished toxicities.

TABLE 1

Current clinical trials (2010) using IFN therapeutics

Therapeutic:	Disease:
Peginterferon	Chronic Hepatitis B, Hepatitis C infections
Albumin-IFNα-2b	Chronic Hepatitis C, HIV, Multiple Sclerosis
Anti-CD20-IFNα	B cell lymphoma
Adenovirus- IFNγ	B cell lymphoma, melanoma
Interferon Lozenges	Chronic Hepatitis B, Influenza A, Chronic cough in Chronic Obstructive Pulmonary Disease

Source: www.clinicaltrials.gov

ENHANCED DELIVERY OF IFNS

IFN as an Anti-Cancer Agent: Gene Therapy & Targeted Injections

Adoptive immunotherapy is a promising cancer treatment in which antigen-specific cytotoxic T lymphocytes (CTLs) are adoptively transferred into patients for the treatment of cancer and viral infections. Numerous strategies have been investigated as a means to provide CTL stimulation in vivo, and several of these include the forced expression of IFN proteins. For example, adenovirus-encoded IFN has been used to express IFN-γ in both dendritic cells, for paracrine delivery of IFN to CTL, or in the T cells themselves for autocrine delivery.[12,13] The same adenoviral IFN-γ is currently being injected intra-tumorally in combination with activated CTL to treat patients with late-stage metastatic melanoma (www.clinicaltrials.gov). Similarly, adenoviral-IFN-β is being tested for its ability to aid in the immuno-therapeutic response to glioblastoma multiforme.[14]

Collectively, these results illustrate the potential for adenovirus-encoded IFN proteins to impair tumor growth, suggesting that this is a therapeutic strategy that warrants further investigation. As with all other IFN therapies, however, the onset of adverse side effects may limit the use of IFN gene therapy approaches in cancer patients. One approach to overcoming this problem is targeted delivery of IFNs directly to the tumor site. This is being pursued in numerous ways, including intra-tumoral injection of unfolded IFN proteins (SURe-PD Cancer Therapy, PBL Therapeutics). Post-injection, unfolded IFNs fold into their correct conformation at variable

rates, providing sustained release of active proteins, thereby diminishing unwanted side effects of therapy and prolonging tumoricidal benefits. Another approach that may prove valuable for disseminated tumors is that of IFN coupled to PEGylated colloidal gold nanoparticles, which accumulate locally in the neovasculature of tumor beds, again providing targeted delivery of IFN to growing tumors (CytImmune Technologies).

Liposome & Microsphere Delivery of IFNs

Liposomes are promising therapeutic delivery vehicles due to their inherent low toxicity and ability to significantly improve the PK profiles of unstable drugs and biologics. Liposomal IFN-α preparations have been under investigation for decades, as they provide sustained release of entrapped IFN in vivo, thereby circumventing much of the severe serum fluctuations that accompany injection of unmodified IFNs.[2] A drawback to liposomal delivery of IFN is the relatively poor entrapment efficiency, as some reports have shown incorporation of only 2% to 25% of the starting IFN protein, depending on the preparation method.[2] More recently, trapping efficiencies of up to 80% were reported due to the use of polyvinylpyrrolidone K30.[15]

Synthetic microspheres have also gained attention as drug delivery vehicles in recent years. Microspheres made from polylactide-co-gylcolic acid (PLGA) or poly-DL-lactide-poly(ethylenegylcol) (PELA) are biologically inert and able to provide sustained release of biologics, such as IFN-α.[2] As with liposomal preparations, a low efficiency of IFN entrapment can hinder the use of this approach. To overcome this problem, alternate microsphere formulations have been attempted, such as using a core of calcium arginate to load the IFN protein, followed by encapsulation into an outer PELA shell. This technique yielded promising results, as it showed a sustained release of IFN-α over a period of 13 days.[16] PEGylated IFN-α2α has also been used in PLGA microsphere preparations; addition of the PEG moiety greatly increased the IFNα2α release rate as compared to that seen for the unmodified IFN-α2α.[17] Continued exploration of alternate delivery methods could circumvent a major obstacle in the field of IFN therapeutics, as research to date shows a promising ability to prolong the release of IFN proteins, which should translate into enhanced clinical efficacy and decreased incidence of side effects.

Alternative Delivery Routes & Methods

The route of administration and the method of delivery can impact clinical efficacy of IFN therapeutics. One example of this is the use of a pump system (Medtronic Paradigm Pump) previously approved for insulin use, that is undergoing clinical trials for continuous subcutaneous delivery of IFN-α2b in concert with oral ribavirin for treatment of HCV (www.clinicaltrials.gov) (Table I). Use of the pump provides a constant, sustained dose of IFN without the fluctuations in serum levels. Although technically demanding to use, as it requires surgical implantation, pump-mediated delivery of IFN eliminates the need for repeated patient injections in the clinic. Another delivery advance is the single-use autoinjector, a prefilled syringe for delivery of IFN-β1a that is in Phase III trials for the treatment of multiple sclerosis. Use of autoinjectors instead of standard needles eliminates overfilling, increases patient compliance, and reduces the risk of dosage error.[18] Thus, the application of mechanical delivery systems already in use for other drugs and biologics can provide a rapid improvement in the use of IFNs for a variety of diseases.

Transdermal & Oral Delivery Methods

Delivery of IFN through transdermal patches is an appealing delivery route that is being explored as a means to provide constant IFN levels over a period of weeks. In one study, the use of skin microporation was coupled with iontophoresis, an active transport method that applies an electric field to drive movement of ionized molecules across the skin, showed successful delivery of relatively high amounts of IFNα-2b in rats.[19]

Iontophoresis has the unique benefit of allowing for some degree of control over delivery rates, as these would vary according to the amount of charge applied. Electroporation of skin utilizes ultra-rapid electric pulses that create aqueous pores, thereby permitting transfer of hydrophilic compounds.[20,21] Use of microneedles, or micropiles, to painlessly increase skin permeability for application of extended releases of IFN has also shown encouraging results in animal studies.[22] Lastly, oral-mucosal delivery of IFN is being explored as a means to combat influenza infections and oral ulcers (www.clinicaltrials.gov). This is being accomplished through the use of IFN lozenges (Amarillo Biosciences) that provide a low-dose of IFN in an inexpensive and easy-to-use formulation.

SUMMARY

The clinical application of IFNs to a variety of diseases has been the subject of intense research for the past 50 years. However, in order to harness the enormous potential of IFNs as valid therapeutics, limitations involving their short half-lives and their propensity to induce numerous toxicities must be overcome. In this review, we summarized several of the approaches that have been and are being investigated to overcome these challenges. Much of the work in this area has focused on improving the

delivery of IFN proteins, to achieve a sustained-release pattern that will both eliminate the current need for repeated patient injections and will reduce the incidence of unwanted side effects. The breadth and variety of experimental approaches are impressive, and as many have shown in promising preclinical and early clinical trial results, it is likely that continued work in this field will yield continued positive results in patients.

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BIOGRAPHY

Mr. Shujath is currently the Chief Marketing Officer of PBL InterferonSource. Before joining PBL, Mr. Shujath was Global Marketing Manager at GE Healthcare, Field Application Scientist at Cellomics, Scientist at Bayer Healthcare, Research Associate at Yale University, and Research Technician at Tufts University School of Medicine. He earned his BS in Biology from Tufts University and his MBA in Marketing from the College of Business at the University of New Haven.

DRUG DELIVERY Executive

Herman Mitchell, Global Marketing Director, Pharmaceutical Chemicals

Avantor Performance Materials

"This is an exciting time as we now have the opportunity to realize our full potential by enhancing our product lines and global supply chain to better serve our customers around the world. We are looking into different investments and acquisitions that will help us meet our growth strategy, which ultimately will benefit all of our customers."

AVANTOR™ PERFORMANCE MATERIALS: NEW HEIGHTS, NEW CHALLENGES & NEW BREAKTHROUGHS

Avantor™, formerly Mallinckrodt Baker, manufactures and markets high-performance chemistries and materials around the world under two well-known and respected brand names, J.T.Baker® and Macron™ Chemicals (formerly Mallinckrodt® Chemicals). These products are widely used in biotechnology and pharmaceutical production; microelectronics and photovoltaic manufacturing; and in research, academic, and quality control laboratories. An affiliate of New Mountain Capital acquired Mallinckrodt Baker in August 2010, and the company was renamed Avantor Performance Materials this past October. Then, in November, the company announced that in March of 2011, it will change the Mallinckrodt® Chemicals brand name to Macron™ Chemicals. Drug Development & Delivery recently interviewed Herman Mitchell, Global Marketing Director, Pharmaceutical Chemicals, to discuss these new developments and how they will impact pharmaceutical customers.

Q: Who is New Mountain Capital and what is their affiliation with Avantor Performance Materials?

A: New Mountain Capital is a New York-based private equity firm investing for long-term capital appreciation through direct investment in growth equity transactions, leveraged acquisitions, and management buy-outs. For more than a year, New Mountain worked closely with Raj Gupta, former Chairman and CEO of Rohm and Haas, and other industry executives to find a new platform to build into a leader in high-growth, high value-added niches of the specialty chemicals and materials industry. New Mountain chose Mallinckrodt Baker, now called Avantor Performance Materials, because of its position as a stable business with a large runway for growth in the technology-driven markets that it serves (pharmaceuticals, biotech, and microelectronics).

