Drug Delivery Technology®

October 2010 Vol 10 No 8

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Nuchal Apo Therapy for Parkinson's

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

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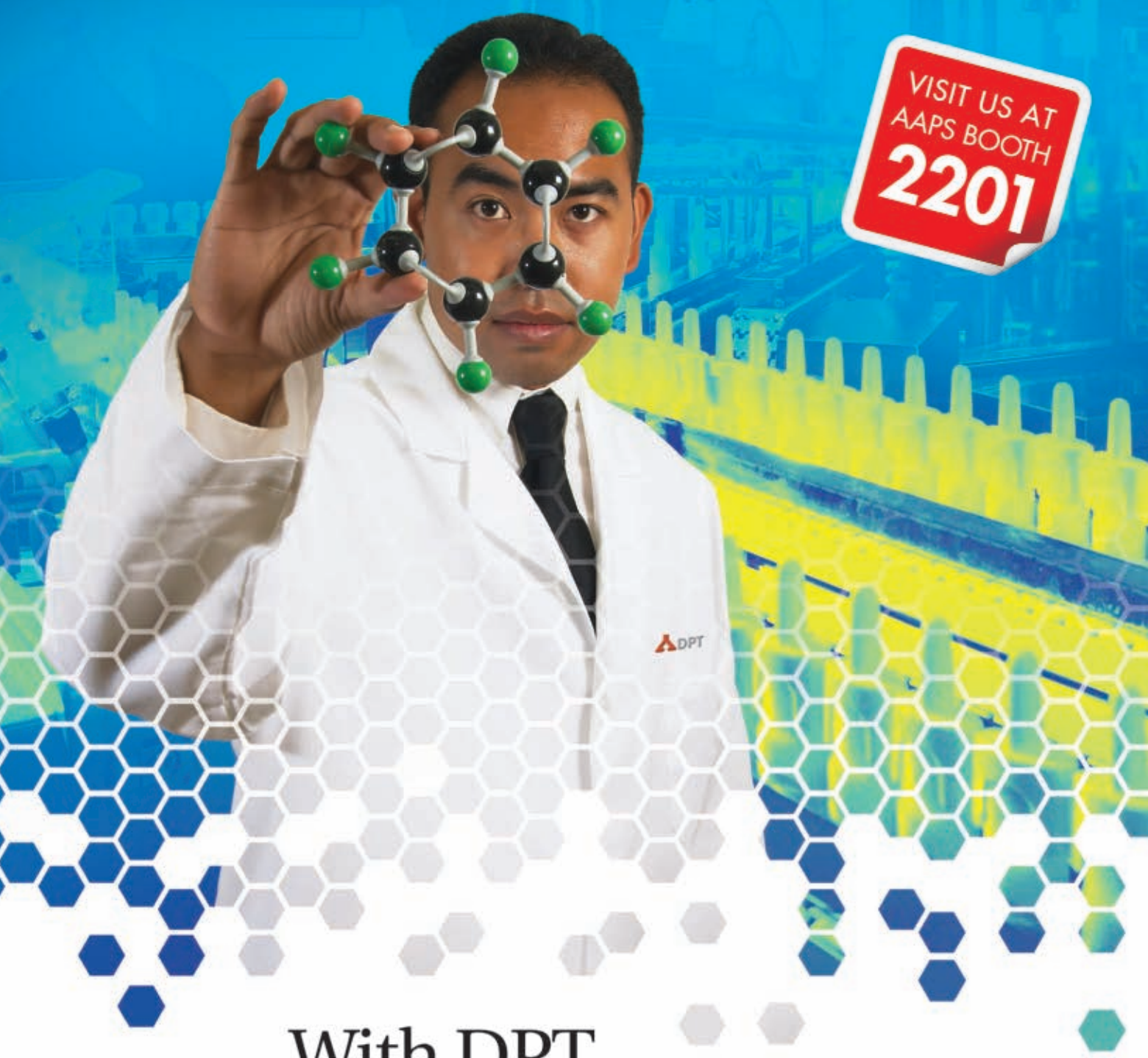

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Game-Changer for Parkinson's?

"As discussed, therapeutic drug effect with nuchal Apo therapy follows physiologic lines as it begins at the cutaneous free nerve endings; continues by peripheral nerves to cervical nerve roots and spinal cord; then, from brainstem structures (substantia nigra) via ascending nigra-striatal pathways, to striatum and other downstream structures."

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Market News and Trends

Genzyme & Isis Pharmaceuticals Announce Positive Phase III Data

Genzyme Corp and Isis Pharmaceuticals Inc. recently announced the Phase III study of mipomersen in patients with heterozygous familial hypercholesterolemia (heFH) met its primary endpoint with a 28% reduction in LDL-cholesterol, compared with an increase of 5% for placebo ($p < 0.001$). The trial also met all of its secondary and tertiary endpoints. Frequently observed adverse events were injection site reactions, flu-like symptoms, and elevations in liver transaminases, as seen in other mipomersen studies.

This double-blind, placebo-controlled Phase III study was designed to test the efficacy and safety of adding mipomersen to stable lipid-lowering therapy. Patients were randomized 2:1 to receive a 200-mg dose of mipomersen or placebo weekly for 26 weeks. The trial included 124 adult heFH patients at 26 sites in the US and Canada. All of the patients had pre-existing coronary artery disease and LDL-C levels greater than 100 mg/dL, and were taking a maximally tolerated dose of a statin, as well as additional lipid-lowering drugs in most cases. Prior to study enrollment, 78% of patients had previously experienced at least one cardiovascular event, and 49% had more than one previous cardiovascular event.

Patients treated with mipomersen had an average LDL-C at baseline of 150 mg/dL. These patients had an average LDL-C level of 104 mg/dL at the end of the study. 45% of the mipomersen-treated patients achieved LDL-C levels of less than 100 mg/dL, a recognized treatment goal for high-risk patients. The reductions observed in the study were in addition to those achieved with the patients' existing therapeutic regimens.

The trial met all of its secondary and tertiary endpoints. Patients treated with mipomersen experienced a 26% reduction in apolipoprotein B compared with a 7% increase for placebo; a 19% reduction in total cholesterol compared with a 4% increase for placebo; and a 25% reduction in non-HDL cholesterol compared with a 4% increase for placebo (all $p < 0.001$).Reductions were observed in other atherogenic lipids, including Lp(a) by 21% compared with no change for placebo ($p < 0.001$). Apo B and Lp(a) are both generally accepted risk factors for cardiovascular disease. Study results are based on an intent-to-treat analysis (full analysis set). As seen in other mipomersen studies, the most commonly observed adverse events were injection site reactions (93% for mipomersen compared with 42% for placebo) and flu-like symptoms (49% for mipomersen compared with 32% for placebo).

