Drug Development® & Delivery

July/August 2011 Vol 11 No 6 www.drug-dev.com

Adaptive Focused Acoustics

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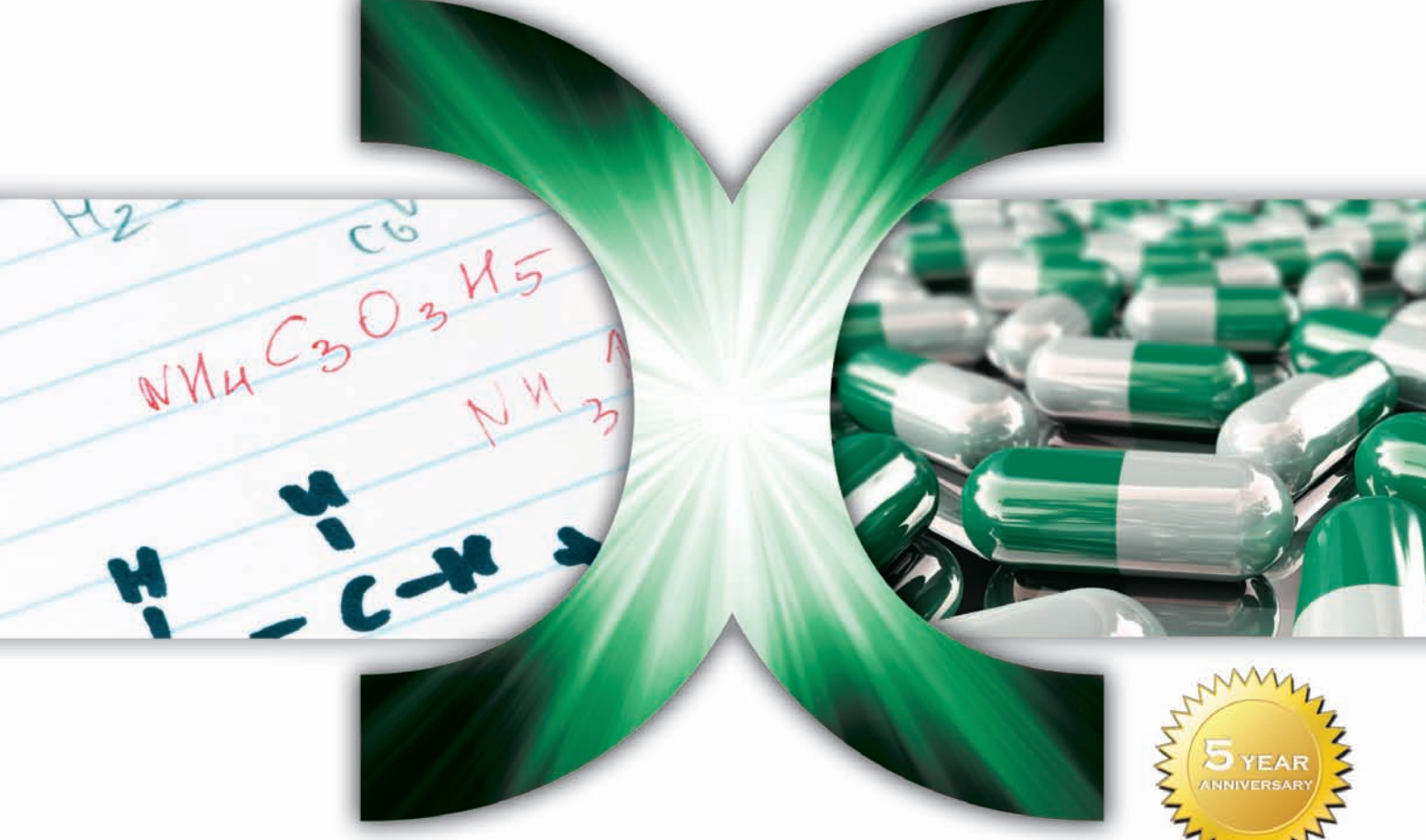

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Drug Development & Delivery

July/August 2011 Vol 11 No 6

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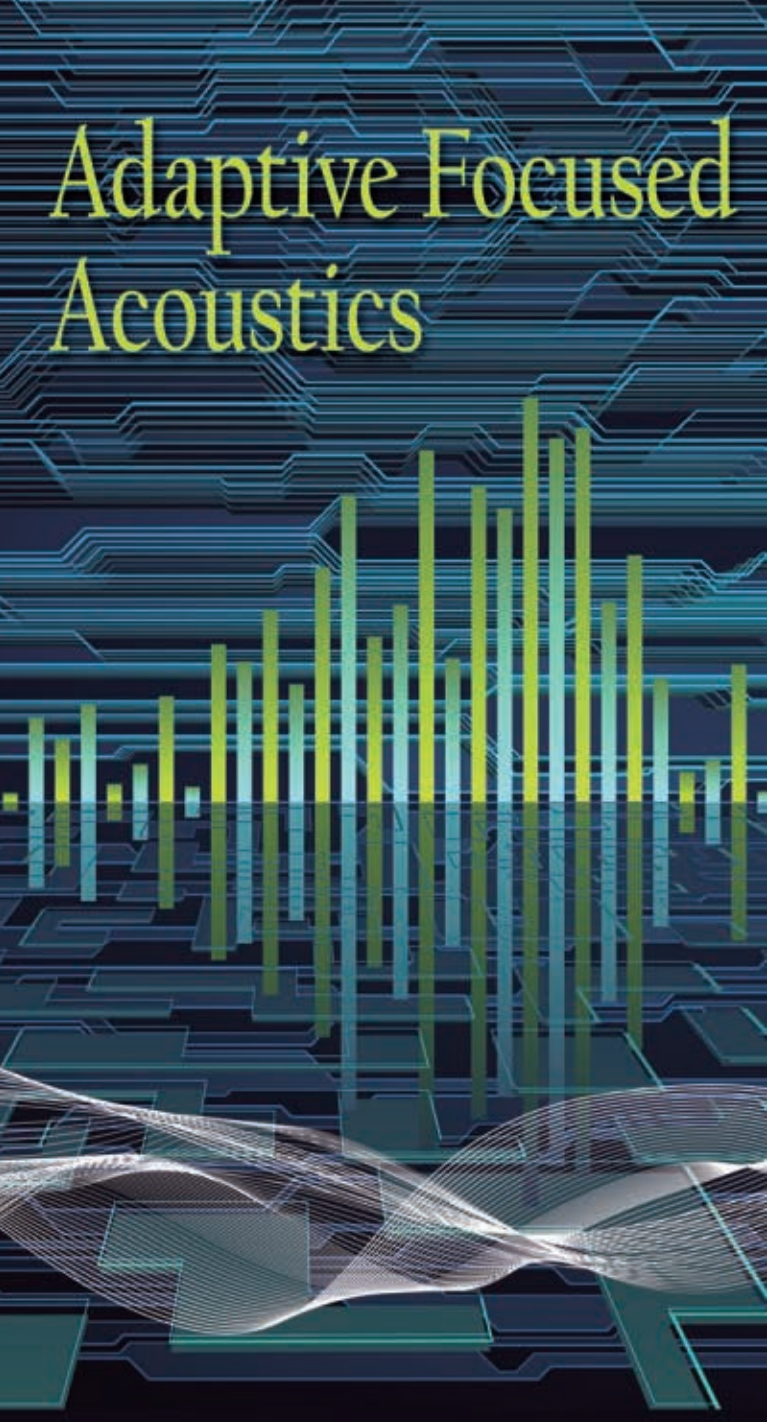

"A possible technique to mitigate this risk is reduction of the suspension's particle size. However, there are few currently available methods to quickly reduce particle size across a range of sample volumes without introduction of potential contaminants due to the use of a reusable probe or degrading the API due to excessive heating. A novel technology, Adaptive Focused Acoustics, has been used to successfully reduce particle size in a controlled manner to make uniform suspensions with low micron or nano-scale particle sizes."

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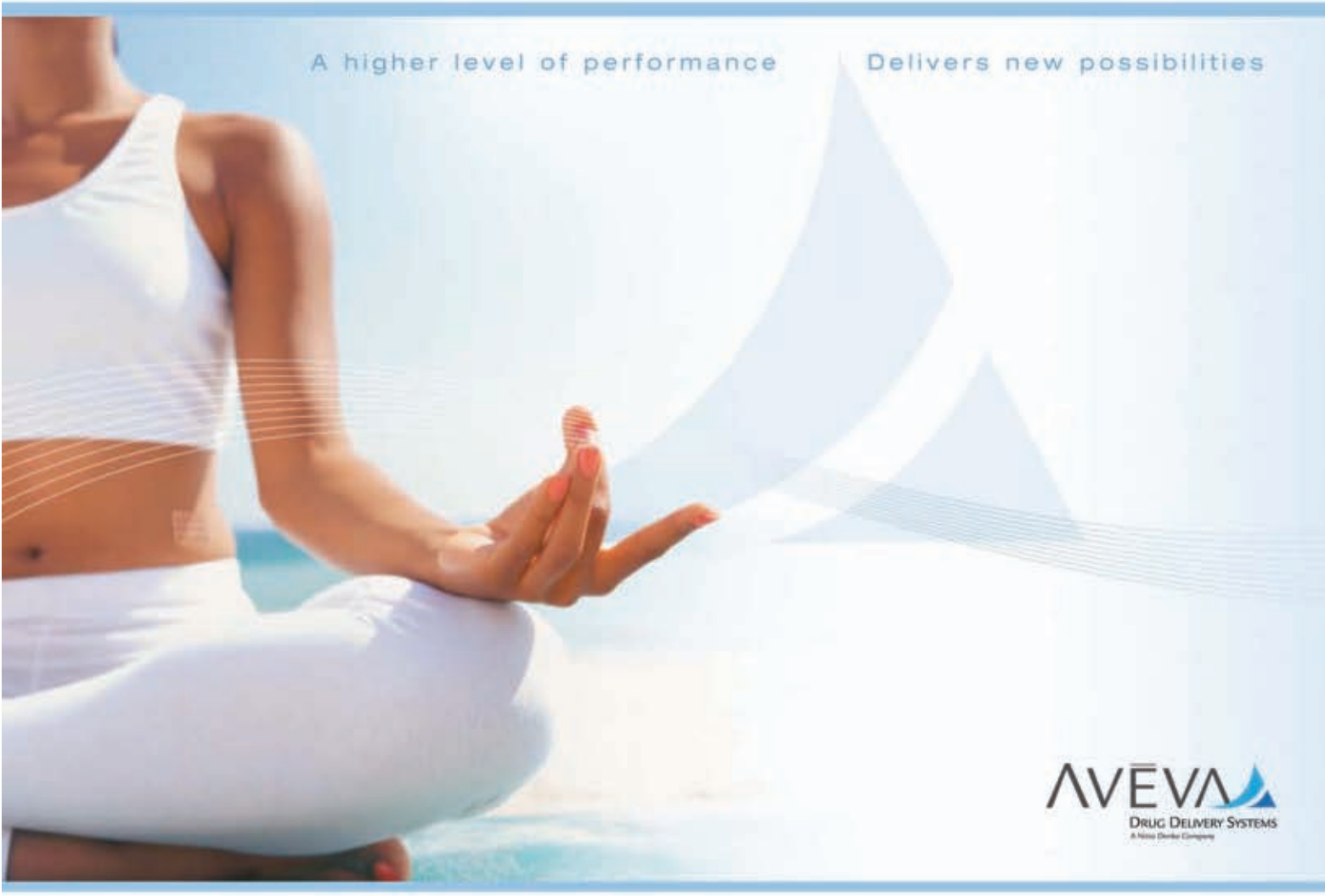
TRANSDERMAL TRANSCENDENCE



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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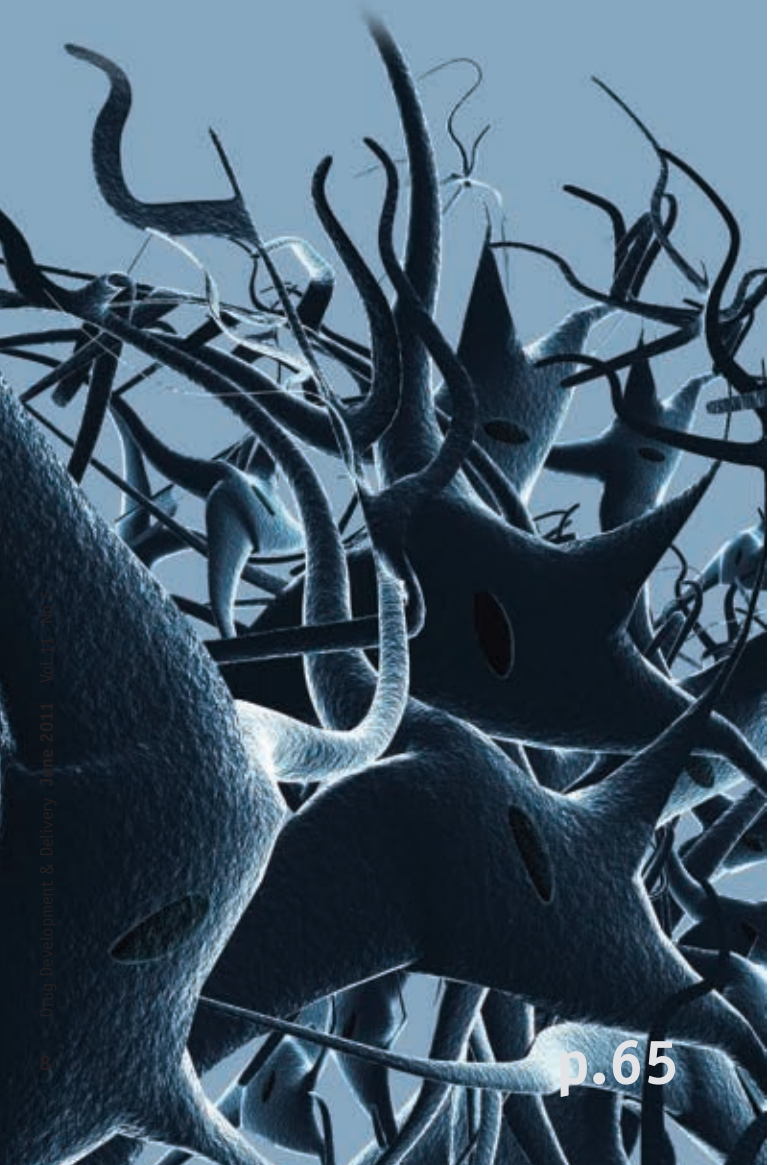
NITTO DENKO GROUP

Neurodegeneration in Multiple Sclerosis

"Current treatment options target the inflammatory component of the disease, and little attention has been given to the neurodegenerative component, which ultimately leads to permanent disability affecting the quality of life for MS patients. The therapy for MS has changed over the past several years as a result of intensive studies and drug trials on animal models. Recent findings in the immunological and pathophysiological aspects of the disease, advances in biotechnology, modern imaging, and improvements in clinical trials have led to a variety of therapeutic approaches."



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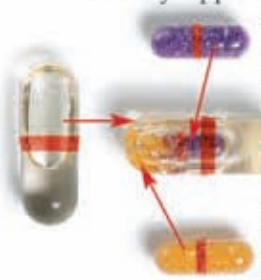
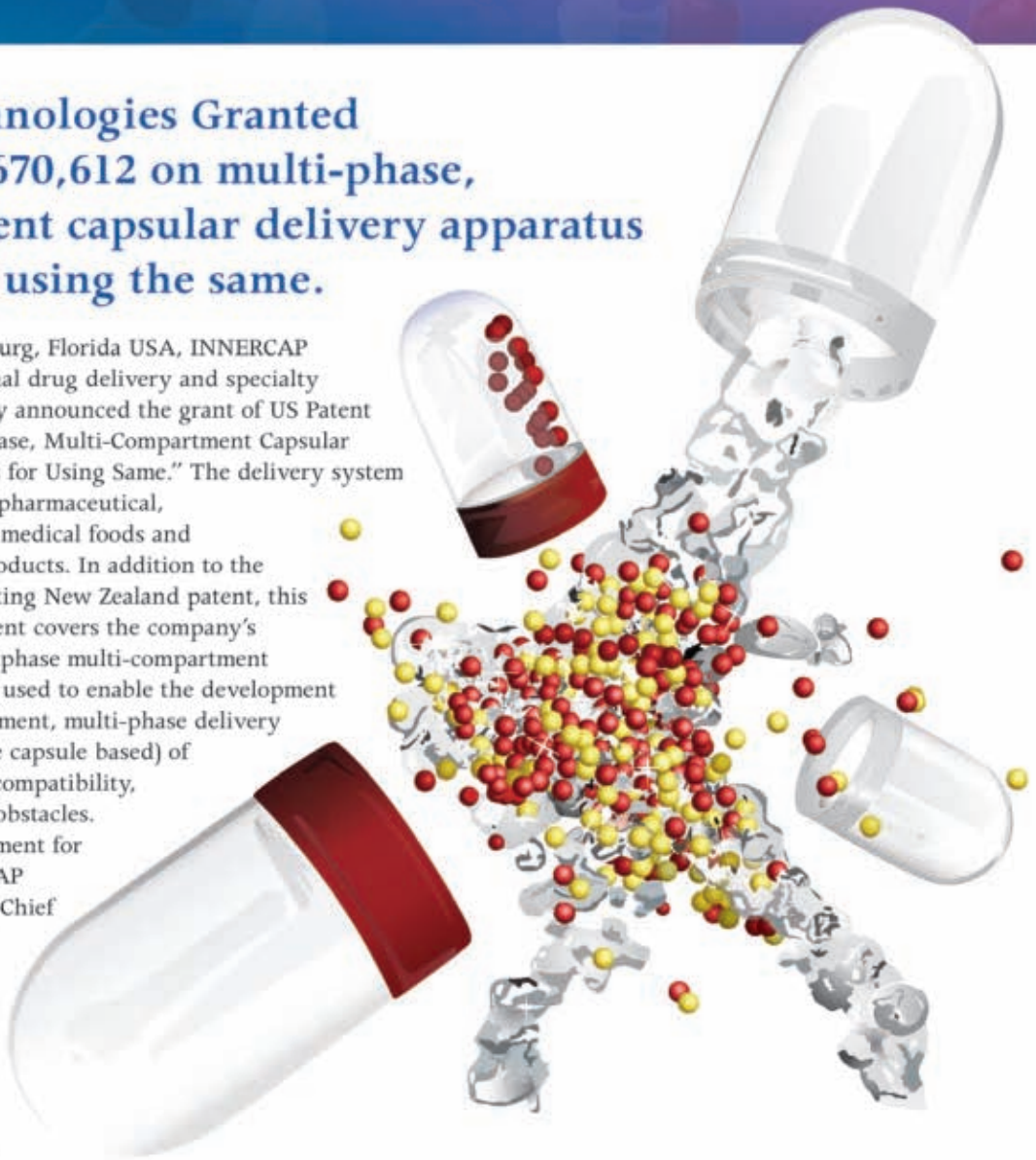
THE ADVANTAGES

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
US and International Patents Pending

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Market News and Trends

Pulmatrix Shows iSPERSE Effectively Delivers Doses of Multi-Drug Formulations

Pulmatrix recently announced that data relating to the preclinical efficacy and multi-drug formulation and delivery capabilities of the company's novel iSPERSE inhaled dry powder drug delivery platform were presented at poster sessions on June 19 and 21, 2011, at The International Society for Aerosols in Medicine (ISAM) in Rotterdam, Netherlands. iSPERSE is a novel dry powder platform that uses certain proprietary cationic salts at tailored ratios to enable delivery of small or large molecule drugs via inhalation for local or systemic applications.

At ISAM, in a poster titled *A Novel Inhaled Dry Powder Delivery Platform; Efficacy of Fluticasone and Salmeterol During Allergic Asthma*, preclinical data on the iSPERSE platform highlighted the potential of this novel technology to support the effective delivery of a two drug iSPERSE formulation that underscores the uniqueness of the platform across a range of patient populations. The iSPERSE platform offers the potential to enable the aerosol delivery of small molecule drugs, drug combinations (including triple drug combinations or higher), and macromolecule drugs (ie, proteins, peptides, etc) at therapeutically relevant doses well in excess of those achievable by traditional dry powder lactose blend technologies.

"These data, as well as other studies we have conducted, clearly underscore the unique and compelling potential of our proprietary iSPERSE platform to create novel dry powder formulations for inhaled drug delivery for local and systemic therapeutic applications," said Michael Lipp, PhD, Vice President of Development and Intellectual Property at Pulmatrix. "iSPERSE formulations have been shown to exhibit desirable properties, including high density and high dispersibility, that can lead to reliable inhaled drug dose delivery across a wide range of relevant flow rates. Additionally, the iSPERSE platform can support the inhaled delivery of single or combination drug formulations as well as a greater capacity to accommodate higher drug loadings and larger drug molecules than conventional inhaled technologies."

In the data presented by Pulmatrix at ISAM, two mouse models of allergic asthma, the ovalbumin (OVA) model and house dust mite (HDM) model, were used to show the utility of Pulmatrix's iSPERSE platform using a well-described inhaled combination, a long-acting bronchodilator, salmeterol xinafoate (SX), and a corticosteroid, fluticasone proprionate (FP). In these studies, animals inhaled FP/SX treatment or placebo by whole body exposure prior to allergen challenge (OVA or HDM). Specific airway resistance was determined by dual chamber plethysmography and was collected at baseline and during methacholine (MCh) challenge following the final iSPERSE-enabled dry powder treatment. Specific airway resistance values were decreased (33% on average) across the range of MCh challenge in both allergen models. To evaluate the effect of the corticosteroid, animals were treated with SX/FP (SX at 2.0% w/w / FP at 13.5% w/w), which resulted in decreased total inflammatory cells marked by reduced eosinophilia assessed by bronchoalveolar lavage. These data highlight the potential efficacy of iSPERSE as a novel dry powder delivery technology platform, as aerosol delivery of SX/FP demonstrated reduced inflammation and airway hyperreactivity.

With completion of comprehensive proof-of-concept validation of the iSPERSE platform along with extensive initial patent filings, Pulmatrix is now advancing a select number of proprietary iSPERSE drug candidates as well as actively pursuing iSPERSE partnerships with pharmaceutical companies to create novel therapeutics.

iSPERSE is a novel inhaled dry powder delivery platform developed by Pulmatrix for use in the delivery of drugs via inhalation for local or systemic applications. iSPERSE uses proprietary cationic salt formulations to create a robust and flexible platform that can accommodate low or high drug loads in highly dispersible particles, yielding drug delivery capabilities not feasible with conventional dry powder technologies that rely on the use of lactose blending or low-density particles. The properties of iSPERSE have meaningful therapeutic and patient benefits, including the potential for single formulations with multiple drugs, effective inhaled drug delivery to patients with normal or impaired lung function, and the use of simple and convenient inhaler devices. iSPERSE offers the potential of a strong safety profile, as, in addition to drug and drug molecules, iSPERSE dry powders comprise exclusively generally regarded as safe (GRAS) salts and small quantities of additional, safe excipients if needed. iSPERSE powders are made via a straightforward, proven one-step spray-drying process capable of high and consistent yields.

Pulmatrix is a clinical stage biotechnology company discovering and developing a new class of therapies for the prevention, treatment, and control of respiratory diseases. Pulmatrix's lead proprietary therapies, called inhaled cationic airway lining modulators (iCALM), are a novel approach to prevent and treat acute exacerbations and improve lung function in patients with chronic respiratory diseases. iCALM therapies have broad potential to treat and prevent a wide range of respiratory diseases, including respiratory infections, such as influenza; ventilator associated pneumonia (VAP), and respiratory syncytial virus (RSV), as well as progressive or chronic respiratory diseases, such as COPD, asthma, and cystic fibrosis.

Hovione & Particle Sciences Inc. Ink Deal to Speed Up Drug Solubilization Projects

Hovione and Particle Sciences Inc (PSI) recently announced a collaboration agreement under which they will pool their technologies together to significantly speed development projects targeting poorly water-soluble drugs. The companies expect to jointly be able to significantly reduce typical project times.

Hovione and PSI are joining their solid solution technologies based on spray-drying capabilities and aimed at targeting ways to maximize the bioavailability of BCS Class II APIs. Development will be fast-tracked at both companies, with PSI developing the solubilization process and resulting drug product for their clients and Hovione managing the scale-up and industrialization of the spray-drying process.

"It is truly incredible how versatile and useful spray-drying technology is," said Dave Hoffman, President, Hovione US Operations. "We have used it from a gram scale to tons, with important time savings on the scale-up to manufacture products where other technologies failed. Teaming up with PSI will give their customers an integrated solution that will allow us to go from drug product and process design to feasibility and development to industrial application in record time."

"We have a variety of drug delivery platforms, some of which are best scaled through spray-drying," added Mark Mitchnick, Particle Sciences' CEO. "Our unique contribution is to develop products that maximize clinical effect, and after that, Hovione takes over with their technological and industrial expertise and regulatory compliance. We will really be able to save our clients quite a lot of time."

Hovione is an international company with over 50 years' experience in API development and compliant manufacture. With four FDA-inspected sites in the US, China, Ireland, and Portugal, the company focuses on the most demanding customers, in the most regulated markets. Particle Sciences Inc is an integrated provider of drug development services, utilizing a broad suite of drug delivery technologies to address a diverse range of challenges. With special expertise in particulate-based formulations and drug/device combination products, it has become a leader in drug delivery development.

3M Signs Development Agreement; Updates Phosphagenics Collaboration

3M Drug Delivery Systems and Radius Health, Inc. recently announced an agreement to collaborate on the development of a transdermal delivery option of BA058, Radius' novel, proprietary PTHrP (parathyroid hormone-related protein) analog, for the treatment of osteoporosis. The BA058 Microneedle Patch will use 3M's patented Microstructured Transdermal System microneedle technology to administer BA058 through the skin, as an alternative to subcutaneous injection. The BA058 patch is expected to combine the ease, convenience, and self-administration attributes of a transdermal patch with the speed and efficiency of a traditional injection. Terms of the agreement were not disclosed.