Q: Why did you pick the name Avantor and what does it signify or mean?

A: We chose Avantor because the name conveys several very important ideals. Avant (as in avant-garde)–meaning the first, the leaders, the innovators–evokes the bold ideas, energy, innovation, and passion that we have as a company. Avant is merged with tor (a synonym for mountain)–signifying our aspiration to

achieve new heights of performance and quality, as well as our affiliation with New Mountain Capital. It's a new day, and our new name sets the tone for helping our customers soar to new heights, take on new challenges, and achieve new breakthroughs.

Q: How does the sale affect your pharmaceutical operations or product manufacturing? Are there any plans to eliminate or phase out any pharmaceutical products?

A: We will continue to produce our products with the high level of quality, purity, and consistency our customers have come to expect from us. We are not planning to eliminate any pharmaceutical products, although those products previously marketed under the Mallinckrodt® brand name will be known under a different name, Macron™ Chemicals, beginning in March 2011.

Q: What happens to the Mallinckrodt® and J.T.Baker® brands going forward?

A: The Mallinckrodt® name was retained by Covidien; so as previously stated, Avantor products sold under the Mallinckrodt® product line brand name will transition to a new brand name called Macron™ Chemicals, effective March 2011. Macron™ brand products are produced under the same manufacturing processes and share the same manufacturing sites and product numbers as the previous Mallinckrodt® brand products. There will be no changes to product numbers, names, or codes. This change is simply a brand name change. The branding of the J.T.Baker® product line will not change as Avantor intends to continue using the J.T.Baker® product line brand name on products currently labeled as J.T.Baker®.

Q: Tell us about the new product brand name?

A: Pronounced MACK-ron, the name incorporates the Greek word for large, implying strength and broad range. The name Macron™ Chemicals embodies the product quality and consistency recognized across the industry and around the world. Macron™ Chemicals brand products have a legacy of safety and trust, a 140-year tradition of the highest standards of quality, purity, and consistency in laboratories and in the demanding pharmaceutical market. Today, the brand's focus is on providing products for everyday laboratory use in environmental testing and university research as well as in food, pharmaceutical, and industrial manufacturing.

Q: How does this transition to a stand-alone organization position Avantor Performance Materials in the market going forward?

A: This is an exciting time as we now have the opportunity to realize our full potential by enhancing our product lines and global supply chain to better serve our customers around the world. We are looking into different investments and acquisitions that will help us meet our growth strategy, which ultimately will benefit all of our customers. Most recently, we announced our intent to acquire RFCL Limited (RFCL) from ICICI Venture. Headquartered in New Delhi, RFCL is a leading manufacturer of laboratory reagents and products for the medical diagnostics market in India. We identified RFCL as an attractive target to build on our current presence in the laboratory and pharmaceutical markets in India. The acquisition gives us the infrastructure to market our J.T.Baker® and Macron™ (formerly Mallinckrodt®) brands of pharmaceutical materials in India, including our J.T.Baker® brand

PanExcea™ high-performance excipients.

Looking ahead, we will continue to enhance our offerings to serve demanding high-tech markets and provide our customers with advanced chemistries and materials that enable performance, increase speed to market, and enhance customer processes. New Mountain will partner with Avantor to enable the management team to execute its international growth strategy through organic initiatives and add-on acquisitions. Our goal is to become a leading global supplier of performance materials. With the support of New Mountain, we have the energy, agility, technical expertise, resources, and focus to rise to new challenges and grow to the forefront of materials technology.

Q: What is New Mountain's strategy for Avantor Performance Materials in the pharmaceutical market?

A: New Mountain's strategy is to leverage the Mallinckrodt Baker reputation and strong market presence to build Avantor Performance Materials into an international market leader in the pharmaceutical industry. We look forward to offering our pharmaceutical customers more advanced chemistries and materials that enable performance, increase speed to market, and enhance customer drug development and manufacturing processes.

Our J.T.Baker® PanExcea performance excipients represent a good example–they combine two or more ingredients that interact at the subparticle level to improve their functionality synergistically. This design feature enhances the desirable aspects and masks the undesirable properties of the individual excipients. The PanExcea™ platform includes both PanExcea™ MC200G for Orally Disintegrating Tablets (ODT) and PanExcea™ MHC300G for Immediate Release (IR) dosage forms.

Avantor is also very active in the purification of traditional and biologic pharmaceuticals. We provide enabling products and services in process chromatography media, purification buffers and solvents, and cGMP-manufacturing of custom aqueous solutions.

Q: How will this acquisition benefit customers in the pharmaceutical market?

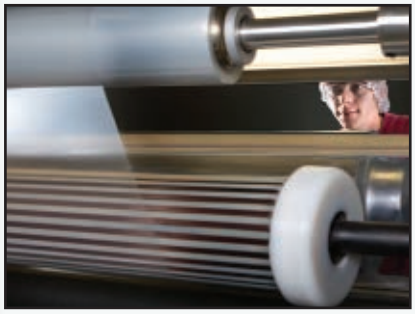
A: We will continue to provide the highest standards in product purity, consistency, and technology innovation, and to bring those values to the pharmaceutical market on a global basis. While we have always been proud of our technological achievement, we have been equally proud of the level of trust we have enjoyed and our reputation for integrity. We look forward to offering our pharmaceutical customers more advanced chemistries and materials that enable performance, increase speed to market, and enhance customer processes.

Q: So what's next for Avantor Performance Materials?

A: Avantor now has the opportunity to realize its full potential by enhancing its product lines and its global supply chains to serve customers around the world. We are really looking forward to what the future holds. To achieve our growth strategy, we will be expanding in our current markets and also have the opportunity to explore expansion into new geographies. ◆

Technology & Services Showcase

Innovative Platforms



Adhesives Research, Inc. has over 20 years of experience developing and manufacturing custom pressure-sensitive adhesive tapes, specialty coatings, films, and laminates for the for the world's leading pharmaceutical companies. We offer the pharmaceutical industry a wide range of coating technologies and adhesive capabilities for transdermal, oral, and topical drug delivery. Based upon proven PIB, acrylic, silicone, and dissolvable film technology platforms, Adhesives Research's skin-friendly adhesives are available with conductive, porous, occlusive, hydrophilic, hydrophobic, gentle, or long-term adhesion functional properties to meet the unique needs of our clients' applications. For more information, contact Adhesives Research at (800) 445-6240 or visit **www.adhesivesresearch.com**.

Performance Excipients

AVANTOR™ PERFORMANCE MATERIALS
Formerly Mallinckrodt Baker

J.TBaker® PanExcea™ performance excipients from Avantor® Performance Materials (formerly Mallinckrodt Baker) are manufactured using novel particle engineering technology and provide multifunctional performance that enables efficient drug development and manufacturing. All products in the PanExcea performance excipients product line comprise highly characterized, widely used GRAS pharmaceutical materials. Full technical and regulatory support is provided for customer applications. These ready-to-use performance excipients are manufactured to provide consistency from lot-to-lot as well as homogeneity throughout the lot, ensuring tablet content uniformity and robust tableting processes. PanExcea performance excipients improve supply chain, manufacturing, and regulatory efficiencies; speed time to market; and reduce ownership costs. For more information contact Avantor® Performance Materials at (855) AVANTOR or visit **www.mallbaker.com/panexcea** to request a free sample.

Licensing & Capabilities

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

Pharmaceutical Solutions

Catalent®

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**.

Technology & Services Showcase

Specialty Pharma

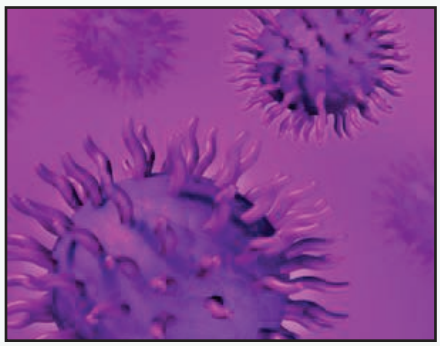
CyDex Pharmaceuticals, Inc. is a specialty pharmaceutical company focused on the development and commercialization of drugs specifically designed to address limitations of current therapies in selected established markets. We have developed a portfolio of product candidates utilizing our drug formulation technology (Captisol® cyclodextrins),which are a patent protected, specifically modified family of cyclodextrins designed to improve solubility, stability, bioavailability, safety, and/or dosing of a number of APIs. To maximize our internal resources, experience, and technology, we are focusing on the development and commercialization of product candidates for use in the acute care hospital setting. For those product candidates that likely will entail more extensive development and commercialization efforts, we partner with established pharma companies. We also outlicense our Captisol technology to third parties. For more information, contact CyDex at (913) 685-8850 or visit **www.cydexpharma.com**.