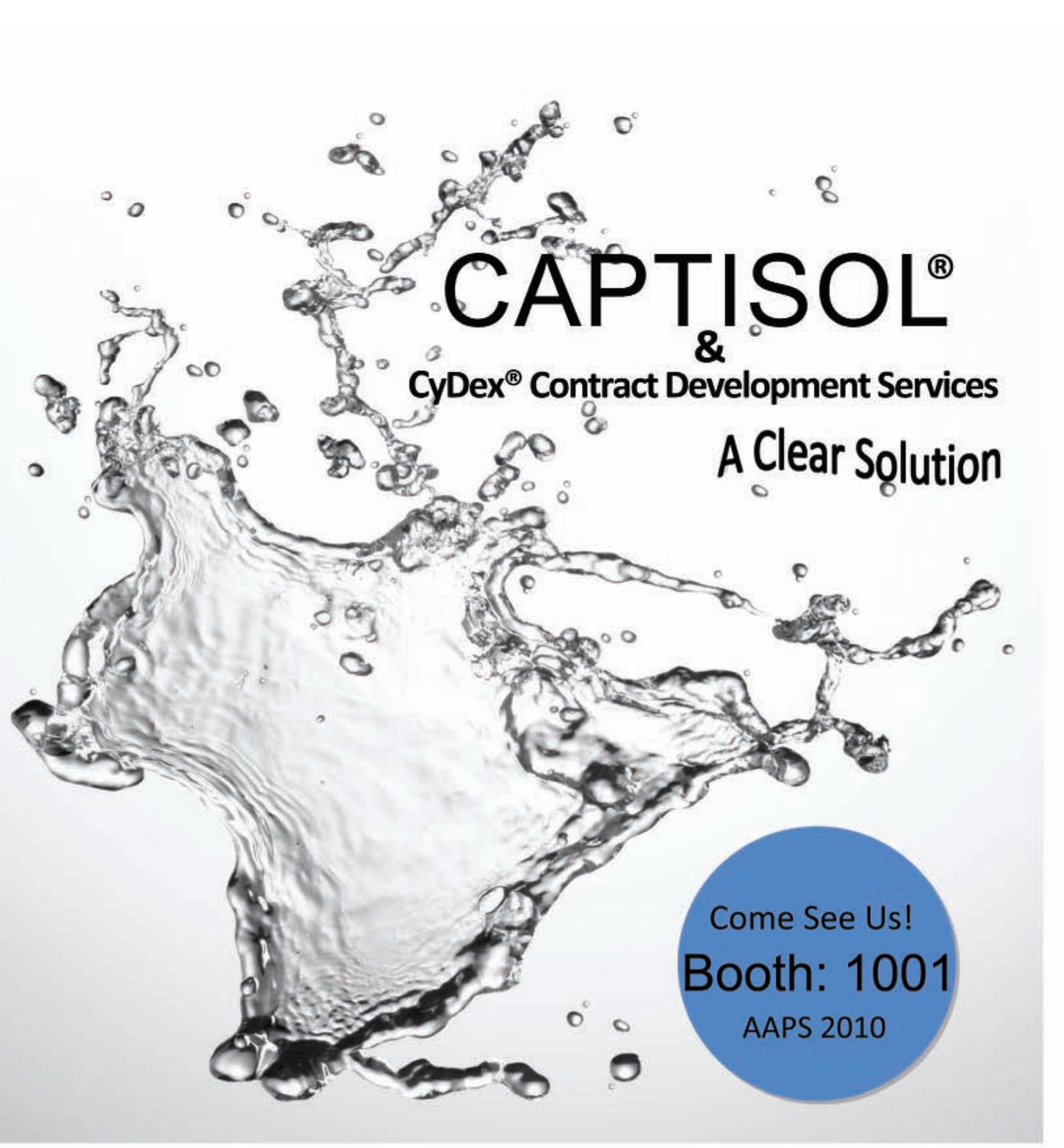
All 41 patients treated with placebo completed treatment. Of the 83 patients treated with mipomersen, 73 completed treatment; nine of the discontinuations were related to adverse events, the nature of which was generally similar to previous studies. Reasons for withdrawal from the mipomersen group were: elevations in liver transaminases (3), injection site reactions (2), non-cardiac chest pain (2), injection site reactions and flu-like symptoms (1), and constipation (1).

In this study, elevations in liver transaminases (ALTs) in patients treated with mipomersen were observed that were generally similar in character with those seen in other studies. Six mipomersen-treated patients (7%) had persistent ALT elevations above 3X ULN during the treatment period. Persistent is defined as consecutive elevations at least 1 week apart. As measured by MRI, mipomersen-treated patients had a modest change in liver fat from baseline (median increase of 4.9%), compared with the placebo-treated patients (median increase of 0.4%). In general, increases in liver transaminases and liver fat appeared to be associated with the greatest reductions of LDL cholesterol. No patients, including those who discontinued the study, had changes in other laboratory tests to indicate hepatic dysfunction, and there were no Hy's Law cases.

Mipomersen is a first-in-class apo-B synthesis inhibitor currently in late-stage development. It is intended to reduce LDL-C by preventing the formation of atherogenic lipids. It acts by decreasing the production of apo-B, which provides the structural core for all atherogenic lipids, including LDL-C, which carry cholesterol through the bloodstream.

Genzyme's initial US and EU regulatory filings for mipomersen will seek marketing approval for the treatment of patients with homozygous FH (hoFH). These initial filings may also include patients with severe heFH. In the first half of 2011, Genzyme expects to submit the initial US and EU filings, and to have made progress toward filing in other major international markets.

Genzyme and Isis have completed all four Phase III studies planned to support the initial filings. As previously reported, the Phase III study of mipomersen in hoFH patients met its primary endpoint with 25% LDL-C reduction, and results were presented at last year's American Heart Association meeting. Genzyme and Isis announced top-line results of the Phase III study in heFH patients in February. The companies last month reported that the Phase III studies of mipomersen in severe hypercholesterolemia and high-risk patients met their primary endpoints with 36% and 37% LDL-C reductions. These four studies will be included in the initial filings. In addition, studies are ongoing and planned to evaluate alternative dosing regimens.



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Kamada & Baxter International Enter Strategic Agreement for the Distribution & Manufacture of Intravenous Liquid AAT to Treat Alpha-1 Antitrypsin Deficiency

Kamada, Ltd., a biopharmaceutical company engaged in development, production, and marketing of specialty life-saving therapeutics, and Baxter International Inc., a global, diversified healthcare company, recently announced they have entered into an exclusive distribution and manufacturing agreement for Kamada's liquid, ready-to-use, intravenous Alpha-1 Antitrypsin Product for the treatment of hereditary Alpha-1 Antitrypsin Deficiency approved by the USFDA on July 1, 2010, for marketing under the trade name Glassia. The companies have also entered into a Technology Sharing agreement for the manufacturing of liquid AAT at a Baxter facility using Kamada's proprietary and patented technology.

Under the terms of the agreements, Baxter will be responsible for marketing and distribution of Glassia in the US, Canada, Australia, and New Zealand. Within the scope of the agreements, Kamada will receive milestone payments of $45 million, including an up-front payment of $20 million. Furthermore, Kamada will also be eligible to receive up to $25 million in aggregate payments upon the achievement of certain milestones. Baxter has a commitment to purchase minimum quantities of Glassia in the range of $60 million that could reach $110 million during the first 5 years of the agreements. Kamada will also be eligible to receive significant royalty payments on net sales of the product produced by Baxter.

The distribution rights and the licensing agreement do not include the inhaled version of Kamada's AAT product, currently in Phase II/III clinical trial in Europe. Nevertheless, under the terms of the agreements, both sides will examine additional cooperation opportunities for the inhaled product. Under this engagement, Baxter will serve as Kamada's exclusive distributor for Glassia in the US.

"This is a great achievement for Kamada," said David Tsur, Chief Executive Officer of Kamada. "Baxter is one of the world's largest biopharmaceuticals companies and has a strong history of creating and establishing market-leading brands, a track-record that makes Baxter our ideal commercial partner for Glassia. The strategic cooperation with Baxter is expected to enable Kamada to reach significantly larger sales volume in the US market with greater profitability margins. The cooperation with Baxter will enable Kamada financial independence and firmness needed for facilitating the development of the next-generation product, the Inhaled AAT."

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Market News and Trends

Particle Sciences & Children's Hospital Boston Cooperate on Translational Medicine Efforts

Particle Sciences Inc. (PSI), a leading pharmaceutical Contract Research Organization (CRO), has been engaged by Children's Hospital Boston to help advance early stage molecules and drug innovations into new therapeutic products for patient care. Under the established framework between Children's and PSI, Particle Sciences provides drug product development services aimed at progressing the specific drug or drug product candidate to the point where it becomes attractive to potential licensees. Under the non-exclusive agreement, Children's retains all rights to the drug product, as well as the data and intellectual property created under this arrangement.

"Particle Sciences is one of several CROs we have chosen to work with," said Erik Halvorsen, PhD, Director of the Technology and Innovation Development Office (TIDO) at Children's. "They bring a great deal of experience to the effort in both drug delivery and analytic method development. Importantly, in an early stage exercise such as this we need our partners to remain flexible and to participate as more than simply fee-for-service providers. Particle Sciences has demonstrated this, and we are happy to be working with them."

The Children's Technology Development Program selects early stage technologies from the world-class staff at Children's and provides enough funding to progress them to meaningful inflection points. This could include activities ranging from establishing preclinical data for an IND submission or a solid preformulation package leading to process scale-up that would enable clinical studies. Along with funding, the program provides expert advisors with appropriate industrial experience.

"We couldn't be more pleased to be involved with this effort," said Dr. Mark Mitchnick, CEO at Particle Sciences. "Children's Hospital Boston is one of the world's great institutions. The technologies we have seen so far reflect the depth one would expect from such a group, and we are thrilled to be able to help commercialize them."

