Drug Delivery Technology®

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Hand-Held Injection's Significant Impact

IN THIS ISSUE

INTERVIEW WITH MEADWESTVACO'S PRESIDENT

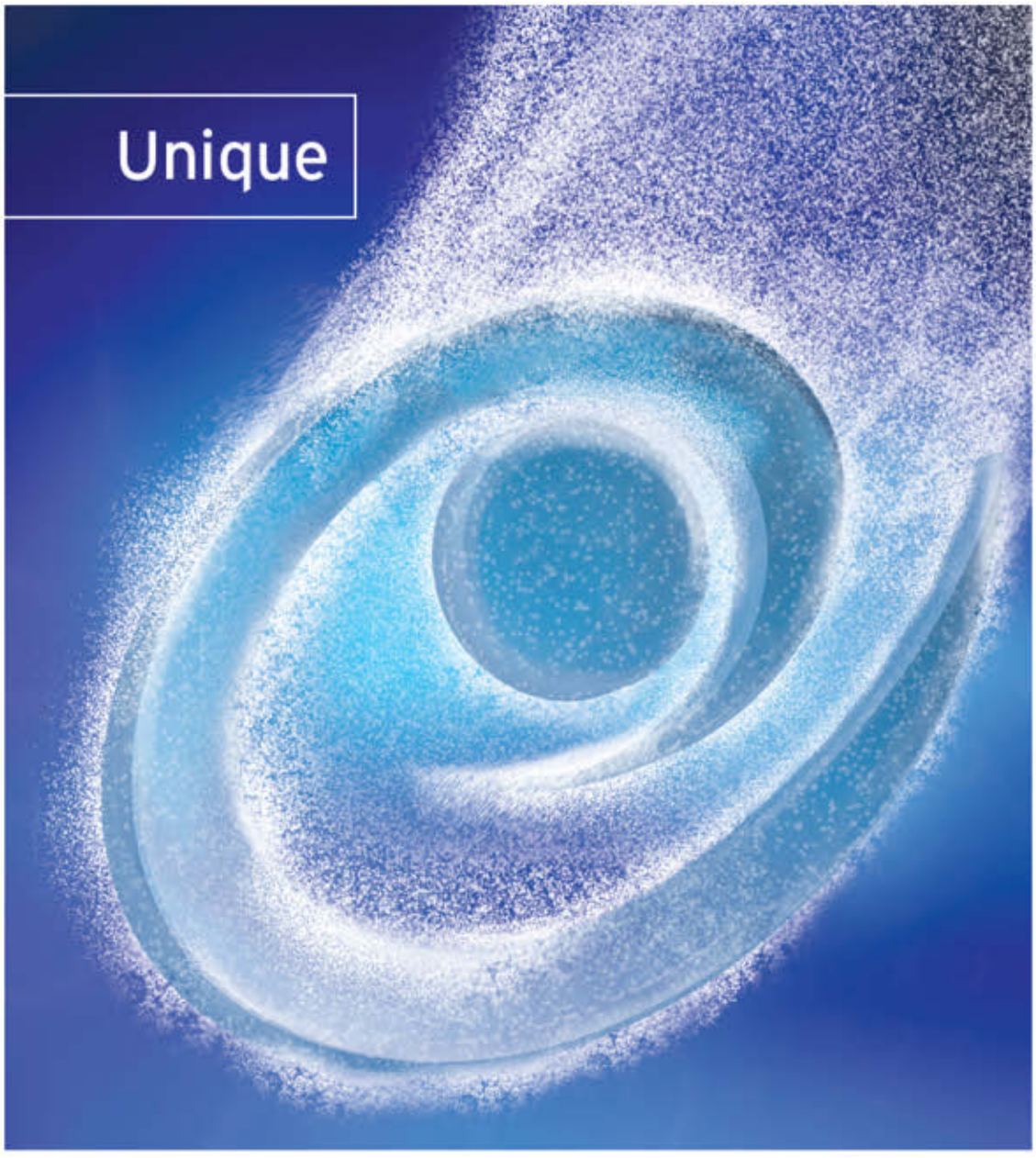
DR. TED LITHGOW

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

Avani F. Amin, PhD
Nanoparticulate Carrier Drug Delivery Systems: A Mini Review of Patented Technologies

Clifford M. Davidson, Esq.
Patent Procurement - Fast Tracking to Protection

Daniel G. Chain, PhD
ANTISENILIN® Monoclonal Antibody Platform to Prevent Accumulation & Neurotoxicity of Aβ in Alzheimer's Brain



Unparalleled taste Flexible dose Versatile release Robust tablet

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Eurand's AdvaTab is an orally disintegrating tablet (ODT) technology that combines superior taste and mouth feel properties in a robust tablet. AdvaTab is unique, offering both high dose capacity and modified drug release making it the most broadly applicable ODT available. Utilization of standard tabletting processes allows for cost-efficient manufacturing and conventional packaging.

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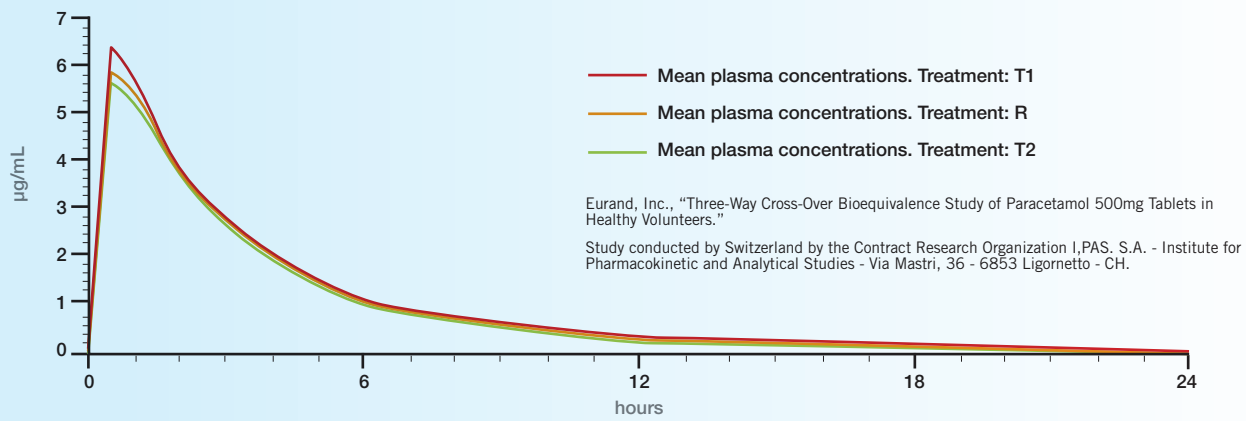
CLINICAL TRIAL RESULTS

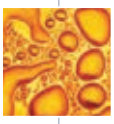
Eurand completed a study of AdvaTab® Paracetamol 500mg in 24 healthy volunteers. The product was administered with and without water versus the reference (Paracetamol) 500mg immediate-release tablets.

Paracetamol three-way comparative bioavailability study



Eurand, Inc., "Three-Way Cross-Over Bioequivalence Study of Paracetamol 500mg Tablets in Healthy Volunteers."

Study conducted by Switzerland by the Contract Research Organization I,PAS. S.A. - Institute for Pharmacokinetic and Analytical Studies - Via Mastri, 36 - 6853 Ligornetto - CH.

AdvaTab® is distinct from other ODT technologies in that it can be combined with Eurand's proprietary Microcaps® technology. The pairing of AdvaTab® with Microcaps® creates products that offer the dual advantage of a patient preferred dosage form, together with a superior taste and smooth mouth feel. This is a critical advantage as the unpleasant taste of drugs is a significant restriction in the application of other ODT technologies.

Patient Advantages:

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- Unparalleled taste
- Convenient oral drug administration without water
- Easier to swallow—AdvaTab® typically disintegrates in less than 30 seconds
- Improved patient compliance

The AdvaTab® Advantage:

- Superior taste-masking
- High dose capacity per dosage unit
- Controlled drug release capabilities
- Robust tablets—packaging choices include both standard bottles and push-through blisters

Partnering with Eurand to market AdvaTab® Paracetamol provides:

- Patent protection
- Product differentiation
- Market expansion
- Product portfolio lifecycle management

AdvaTab® TECHNOLOGY

The proprietary production method used to make AdvaTab® products provides product features that further enhance its performance. Traditional tablets are produced using an internal lubrication system in which lubricant is incorporated throughout the tablet blend, its primary purpose to act as a lubricant between the tablet surface and the metal surfaces of the tablet press. The internal lubricant makes the tablet hydrophobic and necessitates the use of higher tablet compression forces for a given tablet hardness.

AdvaTab® tablets are compressed using a patented external lubrication system in which the lubricant is only applied to the tablet surface. As a result, the tablets are hard and durable, do not require high tablet compression forces during manufacturing and do not repel liquids such as saliva when ingested. Consequently, AdvaTab® tablets are robust, disintegrate rapidly in the oral cavity and the tablet compression step does not lead to breakage of the drug particles.

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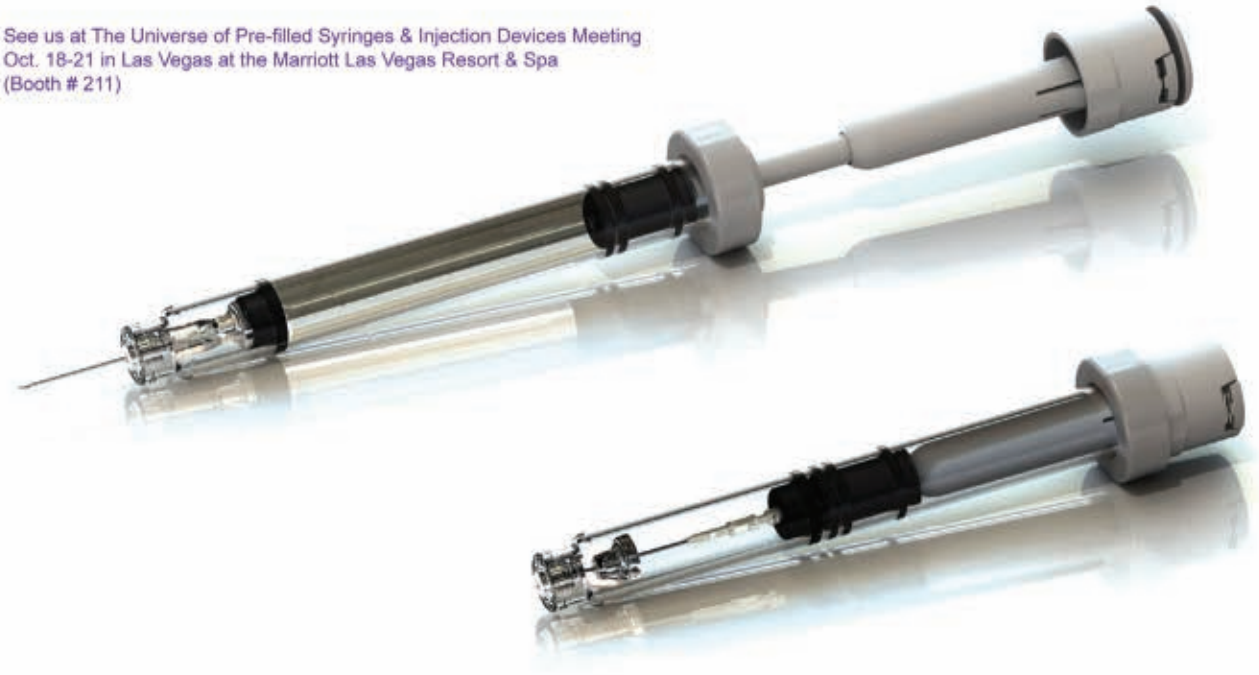

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Home Delivery

"Injectable drug delivery devices are increasingly all about the safe and simple delivery of prescription medication by patients outside of the healthcare facility. The transition of healthcare from hospitals and into the homes of patients is beneficial in reducing financial pressures on healthcare facilities and allowing patients to go about their daily lives with minimal disruption."

p.32

Table Of Contents

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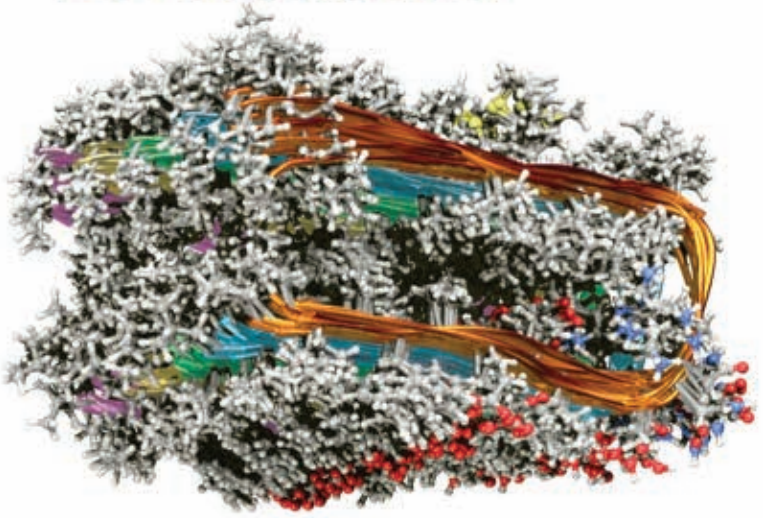

"ANTISENILIN® antibodies are selected on the basis they only bind to epitopes that contain either one of these molecular signatures, thus safely helping to shuttle Aβ away from sites of damage in the brain without the possibility of interfering with the functions of APP on the surface of nerve cells. Moreover, when these drugs are administered via the bloodstream, they do not run the risk of binding APP on the surface of blood platelets, which could potentially cause clotting."

p.64

Table Of Contents

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Market News and Trends

Endo Pharmaceuticals to Buy Penwest for About $168 Million; Submits NDA for Long-Acting, Crush-Resistant Oxymorphone

Endo Pharmaceuticals recently announced actions designed to advance the company's leadership and growth in pain management, including an agreement to acquire all outstanding shares of Penwest Pharmaceuticals for $5.00 in cash per share, or an estimated enterprise value of approximately $144 million at the time of deal close. Penwest has been working with Endo since 1997 on the development and commercialization of OPANA ER and receives a royalty stream on net sales of the product.

"Our acquisition of Penwest sets the stage for maximizing the value of the OPANA franchise and for leveraging Penwest's drug delivery technologies and pipeline across our branded and specialty generics businesses for the benefit of patients," said Julie McHugh, Chief Operating Officer, Endo Pharmaceuticals. "This transaction highlights the growth potential of Endo's core Pain Management franchise, enhances our earnings, and creates significant value for shareholders of both organizations."

Under the terms of the merger agreement, Endo will shortly commence an all-cash tender offer to acquire 100% of the outstanding common stock of Penwest Pharmaceuticals for $5.00 per Penwest share. Endo will acquire any Penwest shares that are not purchased in the tender offer in a second-step merger, which is expected to be completed during the fourth quarter of 2010 at the same price per share paid in the tender offer. The tender offer will be subject to certain closing conditions, including a minimum condition that not less than a majority of shares of Penwest common stock are tendered into the offer. Tang Capital Partners, LP, and Perceptive Advisors LLC, shareholders of Penwest, and Jennifer Good, Penwest's President and Chief Executive Officer, who collectively own 38.6% of fully diluted common stock of Penwest, have committed to tender their shares in the tender offer. The transaction has been unanimously approved by the boards of directors of both companies.

Endo also announced the filing of an NDA with the US FDA for a new extended-release formulation of oxymorphone for the relief of moderate-to-severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. The new formulation was developed in partnership with Grunenthal GmbH. Grunenthal is an independent, global pharmaceutical company with long-time experience in the development of innovative analgesics. This formulation of oxymorphone is designed to reduce accidental misuse and deter certain methods of intended abuse.

"The level of opioid abuse has increased significantly over the past decade in the US and created significant challenges for physicians who prescribe opioids," said Ivan Gergel, MD, Executive Vice President of Research and Development, Endo Pharmaceuticals. "As a responsible company with a long-standing history in pain management, Endo is committed to applying our expertise to deliver a new crush-resistant opioid medication to deter non-medical abuse so that patients who experience moderate-to-severe chronic pain continue to get access to appropriate therapy."

The NDA submission is based on a non-clinical and clinical development program designed to demonstrate that the crush-resistant formulation of oxymorphone addresses attempts to break, crush, extract, powder, and pulverize the product.

NextWave Pharmaceuticals & Tris Pharma Enter Into CNS-Focused Development & Commercialization Agreement

NextWave Pharmaceuticals and Tris Pharma, both privately held companies, recently announced a new collaboration agreement to enhance NextWave's CNS product portfolio utilizing Tris Pharma's unique drug delivery technology for liquid and solid formulations. Tris has reacquired the rights to non-CNS products, including all the OTC products previously licensed to NextWave Pharmaceuticals.

NextWave will commercialize NexiclonXR (clonidine) Extended-Release Tablets and Suspension, which is the first ever 24-hour liquid extended-release product approved by the FDA. NexiclonXR has been cleared for marketing by the US FDA and will be introduced to wholesalers and pharmacies by NextWave in the second half of 2010. NextWave and Tris will also collaborate on the development of three additional CNS products, with an option to expand development to additional products. All products under the agreement incorporate Tris' OralXR+ technology for delivery of suspension or solid dosage forms, which provides up to a 24-hour delivery profile in taste-neutral formulations.

NextWave is an emerging CNS-focused specialty pharmaceutical company that develops and commercializes unique products utilizing proprietary drug delivery technology to address unmet needs in key therapeutic areas, with particular emphasis on the treatment of ADHD and related disorders.

Tris Pharma is a specialty pharmaceutical company focused on the research and development of drug delivery technology-based products. Through its OralXR+ platform, Tris has pioneered the delivery of sustained release in the liquid, chewable/ODT, and strip dosage forms so patients do not have to swallow a pill. Tris' Nobuse platform provides abuse-deterrence for opioids and other abuse-prone drugs. Tris' R&D and manufacturing facilities are located in Monmouth Junction, NJ.

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Market News and Trends

OptiNose Announces Positive Subgroup Analysis Evaluating Efficacy of Fluticasone Delivered With Novel Delivery Technology

OptiNose Inc. recently announced that a subgroup analysis of positive Phase II trial results has been published in the July/August issue of the American Journal of Rhinology & Allergy.

The paper, Impact of Baseline Nasal Polyp Size & Previous Surgery on Efficacy of Fluticasone Delivered With a Novel Device: A Subgroup Analysis, provides results showing that OptiNose's innovative bidirectional nasal device delivering fluticasone, a nasal steroid, is highly effective in progressively reducing the size or eliminating nasal polyps in patients with chronic rhinosinustis (CRS) with nasal polyps. The results also show the drug delivery technology was equally effective in treating patients with newly diagnosed and those with recurring nasal polyps post sinus surgery.

The excellent clinical results achieved offered a unique opportunity for analysis for subgroups with different baseline polyp size. Highlights of the multicenter, randomized, double-blind, placebo-controlled, parallel-group study of 109 adult patients with mild-to-moderate bilateral nasal polyps include the following: (1) patients with large nasal polyps saw significantly greater reduction at 4-, 8-, and 12-week periods with the OptiNose/fluticasone drug delivery technology; (2) the largest nasal polyps showed a mean reduction of 1.69 or 42% at 12 weeks; (3) more than 80% of patients with larger polyps demonstrated size reduction to the degree that they are classified as small polyps; (4) Patients with small nasal polyps realized a significant reduction at 4, 8 and 12 week periods; (4) the smallest nasal polyps showed a mean reduction of 0.56 or 28% at 12 weeks; (5) seven of the 27 patients in this subgroup (26%) completely resolved polyps on both sides of the nasal cavity after 12 weeks of therapy; and (6) the data show that the treatment was just as efficient in non-surgery and surgery subgroups with both experiencing approximate 35% reduction in polyp size.

OptiNose's bidirectional nasal delivery technology significantly improves delivery to the target sites deep into the nose where the openings to the sinuses are located, which is considered essential to achieving clinical effects in CRS with topical treatments. While exhaling into the device, the soft palate automatically closes off the nasal cavity completely. The breath enters one nostril through a sealing nozzle and triggers the release of particles into the airflow, carrying particles beyond the nasal valve to target sites. The air flow passes through the communication posterior to the nasal septum and exits through the other nasal passage in the opposite direction.

Quark Pharmaceuticals & Novartis Sign $670-Million Deal

Quark Pharmaceuticals, Inc., a world leader in the discovery and development of RNAi-based therapeutics, recently announced it has granted Novartis an option to obtain an exclusive worldwide license to develop and commercialize its p53 temporary inhibitor siRNA drug QPI-1002, currently the subject of a Phase II clinical trial.

Quark will receive initially a non-refundable fee of $10 million. In the event that Novartis exercises the option, Quark would receive option exercise fees and milestone payments that could potentially total $670 million. In addition, Quark would be entitled to potential royalties on sales of licensed products.

"We are very pleased to have reached this agreement with Novartis," said Dr. Daniel Zurr, Quark's Chief Executive Officer. "We believe Novartis represents an outstanding partner for Quark. With its world-leading expertise in transplantation and acute care, Novartis will provide invaluable support to the global development of QPI-1002, in development for the prevention of acute kidney injury (AKI) in patients undergoing cardiac surgery and for delayed graft function (DGF) in kidney transplant patients. The gene target of QPI-1002, p53, is a major player in apoptotic cell death; its temporary suppression rescues cells, prevents them from dying in conditions of severe stress, such as ischemia, potentially opening opportunities for Novartis to novel treatments in additional indications."

QPI-1002 is designed to temporarily inhibit expression of the stress-response gene, p53 and is the first synthetic siRNA to be administered systemically to humans. QPI-1002 is being developed for the prevention of AKI in patients undergoing major cardiovascular surgery, and for the prophylaxis of DGF in patients receiving deceased donor kidney transplants. QPI 1002 completed Phase I studies in these patient populations and an independent Data Safety Monitoring Board recommended continuation of QPI-1002 clinical development in both diseases. QPI-1002 was granted Orphan designation by the US FDA and the European Medicines Agency (EMA) for the prophylaxis of delayed graft function in kidney transplant patients.

Quark Pharmaceuticals, Inc., a world leader in novel RNAi discovery and development, has the largest clinical-stage siRNA pipeline in the industry. The company's fully integrated drug development platform spans therapeutic target identification to drug development. Quark's approach to delivery allows targeting of tissues and organs, including the eye, kidney, ear, lung, spinal cord, and brain.

Cetero Research Announces Expansion of TDDS & Dermatology Services to Four Clinical Facilities

Cetero Research, a leading early stage contract research organization (CRO), recently announced the expansion of multiple Clinical Dermatology and Transdermal Delivery System (TDDS) services to four Cetero clinical facilities. Cetero has also enhanced the sophistication of its preclinical analytical capabilities with more sensitive, highly advanced equipment.

"There are very unique complexities surrounding topical and transdermal product development. Cetero's four decades of combined in vitro and in vivo topical pharmacokinetics experience ensures that our clients benefit from rapid, efficient, and early product optimization," said Dr. Thomas Franz, MD, Executive Medical Director of Cetero Research.

With this service expansion, Cetero can now conduct Clinical Dermatology and TDDS multisite studies for adhesion, irritation, and sensitization (A/I/S) trials across its facilities in Miami, FL; St. Louis, MO; and Toronto, Ontario, in addition to its Fargo, ND, facility. Recent FDA guidances for transdermal delivery systems recommend that at least two climatically different sites should be used for assessing patch adhesion performance, and irritation and sensitization potential. Cetero has harmonized the personnel training and specific study processes across the four clinical sites and has successfully conducted A/I/S studies at these multiple sites using identical scoring and performance standards, with the same protocol and comprehensive final report within one full-service package. In addition, Cetero can assist sponsors with these new regulatory recommendations, including compliance with the FDA guidance.