Development & Manufacturing

DPT

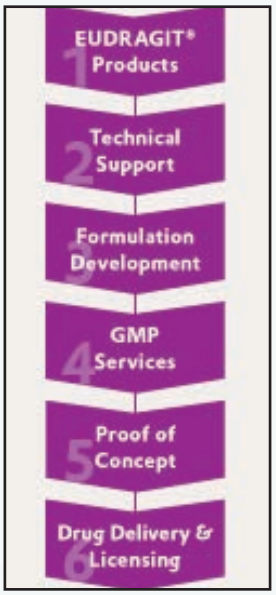
DPT is a contract development and manufacturing organization (CDMO) specializing in semi-solid and liquid dosage forms. DPT provides fully integrated development, manufacturing, and packaging solutions for biopharmaceutical and pharmaceutical products. DPT is the industry source for semi-solid and liquids — from concept to commercialization and beyond. Drug development services range from preformulation, formulation and biopharmaceutical development, analytical development, and validation through process development. Production capabilities include four cGMP facilities, clinical trial materials, full-scale commercial production, controlled substance registration Class II-V, and complete supply chain management. Packaging services encompass engineering and procurement resources necessary for conventional and specialized packaging. For more information, contact DPT at (866) CALL-DPT or visit **www.dptlabs.com.**

Bioavailability Enhancement



Elan Drug technologies' NanoCrystal® technology is a drug enablement and optimization platform applicable to poorly water-soluble compounds. Improved bioavailability provided by NanoCrystal® technology can result in the following benefits: increased rate of absorption, reduction in fed fasted variability, improved dose proportionality, rapid formulation development, and reduction in required dose with smaller and more convenient dosage forms. Five products incorporating this technology are now launched in over 100 markets worldwide with over $1.9 billion in market sales achieved in 2009. With over 1,300 patents/patent applications, NanoCrystal® technology has been optimized and simplified from 20 years in development. Applicable to all dosage forms, products incorporating this technology have been manufactured at commercial scale since 2001. For more information on our platform of technology solutions, contact Elan Drug Technologies at edtbusdev@elan.com or visit **www.elandrugtechnologies.com**.

Pharma Polymers



Evonik Industries is a global market leader in specialty chemicals, offering a broad portfolio of products and services to meet the drug delivery challenges of the pharmaceutical market. Evonik Pharma Polymers manufactures EUDRAGIT® acrylic polymers used for enteric, sustained-release, and protective formulations. The unique functionality of EUDRAGIT polymers can also meet high sophisticated drug delivery requirements (eg, pulsed drug release). We have adapted our services to meet the requirements of the pharmaceutical industry's value chain. As a result, we are able to support our customers in the development process to bring products safely and quickly to the market. From excipients supply to the development of custom tailored drug delivery solutions, our customers benefit from our knowledge and expertise. For more information, contact Evonik Degussa Corp., Pharma Polymers at (732) 981-5383 or visit **www.eudragit.com**.

Technology & Services Showcase

Analytical Testing Services

Gateway Analytical provides analytical testing and consulting services to the pharmaceutical, forensic, and material science industries. By pairing innovative technologies with conventional methods, Gateway Analytical utilizes a forensic strategy to scientific problem-solving. With more than 15 years of experience, you can rely on our expertise in regulatory affairs, product and process development, non-conformance and failure investigations, foreign particulate identification, and more to help solve your toughest challenges. Trust Gateway Analytical to be an extension of your own lab, providing personal attention, high-quality results, scientific talent, and technical expertise to help you get the job done. For more inforation, contact Gateway Analytical at (724) 443-1900 or visit **www.gatewayanalytical.com**.

Excipients & Technology

The MEGGLE Group's Excipients & Technology Business Group supplies the pharmaceutical industry with carrier substances, such as pharmaceutical lactose. With outstanding product quality and intelligent innovations, we have gained a leading global position in the field of lactose and compounds. MEGGLE pharmaceutical lactose, for example, serves as a carrier substance in medicines. It behaves completely neutrally in the human organism and causes no undesired effects due to interaction with other components of the medicine. We also have developed a diversified product portfolio in the more than 50 years that we have been active in the market that contains excipients for granulation and capsule-filling as well as special modern products for direct compaction and dry-powder inhalers. Our customers are predominantly manufacturers of pharmaceutical products and dietary supplements. For more information contact the MEGGLE Group at (914) 682-6891 or visit **www.meggle-pharma.com**.

Silicone Materials

When it comes to drug delivery, NuSil provides numerous solutions that fit a variety of device needs. While most silicone products are customized for individual delivery systems, all are developed with FDA regulatory concerns in mind. In addition to its role as a supplier, NuSil offers research and development capabilities for those looking for proprietary, custom formulations. Regardless of batch size, NuSil delivers quality, high-performance silicone materials based on your unique property requirements, as well as provides precise, custom formulations. NuSil offers an even wider range of silicone material and compound options for transdermal, transmucosal, implanted intrathecal, and external delivery devices, as well as ingestible materials. For more informati on, contact NuSil Technology at (805) 684-8780 or visit **www.nusil.com**.

Development & Delivery Solutions

Founded in 1991, Particle Sciences is an integrated provider of both standard and nanotechnology approaches to drug development and delivery. Through a combination of preformulation, formulation, analytic, bioanalytic, and manufacturing services, Particle Sciences provides clients with a powerful, integrated solution to most efficiently take a drug from discovery to the clinic. Each project has a dedicated team and leader to manage the project from start to finish. With years of experience to draw upon, Particle Sciences can confidently handle difficult APIs, complicated intellectual property terrains, and challenging delivery goals to arrive at the simplest, most efficient solution to the client's needs. For more information, contact Particle Sciences at (610) 861-4701 or visit **www.particlesciences.com**.

Technology & Services Showcase

Manufacturing & Development

Patheon is a leading global provider of contract dosage form development and manufacturing services to the pharmaceutical and biotechnology industries. Employing more than 4,700 highly skilled staff, Patheon's network of modern manufacturing facilities located in North America and Europe offer more than 3 million sq ft of best-in-class capacity. With three facilities in the US, three in Canada, and four in Europe (including two in Italy, one in France, and one in the UK), Patheon is able to meet the international requirements of its customers. Patheon's development and manufacturing capabilities cover prescription (Rx) products in solid, semi-solid, and liquid dosage forms, as well as specialized capabilities in high-potency, cephalosporin, controlled/sustained release, and sterile manufacturing, including aseptic filling and lyophilization. For more information, contact Patheon at (888) PATHEON or visit **www.patheon.com**.

Knowledge Management

PharmaCircle™

PharmaCircle is an innovative knowledge management company specializing in the drug delivery, pharmaceutical, and biotechnology fields, with a current client base ranging from start-up life science companies to world leaders in Big Pharma. Clients choose PharmaCircle's services and content for its comprehensive technical (pipeline, products, molecule, and technology) and business (deals, acquisitions, royalty, licensing, drug revenues, market information, etc) related information and analysis, which are ideal for all segments of small and large companies. PharmaCircle helps facilitate product life cycle management (LCM), partnering, licensing, and competitive intelligence efforts as well as supplements internal efforts and costs at a fraction of the cost if performed internally. For more information, contact PharmaCircle at (847) 729-2960 or visit **www.pharmacircle.com**.

Intranasal Vaccine Device

The new VaxINator™ Intranasal Vaccine Delivery Device offers a rapidly effective method to deliver vaccines or other medications to a patient without the need for a painful injection. The device features a precise 30- to 100-micron spray, has low dead space, attaches to any luer lock syringe, is ideal for lyophilized and liquid drugs, and is latex free. For more information, contact Wolfe Tory Medical at (801) 281-3000 ext. 101 or e-mail mdenton@wolfetory.com, or visit **www.wolfetory.com**.

Development Services

Xcelience® Formulation Development

Xcelience is a premier provider of formulation development and manufacturing solutions with a solid reputation for accelerating early phase small molecule development. Our outstanding quality record, significant drug development expertise, willingness to customize, and disciplined project management enable us to deliver real advantages to clients needing to speed potential drugs to clinical trials. Since 1997, Xcelience has been renowned for reliably expediting drug development. Our formulation development scientists have considerable experience overcoming challenges associated with physical and chemical properties of drug substance, or limited quantities of API, in a manner that results in compounds with improved solubility and bioavailability. Partnering with a specialist like Xcelience for early phase development can significantly reduce product risk and accelerate development timelines. For more information, contact Xcelience at (608) 643-4444 or visit **www.xcelience.com**.

DRUG DEVELOPMENT Executive

HOVIONE

HOVIONE: WHAT IS SPECIAL ABOUT INHALATION APIS?

Carla Vozone, MSc, MBA
Director, Business Development

Hovione

Hovione is internationally recognized as a leader in the manufacturing of high-quality and compliant Active Pharmaceutical Ingredients (APIs). Notwithstanding Hovione's diversification into API Contract Manufacturing and expansion of technology offerings beyond chemistry, such as particle engineering, inhalation formulation development, and dry powder inhalation devices, Hovione has stayed true to the business model of supplying difficult-to-make and specialized off-patent APIs. With a unique portfolio of APIs used in nasal suspensions, pressurized metered dose inhalers, and dry powder inhalers, Hovione has been investing in novel particle design technologies to produce the desired particle characteristics for inhalation drug delivery development. Drug Development & Delivery recently interviewed Carla Vozone, Director of Business Development for Hovione's Generics Business Unit, to discuss what makes Hovione unique in API supply for inhalation, its supportive technologies, and approach to the market.