TransPharma Announces Successful Completion of Phase Ia Clinical Trial of ViaDerm-GLP1 Agonist Indicated for Type II Diabetes

TransPharma Medical Ltd., a specialty pharmaceutical company focused on the development and commercialization of drug products utilizing a proprietary active transdermal drug delivery technology, recently announced the successful completion of a Phase Ia trial of ViaDerm-GLP1 agonist that is being developed for the treatment of diabetes mellitus type II. The Phase I study was a three-way cross over study designed to evaluate the pharmacokinetic (PK) profile and assess safety and tolerability of two doses of ViaDerm-GLP1 agonist in healthy volunteers, as compared to a subcutaneous injection of Exenatide (Byetta). Each volunteer received all three treatments with a washout period of 1 week between treatments.

The results of the study demonstrate ViaDerm-GLP1 agonist to be safe and well-tolerated with a preferable extended PK profile compared to an injection of Exenatide (Byetta). Transdermal application of ViaDerm-GLP1 agonist resulted in therapeutic GLP1 blood levels for approximately 13 hours compared to 6 hours of the injected form. In addition, ViaDerm-GLP1 agonist was demonstrated to be biologically active based on changes in glucose levels during the treatment. TransPharma has initiated enrollment of type II diabetic patients to a Phase Ib clinical trial using its dry form, extended-release state-of-the-art patch formulation of GLP1 agonist.

GLP1 agonists/analogues are a new class of medications for the treatment of type II diabetes that offer improved glycemic control with no risk of hypoglycemia. The first GLP1 agonist drug, Exenatide (Byetta), was approved in 2005 and has already reached sales of over $670 million. The drug displays biological properties similar to human glucagon like peptide 1 (GLP1), a regulator of glucose metabolism and insulin secretion. Currently, the drug is administered twice daily to type II diabetes patients via injections.

"We are very pleased with the results of this study, which demonstrate significant advantages of our ViaDerm-GLP1 agonist over the injectable marketed product," said Dr. Daphna Heffetz, CEO of TransPharma Medical. "We have clearly demonstrated a preferable extended drug PK profile when the molecule is administered utilizing our ViaDerm system. The extended profile may allow for once-daily painless transdermal administration in comparison to the current two daily injections treatment. We are looking forward to the results of the Phase Ib testing."

MonoSol Rx Announces Reckitt Benckiser FDA Approval of Sublingual Film for Opioid Dependence

MonoSol Rx, the developers of PharmFilm technology and a drug delivery company specializing in film pharmaceutical products, recently announced that its partner, Reckitt Benckiser Pharmaceuticals Inc., a wholly owned subsidiary of Reckitt Benckiser Group plc, has received approval from the US FDA to market Suboxone (buprenorphine HCl/naloxone HCl dihydrate) sublingual film for the treatment of opioid dependence.

This is the second US marketing authorization for a prescription product based on MonoSol Rx's PharmFilm technology, closely following the July 2010 FDA approval of the anti-emetic Zuplenz (ondansetron) oral soluble film.

Suboxone sublingual film delivers a convenient, quick-dissolving therapeutic dose of buprenorphine, a partial opioid agonist, and naloxone, an opioid antagonist. The drugs rapidly absorb under the tongue to ensure compliance.

"We are very pleased to announce the approval of Suboxone sublingual film and disclose our important relationship with Reckitt Benckiser," said A. Mark Schobel, President and CEO of MonoSol Rx. "Following the FDA approvals of Suboxone sublingual film and Zuplenz oral soluble film, both within the past 2 months, the agency has clearly accepted our proprietary PharmFilm technology as a viable prescription drug dosage form. The success of Suboxone sublingual film through our collaboration with Reckitt Benckiser is another example of the significant value our PharmFilm technology delivers to leading pharmaceutical companies, and further validates the commercial potential of film drug delivery for this industry. We look forward to working closely with Reckitt Benckiser to prepare for the launch. Upcoming royalty and supply revenues under this agreement are expected to support our pipeline and provide further confirmation of the acceptability of PharmFilm® for future partners."

Suboxone sublingual film was developed under a previously undisclosed collaboration between MonoSol Rx and Reckitt Benckiser Pharmaceuticals Inc., in which Reckitt Benckiser's Suboxone products were formulated utilizing MonoSol Rx's PharmFilm technology. Under the world-wide agreement, MonoSol Rx will manufacture Suboxone sublingual films and Reckitt Benckiser will leverage its existing Suboxone sales force to market the product. MonoSol Rx is eligible to receive pre-launch milestone payments, development fees, supply payments, and royalties on net sales.

IntelGenx Achieves Positive Bioequivalence Results for ED Film Product

IntelGenx Corp. recently announced the completion of a pilot study indicating the successful development of a novel oral film, INT007, that is bioequivalent to a leading branded tablet containing a phosphodiesterase type 5 (PDE-5) inhibitor for the treatment of erectile dysfunction (ED). INT007 has been developed using IntelGenx' proprietary immediate-release VersaFilm drug delivery technology.

This was a randomized, two-period, two-way crossover study in healthy male subjects. The study was designed to determine whether INT007 was bioequivalent to a leading branded PDE-5 inhibitor tablet as measured by industry standard pharmacokinetic measures, peak plasma concentration (Cmax), and area under the curve (AUC). The study results demonstrated that INT007 was within the range of bioequivalency on both of these measures. The study also measured time to peak concentration (Tmax), a common determinant of rate of absorption. IntelGenx' INT007 film achieved Tmax 27% quicker than the oral tablet formulation, indicating a potentially faster onset of action.

"The achievement of bioequivalence in this pilot study solidifies IntelGenx' position at the forefront of immediate-release film development," said Dr. Horst G. Zerbe, President and Chief Executive Officer of IntelGenx. "This is the second VersaFilm project we progressed into the clinic, and the second VersaFilm project that has yielded positive bioequivalence results. Furthermore, this study has demonstrated not only bioequivalence but also a faster onset of action, which could be another advantage versus the current tablet formulation."

Following the successful completion of the pilot study, the company plans to commence scale-up and manufacturing of the pivotal batches required to support a pivotal clinical study and future regulatory 505(b)(2) filing.

Purac to Build New Plant for Biomedical Resorbable Polymers in the US

Purac recently announced the investment in a new manufacturing facility for its biomedical polymers. The plant is intended to support the growing resorbable polymers business of Purac Biomaterials. Purac currently operates a plant for biomedical polymers in The Netherlands. This second facility will be built in the US. The investment for this new plant will be EUR 15 million. The construction of the facility will start in 2011 and is expected to be completed before the end of the year.

"This represents an important step in the biomedical polymer business and shows Purac's continued commitment to this market," said Arno van de Ven, Purac Vice President Chemicals & Pharma. "It provides us with the capability to support the growth of our existing and new business partners."

In addition to an increase in the production capacity, the new facility will bring Purac Biomaterials more flexibility and a more balanced presence in its global markets.

"As an experienced supplier to pharmaceutical and medical device companies, we understand the importance of guaranteed supply continuity," added Menno Lammers, Director of Purac Biomaterials. "Throughout the past several years, the importance of risk management has increased and with this facility we will be in the unique position to provide our customers with dual sourcing."

The Purac Biomaterials business comprises Lactide-based polymers, such as Poly Lactic Acid (PLA) and Lactide/Glycolide Copolymers (PGLA). The technology as developed for Purac's biomedical polymers also formed the basis for Purac's activities in L- and D-Lactides for bioplastics, such as Poly Lactic Acid (PLA).

Trade Shows: Why We Love (Hate) Them

Part 5 of a 6-part series on business models & best practices for navigating the new normal.

By: Derek Hennecke, President & CEO Xcelience LLC

I love trade shows. It's an unfashionable thing to say, but truth be told, I've never been much of a fashionable guy. My wardrobe probably reflects that. Nearly half of my casual wardrobe consists of giveaway pharma T-shirts I got at trade shows.

I know all the negatives about trade shows. I know them down to the well-worn soles of my black leather trade show shoes. They're exhausting, expensive, and disrupt the regular flow of business. They're loud, long, and bad for my diet.