3M also announced that Melbourne drug delivery technology company Phosphagenics Limited is a step closer to commercializing its first-in-class oxycodone pain patch following successful completion of their initial global formulation development collaboration. 3M has refined Phosphagenics' original oxycodone transdermal patch prototype and will commence the development of an improved version that will be used for next stage clinical trials. These trials are scheduled to commence later this year. The development of the new patch has commenced at 3M's laboratory in Minnesota. The Melbourne-developed technology has the potential to revolutionize the delivery of the powerful painkiller oxycodone using Phosphagenics' proprietary TPM transdermal delivery technology.

Evonik Degussa Provides Pharmaceutical Melt Extrusion Technology Services

Evonik Degussa Corporation recently announced the purchase of a Leistritz Nano 16-mm (TSE) Twin Screw Extruder to serve the growing number of customers using pharmaceutical melt extrusion technology. Installed at the Evonik Pharma Polymers Technical Lab in Piscataway, NJ, the new extruder is equipped with a micro-plunger feeding system and precision T-12 K-Tron top feeder. The TSE tackles solubility and bioavailability issues of poorly soluble drug substances, taste-masking, controlled/sustained release, and continuous manufacturing applications.

Twin screw extruders have become the industry standard in the manufacture of pharmaceutical products from feasibility to commercial scale.

"At early stages of melt extrusion formulation development of new molecular entities with limited drug availability, it is essential to use extrusion equipment for the smallest batch size," said Dr. Firouz Asgarzadeh, Senior Technical Manager of Pharma Polymers business line. "The current set allows 30 g to several kg pharmaceutical in melt extrusion batch manufacturing."

Evonik Pharma Polymers, a business line of Evonik Degussa Corporation, manufactures EUDRAGIT® acrylic functional polymers, used for immediate-release, enteric, sustained-release, taste-masking, and protective formulations.

Throughout the past 12 years, Evonik has built a network of global centers of excellence for pharmaceutical melt extrusion and spray-drying to help customers develop formulations for poorly soluble drugs via MemFis (Melt Extrusion Modeling & Formulation Information System), lab trials, and cGMP clinical supplies. Evonik Pharma Polymers provides full formulation development services for melt extrusion of drug substances with appropriate (EUDRAGIT or Non-EUDRAGIT) polymers.

"The market trend is to make molecular entity drugs more bioavailable," said Yann d'Herve, Business Director North America of Pharma Polymers business line. "This latest addition to our state-of-the-art lab provides pharmaceutical formulators access to the latest new platform technology and a means to develop pharmaceutical melt extrusion formulations to bring drugs to the marketplace in a faster and more cost efficient way."

Evonik is the creative industrial group from Germany. In its core business of specialty chemicals, it is a global leader. In addition, it has energy and residential real estate operations, and its performance is shaped by creativity, specialization, reliability, and continuous self-renewal. Evonik is active in over 100 countries around the world.

Avantor Performance Materials Expands Presence in India

Avantor Performance Materials recently announced it has opened a new pharmaceuticals formulation applications laboratory at the RanQ Remedies facility, an established excipient developer and manufacturer based in Sinnar Nashik, India. Following Avantor's recent acquisition of RFCL Limited in India, the opening of this new laboratory shows a strong commitment to growth and expansion in the region.

The new lab, which strengthens a strategic development and manufacturing agreement between Avantor and RanQ, will be used to characterize excipients; perform functional testing; develop and characterize drug formulations; and support customer applications and product implementation.

In addition to an applications laboratory, Avantor has completed construction of a pilot plant onsite at the RanQ facility. The pilot plant will be used to develop and scale-up additional performance excipients to extend Avantor's J.T.Baker PanExcea product line. The PanExcea line includes performance excipients that combine filler, binder, and disintigrant to provide increased excipient functionality for immediate-release and orally disintegrating tablet applications.

"Our partnership with Avantor will allow us to advance our goal of becoming an internationally known, high-quality excipient manufacturer," said Managing Director of RanQ, Sameer Ranadive. "We look forward to developing a broad range of performance excipients to assist customers in the global pharmaceutical industry."

RanQ has extensive process development and manufacturing capabilities and expertise. The company is known for developing premixed and other application-focused pharmaceutical excipients that result in a homogenous mix and co-processed excipients that eliminate the need for wet granulation production stages.

"With our proven excipient innovation experience, beaker-to-bulk packaging flexibility, and Q7A quality systems, RanQ will serve as a strategic pharmaceutical partner in the region," added Avantor Executive Vice President of Pharmaceuticals Paul Smaltz.

"RanQ's capabilities will help us increase the commercialization speed of Avantor's line of J.T.Baker PanExcea performance excipients," said Mr. Smaltz. "By working with RanQ on customer applications, we expect that this alliance will facilitate a rapid introduction of additional novel, high-performance excipients to the global pharmaceutical market."

"This base of applications support complements our other activities in India," said Avantor Executive Vice President of Southeast Asia Sushil Mehta. "Our expanded presence will enable us to quickly develop more unique and effective solutions that help customers increase their speed to market."

"Avantor is a global leader continuing to build upon a legacy of innovation by expanding into new global regions," said Mr. Smaltz. "Our new applications laboratory will allow Avantor to provide additional value to customers who are developing high-volume manufacturing operations in the Southeast Asian region by conveniently testing and developing drug formulations on site."

Avantor is continuing to expand in the Southeast Asia region. The company recently acquired RFCL Limited, a leader in laboratory reagents and consumables as well as products for medical diagnostics. Avantor purchased RFCL because of its current presence in the laboratory and pharmaceutical markets in fast-growing Indian market.

Tekmira's LNP Delivery Technology Enables Proof of RNAi in Man & Clinical Activity

Tekmira Pharmaceuticals Corporation recently provided comments on presented data from a Phase I human clinical trial with ALN-VSP conducted by Alnylam Pharmaceuticals, Inc. ALN-VSP, an RNAi therapeutic for the treatment of liver cancers that utilizes Tekmira's LNP technology, the only RNAi delivery technology supporting multiple clinical candidates being advanced by Tekmira and its partners in several different disease indications.

The most recent ALN-VSP data was presented at the American Society of Clinical Oncology (ASCO) meeting in a poster titled *Phase I Dose-Escalation Study of ALN-VSP02, a Novel RNAi Therapeutic for Solid Tumors With Liver Involvement*. Alnylam disclosed that ALN-VSP was generally well tolerated, demonstrated evidence for anti-tumor activity, and was found to mediate RNAi activity in both hepatic and extra-hepatic tumors.

"Earlier this year, we were excited to see Alnylam's interim clinical data with ALN-VSP, which demonstrated RNAi activity in human tumor biopsies and confirmed that our LNP technology enables bona fide RNAi activity in man. Now, another important advancement has been made in the RNAi field as Alnylam reports that its ALN-VSP data demonstrates anti-tumor activity," said Dr. Mark J. Murray, Tekmira's President and CEO.

"To date, this is the second completed human clinical trial that has reported Tekmira's LNP technology is safe and well tolerated. We anticipate further clinical data being presented from a number of LNP-enabled products over the remainder of 2011. Building upon this momentum, Tekmira continues to innovate and protect our LNP technology with a focus on improvements to LNP potency and tolerability, as well as combining new RNAi payloads with LNP delivery," he added.

Tekmira's LNP technology is enabling the systemic RNAi product pipeline of Alnylam Pharmaceuticals, including the products ALN-VSP, ALN-TTR, and ALN-PCS. As Alnylam disclosed, ALN-VSP was administered to 41 patients at doses ranging from 0.1 to 1.5 mg/kg; a total of 182 doses have been administered, including to one patient who has received 24 doses at 0.7 mg/kg over the course of more than 1 full year, and continues to receive treatment in the study. The Phase I trial was designed as a multi-center, open label, dose escalation study in patients with advanced solid tumors with liver involvement who have failed to respond to or have progressed after standard treatment. The primary objective was to evaluate the safety, tolerability, and pharmacokinetics of intravenous ALN-VSP.

RNAi therapeutics have the potential to treat a broad number of human diseases by "silencing" disease-causing genes. The discoverers of RNAi, a gene-silencing mechanism used by all cells, were awarded the 2006 Nobel Prize for Physiology or Medicine. RNAi therapeutics, such as siRNAs, require delivery technology to be effective systemically. LNP technology is one of the most widely used siRNA delivery approaches for systemic administration. Tekmira's LNP technology (formerly referred to as stable nucleic acid-lipid particles or SNALP) encapsulates siRNAs with high efficiency in uniform lipid nanoparticles, which are effective in delivering RNAi therapeutics to disease sites in numerous preclinical models. Tekmira's LNP formulations are manufactured by a proprietary method that is robust, scalable, and highly reproducible, and LNP-based products have been reviewed by multiple FDA divisions for use in clinical trials. LNP formulations comprise several lipid components that can be adjusted to suit the specific application.

Alliqua Expands Patent Portfolio for Transdermal Drug Delivery Platform

Alliqua, Inc., an advanced biomedical products company focused on the development and manufacturing of proprietary drug delivery and liver health technologies, recently announced it has filed a provisional patent application with the US Patent and Trademark Office to enhance its transdermal delivery technology. The filing was based on positive test results with respect to specific chemical agents that improved the delivery of active ingredients when used in conjunction with the company's hydrogel drug delivery platform. The patent application is directed to specific formulations that management believes will enhance the performance of its platform.

"This patent filing is the second in a series of filings that we hope to continue as we develop additional improvements and processes," said David Stefansky, Chairman of Alliqua, Inc. "These filings are a meaningful step in building our intellectual property portfolio, strengthening our drug delivery platform position, and in increasing shareholder value."

Alliqua, Inc., is an advanced biomedical products company focused on the development and manufacturing of proprietary technologies in the fields of drug delivery, advanced wound care, and liver health preservation. Through its wholly owned subsidiary, Alliqua BioMedical, Inc., Alliqua intends to develop active ingredient and transdermal drug delivery products, primarily utilizing the proprietary hydrogel technology platform of AquaMed Technologies, Inc., Alliqua's subsidiary.

AquaMed manufactures custom hydrogels used for transdermal drug delivery, wound care, medical diagnostics, and cosmetics. These products use proprietary manufacturing technologies that enable AquaMed to produce what is known in the healthcare industry as high water content, electron beam cross-linked aqueous polymer sheet hydrogels. AquaMed believes that it is one of two manufacturers in the world for these gels. Alliqua's third subsidiary, HepaLife Biosystems, Inc., focuses on the development of a cell-based bioartificial liver system, known as HepaMate.

Oxygen Biotherapeutics Approved to Expand Trials for Traumatic Brain Injury

Oxygen Biotherapeutics, Inc. recently announced it has received approval by the Drug Controller General of India to conduct its traumatic brain injury Phase IIb clinical trials known as STOP-TBI. Oxygen Biotherapeutics believes adding clinical investigators in India to its existing clinical sites in Switzerland and Israel will enable the company to conclude the study faster and more economically. The next cohort is expected to begin in the second half of fiscal year 2012.

Dr. Tim Bradshaw, Executive Vice President of Clinical Development at Oxygen Biotherapeutics, believes the addition of India to its existing clinical sites in Switzerland and Israel is an important step in the clinical development plan for Oxycyte(R) PFC. "Traumatic brain injury is a leading cause of mortality and morbidity in India with an estimated incidence of 150 per 100,000. In the city of Bangalore alone, nearly 10,000 individuals sustain brain injury and more than 1,000 die every year. Expanding our trial into countries such as India will help us to accelerate completion of the study."

"We are pleased that we received this approval and look forward to working with our new clinical sites," added Chris Stern, Chairman and Chief Executive Officer of Oxygen Biotherapeutics. "Currently, we are exploring whether to amend the protocol to include patients with milder forms of TBI, and we are developing the processes for manufacturing cGMP Oxycyte PFC for the study. In addition, we are seeking a partner to help us execute the remaining aspects of this trial because we believe that makes strategic sense and is in the best interest of our shareholders and patients."

The STOP-TBI study is a double-blind, placebo controlled dose-escalation study designed to evaluate the safety, efficacy, and dosing parameters of Oxycyte PFC, a novel perfluorocarbon emulsion that is given intravenously to traumatic brain injury patients. The study's first cohort has been completed and the database has been locked.

Headquartered in Morrisville, NC, Oxygen Biotherapeutics, Inc. is developing medical and cosmetic products that efficiently deliver oxygen to tissues in the body. The company has developed a proprietary perfluorocarbon (PFC) therapeutic oxygen carrier that is being formulated for both intravenous and topical delivery.

Recovery Strategies

The New Phase I Entrepreneur

Part 4 of a 6-part series on how not to blow the recovery.

By: Derek Hennecke, President & CEO Xcelience LLC

It's not just the recession. The structure of the drug development pipeline is changing. We have been used to a certain rate of flow through preclinical, Phase I, II, and III. The recession pushed investment into Phase III, and investment in Phases I and II slowed to a trickle. Today, the flow is normalizing, but not yet back to normal. Phase I remains anemic. So what's going on?

For a clue on early clinical research, we need only look as far as Parexel, one of the largest CROs in the country. Even with investment clearly returning to the early stages of drug development, Parexel is shutting down 30% of its Phase I capacity, letting 300 people or about 3% of its workforce go. Parexel wouldn't close down this portion of its business if demand was robust.

This is just one case, and it could be unique to Parexel. It could be a strategic decision, or it could be linked to its recent strategic deal with Pfizer. Indeed the CRO acknowledged the delay in the start of some Phase I investment, which seems to support the idea that the recovery is still tepid. But what I find interesting is that the company defended its decision by saying that there has been a shift among drug makers toward using existing patients rather than healthy volunteers, eliminating a large portion of their business.

More and more drug makers are choosing to conduct Phase I studies in affected populations, as opposed to the traditional path of healthy normals. Obviously, Parexel's CEO is not arguing that drug makers are skipping Phase I, what he's saying is that the target population for Phase I tests has significantly shifted. Phase I is still being done, but maybe there are fewer tests being carried out in this phase.

So, maybe product development strategy has shifted. Until a few years ago, company spend on Phase I studies was increasing; companies approached each Phase I compound as if that compound would succeed, and therefore conducted every possible test.

Now, companies are delaying studies where possible, choosing instead to conduct the bare minimum Phase I studies in accordance with agency guidelines and move more quickly into Phase II. Phase II spend is increasing its slice of the drug development pie, at the expense of Phase I.

So Phase II must be the place to be, right? Not if you're looking for success, anyway. A recent study showed that achieving success in mid-stage development is getting harder than ever. The Centre for Medicines Research analyzed the results of 16 companies with 60% of the global drug R&D budget and found that the success rate of Phase II compounds plummeted from 28% in 2006-2007 to a mere 18% in 2008-2009.

To some extent, we shouldn't be surprised. It makes sense that as time goes on, it will get harder and harder to find new drugs. We've been discovering drugs for the past century. The easy ones have all been discovered. Now, to get a new drug developed, it has to be either completely original or better than anything already out there. It's like we've been farming in the valley for decades, and we're now planting on the mountainside. The investment is higher, and in many cases, the number of successes per attempt are lower. To keep producing at the same rate, we're going to need a lot more investment. But the opposite is happening - companies are reducing R&D to increase returns for shareholders. So success rates are falling.

Taking a closer look at the failures of the past couple of years bears this out. Thomas Reuters Life Science Consulting analyzed the 108 reported Phase II failures from 2008-2010 for new drugs and major new indications of existing drugs (Drug News Perspect. 22, 39-51; 2009; Drug News Perspect. 23, 48-63; 2010; Drugs Today, 47, 27-51; 202).

Of the 108 Phase II failures, just over half failed outright because of insufficient efficacy, meaning that for purely scientific reasons, they were no better than what was already out there. Analyzing the failures by therapeutic indication, we find that 68% fell into four high-risk disease areas: alimentary/metabolism, cancer, cardiovascular, and neuroscience, according to Thomas Reuters Life Science data. Yet, despite therapeutic area risk, I have to wonder to what extent these fatal weaknesses could have been identified with additional predictive Phase I testing. Early identification avoids a whole lot of unnecessary and expensive Phase II testing.

The next biggest chunk at 29% failed for strategic reasons. They pass the scientific test, but just don't cut it for business reasons. Maybe the product is a little bit better than what's already out there, but not enough better to justify the cost of development; or it's in an area that's no longer a strategic market for the

sponsoring company.

The fact is that adding Phase I testing that could predict Phase II failure adds costs to Phase I, and slows down progress, increasing the possibility that a competitor will reach the market first. In this economy, companies focus on near-term success just to live another day, and we don't have the luxury of taking the long view. And so the market shifted toward delayed Phase I testing.

Already though, the market is adapting, as our free market system is supposed to do. Though Phase I remains underinvested, there is opportunity here. Right now, no one is in Phase I. When all the molecules have moved through the system, big pharma will be shopping for more early stage drugs. The few players that have established themselves here will be like the first lasses on the dock when the sailors return from their years on the recessionary seas.

What I foresee is not just the re-emergence of mini-biotechs in Phase I, it's a new type of entrepreneurs – scientifically trained entrepreneurs with a business model that is perfectly suited to the new pipeline and takes advantage of the new lower entry barriers to Phase I trials.

It starts with one biologist and one chemist. Quite often, these will be senior executives made redundant by big Pharma. One plays the role of CEO, and they bootstrap together some capital to take one or preferably two compounds (one lead, one back-up) through the newly simplified Phase I process. The compounds themselves may even be sourced from their former company - many companies would be happy to offload a few compounds for, say, a small cut of profits if it succeeds. They martial the compound(s) through Phase I, where risks have effectively been reduced, then sell it before Phase II, passing it like a hot potato into a phase where odds are it will fail.

Typically, these entrepreneurs would target a small niche (no blockbusters here) and form an LLC structured around a single compound or two. Usually a company like this would involve an investment of about $2 million; more than is considered seed capital, but less than a Series A financing structure, which is the first major round of financing.

The key is to get the compounds for as little investment as possible. That way, the venture capital companies can focus on driving the value of the asset, not the company. A few of these companies will later become Fully-Integrated Pharmaceutical Companies (FIPCos), but not many because of high failure rates.

The business case presented to venture capitalists is a strong one. There is little or no money required for equipment, management teams facilities, and stationary - all the accoutrements that come with a new biotech. The business case can be based almost exclusively on the risk-benefit analysis of the compound itself, and only through Phase I.

This new model is all about the compound, and the early scientific and commercial decision-making process that supports it. Not a penny or a moment is wasted on filling out work orders, supply requisitions, performance reviews, marketing meetings, or corporate strategizing. For scientists themselves, it's a great opportunity to do what they love to do, working in small elite teams of people they like and respect.

For the industry, there is the potential to rejuvenate the very seeds of scientific discovery, providing a new and vibrant source of Phase I drug development to fuel the pipeline, and increase the rate of success in Phase II and beyond. ◆

BIOGRAPHY

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

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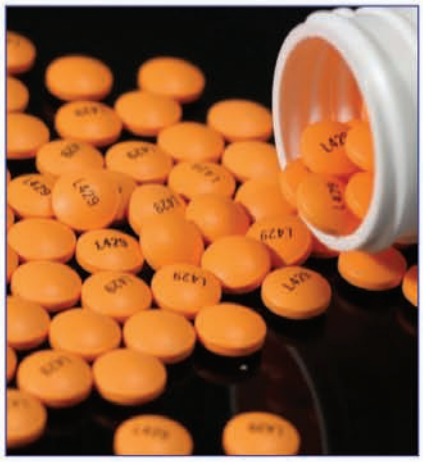

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SPECIAL FEATURE

Transdermal Delivery: Growing Rapidly With the Global Biologics Market

While the first passive delivery transdermal patches were introduced more than 2 decades ago in response to increasing demand for a more comfortable delivery system than needle injections, most transdermal patches today are still restricted to a limited number of molecules that can be delivered through the skin. Additionally, there may be local irritation or sensitization of the skin at the site of patch application, and, not all drugs are even suitable for transdermal delivery. Finally, in comparison with other routes of drug delivery, the transdermal route is relatively more expensive.[1]

Despite these limitations, the global 2010 transdermal market for patches alone reached $9.5 billion.[2] In 2009, the market was valued at $5.6 billion, with the majority of these sales being accrued by products utilizing first-generation patch technologies.[3] And, the transdermal market is poised for even more significant growth as innovative technologies that can deliver drugs beyond the capabilities of conventional patches are being developed. For example, various modes of transdermal drug delivery, such as microneedles, laser microporation, and dermabrasion, are in development to meet the need for a more convenient form of administering larger molecules.

With the advent of such technologies, transdermal delivery potential will continue to grow rapidly with a global biologics market that is forecasted to expand from $120.1 billion in 2009 to $170 billion by 2015.[3]

ALTEA THERAPEUTICS CORP.–DEVELOPING BIOBETTER PATCHES

Altea Therapeutics is developing what it dubs "biobetter" patches for biologic therapeutics by enabling painless delivery through the skin of drugs that until now, were administered only by needle injection, explains Yogi Patel, Director, Business Development at Altea. Altea's PassPort® Transdermal System painlessly creates channels in the dead outer layer of the skin for the delivery of drug from a transdermal patch (Figure 1). The PassPort System can provide a bolus or sustained drug delivery and can co-deliver multiple drugs or vaccines from a single transdermal patch. The technology has several optional features that support patient compliance and reduce the potential for drug misuse, including dose-monitoring, dose-reminder, and dose-lock-out.

"Altea's PassPort Transdermal System has the potential to grow the current market of transdermal patches by replacing injections, and in some cases, even oral agents," says Mr. Patel. For pharmaceutical companies, adapting an approved agent for transdermal delivery offers a lifecycle management approach that provides extension of patent coverage, branding, and market share."

Altea currently has four clinical-stage products in development using the PassPort System: Enoxaparin sodium, exenatide, basal insulin, and fentanyl citrate. In the case of enoxaparin sodium, Altea has completed Phase I clinical studies with a transdermal patch delivering the low-molecular weight heparin for the management of thrombosis, which is currently available as once- or twice-daily

FIGURE 1

The PassPort® System is designed to enable transdermal delivery of biologics and small water-soluble drugs by replacing needle injections with a painless, safe, and easy-to-use transdermal patch.

injections and accounted for more than $4 billion in worldwide sales in 2009. Transdermal Enoxaparin Sodium provides bolus delivery and has the potential to lower the overall cost in the prevention and treatment of blood clots by reducing hospital stays and eliminating home healthcare services required for administering injections, says Mr. Patel.

With partners Eli Lilly & Co. and Amylin Pharmaceuticals, Altea has conducted Phase I clinical trials for transdermal delivery of exenatide, the first approved GLP-1 compound for management of type 2 diabetes. Currently marketed as Byetta®, a twice-daily injection, GLP-1 analogs, or incretin mimetics, are a new approach to managing diabetes. Transdermal Exenatide is designed to overcome the needle barrier associated with the injectable GLP-1 compounds, to enhance compliance, and to enable earlier introduction of GLP-1 in diabetes management, potentially resulting in improved glucose control, weight loss, and fewer long-term complications associated with diabetes, explains Mr. Patel.

Altea also has completed several Phase I clinical studies for a transdermal patch delivering around-the-clock basal levels of insulin for managing types 1 and 2 diabetes. The basal insulin market is currently the fastest growing of all marketed insulin products and is dominated by Lantus® and Levemir®, which combined account for over $6 billion in worldwide sales. Transdermal Basal Insulin is designed to improve glycemic control by maintaining constant levels of plasma insulin throughout the day. In addition, Transdermal basal insulin allows for better management of hypoglycemia by providing the ability to stop insulin delivery upon patch removal.

A Phase I clinical development for transdermal delivery of steady levels of fentanyl to manage chronic, moderate-to-severe pain is also underway. Altea has demonstrated kinetics matching intravenous infusion of fentanyl citrate as well as a demonstrated steady delivery of fentanyl citrate in a multi-day pharmacokinetic study in human subjects. Currently marketed fentanyl patches deliver the base form of the compound, leading to several efficacy and safety issues, says Mr. Patel. Transdermal Fentanyl Citrate is designed to address these concerns by enabling the transdermal delivery of the salt form of the compound. Altea Therapeutics plans to demonstrate these advantages in clinical testing.

"In addition to enabling steady delivery of fentanyl citrate for effective management, the technology has the capability to store the time, date, and dose strength of each patch application and can provide dose-reminder signals. The technology has an optional electronic lock-out feature that can be used to limit dosing," he says.

With advances in more controlled dosing, Mr. Patel expects transdermal delivery to help facilitate the launch of new products and penetrate new markets. As a case in point, in May 2011, Altea Therapeutics entered into a partnership with Handok Pharmaceuticals Co., Ltd to develop transdermal products using the PassPort System in Korea and other East Asian countries.

"Innovation will continue to expand the market opportunity for transdermal delivery of therapeutics, while increasing the safety and efficacy of drugs, and in some cases, enabling the market introduction of a therapeutic that otherwise may never become commercially viable."

3M DRUG DELIVERY SYSTEMS–SOLID & HOLLOW MICROSTRUCTURED TECHNOLOGIES

As more biopharmaceutical products are being developed, the demand for effective and patient-friendly delivery systems is growing. Transdermal delivery of biologics offers pharmaceutical companies ways to efficiently and effectively deliver their drugs without a syringe, offering a means of finely tuning the therapeutic profile or differentiating their products in markets crowded with autoinjectors or syringes. 3M's Solid Microstructured Transdermal System (sMTS) and Hollow Microstructured Transdermal System (hMTS) technologies (Figure 2) have the potential to deliver both therapeutic and emotional benefits to patients, says Tom Martin, a Microstructured Transdermal Systems Platform Business Manager, 3M Drug Delivery Systems Division.

FIGURE 2

3M's Solid Microstructured Transdermal System (sMTS) and Hollow Microstructured Transdermal System (hMTS) technologies have the potential to deliver both therapeutic and emotional benefits to patients.

"In developing one of the first high-volume intradermal delivery systems with our hMTS device that delivers up to 2 mL of formulation, 3M has learned a lot about the potential of intradermal delivery," he says. "In addition to more efficacious delivery of vaccines, we've shown that intradermal delivery can provide very rapid and often highly efficient absorption of large molecules, including antibodies."