"As an independent company, our combination of skills in API manufacturing, particle design, inhalation formulation, and DPI development is unique in the industry. Whether a customer is looking for a catalogue API or for a service, we are able to assemble very quickly a cohesive team able to significantly leverage the scientific and technical content of our customers' drug development programs."

Q: Which technology platforms differentiate Hovione for the supply of APIs used in inhalation?

A: Hovione's expertise in physical particle reduction is not new. In fact Dr. Ivan Villax, the Founder of Hovione, was an authority in corticosteroid chemistry, and since its founding 50 years ago, Hovione has been manufacturing and supplying corticosteroids to the pharmaceutical market. Given the poor solubility of these drugs and their use in topical and nasal drug products, they required particle size reduction, which has been achieved mostly by jet-mill micronization. Air-jet milling has been available for more than 100 years and presents significant issues, which can have a negative impact in today's demanding inhalation formulations and stricter regulatory requirements. It is a high-energy, size-reduction process that breaks down the active substance crystals impacting surface energy and crystal form, originating significant amorphous content that can influence stability of the finished product formulation. Additionally, with some products, it is inefficient and poorly reproducible because of the number of repeat runs to produce the desire particle size distribution, which provides the potential for metal contamination and an increase in the amorphous content, with each repeat run. While the majority of API suppliers and CMOs still use jet mill to reach the targeted specifications, Hovione has developed a proprietary technology by combining homogeneous fluidization with drying, which overcome all the challenges posed by air-jet mill in inhalation drug development. Manufacturing is complemented

by state-of-the-art analytical tools to characterize crystalline forms.

Q: What development challenges do these technologies overcome and what market need does it fulfill?

A: An aerodynamic particle size distribution of 1 to 5 microns and consistent crystal shape and size are required for successful inhalation therapy. For new product development, this is important to maximize the proportion of the drug in the finished product formulation that reaches the target airway site. In the area of generics product development, it is fundamental to demonstrate in vitro and subsequently in vivo equivalence to a reference product. Companies typically face poor consistency of the particle's aerodynamic characteristics as well as significant and variable amorphous content of the APIs they source. These issues have the potential to jeopardize clinical study results and delay development programs. Hovione's technology generates considerable lower energy than air-jet mill and can attain much higher pressures, allowing a d(90) between 1 to 3 microns to be achieved in a single run with a 2% relative standard deviation. The particle reduction process is carried out in a suspension of the API in a suitable anti-solvent, and isolation is carried out by drying. The product is dried by being sprayed through a hot gas, leading to very rapid evaporation that avoids morphology changes. Drug substances with varying hardness can be handled with this technology and with equivalent results. Given this process produces nearly 100% of a known crystalline form, the formulators don't need to be concerned with the amorphous content of the API and its subsequent conversion into an unknown polymorph.

Q: Can you provide an example of an API that has a particular benefit with this technology?

A: I can illustrate the benefits of this technology with fluticasone propionate. Hovione has almost 10 years' experience in the chemistry, crystallization, and air-jet mill particle reduction of this API. Fluticasone propionate is the API used in the blockbusters Advair® and Seretide®, earning GSK sales in excess of $6 billion. Fluticasone propionate is a very difficult product to micronize, requiring multiple runs to obtain the particle size necessary for nasal and pulmonary delivery purposes. Micronization yields a product with amorphous content that can be as high as 45%. This amorphous content creates high product instability in a period of 2 weeks after manufacturing and beyond, during which the amorphous material converts to a crystalline form, reducing the API water content and inconsistently increasing its particle size.

Pressure milling and drying are able in a single run to produce a fluticasone propionate of the targeted particle size at approximately 100% crystalline material. There is virtually no amorphous material in the product and therefore overcomes all the previously mentioned issues. Simultaneously, we are able to easily obtain levels of d(0.5) as low as 1.7 microns with a span of ~1.5 (the width of the distribution curve), in a more reproducible manner.

Q: In addition to its potential use in inhalation, what other dosage forms can benefit from such technology?

A: In reality, all drugs that require an API with a consistent particle size in the range of 5 microns or lower, a reproducible level of a certain polymorph or absence of amorphous material can benefit from this technology. Additionally, this method of downsizing, isolating and drying the API particle brings

complementary options to the drug development work. The spray-drying step can be potentially used to add stabilizers, produce solid dispersions, or to microencapsulate the APIs in excipients, such as polymers and lipids. Moreover, if a sterile product is required and the API has to be processed aseptically, Hovione has the capability of utilizing aseptic spray-drying to produce the required material in a continuous approach. These two enabling technologies used in combination are a powerful tool and avoid handling in separate particle reduction and sterilization (normally done by heat or gamma irradiation). Companies facing the aforementioned challenges in their product development have in Hovione the partner to find the most appropriate solutions using these emerging technologies and simultaneously create strong intellectual proprietary protection around their products.

Q: What is your approach to the market?

A: Even when Hovione is supplying a catalogue API product to a customer, what we strive for is to be a partner to that company. It is inculcated in our DNA to find solutions for our customers. Inhalation is a particularly difficult development area, which I believe leverages this characteristic that is so strongly marked at Hovione. This novel technology we developed allows for product customization depending on the inhalation device used, formulation complexity, single or combination active ingredients, and development purpose (new product or generic). It has been my experience that a one-size-fits-all or use of an apparently equivalent cheaper API often brings delays to the pharmaceutical development, start, and outcome of clinical studies and ultimately delays in filing. We have also been observing particular concern from leading Health Agencies regarding the issues of amorphous content in inhalation drugs. These Agencies often ask questions probing the understanding of the API crystalline form and its behavior during stability. We therefore ensure that the regulatory group is involved in the project teams for customization of APIs to make them best prepared to address in a timely fashion questions to the ANDAs/NDAs.

Q: Hovione has a significant business in Contract Manufacturing for APIs and Particle Design for the pharmaceutical industry. How are you able to capture synergies from those different business models?

A: The know-how we develop for our off-patent API business is fundamental to expand our offerings to our contract manufacturing customers. The engineering and solid-state characterization technologies developed for inhalation, for instance, have given us a really unique expertise. It is only because of our internal innovation program (to develop alternative processes to the conventional micronization with the purpose to overcome quality, stability, and efficiency issues) for our catalogue products that we are able today to offer those novel technologies to all our customers. Those customers are not looking for a product, they are looking for a solution to a problem they have, and we are the right address for that. This doesn't necessarily mean that Hovione will synthesize the API. We offer drug delivery technology options to the customers with a supportive group of professionals that are already advanced in the learning curve because of our own APIs.

Q: You have a growing business in formulation development services, particularly in dry powder inhaler devices and inhalation formulation development. How do those skills leverage your position in the supply of APIs for inhalation?

A: As an independent company, our combination of skills in API manufacturing, particle design, inhalation formulation, and DPI development is unique in the industry. Whether a customer is looking for a catalogue API or for a service, we are able to assemble very quickly a cohesive team able to significantly leverage the scientific and technical content of our customers' drug development programs. This multidisciplinary dynamic provides a strong depth and breadth of understanding in the inhalation field. Customers looking for an API for inhalation can count on a team to adapt the particle requirement to their needs and address analytical challenges and regulatory questions, thus saving time and money to get the product approved. Having one company and one team sharing best practices and combining and integrating every aspect of inhalation drug product development gives us tremendous leverage and flexibility.

Q: Hovione enjoys a strong presence in the API supply market beyond the inhalation field. Can you tell us about your portfolio and how you are responding to the current challenges of the industry?

A: Hovione has been supplying off-patent APIs to the pharmaceutical industry for the past 50 years. Since its inception, Hovione's positioned itself as a supplier of specialized APIs for highly regulated and demanding markets. By specialized, I mean APIs that involve complex chemistry, difficult-to-handle techniques, or those that require tighter GMP controls. Examples include our long-time presence in corticosteroids and tetracycline antibiotics and more recently in injectable-grade contrast media for large-volume parenteral drugs. The increase of lower-cost producers based in China and India in the past decade undoubtedly brought significant challenges to the European-based API industry, and Hovione was not an exception. Notwithstanding those challenges, Hovione has been growing at about 13% CAGR, promoted in large part to the off-patent API business, which currently accounts for about 60% of Hovione's sales. Operating in the API generic sector, which is commanded by a spiral of downward pricing, is surely not easy and requires a daily focus on differentiation, innovation, customer service, quality, cost improvement, and capacity management, achieved with business diversification, such as Contract Manufacturing.

Q: What role do your facilities in China play in addressing the challenges you previously mentioned?

A: Hovione has been present in China with a manufacturing facility since 1986. The first plant built in Macau was inspected by the FDA for the first time in 1987 and multiple times since then. Macau's plant has always been more of a strategic asset than a low-cost manufacturing plant. As Supplementary Patent Certificates are usually not filed in Macau, we make use of this head-start and are also very active in strategic procurement, adding important tools for us to face the highly competitive API generic industry. More recently, Hovione established a joint venture with Hisyn, a Chinese manufacturer based in Zhejiang province. This subsidiary aims at centralizing the production of Hovione's contrast agents and plays a fundamental role in achieving the most cost efficiency in this line of products in order to remain cost competitive. ◆

R&D Discussion Series

The New Role of R&D: Why & How Does it Need to Change?