But you know what? At trade shows, I feel understood. You know how it is when at parties you have to explain what you do for a living? And try to make it sound worthwhile? You follow your listener's expression as it moves from puzzled to glazed. When you catch them glancing, hopefully at the exits, you relent and deftly switch gears to talk about the Buc's latest losing streak.

It's not like that at trade shows. At trade shows, everyone understands and appreciates what I do. They like to talk about it. They maybe even want to know more about it. Everyone else at our industry trade shows has an interesting job too. Not like that guy I met last weekend who extrudes metal at a steel factory. I mean what do you say to that?

I believe deep down we all enjoy this feeling of belonging. At trade shows, we are a community of like-minded people. We don't believe people in white elastic caps and protective goggles look funny, and we think grasping a new facet of microbial chemistry is incredibly neat. We are part of a great and powerful scientific community that is changing the way people live every day. People in the real world just don't understand.

But at trade shows, EVERYONE gets it. We don't have to explain why we do what we do. Everyone knows. I look forward to the AAPS Annual Meeting and Exposition and other trade shows every year. I love the opportunity to reconnect as a profession and as an industry. Okay, and I like the parties too.

So it comes as a great bonus that trade shows are really good for business too. In fact, every year, we generate many successful leads from trade shows. Why is that?

EXTOLLING THE VIRTUES OF FACE TIME

In a world filled with ever-increasing possibilities for communication, we just can't forget the importance of face-to-face business meetings for establishing trust. So many alternatives exist - think teleconferences, virtual meetings, webinars, podcasts, online forums, and blogs - but nothing builds trust and confidence like a personal connection and direct experience.

That might be true of any industry; it is doubly true of ours. In fact, I would argue that our industry is

marketed entirely on reliability. Time and time again, studies show that pharmaceutical companies rate quality and reliability twice as high against all other purchasing factors.

The services we provide may not be a huge cost in the overall scheme of drug development, but the consequences of us failing to carry the ball successfully through our small stage of the process are, quite simply, huge. Clients would be silly to trust us with any portion of their multi-million dollar projects if they didn't trust that we were completely and totally reliable.

You really can't fake reliability in our industry. Pharmaceutical manufacturing industries are completely transparent. Our customers are *inside* our factories. If there are any mistakes in production, client and provider are both immediately aware of them. We wear our quality on our sleeves, so to speak. Our process IS our product. It can't just appear reliable, it must be reliable. But it works the other way around too - it can't just be reliable, it must appear reliable too. If you can't show it, you can't sell it. You have to earn your client's trust.

There's really only one way to do that. You just can't expect anyone to put their trust in your company without looking your people in the eye first. You can't build any significant level of trust on a keyboard. It's not the way we human beings are wired. We need face time to build trust. Trade shows are all about face time.

TRADE SHOWS ADVANCE SCIENCE

The face time at trade shows helps us sell our product, but that's just the beginning. Programs, panels, and poster sessions provide rich opportunities for scientific exchange and continuing education. AAPS and Pittcon, for example, are important venues for our staff, and we try to send as many staffers as we can do without for a week.

Trade shows let us recognize our most talented scientists. In 2009, we were able to produce three posters for the annual AAPS meeting in Los Angeles. This year, we are a little busier with client projects (isn't everybody?), but we still managed to achieve two accepted posters that help highlight our formulation development and manufacturing expertise at AAPS in New Orleans. Look for: Development of an Enteric Coating Process and Stability Evaluation of PCcaps™ (B.V. Kadri, A.M. Johnson, D.M. Cartwright, M.A. Cappucci, P.F. Skultety), and Effect of Excipient and Binary Excipient Characteristics on Filling Using Capsugel's Xcelodose® 120 S Precision Powder Micro-dosing System (B.V. Kadri, B.F. Truitt, C. Hoffman, E. Robles, P. Barros, P. Skultety, D. Edwards).

TRADE SHOWS DEEPEN EXISTING RELATIONSHIPS, BUILD PARTNERSHIPS

Trade shows are about new relationships, but they're also about maintaining and nurturing older ones. We meet with as many suppliers and existing customers as we can. We have customers all around North America, in Europe, Japan, and Australia. Many of them come to these trade shows. Talk about effective use of time and money.

Just the mere fact of getting like minds together can lead to innovation. A few of us CEOs had been mulling over the idea that there were opportunities to improve efficiencies and increase project success by creating strategic alliances among a few of the highest-quality CMCs in the industry. But it wasn't until we rubbed shoulders at the InformEx in San Francisco in 2009 that Chemistry Playbook™ was born. Originally uniting are Cambridge Major, Beckloff Associates, and Xcelience, Chemistry Playbook has now been expanded to include MPI Research and Micron Technologies.

NO COUNTRY FOR OLD MARKETERS

Trade shows force us to refine our message. They make us sit down and think about what we want to say, and how we will say it.

I find the "how" part particularly challenging. After all, our industry trade shows are not like other industry trade shows. You can't kick the tires right then and there in the drug development business like you can at an auto trade show. What we are selling isn't tangible on an exhibition floor.

It seems ridiculous to think that someone might come to AAPS and choose a vendor based on the size of their booth, the charm of a particular employee, or the words on the graphic panels. Yet those details can draw a passing potential client in, or turn them away.

I can tell you that one significant lead came down to the choice of a single phrase on the panel of our trade show booth. We chose to place "API characterization" at the top of our graphics panel, which caused a decision-maker who didn't know us to stop, introduce himself, and ensure that Xcelience was part of his evaluation set. Had we chosen the word "Preformulation," he said he would have walked on by.

These details are all the more challenging in today's market. In the old days, marketing was a considerably more extravagant business. Let's face it - people threw money at the marketing division and hoped good things would happen. It's not just the Great Recession that reversed this trend. It began before the recession - but it has been intensified. Today's marketers are constantly assessing their cost/benefit ratios.

Trade shows are no exception. We want to grab people's attention with innovation and creativity, but not with lavish gifts. (T-shirts, in my book, do not count as lavish, fellow vendors). Our clients are more cost conscious too, and I know when I see a vendor giving away

extravagant gifts I have to wonder if I won't be overpaying for their services to facilitate their corporate lifestyle.

We are extremely excited about our booth at AAPS this year, and I give kudos to Marketing Director Kim Black-Washington for coming up with an innovative X Marks the Spot campaign for AAPS in New Orleans 2010. Stop by Booth 1937 and decide for yourself.

HOW TO MAKE THE MOST OF YOUR TRADE SHOW BUDGET

Yes, you can generate lots of great leads at a trade show, but you can also totally screw up a trade show. Just being there isn't enough. We've seen many a company trash their reputation by sending unqualified sales people, or marketing flash without substance. I won't waste your time giving you the obvious tips about trade shows, like "follow up on leads immediately," which is all over the internet. I'm assuming you're smart enough to have already figured that one out. These are some of the less obvious DOs I've learned from and with my seasoned Vice President, Randy Guthrie, who has more than 30 years of experience at trade shows.

DO HOLD YOUR MARKETING & SALES TEAMS ACCOUNTABLE

Trade show costs can get out of control fast, and they already represent a significant portion of your marketing mix. Define what an acceptable cost per badge swipe and cost per qualified lead are for your organization. (Heck, be clear on what a qualified lead is.) Be clear about return on investment targets and time horizons, and hold your team to it. This means paying as much attention to pre-show promotion and post-show follow-up activities, as it does securing face-to-face time during the trade show.

DO SET EVENT GOALS & OBJECTIVES

Everyone needs to be operating under the same game plan. Are you here to launch a new product, build awareness for a new program or partnership, hire talent, evaluate capital equipment, generate new business, or strengthen existing business relationships? Each year is an opportunity to put your best organizational foot forward. Make sure that your team arrives prepared, not tired or confused.

DO TRAIN YOUR STAFF

Do I really have to say this? We once visited a booth at a past AAPS and, confounded by the Business Development Director's lack of product knowledge, began politely inquiring about his personal background. Turns out he worked in shoe sales a month previously. About turn….

DO KEEP YOUR BOOTH SIZE IN PROPORTION TO YOUR BUSINESS

Put a professional foot forward, but don't overdo it. A classic mistake I've seen is for a new or small company to splurge on a huge booth. To me, any company that comes out of nowhere with a gigantic booth presence is a red flag - either they've grown too fast and are at risk for quality glitches, or they are plumping up the turkey for a near-term sale. Clients prefer to see solid, reliable growth and responsible margins. An over-blown booth is a sign of an out-of-whack marketing budget.