The potential to improve the bioavailability of monoclonal antibodies, drugs that have provided transformational therapeutic benefits to many patients, could be a very significant advance in transdermal delivery.

hMTS uses hollow microneedles that penetrate the stratum corneum to provide efficient delivery of molecules that are traditionally restricted by the constraints of syringe injection. 3M is fast-tracking the development of the fully integrated hMTS device.

"We have tested the hMTS device using a commercial formulation of Humira®," says Mr. Martin. "We delivered the drug with our hMTS device and with the autoinjector that is currently marketed with this product. A full therapeutic dose of Humira (0.8 mL) was delivered and was well tolerated in swine, with the injection site being barely visible after 1 hour. We were also pleased with the PK data, and the hMTS delivery showed

FIGURE 3

IVF Hormone patches have proven most successful when a patient's skin is pre-treated with P.L.E.A.S.E.® Private, a battery-powered hand-held medical laser device developed by Pantec Biosolutions.

slightly faster absorption and better bioavailability than the syringe delivery. We're looking to conduct a follow-up study of more statistical significance."

In addition to hTMS, 3M's sMTS platform has expanded the range of medications that can be delivered transdermally to patients. This is accomplished by using biocompatible, polymeric microneedles to bypass the barrier properties of the stratum corneum and deliver previously undeliverable molecules. With regard to vaccine delivery, the sMTS technology has the ability to provide a faster, more robust immune response than can be achieved by intramuscular injection, says Mr. Martin.

3M's targeted microneedle platform includes biologics, such as vaccines, hormones, treatments for autoimmune diseases, anemia/neutropenia, and osteoporosis. As a matter of fact, 3M recently signed an agreement with Radius Health, Inc. to partner and develop a BA058 sMTS patch as an alternative to subcutaneous injection for the treatment of osteoporosis.

"Transdermal drug delivery with an MTS-like system is growing steadily and will continue to expand," he says. "The MTS platform's ability to provide pharmaceutical companies with a way to differentiate their products, while providing physicians and patients with convenient and efficient administration, make this route of drug delivery an excellent choice for the future."

PANTEC BIOSOLUTIONS–LASER MICROPORATION ADMINISTRATION

Patches and passive transdermal delivery have been on the market for quite some time, and pharmaceutical scientists are constantly striving to add new deliverables to the list of approved transdermal products. A number of companies have pioneered several "needle-free" transdermal technologies to make transdermal administration a more widely used method, especially for peptide and protein delivery.

Pantec specializes in using laser microporation technology to deliver high- and low-molecular weight drugs into the epidermis for local or systemic drug uptake. Its proprietary P.L.E.A.S.E.® (Precise Laser Epidermal System) platform enables needle-free and painless administration of biopharmaceutical drugs, both in varying and individualized dosages, says Christof Böhler, CEO of Pantec Biosolutions.

The platform consists of a hand-held laser device that creates controlled aqueous micropores in the patient's skin through which drugs can be delivered. The micropores do not reach the dermis where nerves and blood vessels reside; however, the micropores are of a sufficient depth to facilitate transdermal drug delivery.

The company's lead compound is the P.L.E.A.S.E.-FSH (follicle stimulating hormone) patch. Currently, FSH is self-administered by the patients for 10 to 12 days by daily subcutaneous or intramuscular injection; FSH stimulates the growth and recruitment of immature ovarian follicles in the ovary during an in vitro fertilization (IVF) protocol.

"When used in conjunction with P.L.E.A.S.E., FSH is transported through the skin and into the systemic circulation, effectively stimulating follicle growth and making the process of IVF easier and more comfortable for women hoping to conceive," says Mr. Böhler. In order to make these hormone patches work, the skin is pretreated with P.L.E.A.S.E. Private (Figure 3), a battery-powered hand-held medical laser device.

At the end of 2010, Pantec achieved proof-of-concept in an exploratory clinical trial using an FSH of 32-kDa patch used with P.L.E.A.S.E. The study investigated the primary pharmacodynamic characteristics, as well as the safety and tolerability, of the newly developed FSH protein patch in 10 oocyte donors and to compare them with the effects of subcutaneous injections of Fostimon® (native urinary FSH) in another 10 oocyte donors.

Due to its size of 32 kDa and physicochemical properties, the urinary FSH hormone cannot permeate intact skin. Therefore, before patch application, the skin was microporated using P.L.E.A.S.E. to create tiny openings in the skin's outermost layer. These micropores allowed FSH to be transported through the skin and into the systemic circulation. The results showed that oocyte donors using the P.L.E.A.S.E.-FSH patch microporation stimulation protocol achieved follicle growth.

In February, Pantec announced the first successful IVF pregnancy using the P.L.E.A.S.E.-FSH patch. A woman conceived after being implanted with a fertilized oocyte from a donor treated with the FSH patch subsequent to skin microporation with P.L.E.A.S.E. The infertility hormone patches are currently entering clinical Phase II trials.

Mr. Böhler says that laser microporation combines several key advantages that set it apart from other transdermal technologies on the market, such as its ability to control drug dose through the variation of pore properties and number, doing so painlessly and with negligible damage to the skin. The company also has been able to microporate hard tissue, such as nails and bones.

"Innovative technologies that are able to deliver drugs with a broader spectrum of characteristics are poised to revolutionize the transdermal drug delivery market and drive significant growth," says Mr. Böhler. "In 3 to 5 years, we see microporation-based transdermal patches entering the market in several therapeutic areas. This will represent a paradigm shift in how to administer large biomolecules safely and efficaciously in the practise and at home."

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FIGURE 4

Skinvisible has developed more than 30 Invisicare products whose formulations cover a range of topical treatment options.

SKINVISIBLE–TOPICAL DELIVERY WITH AN EYE ON TRANSDERMAL

Skinvisible has developed a series of polymer delivery systems called Invisicare® that are designed to enhance product performance. The technology offers controlled release, greater release, superior binding, and skin barrier properties to topically applied products, says Doreen McMorran, Vice President, Business Development for the company.

Invisicare was developed to deliver most actives, including anionic, non-ionic, and cationic actives. To accommodate this wide variety of actives, Skinvisible developed seven Invisicare polymer delivery systems, five of which are a series of polymer complexes. Other Invisicare polymer delivery systems (ie, transdermal, mucosal) are in development. Skinvisible has three US patents and seven comprehensive international Invisicare patents (US, Canada, Australia, China, India, Hong Kong, S. Korea, and Japan; the EU is imminent.) covering the composition, manufacturing, and use/indication.

Skinvisible has developed more than 30 Invisicare products that are available for licensing, including prescription, over-the-counter, and cosmeceuticals products (Figure 4). These formulations cover a range of treatment options, including active agents used for acne, actinic keratosis, anti-fungals, atopic dermatitis, analgesics, anti-inflammatories, and antimicrobials, along with moisturizers, sunscreens, sunless tanners, and various other actives and inactives.

It is important to make the distinction that Invisicare is not a compound, it is a complex. There are no formal bonds formed with any of the Invisicare systems. The polymers and ingredients used in all Invisicare complexes are used for cosmetic and drug delivery. A complex of hydrophilic and hydrophobic polymers, Invisicare is designed for water-based products to carry water-insoluble and certain cationic active ingredients without the use of alcohol, silicones, waxes or other organic solvents.

"Skinvisible has developed proprietary product formulations using Invisicare, which provide greater release of active ingredients, sometimes three to four times greater than branded products. The result is a patent protect formulation with greater efficacy, safety, and marketing claims," says Ms. McMorran.

Invisicare also has the ability to bind active ingredients to the skin, while at the same time allowing the skin to breathe and perspire normally. The result is a protective bond, resistant to wash-off; delivering targeted and controlled levels of therapeutic or cosmetic skincare agents directly onto the skin. Invisicare is moisture activated, reacting to the chemical composition of the outside layers of the skin. Over time, the products wear off as part of the natural exfoliation process.

Lifecycle management is a key benefit that Invisicare offers pharmaceutical companies. Through reformulation, Invisicare provides a new patent (technology) and often additional patent protection for the formulation (product), which prevents the loss of market share and extends the value of the pharmaceutical company's brand, explains Ms. McMorran.

"A lifecycle management strategy using Invisicare also eliminates the need for expensive research and development for new APIs by pharma companies."

Skinvisible has dedicated research and development efforts toward transdermal and mucosal delivery due to the growing need in the marketplace.

"Several blockbuster drugs in hormone therapy, nicotine cessation, and other markets are coming off patent in the next 5 years. Skinvisible is focused on delivering viable lifecycle management solutions for these products," says Ms. McMorran.

She goes on to say that Skinvisible will play a leading role in the drug delivery market throughout the next few years.

"We are experiencing it already. Pharmaceutical companies internationally are cutting back on their own internal research and development, and we have seen a renewed focus on open innovation policies in the pharma and consumer goods industries. Skinvisible fits perfectly into this model."

DOW PHARMACEUTICAL SCIENCES–CUSTOMIZED SKIN PENETRATION

Dow Pharmaceutical Sciences (DPS) has developed proprietary technology for delivering active molecules, both large and small, through the human skin at various rates. Using proprietary technology, scientists can tailor the rate and level of penetration that is measured in an *in vitro* drug transport laboratory using freshly excised human skin (Figure 5).

"At DPS, we develop multiple formulation prototypes that are evaluated for API release and penetration in our drug transport laboratory, and are then optimized for maximum delivery," says Vanlee Waters, MBA, Marketing Manager, Dow Pharmaceutical Sciences. "Increased penetration means less API is required in a

FIGURE 5

Dow scientists can tailor the rate and level of penetration that is measured in an *in vitro* drug transport laboratory using freshly excised human skin.

formulation (lower strength), which can result in a substantial reduction in cost of goods if the API is expensive. A formulation optimized for penetration provides our client's product the best chance for success in the clinic because the API is released from the formulation and delivered to the desired site."

Drugs are delivered through a variety of matrices–lotions, creams, ointments, gels, sprays, foams, and various substrates. DPS designs the delivery system based on the dermatological indication and drug properties, enabling customized skin penetration.

DPS expects transdermal delivery to continue to grow as more drugs are delivered topically to optimize efficacy and maximize safety profiles.

"As a leader in topical drug development, transdermal delivery is part of our core business, and we expect to continue to build our expertise and proprietary technology to enable ideal topical drug delivery," says Ms. Waters.

There are currently a number of DPS transdermal drug delivery systems that have been approved by the FDA, and there are an even larger number of transdermal delivery technologies that are currently in development or clinical trials.

TAPEMARK—PRECISE TRANSDERMAL CONTRACT MANUFACTURING

There are many elements to the transdermal market, including drug development, formulation, compounding, development in active transdermal technologies, and active and passive patch manufacturing. Tapemark is a contract manufacturer with experience in active and passive transdermal patches (Figure 6). The company works with drug and device GMPs, and handles Schedule III – V Controlled Substances, with plans to expand into Schedule II. Tapemark does not offer its own products.

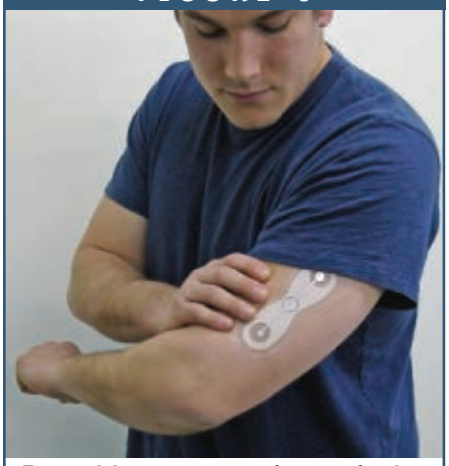
Active patch technologies open the door to larger molecules as well as hydrophilic molecules. Pre-treatments such as dermal ablation and chemical enhancers can be combined with active and passive transdermal patches to assist effectiveness; microneedles can be used as a pre-treatment or as the primary delivery mechanism.

Tapemark works on customer projects using many active transdermal drug delivery technologies, such as iontophoresis, microneedles, dermabrasion, and thermal poration. "In passive drug delivery patches, we have experience with both matrix and reservoir systems," explains Tom Yetter, Vice President of Research and Development for Tapemark. "Because we understand materials, we can identify appropriate materials based on cost, availability, and functionality." Additionally, Tapemark can cut and place electronics and power sources using robotics, and the contract manufacturer has experience in API metering and dispensing. "With our cadre of capable equipment, we offer scalability to work with clinical trial volumes as well as commercial launch volumes," says Mr. Yetter.

No matter the customer, Mr. Yetter says Tapemark is always aware of the how much the client wants to spend. "Because costs are a primary concern, it is important to identify and develop an integrated, one-operation process to manufacture the transdermal patch," he says. Precise patch and component dimensions are influenced by the converting equipment, and expensive materials dictate that Tapemark design for minimum waste, so manufacturability and ultimate cost-effectiveness are ensured by working with customers early in the design process. "We focus on process development, design for Six Sigma, critical quality elements, and more, all leading to improved manufacturability," he says.

Looking ahead, Mr. Yetter says that the transdermal market is driven by various factors; the loss of patent protection for blockbuster drugs is certainly a strong factor, as is the ability of transdermal delivery to avoid the first pass effects of oral drug delivery. "Obviously we see the market growing, with increased focus on active transdermal drug delivery technologies."

FIGURE 6



Tapemark is a contract manufacturer of active and passive transdermal patches.

SUMMARY

The transdermal drug market is growing more slowly than the overall pharmaceutical market, indicating a level of maturity and a lack of new approved products. New technologies may change this dynamic. While the most commonly used transdermal system is the skin patch, microneedle and needle-free technologies are also being explored. Transdermal, and even topical, technologies may be applied for several categories of pharmaceuticals used for the treatment of disorders of the skin or for systemic effect to treat diseases of other organs. Applications include hormone replacement therapy, contraception, insulin, management of pain, angina pectoris, smoking cessation, and neurological disorders such as Parkinson's disease. Technologies that deliver drugs with a broader spectrum of characteristics are poised to revolutionize the transdermal drug delivery market and drive significant growth.

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EXCIPIENT UPDATE

Reviewing Thaumatin's Pharmaceutical Applications

By: Sunita A. Chaudhary, MPharm; Tejal A. Mehta, MPharm, PhD

ABSTRACT

Thaumatin is natural sweetener first found as a mixture of protein obtained from a plant called Thaumatococcus deniellii. It is prepared from the seeds of the plant through various processes. It is 10,000 times sweeter than sucrose, thus it can be used in pharmaceutical formulations and other food items as a sweetener and flavoring agent in very less quantities to avoid the bitter after-taste of artificial sweeteners like sucralose and aspartame. It is a mixture of two types of proteins (thaumatin I and thaumatin II), making it useful as a sweetener and flavor enhancer for taste-masking certain bitter drugs.

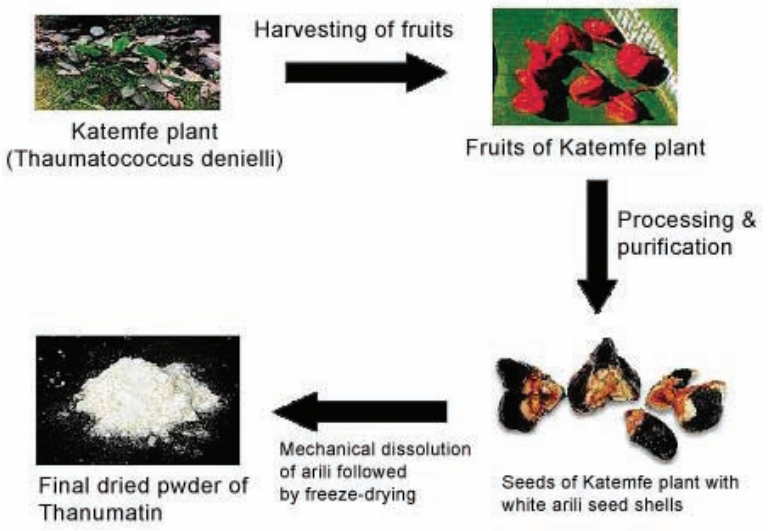
INTRODUCTION

Currently, there is an increasing amount of sweeteners available. Amongst them include natural sweet proteins, which are unique due to their natural occurrence. They have a high-sweetness potency compared to sugar, and decompose into a normal distribution of amino acids upon hydrolysis. Thaumatins were first found as a mixture of proteins isolated from the katemfe fruit of a West African plant (Thaumatococcus daniellii). Thaumatococcus actually means fruit of wonder, and daniellii pays tribute to Dr F.W. Daniell, who was the first person to discover scientific applications of the plant in the 19th century. To date, thaumatin is the only commercially available natural protein sweetener. This all-performance ingredient has many applications in a multitude of fields, particularly in taste modification and flavor enhancement. Thaumatin is a calorie-free protein used as a sweetener and flavor modifier. Some of the proteins in the thaumatin group are natural sweeteners approximately 2000 times more potent than sugar. It is highly water-soluble and stable in heating and acidic conditions and offers a very sweet taste rated to be 2,000 to 10,000 times sweeter than sucrose, depending on purity and concentration. This makes Thaumatin the sweetest known natural substance on earth. The purified extract from the fruit, that naturally contains the different forms of the protein, is collectively called Thaumatin.[1-5] The present review highlights the preparation, properties, and various applications of thaumatin in the formulation development of mouth-dissolving, immediate-release dosage forms.

PREPARATION OF THAUMATIN POWDER FROM PLANT[2-4]

As stated previously, thaumatin is prepared from the katemfe shrub, which is

FIGURE 1



Preparation of Thaumatin From *Thaumatococcus* daniellii Plant

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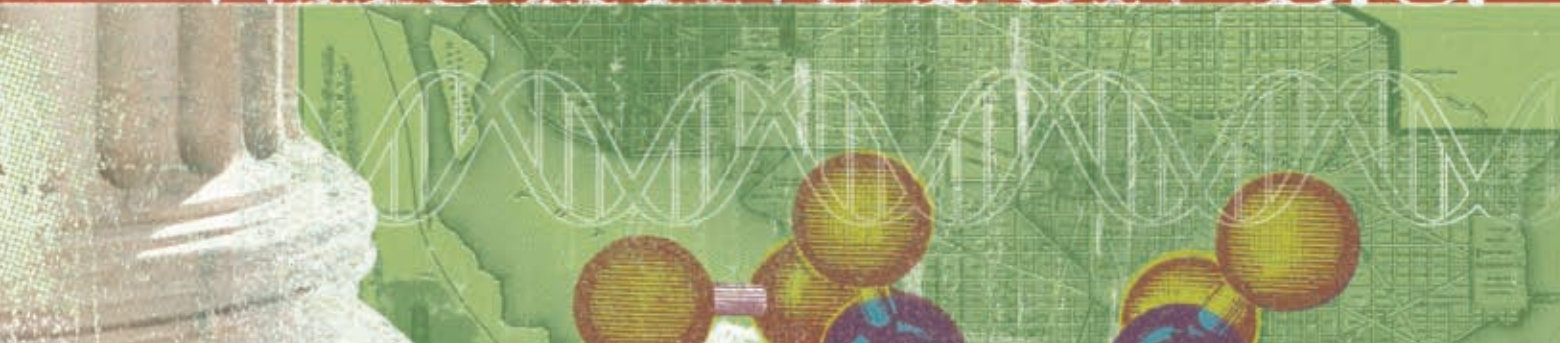


native to the African rain forest. Specifically, thaumatin proteins are obtained from the seed shells (called arili) of its fruits. Processing the plant material and purifying the protein requires a method with scale-up capability. Because the protein can easily dissolve in water, one of the methods includes the dissolution of the fiber parts containing thaumatin by mechanical movement to form the aqueous extraction. Currently, modified technologies are used to separate and extract additional materials at the same time via membrane filtration. The protein is then finally dried to make it ready for storage and transport. Various cleaning steps involved result in products that fully satisfy specific quality requirements. Preparation of thaumatin from the plant is shown in Figure 1.

CHEMISTRY OF THAUMATIN[7-10]

Thaumatin consists of two proteins, Thaumatin I and Thaumatin II. Their polypeptide chains consist of more than 200 amino acids, and their tertiary structures are stabilized by eight disulfide bridges that make them stable (Figure 2). Like other pathogenesis-related proteins, thaumatin is predicted to have a mainly beta structure, with a high content of beta-turns and little helix. The properties are listed in Table 1.

FUNCTIONAL PROPERTIES[5,6]

Thaumatin can be used as a sweetener, taste-modifier, or flavor enhancer, depending on the type of food and the application.

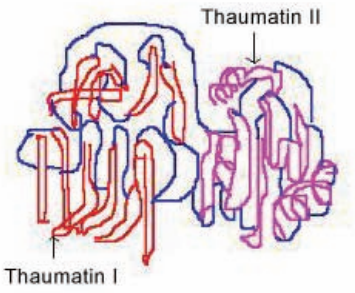
Sweeteners

Although not a sugar, thaumatin offers a very sweet taste and is rated to be 2,000 to 10,000 times sweeter than sugars (1 kg of thaumatin is equivalent in sweetness to 2 to 10 metric tons of sucrose, without the same calories). The taste is characterized by a short delay to the onset of the sweet taste, followed by a very long sweet taste in the mouth. Thaumatin is rarely used on its own, but is rather advantageously blended (0.5 to 2 ppm) with other intense sweeteners to obtain a well rounded and pleasant taste.

Flavor Enhancement

Thaumatin is effective in enhancing a wide range of flavor compounds due to its ability to reduce the aggressive nature of complex flavor compounds. It also provides the opportunity to achieve higher levels of flavor in products without being too aggressive (eg, in coffee-flavored products without generating bitter nodes). In dairy and snack products, enhancement is more complex. In addition to enhancing flavors, it also has a synergistic effect with naturally present or added flavor enhancers, such as 5' nucleotides and monosodium glutamate (MSG).

FIGURE 2



Structure of Thaumatin[11]

Taste-Masking

Thaumatin's masking effects, particularly of metallic or bitter tastes, are an important feature accounting for its widespread use in the human and animal food industries and with high-intensity sweeteners (in particular with saccharin). Thaumatin is particularly effective in masking the metallic aftertaste of saccharin, with this combination being used in a wide variety of products as well as pharmaceuitcals. In citrus fruit products, Thaumatin has shown to be very effective in masking the bitter taste-producing substances of natural flavors from the fruit. It is used in the pharmaceutical industry in antibiotics,

TABLE 1

Structure	Made of one single chain of 207 amino acids that differ from one another by only 5 amino-acids. It has presence of 8 disulfide bridges, which brings about complex 3D cross-linking that may be responsible for the heat- and pH-resistance of Thaumatin.
Composition	It contains a mixture thaumatin I and thaumatin II proteins. Both have similar properties, such as amino acid composition, sweetness profile, and identical amino acids sequence except that they differ from one another by only 5 amino-acid residues.
Molecular Weight	22,000 Daltons
Solubility	Very soluble in water, fairly soluble in ethanol/water mixtures, and insoluble in most common organic solvents.
Stability	Thaumatins as basic proteins are fairly stable. The stability of the protein is due to the presence of 8 disulfide bonds in the molecules. Thaumatin is heat and pH stable and has good stability in freeze-dried form up to 2 years when stored under cool and dry conditions. It is extremely stable to heat and pressure used in processes, such as UHT, pasturization, retorting, baking, and extrusion.
Function	Flavor enhancement, sugar replacement, bitter-masking, mouthfeel enhancement

Properties of Thaumatin

analgesics, antacids, cough syrups, common cold remedies, medicated gums, and pharmaceutical drugs. It acts as powerful masking agent to reduce bitterness and medicinal nodes, after-taste and bitterness of vitamin C, bitterness and astringency of vitamin B2 and B6, and caffeine bitter nodes. A good example of thaumatin's simultaneous action is to be found in applications with vitamin C, often flavored with citrus and sweetened with high-intensity sweeteners. Thaumatin is effective in masking the taste of some pharmaceutical products, such as chewable tablets and suspensions for pediatric use.

Synergism

A clear synergism is shown when using thaumatin in conjugation with highly intense sweeteners and/or flavors. For example, a commercial application has shown a sufficient synergistic effect between thaumatin and aspartame: a thaumatin inclusion of 10 parts per million allowed for a 30% reduction in aspartame to achieve the original sweetness level. In addition to the synergistic effects, thaumatin has also shown improvement in the sweetness profiles of non-nutritive sweeteners and masking the associated after-taste, as well as extending sweetness and flavor profiles. Although thaumatin is the most highly potent form of sweetners available, its use as the only source of sweetness is limited to applications in which the sweetness requirement is less than the equivalent of 10% of sucrose due to its liquorice-like after-taste at higher levels.

Formulation Additives

Thaumatin is used in chewing gum, toothpaste, and mouthwash to help improve and prolong their flavors and cooling effects. It is heat and pH-stable for 6 months and maintains its relation as a sweetner and flavoring agent when used at very low levels (2 to 3 ppm). It will increase the cooling effect of mint flavors, leaving a fresh, clean taste in the mouth. Thaumatin also masks the taste of anti-plaque agents, such as zinc citrate trihydrate. In mouthwashes, the mouthfeel is improved by giving the perception of more body or viscosity. It is tooth friendly, especially for children who are susceptible to tooth decay, as it does not lead to the production of cariogenic acids, which aid in the formation of plaque.

Thaumatin Cousins[12]

There are seven known sweet and taste-modifying stress-induced proteins of plants that have been found to be related to thaumatins, namely Brazzein, Monelin, Curculin, Mabinlin, Miraculin, and Pentadin.

SUMMARY

Thaumatins are novel, naturally occurring excipients from the Thaumatococcus deniellii plant, and exhibit a very high sweetning effect 10,000 times sweeter than current artificial sweeteners. Hence, they offer many significant benefits in pharmaceutical formulation development as lesser quantities are required, after-taste is avoided, and carciogenic effects are non-existent even after prolonged use.