Part 1 of a 6-part series

By: Rosemarie Truman, Executive Vice President, Advanced Clinical

Introduction

Many have said that life sciences companies are experiencing the Perfect Storm. We believe it's more like a tsunami given the number of mass disturbances taking place, from significant changes in the FDA guidelines, massive restructuring, as well as higher costs with lower results in R&D. The result: significant pressure for the R&D function. The new operative term in R&D headlines is transform R&D productivity to address increasing expenses per trial, long cycle times, and improve success rates. And, while R&D transformation is clearly needed, the new role of R&D is, perhaps, not as clear. R&D will need to make mammoth shifts to continue to be at the heart of innovation, ensuring the right drugs, devices, and/or biologics get to market and make the intended impact. The new role of R&D needs to go beyond the medicine and involves discovering and bringing to market differentiated solutions, and not just "me-too" products; focusing on being a thriving center of productivity and operational excellence; ensuring that not only the medicine is great, but it has market adoption at the right penetration rates and payers that want to pay for it; driving and enabling new models of revenue, such as performance-based pay; and cultivating ecosystems that create barriers to entry for competitors. The goal of this discussion is to provide an overview of what key shifts R&D needs to make to bring breakthrough commercial successes to market with the lowest cycle time and total cost of ownership. We also outline the opportunities and challenges that are involved in such a transformation.

The New Business Environment

The recent economic crisis has caused life sciences organizations, including pharmaceuticals, biopharmaceuticals, medical devices, and biotechnology, to reevaluate and shift their business strategies to set a sustainable course for future growth. Throughout the next several years, pharmaceutical companies face more than $125 billion in lost revenue due to patent expirations, competition from generics, as well as new legislation introduced in President Obama's healthcare bill. The impact of the new healthcare bill isn't fully understood, as it will cause an accelerated erosion of revenue and margin, given items such as AIDS Drug Assistance Programs (ADAPs) and various extensions. In addition, many blockbuster drugs are coming off patent with limited/no replacements in the pipeline. This industry crisis, often noted as the Perfect Storm, has forced life sciences companies to focus on: innovating the portfolio, reducing R&D costs, decreasing clinical trial cycle time and ensuring the highest probability of success, every time![1]

Life sciences organizations are reacting in a variety of ways. Many are cutting people and costs. From 2009 to the present, about 100,000 life sciences-related jobs have been permanently

eliminated. Given much of the work hasn't gone away, companies are filling the workforce gap with contract staff and outsourced resources. Several companies are pursuing personalized medicine solutions to create tailored medical products for specific patient populations to ensure comparative effectiveness requirements are met. To hedge bets, many new collaborative relationships are being formed as well. For example, GSK and Pfizer's spin-off of their HIV R&D unit to form a new HIV-focused company will be able to get products to market faster and address a larger population. PricewaterhouseCoopers found that global leaders also are seeking to sell off assets and preserve funds. Additionally, many business leaders have expressed the need to assess their risks and examine alternative strategies.[1, 2]

Yet, many of these measures are a mere temporary fix for the challenges that life sciences companies face. There are still unique challenges and key imperatives facing the industry that require long-term solutions. Over the long term, R&D will have to act on the following key imperatives:

Revenue Replacement: This is needed to bridge the gap between the $125 billion in lost sales from intellectual property protection expirations, and the collective value of products/solutions in the pipeline that could be launched, which total $30 billion. And while an astounding 98% of life sciences CEOs surveyed indicated they are confident their companies will grow revenues over the next 3 years, it will be a significant challenge given revenue and profit erosion. Major life sciences companies, such as Johnson & Johnson, are projected to have up to 50% of sales at risk due to generic erosion throughout the next 5 years.[3] There are three key levers life sciences companies will need to pull:

1. Shift From Product-Orientation to Solutions-Orientation: Shifting from a product mindset to a solutions mindset given the rise of personalized medicine and the requirement to have new business models, such as performance-based pay.

2. Portfolio Optimization: Ensuring both products/solutions in the pipeline, those in the market as well as those that are off-patent and/or have been shelved, have optimal asset utilization and monetization.

3. Patient Centricity: 73% of CEOs believe patients will play a more active role in the development of new products and services.[2] Therefore, the whole model of identifying new products/solutions needs to shift from being medicine-focused to being patient-focused.

Innovation Lever	Definition	Example
Operational Model Innovation	Innovation that improves the effectiveness and efficiency of core processes, technology, as well as organizational models and functions for competitive differentiation.	Trial designs using adaptive and AcPOC; the application/institutionalization of Kaizens and Lean Sigma; technology using an eClinical platform, such as EDC, IVRS GTMS; business intelligence platform integrated across all clinical trials; data harmonization; tech-regulatory standards moving toward e-submission, a foundational component of the platform; talent retention.
Products/Services/Solutions Innovation	Innovation applied to the creation and subsequent introduction of novel products, services, and/or solutions. A solution would include not only innovation from a medical/scientific standpoint, but also in all the aspects of the product, such as the pricing model.	Science innovation that drives new products/services/solutions. Example: product differentiation and variation addressed in protocol development (eg, Vion's special protocol assessment for Onrigin Injection). Other examples include solutions, such as personalized medicine
Business Model Innovation	Innovation in the way companies generate revenue, including which customers are served, what value proposition is offered, and what channels are used to reach customers. The value proposition needs to be higher – comparative effectiveness is a vital factor.	Companies like Novartis have pay-for- performance programs, so patients don't pay for drugs unless they actually work.
Market/Customer Innovation	Innovation that is driven by latent customer/patient wants and needs. Alternatively, customer innovation can proactively shape demand.	Life science companies are shifting from "marketing" to doctors to interfacing directly with patients to let them know the value proposition of their products/solutions. "Voice of the Patient" efforts are underway. Marketing efforts are starting to focus on microsegments. Coupons are being provided to drive demand (eg, Advair).
Collaborative/Open Innovation	Continuous two-way collaboration with external parties to drive increased insight and economic impact. This is innovation to allow open expertise, cost, and benefit sharing. Typically this innovation involves restructuring.	GSK and Pfizer spun off parts of their HIV organizations into a joint venture, called ViiV Healthcare, to share expertise, accelerate time to market, reach more patients, and ultimately gain increased market share.

Table 1. Outline of the innovation levers and some examples in play.

Effectiveness & Efficiency in Research & Product Development: Optimizing the "what" (effectiveness) and the "how" (efficiency) in both the "R" and the "D." From a Research standpoint, this means picking the right products/services, every time that will have market adoption and those which payers will support. In Research, it will be necessary to apply much more analytical rigor using new processes and frameworks. From a Development standpoint, life sciences companies will need to address the unrelenting slippage and productivity losses in product development while at the same time managing increased complexity given new protocol requirements, global trials, etc.

Collaborative Innovation: Proctor & Gamble (P&G), Innocentive and many others have set the standard on breakthrough "open innovation." In fact, P&G saved ~40% of R&D costs with their efforts. Life sciences

companies need to explore four different collaboration models. The key, however, is to first identify where one should collaborate, with whom one should collaborate, why collaboration should occur, and, finally, how the collaboration should take place. The players range from associations, life sciences companies, technology companies, competitors, suppliers, etc.

Change Management: Managing the torrent of change coming from M&A, significant cost and workforce reductions and other re-organizations (shifting 30% of resources from the US to Asia), and new/shifting R&D processes using new technology (eg, EDC) and methods (eg, Adaptive). In light of all these challenges, the industry as a whole is currently making fundamental changes to its operating structure.

Differentiation: Ensuring products/solutions, associated commercial models, as well as the experience patients have with products/solutions are better than others on the market given increased customer, and FDA scrutiny (comparative effectiveness). And if the product/solution does get on the market, providing strong support for payers to pay.[4]

Positioning R&D as a staple of productivity is not without merit. Companies that have strong R&D capabilities and strategies were found to be 73% more profitable.[5] However, foundational to achieving all these imperatives is breakthrough innovation. It is not enough to reduce cycle time if a drug is not approved and payers don't want to pay for it. It is not enough to have a great medical breakthrough if patients and doctors don't recognize the value. It is not enough to have a great product if it is not affordable. Given these circumstances, market share cannot be gained in an over-crowded market. Life sciences companies need to develop a portfolio of five types of innovation (see Table 1):

1. Operational models that reduce cycle time, control costs, and ensure a high probability of success.
2. Solutions that are differentiated and build durable patient-centered relationships.
3. Business models that create long-term value propositions.
4. Market/patient models that create net new experiences in standard of care.
5. Open innovation that creates collaborative relationships that allow increased insight and economic impact.

While taking into account all levers that can formulate an innovation blueprint, how can your company develop a balanced portfolio to drive sustainable growth? By making R&D the innovation steward to integrate and drive all types of innovation.. ◆

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Rosemarie Truman, PhD

Executive Vice President Advanced Clinical

Dr. Rosemarie Truman is the Executive Vice President of Advanced Clinical. She has 19 years of global strategy and transformation solution sales and execution experience working with C-suites and Board of Directors as well as senior leadership teams of leading companies in nearly every industry segment. At Advanced Clinical, Ms. Truman uses her strategy consulting background and "growth breakthrough innovation" experience to conceptualize and implement a new industry-changing framework for life sciences companies called Industry Leading R&D Performance (ILRDP). Ms. Truman completed PhD work in Software Engineering from Oxford University. She completed an Executive "Mini-MBA" Program, sponsored by Booz Allen & Hamilton, with instructors from Harvard Business School and INSEAD, and graduated Magna Cum Laude from Smith College and Princeton University while earning undergraduate degrees in Mathematics, Economics, and Industrial Engineering and Operations Research.