This year's AAPS in New Orleans is lining up to be a good reversal from the lower traffic that we saw in Los Angeles and Atlanta the past 2 years. Hiring is picking up, and more people are shopping for equipment. I'm expecting to see more new faces, and more old faces back. The convention hall in New Orleans is massive - aren't they all? - so hopefully our convention won't be placed at the end of the pier like Pittcon in New Orleans in 2008. But even if it is, hey, it's November in New Orleans, and it will be a nice walk. Best of all, once we clear the pier/convention halls, turn right and there is the French quarter. Not bad, and it sure beats trying to find a taxi at 5 PM when the convention ends.

At the time of writing, I'm also looking forward to the CPhI/ICSE, held in Paris in early October this year. Both promise to be very, very bad for my diet, but good for my wardrobe. My fall will be rich in trade shows. There will be many long hours on my feet, but you will see a bounce in my step. Hope to see you there.◆

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 Company Performance

By: Josef Bossart, PhD

In the previous issue's article, *Decade in Review - Drug Delivery Product Sales*, we examined sales of DDEPs (drug delivery enabled/enhanced products) throughout the past decade and observed there were quite a few "billion dollar babies." We noted many of these top DDEPs were developed by Big Pharma companies using internal or "public domain" drug delivery technologies. So how has this impacted the revenue and profits of drug delivery companies that provide partners with proprietary technology resources and drug delivery-enabled products?

First, let's review the limitations of this month's article. The period of coverage for this article is 2000 through the end of 2009. In some cases, the period is shorter because the companies were sold or acquired prior to 2010. The companies reviewed are limited to publicly traded drug delivery companies for which drug delivery was their sole or most significant business initiative. Public companies are the only ones for which there is consistent pipeline and financial information available. Private companies typically operate at a different scale, where public funding is not required, and they rarely publish their financial results.

Drug delivery companies for the purpose of this article are companies with proprietary drug delivery technology made available to other companies as technology or products. Excluded are companies that use drug delivery technology to solely develop products for their own commercialization efforts. Without this restriction, we would need to include Big Pharma companies, such as GlaxoSmithKline and AstraZeneca,

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given their significant portfolios of internally developed drug delivery products.

This article focuses on the past decade, not the 1990s. Drug delivery companies that largely defined the industry in the 1990s (eg, Alza, Elan, and Biovail) are not included. Alza really ceased to be a drug delivery company according to our definition by the late 90s, and Biovail did so early in the 00s. Elan is a special case; it certainly has a thriving drug delivery service business, but at this point, it is more than 40 years old and is really not representative of the current generation of drug delivery companies. Additionally, the financial results for the Elan drug delivery division are hard to fully grasp for the early part of the 00s given their corporate initiatives in the areas of biotechnology and financial engineering. A few other drug delivery companies, notably Eurand and Flamel, are not included because financial information for the full decade is unavailable even though they are currently listed on one of the US exchanges.

All of the figures used in this article were sourced from company filings with the US Securities and Exchange Commission (SEC). Pipeline information was sourced from SEC filings, company websites, and press releases, and then checked against the PharmaCircle database to ensure completeness and accuracy.

PERFORMANCE PARAMETERS

There are many ways to measure company performance. In this article, we'll look at parameters most obviously related to value creation: market capitalization and profitability. As we'll see, most drug delivery companies are "emerging" entities in that they do not regularly turn a profit and are still heavily invested in research and development.

There is one additional point worth clarifying: market capitalization. We'll be looking at market capitalization (share price multiplied by reported shares outstanding) rather than share price. While investors may focus on share price, market capitalization better captures enterprise value. Table 1 provides a summary of core financial and corporate parameters for 15 public drug delivery companies.

TABLE 1

Company	Founded/IPO	Market Cap Gain/Loss (000s)	Cumulative Net Income (000s)	FDA-Approved NDA Products Internal/Contract	Other Marketed Products	Years Since Founding	Commercial Operations
Acusphere	1993/2003	($139,218)	($306,085)	0/0	0	16	N
Antares[1]	1979/1996	$88,922	($121,599)	0/1	5	30	N
Alkermes	1987/1991	($291,881)	($103,499)	1/2	0	22	Y
Alexza	2000/2006	($79,379)	($348,860)	0/0	0	9	N
Aradigm	1991/1996	($390,241)	($273,554)	0/0	0	18	N
Atrix[2]	1986/2004	$630,902	($91,145)	2 (5)/0	5	18	N
CIMA[3]	1986/1994	$280,664	$23,314	0/7	3	18	N
DepoMed	1995/1997	$193,950	($150,710)	2/0	0	14	Y
Durect	1998/2000	($390,817)	($303,230)	0/0	0	11	N
Emisphere	1986/1991	($737,300)	($359,540)	0/0	1	23	N
Halozyme	1998/2004	$429,526	($58,361)	0/0	2	11	N
Middlebrook	2000/2003	($126,530)	($320,481)	1/0	0	9	Y
Nektar	1990/1994	($22,120)	($1,132,143)	1/7	2	19	N
NexMed	1994/2000	($231,020)	($156,395)	0/0	1	15	N
Noven[4]	1987/1988	($47,503)	$81,888	4/0	1	22	Y
Penwest	1991/1998	($123,844)	($198,495)	1/0	3	18	N

1) Earliest genesis, Medi-Ject Corporation, founded in February 1979. **2)** Incorporated as Vipont Research Labs, August 1986. Acquired 2004 by QLT. Five products in terms of approved NDAs, but only 2 brands (Atridox and Eligard - 4 strengths). **3)** Acquired 2004 by Cephalon. **4)** Acquired 2009 by Hisamitsu.

Founded/IPO presents the dates reported by the companies as their year of founding or incorporation, and the year they were first listed on a US stock exchange. The founding year can be deceptive as a few of the companies were not formed as drug delivery companies. The Initial Public Offering dates are misleading in a couple of cases in which a company went public via a reverse merger with a publicly traded shell company.

Market Cap Gain/Loss presents the difference in company market capitalization between the first quarter of 2000 or the first year a company became public, and the last quarter of 2009.

Cumulative Net Income Gain/Loss refers to the cumulative net income reported by each company throughout the period of 2000 through 2009. Net Income is the net gain or loss the company reported as applicable to the common shareholders. In some cases, this includes gains and losses related to corporate initiatives not necessarily focused on drug delivery activities, but surely intended to support the overall corporate objectives.

FDA Approved Internal/Contract NDA Products refers to the number of products approved between 2000 and 2009 for which the drug delivery company had a pivotal role in product conception and/or development. Beyond the obvious products developed entirely by a drug delivery company, Internal Products include products such as Nektar's Exubera, which was conceived internally by Nektar and then partnered with Pfizer (even though Pfizer carried the largest part of the development costs and responsibilities). Another Internal Product would be Penwest's Opana ER, which was developed in partnership with Endo. Contract Products refer to products for which the drug delivery company provided technology, know-how, and resources but were products commissioned by a partner. Examples include Alkermes' Nutropin Depot and Risperdal Consta, and Nektar's Pegasys and Somavert.

Other Marketed Products includes products approved outside the US, and non-NDA products [ANDA, 510(k)] approved in the US.

Commercial Operations makes note of whether the company had a sales and marketing operation targeted to physicians or other end user at some point in the decade.

It will be noted that not all company figures continue through the end of 2009. Atrix, CIMA, and Noven were all acquired in the past decade, and their figures are complete through to their date of acquisition. Their final market capitalization value is considered to be their acquisition price.