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BIOGRAPHIES

Dr. Tejal A. Mehta is a Professor in the Department of Pharmaceutics, Nirma University. Dr. Mehta has 13 years of teaching and 7 years of research experience. She has 7 national and 14 international publications in her credit and has delivered lectures and authored a chapter in a multi-author book on novel drug delivery systems. She is a recipient of a best paper award in 2004 granted by the Association of Pharmaceutical Teachers of India for publishing a paper in the Indian Journal of Pharmaceutical Education.

Ms. Sunita A Chaudhary is a Lecturer in the Department of Pharmaceutics, Saraswati Institute of Pharmaceutical Sciences, Dhanap, Gandhinagar. She has 3 years of teaching experience and has 4 international publications to her credit. She is continuing her PhD at Nirma University under the guidance of Dr. Tejal A. Mehta.

Delivering Quality in Personal Dosimetry Devices

By: Erik Wittenzellner & Erik Berndt

Insulin pens and auto-injectors that allow patients to inject themselves are finding increasing acceptance among the patient population. The devices are subject to strict quality monitoring and government regulation. Maintaining high-quality and full compliance with regulations requires the use of automated testing systems that reduce operator influence and provide reproducible results at a low cost. Triggering force and time, ejection time and speed, as well as the length of the extended injection needle and other forces must be measured with great accuracy to ensure quality. Regulatory compliance may also require that test results be archived for review subsequent to the testing process.

INSULIN PENS

Diabetes represents a large and growing market in the United States, affecting more than 20 million Americans and growing at three times the rate of population growth. Treatment of diabetes involves diet, exercise, and regular doses of insulin, and approximately 4.2 million patients with diabetes use insulin. Traditional insulin delivery injection methods using hypodermic syringes face environmental and physical barriers to widespread use, especially by children or patients with physical challenges.

Pen injector devices containing insulin in prefilled cartridges have been designed to make injections easier and more flexible. Pen injectors eliminate the need for drawing up from an insulin vial. The dose is dialed up on a digital scale. The devices may be particularly useful for insulin administration away from home, at school, or on holiday. Pen injector devices are useful in children on multiple injection regimens or fixed mixtures of insulin but are less acceptable when free mixing of insulins is used.

In insulin therapy, the insulin is generally injected subcutaneously using prefilled syringes or insulin pens. These pens are similar to a ball-point pen and are filled with insulin cartridges. So-called disposable pens are discarded when the cartridges are empty, whereas reusable pens can be used repeatedly over years. The standard DIN EN ISO 11608,

FIGURE 1

The zwicki-Line Z0,5 TN testing machine with additional torsion drive measures various functions of the insulin pen, eg: dosage setting, triggering force, stroke, and dose, in a continuous process.

FIGURE 2

In the tests on the insulin pens, the specimens are fed automatically via the "roboTest R" handling system.

Parts 1 to 3, is used in quality assurance testing for insulin pens and cartridges.

Special pen injection needles of small size are available and may cause less discomfort upon injection. Pen injectors of various sizes and types are available from several pharmaceutical companies, including Eli Lilly & Co. Eli Lilly offers the Humalog® KwikPen™, a reusable pen that may be refilled with disposable insulin cartridges. The KwikPen device uses a prefilled cartridge and is available for one-time use. Lilly has other products (HumaPen LUXURA®, HumaPen® MEMOIR™) that are reusable. Some patients prefer the convenience of the disposable pen while the reusable pen is available for patients who reside in countries with reimbursement systems that are set up to support reusable devices.

Testing plays an integral role in bringing insulin pens and autoinjecters to market and ensuring quality in the manufacturing process, according to Mike Roe, Senior Engineering Consultant, Delivery Devices Research & Development at Eli Lilly& Co.

"We run a number of different tests on these devices - from evaluating the close actuation force and the cap removal force to determining twisting forces that the patient will apply to the device in usage," he said.

Zwick has introduced a testing system based on a zwicki-Line Z0,5 TN (Fmax 0.5 kN) table-top testing machine with additional torsion drive (Fmax 2 kN) for automated testing of insulin pens.

"We use a torsional system from Zwick USA to evaluate twisting forces," Mr. Roe added. "The outcomes of these tests help us with development work in the areas in which patients interface with our pens."

This system also permits various functions of the insulin pen, eg; dosage setting, triggering force, stroke, and administered dose, to be measured in a continuous process.

"We also conduct tests that support our evaluation of processes in manufacturing, such as the determination of gliding forces and measuring sealability of the device - where we look at preventing leakages," said Mr. Roe.

The test methods of the two test axis can be modified and combined as desired. Specimens are fed in automatically via the "roboTest R" handling system. The insulin pens are fed into the testing machine from the associated magazine (capacity up to 50 specimens) with the aid of the autoEdition2 automation software.

Automatic feeding and testing eliminates concerns about operator influence upon the test results. The higher specimen throughput rate makes the test process considerably more efficient. Manual tests can also be performed at any time.

AUTO-INJECTORS

Auto-injectors are similar in design to insulin pens; however, there is no dosing, and fluid injection is always triggered automatically by a spring when

the injector is pressed into place. A typical application example is the acute treatment of anaphylactic shock in allergy sufferers. Automatic injection devices are useful for children who have a fear of needles. Usually, a loaded syringe is placed within the device, locked into place, and inserted automatically into the skin by a spring-loaded system. Among the benefits of auto-injectors is the needle is hidden from view and inserted rapidly through the skin. Automatic injection devices for specific insulin pen injectors are now available.

Military forces and emergency response teams are also issued special auto-injectors that can deliver drugs, such as morphine and atropine. These devices are subjected to different environmental conditions due to the global theaters of operations in which they might be used. The quality of the devices in use and those in long-term storage must be checked regularly.

High-performance quality monitoring, which also includes the testing of these products according to the federal and state pharmaceutical and technical rules, is intended to optimize functional reliability and safety as well as supply management.

Measurements of the triggering time and the ejection duration for the active ingredient solution previously could only be made manually.

The market and regulatory environment required a testing machine for automatic determination of the triggering force, triggering time, ejection time/speed, active ingredient profile, and length of the extended injection needle. Testing on two-chamber auto-injectors should also be possible. A testing machine from the zwicki-Line with a special specimen grip and a carousel to accommodate the active ingredient was developed to achieve this goal. This carousel is used for testing two-chamber auto-injectors.

After triggering of the injector and collection, the mixture ratio or "ejection profile" over time can be evaluated. The key parameters, such as the triggering time, ejection time, and the length of the extended needle, are measured using two lasers.

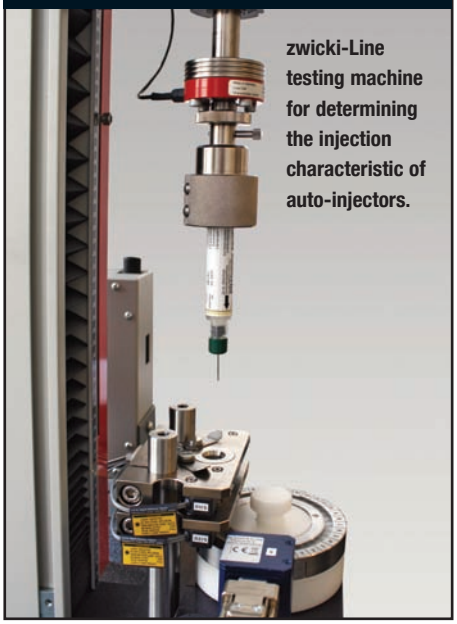
MAINTAINING RECORDS

Production of pens and auto-injection devices requires compliance with regulations, such as FDA 21 CFR Part 11 and Annex 11 of the EU GMP directive when using electronic recordings and signatures in the regulated environment.

"We operate with GMP standards and with good lab practice standards," said Mr. Roe.

Practically speaking, Part 11 requires drug makers and medical device manufacturers, biotech companies, and other FDA-regulated industries to implement controls, including audits, system validations, audit trails, electronic signatures, and documentation for software and systems involved in processing electronic data that are required to be maintained by the FDA predicate rules or used to demonstrate compliance to a predicate rule.

FIGURE 3



zwicki-Line testing machine for determining the injection characteristic of auto-injectors.

"Testing helps us evaluate quality and ensure consistent delivery from one manufacturing site to another. The manner in which the software organizes data and aids with statistical analysis is helpful to us in complying with regulation," explained Mr. Roe.

Zwick offers a solution for maintaining full compliance with FDA 21 CFR Part 11 during the design and test of auto-injection devices with its testXpert® II testing software. The Expanded Traceability option offers all tools required to fulfill the requirements set forth by the FDA in 21 CFR Part 11 in combination with organizational measures and procedure instructions in the

respective company.

The Electronic Records function permits complete, tamper-proof documentation of all actions and modifications performed in testXpert II. The user defines the degree of actions to be logged and justified according to his specifications, which can originate from his QM manual or external requirements. In a specific case, this could involve recording every change in a parameter relevant to testing, eg, the test speed, in its entirety in an audit trail.

The Electronic Signatures function permit the assumption of responsibility to be documented and simultaneously allow the conversion to a paperless laboratory as the signature on a document can be replaced with a digital signature of the test series by means of entering the user ID and password in testXpert II.

"Electronic record-keeping is of great importance to us," said Mr. Roe. "The software for Zwick systems has a traceability function that enables one to easily determine who was logged on, what tests were conducted, and what data was generated. It is comparable to the black box in commercial aircraft in that it provides a complete record of what occurred from the moment a user logs on to when they log off."

The software also offers the ability to control access to the system. Various levels of logins are possible that enable the completion of different functions. This is helpful when a range of personnel, such as engineers, technicians, and lab managers, may each have a need to use the system and have varying requirements for usage.

Zwick additionally offers a qualification service package (DQ/IQ/OQ) to assist with validation, the key component of which is the technical verifiability of individual systems and devices.

Zwick assists its customers in the qualification of materials testing systems in individual steps in the form of comprehensive, individually adapted qualification documentation according to the GAMP® guide and currently valid guidelines, as well as in the practical implementation on location.

"With Zwick systems, there is no programming involved in setting up the test that you want to run. The software also has existing routines set up for statistical analysis, which makes the volumes that we are handling manageable," said Mr. Roe.

"Eli Lilly started using Zwick testing equipment in 2002 and now has a large number of systems installed around the world. When we are developing new testing protocols, it is invaluable to us to be able to employ the same root program globally and know that we will get consistent results because the testing platforms are consistent and reliable. This greatly simplifies validation of manufacturing processes from site to site. ◆

BIOGRAPHIES

Erik Wittenzellner is a Senior Applications Engineer for Zwick USA. Applying deep skills in the support of test system control electronics, Mr. Wittenzellner works in concert with customers to develop novel test procedures for a wide range of medical applications. He has been integral to concept development for fixtures that support torsional testing of insulin pens. Understanding the importance of applying built-in platform flexibilities, Mr. Wittenzellner frequently lends his expertise in testflow development to address the unique needs of individual customers.

Erik Berndt is the Industry Manager - Medical for Zwick/Roell AG and Head of the company's Competence Center for the Medical Industry. A Mechanical Engineer as well as a Textile Engineer, Mr. Berndt was previously in research & development for Paul Hartmann AG, a premier provider of medical textile products for wound care, surgical and healthcare applications, and patient diagnostics. Prior to his role at Paul Hartmann AG, Mr. Berndt was the Head of Research - Medical Textiles/Biomaterials at ITA, RWTH Aachen University in Aachen, Germany.

NANO-SUSPENSION FORMULATIONS

Adaptive Focused Acoustics for the Formulation of Suspensions & Nano-Suspensions

By: Srikanth Kakumanu, PhD, and James Bernhard

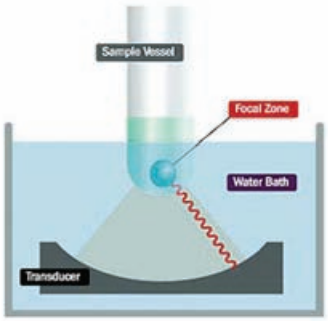
INTRODUCTION

The majority (~90%) of new chemical entities (NCEs) discovered by the pharmaceutical industry today are poorly soluble or lipophilic compounds; as are about 40% of existing drugs in the market.[1,2] Consequently, this can create major challenges in drug development due to poor solubility, short biological half-life, poor bioavailability, prominent adverse effects, and stability of NCE's. Therefore, to evaluate these compounds at the preclinical stage, the compound is often dosed orally as an aqueous-based suspension, as a solution formulation may not easily be obtained without either toxic levels of excipients and/or considerable resources (i.e., impractical at an early stage when evaluating a high number of compounds). A potential downside to this approach is that dosing a suspension may have detrimental in vivo consequences such as decreased bioavailability and higher inter-subject variability when compared to dosing a solution formulation. A possible technique to mitigate this risk is reduction of the suspension's particle size. However, there are few currently available methods to quickly reduce particle size across a range of sample volumes without introduction of potential contaminants due to the use of a reusable probe or degrading the API due to excessive heating. A novel technology, Adaptive Focused Acoustics™ (AFA™) (developed by Covaris Inc., Woburn, MA, USA) has been used to successfully reduce particle size in a controlled manner to make uniform suspensions with low micron or nano-scale particle sizes. This article describes how this controlled and broadly applicable technique is a scalable process that is more suitable over current methods at producing reduced particle size suspensions for achieving improved bioavailability and less variability in exposures.

CURRENT PROCESSES & LIMITATIONS

Micronization is employed to help address the low solubility issue by improving dissolution rate and its consequent bioavailability.[3] The typical processes to formulate a simple suspension for preclinical oral dosing are sonication, homogenization, microfluidizers, stirring, and/or the use of excipients, such as the addition of surfactant wetting agents and polymers to promote homogeneity. A basic sonication bath can produce inconsistent results due to the unfocused and random nature of the sonic waves. These baths are limited in the peak power density achievable, and typically have "hot or cold spots." Additionally, temperature-sensitive compounds are subject to heating in this process due to the need for high overall energy input to achieve the desired micronization effect. Mechanical homogenization is not ideal for small-scale volumes when compound is limited. It also promotes foaming in the formulation and makes cross-contamination a possibility. Additionally, operator to operator variability may be introduced. Like sonication, it can cause heating of temperature-sensitive compounds when used at higher intensity or for a significant amount of time. Microfluidizers produce very large

FIGURE 1



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What do you *really* know about end-users of drug delivery technologies?

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amounts of heat and enable cross-contamination in the processing chamber. The sample must be cooled with a heat exchanger after processing. Additionally, the sample frequently must be passed through the system multiple times, and it is not uncommon to lose material in the process. Compounds may also be milled prior to formulation as an additional micronization step. This adds more time to the process and introduces loss of yield from the additional step. These techniques have issues, such as a broad size distribution in the drug particle produced, thermal degradation of the material, and contamination.

Wet milling, high-pressure homogenization, and microfluidizers are also used to produce nano-suspensions in-situ. The additional energy required in these processes exacerbates the issues mentioned above. Development of a proper formulation to stabilize the nano-suspension may be required. Limitations of these techniques related to the need for cleaning to avoid cross-contamination and/or a larger minimum volume needed to process material make it difficult to directly generate in-situ nano-suspensions with reasonable throughput for testing multiple iterations of formulations at a small scale.

ADAPTIVE FOCUSED ACOUSTICS: PROCESSING & INSTRUMENTS

A more effective and versatile technique applicable to making suspension formulations of drugs with limited aqueous solubility is needed that overcomes all these limitations. A broadly based technology applicable to this class of molecule could have a tremendous impact on discovery effectiveness.[4] The Covaris AFA technology is a self-contained, scalable, isothermal, and controllable process which is applied to generating reduced particle size suspensions of narrow distribution without degrading materials or allowing cross-contamination, and achieves 100% material recovery.

TABLE 1

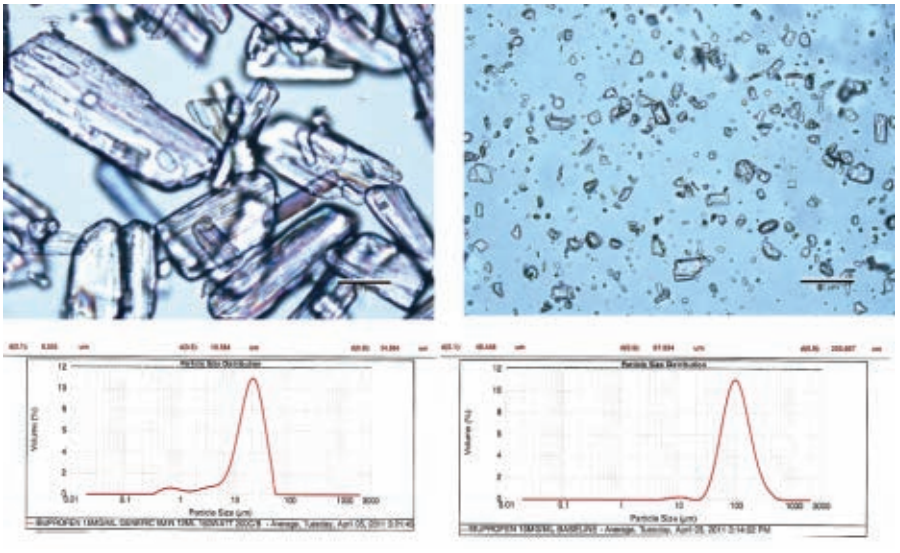
Parameters	Ibuprofen (microns)	Cinnarizine (microns)	Indomethacin (microns)	Griseofulvin (microns)
Baseline	203.67	149.17	239.88	44.45
2 ml, 5 min	12.55	37.29	20.88	16.86
12 ml, 5 min	33.35	41.73	38.32	31.45
18 ml, 10 min	39.53	43.00	28.73	31.01

d90, Particle Size 15 mg/ml

The Covaris AFA technology evolved from therapeutic lithotripsy (such as kidney stone treatment) and diagnostic imaging. The instruments developed by Covaris that incorporate AFA have wide-ranging applications from chemical compound management, DNA shearing for next generation sequencing methods, tissue disruption/homogenization, and formulation preparation. AFA works by sending convergent, high frequency, high intensity acoustic energy waves from a dish-shaped transducer (Figure 1). AFA is a form of mechanical energy. As acoustic/mechanical energy transfers through the sample, the material undergoes compression and rarefaction (expansion). At high intensity with fluid samples, this is typically embodied as cavitation events. Cavitation is the formation and subsequent collapse of bubbles. The acoustic energy applied to a sample causes bubbles to form from the naturally occurring dissolved gases and vapors of biological specimens and chemical fluids. When the energy is then removed, the bubble collapses. As the bubbles collapses, an intense, localized jet of solute (typically water) is created. This jet travels over a very short distance but at a very high velocity (> 100 m/sec). As the number of bubbles is extremely high, the convergent energy density is very high, and the time interval is short (micro seconds), the consequent mixing (acoustic streaming) and/or disruption power capability of the process is substantial. A key point is the precise, reproducible control that is obtainable with the Covaris instrument systems utilizing AFA.

Similar to Covaris AFA, sonication is

FIGURE 2



Before and after (50 x magnification with a 50-micron scale bar) processing of 15-mg/ml Ibuprofen at 12-ml scale.

TABLE 2

Parameters	Ibuprofen (1 mg/ml) (microns)	Ibuprofen (15 mg/ml) (microns)	Ibuprofen (100 mg/ml) (microns)
Baseline	203.67	203.67	203.67
2 ml, 5 min	12.55	19.03	29.54
12 ml, 5 min	33.35	34.88	37.78
18 ml, 10 min	39.53	34.04	35.53

Ibuprofen d90, Particle Size as a Function of Concentration

also an acoustic-based process. It has been used for a number of years in the life sciences industry; however, it is intrinsically distinct from AFA for a number of reasons. One key to the difference lies in the operating wavelength of each system. Sonication has a wavelength of 10's of centimeters. This results in unfocused energy scattering, reflecting, and in many instances producing "hot spots", which may readily damage some biological or chemical samples. By contrast, AFA wavelengths are short and focusable. This allows AFA to be both focused to a localized area of the sample and to be very efficient. For example, to achieve the identical internal pressure field in a sample, only 0.5 Watts of energy are required from a Covaris system, whereas over 80 Watts would be required from a sonicator system.

MATERIALS & EQUIPMENT

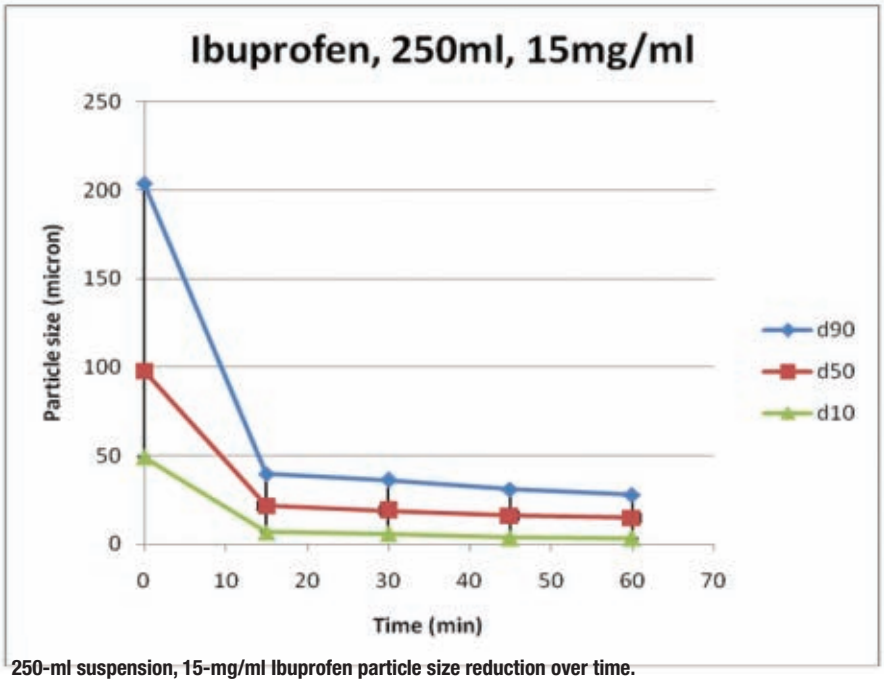
Processing Equipment

- Covaris SF220 High Performance Formulation Processing System
- Parameters are controllable. Parameters for all processes mentioned: 300PIP, 50DF, 200C/B
- Net 150 Watts of power.

Particle Size Instrumentaion

- Nano particle range (Malvern Zetasizer Nano ZS-90)
- Micron particle range (Malvern Mastersizer 2000)

FIGURE 3



250-ml suspension, 15-mg/ml Ibuprofen particle size reduction over time.

Materials

- Ibuprofen, Indomethacin, and Cinnarizine are from Spectrum Chemicals.
- Griseofulvin from MP Bio
- Sodium Lauryl Sulfate (SLS) from Fisher Scientific
- Methyl Cellulose (MC) from Sigma Aldrich
- Water, deionized and purified by a Barnstead water purification system

RESULTS & DISCUSSION

Suspension formulations with particle size reduction from a controlled, broadly applicable technique are essential to achieving reproducible, high quality pharmacokinetic data at the preclinical stage. In these experiments, we demonstrate the ability for rapid particle size reduction in a generic suspension vehicle (0.5% methyl cellulose, 0.1% sodium lauryl sulfate) to a d(90) below 40 µm for Ibuprofen, Cinnarizine, Indomethacin, and Griseofulvin at 15 mg/ml. Ibuprofen concentration was then varied to demonstrate consistent results at 1mg/ml, 15 mg/ml, and 100 mg/ml. All of this was accomplished at three fixed volumes of 2 ml, 12 ml, and 18 ml, which were chosen to encompass the volumes needed for early PK rodent dosing experiments. We then scaled up Ibuprofen to a homogenous 250-ml suspension to demonstrate the scalability of using a flow cell without changing the mechanical attributes of the particle size reduction process.

Many new drug candidates originating from discovery programs are water insoluble with poor bioavailability, often leading to abandoning drug development efforts. The science of nano-suspensions is increasing the number of drug candidates that can be evaluated. Nano sized drug particles have a faster dissolution rate which can lead to faster

or greater absorption. It is an effective and broadly applicable approach that goes beyond addressing water insolubility. Nano-particles can be used in tissue or cell specific targeting, have longer blood circulation capacity, greater stability against enzymatic degradation, and allow for the reduction of unwanted side effects.[5] AFA was demonstrated to be highly effective at creating nano-suspensions, which will directly translate to an increase in the percentage of drug candidates viable for testing. In this experiment, a suspension vehicle (0.1% sodium lauryl sulfate, 0.025% methyl cellulose) was used with a 5-mg/ml concentration of API processed in a 2-ml vial for Ibuprofen, Cinnarizine, Indomethacin, and Griseofulvin. We demonstrate the ability to make low nanometer range suspensions by extending the processing times to 15 minutes. We then scaled up Cinnarizine to 250 ml to demonstrate the scalability of using a flow cell for nano-suspension generation without changing the mechanical attributes of the particle size reduction process.

Process Results (2-ml, 12-ml, 18-ml Batches)

The base line starting d(90) particle size for Ibuprofen is 203.667 µm with 97% of the particles above 40 µm. The samples were then processed for 5 minutes at 150 Watts under AFA. A 2-ml vial (1-mg/ml concentration) produced a d(90) population below 12.554 µm and 100% particles below 20 µm. A 12-ml vial (1-mg/ml concentration) produced 33.353 µm (d90), and 97% of the particles are below 40 µm. In the case of an 18-ml vial, it took 10 minutes for 97% of the particles to get to below 40 µm. Concentrations were increased to both 15 mg/ml and 100 mg/ml of Ibuprofen; in 5 minutes of processing, the d(90) was below 40 µm for the 2-ml and 12-ml vials, and with 10 minutes processing, the 18-ml vials had d(90) populations below 40 µm. These results were repeated for both Indomethacin and Cinnarizine at 15 mg/ml, with slight variations in size distributions. In the case of Griseofulvin at 15 mg/ml, the starting d(90) particle size was approximately 40 µm. The d(90) particle size was brought below 20 µm in 5 minutes for the 2-ml and 12-ml vials, and 10 minutes for the 18-ml vial. The particle size results for the four compounds at 15 mg/ml are listed in Table 1. Table 2 lists the particle sizes for Ibuprofen at 1 mg/ml, 15 mg/ml, and 100 mg/ml. Figure 2 illustrates before and after processing of 15-mg/ml Ibuprofen at the 12-ml volume.