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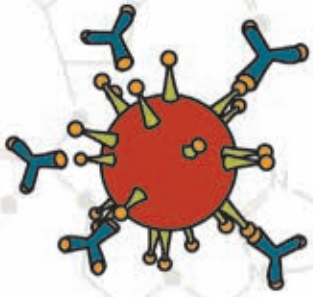

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DOS47 – Killing Cancer by Altering the Tumor Microenvironment

By: Heman Chao, PhD, Chief Scientific Officer, Helix BioPharma Corp.

Introduction

Throughout the past 15 years, the effort in anti-cancer drug research has been directed toward targeted pathway therapeutics. These compounds target one and possibly more intracellular biochemical pathways that have been implicated in tumorigenesis. The rationale for their development is that more targeted therapeutics would provide efficacy while minimizing adverse events. Several compounds have completed clinical testing and have been launched as anti-cancer treatments, including a VEGF inhibitor, bevacizumab (Avastin®), an EGFR antagonist, cetuximab (Erbitux®) and a bcr-abl inhibitor, imatinib (Gleevec®).[1-3] However, although most of these compounds generate measurable benefit, their efficacy is generally modest or, in the case of imatinib, require chronic therapy. New treatment paradigms are needed, especially for solid tumors, such as non-small cell lung cancer (NSCLC).

Most solid tumors arise in a microenvironment that has been altered to enable tumor cells to thrive and proliferate. The changes to the microenvironment are varied and complex and include suppressed host immunity, deregulated inflammation and increased production of cellular growth and survival factors that induce angiogenesis and inhibit apoptosis, as well as a lowering of pH.[4,5] Such changes in the tumor cell microenvironment could be a target for therapeutic intervention.

$$\text{Urea}[(NH_2)_2CO] + 3H_2O \xrightarrow[\text{Urease}]{} 2NH_4^+ + 2OH^- + CO_2$$

Figure 1. Chemical Pathway of Urease Activity

The following will describe an approach to chemically alter a part of the tumor microenvironment with the goal of developing a cancer therapeutic that can be either directly cytotoxic to the tumor cells and/or act synergistically with other

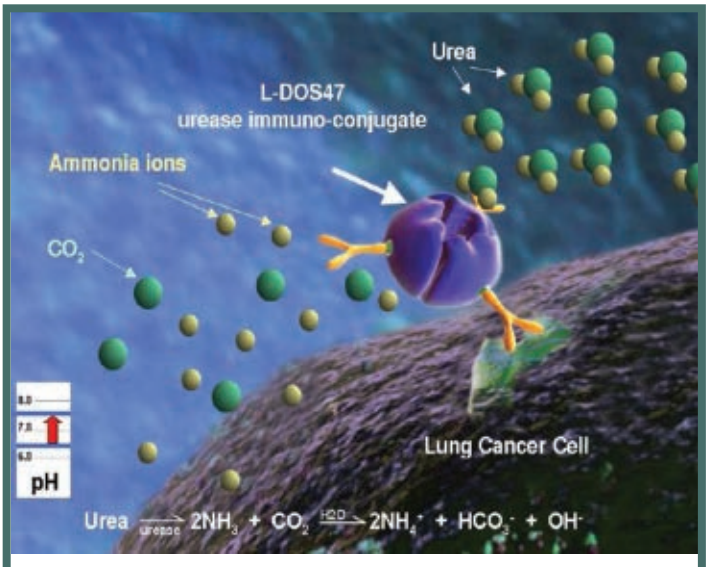


Figure 2. L-DOS47 Mechanism of Action

chemotherapeutic agents to enhance efficacy and/or tolerability.

Altering the Microenvironmental pH as an Approach to Cancer Therapy

Tumor cells create an external microenvironment that is more acidic and hypoxic than the microenvironment surrounding normal tissues.[6] This is a result of altered metabolic pathways and abnormal tumor vasculature. Tumor cells appear to thrive in this environment. In addition, the efficacy of weakly basic chemotherapy drugs is adversely affected by the acidic conditions surrounding tumor cells.[7] It is possible that changes to the microenvironment of tumor cells may actually affect their sustainability and could potentially offer a target for cancer drug development.

DOS47 - Enabling Targeted Alteration of Microenvironmental pH

DOS47 is an oncology platform technology developed by Helix BioPharma, Aurora, Ontario, that offers a new approach to the debilitation and destruction of cancer cells. DOS47 is designed to offer a means of deriving a therapeutic pharmacological effect by acting upon a naturally occurring substance in the body. The technology is based on the principle of using an enzyme to catalyze the metabolism (catabolism) of an endogenous substrate molecule in order to yield metabolites of therapeutic benefit.

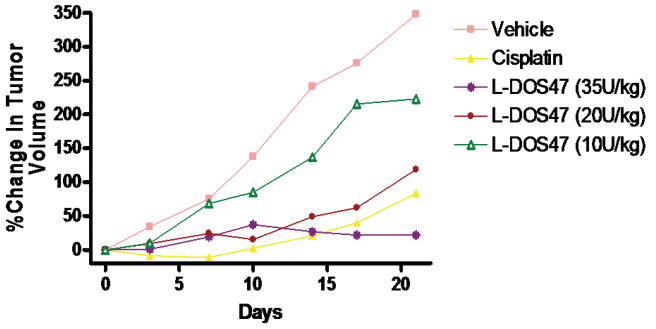


Figure 3. **L-DOS47 In Vivo A549 Xenograft Efficacy**
L-DOS47 doses were injected every other day X 5. 35 U/kg p = 0.0158 significant, 20 U/kg p = 0.0417 significant, 10 U/kg p = 0.3943 not significant.

Cancer cells generally exist and proliferate under conditions of abnormally low interstitial pH (ie, high acidity). DOS47 is designed to induce an increase in pH locally at the site of cancerous cells in the body to create an environment inhospitable to their continued growth and survival.

DOS47 is an enzyme called urease derived from the jack bean that catabolizes the naturally occurring substrate, urea. By inducing the catabolism of urea in the interstitial medium surrounding cancer cells, urease action may promote the production of metabolites, including ammonia and hydroxide ions. These metabolic products of urease activity are believed to stress cancer cells by a combination of effects, including direct toxicity and the induction of an alkaline microenvironment (Figure 1).

Ammonia itself is cytotoxic, a behavior thought to stem from its interference with cell processes, many of which are more pronounced in rapidly growing cells. While ammonia is toxic to cancer cells, the catabolism of urea increases the local pH of the surrounding medium. The increased alkalinity may also counteract the adverse effect of the acidic microenvironment on weakly basic drugs and enhance the uptake of these chemotherapeutics.

Following in vitro studies to understand urease's cytotoxic mechanism of action, in vivo studies were carried out in mouse models of lung and breast cancer to assess the anti-tumor activity of urease. It was demonstrated that urease injections significantly inhibited tumor growth in both models. When combined with weak-base anti-cancer drugs, the increased pH resulting from the catabolism of urea enhanced the activity of the chemotherapeutic agents.[8]

Because DOS47 activity is potentially toxic to any cell in the body, the molecule must have a targeting mechanism that very specifically targets the tumor cell type of interest.

Otherwise, unwanted side effects would be generated due to off-target activity.

With the aim of recreating the anti-tumor response in vivo to urease injection, DOS47 was designed to be combined with highly specific antibodies that could effectively deliver the drug to solid tumor cells. Antibodies whose antigens are highly expressed on a particular tumor cell type can be joined to DOS47 by a chemical linker and subsequently serve as a highly-specific targeting agent, whether or not the antibody has any intrinsic therapeutic activity. The local delivery of DOS47 to tumor sites promises to limit the cytotoxicity to the tumor cells themselves. Additionally, DOS47 can be administered simultaneously with other chemotherapeutics with the possibility of enhancing weak-base anti-cancer drugs locally at the tumor site.

L-DOS47 - Altering the Microenvironment of Non-Small Cell Lung Cancer (NSCLC) Solid Tumors

L-DOS47 is a novel immuno-conjugate therapeutic designed for the treatment of lung adenocarcinoma, a sub-type of NSCLC. L-DOS47 is a combination of the DOS47 urease drug compound and a NSCLC-specific single domain antibody, AFAI.