This multi-site, one-CRO advantage also extends to special population needs, such as post-menopausal females. By utilizing multiple clinical sites when needed, Cetero can ensure complete study enrollment.

"Our team understands how critical factors, such as dose application and removal, skin conditions and diseases, lifestyle history, and adverse event assessment (skin and systemic) will impact how the skin absorbs a compound, ensuring the design of studies to control for those details," said Dr. Alan Copa, President of Clinical Operations - Fargo for Cetero Research. "This understanding, combined with our advanced technology, allows our integrated team of dermatology experts to seamlessly leverage their knowledge into the design and performance of clinical trials."

In addition to adding functionality at its clinical facilities, the Pre-Clinical Dermatology Research Laboratory has expanded its analytical capability with the addition of two MicroMass LC/MS/MS systems to complement its current four LC/MS and four LC/UV and GC/MS systems. The LC/MS/MS systems provide the additional level of analytical sensitivity and selectivity needed to evaluate the in vitro dermal absorption of the most challenging compounds currently in development or production. This new equipment will allow the Pre-Clinical Dermatology Research Laboratory to further expand its ability to conduct testing of in vitro percutaneous absorption and semi-solid release to GLP standards, including analytical method development and validation.

Market News and Trends

LifeCycle Pharma Receives SPA From FDA for LCP-Tacro Pivotal Phase III Study in De Novo Kidney Transplant Patients

LifeCycle Pharma A/S recently announced receipt of agreement with the US FDA on a Special Protocol Assessment (SPA) of its pivotal Phase III study, Study 3002, for LCP-Tacro in patients, who have just received a kidney transplant (de novo transplant patients).

"The SPA Agreement for Study 3002 of LCP-Tacro is a very significant achievement for LCP," said William Polvino, President & Chief Executive Officer of LifeCycle Pharma. "We have now received a formal green light from the FDA as to our proposed clinical study design and are now well-positioned to move forward with the study start. Further, we have achieved increased clarity on the costs and timing to regulatory approval. LCP reaffirms its expectations of a target NDA filing in the first quarter of 2013, and we anticipate study initiation in the third quarter of this year."

"The optimized and patent-protected formulation used in LCP-Tacro provides desirable once-daily dosing of tacrolimus and is intended to reduce the peak-to-trough variability in blood levels," added Dr. John Weinberg, Senior Vice President, Commercial Development and Strategic Planning. "We are optimistic that LCP-Tacro will provide important patient benefits compared to existing treatments, will be a valuable addition to the therapeutic regimens available to transplant physicians, and has significant market potential."

The LCP Study 3002 is a randomized, double-blind, multicenter study that will compare once-daily LCP-Tacro against the current market-leading comparator, twice-daily Prograf in de novo kidney transplant patients. A 12-month treatment period will be followed by a 12-month blinded extension. The primary endpoint of the study will be to demonstrate the non-inferiority of LCP-Tacro, compared to Prograf, on kidney graft function (biopsy proven acute rejection, graft failure, death, or loss to follow up) at 12 months. Secondary endpoints will include safety, tolerability, and renal function assessments. The study will be conducted at approximately 75 to 100 transplant centers, primarily in the US and Europe.

LCP has developed LCP-Tacro as an optimized version of the highly successful transplant drug, tacrolimus (Prograf). Worldwide sales of Prograf were about $2 billion in 2009. Tacrolimus is a leading immuno-suppression drug used for the prevention of transplant allograft rejection after organ transplantation. LCP-Tacro is being developed as a once-daily tablet version of tacrolimus, with improved bioavailability, consistent pharmacokinetic performance, and reduced peak-to-trough variability when compared to currently approved tacrolimus products. Transplant patients need to maintain a minimum blood level of tacrolimus for the prevention of transplant allograft rejection, but excessive levels may increase the risk of serious side effects, such as nephrotoxicity and opportunistic infections. Therefore, tacrolimus levels need to be managed carefully, and transplant patients are typically obliged to make frequent visits to the hospital for monitoring and dose adjustments after receiving a new organ.

3M Integrated Dose by Dose Counter Receives FDA Approval

The FDA has granted approval to a new inhalation product utilizing the 3M Integrated Dose by Dose Counter. The product, which also incorporates 3M's Fluorinated Ethylene Polymer (FEP) coating, received FDA approval after a one-cycle review of the New Drug Application.

The Integrated Dose by Dose Counter helps prevent patients from running out of medication in their metered-dose inhalers by providing an accurate count of how much medication remains. The device is displacement driven and utilizes a novel split-count design that matches dose counter actuation as closely as possible to valve travel to prevent under-counting and to minimize the potential for over-counting due to misuse. The counter utilized global patient research during development, resulting in a device that is easy for patients to use, requiring no additional training, and that retains a familiar look and feel. The 3M Integrated Dose by Dose Counter is compatible with most valves and customizable to meet partners' requirements.

An additional component of the newly approved product, the FEP-coated canister, helps reduce drug deposition to improve chemical and physical stability. Whether formulated as a suspension or solution, the API in pressurized metered-dose inhalers can interact with the container closure system. The FEP coating, however, helps prevent deposition of the API on canister walls and reduces canister-formulation interactions.

"The approval of this new product following a one-cycle review is a testament to the quality of our dose counter and FEP coating, as well as a demonstration of our expertise in regulatory documentation," said Robert Odenthal, Vice President of Respiratory Business. "3M is pleased to help bring this product to market successfully."

SurModics Signs License Agreement With Clinuvel Pharmaceuticals

SurModics, Inc., a leading provider of drug delivery and surface modification technologies to the healthcare industry, recently announced it has entered into a license agreement with Clinuvel Pharmaceuticals Limited of Melbourne, Australia. Under the agreement, the company's SurModics Pharmaceuticals unit has licensed certain aspects of its biodegradable polymer implant technology to Clinuvel for the treatment of sun-induced skin disorders. Terms of the agreement were not disclosed.

SurModics and Clinuvel have been collaborating on the development of Clinuvel's sustained-release SCENESSE (afamelanotide) implant formulation for several years. The implant is being developed as a prophylactic treatment for a range of UV and light-related skin disorders. Clinuvel's implant is currently being evaluated for a variety of skin disorders in several clinical trials in Europe and Australia. In addition, Clinuvel has recently announced initiation of a Phase II trial in the United States for the treatment of erythropoietic protoporphyria (EPP), an orphan disease that affects around 3,000 Americans. Independent estimates from RBS (Royal Bank of Scotland) place SCENESSE's potential market for all UV-related disorders being investigated by Clinuvel in excess of seven million patients worldwide.

SurModics' biodegradable polymer drug delivery technology enables the drug afamelanotide to be released in a sustained and tightly controlled manner. This elegant release stimulates the production of melanin in the patient's skin, to protect the patient from UV and light exposure.

Clinuvel's SCENESSE (afamelanotide) implant is currently in clinical trials for erythropoietic protoporphyria (EPP, or sun intolerance) - Phase III OUS, Phase II US; actinic keratosis (AK) and squamous cell carcinoma (SCC) in organ transplant recipients (skin cancers) - Phase II OUS; and polymorphous light eruption (PLE, commonly known as sun poisoning) – Phase III OUS.

SurModics' vision is to extend and improve the lives of patients through technology innovation. The company partners with the world's foremost medical device, pharmaceutical, and life science companies to develop and commercialize innovative products that result in improved diagnosis and treatment for patients.

Patent Procurement – Fast Tracking to Protection

By: Clifford M. Davidson, Esq.

Throughout the past decade, patent practitioners and inventors alike found that the USPTO was turning more and more into a black hole in which a patent application was deposited, never to come out on the other side as a granted US Patent. Due to many factors, including Court Decisions and USPTO policy changes that made it more difficult to obtain allowances, higher costs for patent procurement relative to past times due to multiple rejections of the same patent application by the USPTO, a loss of experienced patent examiners at the USPTO and an overburdening of relatively green patent examiners due to government budgeting, and finally, a slowing and stagnating economy, I have witnessed a growing reluctance on the part of specialty pharma and drug delivery companies to spend the time and money to prepare and file patent applications that would cover potential new products. Who could blame pharma companies for cutting back on patent filings in the face of the USPTO rejecting about two-thirds of patent filings in the pharmaceutical arts? Even the patent examiners I have spoken to throughout the past few years seemed disappointed about not being able to allow more patent applications, and they spoke in hushed terms about the risks to their careers if a patent application they allowed was sent back via the USPTO quality review system.

The situation is changing. The USPTO reports that patent grants are up 35% over 2009. More is being done to find ways to have patents examined faster and by more experienced examiners. On a personal level, I have noticed a much more robust rate of allowances in recent months.

Does that mean patent applications are moving through the system rapidly? Not necessarily. According to USPTO statistics, for the pharmaceutical arts, it is now taking approximately 22.5 months from filing a utility patent application in the USPTO to a first office action (which is rarely an allowance). It is taking on average about 35.1 months total until a final disposition of a patent application (allowance or final rejection). According to Prof. Dennis Crouch, the 66,000 patents issued from January 10, 2010 to April 27, 2010 had an average prosecution pendency of 3.8 years from filing or 4.8 years from the earliest US priority date. For applications with at least one non-provisional US parent application, the average pendency was 7.0 years from the earliest US priority date. (Patently - O posting, May 3, 2010). In many instances, that timeframe may simply be too long to provide maximum usefulness of a patent in the pharmaceutical arts. For example, if a product for which approval is sought from the FDA as an NDA or a paper NDA is commercialized, and the ANDAs can be filed prior to a patent listing in the FDA Orange Book, then the value of a patent for the NDA holder is significantly reduced.

Without question, it would be desirable for specialty pharma and drug delivery companies to have a mechanism by which review of a patent application can be obtained quickly, and better yet, with a better chance of approval. There is such a solution!

The USPTO has established procedures under which the examination of a patent application may be accelerated. Under one of these procedures, the USPTO will advance an application out of turn for examination if the applicant files a grantable petition to make special under the accelerated examination program. According to USPTO statistics, close to 40% of accelerated patent applications are allowed via a first office action, and about 60% of accelerated patent applications are ultimately allowed. This is a far cry from the rather daunting statistics of allowances in the recent past.

ACCELERATED EXAMINATION PROGRAM

Under the new USPTO accelerated examination program, applicants must submit a complete patent application along with a petition and requisite fees, a pre-examination search, and an accelerated examination support document (AESD). The patent application must be submitted electronically via the EFS-Web system. It can have three or fewer independent claims and no more than 20 claims total. The application must be directed to a single invention; if the examiner deems the claims to cover more than one invention, the applicant must agree to elect a single invention without traverse. The applicant must also agree to an interview with the examiner to discuss any outstanding issues arising in the examination process.

The initial review of requests for accelerated examination is conducted in the Office of Initial Patent Examination (OIPE), where the application is reviewed for compliance with all of the filing requirements other than the review of the pre-examination search and the accelerated examination support document (which are reviewed in the Technology Centers by the Special Program Examiner office). Assuming these documents are prepared in acceptable fashion, the application will be accepted in the accelerated examination. The examiner will fully consider the AESD in the process of conducting a complete examination of the application, including an independent search.

The pre-examination search must include a classified search of the US patents and published patent applications in the class and subclass where the claimed invention is most likely to be classified in the current US Patent Classification. The search is supposed to cover the subject matter of the independent claims using terms recognized in the art given their broadest reasonable interpretation, and should consider individual features by themselves and combinations of features. The USPTO also requires a text search of foreign patent documents.

The AESD must be filed with the application and a petition to make special. The AESD must include (1) an information disclosure statement (IDS) citing each reference deemed most closely related to the subject matter of each of the claims, and for each reference cited, the accelerated examination support document must include an identification of all the limitations in the claims that are disclosed by the reference specifying where the limitation is disclosed in the cited reference; (2) a detailed explanation of how each of the claims are patentable over the references; and (3) a concise statement of the utility of the invention as defined in each of the independent claims, and a showing of where each limitation of the claims finds support in the written description of the specification.

WHAT ARE THE COSTS?

In order to ensure acceptance of the request for accelerated examination, the first step is to obtain a proper pre-examination search. Searches typically done by pharma companies, or quick searches by patent counsel, will not suffice. We have been finding that an acceptable search generally costs in the $2,000 to $4,000 range.

The second step is the preparation of the AESD. This document must be carefully crafted to ensure compliance with the USPTO requirements previously mentioned. It also must be carefully crafted to avoid pitfalls that I will discuss further in this article. Generally, we have been finding that the AESDs we are preparing cost in the neighborhood of $4,000 to $14,000, depending upon (1) the complexity of the invention; (2) the closeness of the prior art uncovered in the search and the complexity of the arguments that must be prepared and submitted; and (3) any miscellaneous prior art surprises that come along the way that need to be dealt with. These costs are exclusive of the costs for preparing the patent application and the set of claims for the accelerated case.

WHAT IS THE STRATEGY?

In many cases, the goal of the accelerated examination is to obtain a patent with useful claims, not necessarily the broadest claims. The fact that the allowance rate is so high is indicative of the fact that most filers are following this path.

Inventors and pharma executives are often reluctant to go this route. They see the broad claims that may possibly define over the prior art, and want it all and want it now. Unfortunately, that is not the way the USPTO is operating these days. Examiners are much less reluctant to allow patent claims that don't appear to aggressively cover every possible alternative embodiment of an invention (including those never described in the patent filing). Therefore, one useful strategy is to draft a set of claims that cover the commercial product in a narrow but useful manner that captures design-around formulations, where there is a clear story as to patentability over the prior art. Such claims are much more likely to result in allowable subject matter.

There are a number of benefits to obtaining a narrow(er) patent claim. First, it is less likely that patent prosecution estoppels have been incurred, leaving the possibility of a wider range of infringement under the doctrine of equivalents. Second, it is often the case that the narrower the claim, the less the applicability of prior art. That leads to a quicker allowance and a more difficult invalidity argument by, eg, an ANDA filer.

Does the fact that the accelerated application includes narrower claims mean that you cannot obtain broad patent coverage? No. It is often the strategy that broader claims are also filed in a "sister" patent application filed before or after the accelerated case. In fact, it is often the case that multiple cases are filed simultaneously, for example, (1) covering the product narrowly; (2) covering the (approved) method of treatment using the product; and (3) covering aspects of the product broadly, among other things. In this way, one achieves the best of all worlds.

WHAT ARE THE DOWNSIDES?

There are at least two downsides against the accelerated examination system. First are the costs involved. One can generally expect to spend about $5,000 to $15,000 more to initiate the accelerated examination as compared to filing a conventional US application taken up in turn.

The larger downside to the accelerated examination system is the necessity for the applicant to perform extensive searches for the examiner and then provide commentary concerning the patentability of the claims over the results of such searches in significant detail. This in turn creates issues of estoppel in litigation with respect to taking interpretations that may contradict positions taken in the accelerated case. Second is the fear of charges of inequitable conduct relating to a variety of steps in the process, such as failure to conduct a proper search, or misrepresentation of the prior art, or failure to identify the best art (albeit in the eye of the challenger).

WHAT ARE THE BENEFITS?

There are significant potential benefits to the utilization of the accelerated examination system. One such benefit is a quick time to the uptake of the case by a patent examiner. We have seen some cases

receiving office actions within 2 to 3 months of acceptance of the accelerated application. For some pharma situations, the quick review provides the possibility of obtaining a patent much, much quicker than otherwise. It also provides a better gauge on whether to spend money on foreign patent filings. An additional benefit is found in the USPTO statistics; it appears the USPTO is more willing to quickly allow cases rather than going through multitudes of rejections.

ARE THERE ANY OTHER WAYS TO FAST TRACK A PATENT APPLICATION?

There are indeed other ways to fast track a patent application with the USPTO, but these are situation-specific and will not be useful in many cases. For example, the USPTO has entered into a Patent Prosecution Highway (PPH) work-share program (agreements) with foreign patent offices (including the European, Japanese, UK, German, Danish, Korean, Hungarian, Australian, Canada, Finland, and Singapore) patent offices to expand the existing. PPH agreements streamline the patent system and promote expeditious patent examination among participating offices by allowing patent examiners to avail themselves of work from other patent offices. Under existing PPH agreements, an applicant receiving an allowable determination from one patent office on at least one claim in an application may request that the corresponding application filed with another office advance for faster examination. By coordinating patentable results between both nations' offices, applicants can expect to obtain patents in both nations more quickly. For US applications, this is only useful if, for example, a favorable conclusion has been reached with one of the aforementioned foreign patent offices.

PROJECT EXCHANGE

The USPTO has also enacted a program called Project Exchange, wherein any applicant with more than one application, filed prior to the inception of the program, currently pending at the USPTO can receive expedited review of one application in exchange for withdrawing an unexamined application. The expanded Project Exchange will be limited to 15 applications per entity through December 31, 2010.

CONCLUSION

Accelerated review of patent applications is a useful and important alternative to the typical slow churn of the USPTO in reviewing pharma patent filings. Accelerated examination is one useful procedure. If you have patent application(s) that have been pending for awhile, the PPH or Project Exchange may provide an alternative and cheaper way to obtain quick review. Finally, there are yet other ways to obtain expedited review, for example, via petitions to make special based on applicant's health or age. Other petitions to make special (ie, based on manufacture, infringement, environmental quality, energy, recombinant DNA, superconductivity materials, HIV/AIDS and cancer, countering terrorism, and biotechnology applications filed by small entities) will be processed using the revised procedure for accelerated examination. ◆

BIOGRAPHY

Clifford M. Davidson, Esq. is a founding partner at Davidson, Davidson & Kappel, LLC, an Intellectual Property law firm with offices in New York City and Frankfurt, Germany. He counsels pharmaceutical clients in pharmaceutical patent-related matters, including patent prosecution, freedom to operate and infringement opinions, due diligence and tech-transfer, and litigation (including ex parte and inter partes proceedings worldwide). He has assisted specialty pharma and drug development companies to create significant patent portfolios, and the patents he has written and the patent portfolios he has created have been recognized as creating significant value for his clients. He has written patents covering virtually all areas of drug development, and has pioneered strategic patent focus on the pharmacokinetic profiles and the pharmacologic activity of drug/drug formulations. Mr. Davidson earned his BS in Pharmacy and his JD from Rutgers University and is a member of the New York and New Jersey Intellectual Property Law Associations, the American Pharmaceutical Association, and The Controlled Release Society. His area of expertise includes new chemical entities; new pharmaceutical formulations (including controlled-release oral dosage forms, injectables, transdermals, ophthalmics, inhalation, intranasal, sublingual, suppository, and implantation administration); new combinations of previously known drugs; new modes of administration of previously known drugs; method of treatment; pharmaceutical excipients; and methods of preparation.

REFORMULATING SUCCESS

Looking for Gorillas

Part 4 of a 6-part series on business models & best practices for navigating the new normal.

By: Derek Hennecke, President & CEO Xcelience LLC

Do you know what keeps me up at night? It's not the pace of this recovery. It's not the search for good employees to join our team. Don't tell my VP of Sales, but it's not sales either. My greatest concern is the things I may not see - the major market developments that come out of left field. I'm talking about what Netflix did to DVD rentals. What the iPhone did for the cell phone market. What the GPS in your car did for your marriage (or was that just me?). I believe it is my job as CEO to see, anticipate, and capitalize on these game-changers.

It's not just about riding the waves of change for maximum growth - though it's that too. Increasingly in the new normal, seeing these game-changers coming is about staying alive. No matter how well you do what you do, if the rules of the game get pulled out from underneath you, your company is going to hit the rocks.

EVEN THE GURUS MISS SOMETIMES

Even the big guys have been known to miss these great galactic shifts. The guys you think don't ever miss a beat. Did you know that years ago, Bill Gates wrote letters to Steve Jobs begging him to allow the cloning of Apple hardware? If Mr. Jobs had agreed, Apple's operating system might have become the de facto universal standard - the one everybody wrote software for - a role that fell to Windows instead.

Apple missed out on the fortune that Microsoft created for its shareholders. It's one of history's greatest business blunders, made by one of history's greatest entrepreneurs, and it nearly dealt a fatal blow to the company. But the Web came along and Apple reinvented itself as a maker of slick and sexy computing devices that became all the rage.

How could even Steve Jobs miss such an obvious opportunity? When we talk about obvious things that people ignore, we often use the phrase, "the elephant in the room." Something so patently obvious that everyone is aware of it but no one mentions it, usually because it's inconvenient or awkward. Yet believe it or not, sometimes people don't talk about the elephant in the room because they simply don't see it.

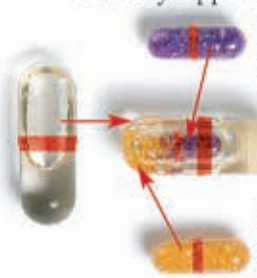
No, really. They don't see it. More often than you think. A lot more often. There should be a book about this phenomenon. And in fact, there is. Cognitive neuroscientists Christopher Chabris and Daniel Simmons have written about our ability to miss the obvious with stunning clarity in their book, *The Invisible Gorilla*.

Mr. Chabris and Mr. Simons created a 1-minute film of students passing a

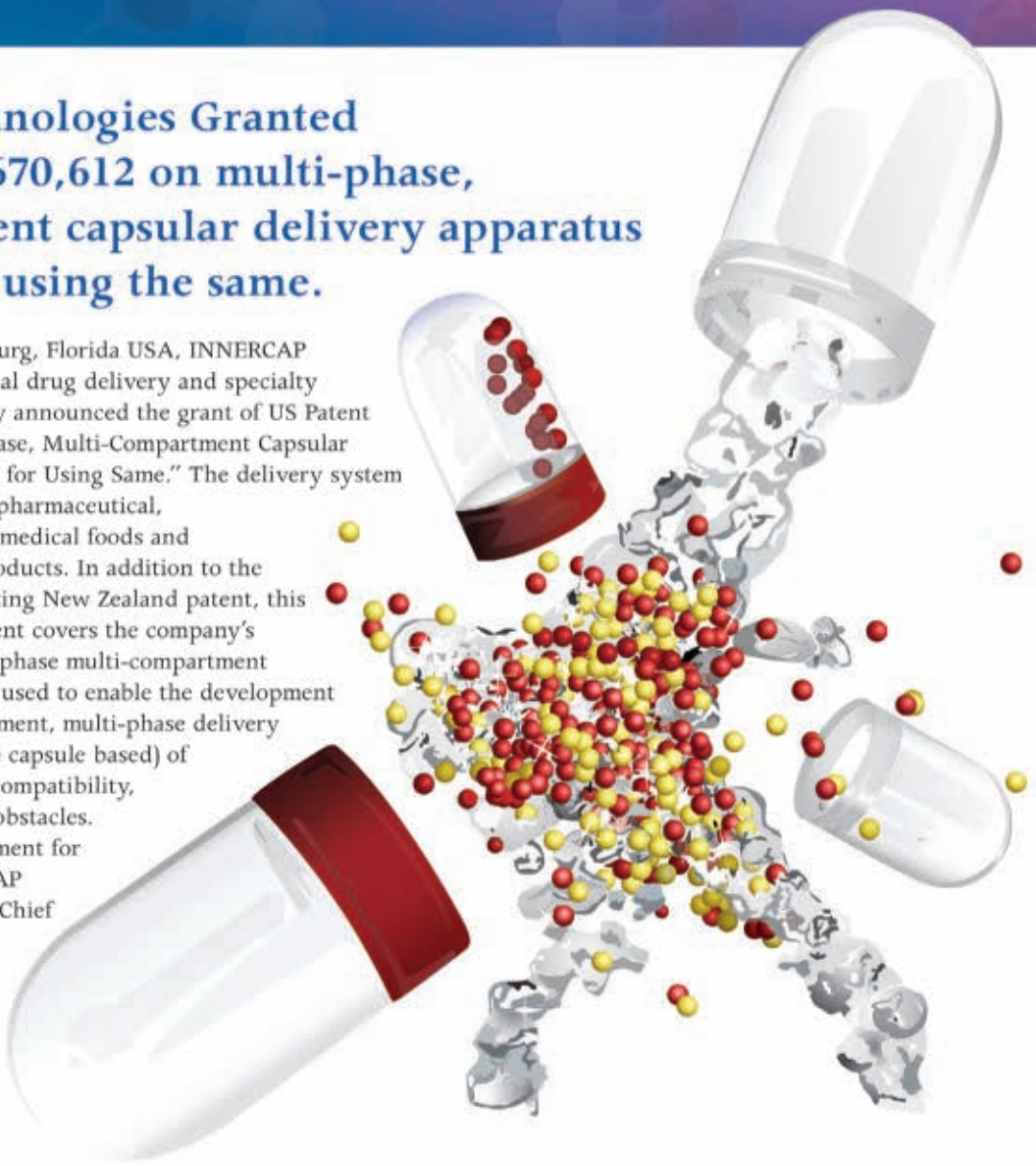
THE ADVANTAGES

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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basketball back and forth. The film was uneventful, with the exception of the brief appearance of a man wearing a gorilla suit. It wasn't exactly an elephant in the room, but it was, one might expect, equally hard to ignore. The man in the gorilla suit saunters through the basketball tossers, beats his chest, and then leaves. He appears in the film for a full 9 of the 60-second flick. Subjects were invited to view the film, and count the number of times the basketball was passed between the students. Then, when the film was finished, they were asked if they had seen the gorilla.