TABLE 3

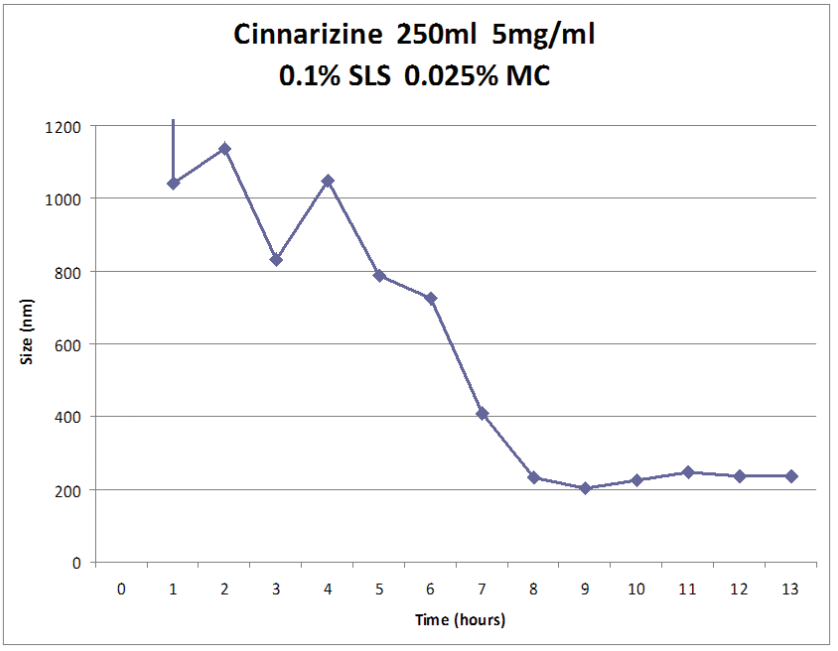
Parameters	Ibuprofen	Cinnarizine	Indomethacin	Griseofulvin
Baseline	203.67 microns	149.17 microns	239.88 microns	44.45 microns
15 minutes	110 nm	280 nm	127.4 nm	100 nm
30 minutes	97 nm	56.85 nm	20 nm	90 nm

2-ml Nano-suspension, Average Particle Size 5 mg/ml

Generic Scale-Up for Ibuprofen: 250-ml Batch

The base line particle size of the Ibuprofen is d(90) 203.667 µm and d(50) 97.834 µm, and almost 95% of the particles are above 40 µm. Scaling up to a volume of 250 ml at a flow rate of 30 ml/min at 15 minutes produced 90% of the particles below 40 µm; d(90) 39.726 µm, d(50) 21.701 µm, and d(10) 6.805 µm. At 30 minutes, 93.57% of the population are below 40 µm; d(90) 36.328 µm, d(50) 19.055 µm, and d(10) 6.023 µm. At 45 minutes, 98.31% of the population are below 40 µm; d(90) 31.091 µm, d(50) 16.167 µm, and d(10) 3.583 µm. At 60 minutes, 99.39%% of the particles are below 40 µm; d(90) 28.005 µm, d(50) 14.843 µm, and d(10) 3.351 µm. Therefore, assuming a linear conversion ratio where 2 ml is scaled up to 250 ml, it should take 10.41 hours to attain < 40-µm particles. In practice, it required 15 minutes to achieve the desired result, thus demonstrating a favorable scaling factor over 40 times more efficient when processing the higher volume of material. Figure 3 illustrates this particle size reduction over time. Homogeneity and stability was demonstrated by sampling from the 250-ml suspension at the top, middle, and bottom

FIGURE 4



250-ml nano-suspension, 15-mg/ml Cinnarizine particle size reduction over time.

depths. The suspension aliquots were analyzed by HPLC using a stability-indicating method as a guide.[6] At the first measured time point of only 15 minutes, the samples showed that the suspension was homogenous, having a relative standard deviation of only 0.40%. This was maintained through 60 minutes, where the samples had an RSD of 0.38%. The Ibuprofen was chemically stable, showing no impurity growth over the 60 minutes of processing.

Nano-Suspension Process Results (2-ml Batches)

In 15 minutes, nano-suspensions were generated with an average particle size ranging from 100 - 280 nm and at 30 minutes, a range of 20 - 97 nm was achieved. Results are listed in Table 3. The SF220 enables generation of nano-particles and the practical screening of potential formulations to stabilize them in the same step at small scale without the uncontrolled heating, sample loss, and/or higher volume requirement of other nano-suspension generation techniques. This saves time and eliminates compound waste.

Nano-Suspension Scale-Up for Cinnarizine (250-ml Batch)

Following 1 hour of processing, a 250-ml suspension (which started at 200 µm), a 1-µm particle size was achieved, and by 9 hours, it stabilized at approximately 200 nm. The suspension vehicle used was 0.1% sodium lauryl sulfate, 0.025% methyl cellulose in water. The surfactant concentration was significantly below the CMC range. Figure 4 illustrates this particle size reduction over time.

CONCLUSION

Adaptive Focused Acoustics (AFA) technology enables an instrument that capably and effectively results in reproducible suspension formulations at both the micron and nono-scale size range. Routine, high throughput preclinical formulation efforts aimed at screening early stage compounds in PK studies can thus be completed in a self-contained, controlled, and partially automated fashion. In this area of preclinical formulation, use of the Covaris SF220 system will improve the overall quality of experiments by reducing formulation preparation errors and dosing variability, while offering rapid, standardized protocols to reduce particle size. Formulation development is enhanced with a novel tool that allows for faster results with less material that is scalable.

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BIOGRAPHIES

Dr. Srikanth Kakumanu earned his PhD from the Department of Biomedical Engineering and Biotechnology at University of Massachusetts in 2010. Since June, 2010 he has been working as Research Scientist at Covaris Incorporated, where he heads the research in the application of Adaptive Focused Acoustics in formulations (Dissolution, Micronization, Nano-suspension and Liposome production) and Cell lysis. His major focus of research is scaling the AFA process to pilot scale and continuous flow sample volumes.

James Bernhard is a Senior Scientific Associate in Pharmaceutical Development at Vertex Pharmaceuticals in Cambridge, MA. He is a member of Pharmaceutical Chemistry in the Materials Discovery and Characterization group. His areas of research include solid form discovery and selection as well as formulation development at the preclinical stage. He also is focused on both developing and implementing new technologies for materials processing.

RCM

IMPLEMENTATION

A Guide to Revenue Contract Management System Implementations: Avoid the Pitfalls & Optimize Your Opportunities

By: James Burke, Vice President, Revenue Contract Management & Richard Butler, Managing Consultant

INTRODUCTION

A multitude of business drivers are leading Life Sciences companies to evaluate and implement Revenue Contract Management (RCM) solutions. These include the need to ensure compliance in an ever-changing regulatory landscape, a systematic approach to commercial and government contract administration, and the need for business intelligence required to effectively evaluate and implement innovative contracting strategies. Historically, the RCM system landscape consisted of a variety of systems/modules that were challenging to integrate. In today's environment, contracting software suites are available on the market that bring together all of the pieces required to proactively monitor contract performance, enabling superior decision-making, yielding competitive advantage. Regardless of whether you have, are, or will be implementing an integrated RCM solution, there are critical success factors that should be made part of your implementation strategy to meet these needs and achieve your business objectives.

When establishing an implementation strategy, there are various questions that will drive your implementation strategy. Some include: What business areas and corresponding modules drive the quickest path to ROI or compliance? What resources will this demand from your organization? How will that impact your operations? What is your current systems landscape? These questions are very individualized, and the answers unique to each project will establish the high level schedule and plan for the overall project. While these strategic questions are important for setting the overall tone for the project, there are other tactical elements that if not addressed early, can lead to delays and cost overruns later in the project. In the following sections, we'll highlight some of these elements, which if not addressed early, can add risk to an already complicated project. In addition to avoiding risk, addressing these elements early and with proper diligence will create opportunity to expand the value proposition presented by the implementation of an integrated RCM solution suite.

ENSURING CLEAR EXPECTATIONS FOR DELIVERABLES

One of the leading causes of ongoing delays within a project is prolonged review cycles for deliverables. The cause of these delays typically have nothing to do with the content of the deliverables themselves, but are instead caused by a lack of clarity surrounding what to expect during each phase of the project. Because integrating a RCM system typically involves primarily configuration of off-the-shelf software, the project typically follows a system development lifecycle that is somewhat different than the traditional custom development lifecycle (SDLC). For example, when working with an off-the-shelf package, the role of the requirements document is considerably different, as there already exists a baseline of functionality to be delivered. Similarly, the design specification needs to focus on a comprehensive inventory of switches and parameters that will affect the functionality of the application.

One element that is consistent from a traditional SDLC to a packaged software approach is traceability. Although the style of content and level of detail may be different, it is still critical to ensure that each requirement gets addressed via a design element, and consequently is verified through the successful execution of a test script. In order to ensure traceability is carefully managed, a database-driven approach to managing requirements, such as the one illustrated in

Figure 1, is extremely valuable.

Regardless of the method used to manage requirements traceability, the structure and linkages that they conceptually represent are critical for all document reviewers to understand at the inception of a project. To avoid potential confusion and long review cycles during the project, it is always best to:

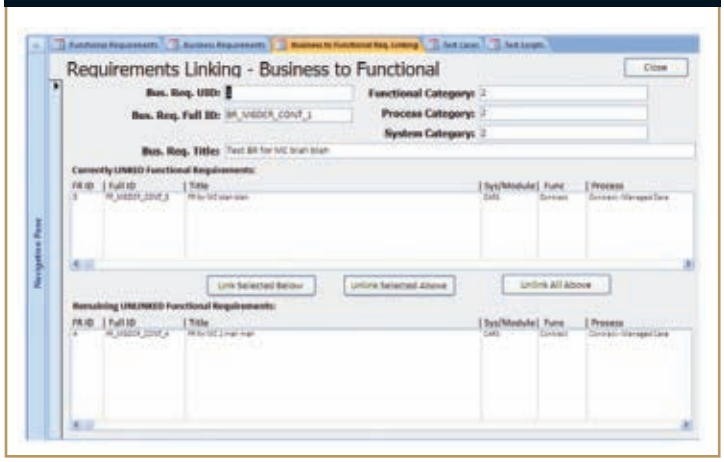
- Review the complete list of deliverables, highlighting the traceability links between each document.
- Provide templates of each of the key deliverable documents to allow users to familiarize themselves with the format and flow of the document.
- Provide examples of the expected level of detail within each document.
- Illustrate the complete lifecycle with a handful of sample requirements, showing how the evolution of those requirements would be represented in each of the key deliverables.

By taking these key steps early in the project, the deliverable review cycles are typically shortened. If not undertaken early, the activities will still be required - but will occur at various points throughout the project, potentially repeatedly, and will often result in project delays.

IDENTIFYING CHANGE MANAGEMENT NEEDS

The implementation of new technology is often the key focus, if not the only focus of many organization's change initiatives. To be truly successful, however, initiatives must recognize and incorporate additional elements to realize business benefits promised by the technology platform. These elements, consisting of strategic alignment, organizational evaluation/redesign, and business process transformation are typically grouped under the common heading of Change Management. The degree and rate of change that your organization can successfully absorb must be carefully managed. Identifying this throughout the project lifecycle can be a workstream in and of itself. Some manufacturers have chosen to do just that and create a sub-project, or third-party team, to manage this crucial aspect of implementation. Framing and tracking change as it relates to people, processes, and technology can provide senior management a dashboard and detailed view of gaps and challenges as they are identified. This approach facilitates a proactive model versus reactive where you begin to address the issues in the latter stages of the project when it may be too late or the effort and cost to do so has grown substantially. The time to course-correct your implementation strategy is along the way, not after you've deployed.

FIGURE 1



DEFINING THE DATA MIGRATION STRATEGY

Too often, the data migration strategy is phrased in all-encompassing terms, such as "convert everything" or "clean-slate approach." Converting data is often a costly proposition, and the results achieved often fail to meet expectations. Therefore, preparing a comprehensive data conversion strategy involves examining every sub-element of data that has the potential to be converted. During this examination, the focus needs to remain on the intended use of the data; will it be used for actual transactional processing, or just for reporting purposes? To determine if the effort and cost of converting the data justifies the benefits, several dimensions of that cost need to be considered:

- **Converting** – The actual translation between data structures
- **Cleansing** – Removing unused or inappropriate data entries from the data to be converted
- **Completing** – Identifying "fill-in" values for fields and elements that were not tracked in the legacy system
- **Compensating** – Finding ways to store data that will not be converted over completely but cannot be lost

Often times, project teams fail to address these questions until the actual data migration activities have commenced. At that point, the project schedule is often rushed, or the team examining the data migration plan represents a subset of issues. In either scenario, the question of data migration strategy can end up addressing the needs of only a subset of people, or result in a costly investment of time and dollars into converting data that will never be used.

ESTABLISHING A DETAILED TEST PLAN

Testing of a configured custom off-the-shelf (COTS) system should be managed differently from a custom developed system, although your functional requirements will still translate into Test cases that should outline realistic aspects of your business operations. You will find that your functional requirements will be a blend of out-of-the-box (OOTB) functionality, blended with specific processes in which the system was configured to support them. Focus on flexing your specific business processes end-to-end regardless of whether it is OOTB, configured, or customized. This approach is critical to finalize the circle of traceability from your business requirements to functional requirements to test cases to test scripts/iterations.

The gaps found in most test plans that have gone awry are not found within the content of the test cases themselves. Rather, the greatest risk area when developing the test plan lies not in what will be tested, but how it will be tested. To truly have a successful test plan, it must address key questions that go beyond the scope of scripts:

FIGURE 2

- Who will test? - Know who your test team is, and what they will need in terms of education and access.

- Where will they test? - Ensure the hardware/software environment is strictly controlled and segregated from active development.

- What will they test? - A testing plan must be fully load-balanced between team members before you can be confident in the make-up of your team.

- When will they test? - Understand the sequence of the scripts within a typical business scenario and use that to schedule execution and interim refresh and reload activities.

- How will they handle errors? - A clear and well-understood procedure for reporting errors will not only prevent chaos among the testing team, it will be an invaluable source of statistics for project sponsors.

When projects are being planned, the amount of time being allocated for testing is often well below what would otherwise be desired or recommended. To make matters worse, these timelines are often condensed during project execution to make up for lost time. Only through a detailed and comprehensive test plan can you prevent this stage of your project from descending into chaos.

CUTOVER PLANNING

Although often represented by a single-day milestone on a project plan, the process of going live is never a simple "flip-of-the-switch" activity. There are several activities that need to be coordinated and executed within a specific sequence. Timing of the initial data load, when to establish the first run of the interfaces, when the first financial transactions will run - these are all "mini-milestones" that fall within a multi-day plan leading to the point where you claim success. When developing this plan, there are several considerations that your organization needs to take into consideration:

- What is the tolerance for downtime?

- Can or should parallel processing be leveraged?

- What important cutoff dates exist and how would they figure into this plan?

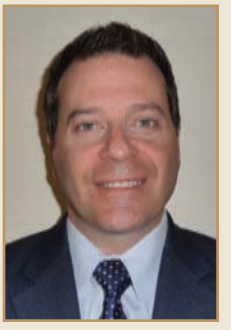
- What is the contingency/rollback plan?

One important consideration when developing a cutover plan is the involvement of stakeholders from both inside and outside of the organization. Even if their interaction with your group is not changing, understanding in advance why things could potentially be delayed or have problems during the go-live period is far better than "surprising" your customers. Ideally, all stakeholders should be well aware of your plans from far earlier in your project lifecycle. A strong communications plan provides the foundation for this awareness by the identification of all stakeholders and how they will impact, or are impacted by the project. Identifying the key groups that provide inputs and consume outputs of your process can help you leverage these organizations and customers as partners in the testing process. Understanding their needs can provide innovative ways for you to transform how you serve them, making them a partner in change management activities. By closely partnering with them, they will be prepared to work with you throughout the go-live process and be there to congratulate you when you bring it to a successful conclusion.

Implementation of any enterprise system can be a minefield fraught with danger. Like any risky proposition, the only way to succeed is through careful planning and analysis up-front. By taking the time early in the process to establish a disciplined, informed, and forward-thinking implementation approach to the key areas discussed in this article, you can mitigate the associated risks and deliver a successful solution that ultimately meets your financial and business objectives.

BIOGRAPHIES

Jim Burke is VP of Revenue Contract Management Solutions for ALSCG. Mr. Burke joined Alliance in 2004, bringing with him an extensive background of over 8 years in contract management, including experience from contract management systems implementation projects at over 10 life sciences companies. Since joining, he has expanded the Contract Management practice to virtually all of Alliance's pharmaceutical clients, with projects ranging from managed support initiatives to custom solution development and business intelligence projects. Prior to joining Alliance, he was a Director in iMANY's Professional Services organization.



Richard Butler is a Managing Consultant of Contract Management Solutions for ALSCG. Mr. Butler has almost 20 years of experience implementing enterprise solutions, including Contract & Revenue Management, Contract Lifecycle Management, Sales & Marketing, Master Data, and Reporting & Analytics systems. His strengths focus on delivery assurance and management of these solutions acting as a value driven, trusted advisor to our clients.

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ADHESIVE TECHNOLOGIES

Advanced Adhesive Technologies Deliver Enhanced Performance Capabilities to Transdermal Product Designs

By: Jeffrey Purnell, PhD

INTRODUCTION

Custom adhesive manufacturers have been meeting the specialized bonding challenges of transdermal drug delivery systems (TDDS) for more than 3 decades. Knowledge gained from years of understanding the pharmaceutical industry is fueling the development of new adhesive technologies with sophisticated, value-added functionality to deliver an enhanced range of performance capabilities to pharmaceutical drug delivery device developers.

The pressure-sensitive adhesives (PSAs) used in TDDS are commonly acrylic, silicone, or polyisobutylene (PIB) formulations.[1] The selection of an adhesive is based upon a myriad of desired performance and compatibility factors, some of which include drug and component compatibility; adhesive performance to a wide range of substrates; bioavailability and drug flux rates; and parameters to ensure skin-friendliness, such as wear properties, moisture-vapor transmission rates (MVTR), non-sensitizing, and non-cytotoxic.[2]

These base technologies remain well used and relevant today; however, the launch of new generic product patches and treatments for chronic conditions targeting diverse patient populations are driving the demand for improved skin-friendly adhesive formulations. Developmental "active" transdermal technologies will also require higher-performing component materials with enhanced capabilities. The following will discuss how new adhesive and polymer technologies will improve the patient experience for wear and comfort, and introduce emerging technologies that will deliver enhanced capabilities for the next generation of transdermal controlled-release applications.

STRONG ADHESION, GENTLE REMOVAL

Human skin is an extremely variable substrate. As a general rule, adhesives for transdermal patches are formulated to present aggressive bonds with flexibility and conformability to ensure the patch remains firmly in place without lifting or fall-off to ensure a therapeutic dose. The adhesive/skin bond must withstand physical activity, constant friction from clothing, periodic moisture exposure, and varying degrees of skin porosity and oil levels, without shifting or moving. The majority of transdermal patches available today are daily-wear devices that are typically removed within 24 hours of application; however, formulators are developing extended-wear patches designed to be worn for multiple days.

Controlled Breathability

It is important that the adhesives selected for a transdermal device promote skin breathability to ensure a healthy environment for proper dosing and patch

FIGURE 1

comfort. Controlled hydration is a desirable attribute at the adhesive/skin interface for enhancing drug flux while preventing macerated skin. The latter condition can potentially affect drug bioavailability while causing the skin to become weak, increasing the possibility of tearing, resulting in pain during device removal.

Of the adhesive chemistries used for TDDS, acrylics provide the highest MVTR levels, followed by silicones with PIBs offering the lowest MVTR rates. In many cases, drug compatibility dictates the adhesive chemistry chosen. Several approaches are used to improve MVTR. These include substrate selection, adhesive coat weight, and zone or pattern coating. Performance properties can be improved by utilizing an adhesive coat weight of less than 30 microns. However, this approach can reduce the mass of the adhesive, compromising the ability to achieve a reliable skin bond. Techniques such as zone or pattern coating to provide adhesive-free areas and mechanical poration, are processes that can prepare an adhesive for improved moisture transmission when used in combination with high MVTR substrates to enable breathability.

TABLE 1

Attribute	LTA 1	LTA 2	LTA 3
1-hour forearm peel	2-10 oz/in	4-14 oz/in	3-6 oz/in
24-hour forearm peel	2-10 oz/in	4-16 oz/in	6-8 oz/in
Δ peel (1-24 hours of wear)	Insignificant	Max 2 oz/in	Max 2 oz/in
Pain upon removal (Wong-Baker Faces Pain Scale)	0-2	1-3.5	0-2
% peel retention on re-attachment	80%	70%	85%
Residue on skin	no	no	no
Skin cell removal (based on Skin Cell Removal Assessment Scale)	0	0	<2
MVTR - upright Payne cup (g/m^2/day) 2 mils PSA on 1 mil PU	450	750	1300
Gamma sterilization resistance	Good	Fair	Excellent
Cytotoxicity (Direct Agarose overlay)	Non-cytotoxic	Non-cytotoxic	Non-cytotoxic
Primary Skin Irritation - ISO	Negligible (0.2)	Negligible (0.4)	Negligible (0.0)

Attributes of Adhesives Research Non-Silicone Skin-Friendly/Gently Removing Adhesive.

Downside of Aggressive Skin Bonds

While aggressive adhesion ensures a secure bond to skin for addressing dosing concerns, it can potentially cause discomfort upon patch removal. In these situations, the adhesive removes skin cells and/or hair when the device is pulled away. Additionally, an adhesive that releases uncleanly may leave behind an unwanted residue on the skin that is difficult to remove.

As more patch products become available for diverse consumer populations with skin of varying ages and conditions, developers are seeking adhesive technologies that continue to demonstrate high levels of reliable adhesion, but with a more gentle removal experience for the user. This is becoming more evident as designs for longer-wear applications are being considered. Also a factor, is the emergence of new transdermal treatments for chronic conditions that require repeated patch placement to a specific skin site. As more active transdermal treatments employ mechanical preparation of the skin prior to, or as part of a treatment regimen, the need for more adhesive choices providing low- to no-pain removal is growing.

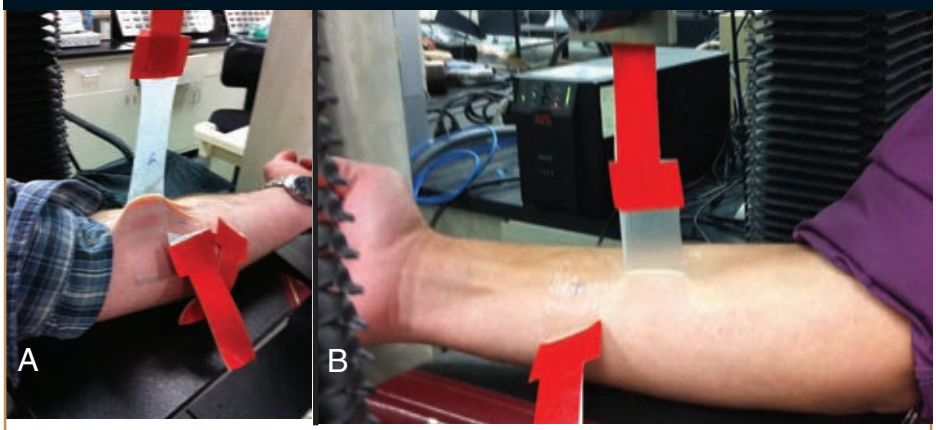
The pain experienced during device removal is difficult to measure precisely because the sensation is influenced by a wide range of factors. The well-known Wong-Baker FACES™ Pain Scale is one of the industry indexes used to quantify pain intensity as shown in Figure 1.[3] This system can be utilized for ranking the pain an individual experiences on a scale of 0 to 5, with 5 being the highest. Ultimately, the lowest possible Wong-Baker FACES pain rating during device removal is desired while maintaining the appropriate wear performance.

Skin-Friendly Adhesive Choices

While a number of adhesive technologies available on the market today claim to have skin-friendly properties, the majority fall short in addressing the specific needs of transdermal patch product design.

Silicone gel adhesives commonly used in advanced wound care applications, are in theory, a good material choice for short-term wear transdermal applications, but may require a minimum adhesive thickness of 80 microns to successfully bond to skin, causing a thicker edge for a patch to "grab" clothing or other materials. However, many silicone gel adhesives are susceptible to damage caused by common sterilization techniques incorporating gamma radiation that negatively impact

FIGURE 2A&B



A) Shows peel test with standard skin-friendly adhesive. B) Shows the same peel test occurring with Adhesive Research's gently removing skin-friendly adhesive.

TABLE 2

Assessment Scale	Description
0	Few visible skin cells, <1% patch area
1	Some visible skin cells, <10% patch area
2	Some visible skin cells, <50% patch area
3	Nearly full coating of skin cells, but still some tack to the PSA
4	Full coating of skin cells, no tack left on the PSA
5	Full coating of skin cells, many body hairs. Visible layer (damage) of skin removed from the forearm.

Skin Cell Removal Assessment Scale

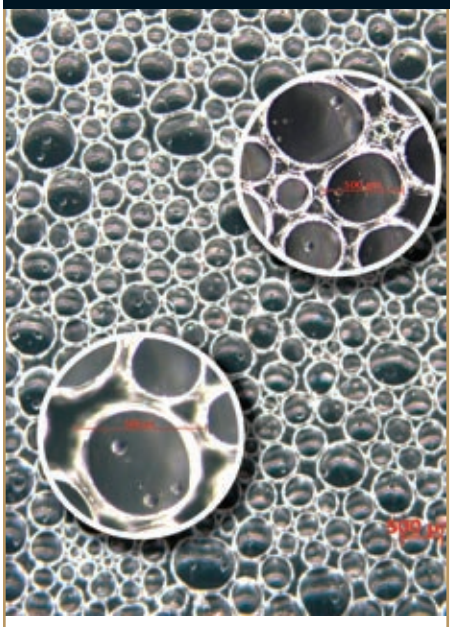
adhesion bond levels to skin.