ANALYSIS

There are only a few companies included in Table 1 that were founded in the past

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TABLE 2

Company	Market Cap Gain/Loss (000s)	Cumulative Income (000s)
Acusphere	($139,218)	($196,478)
Antares	$45,764	($56,756)
Alkermes	($521,373)	$195,953
Alexza	($79,379)	($298,046)
Aradigm	($126,005)	($133,012)
DepoMed	($51)	($79,090)
Durect	$47,298	($117,608)
Emisphere	($96,614)	($159,898)
Middlebrook	($126,530)	($255,139)
Nektar	($225,363)	($611,374)
NexMed	($108,778)	($86,523)
Noven	($113,704)	$24,988
Penwest	($231,262)	($140,694)

decade. The youngest companies are Alexza and Middlebrook, which were both founded in 2000 and went public in 2006 and 2003, respectively. The markets have been largely unreceptive to IPOs throughout the past few years, with a particular disinterest in biopharma companies lacking a clear path to products or near-term profitability. For at least the past few years, the public markets have been beyond the reach of earlier stage drug delivery companies, a situation quite different from a decade earlier when companies like DepoMed, Durect, and Nektar went public only a few years after formation.

A quick glance at Table 1 shows too much red ink in the Market Cap and Net Income columns. It can be argued the Table 1 Market Cap figures are a little misleading in that the beginning of 2000 was right in the middle of the tech bubble, and markets have appropriately corrected themselves since then. A similar argument can be made concerning net income. As companies develop, they progressively move from losses to profits. To address this argument, Market Cap and Net Income figures for the 6-year period from 2004 through 2009 are presented in Table 2 to provide a base market capitalization when the markets were not as frothy.

What we see in Table 2 is more of the same. In terms of Market Cap, the overall net/net is the same even though a couple of companies have moved from negative to positive, while others have gone the other way. Durect is notable in that it has recorded a net increase in market capitalization throughout the past 6 years versus a large drop for the full decade. Halozyme is well ahead in terms of market capitalization throughout this period and may point to how a drug delivery company can be successful, at least in terms of market valuation.

Regardless of what period of time is examined, there is a consistent sea of red with respect to net income. The numbers don't seem to support the suggestion that drug delivery is a fast and low-risk path to market valuation and profit for a biopharma company. Many of the companies that have been in business for a dozen years or more not only have significant cumulative losses, but even now continue to post annual losses. Three companies (CIMA, Noven, and Alkermes) have posted annual net positive incomes for at least a few years. CIMA must be considered a model for any drug delivery company in the way they were able to parlay their ODT platform into numerous partnerships, products, and modest profits before their acquisition by Cephalon. While this is how the drug delivery business model is supposed to work, they are among the very few companies that were able to profitably execute it.

Noven posted a relatively small but consistent annual net income for almost the full decade; the only exception being 2007 when they made investments in developing a commercial infrastructure. Noven's profitability however was derived from their partnership interest in the Novogyne joint venture with Novartis that marketed hormone replacement therapy products based on Noven technology. On a stand-alone basis, the drug delivery service business did not provide a consistent annual profit.

Alkermes has posted a positive net income throughout the past 6 years, but is still in the hole for the decade. Prior to last year, Alkermes had put together 4 consecutive years of positive net income, largely on the basis of license fees related to its now terminated deal with Cephalon for Vivitrol. As Alkermes gears up to commercialize Vivitrol for a potential alcohol abuse indication, it will be interesting to see if they can get back to a positive net income. Alkermes' profitability will also depend on its ability to replace the Risperdal Consta partnering income stream with internal or contract drug delivery products.

How much do approved products contribute to market capitalization growth and positive net income? Each reader can come to his/her own conclusions, but it seems as though approved products are a necessary but not necessarily sufficient condition for value creation. A number of companies with approved products are still looking for a profitable year. And a number of companies that have been around for more than a decade are still waiting for their first FDA-approved NDA product. Apparently, developing DDEPs for one's own account or in collaboration with a partner isn't as quick or simple as is often suggested for Drug Delivery.

REFLECTIONS

Looking at the figures in Tables 1 and 2, one is reminded of the advice that when you find yourself in a hole: the first thing you should do is stop digging. But is it really as easy as that?

The drug delivery icons Alza and Elan had dug themselves rather deep holes and were in business for more than 20 years before they started reporting consistent profitability. Alza certainly didn't follow a straight line to success. Founded in 1968, Alza was at one point majority owned by Ciba-Geigy, at another perched on the edge of bankruptcy, and only in 1981 realized its first significant commercial success with the approval of Transderm Nitro. It was in their 32nd year of existence that Concerta, the catalyst for Alza's acquisition by J&J, was approved.

Similarly, Elan really only hit its stride 20 years after founding when in 1989, Cardizem SR, it's SR formulation of diltiazem, was approved by the FDA and became a major product for Marion Merrill Dow. After some success in the early 90s, Elan was almost done-in by financial maneuverings in the late 90s and a big corporate investment in biotechnology. For the past 7 years, Elan has managed to produce a positive net income for its drug delivery business. But this of course is

almost 4 decades after the company's founding.

Among the 12 remaining independent public drug delivery companies listed in Table 1, Alkermes seems to be the most likely to succeed, more as a specialty pharma than drug delivery company. Alkermes is increasingly targeting its resources to developing an internal pipeline, while forgoing in large part the partnering activities it depended on for most of its first 2 decades.

Nektar has managed to dig the deepest hole of any drug delivery company throughout the past decade. The company has certainly stopped digging, at least in terms of its contract drug delivery services. The corporate strategy of being the premiere drug delivery technology services company that was unveiled in early 2003 with the renaming of the company is no longer operative. Since early 2007, the company has increasingly focused itself on developing a portfolio of internal pipeline products rather than providing technology and know-how for client products. It's likely that Nektar will need to dig itself in deeper, to the tune of about another $500 million, before it can hope to think about working its way back up.

A few companies seem to have more limited options. With financing hard to find, and more red ink likely to show up on the bottom line, it's not clear what they will do. A couple of drug delivery companies not included in Table 1 seem to be in a death spiral, reduced to issuing more and more stock at lower and lower prices in hopes of reaching a validating milestone. Two of the companies listed in Table 1, Acusphere and Middlebrook, have recently gone through bankruptcy or are in the middle of major restructuring.

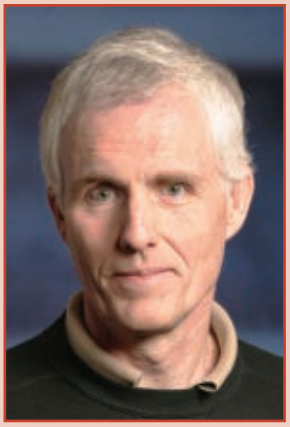
So is the drug delivery company business model broken? It depends on what you consider to be the drug delivery business model and how you measure success. Arguably, survival in this environment is a success of sorts, although it still needs to be a step to profitability. Historically, a few drug delivery companies have been successful, and a couple spectacularly so. But these successful companies have each done it their own way. If there is a common denominator to success, it seems to be that real corporate value is realized through being acquired. Alza seemed to believe that continued profitability and increasing market valuation as a drug delivery service company was not possible and made the decision to move into the specialty pharma space. Could Alza have continued as a profitable drug delivery company? Perhaps it could have, but only by refreshing its technology portfolio. And Cima, by developing a buccal fentanyl product that was to become Fentora, realized that drug delivery service alone was not a long-term option for profitability and market valuation.

More recently, we have seen Noven move away from a drug delivery service and product model to embrace a specialty pharma marketing approach. This led directly to its acquisition by Hisamitsu in 2009. DepoMed is implementing a hybrid approach that involves creating drug delivery-enhanced products it "shares" with licensing partners. This sharing involves DepoMed retaining limited commercialization rights to its products while still benefiting from up-front partner license fees. This seems to be pointing to a time at which DepoMed either fully transitions into a specialty pharma company with sales and marketing resources, or it creates such an attractive product that it is bought out by a much larger company. Alexza seems to have adopted a related strategy, partnering its most advanced product while intending to build a US-based sales force to commercialize follow-on pipeline products.

It's not obvious how other companies are intending to dig themselves out. Most are still committed to providing marketing partners with drug delivery-enhanced products and technology in exchange for license fees and royalties or a profit share. It's hard to imagine that the financial rewards will be any greater in this decade than the past.

The hole that many companies have managed to dig will not easily be crawled out of by doing more of the same. If the industry's future depends on developing next-generation version 2.0 and 3.0 drug delivery products, it also depends on building version 2.0 and 3.0 drug delivery business models. The strategies of Alza and Elan probably won't succeed in this millennium. ◆

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 drug delivery 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.