Get this: about half of the subjects were absolutely certain there had not been a gorilla. They were dead sure. They would have seen it. They were completely shocked to learn of its existence, and many insisted on seeing the film again because they were so certain they would have seen a gorilla on the court.

The Invisible Gorilla argues that this an example of our ability to place undeserved trust in our own instincts and intuition. We just assume that if there was a gorilla in the room, we would see it. Ignore it, maybe, but see it, definitely. It is all part of our undue confidence in ourselves, the things we see and our ability to interpret them accurately.

TO SPOT A GORILLA, ASKING YOUR CUSTOMER ISN'T ENOUGH

So look around you now. How do you spot a gorilla in an industry? Do you ask the customer what else you can do for him? Unfortunately, it's rarely that easy. Gorillas are surprisingly sneaky, and often the customers themselves don't see them. I know what I'm talking about. I've missed the gorilla before. I was a Blockbuster investor.

Ten years ago, Blockbuster seemed like a pretty good business model. If you interviewed their customers, I'm sure most of them would have reported themselves to be satisfied. In hindsight, even that seems dumb. Remember all those late fees? Did you ever have to make a special trip to Blockbuster to get a video or DVD returned before midnight so you wouldn't get dinged for another day? What kind of customer-friendly model is that? On top of it, their stock was 90% new releases. But I accepted the situation like Canadians accept snow storms. What can you do? I would've told you I was a happy customer if you'd have asked me.

Then along came Netflix and showed me a world where any movie I wanted was available and delivered right to my mailbox, and many could be streamed to my TV. I could watch old Dr. Who reruns from dawn to dusk if I wanted. Then along came DVR capability, and I could rent new-release movies with the click of a remote button for roughly the same price as a trip to Blockbuster. Through all these massive changes in the movie rental landscape, Blockbuster was still doing battle with Hollywood Video as if that was where the war for our movie dollars was raging. By the time the first Red Box appeared at the corner offering quick access to new release movies for a buck, the battle was pretty much lost.

Maybe, like Apple, Blockbuster will re-invent itself and come back newer and better than ever, but I'm not seeing it. Blockbuster was a happy camper a few years ago, but now the business model has been completely renovated, and late entry to the DVD mail-out business and corner convenience kiosks aren't cutting it. Blockbuster missed it!

If you were Mr. Blockbuster 10 years ago, you might've been looking for ways to improve your business by examining your customer satisfaction surveys. But you still would have missed it.

In the drug development industry, we all know it's essential to keep on top of what's out there. Our customers will often tell us about those things that are already out there that we want - we simply have to keep buying equipment and re-investing into new capabilities. The challenge is to dig really deep and find or at least recognize the arrival of the great new game-changing idea.

THINK OF WAYS TO KEEP YOUR CUSTOMERS HAPPY THAT EVEN YOUR CUSTOMERS HAVEN'T THOUGHT OF YET

Sure, technology made the breakthrough that decimated Blockbuster, but it came because Netflix saw how Blockbuster was failing to make their customers as happy as they really could be by miring them in late fees and limiting selection. So Netflix built a technology that eliminated these shortcomings, and then went out to offer more than we customers ever dreamed of.

The lesson here is that just because your customers say they're happy, doesn't mean they'll stick with you. Your job is to try to think of ways to keep your customer happy that even your customers haven't thought of yet.

Disruptive technologies - like DVR capability and Netflix on your Wii - will never come from the standard customer satisfaction surveys. If there is a way to make customers happy that customers haven't thought of, that's where the change will come from.

The marketplace is littered with

examples of companies that missed these gorillas, even as they sauntered through their field of vision. Why didn't Sony, the creator of the Walkman, launch the iPod? Stable companies and industries are being upstaged by disruptive innovation and new competition today more than ever. It's as much a part of the New Normal as tighter credit.

Powder in capsule (PIC) is an example of a disruptive technology in our industry. Is it the new normal? There are certainly those who argue that PIC can't replace all traditional formulations. At Xcelience, we believe that PIC is not the solution to all APIs, and every responsible scientist has to carefully decide what the best approach is for a given project. Still, I wouldn't consider PIC a gorilla in the industry. You absolutely need a PIC in your arsenal in our business. It's part of maintaining a full tool box.

Is the gravitation toward production in China a game-changer? Maybe. Maybe not. Shareholders of late are showing increasing wariness of this approach. Charles River (CRL) was probably thinking that it had a disruptive change when it made a bid for the Chinese company, Wuxi. But CRL shareholders revolted at the price tag. Drug companies around the world are suffering from a basic problem - lack of funding for early stage drugs. Is China really the miracle pill that will solve these ills?

CONSIDER EVOLUTIONARY CHANGES IN YOUR CUSTOMER HIM OR HERSELF

Have you ever been in a hotel where you had to unwrap a paper-clad drinking glass? Ever wondered why they do that? It's a classic case of an industry whose clientele has changed, without the industry noticing. In fact you have to dig pretty far back to find the rationale for this habit.

Hotel chains got their big boost when President Eisenhower constructed a vast network of interstate highways across America, giving middle-class Americans their first real opportunity to travel the country. These nascent travelers were a little nervous - they were concerned about safety and cleanliness and didn't want too many surprises. Holiday Inn and other chains supplied both. They gave Americans all the sameness they could want, clothing their drinking glasses in paper and covering the toilet seat in odd sanitized wrappers to make people feel safe. Later, they added things like telephones in the toilet stalls. Remember those? These things were once the signs of a quality hotel.

Of course nowadays, a toilet wrapped in paper is a little scary, if you ask me. So why do some hotels still persist in doing this? They simply haven't registered that their customer has changed.

In my humble opinion, the hotel industry is a clear example of an industry that could do with some galactic changes to deal with customer satisfaction. Like the Blockbuster customer 10 years ago who got nailed with late fees but still reported to be a happy customer, the hotel clientele shows remarkable client satisfaction. Priceline and Expedia provided a disruptive technology that decimated the local travel agencies, but they provide pretty much the same endless diet of chain hotels. Wouldn't it be wonderful to be able to find obscure hotels - places with character or innovative design? A B&B on the lake around the corner instead of the Holiday Inn? It takes hours to find such a hotel on the Internet, and about the only reliable indicator of quality is outrageous pricing. Yet we all know there are gems out there because we stumble on them usually through word of mouth. Still, most the time, we just end up booking a McHotel through Expedia, accepting our lot like late fees at Blockbuster. What can you do?

In stark contrast to the hotel industry, we have today's Ford. Here is a company that in its recent turnaround showed it's evolving to keep pace with its customers, and in doing so it's probably a step ahead of the competition. The company shocked the North American market last month when it unveiled the re-engineered Explorer. Ford is asking the customer to pay more for less: that is, to pay more for the smaller, more fuel-efficient 4-cyclinder Explorer, and less for the less fuel-efficient V-6 engine. In a complete reversal of the usual pricing strategy, Ford is betting that Americans will pony up more for 237 horsepower than for 290 horsepower, even in a climate of relatively cheap gasoline. Not bad thinking.

How is the CRO customer evolving? Here's just one thread to follow: the number of qualified CMC consultants coming from the Pharma industry restructuring is reaching groundswell proportions. These specialists are bringing a lifetime of experience to their/our clients. They know which provider does what and how well they do it. No longer is size the primary metric to make a safe outsourcing decision. The CRO world is becoming increasingly transparent. Just one implication: it's more important than ever before to keep a golden reputation as the word is carried on more seeds.

SOMETIMES THE GORILLA COMES FROM OUTSIDE YOUR INDUSTRY

When looking for gorillas, broaden your view. It helps to consider your definition of a customer. Sometimes, the game-changer doesn't come from a competitor, or even from the same industry. Consider what happened to the rail and bus systems like Amtrak and Greyhound when Southwest Airlines' low fares started to expand outside of Texas. It wasn't just airlines that took the hit. Southwest was breaking into completely new competitive terrain - the low-budget traveler. The bus and rail systems were caught unprepared.

BETTER YET, BREED YOUR GORILLAS

Research shows that when scientists told subjects in the gorilla experiment about the gorilla, they were indeed more likely to spot the gorilla, but they are no more likely to notice any other unexpected events. In fact, their performance was poorer on some measures. So in a cruel twist of fate, it appears that in looking for gorillas, we may actually become less likely to spot them.

There is only one solution. Rethink the industry and BE the unexpected. DO what no one else has done yet. SEE what your customers want, and invent the solutions no one has thought of yet.

The following are a couple of things we are working on. Our industry has resisted consolidation, where the rest of pharma has been moving clearly in that direction. Consolidation, however, is wrought with pitfalls. The one-stop shop promises simplicity, but it delivers a bumpy road full of quality potholes. In a one-stop shop, some steps in the A-Z drug development process are high-quality, but the best shops don't want to be purchased, so companies are forced to by lesser shops and try to integrate them and improve them. Putting up with these potholes is our industry's equivalent of living with late fees and limited selection. We can do better.

This is what Xcelience is doing with Chemistry Playbook - a unique linkage of independent highly reputed companies that work together to smooth the CMC process without the disadvantages associated with a one-stop shop. Customers can pick and choose which companies in the Playbook they want to work with. When working with the Playbook partners, they enjoy all the benefits of simplified process management from step to step, a single standardized contract across companies, and simplified negotiation. It's our industry's Netflix, only we can't yet deliver it through your TV. We'll work on that.

Here's another idea. Many of our customers want to work simultaneously to gain entrance into both the American and European markets. Xcelience has a joint venture with Penn Pharmaceuticals, which enables us to oversee the combined progress of molecules in both markets at the same time.

These ideas may not transform your living room into a remote-controlled movie theater, or deliver you 253 horsepower. They won't revolutionize how you spend your time waiting in line or in the back of a taxi, like the iPhone did. But they might just give our customers a little more free time to do all those things, because the rest of their work is done! ◆

BIOGRAPHY

Derek G. Hennecke, MBA
President & CEO
Xcelience

Derek G. Hennecke is a founding member of Xcelience and its current CEO and President. He has a long history of growing strong businesses around the world. He balances a scientific and business background with nearly 2 decades of international experience in the healthcare industry and a track record as a highly successful international turn-around manager in the global drug development community. Xcelience is the first company Mr. Hennecke has managed as an owner, having launched a management buy-out from MDS Pharma Services in 2006. The newly formed company immediately embarked on a robust pattern of strong growth. This growth was recognized in May 2008, when Mr. Hennecke was selected as a finalist for the coveted *2008 Ernst & Young Florida Entrepreneur of the Year* award, a nomination based on the demonstration of extraordinary success in the areas of innovation, financial performance, personal commitment to community, and the company's perpetual growth since its official formation. Mr. Hennecke was also recognized as a finalist for the *Ultimate CEO* awards by the Tampa Business Journal in 2008. This is in addition to Xcelience's nomination for *Small Business of the Year* by the Greater Tampa Bay Chamber of Commerce, also this year. Before founding Xcelience, Mr. Hennecke managed the same Tampa-based business while also overseeing a Seattle and a Montreal-based plant as Vice President and General Manager, Pharmaceutics and Biopharmaceuticals. Prior to that, he spent more than 10 years abroad working for the Dutch-based conglomerate DSM. In Montreal, he was GM of a 250-staff Biologics plant for more than 2 years. In Cairo, Egypt, as GM, he oversaw a radical turn-around in an anti-infectives plant that was originally slated for closure. He also spent 2 years in Holland developing new Pharma intermediates, and two years in Mexico as Commercial Director covering Central and South America. He also worked for Roche, both in Canada and Germany. Mr. Hennecke earned his BSc in Microbiology from the University of Alberta in Canada and his MBA from the Erasmus University in Rotterdam, The Netherlands.

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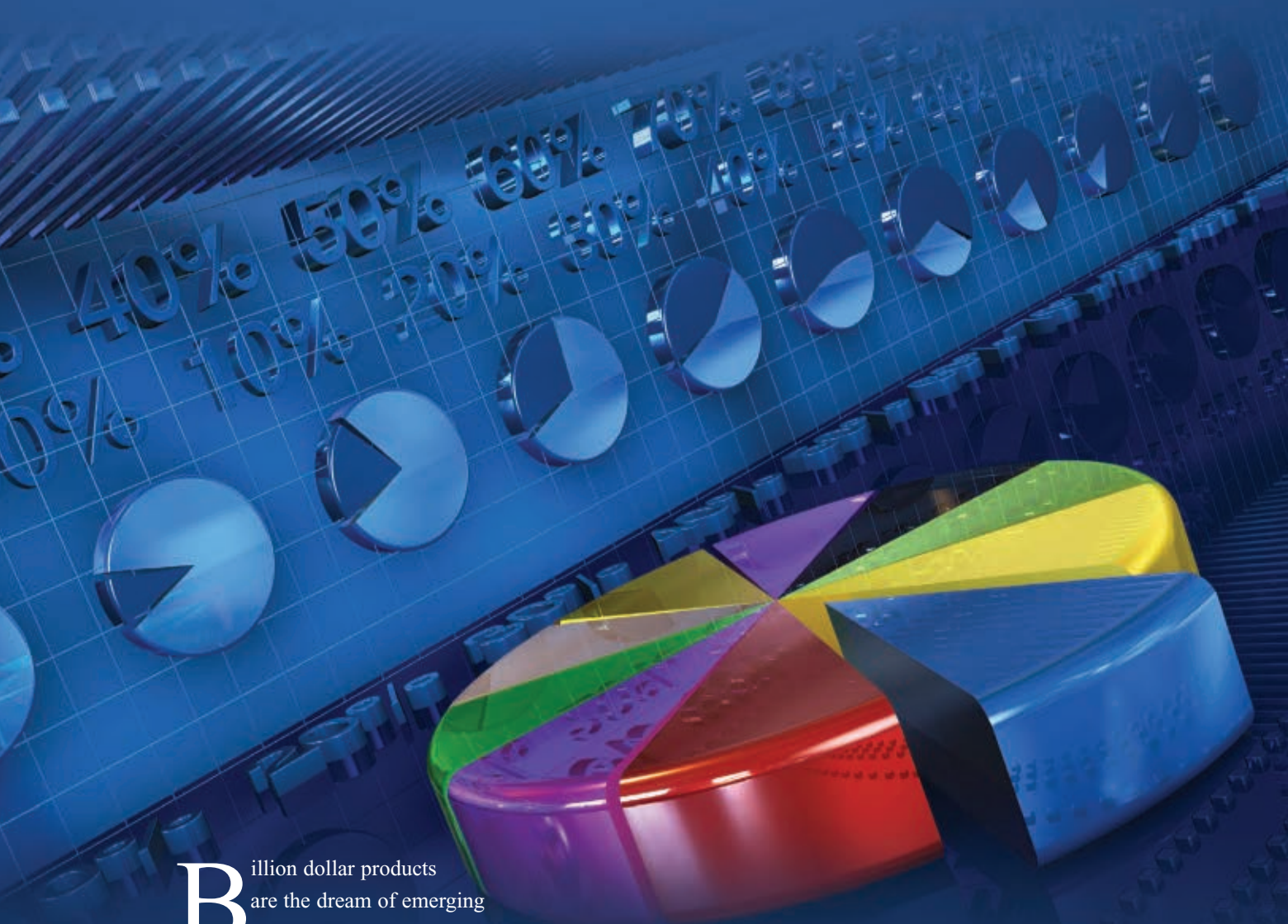
Delivery Report

Decade in Review - Drug Delivery Product Sales

By: Josef Bossart, PhD



Billion dollar products are the dream of emerging and established biopharmaceutical companies. To better understand where product opportunities are headed, it's worth reviewing product sales for drug delivery enabled/enhanced products (DDEP) throughout the past decade. If Procardia XL showed that a DDEP could capture more than $1 billion in annual sales, the past decade has convincingly confirmed that it was no fluke. As we will see, there were many billion dollar babies in the past decade, varying in their therapeutic indications and delivery formats but all remarkable therapeutic and commercial successes.

Let's quickly review the limitations of the data presented in this article. All sales data is imperfect in one way or another; understanding the limitations of data is key to using it effectively. The data used for this analysis is non-proprietary and is available to all readers from a variety of sources. The two most important data sources used for this article are based on either sales figures derived from prescription audits, or company published sales reports. None of these sources provide a truly accurate and comprehensive summary of sales for all DDEPs.

Audited sales based on prescriptions most accurately reflect consumption in a year using sampled prescription numbers and projected costs/prices. The limitations of this approach relate to inaccuracies associated with sampling methods, projections, and estimated prices. In the case of company published sales figures, as often presented in annual reports, the numbers capture the net sales shipped out of the company warehouses in a given year, not necessarily how much product was

actually prescribed. In some cases, these company sales figures can be skewed by stocking events and a change in wholesaler inventory levels. In addition, industry audits often exclude federal drug purchases and certain public institutions that are not serviced through usual distribution channels. The bottom line is that while the sales figures may vary between sources, they are close enough to allow us to get a good sense of overall sales and trends.

This discussion depends primarily on the figures provided by SDI/Verispan VONA (Vector One National Accounts) as published in their annual summary of the Top 200 drugs prescribed in the US. These numbers are available online at the Drug Topics website, and have been made available since at least 2000. The published SDI/Verispan figures include sales and prescriptions for both brand and generic products but are limited to retail prescription sales. They do not include sales dispensed through hospitals and federal facilities. This primarily impacts the reported figures for hospital products and, with only a couple of noted exceptions, does not significantly impact this review of DDEPs. In addition, the SDI/Verispan data is limited to the Top 200 products sold annually in the US, including all prescription pharmaceutical products not just DDEPs. This means products with annual sales of less than about $125 million are not captured in this review. Nonetheless, more than 100 DDEPs are included.

Combining the SDI/Verispan data with sales figures from manufacturer reports and other data providers provides us with a good idea of DDEP sales in the US throughout the past decade. We will by exception take a look at the worldwide sales for several of these products using manufacturer reported sales in which these sales are important and the figures are available. Unfortunately, too many companies report their sales by franchise, that is therapeutic area or general pharmaceutical active, which limits the conclusions that can be drawn concerning the performance of a particular DDEP.

TOP 15 DDEPS (2000-2009)

Table 1 lists the Top 15 DDEPs in terms of sales for the past decade. In addition to individual product sales, Table 1 estimates inflation adjusted sales totals for the Top 15 DDEPs and all 108 DDEPs covered by the SDI/Verispan VONA Top 200 list. The Neulasta US sales are not included in the SDI lists and are sourced from Amgen's 10-K filings. The inflation adjusted figures (2010 millions) assume a 7% annual price increase for each of the products, and attempts to provide the reader with a sense of what full decade sales represent in terms of 2010 dollars.

TABLE 1

Products	Company	Year Introduced (US)	Total Sales 2000-2009 (millions)	Total Sales 2000-2009 (2010 millions)
1. Advair Diskus	GlaxoSmithKline	2000	$22,703	$30,084
2. Effexor XR	Pfizer	1997	$19,804	$27,742
3. OxyContin	Purdue	1995	$16,206	$23,117
4. Neulasta	Amgen	2002	$14,615	$18,922
5. Adderall XR	Shire	2001	$7,789	$10,167
6. Toprol XL	AstraZeneca	1992	$7,529	$11,064
7. Concerta	J&J	2000	$7,472	$10,081
8. Nasonex	Merck (Schering-Plough)	1997	$6,552	$9,193
9. Wellbutrin XL	GlaxoSmithKline	2003	$5,876	$7,780
10. Wellbutrin SR	GlaxoSmithKline	1996	$5,833	$10,070
11. Duragesic	J&J	1990	$5,589	$8,617
12. Flonase	GlaxoSmithKline	1994	$5,235	$8,485
13. Detrol LA	Pfizer	2000	$4,654	$6,277
14. Combivent	Boehringer Ingelheim	1996	$4,436	$6,216
15. Spiriva	Boehringer Ingelheim	2004	$4,382	$5,208
All DDEPs in SDI Top 200			>$250,000	>$350,000

Top 15 DDEP by Sales, 2000 to 2009 (USA)

The $250 billion sales figure for all DDEPs in Table 1 captures 80% or more of all US DDEP sales in this period. The products that compose the remaining 20% of sales are those individual DDEPs with sales of less than $125 million annually. While there may be more of these products, their contribution to total sales is proportionately much less.

The top DDEP on the list is Advair. This inhalation product, used for the treatment of asthma and chronic obstructive pulmonary disease (COPD), has averaged more than $3 billion in annual sales in the US since its launch in 2000. Globally, GlaxoSmithKline has reported sales in excess of $45 billion throughout the past decade, or more than $60 billion when inflated to 2010 dollars.

Products holding the Nos. 2 and 3 positions are oral sustained-release DDEPs. While the almost $20 billion in US sales recorded by Pfizer's Effexor XR put it more than $3 billion ahead of Purdue's OxyContin, it is likely that this would not have been the case had OxyContin not faced mid-decade generic issues. Since legally resolving these issues, OxyContin US sales have rebounded to over $3 billion annually and look to capture similar sales for at least the next 2 years, while Effexor XR faces generics in 2010.

The No. 4 product on the list is Neulasta, a PEGylated version of Amgen's Neupogen, with decade-long US sales of more than $14 billion. On a global basis, Neulasta has reported full-decade sales of over $18 billion.

The products ranked Nos. 5 through 7 are all oral sustained-release formulations of previously approved actives targeted to improved dosing convenience and somewhat better therapeutic performance. These products represent the classic vision of a drug delivery product; improved therapeutic performance by reducing the doses per day. In the case of Adderall XR and Toprol XL, Shire and AstraZeneca were able to profitably extend their product franchises in the face of generic threats by means of these DDEPs. Concerta, an oral sustained-release formulation of methylphenidate, permitted Alza to break into the specialty pharma space with limited risk and expense by formulating an approved and off-patent pharmaceutical active using its well-validated OROS technology.

In a similar fashion, the Wellbutrin franchise was profitably extended with the introduction of Wellbutrin SR in 1996, a twice-daily oral dosage form of bupropion, and then again in 2003 with once-daily Wellbutrin XL. Combined, these two products have extended the branded franchise for Wellbutrin a dozen years and contributed

SIDEBAR

WHAT IS A DDEP?