Hydrogels and hydrocolloids can also be formulated for gentle removal; however, the adhesive properties of these formats change significantly as they absorb water, often resulting in adhesive/skin bond failure. These formats also may require a thick application of the material in a layer greater than 80 microns to ensure a reliable bond. As mentioned previously with silicone gel formats, a heightened edge can result in snagging and uplift of a patch.

Adhesives Research (AR) is addressing the growing need for skin-friendly adhesives while overcoming the thickness issues of gel formats through the development of a new gently removing PSA technology. This non-silicone, high-MVTR, customizable PSA technology maintains aggressive, intimate skin contact for up to five days with pain- and residue-free removal. The adhesive is formulated to cleanly release from hair and the top layer of skin with a pain index < 2.5 on the Wong-Baker FACES Pain Scale. For comparison purposes, a standard skin-friendly adhesive has a pain index rating of 4 to 5 based on internal studies. Some of the formulations based on this technology exhibit good to excellent ratings for resistance to gamma sterilization techniques, which is an important consideration in active patch designs utilizing microneedles, abrasion, or other techniques to prepare the skin prior to, or as a step in the proper application of a patch. Three versions of this technology are currently offered, and the properties are outlined in Table 1.

An internal study was conducted on test subjects utilizing several formulations of AR's skin-friendly technology with the intention of measuring the pain experienced upon removal of the tape. The samples of each adhesive were applied to the test subjects' forearm and left in place for 24 hours as illustrated in Figure 2 A and B. Upon removal, the samples were peeled back at an angle of 90°, and the peel speed was 12 inches/minute in a tensile tester. The pain level was evaluated using the Wong-Baker FACES Pain Scale. The amount of skin cells remaining on the adhesive after peeling from the forearm was also noted and graded on a 0 to 5 scale as per the ranking guide in Table 2.

FIGURE 3



Adhesives Research's porous pressure-sensitive adhesive forms isolated channels to offer improved exchange of gases and fluids.

TABLE 3

Adhesive Construction	MVTR (g/m^2 day) Adhesive (laminated to nonwoven)
ARcare® 92205	8900
ARcare® 92174	8800
ARcare® 92556	9000

MVTR Testing Results for Porous Adhesive[4]

POROUS ADHESIVES

As previously mentioned, coating techniques can be applied to improve the MVTR values of a PSA for skin-bonding applications. The concept of a porous adhesive serving a dual role for skin bonding while increasing device functionality is relatively new to the pharmaceutical industry.

AR's porous technology is a super porous PSA offering hundreds of micrometer-sized open pores or cells in a low-density, highly permeable structure. The pores range in diameter from approximately 200 to 500 microns as shown in Figure 3. The distribution of pores throughout the matrix results in 30% to 50% porosity, and a finished film thickness of 2 to 8 mm. The porous adhesive formulation is completely customizable for each application.

The adhesive's pores form isolated channels through the adhesive as shown in Figure 3. These channels enable the free exchange of gases and fluids from one substrate to the next through the Z direction of the adhesive to offer enhanced high MVTR rates. As seen in Table 3, the porous adhesive's MVTR of about 9000 g/m²/day is extremely high when compared to conventional solid film PSAs that typically demonstrate MVTR of tens to several hundred g/m²/day.

CHARGING FORWARD WITH ELECTRICALLY CONDUCTIVE PSAS

Transdermal product developers continue to explore the opportunities for iontophoretic delivery to broaden the range of therapeutic compounds possible for transdermal delivery. In iontophoretic patches, electrically conductive PSAs transmit an electric current through layers of a device while bonding electrical components within the patch. The rate of drug delivery is controlled by the strength of the electrical current to transport the drug rapidly and accurately, via on-demand dosing or patterned/modulated drug delivery.[5] In some versions of these devices, the electrically conductive layer may contain conductive fillers to lower the resistance of the interface and to form electrical connections.

The benefits of AR's homogeneous, carbon-based electrically conductive PSA technology have been well proven in the electronics industry for more than 20 years. Controlled-release applications that require electrical conductivity for successful drug delivery can capitalize on the many performance capabilities this technology has to offer. Reliable electrical interconnections are achieved through the uniform dispersion of conductive particles within the adhesive matrix to form strong carbon chains. These chains provide good point-to-point conductivity and flexibility to move with the adhesive for uninterrupted electrical interconnections. The conductive fillers may be composed of a number of materials, such as nickel, silver, and carbon, or a combination of these. Adhesives may be formulated from acrylic-, silicone-, or rubber-based polymers, including skin-friendly formulations, to ensure the maximum flexibility in product design and compatibility with a device's APIs and other components.

Depending upon the application, a number of adhesive or film formulations can be created in combination with the carbon particles to achieve the desired outcome:

- Carbon-filled adhesive matrix
- Carbon- and metal-filled adhesive matrix
- Carbon and silver compound adhesive
- Adhesive-embedded composites for X-Y vs. Z conductivity control
- Conductive films and laminates

In recent years, advancements in conductive PSAs enabled formulators to tailor the adhesive's physical properties for resistivity, conductivity, and a number of environmental stresses, including moisture resistance. For example, the Adhesives Research conductive technology can achieve Z-axis resistances from a few milli-ohms to a few ohms reliably, and can be produced in thicknesses ranging from 25 to 100 microns. This technology is also proven for use in fine pitch connections where X-Y isolation is critical, and provides reliable connections down to 300 x 300 microns.

SUMMARY

TDDS continue to deliver patients increased compliance by providing predictable and reliable therapeutic dosages without limiting a patient's normal daily activities, driving drug manufacturers to continue to expanding the scope of this drug delivery system. As the scope widens, adhesive manufacturers are responding by developing a range of skin-friendly and API-compatible formulations for improved comfort and wear with less discomfort during removal. Versatile in their chemistry and form, PSAs are critical components in achieving intended outcomes, such as sustained skin adhesion, component bonding, electrical component bonding and assembly, moisture seals, and drug envelopments. While pharmaceutical product developers explore new methods for delivering a wider range of drugs through passive and active systems, PSA manufactures will continue to push the capabilities of their technologies to meet the unique challenges of new and emerging transdermal applications.

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BIOGRAPHY

Dr. Jeffrey Purnell is currently the Medical and Pharmaceutical R&D group leader for Adhesives Research and has contributed to the company's product development initiatives for 5 years. In 1994, he was awarded an Alexander von Humboldt Fellowship and conducted research at the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany. Dr. Purnell earned his PhD in Chemistry from the Pennsylvania State University (University Park, PA) and his BS in Chemistry from Shepherd College (Shepherdstown, WV).

DRUG DEVELOPMENT
TYRX Executive

TYRX: Combination Drug-Device Products That Help Prevent Surgical Infections Associated With Implanted Medical Devices

Robert White

President & CEO

TYRX

"We expect to penetrate approximately 2% of the CRM market this year with our first product, the AIGISRx Antibacterial Envelope, and are now introducing or completing development of similar products for other procedures with high infection risk, including hernia repair, orthopedic procedures, and other device implants. Collectively, we believe the total revenue potential for TYRX in the surgical infection control arena is well over $100 million per year within 5 years."

Since its inception in 1998, TYRX has focused on a singular goal - the creation of cost-effective solutions to serious medical problems associated with surgically implanted medical devices, specifically the prevention of serious surgical site infections. The company's products are drug-device combinations based on a novel polymer platform technology that offers a wide range of applications that add value to established medical devices. TYRX's first commercial product, the AIGISRx® Antibacterial Envelope, specifically addresses increasing infection rates associated with the implantation or replacement of cardiac rhythm management devices, such as pacemakers and defibrillators. Since its FDA clearance in 2008, the AIGISRx device has been successfully used in nearly 20,000 patients, and published clinical results have shown significant reductions in infection rates, especially in patients at greatest risk. TYRX has also received FDA clearance for AIGISRx® ST, an antibacterial product for the surgical repair of damaged or ruptured soft tissue, and the company is developing a range of additional products, including a next-generation, totally resorbable AIGISRx. Drug Development & Delivery recently interviewed Robert White, President and CEO of TYRX, to discuss the company's proprietary technology and products as well as the market outlook for such drug-device combinations.

Q: What is the market opportunity related to surgical infections?

A: Bacterial infections have become a major, growing problem for hospitals, as rates and seriousness of infections have increased significantly in recent years. This has led to hospital costs in the billions of dollars relating to the treatment of infections. With the growing focus on patient outcomes and quality indicators, not only hospital administrators and doctors, but also Medicare and other third-party payers are paying increased attention to infection control. Our customers view surgical infections as analogous to plane crashes: while somewhat infrequent, they are costly; everyone hears about them when they occur; they require a lot of "clean-up" both with the patient and hospital administration; and unfortunately people die. Awareness and pressure to reduce

infection rates is rising because a single infection can lead to more than $100,000 in expense and cause significant morbidity and mortality. In fact, studies have shown that the in-hospital mortality for implanted patients when infection occurs is 4.7% to 11.5%, depending on the device type; this incidence is 8.4- to 11.6-fold the mortality without infection. Overall mortality after one year increased to 24% to 33% for those incurring infection, approximately two-fold the mortality rate for non-infected patients. That's the equivalent of a lot of 747 crashes each year in the US alone.

With respect to our initial market focus on the implantation of Cardiac Rhythm Management (CRM) devices, there are roughly 580,000 implants performed in the US alone each year. Two-thirds of these patients have at least one risk factor for infection, such as device replacement or heart failure. Today, roughly 2% of them experience a major infection associated with their surgical procedure, and this infection rate is increasing even faster than the number of devices implanted. We expect to penetrate approximately 2% of the CRM market this year with our first product, the AIGISRx Antibacterial Envelope, and are now introducing or completing development of similar products for other procedures with high infection risk, including hernia repair, orthopedic procedures, and other device implants. Collectively, we believe the total revenue potential for TYRX in the surgical infection control arena is well over $100 million per year within 5 years.

Q: What is the technology basis for TYRX's products?

A: TYRX was founded based on novel polymer technology (developed at Rutgers, The State University of New Jersey), which is a collection of modified tyrosine-based polymers known as polyarylates that have unique properties for drug delivery. Our world-wide license to this technology portfolio covers not only drug delivery applications, but a broad range of resorbable materials. From Baylor College of Medicine and The University of Texas M.D. Anderson Center, TYRX has also received an exclusive license to combination drug patents and associated technologies addressed to the problems of post-surgical infection and fibrosis. Leveraging these technologies, we are able to create a wide variety of products addressed to specific surgical needs. Our first products are polymer-coated devices impregnated with two antibiotics, minocycline and rifampin, that when used in combination creates a proprietary formulation that elutes over a period of days. These antibiotics have been shown in in vivo preclinical studies to reduce infection by organisms representing the majority of the infections reported in cardiac device-related endocarditis, including "superbugs" or MRSA.

Q: You have already commercially launched your first product? Tell us about it.

A: In 2008, we commercially released the AIGISRx Antibacterial Envelope, which is a polypropylene mesh envelope coated with our polyarylate polymer and impregnated with our minocycline/rifampin antibiotic combination. Designed specifically for helping to manage infection risks associated with the implantation or replacement of cardiac devices, the pacemaker, defibrillator, or CRT is placed within the envelope prior to implantation. Once implanted,

the polyarylate polymer mesh coating controls the release rate of the antibiotics to prevent infection not only during the implant procedure but for 7 to 10 days post-implantation. While the current AIGISRx Antibacterial Envelope remains in place even after the drugs are fully eluted, we are now developing a next-generation, totally resorbable version.

Q: What has been the clinical experience with the AIGISRx Anntibacterial Envelope?

A: We have now successfully implanted the AIGISRx device in nearly 20,000 patients. We recently published our first human clinical trial data from 642 patients, showing a 99.5% rate of successful implantation and 70% fewer infections than were seen in some previous studies within the highest risk cohort of implantable defibrillator replacements. The study also showed no infections in the lower risk groups of patients receiving initial implantations of pacemakers or implantable defibrillators. As good clinical data will drive market uptake for this product, we have also recently completed site enrollment in two major new studies with 50 clinical sites, designed to measure infections and mechanical complications associated with implantable defibrillators. A total of 4,300 patients will eventually be enrolled. We believe the commercial prospects for this product are excellent; there is no other option other than AIGISRx for lowering the risk of infection related to cardiac device implantations beyond traditional prophylaxis approaches.

Q: What other products do you have in your pipeline?

A: In late March 2010, we received another FDA clearance for a second antibacterial product called AIGISRx ST. This product is designed for use with the surgical repair of damaged or ruptured soft tissue, such as hernia repair or abdominal wall repair, where infections are common. While these and many other potential products address anti-infective needs, we believe our technology also has other drug delivery applications, including pain management. This is a huge opportunity given both the number of surgeries worldwide and the lack of good technology for managing acute post-operative pain.

Q: Your initial products were approved via the 510k process. With that process in flux at the FDA, what regulatory challenges is TYRX facing for its new products?

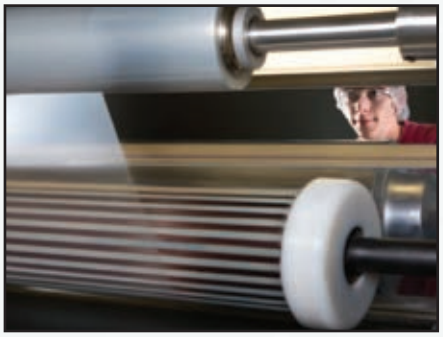
A: I believe the changing 510k process will certainly be a challenge for the medical device industry generally, and gaining regulatory approval in the future will likely require more rigorous data requirements than it has for many device products in the past. For that reason, as well as to support the educational process that will drive our commercial success, TYRX has made it a priority to gather the appropriate data to ensure our regulatory applications are robust upon submission. Companies who are able to combine solid science, robust clinical data, and a thoughtful FDA strategy should be able to navigate the regulatory changes at hand. At the same time, these changes will likely have a cost to companies, including TYRX, in terms of time to market, as well as financially. The regulatory barrier to market has indeed gone up, for us as well as for others. ◆

Technology & Services Showcase

DPI Capabilities

3M Drug Delivery Solutions is a trusted global leader, providing proven technologies and services while continuously expanding the range of drug delivery, such as our Dry Powder Inhalers (DPIs). Designed to overcome the traditional challenges associated with DPI delivery, 3M™ Taper and Conix™ DPIs are patient friendly and highly efficient to help ensure a therapeutic dose is delivered. The 3M Conix DPI uses reverse-flow cyclone technology to effectively utilize the patient's inhalation energy to aerosolize the drug, while the 3M Taper DPI applies active aerosolization to the drug to provide efficient delivery of a respirable dose. 3M can evaluate, within 1 week, feasibility of delivering your drug with the 3M Taper Dry Powder Inhaler. Learn more at www.3m.com/taperdpi or visit **www.3m.com/dpi** to explore all of our DPI capabilities.

Innovative Platforms



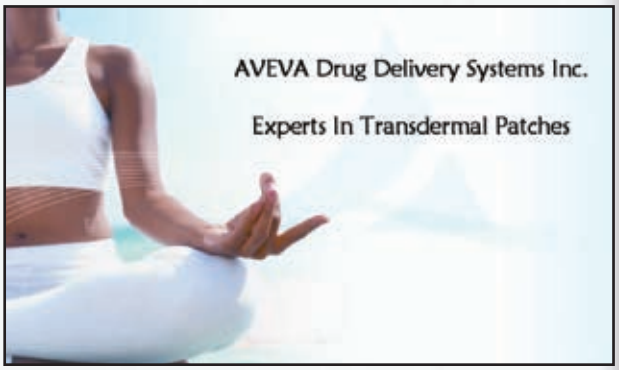
Adhesives Research, Inc. has over 20 years of experience developing and manufacturing custom pressure-sensitive adhesive tapes, specialty coatings, films, and laminates for the for the world's leading pharmaceutical companies. We offer the pharmaceutical industry a wide range of coating technologies 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**.

Specialty Pharma

APTALIS | Pharmaceutical Technologies

Aptalis Pharma Inc. is a privately held, leading specialty pharmaceutical company providing innovative, effective therapies for unmet medical needs, including cystic fibrosis and gastrointestinal disorders. Aptalis has manufacturing and commercial operations in the US, the European Union, and Canada, and its products include ZENPEP®, CANASA®, CARAFATE®, PYLERA®, LACTEOL®, DELURSAN®, and SALOFALK®. Aptalis also formulates and clinically develops enhanced pharmaceutical and biopharmaceutical products for itself and others using its proprietary technology platforms, including bioavailability enhancement of poorly soluble drugs, custom-release profiles, and taste-masking/orally disintegrating tablet (ODT) formulations. For more information, visit Aptalis at **www.AptalisPharmaceuticalTechnologies.com**.

Licensing & Capabilities



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

Technology & Services Showcase

Drug Delivery Solutions

BD Medical - Pharmaceutical Systems provides high-quality, customized, clinically proven drug delivery systems and self-injection technologies to help pharmaceutical and biotechnology customers' injectable drugs reach their full potential. BD has over 100 years of experience in manufacturing and processing technology for parenteral drug delivery systems and has developed an in-depth understanding of the pharmaceutical industry's requirements. BD has leveraged this experience when developing advanced drug delivery systems that span from small-scale clinical through large-scale commercial programs. With a broad range of innovative systems and services, BD Medical - Pharmaceutical Systems provides pharmaceutical companies with support and resources to help them achieve their goals. For more information, contact BD at (800) 225-3310 or visit **www.bd.com/pharmaceuticals**.

Pharmaceutical Solutions

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

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**. (913)685-885

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For more information, contact Delta Industrial at (800) 279-3358 or visit **www.deltamodtech.com**.

Technology & Services Showcase

Combination Capsule Technology

InnerCap offers an advanced patented multi-phased, multi-compartmentalized capsular-based delivery system. The system can be used to enhance the value and benefits of pharmaceutical and biopharmaceutical products. Utilizing two-piece hard shell capsules, the technology offers the industry solutions to problems affecting pharmaceutical companies, patients, and healthcare providers. The delivery system will be licensed to enhance pharmaceutical and biopharmaceutical products. It is a very effective way to deliver multiple active chemical compounds in different physical phases with controlled-release profiles. The delivery system provides the pharmaceutical and biopharmaceutical industries with beneficial solutions to the industry's highly publicized need to repackage and reformulate existing patented blockbuster drugs with expiring patents over the next 5 years. For more information, contact InnerCap Technologies, Inc., at (813) 837-0796 or visit **www.innercap.com**.

Drug Development & Delivery

LTS Lohmann Therapie-Systeme AG is a world-class developer and manufacturer of transdermal systems, oral film drug delivery systems, and adhesive laminates. We use leading-edge technology to manufacture developed products on a large and cost-effective commercial scale. LTS develops products from inception through commercialization in our facilities in Germany and the US under GMP conditions, both approved by the FDA and European Authorities. Our partners include many of the world's successful pharmaceutical, consumer healthcare, medical device, and diagnostic companies. Our resources include research & development, clinical pharmacology, technology transfer, analytical, regulatory affairs, quality assurance, operations, and product support. For more information, visit LTS Lohmann Therapie-Systeme AG at **www.ltslohmann.com**.

Albumin Fusion Technology

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

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 information, contact NuSil Technology at (805) 684-8780 or visit **www.nusil.com**.

Technology & Services Showcase

Development & Delivery Solutions

PARTICLE SCIENCES
DRUG DEVELOPMENT SERVICES

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**.

Knowledge Management

PHARMACIRCLE™

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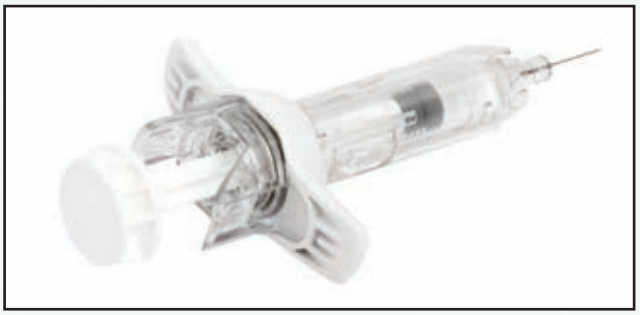
Passive Safety Device



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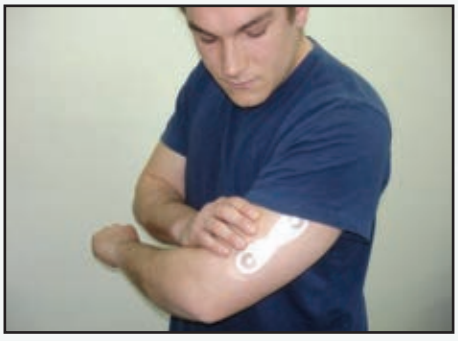

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MARKET BRIEF

Biosimilars: Pathway Still Unclear

By: Katheryn Symank, Industry Analyst, Frost & Sullivan

INTRODUCTION

The 1-year anniversary of the signing into law of healthcare reform as established by *The Patient Protection and Affordable Care Act of 2010* (as amended by the *Health Care and Education Reconciliation Act of 2010*), has just passed. One major aspect was the inclusion of the *Biologics Price Competition and Innovation Act of 2009* (BPCIA), which set up an abbreviated regulatory pathway for the approval of biosimilars. With the looming expiration of patents for several major biopharmaceuticals worth over $60 billion in annual revenue, biosimilars are expected to become a major emerging market in the US. Yet, many factors such as the actual approval guidelines the FDA will use remain unknown. In the US, there is great demand for biopharmaceuticals, which tend to be significantly more expensive than small molecule drugs with annual costs of therapy ranging from hundreds of dollars to thousands of dollars per year. Many hope that the addition of competition from biosimilars could save patients, Medicare, Medicaid, and other payers billions annually.

BPCIA: KEY POINTS

The BPCIA allows for abbreviated applications for products that are biosimilar or interchangeable to a reference biopharmaceutical. Biosimilars must be considered "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and has "no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product." According to the legislation, a product is considered interchangeable if:

- It meets the criteria for being biosimilar to the reference product.
- It can be expected to produce the same clinical result as reference product in any given patient.
- The risk in terms of safety or diminished efficacy when switching or alternating between use of the biological and reference product is not greater than the risk of using the reference product without such alteration or switch.

Ultimately, a product approved as interchangeable could be substituted for the reference product by a licensed pharmacist without consent from the prescribing physician, whereas a product identified as a biosimilar would not.

Although the BPCIA gives some general framework guidelines, one of the great mysteries surrounding the US biosimilars pathway is what exactly the regulatory guidelines are. The FDA has been tasked with determining what these regulatory standards will be and what types of scientific tests or trials will be required. The legislation does state that companies using the abbreviated biosimilar pathway must include analytical studies to show "high similarity" to the reference product, animal data (including toxicology profile), and clinical studies. However, the law also put in an interesting clause that gives the FDA the authority to waive any or all of these requirements if they are deemed "unnecessary." The question remains

whether or not the FDA will exercise the right to waive requirements. Most likely, the FDA will approach regulation requirements on a case-by-case basis, depending upon the complexity of the product.

One of the most contested provisions in the BPCIA is the number of years of exclusivity an originating biopharmaceutical should get. As it currently stands, reference biopharmaceuticals are granted 12 years of exclusivity. The Generic Pharmaceutical Association has publicly stated that they considered this to be an "excessive" exclusivity period and appears to favor name brand products, whereas other organizations like the Pharmaceutical Research and Manufactures of America (PhRMA) has argued that the 12-year period is needed to promote innovation and to recoup research and development costs. Recently, this debate has been rekindled. Included in President Obama's proposed Health and Human Services (HHS) budget for 2012 is a proposal to reduce the exclusivity period from 12 years to 7 years. Ultimately, it remains unclear as to whether this provision will be approved by congress or not.

BIOSIMILARS IN EUROPE

In terms of what the actual regulatory standards will be, one possible scenario is that the FDA will borrow the guidelines used by the European Medicines Agency (EMA), the European Unions equivalent to the FDA. Europe has had biosimilar regulatory approval since 2005 with guidelines set up in The EMEA Guideline on Similar Biological Products (October 30, 2005). The EMA clearly recognizes that biosimilars are not recognized as generics. Specifically, it states that "it should be recognized that, by definition, similar biological medicinal products are not generic medicinal products." As such, the EMA uses a cautious approach for the approval of biosimilars. To get approval, a biosimilar must submit quality assurance, safety, and efficacy tests. In addition, biosimilar manufacturers are required to submit post-marketing tests. The EMA has set up distinct regulatory guidelines for different therapeutic classes. For instance, there are different guidelines specific for each of the following:

- Insulin
- Somatropin
- Gransulocytic-colony stimulating factor (G-CSF)
- Erythropoietin
- Low molecular weight heparins
- Interferon alfa-3a.

Recently, the EMA released a draft guideline for study requirements for biosimilar monoclonal antibodies in Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies.

WILL ABBREVIATED PATHWAY BE UTILIZED?

Taking into consideration all potential studies, both animal and clinical, that will

FIGURE 1

U.S. Patent Expirations of Selected Biopharmaceuticals

Product Name	Company	US Patent Expiry
Enbrel	Amgen/Pfizer	2011-2019
Epogen	Amgen	2012-2015
Procrit	Centocor Ortho Biotech	2013
Avonex	Biogen Idec	2011-2015
Rebif	EMD Serono Inc.	2013
Humalog	Eli Lilly and Company	2013
Neupogen/Neulasta	Amgen	2013-2015
Cerezyme	Genzyme	2013
Rituxan	Genentech/Roche	2015
Lantus	Sanofi-Aventis	2010-2015
Humira	Abbott	2016-2017

A list of expiration dates for selected biopharmaceuticals in the US.

probably be required for a biosimilar to demonstrate its "high similarity" to a reference product, the likelihood of companies using the abbreviated biosimilars pathway comes into question. In addition to the considerable expense the companies will have to pay for the trials and application process, the first biosimilar approved only receives 1 year of exclusivity. Moreover, there are is much uncertainty regarding the patents for some of the complex biopharmaceuticals. It stands to reason that many companies will opt to file a BLA instead of an aBLA. Filing the application for a new product will give the product the same rights as a branded-biopharmaceutical, and in theory, command a higher-price than a biosimilar.