ES1 is a petameric and highly avid form of the AFAI antibody that is highly specific to a variant form of the well-known antigen, carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6 or CEA6) on non-small cell lung adenocarcinomas.[9] ES1, when compared with other forms of the AFAI antibody, was shown to be more lung carcinoma sensitive, particularly those poorly differentiated adenocarcinomas that are usually associated with distant metastasis, and less immunoreactive with normal tissues.[10]

The treatment of NSCLC is a significant unmet medical need, with lung cancer accounting for the most cancer-related deaths in most men and women in the United States. The 5-year survival rate for all stages of lung cancer combined is only about 16%.[11] NSCLC accounts for 85% of lung cancer diagnoses, of which 35% to 40% are hard to treat adenocarcinomas.[12,13]

For most patients with NSCLC, current treatments do not cure the cancer. Despite treatment with new agents like Avastin and Erbitux, patients generally receive the limited benefit of one or two months of additional median survival. The targeted alteration of the NSCLC adenocarcinoma microenvironment to kill cancer cells shows promise as a new paradigm for treating solid tumors and satisfying the unmet medical need.

With its precise targeting, L-DOS47 operates with an unprecedented mode of action, taking advantage of the localized delivery of urease to cause alkalinization of the tumor cell microenvironment,

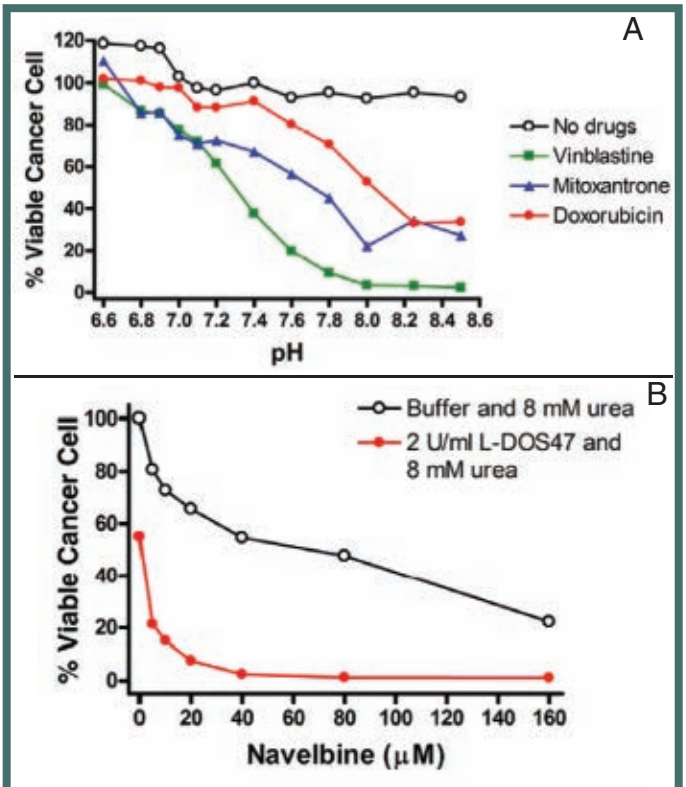


Figure 4 A&B. **The Effect of L-DOS47 on Tumor Cells in Combination With a Chemotherapeutic Agent**
The cytotoxic effect of weakly basic drugs is directly related to the solution pH (Figure 4a). At an acidic tumor pH (< 6.8), the effectiveness of weakly basic drugs is significantly reduced. L-DOS47 can dramatically raise the effectiveness of these drugs (eg, navelbine, Figure 4b). This synergistic effect is directly related to its enzymatic properties of generating ammonia from urea and raising solution pH.

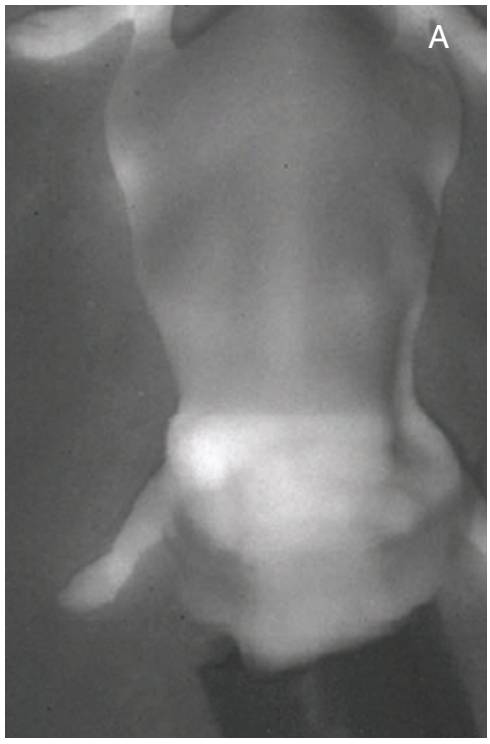
deliver ammonia toxicity to NSCLC tumor cells and, in combination with other anticancer drugs, potentially enhance the effect of chemotherapeutic agents (Figure 2). L-DOS47 has the potential to both stop and reverse the progression of NSCLC adenocarcinomas in those patients with few options.

In preclinical trials, L-DOS47 was tested in vivo in A549 xenograft models of NSCLC (Figure 3). In these studies, the combined effect of ammonia toxicity and an increase in pH was demonstrated to be cytotoxic to cancer cells alone and in combination with chemotherapeutic agents (Figures 4a & 4b). Imaging studies using A549 xenografts and intravenously given labeled L-DOS47 demonstrated the high affinity and high specificity of the AFAI antibody, with histological evidence showing that the drug molecule preferentially accumulated and persisted at the tumor site for well over 72 hours (Figures 5a & 5b). With its ability to preferentially target NSCLC adenocarcinoma cells and to drive local anticancer cytotoxicity, L-DOS47 holds promise as a new treatment as it moves into the clinic.[14]

L-DOS47 is in late preclinical development, and the company's most recent disclosures indicate a US submission of an Investigational New Drug Application (IND) and a European submission of a Clinical Trial Application (CTA) are upcoming. The US Phase I clinical trial is intended to assess the safety of L-DOS47 in patients who have received multiple chemotherapeutic regimens to treat solid tumors. The European Phase I/II clinical trial, to be performed in Poland, is intended to assess the safety and efficacy of L-DOS47 alone and in combination with other drugs in patients with advanced lung adenocarcinoma.

Discussion

Cancer is a highly complex pathology and, unlike other diseases, it is not wholly gene specific. Rather, to manage the



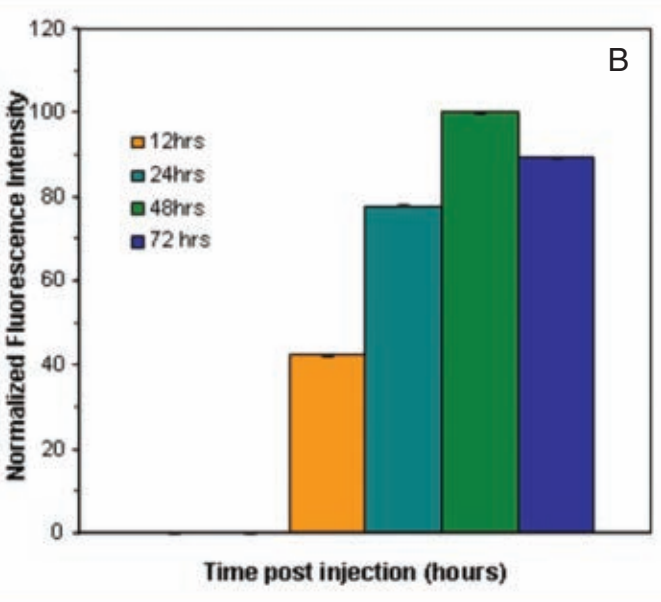


Figure 5 A&B. **L-DOS47 Fluorescent Imaging Study**
Inactivated L-DOS47 labelled with Cy5.5 was injected in nude mice bearing A549 xenograft. The tumor and major organs were harvested for imaging. Relative signal intensities were used to measure biodistribution, half life, and accumulation. A representative picture of a tumor bearing mouse 72 hrs post injection of the labelled material is presented. Summary result showing signal accumulation in tumor (ex vivo) as a function of time is shown. Detectable L-DOS47-Cy5.5 began at 12 hrs and persisted beyond 72 hrs.

variety of molecular and cellular processes that contribute to the development of cancer, you need to go after the disease from different fronts. DOS47 is an example of a drug with several approaches in a single molecule. When attached to highly specific antibodies, DOS47 is intended to essentially become a highly targeted sledgehammer that makes the microenvironment of the tumor inhospitable to survival and growth. The urease in DOS47 effectively catabolizes endogenous urea to produce two anticancer agents: a cytotoxic substrate, ammonia, and a change in pH that is hazardous to cancer cells while offering favorable conditions to some chemotherapy drugs.

L-DOS47 is a compelling validation of the novel approach of the DOS47 platform. L-DOS47 is a promising therapeutic for the treatment of NSCLC, a market where there are limited options and where there is a significant need for new agents. Beyond L-DOS47, the DOS47 platform technology is potentially broadly applicable across a variety of solid tumors and, with the right specific antibody, can extend its therapeutic value to other indications. Looking forward, there is now the possibility to build upon the preclinical success of L-DOS47 with other DOS47-based cancer drugs. ◆

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Chief Scientific Officer
Helix BioPharma Corp.

Dr. Heman Chao is currently the Chief Scientific Officer of Helix BioPharma Corp. of Aurora, Ontario. He is a co-inventor of the DOS47 technology. Prior to his current position, Dr. Chao was President of Sensium Technologies, a Helix BioPharma Corp. subsidiary from 2004 until it was incorporated into Helix in April 2008. Before joining Helix, he was a Research Fellow in the Protein Engineering Network of Centres of Excellence in Canada.