This article uses the acronym DDEP for drug delivery enabled/enhanced products. For the purpose of this article, a DDEP is a pharmaceutical product used for the treatment of humans and incorporates a drug delivery technology to alter the absorption, distribution, metabolism, and/or excretion of a pharmaceutical active with the intention of enabling and/or enhancing its therapeutic benefits. DDEPs are restricted to products that utilize non-toolbox formulation technologies. By non-toolbox, we refer to drug delivery and formulation technologies that are proprietary, if not patented, and are not generally accessible to all companies. Examples of these non-toolbox technologies are PEGylation, Oral Dissolution Technologies (ODT), and Transdermal Patches, all of which are available from multiple sources but generally require certain proprietary materials or know-how. One technology not included in our definition of DDEPs is enteric coating, particularly as used to avoid gastric degradation. Accordingly, products such as proton pump inhibitors are excluded from this analysis. The purpose of defining a DDEP in this manner is to provide a reasonable break between drug delivery and simple formulation-impacted pharmaceutical products. This is a sliding definition. What was considered a breakthrough drug delivery technology when first introduced is often considered a toolbox or formulation technology a decade or two later.

almost $18 billion in 2010 dollars to GlaxoSmithKline revenues in the past decade alone. The interesting twist of course is that Wellbutrin XL was developed by Biovail, but licensed to GlaxoSmithKline in a remarkable win-win for both companies.

The remaining products in the Top 15, with the exception of Detrol LA and Duragesic, are a collection of nasal and pulmonary DDEPs that address a variety of airway indications, including asthma, COPD, and allergic rhinitis. With average annual sales in the range of $1 billion, these billion dollar babies have proven to be very profitable investments.

BEYOND THE TOP 15 PRODUCTS

The Top 15 products account for about 56% of all US DDEP sales captured by the SDI/Verispan Top 200 list. Product Nos. 16 through 30 account for an additional 18% of sales. In total, the Top 30 DDEP products account for about three-quarters of all DDEP US sales in the period 2000 to 2009.

Beyond the Top 15, no products cracked the $1 billion mark in average annual sales, with Ambien CR the closest reporting US sales of $963 million in 2009.

One product that hasn't been included in the list, and possibly should, is Abbott's Tricor. Approved in 2004 as another reformulation of fenofibrate, this time with Elan's NanoCrystal technology, Tricor recorded US sales topping $1.2 billion in 2009. With total sales in excess of $6 billion for the period 2000 to 2009, the Tricor brand would be No. 9 on the Top 15 list if it were a single product in terms of formulation and dosage. Assuming all US Tricor sales since 2005 are NanoCrystal formulated, we end up with Tricor sales of $4.1 billion, which would place it at No. 17 on the list of top DDEPs for the past decade.

Two notable products that didn't make the Top 15 are PegIntron and Pegasys, PEGylated versions of Interferon Alpha used for the treatment of hepatitis B and C. While these products posted strong sales when first launched on the US market in 2001 and 2002, they have in some ways have become victims of their own success by effectively treating and "curing" a large proportion of the hepatitis C population in the US. While combined sales of both products combined topped $500 million in the US this past year, their combined global sales reached almost $2.5 billion, with a strong contribution from Asia, where hepatitis C remains a medical challenge.

Although not included in this review, the drug-eluting stents from Cordis and Boston Scientific would have made the US Top 15 list with cumulative US sales in excess of $5 billion each in the past decade. Approved and launched in 2003 and 2004, the Cypher and Taxus stents quickly became billion dollar babies, with sales of each product approaching or exceeding $2 billion annually in the US. Sales of both products tumbled in 2006 following reports of late thrombotic events associated with their use. By 2009, Cordis reported US coated stent sales of only $245 million annually, while Boston Scientific was somewhat ahead with reported sales of $431 million for their stent franchise in the US.

REFLECTIONS

The observant reader will have noted that almost all of the products on the list were developed by Big Pharma based on a previously approved active. We'll consider Purdue, Amgen, and Shire as Big Pharma given their global reach, their experience in developing pharmaceutical products, and their considerable resources. The two notable product exceptions are Concerta, developed by Alza prior to its acquisition by J&J, and Wellbutrin, developed by Biovail and then licensed to GlaxoSmithKline.

Perhaps more important is the realization that the majority of these products were developed without the direct or even indirect involvement of a drug delivery technology partner. Of the Top 15 products, only four depended on drug delivery company technology contributions; Neulasta (PEGylation), Concerta (OROS), Wellbutrin XL (Smartcoat), and Duragesic (DTrans). The remainder of the DDEPs were developed using in-house or with off-the-shelf technology resources. This significantly impacts on the economics of the drug delivery business model as we will discuss in next issue's article examining the performance of drug delivery companies throughout the past decade.

With 11 DDEPs recording average annual US-only sales greater than $1 billion, the opportunity for DDEPs seems significant. But how do these products rank in terms of all US pharmaceutical products sales?

The top three DDEPs listed in Table 1, Advair Diskus, Effexor XR, and OxyContin, rank Nos. 4, 6, and 12, respectively, on the list of all pharmaceutical product sales for the past decade. Neulasta is in the top 20, but thereafter the next DDEPs only rank in the forties (Adderall XR and Toprol XL). Numerically, DDEPs accounted for about one-quarter of all pharmaceutical products ranked in the Top 200 SDI/Verispan Retail Products in the past decade. In terms of sales, this DDEP group accounted for about 19% of product sales.

So where are DDEP sales heading? What will a billion dollar baby look like this decade? There were a total of 12 DDEPs that hit the billion dollar mark in annual US sales at least once in the period of 2000 to 2010. Only five averaged more than a billion dollars in annual sales over that period. On an inflation adjusted basis, assuming a 2010 dollar value, I expect we will see fewer billion dollar babies in this decade. There are a few underlying reasons to consider.

Generics are even more aggressive. This means DDEPs will have shorter periods of market exclusivity with the knock-on effect of a reduced period to reach the billion dollar mark. You don't grow from zero to a billion in a couple of years; market growth takes time and investment.

Markets are more congested than ever. Three of the Top 15 DDEPs are sustained-release formulations of antidepressants. At the time of their introduction, there were relatively few significant competitors. Going forward though, any new drug delivery enhanced antidepressant will need to deal with both branded and generics versions of these products. It's hard to see any DDEP in this type of mature market hitting the billion dollar mark without a significant increase in prices or treated patients. Hitting the billion dollar mark may be easier in markets that are less mature and have fewer optimized competitors.

Pharmaceutical products are more often optimized with respect to dosing. The opportunity to introduce a dose-enhanced DDEP is limited by the number of products that have not already been dose optimized. Too many of the large market products now arrive in oral once-daily dosing presentations to allow for many additional product opportunities of this type.

With respect to drug delivery companies developing billion dollar babies, remember, Big Pharma doesn't leave money on the table. Whereas Biovail was able to finesse both J&J and GlaxoSmithKline by developing once-daily versions of tramadol and bupropion, don't expect it to happen again. If a Big Pharma company doesn't introduce a once-daily formulation of a product at launch, expect them to have it in their pipeline.

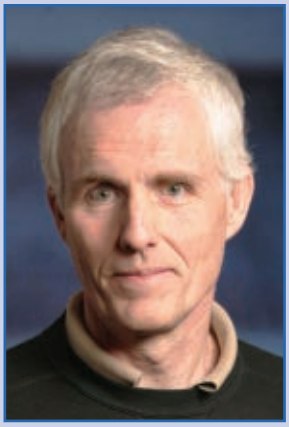
So where are the opportunities for billion dollar, or even half-billion dollar babies? Something old and something new is an apt description. The new relates to indications and technologies. There is significant opportunity to be found in the treatment of challenging therapeutic indications, such as cancer, Alzheimer's, Parkinson's, and multiple sclerosis. DDEPs that can raise the level of therapeutic outcomes for these indications are almost certain to reach or exceed the billion dollar mark. While these are not large populations, the pricing flexibility is significant. In the area of new technologies, there is still the need for better non-injectable delivery forms. The ability to more conveniently administer medications, such as peptides, proteins, and antibodies, would not only expand market use but also permit higher prices.

The old refers to inhalation technology. Inhaled products promise to deliver billion dollar sales for the foreseeable future. Inhalation products, like recombinant proteins, are not at risk of simple generic competitors because of the lack of FDA guidelines for Abbreviated New Drug Approvals (ANDAs). This means generic inhalation products need to go through a clinical development program, with no assurance they will be able to claim bioequivalence and be substitutable for the branded product. This has helped inhalation products targeted to the treatment of asthma and COPD capture one-quarter of the Top 20 DDEP spots, even though most of them were approved in the 1990s or early 2000s.

Another "old" opportunity is repositioning and enhancing the performance of approved actives (enhancing, expanding, and transforming). The three best examples of this, all billion dollar babies on a global basis, are Duragesic, PegIntron/Pegasys, and Taxus/Cypher. These five products helped redefine the standard of treatment far beyond a simple improvement of convenience and point to future opportunities.

There are opportunities to create many more DDEP-based billion dollar babies with imaginative approaches targeted to products and technologies. The question is whether the industry is up to the challenge. These will require developing next generation approaches, what would be a version 2.0 in software terms, not simply an updated version 1.1 or 1.2 of what we have now. ◆

BIOGRAPHY



Dr. Josef Bossart is Managing Director of Pharmanumbers LLC, a boutique research and consulting group providing the biopharmaceutical industry with analysis and insights that improves business outcomes. In addition to issuing industry under its Bionumbers division, Pharmanumbers provides strategy consulting and forecasting support for emerging and commercial-stage biopharma companies. Dr. Bossart has more than 3 decades of experience in the biopharmaceutical sector, including senior sales, marketing, business development, and management positions with Enzon Pharmaceuticals, GeneMedicine, US Ethicals, and Rhône-Poulenc Rorer. Dr. Bossart earned his PhD in Medicinal Chemistry from The Ohio State University, College of Pharmacy.

The material in this report is expanded upon in the upcoming Bionumbers report, DDEP 2010 - A Comprehensive Review of the Development and Commercial Parameters that Impact Drug Delivery Enabled and Enhanced Products.

SPECIAL FEATURE

Injecting Hand-Held Delivery Devices Into the Home

Injectable drug delivery devices are increasingly all about the safe and simple delivery of prescription medication by patients outside of the healthcare facility. The transition of healthcare from hospitals and into the homes of patients is beneficial in reducing financial pressures on healthcare facilities and allowing patients to go about their daily lives with minimal disruption.

Although a relatively underdeveloped market at present, injectable drug delivery has a substantial pipeline and (with significant strides in development of nanotechnology and DNA drug delivery throughout the past 5 years) is set to be an important component of the future pharmaceutical landscape, according to a Business Insights report.[1] Thus, annual sales of injectable products will reach $49 billion by 2014. Therapeutic areas in which adherence is a significant issue present major opportunities for injectable delivery. Current key market successes, such as Risperdal Consta, demonstrate the role injectable delivery plays in overcoming such adherence problems, and its future potential in mental health, diabetes, and HIV are set to ensure its continued success.

There are more than 20 billion injections administered worldwide. While most are still administered with a traditional needle (60%), safety syringes represent approximately 26%, and pen injectors around 13%, indicating a movement toward safer and easier-to-use alternative delivery systems. As needle-free represents less than 1% of the market, industry insiders believe it has the most potential for growth and expansion, especially with newer and more technologically advanced options becoming available. According to Kalorama Information, demand for new delivery options, particularly for biologics, will cause an expansion of the $2.7-billion needle-free technology market.[2]

Also demonstrating their potential for new product opportunities in injectable delivery are drug/device combination products. According to Research and Markets, the market for drug/device combinations currently stands at approximately $10.6 billion. With an expected growth of 11.8% throughout the next 5 years, this segment could be worth more than $18.5 billion by 2014.[3]

In this annual report on the hand-held injection market, *Drug Delivery Technology* spoke with several industry players about the rise in home healthcare, the opportunities for innovative injectable delivery options, and how companies can differentiate their products in what is expected to become a highly competitive market.

FIGURE 6

Unilife's before-and-after shot of Unifill

ANTARES PHARMA, INC.– FACILITATING THE SHIFT TO HOME TREATMENT

The current hand-held injection market is being driven by the development of new therapies that require administration via the parenteral route, the interest for cost-effective healthcare delivery, and patients' desires for the comfort and convenience of administering injectable therapeutics at home. Antares Pharma is addressing these issues by introducing products that facilitate the shift in treatment setting from the hospital or physician's office to the patient's home (Figure 1).

"Our injection systems enable patients to self-inject their medicines safely, comfortably, conveniently, and reliably," says Robert F. Apple, Executive Vice President and President of the Parenteral Products Division.

In the past year, Antares announced the early market acceptance of TJet®, its reusable injection device for the delivery of human growth hormone (hGH) in children. Additionally, the company commenced a development program for VIBEX™ MTX for the treatment of rheumatoid arthritis in collaboration with Uman Pharma. And, Antares continues its collaborative partnership with TEVA in the form of advancing epinephrine and other undisclosed products.

According to Mr. Apple, patient response to Tjet has been highly positive, and in the 12 months since Tjet approval, TEV-TROPIN® prescriptions have increased more than 55%.[4]

"A substantial portion of the growth is attributed to availability of Tjet, with approximately half of new patients starting on TEV-TROPIN choosing Tjet over alternative administration options," he says.

With regard to its newest development program, VIBEX MTX, Antares has conducted preclinical studies demonstrating highly reproducible pharmacokinetics and excellent injection site tolerance when methotrexate was delivered using the auto injector VIBEX technology, explains Mr. Apple.

Methotrexate is the most commonly prescribed disease-modifying anti-rheumatic drug, used in an estimated 70% of rheumatoid arthritis patients. Methotrexate is started at a low dose, generally 7.5 mg given orally, once a week, and titrated up for greater therapeutic effect, or until the patient incurs side effects. The maximum oral dose given is generally 20 to 25 mg per week. Studies have reported as many as 30% to 60% of patients experience gastrointestinal side effects with oral methotrexate, preventing further dose escalation or requiring discontinuation in some patients. Also, the extent of oral absorption of methotrexate varies considerably between patients and has been shown to decline with increasing doses, which may also contribute to insufficient therapeutic response even after dose escalation. Switching patients from oral to parenteral methotrexate improves absorption and has been associated with improved therapeutic response. Additionally, some studies have shown a lower incidence of gastrointestinal side effects in patients who were switched from oral to parenteral methotrexate.

FIGURE 1

Antares' Assortment of AIS Injection Devices

The key limitation with injection methotrexate as currently offered is the need for patients to make weekly visits to the doctor's office for the intramuscular injection.

Mr. Apple believes VIBEX MTX will allow more patients to be titrated and tolerate an effective dose of methotrexate.

"VIBEX MTX will be a cost-effective approach to maximizing the therapeutic potential of methotrexate while also avoiding the cost associated with injections in the physician's office," he says. "In addition to maximizing therapeutic results with methotrexate before adding biologic therapy, VIBEX MTX will be a very important option for rheumatoid arthritis patients who are not ideal candidates for biologic therapies. We have recently filed a patent application around the VIBEX MTX product and are proceeding with plans for clinical studies, and depending on the results, we may be in a position to file an application with the FDA to commercialize VIBEX MTX."

Antares is cognizant of the challenges presented by auto-injectors when injecting viscous therapies. Mr. Apple says that conventional auto-injectors are inadequately powered, which could result in unacceptably long ejection times–beyond that which patients would accept. The design of these systems cannot tolerate the forces required to expel viscous materials within an acceptable time without risking breakage of the glass syringes.

"Our approach attenuates peak impact force at initial trigger point, while maintaining elevated force through the entire stroke, producing a smooth and rapid injection without PFS breakage," he says.

Antares' approach to development and commercialization is based on listening to the needs expressed by healthcare professionals and patients.

"We are evaluating several drug candidates that would be enhanced by an injection device," adds Mr. Apple.

FIGURE 2

BD's Physioject™ Disposable Auto-Injector

"Candidates that fit our existing platforms score higher in our evaluation. If the opportunity is significant but requires different technology, we will develop it internally or in-license the technology. Development and/or commercialization would then occur independently or in collaboration with a partner."

BD MEDICAL-PHARMACEUTICAL SYSTEMS–DEVICE CUSTOMIZATION FOR INJECTABLE THERAPIES

Self-administration of medications is needed to effectively serve the evolving biotechnology drug market. An aging patient population and increasing managed care initiatives are driving the need for home healthcare, especially for patients with chronic diseases. To improve health outcomes, it is critical the devices delivering drug therapies are intuitive and easy to use.

BD has developed multiple product platforms to enable safe and easy administration of injectable drugs. Product offerings include prefillable syringes and self-administration systems, such as liquid pens, dry drug pens, pen needles, auto-injectors, and patch pumps.

Challenges face the pharmaceutical industry on multiple fronts. From a drug standpoint, some issues include the delivery of high-viscosity molecules, highly sensitive drugs, particle suspensions, and large injection volumes. These complex drug characteristics make it critical for pharmaceutical companies to choose the right delivery system to protect and deliver their drug. The self-injection device must integrate seamlessly with the primary container, while meeting patient needs. Complete reliability and integrity of the total delivery system (drug, container, and device) must be achieved.

BD's solutions to these challenges include pen needles designed to meet both technical drug delivery requirements and patient needs. BD also offers primary containers that protect the drug. For example, the BD Hypak™ for Biotech is a glass prefillable syringe system that offers a tighter set of specifications on critical syringe barrel attributes to meet the more stringent and emerging needs of the biotech market, says Chris Del Giudice, Product Manager, BD Medical-Pharmaceutical Systems. Finally, BD develops devices aimed at protecting the primary container and making it easy to self-administer therapies.

As a manufacturer of both prefillable syringes and self-injection devices, BD offers scientific support to ensure a drug is compatible with the primary container.

"We offer expertise in choosing the right primary and secondary delivery systems, integrate the two systems to ensure robustness, and design self-administration devices that are integrated with the primary container," says Megan Lan, Senior Product Manager.

Taking a system-based drug delivery approach, BD has strived to increase the robustness of its products to protect and accurately deliver injectable drugs. The company's first disposable liquid auto-injector, BD Physioject™ Auto-Injector (Figure 2), illustrates this system-based approach. It is a prefilled syringe/disposable auto-injector combination product, which was developed to offer greater convenience to the self-injecting patient.

"As the pharmaceutical model shifts from blockbuster drugs to more targeted therapies, BD is adapting to offer customized solutions to meet our customers' drug delivery needs," says Ms. Lan. "BD is also continuously investing in new product development and optimizing operational capabilities to effectively serve the market."

BIOJECT INC.–PURSUING NEEDLE-FREE INJECTION WORLDWIDE

The entry and rise of new DNA-based vaccines will require Needle-Free Injection delivery options, and Bioject plans on being at the forefront of this opportunity. And the company is on the right course. In the past year, Bioject's intradermal needle-free delivery system was tested by the World Health Organization in a clinical trial in Oman with Polio Virus vaccine.

"Based on the findings, as reported in the New England Journal of Medicine, we have evidence that demonstrates potential cost-savings when using intradermal needle-free injection delivery technology as compared with typical full-dose injections," says Dr. Richard Stout, Bioject's Executive Vice President and Chief Medical Officer.[5]

In addition to vaccines, Bioject is targeting chronic diseases and therapeutic treatment regimens that require multiple injections daily, weekly, or monthly over several months to many years. These include hematopoietics, anti-inflammatory disease, multiple sclerosis, human growth hormone, and fertility.

Bioject provides a range of Needle-Free Injection devices, all using its patented pressure profile. The gas-powered Biojector® delivers up to 1 ml. The Iject®, which is in development and is a single-use, glass, prefilled, needle-free disposable device, can also deliver up to 1-ml injections.

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Spring-powered, needle-free ZetaJet™, with auto-disable syringe, can deliver between .05 ml and 0.5 ml (Figure 3). In April 2009, the device was FDA 510(k) cleared for general use for both subcutaneous and intramuscular injections, and is being used investigationally for intradermal injections. Bioject is in the process of exploring partnerships to leverage this technology worldwide.

Also in development is an intradermal, multi-dose injection device, the Jupiter Jet. Applications for this device include dermal fillers, long-acting insulin, and other low-volume injections given in multiple applications.

Of the aforementioned products, the Biojector and ZetaJet are currently on the market. The others could be on the market within 24 to 36 months; once a partner is found, the two companies will jointly pursue an appropriate development and regulatory strategy, explains Ralph Makar, RPh, MBA, President and CEO of Bioject.

Finding the right long-term strategic partnerships is a challenge for Bioject.

"We must focus on partnerships that aim to fully leverage the technology and capitalize on the opportunity at hand," explains Mr. Makar. "In terms of customer focus, Bioject seeks to expand partnerships with pharmaceutical, biotechnology, vaccine companies, and organizations in developing countries."

Increasing regulatory/political pressures over sharps waste and needle disposal present opportunities for Bioject. As a result, the company is actively engaged in growing its business with the military, public health clinics, and within government mass immunization programs.

"We believe that needle-free technology will begin to expand significantly in the coming years, says Mr. Makar."

DUOJECT—USER-FRIENDLY RECONSTITUTION

As today's hand-held injection market trends are increasingly focused on home care and self-medication products, Duoject's goal is to introduce devices that are safe and intuitive for the end user. Pursuant to this, Duoject continues to focus on reconstitution systems and has developed devices that work with pen injectors, such as its PenPrep XR device or the more recent Actuator reconstitution device for double-chamber cartridges.

"Through our 25-years of experience in the reconstitution field, we have built strong relationships with other medical device manufacturers in the industry. We have been approached by other hand-held injection leaders in the market to help expand their capabilities by adding reconstitution as part of their offering to the market," says Dan MacDonald, Vice President of Engineering Services at Duoject.

To address the growing market for self-administration and home care, Duoject is completing design work on a single-use device that will automatically protect the needle before and after injection, and will be auto disabled to eliminate reuse, ensuring user safety and convenience. This device will be available for liquid- and lyophilized-based drugs. Mr. MacDonald expects the product to be available to the market by the end of this year.

Duoject has also continued R&D work on its Smart-Rod Plus technology, which enables reconstitution of drugs lyophilized in staked-in needle syringes (it can also be used with luer-lock syringes). The advantage is that the drug is reconstituted and administered with minimal loss of product. The drug remains in the syringe during reconstitution steps and the staked-in needle ensures the lowest possible hold-up during delivery to the patient.

"More and more companies are seeing the minimal drug loss benefits of lyophilizing right in the syringe, eliminating the added cost associated with overfilling their product," says Mr. MacDonald.

In addition to increased home care, there is a growing trend in the market to use coated stoppers in drug vials, creating a barrier between sensitive drugs and potential leachables in the rubber formulation. These coatings are generally harder to pierce with a simple plastic spike and can cause transfer failures if the device is not optimized to work with these components. Duoject has designed the E-Z-Link reconstitution device to address this potential failure by incorporating a fully protected stainless-steel needle as part of its fluid path (Figure 4). The needle is protected from the end user throughout the reconstitution process and can be adjusted in gauge size and length to accommodate specific product viscosities and stopper

FIGURE 3

Bioject's spring-powered, needle-free ZetaJet™ with auto-disable syringe can deliver between .05 ml and 0.5 ml.

FIGURE 4

Duoject's E-Z-Link

septum thicknesses and coatings.

E-Z-Link features sequential activation steps in its design that help guide the end user through the reconstitution process.

"A challenge in designing effective delivery devices is to make them as user-friendly as possible," says Mr. MacDonald. "E-Z-Link is designed in such a way that the end-user is required to perform a specific step first, which once completed, will then reveal the next step to perform."

B&O MEDICOM–DIFFERENTIATED TECHNOLOGIES FOR DRUG DELIVERY

Industry interest in hand-held injection technologies that differentiate the drug is beginning to grow significantly, says Paul Erik Fabricius, Senior Design Manager for Bang & Olufsen Medicom. In response, Medicom is focusing on delivering services that lead to differentiated solutions for pharmaceutical companies.