WHAT COMPANIES ARE EXPECTED TO COMPETE IN THIS MARKET?

Biosimilars are complex, large molecules that require a great amount of technical expertise and specialized equipment to manufacture. It is estimated that the average cost to build a biopharmaceutical manufacturing plant is around $400 million. Biosimilars, like biopharmaceuticals, are expensive to manufacture. Some experts estimate that it will cost over 50 times more to produce a biosimilar than a small molecule generic medication. As a result of these significant hurdles, only a select group of companies will be able to compete in the biosimilars market. These companies are likely to be large pharmaceutical companies, large generic companies, and biopharmaceutical companies. Some companies already working in this area include:

- Sandoz/Novartis
- Teva
- Merck
- STC Biologics, Inc.
- Lonza Group AG
- Hospira Inc.

SUMMARY

Biopharmaceuticals are often hailed as one of the greatest breakthroughs of biotechnology. In terms of financial success, several biopharmaceuticals have reached blockbuster status. According to IMS Health, biopharmaceuticals collectively generated sales of $130 billion globally in 2009. As demand for these expensive and often life-saving medications increases, so does the interest in making less-expensive biosimilars available to Americans. However, until the FDA firmly establishes regulatory guidelines, the actual process remains a mystery. Despite this, many industry experts anticipate that some companies will still submit aBLAs, and the FDA will actually evaluate these applications on a case-by-case basis.

BIOGRAPHY

Katheryn Symank is a Industry Analyst with the Frost & Sullivan North American Healthcare team. She focuses on monitoring and analyzing emerging trends, technologies, and market behavior in the Pharmaceutical and Biotechnology industries. Since joining Frost & Sullivan in February 2007, Mrs. Symank has completed several research studies and consulting projects with recent works focused on monoclonal antibodies, stem cells, osteoporosis, lifestyle disorders, and respiratory diseases. Prior to joining Frost & Sullivan, Mrs. Symank worked for 7 years in pulmonary pathology at the University of Texas Health Science Center in San Antonio, where she studied bronchopulmonary dysplasia. She earned her BS from Texas A&M University in Molecular and Cell Biology and her MS from the University of Texas at San Antonio in Biotechnology.

The Zeta Potential & its Use in Pharmaceutical Applications - Part 1: Charged Interfaces in Polar & Non-Polar Media & the Concept of the Zeta Potential

By: David Fairhurst, PhD, Robert W. Lee, PhD

INTRODUCTION

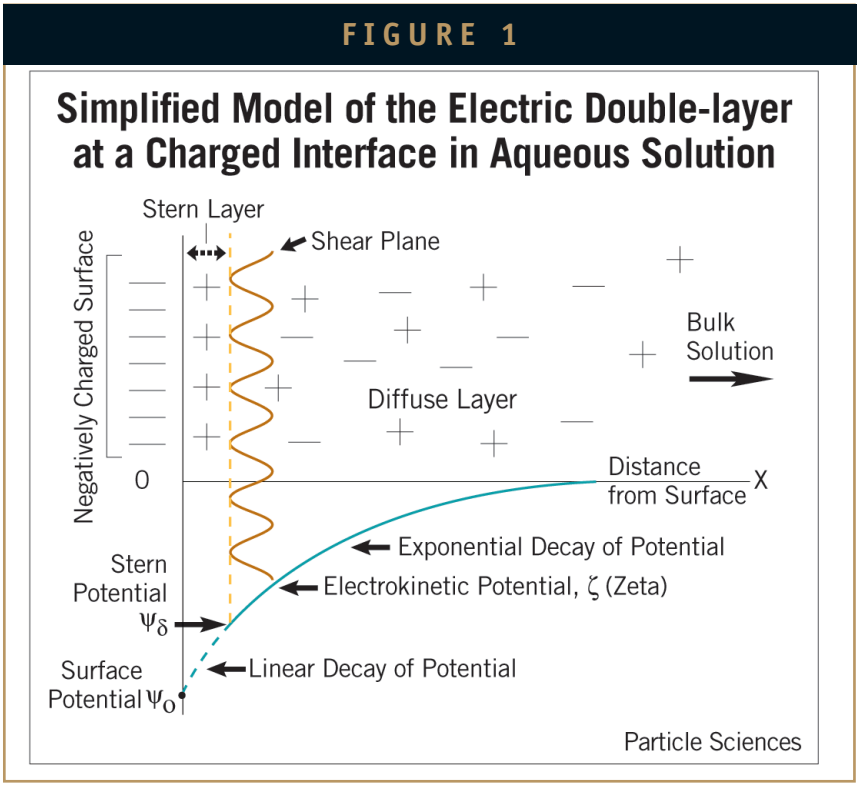
What is the zeta potential (ZP) and why measure it? In order to address these questions, we must first briefly discuss the two fundamental parameters that control the nature and behavior of every system in which one phase is dispersed in another phase; the phases are distinguished by the terms disperse phase (for the phase forming the particles) and the dispersion medium (for the fluid in which the particles are distributed). The two fundamental parameters are the extent of the interface of the disperse phase and the interfacial chemistry of the disperse phase, respectively.

The physical nature of a dispersion depends on the respective roles of the constituent phases; there are numerous examples of dispersed systems, including foams (gas-in-liquid), emulsions (liquid-in-liquid), and aerosols (solid- or liquid-in-gas), that have found application in pharmaceutics. In this review, we shall focus on the most widely formulated type of dispersion - suspensions (solid-in-liquid). The physico-mechanical and physico-chemical characteristics that constitute the two respective fundamental parameters are summarized in Table 1. The reader may well be acquainted with the measurement of one, or more members, of the former group. However, the interfacial chemistry is often a neglected parameter (particularly in pharmaceutical applications) even though in formulation of suspensions, it is as important as (and sometimes more so than) the interfacial extent.

The ZP is a parameter (symbol ζ), which is related to the surface charge, a property that all materials possess, or acquire, when suspended in a fluid. The sign and magnitude of ZP affects process control, quality control, and product specification; at the simplest level, it can help maintain a more consistent product and at a complex level, it can improve product quality and performance. At the very least, its measurement answers the question: Is the electrical charge on the material particle positive or negative? This information is often sufficient to suggest further steps in formulation or processing. The next higher level of inquiry has to do with quality control: Has the product sufficient electrostatic repulsion to maintain its stability?

The ZP is particularly useful to predict the resistance of an electrocratic (ie, governed by electrostatics) dispersion to coagulation by electrolytes by determining

FIGURE 1



the critical ZP (ie, the value of ZP below which the suspension is coagulated). It is often used in determining the critical coagulation concentration (CCC) of an electrolyte (the minimum concentration required for the onset of coagulation); the CCC is proportional to ζ^4/z^2 (where z is the electrolyte counterion valence). However, the ZP has limited value in systems that are completely sterically stabilized, but it is useful in monitoring the adsorption of a nonionic surfactant, or macromolecule, onto a charged particle surface.

THE ORIGIN OF CHARGE IN POLAR MEDIA

All materials will spontaneously acquire a surface electrical charge when brought into contact with a polar medium (ie, water).[1] Generally, an interface in deionized water is negatively charged, but there are materials that can be positively charged. A few examples are shown in Table 2. The various charging mechanisms are:

1. Affinity differences of two phases for electrons
2. Ionization of surface groups
3. Differential ion adsorption from an electrolyte solution
4. Differential ion dissolution from a crystal lattice
5. Surface anisotropy
6. Isomorphous substitution

Mechanism (1) is responsible for the development of the contact potential between dissimilar metals and is important in, for example, corrosion and thermoelectric effects.[2] For all liquid-liquid interfaces and most solid-liquid interfaces that comprise normal particulate suspensions, this mechanism is of little significance. An exception, though, are metal sols in which it is a dominant process in initially determining the surface charge at the metal-solution interface. Nanoparticulate metal sols are currently being studied in wide variety of applications because they offer greatly enhanced performance capabilities. In biomedical applications, nanosilver particles have been found to be highly efficient germ killers and are now used in FDA-approved wound dressings; sols of gold nanoshells when irradiated with NIR wavelengths (that pass harmlessly through soft tissue) absorb the radiation and generate sufficient heat to burst the walls of cancerous cells. Because all metallic nanosystems are initially created as sols (ie, colloidal dispersions), their inherent surface charge is critical to any further processing or use.

Mechanism (2) is commonly observed with all metal oxide surfaces (M-OH) as well as materials that contain carboxylic acid - and amine-containing functional groups. In this latter category are proteins, ionic polymers, and polyelectrolytes, many of which are widely utilized in pharmaceutical formulations. They acquire their charge mainly through ionization and/or dissociation. The ionization of these groups (degree of charge development) and the net molecular charge (and thus sign, either positive or negative) depends strongly on the pH of the solution in which they are dispersed.

In mechanism (3), a net surface charge arises through the process of unequal adsorption of oppositely charged ions and may result in either a net positive or net negative surface. Many lyophobic material suspensions (ie, polymer latexes and APIs) fall into this category.

Surfaces that are already charged (ie, by ionization) show a preferential tendency to adsorb counterions (ions of opposite charge to that of the surface - see later section on the Electric Double-Layer), especially those of high valence. It is possible, however, for such adsorption to cause a reversal of charge. If surfactant ions are present, their adsorption will tend to determine the net surface charge. Hydrated surfaces, such as protein and polysaccharide, adsorb ions less readily than hydrophobic (ie, lipid) surfaces.

Ionic solids, such as calcite ($CaCO_3$), hydroxyapatite [$Ca_5(PO_4)_3(OH)$] and barite ($BaSO_4$) can acquire a surface charge via mechanism (4) by virtue of unequal dissolution of the oppositely charged ions of which they are composed. Addition of small concentrations (ca 10^{-3}M) of Ca^{2+} ions (by using for example, $CaCl_2$) can be used to adjust the net charge of a suspension of $CaCO_3$; the hardness of water becomes a factor that must be considered.

The Ca^{2+} ion is referred to as a potential-determining ion for the system to distinguish it from ions, such as Cl^-, NO_3^-, and K^+, that are termed indifferent ions because they are not expected to have any special interaction with the surface. In a similar manner, H^+ and OH^- ions are potential-determining for metal oxide and hydroxide suspensions.

Between these two extremes is what are termed specifically adsorbed ions because they appear to interact in some particular (chemical) way with the surface; surfactants

TABLE 1

Fundamental Parameters that Control the Nature and Behavior of all Particulate Suspensions

Interfacial Extent	Interfacial Chemistry
Particle Size and Distribution	Surface Charge
Particle Shape/Morphology	Nature/Type of Group(s)
Surface Area (External/Internal)	Number and Distribution
Porosity	Dissociation
	Preferential Adsorption
	Hydrophobic/Hydrophilic Balance
	Surface (Interfacial) Tension
	Contact Angle

Particle Sciences

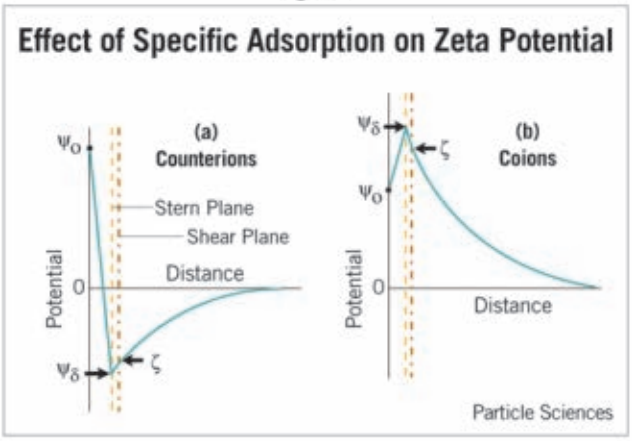
TABLE 2

Charge On Materials in Neutral Water

Positive	Negative
Ferric Hydroxide	Au, Ag, Pt
Aluminum Hydroxide	S, Se
Chromium Hydroxide	As_xS_y, PbS, CuS
Thorium Oxide	Stannic Acid
Zirconium Oxide	Silicic Acid
Basic Dyes (Methylene Blue)	Vanadium Oxide
Base Proteins (Protamines, Histones)	Acidic Dyes (Congo Red)
	Starch
	Viruses, Microbes
	Acid Protein (Casein)

Particle Sciences

FIGURE 2A&B



and polyelectrolytes fall into this category.

Mechanism (5) arises from the simple fact that most crystal lattices are anisotropic. Charge development occurs because of n and p defects in the crystal. This results in surface defects and, in the case of mineral oxides, a plethora of amphoteric hydroxyl groups that can undergo reaction with either H^+ or OH^-. One pharmaceutically useful material in this group is the silicas.[3] This is because, depending on how it was manufactured (synthetic) or processed (natural), the surface properties range from strongly hydrophilic (showing zero contact angle and a thick equilibrium wetted film) because of the surface silanol (-SiOH) groups to strongly hydrophobic (the surface siloxane groups, -Si-O-Si-, have ether-like properties). The silanol groups are weakly acidic, hence, the surface charge of the hydrophilic silicas tend always to be negative.

The oxides of most di- and trivalent metals (ie, MgO and Al_2O_3, respectively) are amphoteric; any dissolution tends to be in the form of the hydroxide, dissociated into its constituent ions (ie, $Mg^{2+} + 2OH^-$). In formulation, swings in solution pH must be avoided because it can cause re-precipitation back onto the oxide surface in a different chemical form thus altering the surface chemistry and hence charge.

Mechanism (6), isomorphous substitution, is a more extreme case of mechanism (5). It occurs in alumino-silicate clay materials (ie, montmorillonite and vermiculite), where a large negative charge is initially developed on the clay crystallite because of the difference in valence between the Al^{3+} and the Si^{4+} ions.[4] However, isomorphous substitution with varying proportions of minor elements leads to a dizzying variety and complexity of minerals.[5] It is this diversity of crystal chemistry that gives rise to the differences in morphology - from the microscopic needles of palygorskite clay to the massive sheets of muscovite mica. Thus, the net surface charge of any clay is a weighted mean of the various exposed faces, and it critically depends on the clays' prehistory. Hence, care must be taken in formulation when using clays; it may not be possible to substitute or replace one clay from a given manufacture with another from a different manufacturer or supplier. It is critically important that the ZP versus pH profile be determined for suspensions of any clay material.

ELECTRICAL PROPERTIES IN NON-AQUEOUS MEDIA

In solvents with moderate dielectric constants (>10 cf ~80 for water), at least some degree of ionization is possible, and charging mechanisms parallel to those in water can occur. Examples include LMW alcohols, amines, aldehydes, and ketones; they are referred to as leaky dielectrics. Ionic surfactants (ie, Aerosol OT) and some simple ionic salts (ie, LiCl) can dissociate to some extent in such media.

However, the inability of an electrolyte to ionize in fully nonpolar media (solvents of very low dielectric, ~ 2, such as alkanes) has led to a mistaken belief that particles dispersed in such a medium cannot acquire a charge. However, carbon dispersed in benzene develops an appreciable positive surface charge in the presence of calcium alkyl silicate, or a negative surface charge using quaternary ammonium picrate. The sign of charge is opposite what would be expected if the charging mechanism were the adsorption of the conjugate larger ion. Thus, electrostatic forces are important and can play a key role in stabilizing non-aqueous suspensions, but the charging mechanism is not the same as in aqueous dispersions.[6,7] In non-aqueous media, it arises through the formation of ions in adsorbed films on the particle surface where acid-base (or electron donor-acceptor) interactions occur between the particle surface and the dispersing agent.[8,9] A solute that is an electron acceptor (or Lewis acid) will interact with an electron donor (or Lewis base) whether it finds that base on a substrate surface or in the solvent. Thus, acidic (ie, polyvinyl chloride) or basic (ie, poly[methyl methacrylate]) polymers are very effective suspendants of particles in non-aqueous media.

This is an extremely complex subject but very important technologically in electrophotography, electrophoretic displays (*vide* the Amazon Kindle), and electrodeposition of specialty coatings.[10] The industrial importance of electrical charges and surface charging in non-aqueous media has been extensively reviewed; it is of considerable interest in paints and coatings, lubrication technology, agrochemical, and cosmetic formulations and in the development of high-performance ceramics and magnetic recording hardware.[11] In pharmaceutics, it impacts the stabilization of APIs in propellant for drug delivery (to be discussed in Applications of ZP in Part 2).

Traces of polar impurities, especially water, play a key role; not only the magnitude but also the sign of ZP depend on the presence and amount of traces of water.[12-14] Thus, in any non-aqueous application, is it critically important to determine the water content of all components.

THE ELECTRIC DOUBLE-LAYER

It is first important to recognize that the solvated size of a particle is not the same as the dry size found, for example, in electron micrographic images. The extent of this solvated layer is influenced by the solution conditions, such as composition (ie, pH, ionic strength) as well as temperature and pressure, and it encompasses what is termed the electric double-layer that exists at charged interfaces.[15] The boundary between the edge of this

solvated layer and bulk liquid is termed the shear plane. It needs to be emphasized that it is this total solvated particle size that is measured by dynamic light scattering.[16]

Regardless of how charge separation is generated, the distribution of electrical charges at the interface is different from that in the bulk liquid phase. A structure called the electric double-layer will be developed such that the surface charge is neutralized by an adjacent layer in solution containing an excess of ions of opposite charge to that of the surface, ie, counterions. Ions of the same charge as the surface are termed coions. The theory of the electric double-layer, (EDL) is extremely complex and beyond the scope of this review; it deals with this distribution of counterions and coions around a charged particle in solution and hence with the magnitude of the resulting electric potential differences that occur in this region.[17,18]

The simplest model for the EDL, shown schematically in Figure 1, is that of Stern.[19] The EDL can be regarded as consisting of two regions or layers (hence the term electric double-layer): a region closest to the surface (the Stern layer) that is considered immobile (and it may include adsorbed ions) and an outer region (the diffuse layer) that allows diffusion of ions that are distributed according to the influence of electrical forces and random thermal motion.

The electric potential decreases linearly from ψ_0 (the actual thermodynamic surface potential) to the Stern potential, ψ_d, and then it decays exponentially to zero in the diffuse layer. It is described in the most simple mathematical model in the following equation:

Equation 1.

$$\psi = \psi_d \exp[-\kappa x]$$

Where x is the distance from the material surface, and κ, called the Debye-Hückel parameter, is defined in the following equation:

Equation 2.

$$\kappa = [2e^2 N_A c z^2 / \varepsilon\varepsilon_0 k_b T]^{1/2}$$

Where e is the protonic charge, N_A is Avogadro's number, c is the concentration of electrolyte of valence z, ε is the dielectric constant, ε_0 is the permittivity of free space, and k_b is the Boltzmann constant.

κ^{-1} is called the Debye length and is a measure of the thickness of the electric double-layer. For a single symmetrical electrolyte in water at 25°C, it can readily be computed from the following equation:

Equation 3.

$$\kappa^{-1} = 0.3041 / Z C^{1/2}$$

For aqueous electrolyte solutions, κ^{-1} is in the range of a few tens of nm. Hence, it can be seen that the electric potential depends (through κ) on the ionic composition of the medium. If κ is increased (the electric double layer is compressed), then the potential must decrease.

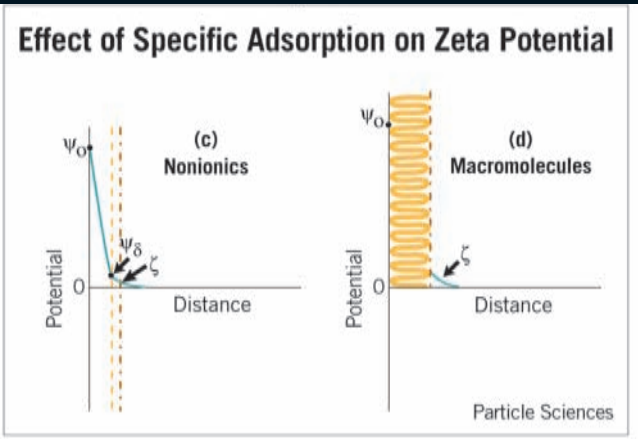
Unfortunately, the fundamental interfacial property ψ_0 (and hence, charge density, σ_0) is fundamentally inaccessible.[20] However, what can be derived (and ultimately measured) is an electrokinetic potential termed the ZP. This quantity is defined as the potential at the shear plane - so called because any relative movement of the surface with respect to solution will cause some of the counterions to be sheared off, resulting in only partial compensation of the surface charge. The location of the shear plane is never precisely known (estimates range from ~1 nm to ~10 nm) because in addition to ions, a certain amount of solvent will also be bound to the charged surface. In reality then, rather than a mathematical plane, it is a region of rapidly changing viscosity (and, possibly dielectric). Thus, ZP is not well defined. Nevertheless, it has become a very useful experimental parameter to monitor electrokinetic behavior of suspensions, especially changes in such behavior.[21]

THE RELATION BETWEEN ZP & SURFACE CHARGE

While it is apparent from the aforementioned that ZP is not the actual thermodynamic (or surface) potential, in theoretical calculations, it is frequently taken to be identical with the Stern potential. Any difference between the Stern potential and ZP will be most pronounced when the real surface charge is very high (ie, completely dissociated COOH groups on polymer latex particle) or at high electrolyte concentrations (ie, physiological saline).

When specific adsorption of charge carriers takes place at a surface, counterion adsorption usually predominates over coion adsorption. Examples would be Ca^{2+} adsorbed on a negatively charged silica surface or PO_4^{3-} on a positively charged alumina surface. With polyvalent and, certainly, surface-active counterions, it is even possible for a reversal of charge to take place within the Stern player, ie, for surface potential and Stern potential (and hence ZP) to have opposite signs (Figure 2 A&B). Further, the adsorption of nonionic (ie, polyoxyethylene-based) surfactants would result in a ZP being close to zero (Figure 2 C&D). Adsorption of surfactants occurs

FIGURE 2C&D



primarily through hydrophobic bonding. Also, as the MW of any macromolecular species increases, it results in the shear plane being located at a larger distance from the Stern plane and, in consequence, ZP being significantly smaller than ψ_d. All these types of charge-modifying agents are used extensively in formulations of suspensions.

Thus, it is entirely possible that a surface can have an inherent (thermodynamic) charge but have no measurable ZP and vice-versa.[22] This does not mean to imply that the ZP measurement is not useful. On the contrary, ZP is in the practical sense the effectiveness of the particle surface charge in solution. While ZP may derive initially from the fundamental number of surface sites (how many, what type, etc), more importantly, from a practical application, are the solution conditions themselves because they control the resulting final sign and magnitude of ZP. The consequence of this to the process of dispersing particles is critical. And importantly, it is useless to quote a ZP value without specifying the suspension conditions under which the measurement was made.

Most suspensions are prepared at some fixed concentration of solids, and because it is necessary to dilute the original material for ZP measurement (Part 2 will cover methods and techniques for measuring ZP), this matter also impacts very much the sample preparation required for ZP measurements. The question then becomes whether one dilutes into pure (distilled/deionized) water under some fixed conditions of pH and specific conductance, and monitors the change with time. This will impact the situation when performing a pH titration. In which direction should the titration be carried out? Does one start at neutral and increase pH to some highly basic condition and then titrate back down to neutral and then continue to decrease the pH to some highly acid condition; or does one go backward and forward? While this may seem to be taking a rather nit-picking approach, it has been demonstrated that ZP measurements of $CD4^+$ T-Cells as a function of pH can reflect different rates of the respective ionization and association that occur in the surface functional groups as a consequence of the different changes in the hydration-dehydration reactions involved.[23] Or, does one dilute into the supernatant of the colloidal system itself by checking first the solution conditions (pH, conductivity, and the interfacial tension)? No matter what, in order to study the effect of adding any charged moiety, it is imperative to start with solution conditions giving an initial constant ZP so that only one variable is changed.

Part 2 will conclude by covering techniques available to measure ZP and as well as provide some applications to illustrate its usefulness.

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BIOGRAPHIES

Dr. David Fairhurst is a Corporate Research Fellow at Particle Sciences Inc. He earned his PhD in Physical Chemistry in 1968 from Liverpool Polytechnic, UK, where he was also a Lecturer (in Physical Chemistry) for 4 years. He spent 2 years as a Visiting Associate Professor in the Center for Surface and Coatings Research at Lehigh University and subsequently held senior research positions with the UK Chemical Defense Establishment, Porton Down and with Union Carbide Corporation, USA. The work encompassed exploratory and basic research, product formulations, and development and technical services. He has spent the last 40 years in using colloid and surface chemistry to solve problems in industrial and pharmaceutical applications and has published more than 100 technical papers, scientific articles and book chapters in the open literature. Prior to joining PSI in 1993, he was, for 7 years, Director of Applications at Brookhaven Instruments Corporation and is an internationally recognized authority on dispersion and emulsion technology and in the assessment and characterization of particle size.