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Need to Know

By: John A. Bermingham

Six weeks after graduating from college, I received the dreaded *Greetings from the United States Government and friends and neighbors*… I was given a date to show up on Polk Street in Chicago for my pre-induction physical. I passed with flying colors, so to speak.

Shortly after that, I received a second communication in the mail from Uncle Sam to report back to Polk Street on a specific date to be formally inducted into the Army and that I would receive an all expenses paid 8-week basic training course at beautiful Fort Leonard Wood, MI. I decided to sign on for a 3-year enlistment so that I could choose what I wanted to do for my time in the Army rather than become an infantry man for 2 years as a draftee.

I asked the Army recruiter what the longest electronics school was that the Army had to offer and, after he reviewed a very thick document, he told me the longest electronics school was Cryptography (codes) at Fort Monmouth, NJ, 54 weeks in duration. He said that with basic training, 30-day leaves, and holidays, I could expect it would be 18 months before I graduated from Cryptography school. Half of my enlistment would be chewed up before I knew it! I signed right up.

I eventually ended up just south of the DMZ in Korea assigned to the 226 Signal Company with the 4th Missile Command. I had two security clearances, Top Secret Cryptography Code Access and Top Secret SAS (nuclear release codes). I also had a very clear understanding of what *need to know* meant.

Simply put, if you have a legitimate need to know the information, then you get the information. If not, then you do not get the information. It doesn't matter what your security clearance is. This need-to-know concept, albeit difficult to deal with at times, has carried over to my business life, particularly when I became a CEO.

My management style is to be an open, honest, and communicative CEO. I want our people to know what is going on in the company, and I hold regular Town Hall Meetings to make certain that first-hand information flows throughout the company. But not everyone needs to know everything all of the time. There is information that your management cannot or does not want to share with you and information that you cannot or do not want to share with others.

That is where things can get dicey. Can you be open, honest, and communicative while holding information back from people? The answer is yes. You can do this by telling people that you will always communicate with them in an open and honest manner. But you must also tell them that there will be times when you have to keep certain information or answers to questions confidential for the benefit of the company. When the time comes that you are able to release the information or answer the question, you will do so.

With that understanding, when there is a request for information that you cannot share or a question asked that you cannot answer for confidentiality reasons, you can tell the person or people that you cannot share that information or answer that question at that time for confidentiality reasons. That is being open, honest, and communicative and people understand and appreciate your candor. You get in trouble when you answer with misinformation or an out and out lie. People will quickly view you as someone who has a *need to go*! ◆

Biography

John A. Bermingham is 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.

THE ADVANTAGES

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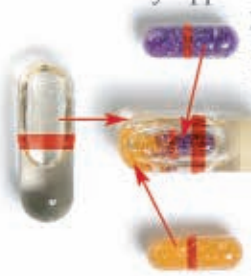
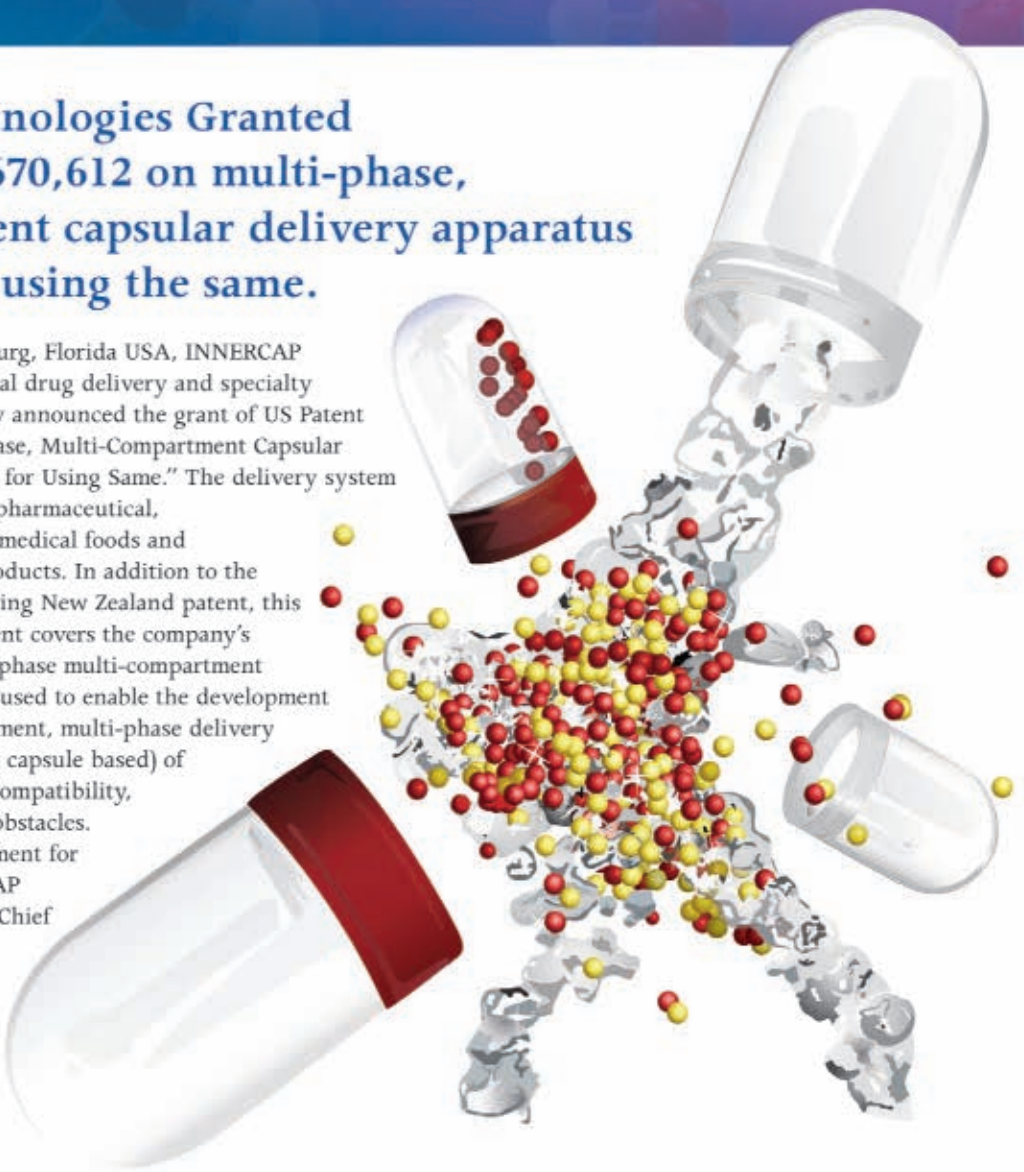
INNERCAP® Technologies Granted US Patent No. 7,670,612 on multi-phase, multi-compartment capsular delivery apparatus and methods for using the same.



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:

INNERCAP® TECHNOLOGIES, INC

United States Patent No. 7,670,612
US and International Patents Pending

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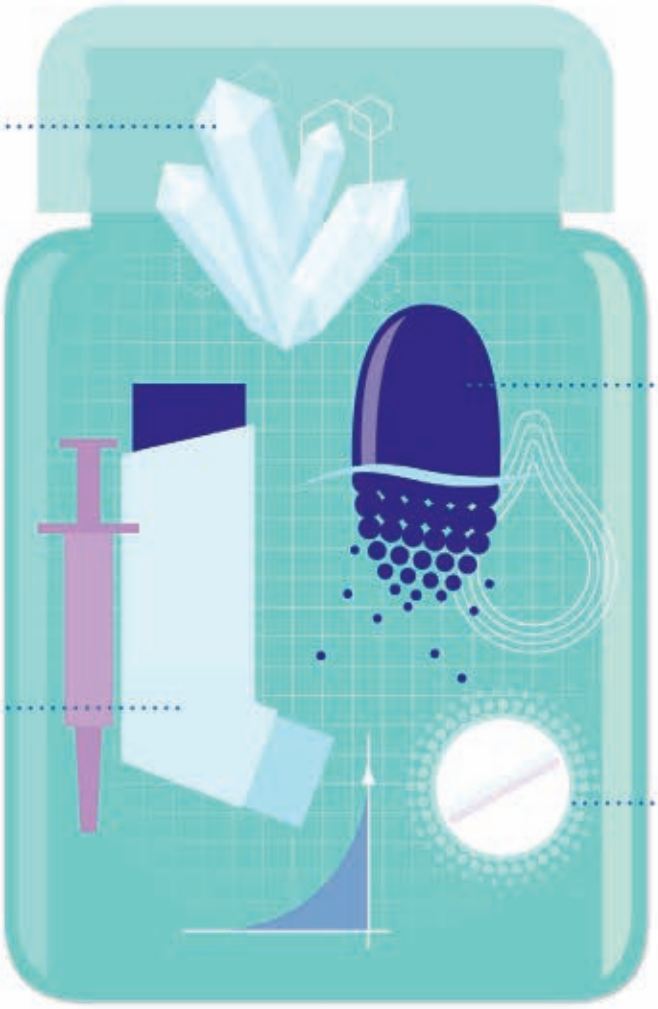

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