In the past year, the company has refocused its efforts to position itself as a provider of advanced drug delivery device development services. The focus is to assist organizations in their efforts to bring complex, competitive injection projects to the market quickly.

The LEVA disposable auto-injector is a key product for Medicom (Figure 5).

"Its design is differentiated in the market as it has a short and flat shape, making it very ergonomic to hold and to use," says Mr. Fabricius. "The design moves the product away from shapes normally associated with injection, pain, and needles."

To date, Medicom is negotiating with several pharmaceutical companies regarding commercialization of LEVA.

In addition to its focus on technologies that differentiate the delivered drug, Medicom is also interested in the area of easy and safe lyophilized drug delivery with a specific focus on automated reconstitution and in more advanced delivery platforms featuring electronics.

"Integrating mechanics, electronics, and connectivity can add additional value to the disease management solution," says Mr. Fabricius.

Medicom is currently working on what Mr. Fabricius dubs a "revolutionary new concept" in the area of lyophilization, which will bring the ease-of-use close to the level now found in more traditional auto-injectors. He is cognizant of the challenges and complexities of bringing advanced delivery devices to market, but says that working with a team of external partners, internal specialists, and the client are keys to create a foundation for successful development.

UNILIFE CORP.–ENSURING SAFETY IN SELF-ADMINISTRATION

The home injection market is driven by the three Ps: pens, pumps, and prefilled syringes. And each of these device categories is driven by ease of use, flexible storage, accurate dose administration, and convenient disposal. Unilife is addressing these key drivers by specializing in the development of prefilled and general-use syringes with passive and fully integrated safety features, specifically designed for healthcare workers or patients that self-administer prescription medication (Figure 6).

"All of our products allow operators to control the speed of automatic needle retraction directly from the body into the barrel simply by relieving thumb or finger pressure on the barrel upon the full delivery of the dose," says Stephen Allan, Vice President of Marketing and Communications at Unilife.

For instance, the Unitract™ 1-mL syringes can help patients self-administer drugs, such as insulin, that are supplied in vials. Unifill prefilled syringes are a primary container with passive integrated safety features integrated in the glass barrel. The syringes are designed for integration into the fill-finish systems used with standard prefilled syringes to help minimize packaging, transport, and storage costs. The Unifill syringe looks and operates similar to a standard prefilled syringe, but virtually eliminates the risk of needlestick injury or splatter as operators can control the speed of needle retraction directly from the body into the barrel. It is then locked in place, and ready for compact, convenient disposal.

"Many once saw the full integration of safety features within the glass barrel of a prefilled syringe as an impossible task," says Mr. Allan. "As a primary container, it was thought that the additional components would conflict with fundamental device requirements, such as material stability and dose delivery. Our proprietary technology is uniquely positioned to address such issues."

To date, Unilife has agreed to a list of therapeutic drug classes, including vaccines and anti-thrombotic agents, where sanofi-aventis has the exclusive right to negotiate the purchase of Unifill syringes. Mr. Allan expects the Unifill syringe ultimately will be used across a number of the more than 12 therapeutic drug classes where prefilled syringes are currently used.

Unifill syringes will be available for supply to pharmaceutical customers in 2011, following the completion of a new global headquarters and production center in York, PA, and the qualification of the automated assembly system.

Mr. Allan expects that the new facility will enable Unilife to keep pace with the growing demand from the prefilled syringe sector. There are more than 2.5 billion prefilled syringes used each year, with the market growing at more than 10% per year, he says.

"There are now more than 65 products available in a prefilled syringe format. We also expect a number of new pipeline drugs to be launched in a prefilled syringe format. Many of these drugs will be within therapeutic classes where prefilled syringes are not currently used. We are aware of approximately 25

FIGURE 5

MedicomNordic's LEVA Auto-Injector

pharmaceutical companies that are now benefiting from prefilled syringes' industrial and marketing advantages."

Mr. Allan also hopes pharma will benefit from the company's Unifill Select, another ready-to-fill syringe with passive, integrated safety that is suitable for use with drugs, such as vaccines requiring intramuscular injection. He says the patented pipeline product will allow pharmaceutical companies to package the prefilled syringe with a sample of luer needles in a "ready-for-injection" kit.

"Healthcare workers would be able to attach a needle up to 1.5 inches in length based upon the requirements for the patient who will be receiving the injection."

Unilife is in preliminary discussions regarding the commercialization of this device.

"We will work in tandem with our partners in the pharmaceutical and healthcare markets to protect those at risk of needlestick injury, enhance patient care, and prevent disease," says Mr. Allan.

ZOGENIX, INC.–DRUG/DEVICE COMBINATION FOR MIGRAINE PAIN

Zogenix's FDA approval and subsequent commercial launch of SUMAVEL™ DosePro™ into the prefilled, single-use, disposable, needle-free injection delivery market is positive news for the industry. After technology development and clinical evaluation, SUMAVEL DosePro was made available to patients who require the speed and efficacy of subcutaneous sumatriptan to treat their migraines without a needle-based injection.

SUMAVEL DosePro (sumatriptan injection) was approved as a drug/device combination and was launched this past January with co-promotion partner, Astellas US Pharma, Inc.

"With DosePro as the delivery platform, physicians can now offer this as an additional treatment for self-administration at home or anywhere that is convenient," says Dr. Stephen Farr, President and Chief Operating Officer at Zogenix, Inc.

The technology was first developed by Weston Medical under the Intraject name, transferred to Aradigm, and then acquired by Zogenix in 2006. Zogenix finalized the design of DosePro and completed commercial manufacturing scale-up. DosePro uses conventional container closure materials to store the prefilled drug (using borosilicate glass). The system has also been designed to be extremely simple and intuitive to use, requiring only three steps–snap, flip, and press, explains Dr. Farr.

Several clinical studies have been completed using DosePro. One study showed that 98% of patients were able to use the product correctly the first time when administered at home. In an Internet-based patient feedback program, 7 out of 9 prefer SUMAVEL DosePro to their oral medications; almost 90% will or might continue using the product; and 3 out of 4 patients would recommend others speak to their doctor about SUMAVEL DosePro, says Dr. Farr.

While the uptake of SUMAVEL DosePro with neurologists and headache specialists indicate favorable acceptance, Zogenix continues to invest in making improvements to the next generation of DosePro, including expanding the fill volume of the glass capsule from 0.5 mL to 1 mL.

"This will broaden the range of drug volumes that DosePro can deliver, making it a true platform technology with applicability to a range of drug formulations, including proteins, peptides, and small molecules, irrespective of viscosity," says Dr. Farr.

Successful delivery of large molecules *in vitro* and *in vivo* has demonstrated bioequivalence to conventional needle-based systems, with no deleterious effect on molecule integrity or system compatibility/stability while at the same time being preferred by patients over a conventional needle-based injection, he adds. Zogenix is developing DosePro for use with drugs in the areas of CNS and pain.

"Because the DosePro design lends itself to any disease state that requires simple, easy-to-use administration, Zogenix is also working with other biotech and pharmaceutical companies to explore the use of DosePro for a variety of applications," says Dr. Farr.

FIGURE 7

Zogenix's SUMAVEL DosePro (sumatriptan injection) Needle-Free Delivery System

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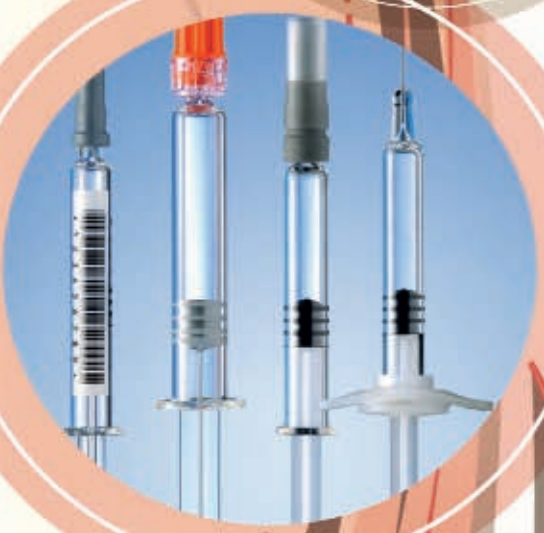

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NANOPARTICULATE DELIVERY

Nanoparticulate Carrier Drug Delivery Systems: A Mini Review of Patented Technologies

By: Avani Amin, PhD; and Mohit Shah, MPharm

INTRODUCTION

Novel formulations and alternate routes for drug delivery broaden the potential for therapeutic applications of treatments by allowing delivery to previously inaccessible sites in the body. In contrast to developing newer active pharmaceutical ingredients, introduction of novel formulations greatly reduces the risk, time, and capital invested in new drug development. Nanoparticulate drug delivery systems (NPDDS) have exhibited enormous potential in the healthcare, pharmaceutical, and biomedical industries. Nanotechnology has changed the scale and methods of drug delivery systems and provides huge potential for development in these areas. NPDDS can enable reformulation of existing drugs by extending product life cycles, increasing profitability, expanding intellectual property estates, and discouraging competition during a drug's most valuable years.

The rise of nanotechnology has changed the face of treatment of previously incurable conditions such as cancer. In cancer therapy and diagnosis, NPDDS can serve many targeted functions in chemotherapy, radiotherapy, immunotherapy, thermotherapy, imaging, photodynamic therapy, and anti-angiogenesis. The inherent size of nanoparticles facilitates their vascular permeability, retention time, intracellular uptake, and biological affinity and provides significant advantages in the delivery of anti-cancer agents.[1,2]

Today, there exists a variety of nanocarriers, such as solid lipid nanoparticles (SLNs), liposomes, niosomes, dendrimers, gold nanoshells, nanorobots, carbon nanotubes, quantum dots, magnetic nanoparticles, nanocrystals, nanorods, and more, that have been successfully targeted to various organs of the body, including the brain (Figure 1).[3-5] These emerging nanoparticulate carrier technologies focus on the following areas:

- Improving solubility and bioavailability of poorly water-soluble drugs
- Enhancing circulatory persistence of drugs
- Targeting drugs to specific cells
- Achieving controlled/sustained-release delivery systems
- Improving drug loading
- Improving performance in various gastrointestinal conditions
- Improving stability in biological environments for proteins and peptides
- Protecting drugs against degradation

Market reports suggest that the total market for nanotechnology-enabled drug delivery systems will reach $26 billion by 2012 and potentially $220 billion by 2015, compared to its size of $3.39 billion in 2007.[6]

The aim of this mini review is to compile some patented nanocarrier-based drug delivery technologies marketed by pharma giants and to highlight their applications and express their novelty. The technologies are summarized in Table 1, and some are described in brief herein according to their route of administration.

INJECTABLE TECHNOLOGIES

Abraxis Bioscience Inc.

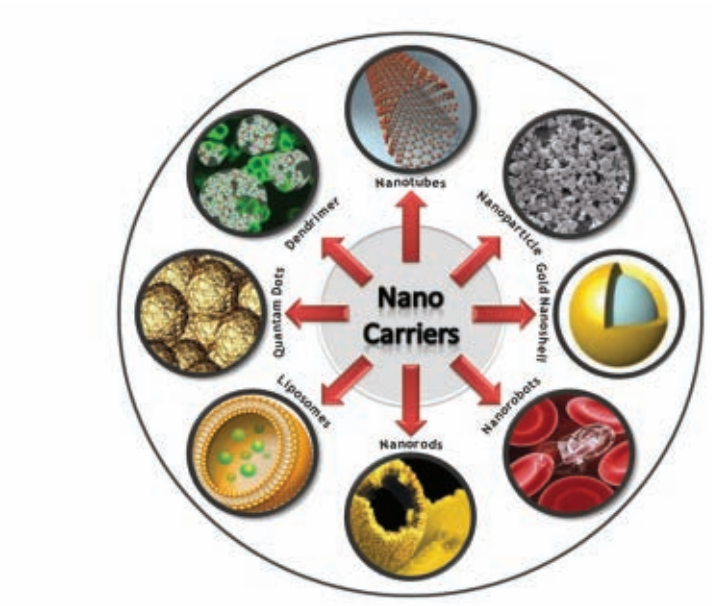
Abraxis introduced the world's first FDA-approved protein-based nanoparticles, Abraxane™ (paclitaxel protein-bound particles) injectable suspension, based on its proprietary nanoparticle albumin bound (nab™) technology for the treatment of breast cancer. Compared to solvent-based paclitaxel, Abraxane nanoparticles are proven to deliver a 49% higher dose of paclitaxel. Furthermore, these nanoparticles have added advantages, such as reduced infusion time, reduced solvent-related toxicity, and elimination of the need of special intravenous tubing and premedication required to prevent solvent-based hypersensitivity reactions.[7]

Access Pharmaceuticals Inc.

Access developed a Cobalamin™ Mediated Disease Targeting Technology that provides a proof-of-principle of vitamin-mediated targeting of cancer cells. This technology could further be extended for the treatment of rheumatoid arthritis, psoriasis, acute leukemia, lymphomas, Crohn's disease, ulcerative colitis, and multiple sclerosis. In preliminary studies, the company focused on targeting Cobalamin folic acid, biotin, and analogs of these substances. The studies suggested that a drug's affinity toward diseased cells and efficacy can be amplified by attaching Cobalamin or encapsulating the drug in a nanoparticle coated with Cobalamin. Access is currently developing applications of this technology in the area of oncology as well as other diseases.

Another nanoparticulate technology from Access is ProLindac™, a nanoparticulate prodrug of Diaminocyclohexane Platinum (DACH Platinum) in which the cytotoxic agent (DACH platinum) is bound to a water-soluble, biocompatible copolymer backbone, called hydroxypropylmethacrylamide (HPMA). This approach allows ProLindac to avoid use of the oxalate group, which is believed to give rise to the severe neurotoxicity associated with oxaliplatin, another blockbuster prodrug of DACH Platinum marketed by Sanofi-Aventis under the trademark Eloxatin™ or by Medac GmbH under the trademark Oxaliplatin Medac™. ProLindac releases platinum much more rapidly in a slightly acidic environment compared to an environment of the body's normal physiological pH. This increases selectivity of Prolindac toward the tumor cells as they are usually more acidic than normal tissue. The Phase I study of ProLindac demonstrated at least five times more bioavailability of DACH Platinum compared to oxaliplatin. Moreover, this technology did not demonstrate acute neurotoxicity, which is commonly associated with oxaliplatin.[8]

FIGURE 1



Various nanoparticulate carriers for drug Delivery

Biophan Technologies Inc.

Biophan has developed nanomagnetic carriers that precisely deliver drug to the target site and activate it in that area only. This can facilitate a high local dose with low systemic concentration, improved safety profiles, reduced toxic side effects, and delivery of clinical doses in excess of what is currently possible. In this technology, the anti-cancer drug particles are attached to the surface of the magnetic nanocarriers and injected into the bloodstream. These nanoparticles are targeted to the tumor location by applying a magnetic field; the drug release from the carrier is facilitated by electromagnetic signals. The major drawbacks of the most effective anti-cancer agents (ie, toxicity and lack of discrimination) can be effectively solved by targeting them to a particular site using this technology.[9]

IMPLANTABLE TECHNOLOGIES

Nanotechnology improvises the benefits of implants and makes it suitable for treatment of incurable diseases like cancer. Among the first nanoscale devices to show promise as anti-cancer therapeutics were structures called nanoshells by NanoMarkets.[10] These

TABLE 1

COMPANY	TECHNOLOGY / PRODUCT	FORMULATION / PURPOSE
Abraxis Bioscience Inc.	Abraxane™	Particles for injectable suspension
Access Pharmaceuticals Inc.	Cobalamine™ Mediated Targeting	Nanoparticle/Polymer
	Cobalamine™ Mediated oral Delivery	Absorption enhancement and drug protection
	ProLindac™	Nanoparticle/Polymer
Aphios Corporation	Taxosomes™	Paclitaxel nanosomal formulation
Azaya Therapeutics	Protein Stabilized Liposome (PSL™)	Improve solubility, protectivity, and reduce toxicity
Biophan Technologies Inc.	Guided Drug Delivery	Magnetic nanoparticles
Calando Pharmaceuticals, Inc.	CYCLOSERT™, RONDEL™	Nanoparticles for cancer targeting
Cerulean Pharma, Inc.	Nanocell™ Technology	Immediate release and controlled release nanoparticles for atherosclerosis, rheumatoid arthritis, cancer, and inflammatory bowel disease
Cornerstone Pharmaceuticals	Emulsiphan Selective Delivery Platform	Nanoemulsion for cancer targeting
Dendritic Nanotechnologies, Inc.	Priostar®, Starburst®	Dendrimers
Elan Drug Technologies	NanoCrystal® Technology	Solubility enhancement
Interstitial NS	NanoMAP Technology	Micro-array patch
Intezyne Technologies, Inc.	IVECT™ Platform	Polymeric crosslinking and encapsulation technology
Keystone Nano, Inc.	NanoJackets™	Nanoparticles for cellular, cancer, and tissue imaging
MagForce Nanotechnologies AG	Nano-Cancer® Therapy	Magnetic nanoparticle for cancer therapy
Nanobiotix	NanoXray™	Nanoparticles for cancer targeting
Nanospectra Biosciences, Inc.	AuroLase™ Technology	Nanoshell for cancer therapy
Nanotherapeutics Inc.	NanoCOAT™	Solventless encapsulated nanoparticles
	NanoDOX™	Doxycycline gel for chronic wound
	NanoDRY™	Micronized powder
	NanoGENT™	Inhaled gentamycin formulation
	NanoQUAD™	Micronized powder for absorption enhancement
NanoVentures Australia	Surface Acoustic Wave Technology	Atomized fluid for inhalation
Novavax Inc.	Estrasorb™ and Androsorb™	Micellar nanoparticles for hormone replacement
pSivida Corp.	BioSilicon™ Technology	Biodegradable implant
SoluBest	Solumer™	Inclusion complex for bioavailability enhancement
Starpharma	VivaGel™	Microbicide gel

Nanotechnology-Based Marketed Products

nanoshells typically have a silicon core that is sealed in an outer metallic core. By changing the wall-to-core ratio, the shells can be precisely tuned to scatter or absorb very specific wavelengths of light. For example, gold-encased nanoshells have been used to convert light in to heat, enabling the destruction of tumors by selective binding to malignant cells.

pSivida Corp.

pSivida has introduced a Biosilicon™ product, which is a nanostructured material that effectively stores an active compound in nanosized pockets and releases minute amounts of drug as the silicon dissolves. This nanotechnology-based product demonstrates various advantages over conventional technologies like higher drug loading, ability to accommodate different sizes of molecules by modifying the nanostructured pores, ability to control drug release for months, and complete bioerodibility. A unique semiconductor property of this biosilicon technology also facilitates construction of smart processor controlled drug delivery. This technology imparts heat and radiation stability to the formulation, facilitating manufacturing and sterilization processes.[11]

ORAL TECHNOLOGIES

Successful implementation of oral administration requires the active ingredient to remain unaltered during transit throughout the gastrointestinal tract and to possess the requisite physicochemical features (typically low molecular weight, lack of charge and some lipophilicity) that allow it to be absorbed readily across the intestinal wall to be delivered to the bloodstream. For many active materials, particularly peptides and proteins, oral administration is currently not an option, as the level of uptake is only less than 1% of the administered dose. Nano-enhanced drugs could make a big difference in increasing oral bioavailability, reducing undesirable side effects, and decreasing degradation. By improving bioavailability, nanotechnology helps increase the yield of drug development and to treat previously untreated conditions by targeting or localizing the drug molecule.

Solubest Ltd.

Solubest introduced a versatile nanotechnology platform, Solumer™, based on the creation of a novel inclusion complex of water-insoluble compounds, which increases solubility, absorption, bioavailability and chemical and biological stability of a wide spectrum of molecular candidates. Its unique design allows pH control of drug release, which is advantageous for the drugs that are pH sensitive, require consistent onset of action and render stomach-related side effects. The simplicity and effectiveness of the formulation led to the design of Solumer-based products like SoluFeno™ (Fenofibrate), SoluAzi™ (Azithromycin), and SoluItra™ (Itraconazole), which exhibit superior absorption patterns than commercial products.[12]

Access Pharmaceuticals, Inc.

Similar to intravenous formulations, Access also developed Cobalamin™ - mediated oral drug delivery technology, which not only enhances absorption property but also provides drug protection. The Cobalamin-mediated nanoparticles demonstrate larger distribution, higher transport capacity, and receptor-mediated uptake. As the Cobalamin-mediated oral drug delivery technology utilizes the body's natural vitamin transport system, the oral absorption and bioavailability of many biotech products (such as proteins, peptides and antibodies, as well as both small and large molecules belonging to BCS class III and IV with poor membrane permeability) can be improved using this technology. Cobalamin-coated insulin-loaded dextran nanoparticles, given orally, provide a glucose lowering effect that is slower in onset and longer in duration than intravenous insulin.[8]

Nanotherapeutics, Inc.

To overcome the problems of poor oral bioavailability, Nanotherapeutics developed powder processing technologies, NanoDRY™, NanoCOAT™ and NanoQUAD™, which improve consistency of absorption and bioavailability, and reduce the required dose and dosing frequency. The NanoDRY™ process uses a low-shear method for rapidly forming dry particles of controlled size and shape for efficient and reproducible delivery of small and large molecules. The process is well-

suited to formulate nanoparticles or microparticles of low molecular weight compounds, insoluble drugs, drug salts, peptides/proteins, and DNA. The NanoCOAT™ process is a patented solventless encapsulation system for coating micron and sub-micron size powders in which a core nanoparticle/microparticle is encapsulated with a thin layer of a coating material, such as a surfactant or a biodegradable polymer, which modify the rate of release of an active component, improve dispersion/flow properties and increase absorption into the systemic circulation. The ability to control drug-release kinetics using a broad variety of coating materials, reducing the polymer load compared to traditional polymeric microspheres, and providing with a cost-effective and rapid manufacturing process under sterile cGMP conditions are the added advantages of NanoCOAT™ technology.

The NanoQUAD™ technology is a cryo-mill process to formulate nanoparticles that exhibit rapid dissolution rates, increased oral bioavailability and more rapid absorption of active drug substances, while minimizing fed-fasted effects. These nanoparticles are also stabilized against agglomeration by surface adsorption of selected GRAS-approved stabilizers.[13]

TOPICAL & TRANSDERMAL TECHNOLOGIES

Nanomaterials provide a unique opportunity for topical delivery of active compounds due to their small size and ability to enter human tissues and cells rapidly. Taking advantage of these properties, many pharma industries have developed nanotechnology-based drug delivery systems for topical applications. Apart from what is listed further on, delivery of nicotine and hormones for contraceptives using nanotechnology has also become popular via transdermal patches.[13]

Novavax Inc.

Novavax has developed micellar nanoparticle technology-based hormone replacement therapies called Estrasorb™ and Androsorb™; the former received FDA approval in 2003. Estrasorb™ is a transdermally absorbed, microencapsulated estradiol used as an estrogen replacement therapy, while Androsorb™ is designed to deliver testosterone through the skin for testosterone replacement therapy.[14]

Interstitial NS

Interstitial developed the NanoMAP platform to enable the delivery of nanostructured large molecular drugs, including pharmaceuticals, therapeutic proteins, hormones, and vaccines, using micro-array patches. NanoMAP technology can also be optimized for immunotherapy and delivery of proteins and antimicrobials for wound repair, such as burns and skin cancer.[15]

Nanotherapeutics, Inc.

Nanotherapeutics has developed NanoDOX™, a 1% Doxycycline Monohydrate Hydrogel topical gel intended for direct contact with the wound and is applied to the entire surface of the wound bed. A secondary dressing, such as gauze or non-adhering dressing, is applied to cover the topical NanoDOX™ and wound tissue, allowing it to provide a moist, wound-healing environment.