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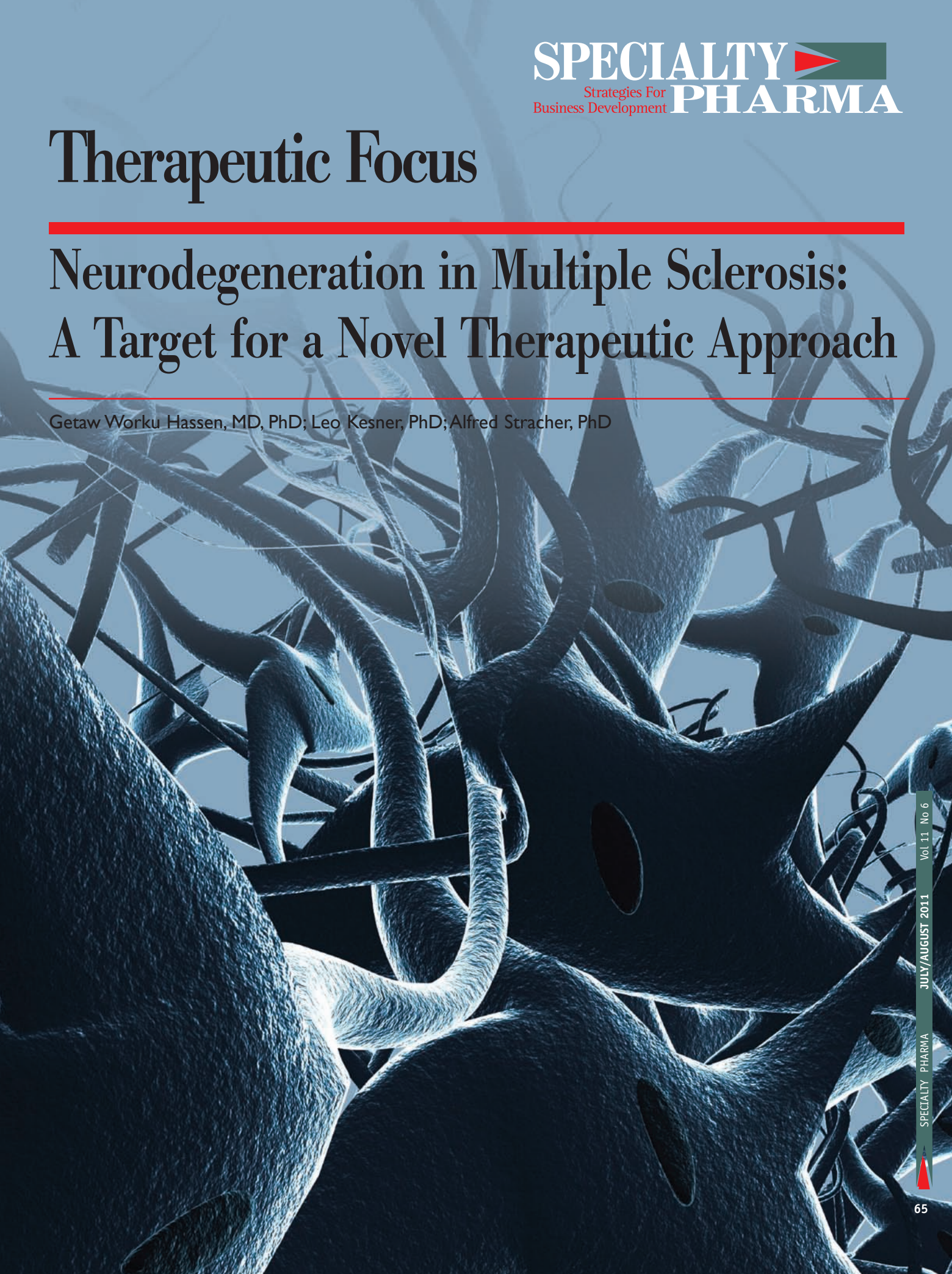
SPECIALTY PHARMA
Strategies For Business Development

Therapeutic Focus

Neurodegeneration in Multiple Sclerosis: A Target for a Novel Therapeutic Approach

Getaw Worku Hassen, MD, PhD; Leo Kesner, PhD; Alfred Stracher, PhD



Abstract

Multiple sclerosis (MS) is a chronic disease that results from inflammation and neurodegeneration. The current treatment strategy for MS involves anti-inflammatory drugs and disease-modifying agents that do not target the neurodegenerative component of the disease. Axonal injury has been shown to be the major correlate of neurodegeneration that eventually leads to permanent disability. Axonal injury is believed to result from cytoskeletal protein degradation by proteases such as calpain. Targeted calpain inhibition may play a pivotal role in the treatment of MS. In this review, we discuss the role of proteases and protease inhibitors as a therapeutic option for the treatment of MS.

Introduction

Multiple sclerosis is a chronic disabling disease of young adults that consists of inflammatory and neurodegenerative components.[1] It is the major cause of non-traumatic disabling disease of young individuals.[2,3] Demyelination associated with inflammation with relative sparing of axons is considered the pathologic hallmark of MS.[2] Studies using MRI and histopathological techniques have emphasized the role of axonal injury in addition to the well-known demyelination and inflammation.[4-10]

Currently, the consensus on the pathogenesis of MS is that autoreactive T-cells, activated in the periphery, cross the blood-brain barrier (BBB) into the central nervous system (CNS), where they re-encounter antigens presented by antigen-presenting cells (APC).[11,12] This process causes secondary influx of additional lymphocytes and blood-born macrophages to the inflammatory site.[13-15] The inflammatory cells produce nitric oxide (NO), tumor necrosis factor (TNF)-alpha and proteases, including calpain that individually or together contribute to the destruction of myelin and eventually cause axonal injury.[16-18]

Calpain has been implicated in myelinolysis.[19] It is significantly elevated in the white matter of MS patients and is increasingly expressed in the inflammatory cells in MS lesions, suggesting a role in the pathogenesis of the demyelinating disease.[20, 21]

Demyelination leads to impairment or loss of axonal conduction. In demyelinated axons, increased expression and redistribution of particular Na^+ channels temporarily restore axonal conduction, a process leading to increased influx of Ca^{2+} ions that ultimately activates enzyme cascades, including axonal calpain.[22-24] Axonal injury in MS was first described by Charcot in 1868. Although damage to the axons has been described as a key factor for disability in MS, much less is known about the pathogenesis of the axonal damage.[25] These have been recently studied and shown by brain imaging, histopathological and axonal transport studies.[7,8,10,26-30]

Improvements of MS symptoms are, in part, the result of increased expression of Na^+ channels. The increased sodium influx leads to the activation of sodium-calcium-exchanger (NCX) at the axons. This process leads to increased influx of noxious Ca^{2+} that ultimately activates different enzyme cascades, including axonal calpain.[22-24,31-33] The abnormal and prolonged activation of axonal calpain has been proposed as a major component in the pathophysiology of axonal injury in MS and experimental autoimmune encephalomyelitis (EAE), which ultimately leads to degradation of cytoskeletal protein, such as alpha-spectrin, resulting in neurodegenaration and subsequently to permanent disability.[33-35] In fact, in chronic forms of MS, especially secondary-progressive MS and EAE, the severity of the disease and degree of permanent disability corresponds more to the extent of axonal damage than myelin damage.[4,5,8 36-41]

Current treatment options target the inflammatory component of the disease, and little attention has been given to the neurodegenerative component, which ultimately leads to permanent disability affecting the quality of life for MS patients.[1,42] The therapy for MS has changed over the past several years as a result of intensive studies and drug trials on animal models. Recent findings in the immunological and pathophysiological aspects of the disease, advances in biotechnology, modern imaging, and improvements in clinical trials have led to a variety of therapeutic approaches. Scientists and physicians have tried combination therapy in order to act on different aspects of the disease.[11,43] This approach reduces the side effects of the individual drugs and potentiates the pharmacological efficacy of the treatment. All current treatment options are immunosuppressive or immunomodulators, affecting predominantly the inflammatory component of MS. These drugs do little or nothing to protect the axonal injury, the major correlate of permanent disability. Their efficacy is limited in the late stages of the disease in which axonal injury predominates. It is crucial to develop a drug that is more effective and with a different mode of action for preventing axonal injury.

Several protease inhibitors have been tested as potential therapeutic agents in EAE and other animal models of neurodegenerative diseases.[44-48] One limiting factor for using protease inhibitors has been their inability to cross the BBB.[46,48] Consequently, developing calpain inhibitors with improved characteristics has been a focus of intensive research.

Future Treatment Strategies & Options

MS is a disease characterized by inflammation and neurodegeneration, especially in the late phases. Most drugs currently available target the inflammatory aspect of the disease. In patients with secondary progressive MS, disability results from accumulation of axonal injury and neurodegeneration. Targeting neurodegeneration for the treatment of MS is of paramount importance. Proteases, especial calpain, have been implicated in the pathophysiology of MS and other neurodegenerative diseases. Calpain has been implicated in the pathophysiology of axonal injury and neurodegeneration in MS and has been a focus of intensive research in developing agents that inhibit calpain and suppress or ameliorate MS.

Calpain is involved in both inflammatory and neurodegenerative components of EAE, an animal model of MS. Calpain inhibitors have been successfully tested in the treatment of animal models of MS.[44-46, 49-57] Studies from our laboratory with the novel calpain inhibitor and other groups have demonstrated the effect of calpain inhibitor in suppressing inflammation and demyelination as well as axonal injury. Ongoing efforts have been made to develop protease inhibitors with improved properties. Our laboratory has been working on developing targeted protease inhibitors for a better action. We have developed several protease inhibitors with different characteristics. Here, we describe one of the protease inhibitors (CYLA) and its specificity with regard to organ systems.

Cysteic-Leucyl-Argininal (CYLA)

Taurine (2-aminoethanesulfonic acid) is a β-amino acid that relies upon a Na^+-dependent transport system to pass through cell membranes.[58] Two distinct Na+-dependent high-affinity taurine transporters have been cloned. The brain synthesizes only limited amounts of taurine and thus significant amounts must be transported into those parts of the brain that require it.[59] Cysteic acid (α-amino-β-sulfo-propionic acid) shares structural similarities with taurine. It is a competitive inhibitor of taurine transport and thus utilizes the same transport mechanisms.[60,61] Cysteic acid has a carboxyl group in addition to the sulfonic acid and amino groups. This provides another functional group, not required for transport, to which other compounds, such as the calpain inhibitor leucyl-argininal, can be attached. Neurodur is synthesized by attaching cysteic acid to the leucyl-argininal of leupeptin. This enables Neurodur to use taurine transporters to cross the BBB. The striking feature of Neurodur at crossing the BBB, its ability to permeate across cell membranes, and the availability at the CNS are essential for reducing calpain activity. The effect of Neurodur in suppressing inflammation, demyelination, and protection of axonal injury in acute and chronic EAE has been shown in our previous works.[62,63]

Results from our studies have shown increased expression of calpain in EAE. Treatment with a novel calpain inhibitor from our laboratory, CYLA, demonstrated significant suppression of calpain expression within the inflammatory cells, reduced tissue calpain content, and suppressed axonal injury in chronic EAE. In addition, markers of axonal injury and calpain content within neurons were significantly reduced with the treatment by CYLA.[62,63] The results of our studies suggest that calpain is involved in both components of MS, and treatment with calpain inhibitor led to significant improvement of the disease. Moreover, calpain is involved in the late phase of the diseases, leaving a window of opportunity for therapeutic intervention. This makes protease inhibitors interesting as they could be given at a later time and still be effective. In one study, protective effect of calpain inhibition was shown up to 6 hours post focal ischemia in rats.[64]

Current anti-inflammatory and disease-modifying agents can only be useful in suppressing the inflammation to ameliorate the disease temporarily. It would be more beneficial for patients to be able stop the progression of the disease rather than treating the acute exacerbations. Our drug has those two advantages, ie, targeting both inflammation and neurodegeneration. In addition, it also has the advantage of crossing the BBB making it suitable for chronic stages of MS in which injury to the axons occur behind the relatively intact BBB.

Previously, it was believed that axonal injury, the major correlate of permanent disability, was prevalent in the late stages of MS. Modern imaging techniques and improved histological methods have shown the involvement of axonal injury in the acute phase of the disease as well.

In addition, remyelination also depends on intact axonal transport because some myelin components are transported via axonal movement.[65,66] Impaired axonal transport might lead to inadequate or absence of remyelination. We have observed axonal injury in early stages of EAE using APP immunostaining. This suggests that the impaired remyelination maybe due to axonal injury, impaired axonal transport of myelin components, and impaired remyelination.

Impaired remyelination triggers increased expression of sodium channels, increased influx of calcium into the neurons, abnormal and prolonged activation of calpain, and worsening of axonal injury, resulting in neurodegenration. Therefore, early application of protease inhibitors may be necessary in preventing axonal injury and improving remyelination.

CYLA, is a calpain inhibitor with the additional ability to cross the BBB, making CYLA a suitable agent for the treatment of MS, particularly in the chronic stages in which repeated axonal injury is believed to occur more or less behind closed BBB.

Conclusion

Given the multiple therapeutic indications for calpain inhibition in various neurodegenerative and other disorders, an achievement of selective inhibition of these enzymes is an important pharmacological goal. Combination of drug groups, each with a different mode of action, can be used as supplemental agents to the existing MS drugs. This leads to the use of individual drugs in a minimum dose that would result in fewer side effects and in a synergistic effect of the combination of the individual drugs.

Given the role of calpain in the pathophysiology of MS, calpain inhibitors bear a potential for the treatment of MS. More studies using relapsing-remitting disease models are necessary to better show their usefulness in a model that reflects the natural course of the majority of MS patients.

Acknowledgement

The authors would like to thank Drs. Lynette Sheffield and Ronald Shaw for proofreading the manuscript.

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Dr. Getaw Worku Hassen graduated from Johannes Gutenberg University School of Medicine, Mainz, Germany in 2000 and joined the Department of Neurology of the University Hospital until 2002. He then joined the School of Graduate Studies in Neural and Behavioral Science at SUNY Downstate Medical Center and earned his PhD in 2006. During his graduate year, Dr. Hassen conducted experiments using targeted-calpain inhibitors in the treatment of multiple sclerosis using animal models. Two papers are published from this project. Dr. Hassen continued his clinical training in the Departments of Surgery at Maimonides Medical Center and Emergency Medicine at Metropolitan Hospital Center from 2006 till 2010. He is currently Assistant Professor in Emergency Medicine at NYMC, Metropolitan Hospital Center and a Clinical Instructor in the Department of Neurology at SUNY Downstate Medical Center. Current projects include the use of targeted-calpain inhibitors and hypothermia in retinal ischemia and collaborative studies in animal models of Huntington's and Parkinson's disease.

Leo Kesner, PhD

Active Member
Graduate School at Downstate Medical Center

Dr. Leo Kesner is an active member of the Graduate School at Downstate Medical Center. He participates in research at several levels and supervises the research of Graduate Students. He is a graduate of The Bronx High School of Science, City College of NY (Chemistry) and Downstate Medical Center (Biochemistry). He has spent sabbatical periods at Rockefeller University and Bern, Switzerland. Dr. Kesner has 52 scientific publications to his name and 9 patents. Drs. Kesner and Stracher have formed two corporations to assist in commercializing their inventions, one called Ceptor and the other Protor. The patents protect substances designed to couple a targeting agent to a pharmaceutical agent. This provides for greater and more selective tissue penetration. In the case of a calpain inhibitor, it is designed to penetrate the blood-brain barrier and blood-retina barrier.

Alfred Stracher, PhD

Past Chairman
State University of New York Downstate Medical Center

Dr. Alfred Stracher earned his PhD in Chemistry from Columbia University in 1956. He carried out post-doctoral studies at the Rockefeller Institute with Dr. Lyman Craig for 2 years and spent a third year at the Carlsberg Laboratory, Copenhagen in the laboratory of Linderstrom-Lang. He joined the State University of New York Downstate Medical Center as an Assistant Professor of Biochemistry and in 1972 was appointed Chairman of the Department until he stepped down in 2006. His research has focused on degenerative diseases, particularly neuromuscular and neurological. He has studied the potential of using protease inhibitors as therapeutic agents in a variety of these diseases and has shown beneficial effects in animal models of Duchenne Muscular Dystrophy, Multiple Sclerosis, Parkinson's Disease, Hearing Loss, Huntington's Disease, and Traumatic Brain Injury. He has also developed a means of targeting these low molecular weight, orally administered inhibitors directly to the CNS and/or skeletal muscle, and in the case of the CNS, the drugs are carried across the BBB readily. Dr. Stracher was appointed as Distinguished University Professor in 1998 for his outstanding contributions to science.

Executive Summary

Steven Bettis
President & Co-Founder
Eyetech Inc.

Eyetech Inc.: Employee-Owned Biotech Dedicated Exclusively to Retinal Diseases

The treatment of ocular diseases has emerged as an area of explosive growth and investment for biopharmaceutical companies of all sizes. Since the 2005 launch of Macugen® (pegaptanib sodium injection), the first anti-VEGF therapy for the treatment of neovascular age-related macular degeneration (AMD), an entirely new market has opened for therapies with the same mechanism of action. After decades of suboptimal treatment for this leading cause of blindness, retina specialists now have several pharmacotherapies with the potential to delay vision loss and even improve vision in some patients. When the burst of activity in anti-VEGF therapy left the future uncertain for Macugen, employees of (OSI) Eyetech, the company that had developed and launched Macugen alongside Pfizer Inc., decided to take the product they believed in so fiercely into their own hands. Eyetech Inc. was relaunched in August 2008 as a 100% employee-owned and -operated company with rights to market and sell Macugen in the US. Unique among biotechs as a company dedicated solely to diseases of the retina, Eyetech is now turning its attention to a major limitation of current anti-VEGF therapies: Their frequent administration (every 4 to 6 weeks) by injection into the eye. This delivery paradigm is a burden for physicians and patients alike, and also has safety implications. To overcome this treatment barrier, Eyetech is developing a sustained-release formulation of Macugen in partnership with SurModics Pharmaceuticals, Inc. Specialty Pharma caught up with Steven Bettis, President and Co-Founder of Eyetech, to learn more about the company's remarkable inception, ongoing efforts to improve the administration of Macugen, and how the treatment landscape of retinal diseases is changing for the better.

Q: ***How has Macugen changed the AMD treatment paradigm?***

A: As the very first VEGF-inhibitor approved for use in the eye, Macugen revolutionized the treatment of wet AMD, a disease that previously had very limited treatment options. AMD is the leading cause of vision loss, so the approval of Macugen was a huge triumph for retinal specialists and their patients. In terms of its impact on the broader landscape, I'd say our approval attracted the attention of a lot of other companies that saw great potential in the retinal disease space - not only for AMD but also for other diseases that could be treated in a similar way, such as retinal vein occlusion (RVO) and diabetic macular edema (DME). After our approval, we quickly saw a major surge in the market for retinal disease treatments. Of course, the heightened competition is tough for us at times, but we look at it as an incredible opportunity for the doctors and patients we serve. It reminds me of where oncology was 20 to 25 years ago. With so much attention on retinal diseases and so many new treatments becoming available, I believe we'll see a shift from a monotherapy approach to a cocktail approach, in which doctors can tailor the protocol to an individual patient's needs.

Amidst all this, I'm confident Macugen remains a critical piece of the puzzle. Macugen is the only selective anti-VEGF therapy, which means it targets VEGF-165, a specific receptor that plays a key role in the

formation of new blood vessels and increased leakage of blood vessels. Because AMD and other retinal diseases are treated chronically, we believe Macugen is an important alternative to non-selective therapies that expose a broader range of VEGF receptors to therapy.

Q: *What are your development plans for Macugen in AMD?*

A: Right now, one of the major limitations of anti-VEGF therapy is that patients need to receive frequent injections. The FDA-approved dosage regimen for Macugen is once every 6 weeks (or about 8 times per year) and for Lucentis, one of our competitors, it's once every 4 weeks (or 12 times per year). The frequent injections are cumbersome on many levels. It's uncomfortable and inconvenient for patients, it's a scheduling burden for physicians, and it exposes patients repeatedly to complications from injections, including a low risk for an infection known as endophthalmitis. And we know that if patients miss or delay a dose, their vision can decline.

To overcome this limitation, we're working with a world-renowned drug delivery company called SurModics to develop an extended-release formulation of Macugen based on microparticle technology. The product, now known as pegaptanib ER, would be delivered by intravitreal injection just like Macugen, but with the goal of decreasing the dosing frequency from every 6 weeks to once every 4 to 6 months. The successful development of pegaptanib ER would be a phenomenal step for both patients and physicians because it would reduce the number of injections to just a handful per year.

In the meantime, while frequent dosing remains the status quo, we're taking steps to help ensure safety and comfort for patients. Eyetech developed and introduced Luer Lok® syringe delivery, an FDA-approved prefilled syringe designed for intravitreal injection of Macugen. The entire syringe package is terminally sterilized for delivery safety and contains an improved, detached 30-gauge needle for comfort and consistency.

Q: *Can you describe the partnership with SurModics?*

A: SurModics is a leading drug delivery company that has extensive experience in microparticle technology, which uses bioresorbable, polymeric particles to encapsulate a therapeutic agent and enable its gradual release over an extended period of time. We're thrilled to be working with a world-class team of scientists at SurModics to apply this leading-edge technology to Macugen.

Under a licensing and development agreement, Eyetech has the worldwide rights to the Macugen Microparticles program. SurModics owns a patent (US Patent No. 6,706,289) that expires in 2021, and has also filed for additional foreign patents. Eyetech has filed for three patents in the US and internationally, which, if issued, will expire in 2026.

Q: *Is Eyetech developing Macugen beyond AMD?*

A: Our core focus is in AMD, and we continue to see growth in that category. At the same time, we're committed to exploring the breadth of Macugen's potential. A Phase III study of Macugen in patients with DME, a common complication of diabetes, met its primary endpoint of the number of patients treated with Macugen who gained greater than 10 letters of vision at 1 year compared to patients who received a sham procedure. This study was conducted by Pfizer Inc, which markets Macugen outside the US. Based on positive results, Pfizer is seeking regulatory approval of Macugen for the treatment of DME in the European Union.

Q: *What sets Eyetech apart from other biotech companies?*

A: Without a doubt, it's our people who set us apart from other companies. There was a point at which the future of Macugen was hanging in the balance, and our employees said, "This is a product we believe in. We're going to keep it alive." And that's when we made a bid for the business. Since then, our staff has increased almost three-fold, Macugen sales have accelerated each year, we're investing in new R&D, and we're forging relationships with new customers every day. Working at Eyetech is not just a job. It's a day-in, day-out commitment to our motto: Science. Vision. Hope. We're passionate about our product because it serves an unmet need in retinal disease. And that's a sentiment that's shared at every level of our business. ■

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Crunch Time: Obtaining the Finacial Commitment

By: John A. Bermingham

My past two articles have discussed two of several important factors regarding a company start-up, the *Escalator Test* and *The Rest of the Story*. Now for *Crunch Time*! Obtaining the financial commitment from an investor.

Our company, AgraTech International is now in that position. We have refined our Escalator Pitch to an informative 3- to 4-minute overview of the company, have professionally printed and bound our Executive Summary and Business Plan, and have a 14-slide Power Point Presentation ready to go for our investor meetings.

Why only 14 slides? Because an investor only wants to see 13 to 15 slides in a meeting of this nature. If the investors have interest following the presentation, they will then ask for subsequent meetings for due diligence, and you will be expected to present significant amounts of information and to answer a great deal of questions at that time.

One thing to always keep in mind is that an investor does not bet on the race horse. The investor bets on the jockey. Therefore, the investor wants to be impressed by you, not the Power Point. The tough part is getting the investor to respond to your solicitation for a meeting. This is what AgraTech is currently facing, and it is important not to become discouraged.

Sending your Executive Summary and Business Plan directly to venture capitalists is a good way to get started, but doing that alone will have limited results. You must follow up your mailing (or e-mailing) with phone calls to those venture capitalists. Venture Capital companies get loads of business plans each week, and many are never read due simply to the volume. A call to the venture capitalist saying that you are following up on your mailing often results in a response of, "I don't recall seeing it." That's probably true because your mailing is probably somewhere down in the pile of business plans on his or her desk with more plans being stacked on top daily. Or it is on the desk of a junior associate who is doing the same thing.

So you will probably have to re-send your documents again directly to the person you spoke with and then follow up with yet another phone call to that individual. But this time, your odds are greatly increased for having your information at least read.

Another method for raising money is to network with financial advisors, investment firms, law firms, accounting firms, work-out firms, and companies that are already in your industry. They can be a wealth of information and will recommend venture capitalists, angel investors, and high net worth individuals who might be interested in making an investment in your company. Also, companies already in your industry may look to invest in your company for an equity position.

Finally, do not resist the idea of offering a success fee to these firms who may recommend an investor who actually does invest in your company. The Lehman formula is pretty standard in this area and can be found on any Internet search engine. AgraTech is conducting all of the above strategies right now, and we are beginning to see positive results. So, if you are interested in making a hundred thousand or so in a success fee for finding an investor for us, let me know! My e-mail is John.Bermingham@agratech.net. Perhaps I can return the favor to you one day. ◆

BIOGRAPHY

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

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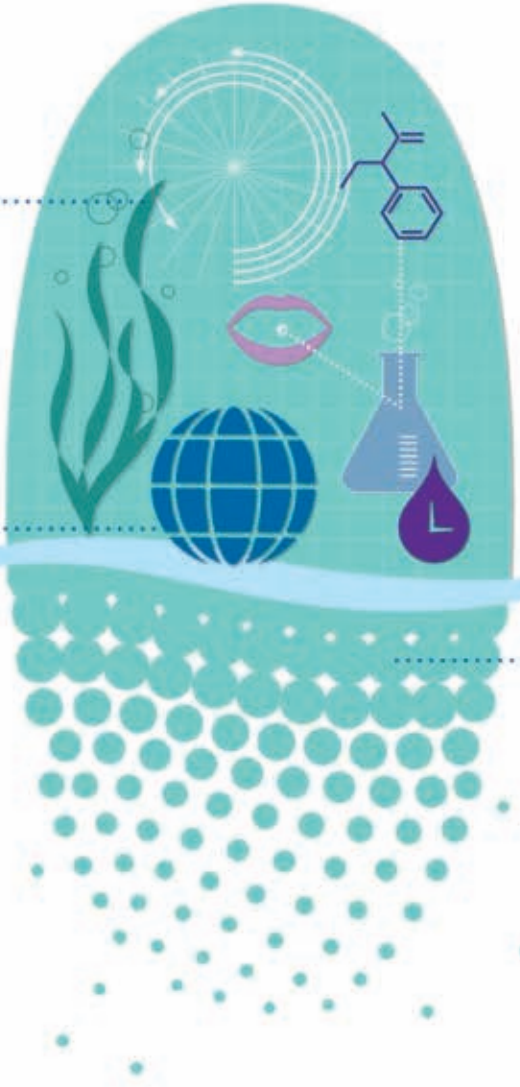

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