Very Fine Chitosan Microparticles With Narrow & Controlled Size Distribution Using Spray-Drying Technologies

By: Sandrine Gautier, PhD; Cordin Arpagaus, PhD; Nina Schafroth, PhD; Marco Meuri; Audrey Deschamps, PhD; Véronique Maquet, PhD

INTRODUCTION

This article highlights how high-tech spray-drying techniques and a novel biopolymer of non-animal origin can be combined for the production of pharmaceutically relevant bioadhesive microparticles with controlled particle size lower than 5 micrometers and a cationic surface charge, ideally suited for mucosal controlled drug delivery and vaccination. Chitosan is a bioresorbable biopolymer made of D-glucosamine and N-acetyl-D-glucosamine (Figure 1). Chitosan of mushroom origin is now commercially available for medical and pharmaceutical applications under the trade name KiOmedine-CsU®.[1] It is produced according to cGMP and provides outstanding quality and consistency.[2] The KiOmedine® ultra-pure chitosan range features a lower molecular weight range (ie. 30,000 to 200,000) than that of the usual shellfish chitosan.

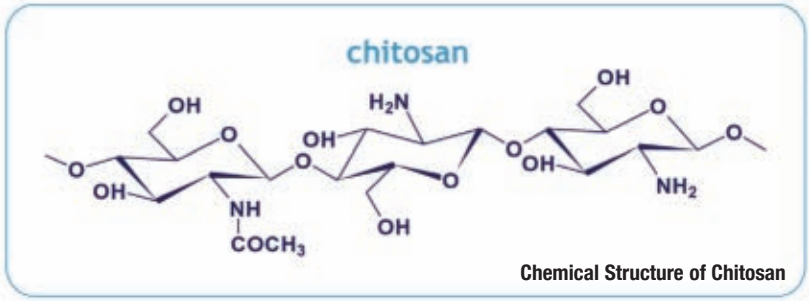
Chitosan is increasingly used as a safe excipient in advanced pharmaceutical formulations, with unique functionalities such as enhanced mucoadhesion, enhanced drug bioavailability, enhanced biological barrier permeability, and bioresorbability.[3-6] Chitosan is a positively charged biopolymer able to electrostatically interact with the negative charge of mucosal layers and of the mucus. Studies demonstrated that drug absorption is not only enhanced by chitosan mucoadhesion, but also by its ability to transiently open tight junctions between mucosal cells.[7,8]

Well-defined micro- and nanoparticles are of particular interest because they enable control of the delivery rate, targeting, drug protection, or prevention of side-effects. Chitosan has successfully been applied for the encapsulation of small molecules and biopharmaceuticals, such as peptides and proteins, DNA, and RNA.[9-15]

Chitosan-based microparticles with a diameter lower than 5 micrometers are efficient for the delivery of drugs via mucosal administration routes.[16-18] Table 1 shows recent results of in vivo administration of chitosan-based microparticles, all stressing the importance of controlling the microparticle features (particle size distribution, surface properties, encapulation rate, release profile) for successful and controlled drug delivery. Sublingual administration of antigen-loaded chitosan particles (diameter from 800 nm to 3 micrometers) was found to enhance tolerance induction in mice with established asthma through improved uptake and presentation by oral dendritic cells.[19] Following intratracheal administration in rats, budesonide-loaded chitosan microspheres showed excellent lung deposition compared to conventional formulations.[20] Clarithromycin microspheres were found to yield high accumulation of the drug in the stomach due to good mucoadhesion with the stomach mucosa.[21]

Spray-drying is the preferred technique to prepare microparticles for pharmaceutical applications because it is a scalable, rapid, controlled, clean, and economic process.[22-24] The preparation of very fine microparticles remains a technical challenge in general. Büchi Labortechnik AG has recently developed the Nano Spray Dryer B-90 (Figure 2), which enables the

FIGURE 1



Chemical Structure of Chitosan

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production of submicron particles. It was designed to evaluate drying during the early stages of product development of small sample amounts at high yields. The system is suitable for a variety of applications, including spray-drying solutions, nanoemulsions, nanosuspensions, structural transformations, or micro- and nanoencapsulations. By means of a piezoelectric-driven spray head, millions of precisely sized tiny droplets are generated every second. The dried particles are separated by an electrostatic particle collector with excellent particle recovery rates even for nanoparticles of milligram sample amounts.

Many publications report the optimization of the spray-drying process of chitosan with various drugs and additives, along with in vitro release profiles and bioadhesion tests.[13,25-37]

In this study, chitosan microparticles with a narrow distribution and a controlled diameter lower than 5 micrometers were prepared using the Mini Spray Dryer B-290 and the Nano Spray Dryer B-90, and KiOmedine-CsU ultra-pure chitosan of various molecular weights.

MATERIAL & METHODS

Mini Spray Dryer B-290

Solutions of 1% w/v ultra-pure chitosan [KiOmedine-CsU, average viscosimetric molecular weight (Mv) 67,000, degree of acetylation 16 mol%, KitoZyme, BE] in 1% acetic acid were prepared with or without addition of sodium tripolyphosphate (TPP) (12% w/w), and bovine serum albumin (BSA) (0.5% w/w) as the model protein. The atomization parameters of the Mini Spray Dryer B-290 included the following:

- Inlet temperature: 160°C
- Outlet temperature: approx. 90°C
- Feed rate: 600 ml/h
- Drying air flow rate: 100% aspirator rate (approx. 40 m^3/h)
- Air spray flow: 600 l/h

The microparticles were observed by scanning electron microscopy (SEM) using an SEM JSL-840A. The particle size distribution was analyzed using laser diffractometry on a Mastersizer 2000 equiped with a Hydrosizer 2000 module (Malvern Instruments, UK).

TABLE 1

Administration Route	Applications (In Vivo Model)	Drug	Ref
Oral	Antiinflammatory	Aceclofenac	[37]
	Vaccination (mice)	Tetanus toxoid	[38]
	Vaccination (mice)	Diphteria toxoid	[39]
	Stomach ulcer (rat)	Clarithromycin	[21]
Nasal	Brain disease and damage (rat)	Cyclopentyladenoside	[40]
	Antiepileptic (sheep)	Carbamazepine	[39]
	Vaccination (mice)	Diphteria toxoid	[49]
	Antimietic (rat)	Ondansetron	[41]
Pulmonary	Antiinflammatory (rat)	Budesonide	[20]
Sublingual	Allergy (mice)	Protein antigen	[19]
Vaginal	Antibacterial (vitro)	Acriflavine	[29]
Bone implantation	Osteomyelitis (rat)	Vancomycin	[42]
Intramuscular	Osteomyelitis (rat)	Ciprofloxacin	[43]
Ocular	Anesthesia (vitro)	Tetracaine	[25]
Intraperitoneal	Antihistaminic (rat)	Ketotifen	[31]

Published in vivo studies on chitosan-based microparticulate drug delivery through various administration routes

Nano Spray Dryer B-90

Solutions of 0.1 w/v % chitosan (KiOmedine-CsU, Mv 30,000 and 50,000) in 1 v/v% acetic acid were prepared without TPP and without BSA. The atomization parameters of the Nano Spray Dryer B-90 included the following:

- Inlet temperature: 120°C
- Outlet temperature: 55°C
- Feed rate : approx. 50 ml/h
- Drying air flow rate : 130 l/h
- Spray mesh size: 5.5 micrometers

Particles were observed by SEM using an SEM JSL-840A. Three photographs were scanned per sample. The average particle size was calculated from 20 particles for each photograph (Figure 3).

Novel Formulations to Improve the Control of Emesis

By Anthony Recupero, PhD, Senior Director, Business Development

EURAND | Pharmaceutical Technologies

Reformulation is a key strategy for product development and helps address the challenges of the current market, such as longer new chemical entity (NCE) development timelines, fewer new drug approvals, increasing costs, looming patent expirations and the threat of generic erosion. Today, offering convenience in dosing or administration alone is no longer a sufficient product differentiator in the marketplace, but must be included as part of the overall product formulation strategy. Other parts of the formulation strategy might include improving solubility / bioavailability to enhance efficacy, reducing side effects, or taste masking.

Addressing Unmet Needs

Drug reformulation can help address the unmet needs of patients and prescribers by improving patient acceptance of and adherence to prescribed treatment regimens. In the treatment of emesis, improved efficacy and extended delivery of antiemetic therapy are desirable therapeutic improvements over many current treatments in the antiemetic category. These improvements may also help ease patients' nausea and vomiting-related fears as they undergo difficult, but beneficial, treatments or procedures (e.g. chemotherapy or radiotherapy), thereby helping them maintain their willingness to continue with such treatments.