PULMONARY TECHNOLOGIES

Currently, most commercial pulmonary drug delivery systems can deliver particles in the form of dry powder in the micron range to specific regions of the lungs; however, bioavailability may be limited due to the size, and hence surface area, of the particles. The use of nano-sized particles allows for delivery to specific regions and increases bioavailability due to the increased surface area, enabling administration of lower doses. Baxter Healthcare, MannKind Corporation, and Aradigm Corporation have introduced many commercialized nanotechnology-based pulmonary delivery systems for the administration of medication for a number of applications, especially for delivery of anti-asthmatic drugs and hormones, such as insulin.

The Australian nanotechnology firm NanoVentures Australia along with Monash University have developed a novel mechanism for generation of liquid aerosol drugs. The proprietary SAW (Surface Acoustic Wave) generated mechanism allows fluids to be atomized as precisely controlled droplets, making them ideal for a new generation of inhaler

devices. Furthermore, dose-to-dose reproducibility, efficient delivery, flexible dosing, and low cost due to few moving parts make these inhalers suitable for delivery of variety of drug molecules.

Interstitial NS

Interstitial NS' pulmonary nanoparticulate delivery technology, based on SAW technology, is currently under development for the delivery of insulin, erythropoietin and gene therapy for the treatment of cystic fibrosis.[15]

Nanotherapeutics Inc.

Nanotherapeutics is developing an inhaled version of the injectable drug gentamicin, a broad-spectrum antibiotic, to be used as a first-line therapy for pneumonic plague and tularemia, Category A bioterrorism agents. Using its novel particle formulation, the company has developed NanoGENT™, an inhaled dry powder formulation of gentamicin, to provide early treatment for exposure to biological warfare agents, as well as tuberculosis and other respiratory infections. In the event of an accidental or deliberate exposure to these agents, non-invasive drug delivery systems, such as improved inhaled and nasal delivery would be especially beneficial for administering wide-spread immediate post-exposure prophylaxis and treatment using disposable multi-dose inhalers with adequate shelf-life stability.[13]

SUMMARY

Nanotechnology-enabled drug delivery technologies have improved conventional technologies by altering key formulations and parameters of drugs, such as solubility, bioavailability, stability and targeting to desired site. NPDDS have opened avenues and exhibited enormous potential for alternate routes, such as nasal, buccal, topical, transdermal, ocular and vaginal, for local and targeting actions. Moreover, these nanocarriers have exhibited promising results for the delivery of genetic material, enzymes, hormones and vaccines at the cellular level as well as for imaging and diagnostic purposes.

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BIOGRAPHIES

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Mohit Shah is a research scholar and has earned his MPharm from Nirma University. He has 3 years of research experience and has published two papers in international journals. He has worked on rapidly disintegrating systems and gastro-retentive drug delivery systems. Currently, Mr. Mohit is actively working in the area of novel bioadhesive drug delivery systems to earn his PhD.

GASTRO-RETENTIVE DELIVERY

Controlled Release of Cinnarizine Using Gastro-Retentive Emugel Beads of Calcium Alginate

By: Bhupendra G. Prajapati, MPharm; Rakesh P. Patel, PhD, MPharm; Kalpesh L. Vaghasia, MPharm

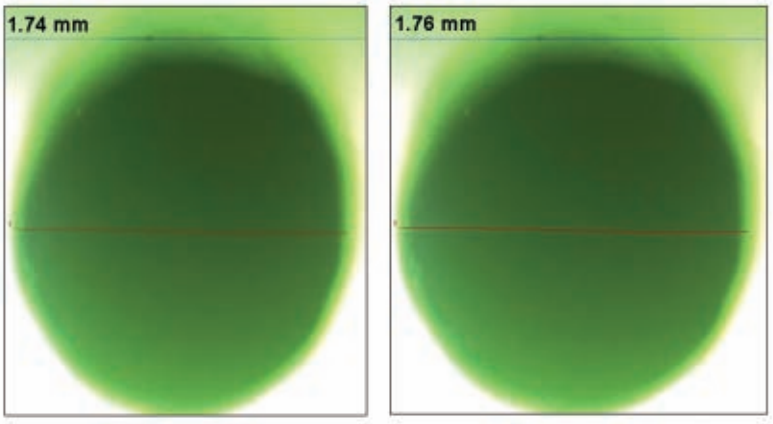
ABSTRACT

Gastro-retentive emulsion gel (EMG) beads of calcium alginate capable of floating in the gastric environment were developed using an emulsion-gelation method, and their release properties were investigated. Attempts to modify the drug release were made by additives during bead formation as well as hardening with glutaraldehyde. The cinnarizine-loaded EMG beads were found to float in simulated gastric fluid. The EMG beads were prepared using different concentrations of sodium alginate, calcium chloride, floating agents ($CaCo_3$, $NaHCo_3$, and liquid paraffin/peppermint oil), and sustained-release agents (HPMC K4M, HPMC K100M, and Acrycoat L 100). Optimization was achieved based on floating lag time, % drug entrapment efficiency, floating time, average diameter, and in vitro dissolution study. The additive glutaraldehyde had a significant effect on drug release when used to harden the beads. The results suggest that EMG beads are suitable carriers for gastro-retentive floating drug delivery.

INTRODUCTION

Gastric emptying is a complex process that is highly variable and makes the in vivo performance of drug delivery systems uncertain. To overcome this physiological problem, several drug delivery systems with prolonged gastric-retention time have been investigated.[1-3] Attempts are being made to develop a controlled drug delivery system that can provide therapeutically effective plasma drug concentration levels for longer durations, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration at a steady state by delivering drug in a controlled and reproducible manner.[4] A wide variety of natural and synthetic hydrophilic polyionic systems such as alginates have been investigated for preparation of multiple-unit floating dosage forms (FDFs).[5] Retention of drug delivery systems in the stomach prolongs the overall gastrointestinal (GI) transit time, thereby resulting in improved oral bioavailability of the basic drugs that have poor solubility in higher pH, and of drugs susceptible to circadian variations. Sodium alginate, a material used for making gel beads, has been used as a food additive, and its properties have been well studied.[6,7] It has also been used for achieving sustained release of drugs, targeting gastric mucosa, and increasing the bioavailability of drugs due to its ability to form a stable and bioadhesive gel with calcium ions.[8-13] Calcium-induced alginate gel beads (Alg-Ca) have been developed in recent years as a unique vehicle for drug delivery. Alg-Ca is rapidly formed by gelation of alginic acid in the presence of calcium ions and is able to incorporate some compounds such as drugs or polysaccharides in the gel matrix.[14,15] Other gastro-retentive studies

FIGURE 1



Photograph of Beads

have been conducted in attempts to improve controlled drug release or to achieve site-specifc delivery.[16,17] The role of mucoadhesives, the floating properties of the alginate gel forms, as well as the effect of varying the dosage have been investigated. In this study, Alg-Ca gel beads were prepared, which are capable of floating in gastric fluid. Because cinnarizine (an anti-allergic agent, calcium channel blocker, and histamine H_1 antagonist) is absorbed in the proximal part of the GI tract, is stable in acidic pH, and has a narrow therapeutic absorption window in the GI tract, it meets the primary criterion for selection as the drug candidate to be formulated as a floating multiple unit dosage form. Following oral administration, peak plasma levels of cinnarizine are obtained in 1 to 3 hours. It is known to have a half-life of about 4 hours before it completely disappears from the plasma. Cinnarizine is completely metabolized; about one-third of these metabolites are eliminated in the urine, and two-thirds in the feces.[18,19]

MATERIALS

Cinnarizine was purchased from Rakshit pharma, Mumbai, India. Sodium alginate, liquid paraffin, and calcium chloride were purchased from S.D. Fine Chemical, Mumbai, India. Acrycoat L100 D was received as a gift sample from Coral Pharma Chem Ahmedabad, India. All other ingredients were of laboratory grade.

METHODS

Preparation of Beads by Ionotropic Gelation Technique

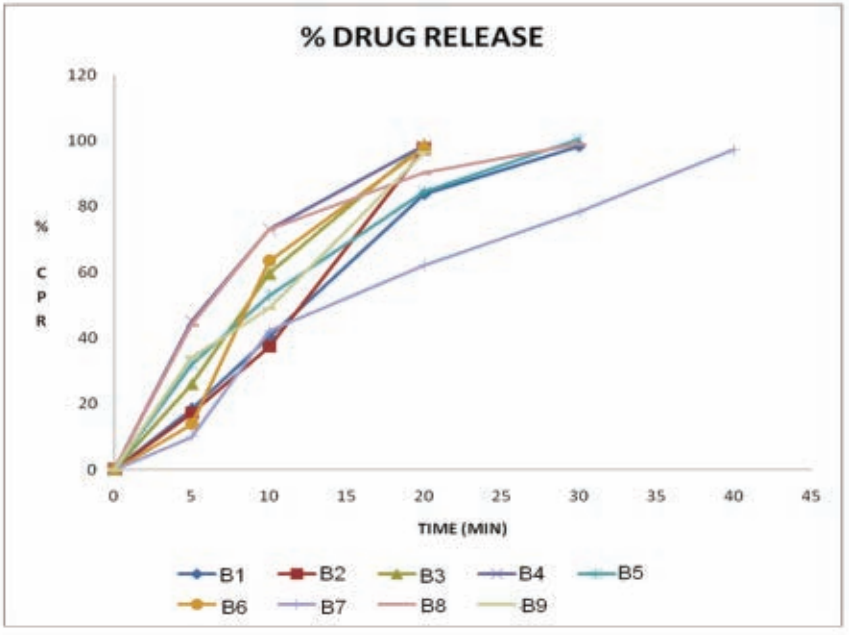
Conventional calcium alginate beads were prepared via ionotropic gelation (IG) method. Alginate solution was prepared in water containing dispersed drug. To this mixture, HPMC solution was added. The gas-forming agents, calcium carbonate or sodium bicarbonate or combination of sodium bicarbonate and citric acid, were then added.

TABLE 1

MATERIALS	B1	B2	B3	B4	B5	B6	B7	B8	B9
Cinnarizine (mg)	300	300	300	300	300	300	300	300	300
Sodium Alginate (%)	2	3	2	2	2	3	2	3	2
$CaCO_3$ (%)	2	2	3	-	-	-	-	-	-
$NaHCO_3$ (%)	-	-	-	3	3	2	-	-	-
$NaHCO_3$:CitricAcid	-	-	-	-	-	-	3:1	3:1	3:1
HPMC K4M (%)	-	-	-	1	1	1	1	1	1
$CaCl_2$ (%)	5	5	5	5	10	5	5	5	2

Calcium alginate gel beads by ionotropic gelation technique (IG Beads).

FIGURE 2



Release Profile of Batch (B1 to B9) of Cinnarizine Beads

TABLE 2

MATERIALS	B10	B11	B12	B13	B14	B15	B16	B17	B18	B19	B20	B21
Cinnarizine (mg)	300	300	300	200	200	200	200	200	200	600	600	600
Sod. Alginate (%)	3	3	3	3	3	3	3	3	2	3	3	3
Liq. Paraffin (ml)	20	15	15	-	-	-	24	20	24	24	24	20
Peppermint Oil (ml)	-	-	-	15	20	15	-	-	-	-	-	-
HPMC K4M (%)	1	1	1	2	2	2	-	-	-	-	-	-
HPMC K 100 M (%)	-	-	-	-	-	-	1	2	1	-	-	-
Acrycoat L 100 (mg)	-	-		-	-	-	-	-	-	1200	1000	1200
Glutaraldehyde (%)	-	-	-	-	-	-	-	-	-	2	2	2
$CaCl_2$ (%)	5	5	10	2	2	5	2	2	5	2	2	2

EMG beads of calcium alginate

The resulting solution was dropped through a 20-gauge needle into calcium chloride solution. The distance from the needle to the surface of calcium chloride solution was fixed to 10 cm. The gel beads formed were allowed to stand in the solution for 20 mins before being separated and washed with distilled water. The beads were dried at 37°C for 12 hrs. Finally, the dried beads were filled into the hard gelatin capsule. The formulation combinations are presented in Table 1.

Preparation of Beads by Emulsion-Gelation Technique

The EMG beads of calcium alginate were prepared via emulsion-gelation method.[20] The alginate solution containing dispersible drug was prepared, and HPMC and/or Acrycoat L 100 was then added. Liquid paraffin/peppermint oil was added and stirred at room temperature until the emulsion was formed. The resulting solution was dropped through a 20-gauge needle into the calcium chloride solution. The beads were allowed to remain in the same solution for some time to improve their mechanical strength. The EMG beads were treated in the same manner as the previous method. Few batches were treated with 2% (v/v) glutaraldehyde for 2 hrs prior to washing and drying at 37°C for 12 hrs. Finally, the dried beads were filled into the hard gelatin capsule and stored in a well-closed container. The formulation combinations are presented in Table 2.

EVALUATION

Drug Entrapment Efficiency of Floating Beads

The prepared beads were evaluated for percent drug loading and drug entrapment efficiency. An accurately weighed sample of beads (500 mg) was crushed in a mortar and added to 100 ml of 0.1N HCL pH 1.2. This mixture was centrifuged at 5000 rpm for 30 minutes, filtered, and analyzed spectrophotometrically at 254 nm. Blank beads were treated similarly. The percent drug loading was calculated (Equation 1) by dividing the amount of drug in the sampled beads by the weight of beads.[21]

Equation 1.

$$\text{Encapsulation efficiency (\%)} = AQ/TQ \times 100$$

Where AQ is the actual drug content of beads, and TQ is the theoretical quantity of drug present in beads.

Particle Size Analysis

All batches of the prepared beads were observed under Leica DMIL inverted fluorescence microscope to study their shape and size. The beads were viewed under microscope with magnification of 45X.

Floating Properties

The time between the introduction of the beads into the medium and its buoyancy to the

upper one-third of the dissolution vessel (buoyancy lag time) and the time for which the formulation constantly floated on the surface of the medium (duration of buoyancy) were measured.[22]

In Vitro Dissolution Studies

The release profile of different batches of beads was determined using the United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl (pH = 1.2), at 37°C ± 0.5°C at 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at different time intervals. The samples were replaced with fresh dissolution medium of the same quantity. Drug release was analyzed at a 254-nm wavelength using 0.1N HCl as a reference standard by a Shimadzu UV1700 double beam ppectrophotometer.

RESULTS & DISCUSSION

The mean diameter and entrapment efficiency (EE) of the CNZ-loaded calcium alginate beads, EMG beads at different alginate-to-CNZ ratios, are presented in Table 3. The mean diameter of the CNZ-loaded gel beads ranges between 1.41 ± 0.05 mm and 1.79 ± 0.65 mm. The average size of the beads increased slightly as the amount of CNZ and/or oils increased. The hardening agent caused a decrease in bead size as it promoted the formation of cross-links between the alginate molecules.

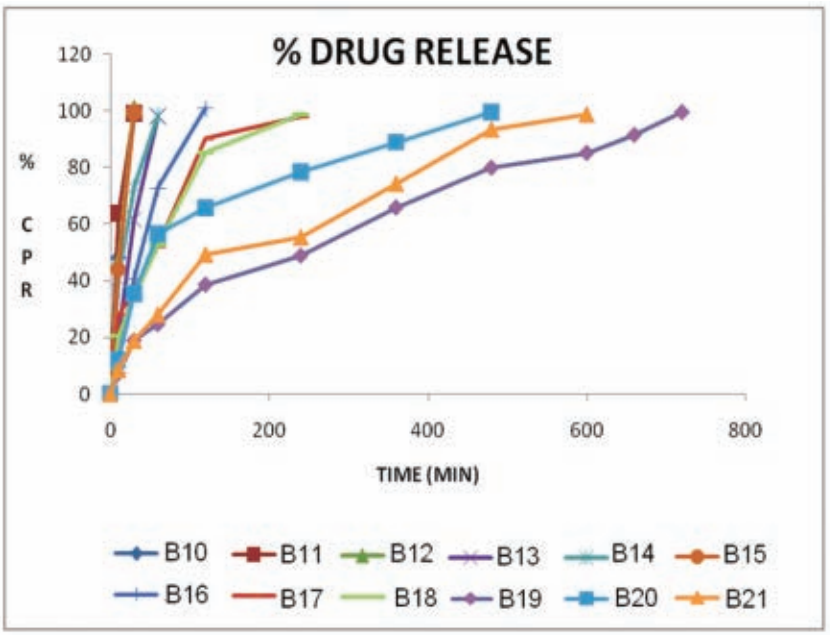
The EE of the beads was calculated from the fractional amount of drug remaining in the beads. As shown in Table 3, the EE of IG beads and EMG beads without any additive ranges from 41.46% and 59.45%, while that of the EMG beads with additive ranges from 40.26% to 79.57%. The EE increased slightly as the amount of drug loading increased. Conversely, the EE decreased by half when the beads were soaked in the hardening agent for 2 hrs.

Study of the initial Batch 1 to 6 prepared using gas-forming agents $CaCO_3$ and $NaHCO_3$ in the range of 2% to 3% showed no floating property in SGF. Change in gas-forming agent to $NaHCO_3$:citric acid in the ratio of 3:1, showed around 2 hrs of lag time, which was still too high. Out of all the formulations, B8 showed the highest floating time (7 hrs). This batch was utilized for further optimization.

Notably, if sufficient amount of oil was added (ie, liquid paraffin/peppermint oil), the EMG beads floated within 5 to 20 mins and remained floated for a long time.[21] The results of floating lag time can be correlated to the relative density of oil used. This is probably due to the decreased density of the beads by loading oils. The floating lag time and floating time both improved by increasing the amount of oil in the formulation, ie, floating lag time decreases and duration increases.

Results of batch B10 to B18 shows that

FIGURE 3



Release Profile of Batch (B10 to B21) of Cinnarizine Beads

the addition of hydrophilic, high viscous polymers like HPMC K4M and HPMC K100 shows a negative impact on floating lag time but improves duration of floating time. Floating time was further improved by replacing the hydrophilic polymer with a hydrophobic polymer like acrycoat L100 (batch B19 to B21).

In Vitro Dissolution Profile

The drug-release profiles were presented by plotting the amount of CNZ released against time. Figures 2 and 3 illustrate the release profiles of CNZ-loaded IG beads and EMG beads, respectively. Lag time was within 5 mins observed for batch B19 to B21. The release of CNZ from IG beads was rapid; about 80% of CNZ was released within 20 to 30 mins, in all ratios of alginate to CNZ. This is probably due to the fact that diffusion of dissolution medium is easy through the calcium alginate structure. The EMG beads containing liquid paraffin produced slower drug-release profiles compared to IG beads. It is likely that the oil, which was dispersed in the structure of EMG beads, obstructed the dissolution channel of CNZ. Consequently, the drug release was prolonged; about 80% of CNZ was released within 100 to 120 mins using hydrophilic swellable polymers. Because the drug release was quick and was not harmonious for floating drug delivery, modification of the EMG bead formulations was needed. The hardening agent is commonly used to strengthen the bead structure as well as to modify the release behavior. In this study, a hardening agent was used to delay the drug release from EMG beads. Figure 3 shows the effect of the hardening agent, glutaraldehyde, on CNZ release from EMG beads containing liquid paraffin oils. The CNZ release from EMG beads containing 24 ml of liquid paraffin and 1200 mg of Acrycoat L 100, which were soaked in 2% glutaraldehyde for 2 hrs, resulted in prolonged drug release compared to the release of CNZ from EMG beads without cross-linking. The release from EMG beads was significantly different when the amount of Acrycoat L 100 D was varied. It was suggested that the Acrycoat L 100 D was only dispersed in the EMG structure and did not interact with the calcium ion or carboxylic group of alginate. In addition, the drug release retarded when the Acrycoat L 100-to-alginate ratio was increased (Figure. 3). It was suggested that the addition of Acrycoat L 100 at a higher amount resulted in a matrix with more hydrophobicity, which consequently delayed the diffusion of drug from the beads.

TABLE 3

Batch No.	Floating Lag Time	Drug Entrapment Efficiency (%)	Mean Particle Size (mm)	Floating Time (Hrs)
B1	No Float	47.67	1.45±0.03	No
B2	No Float	54.90	1.54±0.06	No
B3	No Float	50.31	1.48±0.05	No
B4	No Float	44.95	1.56±0.08	No
B5	No Float	41.46	1.63±0.06	No
B6	No Float	43.32	1.64±0.04	No
B7	1.3 hrs	51.00	1.43±0.02	3.35
B8	2 hrs	59.45	1.49±0.04	7.00
B9	2 hrs	53.96	1.46±0.06	6.55
B10	7 mins	57.12	1.67±0.01	6.45
B11	8 mins	60.34	1.63±0.07	13.15
B12	5 mins	66.87	1.41±0.05	9.45
B13	15 mins	50.34	1.54±0.09	2.30
B14	20 mins	45.55	1.76±0.07	1.40
B15	15 mins	40.26	1.65±0.04	2.10
B16	10 mins	75.65	1.76±0.12	10.50
B17	20 mins	79.57	1.64±0.32	9.40
B18	13 mins	76.69	1.78±0.43	8.00
B19	5 mins	75.87	1.76±0.07	19.20
B20	5 mins	70.45	1.79±0.65	17.15
B21	5 mins	73.00	1.73±0.37	18.18

Evaluation of various cinnarizine floating beads

CONCLUSION

The optimized gastro-retentive EMG calcium alginate beads can float in the gastric condition and control drug release. The enhanced buoyancy property of EMG beads of calcium alginate makes them an excellent candidate for intragastric floating drug delivery systems.

GASTRO-RETENTIVE DELIVERY

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BIOGRAPHIES

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DRUG DELIVERY Executive

ISP

Mr. Philip Strenger
Senior Vice President
Global
Pharmaceuticals

ISP Pharmaceuticals

"At ISP, we are addressing the solubility issue on a number of fronts. We are combining our expertise in material science and our broad portfolio of ingredients as a foundation to help pharmaceutical companies improve traditional formulation techniques and to work with emerging formulation approaches."

ISP Pharmaceuticals: Addressing Drug Solubility Challenges & Energizing the Drug Commercialization Process

At CPhI 2009 in Madrid, Spain, ISP Pharmaceuticals announced it had embarked upon a Drug Solubility Initiative in support of pharmaceutical companies working with drug actives that exhibit poor solubility. The company indicated the Initiative would be a multi-faceted approach that would include R&D, the development and application of a broad portfolio of ingredients for use in solubilization, as well as formulation services designed to enhance solubility. Drug Delivery Technology recently interviewed Philip Strenger, Senior Vice President - Global Pharmaceuticals for ISP, to discuss the new Drug Solubility Initiative and his business' approach to helping the pharmaceutical industry rapidly and economically commercialize drugs based on poorly soluble actives.

Q: You have been talking about the ISP Pharmaceutical business differently recently. Can we start with an overview of your offering to the pharmaceutical industry?

A: Today's ISP Pharmaceuticals is a global business providing technology, products, and services in three major areas: excipients and coatings, drug synthesis, and drug solubilization. We are committed to helping advance the commercialization goals of the world's producers of pharmaceuticals and dietary supplements. In the area of excipients, ISP offers a range of products, including Polyplasdone® crospovidone for rapid disintegration and enhanced drug dissolution, and Plasdone® povidone for high-performance tablet binding. Our Advantia® Coatings Systems are used to enhance quality and performance via film coating of pharmaceutical and dietary supplement oral solid dosage forms. In the area of drug synthesis, the ISP Fine Chemicals business is a contract manufacturer of key starting materials, regulated intermediates, and active pharmaceutical ingredients. We also supply high-purity Tetrahyrdofuran as a solvent for drug synthesis. In the area of drug solubility, ISP has one of the most comprehensive offerings to the pharmaceutical industry. This offering features a range of ingredients that include Polyplasdone® disintegrants, Plasdone® polymers for solid dispersions, and cyclodextrins. The business also offers development services for spray-dried solid dispersions, and support for melt-extrusion technology.

Q: What are the issues affecting the pharmaceutical industry stemming from poorly soluble active ingredients?

A: Currently, the industry estimates that more than 60% of drugs in the pharmaceutical developmental pipeline present solubility issues. That is a significant number and affects literally billions of dollars of investment in drug development. Today's solubility dilemma exists, in part, because of the use of high throughput screening that focuses on compounds with high receptor affinity and selectivity at the expense of biopharmaceutical properties for formulation or delivery. We're working with these poorly soluble compounds because they are where the "action" is in new drug candidates. However, we are finding that the solubility of a compound is a critical determinant in its success or failure as a drug candidate.

Poor solubility has both economic and therapeutic issues throughout the commercialization process. In the development phase, poor solubility can lead to inadequate exposure in both efficacy and toxicity studies. It will result in a lower degree of absorption of a drug in the GI tract, meaning higher dosage level requirements and lower bioavailability. Higher dosages required to compensate for poor solubility can lead to side effects, food effects, and intersubject variability. It can drive up overall costs for drug development and production and can lead to poor compliance by patients because of the high doses required to achieve a therapeutic effect. So what may, on the surface, seem like a technical issue suddenly affects virtually every aspect of a drug in development and use in the marketplace.

Q: Tell us about ISP's Drug Solubility Initiative.

A: At ISP, we are addressing the solubility issue on a number of fronts. We are combining our expertise in material science and our broad portfolio of ingredients as a foundation to help pharmaceutical companies improve traditional formulation techniques and to work with emerging formulation approaches. Currently, ISP has one of the largest portfolios of ingredients in the industry for use in solving solubility issues. This is an active area for new technology development for us. We are conducting research on the issue of solubility and communicating the results of this research to our customers and the industry at large. One major component of the Initiative is working with emerging technologies, such as solid dispersions. Currently, we have a business unit within ISP Pharmaceuticals that provides R&D and manufacturing services for spray-dried dispersions of poorly soluble actives. The Initiative also includes the establishment of alliances with other companies involved in technologies for solubilization, such as the one we developed with hot-melt extrusion equipment company Coperion GmBH. It will also include education and outreach programs to the industry, such as our Solubility 2010 program we recently held in Europe. Beyond this, the Initiative will see us expanding our facilities and personnel dedicated to solubilization efforts.

Q: What ingredient technology are you working with in your Drug Solubility Initiative?

A: ISP's ingredient portfolio includes technology for improving the solubility in oral and injectable dosage forms. The choice of ingredients in a tablet formulation can have a significant effect on the rate and extent of drug dissolution. Our Polyplasdone XL-10

superdisintegrant enhances the rate and extent of drug dissolution. In a recent study, tablets with Polyplasdone XL-10 crospovidone had significantly faster drug release for 12 of 13 drugs in the recommended dissolution media compared to tablets with other superdisintegrants.

Our Plasdone K and S-630 polymers are used in the manufacture of solid dispersions. Solid dispersions can be prepared via spray-drying or melt-extrusion. Pharmaceutically acceptable polymers are ideal to create this matrix. Proper polymer selection is critical to impede diffusion and inhibit any tendency for nucleation and crystal growth that limits solubility.

Plasdone K polymers are also used for preparation of liquid softgel fill formulations with high-use levels of drug actives. In formulation of softgels, it is often challenging to prepare a homogeneous suspensions and solutions with high levels of actives and minimize capsule size. Plasdone K polymers have been shown to enhance the solubility of actives and provide for highly concentrated solutions.

Our ingredients also include CAVAMAX®, CAVASOL®, and CAVITRON® cyclodextrins that are used to form inclusion complexes with poorly soluble actives to improve bioavailability. Drugs with poor bioavailability typically have low water solubility or tend to be highly crystalline. Cyclodextrins are water soluble and form complexes that hide most of the hydrophobic functionality of the drug actives, and they prevent crystallization of active ingredients by complexing individual molecules so that they can no longer assemble into a crystal lattice.

Our line of solubilizing ingredients also includes products that are designed for injectables. Plasdone C povidone provides crystal inhibition, while Pharmasolve® and 2-Pyrol® solvents are very strong solubilizers.

Q: What expertise does ISP bring to the table in developing technology and solutions for drug solubility issues?

A: ISP's many years of work with excipient technology has helped us acquire significant expertise in several different approaches to enhancing solubility for drug actives. Throughout the past 5 years, we have worked with more than 100 drug actives, examining the potential for solid dispersions to improve solubility, and as a result, bioavailability. Every drug active will have its own range of requirements, and each project will have physical and cost parameters within which we must work. We believe that by developing a database of solutions, we can help pharmaceutical companies develop workable commercial solutions, rapidly.

With pharmaceutical scientists in nine pharmaceutical laboratories dedicated to research and technical service support, we routinely assist customers with excipient selection and formulation development. We have developed expertise in the formulation of oral solid dosage forms and have core capabilities in tablet formulation and tablet process technologies.

Q: Can you tell us more about ISP's capabilities for solvent spray-drying?

A: ISP offers technology development and contract manufacturing services to enhance the bioavailability of drugs via solid dispersion technology at our Columbia, Maryland, facility. The benefits of

spray-drying include control of particle size and bulk density of a drug formulation, elimination of crystalinity, and enhanced bioavailability and product stability.

From this site, ISP offers a number of R&D services starting with feasibility studies from proof-of-concept to full-scale design of experiments to select the optimum delivery system for a drug active. Once we've ascertained that spray-dry technology is optimal for a drug active, we can provide scale-up and clinical trial manufacturing under cGMP conditions. We do pilot-scale to mid-size spray-drying in a facility that also includes secondary drying, tabletting, capsule filling, and film coating. This business unit is also capable of full-scale commercial production on selected projects.

Q: Why did you decide to develop an alliance with Coperion GmbH in the area of hot-melt extrusion technology?

A: Coperion has more than 2 decades of expertise in implementing twin screw extrusion systems for the pharmaceutical industry. The hot-melt extrusion (HME) process is just now becoming accepted in the pharmaceutical industry as a viable method of producing a range of solid dispersion form drugs. And while many pharmaceutical laboratories have hot-melt extrusion facilities, these are typically primary at the lab scale. However, one of the major issues in developing this technology is scalability beyond the lab stage.

In our alliance with Coperion, we are focusing our efforts on polymer performance requirements needed for optimal performance. Hot-melt extrusion features combinations of drugs, polymers, and plasticizers into various final forms to achieve designated drug-release profiles. Individual components are mixed and then processed in a controlled environment of temperature and shear within the extruder, to create the final material. HME is a viable method to prepare granules, solid dispersions, sustained-release tablets, and transdermal and transmucosal drug delivery systems. Benefits from the HME approach include fewer processing steps, no requirements on the compressibility of the drug actives, more uniform dispersion of the drug particles, and improved bioavailability of poorly soluble drug actives.

Q: What do pharmaceutical formulators stand to gain from ISP's Solubility Initiative?

A: By providing solutions, we can assist in reducing development timelines and the costs required to introduce new drugs while helping bring products to market more rapidly. We can help reduce dosage costs. We can improve efficacy of the drugs and enhance convenience and compliance at the patient level. From a business standpoint, we can imagine creating new methods to reformulate failed or discontinued drugs, and we can help develop new delivery technologies that can extend the patent protection of existing drugs. By solving the solubility dilemma, pharmaceutical companies will be able to offer better healthcare to the people of the world. And in so doing, will open up new opportunities for better business and improved profitability of the pharmaceutical industry. ◆

Technology Showcase

Excipients & Surfactants

ABITEC is a world leader in the development and cGMP production of high purity lipid-based excipients (that function as solubilizers and bioavailability enhancers) and surfactants for the pharmaceutical industry. ABITEC's products can be incorporated into a broad range of drug formulations and dosage forms, including soft-gelatin capsules, tablets, solid microemulsions, and self-microemulsifying drug delivery systems (SMEDDS). The company offers technical and custom formulation development support with ISO production capabilities to meet bench, pilot, and commercial-scale requirements. For more information, contact ABITEC at (800) 555-1255 or visit **www.abiteccorp.com.**

Licensing Opportunities

Aveva has numerous products for license from its development pipeline along with a full compliment of R&D capabilities to produce transdermal drug delivery systems that fortify R&D 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 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.**

Gelatin-Based Drug Delivery

Banner Pharmacaps is a world leader in patented gelatin-based drug delivery. With global capabilities and continued investment in R&D, Banner is uniquely positioned to support your Rx and OTC pharmaceutical initiatives. Our softgel technologies include controlled-release, enteric, and chewables. Banner chewable softgels (pictured above) offer an excellent mouth-feel and chewing experience as compared to other chewable dosage forms. Chewels® and LiquiSoft™ chewable softgels are suitable for both adult and pediatric populations and offer a more palatable replacement for gritty, chalky chewable tablets or liquid doses. For more information, contact Banner Pharmacaps at (800) 447-1140 or visit **www.banpharm.com.**

Prefillable Delivery Systems

BD Medical - Pharmaceutical Systems is dedicated to developing prefillable drug delivery systems designed to fit the needs of the pharmaceutical industry. BD offers a range of products, including glass and plastic prefillable syringes, a nasal spray system, and a variety of self-injection systems. We deliver cost-effective alternatives to conventional drug delivery methods, which differentiate pharmaceutical products and contribute to the optimization of drug therapy. With a broad range of innovative systems and services, BD provides pharmaceutical companies with support and resources to help them achieve their goals. Our worldwide presence, market awareness, and pharmaceutical packaging know-how allow us to propose suitable solutions for all regional markets and parenteral drug delivery needs. Only BD offers the range and depth of expertise and packaging solutions to guide your drug from early phase development through product launch and beyond. For more information, contact BD at (201) 847-4017 or visit **www.bd.com/pharmaceuticals.**

Technology Showcase

Raman Chemical Imaging

ChemImage provides Raman Chemical Imaging contract services for drug formulation and development scientists needing ingredient-specific particle sizing, polymorph analysis, controlled-release analysis, content uniformity measurements, and more. ChemImage stands behind the pledge to provide our customers with the best quality information and fast sample turnaround time on every project. If you are working to develop nasal, inhalation, topical, transdermal, or controlled/sustained release systems, visit our website to learn how we can help you save time and money, raise your confidence, and lower your risk in moving forward through product development. For more information, contact ChemImage at (877) 241-3550 or visit **www.chemimage.com/branchout.**

Water-Soluble Polymers

POLYOX™ Water-Soluble Resins (NF grades) are nonionic poly (ethylene oxide) polymers. These hydrophilic polymers are available in a wide range of molecular weights that allow for formulation flexibility and are supplied as white, free flowing powders. POLYOX offers a history of successful use in extended-release applications for gastro-retentive dosage forms and other drug delivery systems, such as transdermal and mucoadhesive technologies. POLYOX resins provide a number of benefits, including versatile application in direct compression and granulation, rapid hydration, swelling, and gel formation for osmotic pump technologies as well as hydrophilic matrices. POLYOX meets requirements of the United States Pharmacopoeia (USP) and compliance with US Food Chemicals Codex. For more information on this Controlled Release Alliance product, visit **www.colorcon.com.**

Development & Manufacturing

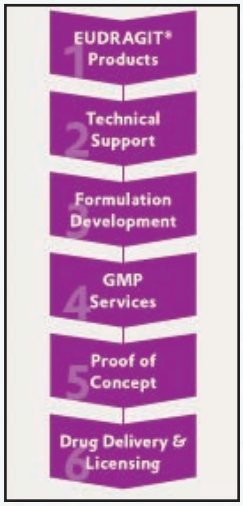
DPT is a contract development and manufacturing organization (CDMO) specializing in semi-solid and liquid dosage forms. DPT provides fully integrated development, manufacturing, and packaging solutions for biopharmaceutical and pharmaceutical products. DPT is the industry source for semi-solid and liquids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

New Auto-Injector Line

Elcam Medical recently launched its Flexi-Q line of auto-injectors for self-medication - the only fully disposable auto-injectors designed for life-cycle management. Flexi-Q DV is designed for drugs in vials in liquid or lyophilized form, and the Flexi-Q PFS is for drugs in prefilled syringes. Both incorporate our unique platform with flexibility in customization: dosage between 0.3-1.0 ml, needle length & gauge, viscosity, injection force, and injection time. Elcam Medical is a leading worldwide OEM supplier of Fluid Management, Drug Delivery, and Vital Signs Monitoring systems and devices. As an OEM partner, we have significant experience in partnering with pharmaceutical companies in many disease states and therapeutic classes. Our dedicated team of auto-injector engineers and technical staff has worked with many leading companies in the field. For more information, contact Elcam Medical at (201) 457-1120 or visit **www.elcam-medical.com.**

Technology Showcase

Pharma Polymers



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

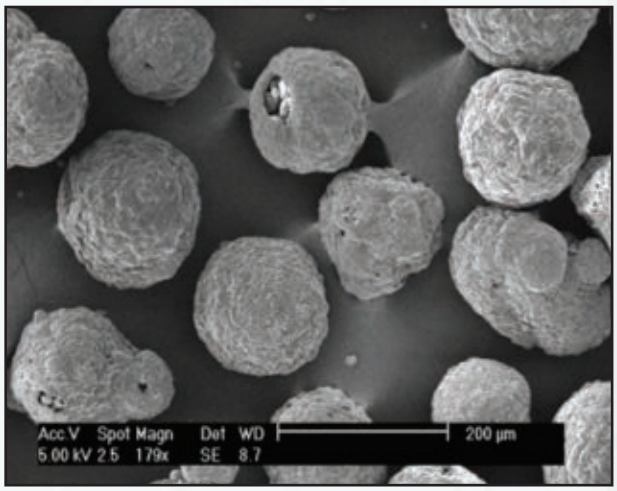
Injection Devices

Haselmeier is a leading designer and manufacturer of pens and autoinjectors for injectable pharmaceuticals with more than four decades of experience. Combining technology, function, and design, Haselmeier offers innovative and flexible platform technologies of disposable and re-usable self-injection delivery systems with many featuring a unique hidden needle design. Working with pharmaceutical companies worldwide Haselmeier develops injection devices of outstanding quality and performance to ensure comfortable and safe injections and meet the requirements of the product and patient. For more information, contact Haselmeier at info@haselmeier.com or visit **www.haselmeier.com.**

Combination Capsule Technology

InnerCap offers an advanced patent-pending 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.**

Performance Excipient



Mallinckrodt Baker's PanExcea™ MC200G performance excipient for Oral Disintegrating Tablet (ODT) applications combines two ingredients for rapid tablet disintegration and dispersion with good taste and texture. Designed for more flexibility at a lower cost, PanExcea MC200G performance excipients enable more API loading capacity while reducing tableting, licensing, and equipment expenses. For more information, contact Mallinckrodt Baker at (800) 943-4747 or visit **www.mallbaker.com/panexcea** to request a free sample.

Technology Showcase

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.**

Development & Delivery

Penwest

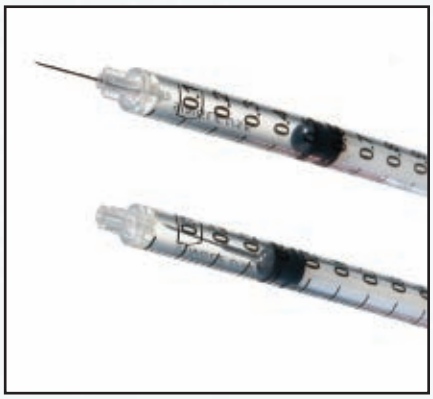
Penwest is a drug development company focused on identifying and developing products addressing unmet medical needs, primarily for rare disorders of the nervous system. The company is currently developing A0001 (alpha tocopherol quinine), a coenzyme Q10 analog demonstrated in vitro to improve mitochondrial respiratory chain diseases. Penwest is also applying its drug delivery technologies and drug formulation expertise to its collaborators' product candidates under licensing collaborations. Penwest's most recent success is Opana ER, an important therapeutic option for the treatment of pain. Its drug delivery technologies include TIMERX, a flexible, approved technology for the development of patented, oral controlled-release products. Penwest's technologies can also be used for delayed release, site-specific delivery, and chronotherapeutics. For more information, contact Penwest at (845) 878-8400 or **bizdev@penwest.com.**

Knowledge Management

PHARMACIRCLE™

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

Prefilled/Clinical Safety Syringes



Unilife Medical Solutions has a range of prefilled and clinical safety syringes suitable for pharmaceutical companies, healthcare facilities, and patients who self-administer prescription medication. Our products incorporate passive and fully integrated safety features that can help customers comply with needlestick prevention laws and encourage single-use and safe disposal practices outside of healthcare settings. The products feature a passive (automated) needle retraction mechanism allowing operators to control the speed of needle retraction directly from the body into the barrel of the syringe. The Unilife Ready-to-Fill Syringe features a glass barrel and is compatible with the manufacturing procedures used to fill standard prefilled syringes. The Unitract 1-mL Insulin Syringe is FDA certified and now being manufactured in the PA facility. For more information, contact Unilife at (717) 938-9323 or visit **www.unilife.com.**

DRUG DELIVERY MWV Executive

PACKAGING'S ROLE IN THE PHARMA SPACE: MEETING THE NEEDS OF GLOBAL CONSUMERS

Dr. Ted Lithgow
President
MWV Healthcare

MeadWestvaco (MWV) provides packaging solutions to many of the world's most admired brands in the healthcare, beauty and personal care, food, beverage, media and entertainment, home and garden, tobacco, and commercial print industries. Specifically in the healthcare space, MWV is a global leader in primary dispensing systems for the consumer and specialty pharmaceutical market. MWV has a strong history of developing innovative technology solutions based on the unmet medical needs of healthcare consumers. The company's solutions come from a deep understanding of the healthcare industry, continual development of consumer research and insights, and ongoing innovation to find the best delivery systems and materials for specific treatments and the individualized needs of patients. Drug Delivery Technology recently interviewed Dr. Ted Lithgow, President of MWV Healthcare, to discuss how healthcare packaging is becoming increasingly sophisticated and innovative. Dr. Lithgow also shares insights on packaging as a critical tool to address poor medication adherence - not following medication regimens as directed - which is a pervasive problem that is increasingly recognized as a considerable source of inefficiency and waste in healthcare systems.

"The pharmaceutical industry remains one of the most profitable and stable industries. In fact, the global market for pharmaceuticals is expected to surpass $1 trillion by 2013. In order for the pharmaceutical industry to continue to grow and innovate, healthcare packaging for the industry must also evolve. That's where MWV comes in."

Q: Can you provide use with a brief overview on MWV's work in the healthcare industry?

A: The pharmaceutical industry remains one of the most profitable and stable industries. In fact, the global market for pharmaceuticals is expected to surpass $1 trillion by 2013. In order for the pharmaceutical industry to continue to grow and innovate, healthcare packaging for the industry must also evolve. That's where MWV comes in. We are privileged to work with a range of small pharma to leading global pharmaceutical companies, creating patient solutions rooted in well-researched technology solutions for patients all over the globe. We place a particular focus on creating unique packaging options that not only promote adherence to medication regimens, but are child resistant and safe, as well as senior-friendly for convenience and ease of use. In the primary space, we are at the forefront of enabling preservative-free solutions and maintaining solution sterility with the latest technology.

Q: How pervasive of a problem is poor medication adherence?

A: It's actually quite a significant problem on a global scale. Data from a recent survey

commissioned by the National Community Pharmacists Association (NCPA) found the following:

- Half of those polled (49%) had forgotten to take a prescribed medicine.
- Nearly one-third (31%) had not filled a prescription they were given.
- Nearly 3 out of 10 (29%) had stopped taking a medicine before the supply ran out.
- One-quarter (24%) took less than the recommended dosage.

This has significant and well-documented consequences. According to the National Council on Patient Information and Education, "patients commonly fail to take their medications as directed, leading to unnecessary hospital admissions and even death, costing the healthcare system as much as $177 billion a year."

Q: How does packaging help address the growing problem of poor medication adherence?

A: Adherence-enhancing packaging is a simple, proven way to realize cost savings, create efficiencies for doctors and pharmacists, and provide tangible health benefits to patients. For instance, let's take a look at adherence packaging's role for intranasal spray products. Studies have shown that intranasal sprays are most effective when used consistently. And, we know patients use the sprays more often when they require fewer daily doses and a convenient dosing schedule. Adherence packaging can help patients better follow their regimens by clearly noting the dosing schedule, which is a further complement with verbal instruction from the doctor and pharmacist.

Q: What does MWV do to ensure that its packaging options are truly adherence-enhancing?

A: Before we even bring a product to the marketplace, we do quite a bit of market research into the use of products. For instance, we typically execute consumer focus groups, conduct in-depth interviews, and foster panel discussions. We always approach our packaging from a consumer insights perspective into what else is needed and how we design it so that it is easy, usable, and helps them in their daily lives.

Q: Outside of adherence packaging, what other products are rising in significance on a global scale?

A: Preservative-free formulations represent a growing trend in prescription and over-the-counter (OTC) nasal spray medications, that's why we've developed PFP N, a preservative-free nasal pump. PFP nasal pumps provide protection to allow removal of preservatives that may cause sensitization. PFP N also protects the integrity and purity of the solution, preventing contamination with use. PFP N is a state-of-the-art preservative-free metered nasal spray pump, designed to keep the medication germ free while allowing patients to achieve the maximum therapeutic effect.
In fact, last year, MWV surveyed 100 pharmacists in the UK regarding their preference for dispensing preservative-free nasal medications. The survey showed that 67% of UK pharmacists have a preference for dispensing a preservative-free drug. This percentage increased significantly to 84% after the benefits of preservative-free drugs were reviewed with these pharmacists. The UK survey results were consistent with US responses surveyed in a September 2009 study by MWV.

Q: When did MWV acquire Calmar? How has Calmar's product line enhanced MWV's Healthcare business?

A: MWV completed its acquisition of Calmar in July 2006; we acquired Calmar Compagnie de Saint-Gobain. The integration of Calmar into MWV ensured we are able to offer pharmaceutical customers around the world market-leading pumps and dispensers. Additionally, MWV now had primary and secondary packaging capabilities that allow us to

provide the complete packaging solution. Through the acquisition, MWV gained the Calmar Center for Excellence for the Pharmaceutical Business Unit in Hemer, Germany. Research and development from the Center for Excellence is continuing to drive innovation of nasal, oral, topical, and otic drug delivery systems for the entire pharmaceutical industry through R&D project management, design optimization, and high-speed component assembly.

Q: MWV is a global company. Can you talk a bit about your work in the healthcare space outside of the US?

A: Sure. We serve customers in more than 100 nations, and we and our customers are significantly increasing our presence in emerging markets. As such, we have grown with our customers, building our capabilities so we can partner with them everywhere they do, or want to do, business. We build our global expertise by transferring knowledge and leveraging best practices to meet local needs or leverage local capabilities.

For example, in 2008 we partnered with Indian pharmaceutical packaging company Bilcare in a joint acquisition of Florida's International Labs. The partnership combines MWV's design and innovation in packaging formats; Bilcare's research and expertise in materials, products, processes, and services; and International Labs' contract packaging services for retail pharmacies and large pharmaceutical manufacturers. We have also formed global partnerships with companies for microbiological testing, sterilization, aseptic filling, and bottles to provide our pump and sprayer customers end-to-end service.

Q: What countries provide the most opportunities for MWV Healthcare?

A: While there is still a lot of growth opportunity in the US, enabling better adherence and life cycle protection, there are nearly twenty times more people in developing areas than in the US and other developed nations. In fact, 70% of the world's economic growth is expected to come from emerging markets. The trend is similar with healthcare. With growing incomes and expanded availability of generic pharmaceuticals, more people in emerging countries have improved access to medication. India is on its way to becoming the world's largest source of generic pharmaceuticals, which is a fast growing category worldwide. We are capturing the opportunity to serve India's consumers, as well as working to leverage its rapidly growing position as a key supplier to the global marketplace.

Q: What are you able to tell us about MWV's future plans for growth in the healthcare industry?

A: I believe companies now understand how packaging can play a significant role in educating patients on their medications while also helping them adhere to their prescription regimens. Growing Packaging's role in the future healthcare space will become even more relevant because MWV has an opportunity to help manufacturers really incorporate packaging into their marketing mix. Five to 7 years ago, pharma simply borrowed a lot of ideas from consumer packaged goods (CPG) companies, particularly around OTC products. If you think about packaging for a CPG brand, it's become a key element of their overall marketing mix. That's not necessarily the case for a lot of pharmaceutical products. Going forward, MWV will place a significant emphasis on helping pharmaceutical manufacturers consider the opportunity it has to leverage packaging to help build brand equity, and ultimately serve as a gateway to customer relationship management.◆

www.frost.com

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

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For more information on growth opportunities in the Drug Delivery market, please contact Johanna Haynes at johanna.haynes@frost.com.

FROST & SULLIVAN

Therapeutic Focus

ANTISENILIN® Monoclonal Antibody Platform to Prevent Accumulation & Neurotoxicity of Aβ in Alzheimer's Brain

By: Daniel G. Chain, PhD, Chairman & CEO, Intellect Neurosciences, Inc.

Introduction

Intellect Neurosciences, Inc. is a Manhattan-based development-stage biopharmaceutical company pioneering the discovery and development of innovative approaches to address the large and unmet clinical need for drugs that can slow down, arrest, and ultimately prevent Alzheimer's disease (AD). With symptoms ranging from forgetfulness to language difficulties, from changes in mood and personality to loss of insight culminating in the destruction of brain cells causing memory loss, AD is a devastating fatal condition afflicting 30 million people worldwide for which there are currently no efficacious disease-modifying treatments.

As a result of Intellect Neurosciences' ability to leverage its robust patent estate with major pharmaceutical companies while simultaneously developing its own internal portfolio of disease-modifying drugs, the company is on track to become a major player in the discovery and development of drugs to treat AD.

Founded in 2005 Intellect's business is based in part on the ANTISENILIN platform that uses highly-specific therapeutic monoclonal antibodies to prevent the accumulation of soluble amyloid-beta (Aβ) protein, the main source of toxicity in the brains of Alzheimer's patients, without impacting normal activities. The accumulation of Aβ clumps (oligomers) in the cerebral spinal fluid (CSF) surrounding the brain is thought to be the starting point in a multi-step neurodegenerative process in which nerve cells die and critical structures of the brain shrink, ultimately resulting in memory loss and learning impairment. By specifically targeting soluble amyloid-beta, to prevent its accumulation and subsequent formation of insoluble plaques, Intellect's ANTISENILIN technology aims to stop the disease in its earliest stages. This pioneering approach has

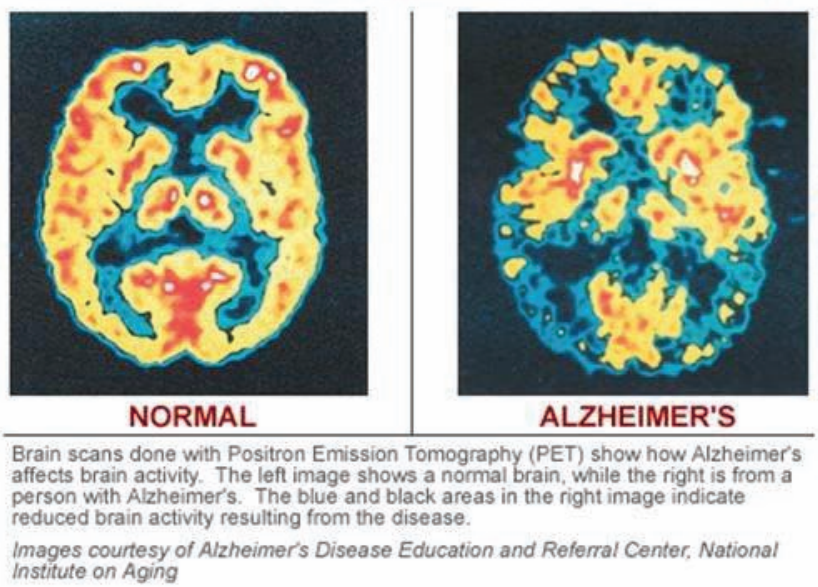

Figure 1. Scan showing amyloid deposits & brain shrinkage of an individual with AD.

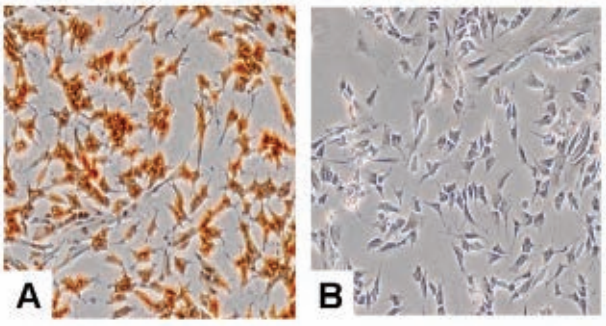

Figure 2. **Binding of antibodies to human nerve cells in culture**
A) Aβ antibodies that are not free-end specific also bind APP on surface of nerve cells.
B) Aβ antibodies that are free-end specific do not bind APP on surface of nerve cells.

gained considerable momentum throughout the past few years, and leading experts in the field have expressed optimism that drugs being developed using the company's proprietary patented technology herald an exciting new era of drug development for safe and effective disease-modifying treatments for AD.

Major global pharmaceutical companies have drug products in Phase I, Phase II, and Phase III clinical trial stages based on the ANTISENILIN technology, which is being licensed from Intellect under worldwide licensing agreements.

Scientific Background

Amyloid-beta is generated from a much larger protein known as the Amyloid Precursor Protein (APP), which is ubiquitously present in tissues throughout the body and especially concentrated in the synapses of neurons in the brain and on the surface of blood platelets. Various important physiological functions are attributed to APP, including the growth and protection of neurons, and activation of blood platelets to cause clotting. APP is embedded at the cell surface with most of the protein facing the outside. It is metabolized by protein splitting enzymes known as secretases. The Amyloidogenic Pathway results from the action of beta secretase (also known as BASE1) that splits APP at one position and gamma secretase that splits it at another, to generate Aβ fragments. Whereas beta secretase always splits at the same position, gamma secretase splits at one of two different positions that are close together so that Aβ fragments exist as two main isoforms that are 40 or 42 amino acids in length. The ratio is influenced by a number of factors, including certain gene mutations that cause an increase in the amount of Aβ42. Over time, accelerated under certain conditions, the fragments tend to change shape from completely soluble alpha helical structures to sticky beta sheets forming clumps of various sizes that are extremely toxic, especially to nerve cells.

We realized the only safe way to remove Aβ protein is to make sure that APP function is not affected. Given almost any substance, it is possible to create monoclonal antibodies that specifically bind to that substance. However, Aβ is almost identical to APP, making it difficult to achieve the required specificity. We overcame this problem by pinpointing the unique molecular signatures at either end of Aβ that are not present in APP - the presence of a free amino (NH2) and carboxyl (CO2) group that result from the splitting of a peptide bond in APP by beta or gamma secretases, respectively.

Addresses Key Safety Concerns

ANTISENILIN antibodies are selected on the basis they only bind to epitopes that contain either one of these molecular signatures, thus safely helping to shuttle Aβ away from sites of damage in the brain without the possibility of interfering with the functions of APP on the surface of nerve cells. Moreover, when these drugs are administered via the bloodstream, they do not run the risk of binding APP on the surface of blood platelets, which could potentially cause clotting.

The concern is that developing antibodies with poor specificity poses unnecessary risk to AD patients, particularly antibodies that bind the mid-domain of Aβ and therefore also bind the APP, an important protein implicated in regulating numerous physiological functions in the brain and other tissues. Examples of antibodies that bind the mid-domain of Aβ are gantenerumab, a fully human antibody (Hoffman La Roche) and solanezumab, an IgG humanized antibody (Eli Lilly). Although we are not yet aware of side effects from these drugs, which are in Phase II and Phase III clinical trials, 4G8, a mouse monoclonal antibody that similarly binds APP and Aβ was shown in vitro to interfere

Figure 3. ANTISENILIN antibodies recognize a unique molecular signature at either end of Aβ.

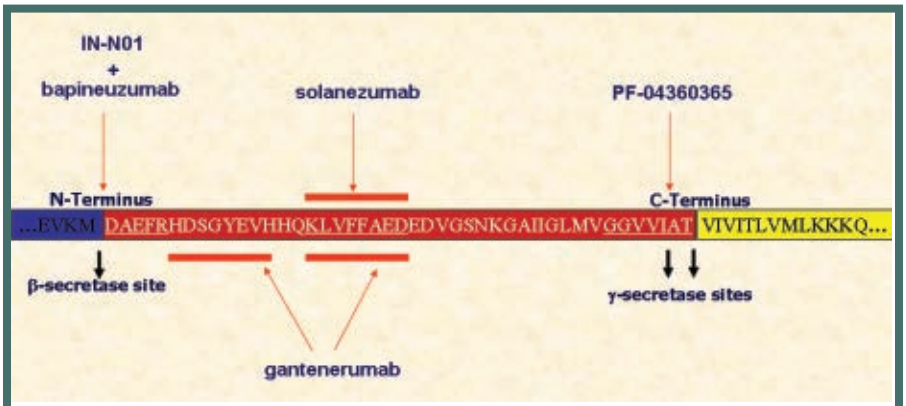

Figure 4. Sequence of amino acids in Aβ and binding regions of various antibodies.

with APP processing, suggesting that non-specific antibodies could yield unexpected results in patients.[1]

Conversely, antibodies uniquely directed to the free-ends of Aβ have the advantage of avoiding this type of risk. Examples are PF-04360365, an IgG2 antibody specifically targeting the C-terminus at position 40, and bapineuzumab, an IgG1 antibody specifically targeting the amino terminus as shown in Figure 3. To date, the ANTISENILIN platform remains the only therapeutic approach that uniquely targets soluble Aβ without binding to APP, thereby promoting the clearance of Aβ away from its sites of damage in the brain while avoiding the possibility to interfere with the functions of APP. These free-end specific antibodies can also be made to bind aggregated forms of Aβ, including oligomers, protofibrils, and Amyloid Plaques.

Bapineuzumab, a prototype for the ANTISENILIN class is being co-developed by Johnson & Johnson and Wyeth/Pfizer (ClinicalTrials.Gov), is currently listing eight open Phase III and one open Phase II clinical trials to test Bapineuzumab administered intravenously or subcutaneously, respectively, in patients with mild-tomoderate AD. According to the website, at least 4,500 patients are expected to be enrolled amongst the different Phase III trials at hundreds of sites in the US and internationally. The first Phase III trials for Bapineuzumab started in December 2007 with additional Phase III trials started in May 2008 and June 2009. The earliest of these trials is expected to be completed in February 2012 based on the most up-to-date public information.

Future Directions

The company is developing IN-N01 as a follow-on generation ANTISENILIN antibody product, which it believes will have better safety and efficacy in a broader population than other products in development. This is being achieved through optimization to reduce effector functions compared to IgG1 and Ig2 molecules. In addition, IN-N01 has an inherent high affinity for soluble Aβ and therefore less likely to cause disaggregation of existing plaque to release toxic fragments back into the circulation.◆

Reference

1. Nikolaev A, McLaughlin T, O'Leary D, Tessier-Lavigne M. APP binds DR6 to trigger axon pruning and neuron death via distinct caspases Nature. 2009;457:981-989.

Dr. Daniel G. Chain

Chairman & CEO, Intellect Neurosciences, Inc.

Dr. Daniel G. Chain serves as Chairman and CEO of the Manhattan-based development-stage biopharmaceutical company, Intellect Neurosciences, Inc., a company he founded in 2005. Fueled by Dr. Chain's interest in the biology of the human brain and his distinguished career in biotechnology, Intellect Neurosciences is pioneering the discovery and development of innovative curative approaches to address the large and unmet clinical need for drugs that can slow down, arrest, and ultimately prevent Alzheimer's disease. Contrary to drugs currently on the market, which only treat symptoms, Dr. Chain aims to create a new class of disease-modifying Alzheimer's drugs that attack the underlying pathologies. In addition to pioneering an antibody-based approach utilized by several major pharmaceutical companies that have products in Phase II and Phase III, he has invested more than a decade to building a diverse drug portfolio based on various technologies that target the first steps leading to the treatment of Alzheimer's disease with the hope that one or more of these drugs will help slow down, stop, or even prevent the disease. Dr. Chain earned his BSc in Biochemistry with honors from the Institute of Biology in London, his PhD in Biochemistry from the Weizmann Institute of Science in Israel, and trained as a post-doctoral research fellow at the Center for Neurobiology and Behavior at Columbia University's College of Physicians and Surgeons in New York. Dr. Chain founded and served as President and CEO of Mindset Biopharmaceuticals, (USA) Inc., in which MPM Capital was the principle investor.

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Executive Summary

Peppi Prasit, PhD
CSO, Co-Founder,
Amira Pharmaceuticals

Amira Pharmaceuticals: Creating High-Value Compounds

Founded in 2005 and headquartered in San Diego, Amira Pharmaceuticals is a small molecule pharmaceutical company focused on the discovery and early development of new drugs to treat inflammatory disease. Its discovery team brings unparalleled insights into bioactive lipid pathways and complex signaling processes controlling many conditions, including asthma, chronic obstructive pulmonary disease (COPD), cardiovascular, and fibrotic diseases. The company has a partnership with GlaxoSmithKline (GSK) for the development of FLAP (5-lipoxygenase activating protein) inhibitors in mid-stage clinical studies for treatment of respiratory and cardiovascular disease. In addition, the company is currently in partnership discussions for its second lead asset, an antagonist of the DP2 (also known as CRTH2) receptor. The drug hunters at Amira are now actively leveraging their history of success to create high-value compounds for the future in the fibrotic disease area. Its lead program in this area is an antagonist of LPA1 (lysophosphatidic acid) receptor that is associated with idiopathic pulmonary fibrosis, scleroderma, and other fibrotic diseases. The company has recently demonstrated that it can develop small molecules with comparable efficacy to a study published in Nature Medicine with LPA1 knock-out mice. This program is expected to enter clinical studies in 2010. Specialty Pharma recently caught up with CSO and Co-Founder Peppi Prasit, PhD, to discuss how Amira combines the rigor of a big pharmaceutical company with the ingenuity and energy of a small company, creating an environment for efficient and effective preclinical and clinical program decisions.

Q: ***Can you provide our readers a little more background on the history of the company?***

A: Most of the scientists who were here in the beginning originally came from Merck. In early 2005, Merck decided to move its research facility from San Diego back to the East Coast. It offered the scientists (both chemists and biologists) new positions, but many of us who had been in San Diego for a while did not want to move. Those of us remaining knew we had to do something, but we did not want to go to any of the existing companies. We were excited by the possibility of starting our own company. I often saw compounds that small, resource-restricted biotech companies were offering up for licensing. There were usually a lot of warts with these molecules and incomplete characterization. We figured that as a group, we probably could do a bit better than most small companies. We should be able to remove some of the obvious warts and probably could also make them into a prized once a day drug.

With the idea of forming a company, we knocked on the doors of VCs and were able to get money together to start the company within 6 weeks. Although the scientists from the Merck San Diego site had been focused on neuroscience, specifically stroke, some of the senior scientists had experience in the inflammation and respiratory area. Our past experience involved working on programs such as Singulair®, so it was natural for us to gravitate toward that therapeutic area.

Q: ***How did you select your first targets?***

A: We knew in the initial stages of the company we wanted to go with a validated target and develop a best-in-class compound. We also asked ourselves which programs our potential partners would be interested in when we had such a compound a year or two later. The first target we agreed on was 5-Lipoxygenase-Activating Protein, better known as FLAP. We believed FLAP was at the cusp of being the next big thing in respiratory disease. There was also data published by Merck many years ago on the human proof-of-concept, which mitigated our risk. Merck did not move forward with its program at the time because Singulair was very safe and effective at 10 mg once a day. Merck's old FLAP program had a couple of warts. The development compound showed a rash side effect and had to be dosed at 125 mg twice a day. We gave ourselves a bar of bringing the dose down to a lower level, making it a once a day compound and improving the safety profile. We cleared that bar in our lead program. We ended up licensing this program to a major respiratory company, GSK.

Once we were in the area, we looked at other respiratory targets that were making people excited and decided on a DP2 antagonist for asthma and COPD. This mechanism also seemed likely to have the ability to raise the interest of potential partners when we had a lead candidate. We heard through the grapevine that there was already human proof-of-concept data. A considerable amount of patent literature had been published. In fact there were 85 patents and patent applications on DP2 antagonists which we had to navigate through to create our own IP space. Our compound would have to be very safe and differentiated from the then leaders in the field. Fortunately, from the inspection of the structures of the leading clinical candidates at the time, they had structural alerts that we think will allow our compounds to sneak through and be best-in-class. Recently, with our Phase1 clinical data as well as the number of interested potential licensing partners, I believe we have achieved our objective.

Q: ***What is unique about these targets?***

A: These two programs are in the bioactive lipid space; leukotrienes and prostaglandins. A FLAP inhibitor will block the synthesis of the leukotrienes, while a DP2 antagonist will block the ability of PGD2 to activate its receptor. These targets have the potential to offer novel oral treatments for asthma and COPD patients. In asthma, this is particularly important because there are a lot of people who still have a phobia of steroids, especially parents of small children. When this fear is combined with a dislike for aerosol, the result is low compliance. In addition, there is the potential that the two mechanisms are additive. In COPD, there is a significant unmet medical need. There are currently no effective treatments available for COPD, so we believe these programs have great potential.

Q: ***In what area does Amira have the greatest potential?***

A: With our two lead programs in the clinic, we were able to change our focus from building the foundation to how we can take the company to the next level. We knew we didn't want to partner every program, so we asked ourselves in which types of disease a small company like Amira can take a drug all the way from concept to the market. While considering new options, I attended a presentation at a scientific conference by a scientist from Massachusetts General Hospital on the role of the LPA1 receptor in idiopathic pulmonary fibrosis, or IPF. Not many people are familiar with the disease, but it impacts approximately 60,000 patients per year in the US. The diagnosis is essentially a death sentence as patients only survive up to 5 years, and most die within the first 2. The only treatment option for patients today is a lung transplantation, and none of the programs in development seem to offer much hope to patients. The data presented included human biopsy and knock-out data in mice, which showed the target, the LPA1 receptor, had a significant role in IPF. The receptor is in the bioactive lipid space, similar to the leukotrienes and DP2 we worked on for our first two programs. We quickly saw we could potentially have a big

impact in this area. Not just being the first-in-class with a novel mechanism, but also something we can fully develop ourselves, and there is nothing like it out there.

Q: ***Why does this target have the potential for a big impact in IPF?***

A: Basically, fibrosis is wound-healing gone wrong. Wound-healing is part of the normal repair process. However, too much of it is not a good thing, and one result is a condition called fibrosis. LPA, and its receptor LPA1, appear to be upregulated in the lung of IPF patients. Additional data using LPA1 knock-out mice also supported the idea that an LPA1 antagonist may be protective. Toward the end of last year, we showed we can obtain similar results with a small molecule in a preclinical setting. The only way to prove it from here is in the clinic, and we expect to enter clinical studies in late 2010. We are very encouraged by the preclinical data as well as the early safety data and look forward to moving the program ahead.

Q: ***How is the team able to move the compounds forward so quickly?***

A: This comes down to creating a working environment where people can be truly creative yet cohesive by sharing a common goal. We live and die by the success of each of the program we embarked upon. Productivity is not measured by the number of compounds made that goes nowhere. Research is definitely not a process-driven thing; it is more of a knowledge-driven opportunism, in my opinion. We choose to work on "tractable" programs. We are very aggressive at killing compounds and not allowing suboptimal leads to linger. We have open, transparent (and sometimes heated) discussion amongst scientists. And of course we have a lot of luck.

Q: ***What is the strategy for developing and commercializing the programs?***

A: As I already mentioned, Amira has already licensed our first program, the FLAP inhibitors, to GSK. Today, we are looking to partner our second program, the DP2 antagonist. With the revenue stream from milestones and other payments around these two programs, we plan to take LPA1 and other programs forward independently. We couldn't pursue any indications that would require a 20,000-patient Phase III trial, but we can look into areas that require a 500-patient Phase III trial. We plan to commercialize these smaller programs on our own or perhaps with a geographical partner.

Q: ***What are the next steps for the company?***

A: The next step for the company is to establish itself as the LPA company. We started our LPA1 program in April 2008 and nominated a candidate and back-up in mid-2009. This is approximately 12 months from the start of the program to candidate nomination, which is in line with the timeline we established with our other programs. This timing is also much faster than industry standards. We expect that by the end of the year, we will be able to begin human trials. We are very proud of this because it is a very novel target, and by definition we at the leading edge. In addition to moving our LPA1 program forward, we are looking to validate additional mechanisms and continue to grow our emphasis on fibrotic disease. We will stick to the same conservative model of focusing on one or two targets at a time. Our track-record has been to discover a safety assessment candidate in approximately 12 months, then take another 12 months to move it into humans. Hopefully, we will continue to keep this pace based on our team's strong experience and, of course, a lot of luck. ◆

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The Mystery of Private Equity Firms

By: John A. Bermingham

Some day, you may have the opportunity to work with or for a Private Equity (PE) firm. What I mean by that is your company may be acquired by a PE firm with you remaining as the CEO, you may be asked by a PE firm to join the management team of one of their portfolio companies, or you may be offered a position as an Operating Partner with the PE firm.

The people who execute the deals are people who generally join a PE firm right out of business school as associates and work their way up to Vice Presidents, Partners, and then Managing Partners. Sometimes a senior executive will go directly from corporate life to a Managing Partner position, but more often becomes an Operating Partner.

An Operating Partner is a person who is an employee of the PE firm and applies his or her past business experience working directly with the troubled portfolio company owned by the PE firm. They are the "fix it" people…..sometimes.

I have been the CEO of five PE-owned portfolio companies, which before I arrived, had a full-time CEO in place overshadowed full time by the PE firm's Operating Partner. In every case, these two people had been in place together for at least one year in the portfolio company, riding the performance of the portfolio company straight down. Here is where the mystery comes to play.

In all five portfolio companies I entered as the turnaround CEO, the previous CEO (handpicked and brought in from the outside by the PE firm's management following the acquisition) had no idea what he was doing, and the Operating Partner was completely ineffective. In four portfolio companies, this had gone on for two to three years. Only one PE firm made the change in the CEO after fourteen months, but the Operating Partner remained for only a few months working with me. Then he left.

I have asked the question many times of PE firms as to why they waited so long to make an obviously necessary CEO change, particularly when they have invested millions (sometimes billions) of dollars into their portfolio companies. It seems to be a situation in which they do not want to admit a mistake in front of their investors, can't admit to a mistake, can't admit that they don't know how to fix the problem, don't know they have a management problem, or all of the aforementioned.

PE firms for the most part have well-educated intelligent people, so why the problem?

My belief is they are all bankers and have no business operations experience. Even the Operating Partners are reporting to the firm's bankers (management), so there is a natural conflict and problem. Bankers win because they own the PE firm.

So if you are offered a company buy-out by a PE firm with you staying on as CEO, make certain you understand who you are selling to and expect to be told how to run your company after the close of the sale! You may also inherit an Operating Partner and eventually be asked to leave so the PE firm can bring in their own person. This could be the Operating Partner. But then again, you will be so rich following the acquisition, who cares? ◆

BIOGRAPHY

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

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