Tapping into the 5-HT3 Receptor Antagonist (5-HT_3 RA) Market Opportunity: Ondansetron

Antiemetics are used to control nausea and vomiting across a broad range of therapeutic indications and in a variety of risk settings (e.g. high, moderate, low emetogenic risk). This category of drugs has seen recent new product entries. Specifically, companies are tapping into the large market opportunity in the 5-HT_3 RA class of antiemetics, a current market size of approximately $705 million and the current mainstay of antiemetic therapy.

In the U.S. antiemetic category, ondansetron dominates the solid oral 5-HT_3 RA segment. Ondansetron is marketed in both generic and branded form. It has several therapeutic indications, including prevention of postoperative nausea and vomiting (PONV), as well as chemotherapy- or radiation-induced nausea and vomiting (CINV and RINV, respectively) in a variety of risk settings. Current oral formulations of ondansetron (liquid, tablet, and orally dissolving tablet (ODT)) are indicated for administration in multiple daily doses, potentially over a series of days. This is due to the pharmacokinetic profile of ondansetron, which has a half-life of approximately 3-6 hours in adults, with a time to peak plasma levels of approximately 2 hours[1].

Long-Acting Formulations Needed

The requirement for multi-dosing can negatively affect efficacy and treatment adherence as well as heighten emesis-related patient anxiety, particularly for patients who have difficulty taking pills within physician-recommended timeframes. In the postsurgical setting, at-risk patients experience deep fear and anxiety about nausea and vomiting, generally viewing it as more troubling than even pain. Not surprisingly then, in a post-operative survey, patients revealed they are willing to spend as much as $100 out of pocket for an effective antiemetic.[2] In the setting of cancer chemotherapy, the experience of nausea and vomiting is one of the most common and distressing side effects of cancer treatment[3, 4] and has been associated with noncompliance with receiving chemotherapy, particularly in the era prior to the availability of current prophylactic drugs.[3,4] By complicating or preventing administration of planned therapies, CINV can lead to poor treatment outcomes and decrease quality of life for patients that have to interrupt or discontinue planned treatment.[5] Similarly, the lengthy duration of radiotherapy—sometimes lasting 6 to 8 weeks—can result in prolonged symptoms of nausea and vomiting that can negatively impact patients' quality of life and contribute to noncompliance with planned radiotherapy treatments.[6]

Although there have been advances with the introduction of combination antiemetic treatment, there is still a need for sustained protection, particularly when patients are faced with prolonged or recurrent treatment during which they are at risk of CINV or RINV, as well as the risk of nausea and vomiting for up to five days after chemotherapy administration and for several days after completion of radiotherapy. Improved adherence to antiemetic regimens and development of extended-release antiemetic drug formulations have been identified as a way to improve patient outcomes.[4]

EUR-1025, An Extended-Release Formulation of Ondansetron

Responding to this need, Eurand is developing EUR-1025, a novel, once-daily, oral formulation of ondansetron that is designed for improved efficacy and increased patient compliance across the many therapeutic indications and risk settings related to nausea and vomiting. EUR-1025 combines immediate-release (IR) and extended-release (ER) components in one capsule.

Although oral dosage forms are preferred by patients, developing an ER formulation of oral antiemetic market leader ondansetron has challenged drug makers. This is because ondansetron is only freely soluble in the acidic pH of the stomach. Using Eurand's Diffucaps® customized release technology (**Figure 1**), EUR-1025 will potentially be the first once-daily, ER oral ondansetron formulation.

In pivotal pharmacokinetic (PK) studies, EUR-1025 provides 24 hours of coverage, eliminating the peaks and troughs in plasma concentration associated with twice- or thrice-daily ondansetron formulations.

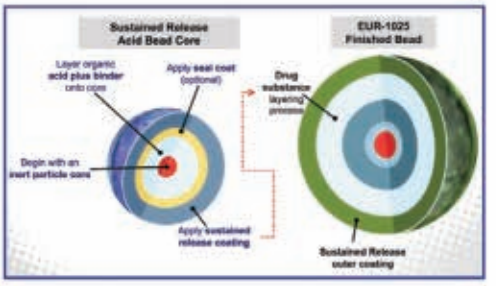

Figure 1. Diffucaps®: Customized Drug Release for pH-sensitive Drugs

The improved PK profile is designed to provide more consistent control of nausea and vomiting, reducing the probability of breakthrough emesis that can occur between IR doses. This, and the fact that it is a single dose, may promote higher patient compliance as well as reduce emesis-related anxiety.

EUR-1025

EUR-1025 is designed to provide 24-hour protection in controlling nausea and vomiting, reducing the probability of breakthrough emesis that can occur between multiple daily doses of currently available immediate-release (IR) oral antiemetics. Eurand is actively seeking partners to market EUR-1025 in the U.S. Contact the author directly at anthony.recupero@eurand.com.

Bioavailability Enhancement Using Diffucaps®

This enhanced formulation of ondansetron was developed using Eurand's proprietary Diffucaps® customized drug release technology, which improves the bioavailability of drugs that exhibit extreme pH-dependent solubility profiles. In this formulation challenge, the Diffucaps technology was optimized to address the specific solubility issues for ondansetron, resulting in improved bioavailability and, thus, once-daily dosing.

The development of EUR-1025 is representative of Eurand's R&D excellence in oral delivery formulation development. With a broad portfolio of technologies, Eurand has had six partnered and proprietary products approved by the FDA since 2001 and has developed more than 40 products for commercialization by partners worldwide. The company is actively seeking partners to market EUR-1025 in the U.S. Visit the company's website at www.eurand.com/contact.html to learn more.

***Anthony Recupero**, Ph.D., is currently Senior Director, Business Development at Eurand where he is responsible for new business development and licensing for North America.*

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Eurand is a global specialty pharmaceutical company that develops, manufactures and commercializes enhanced pharmaceutical and biopharmaceutical products based on its proprietary drug formulation technologies.

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FIGURE 2

Mini Spray Dryer B-290 (left) and Nano Spray Dryer B-90 (right) from Büchi Labortechnik AG

RESULTS & DISCUSSION

Mini Spray Dryer B-290

The goal of this production was to obtain microparticles with a particle diameter between 1 and 5 micrometers. The average particle diameter D (0.5) ranged from 3.2 to 3.5 micrometers, with 63% to 65% of particles in the particle range from 0.5 to 5 micrometers, and 23% to 25% between 5 and 10 micrometers.

SEM pictures showed that microparticles prepared without TPP are spherical with a slightly wrinkled surface (Figure 3). The addition of TPP did not modify the appearance of the particles. They were less spherical when prepared with both TPP and BSA.

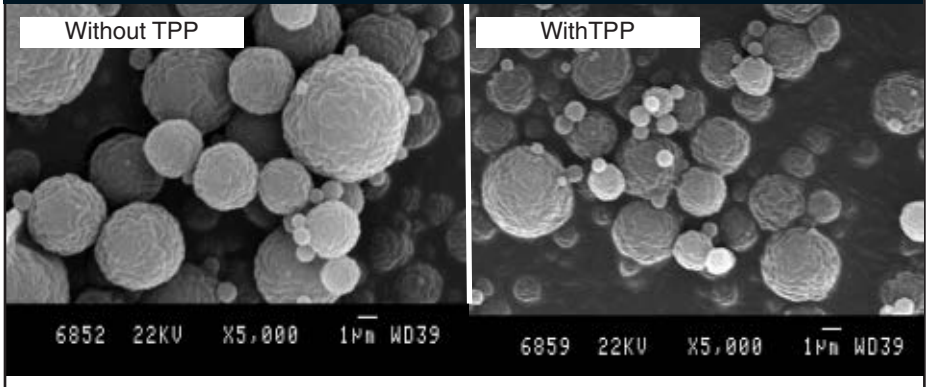
This result is in accordance with studies carried out with shellfish chitosan. For example, chitosan particles with a roughened folded surface and a particle diameter ranging from 1 to 4 micrometers were obtained using a Büchi Mini Spray Dryer B-191 (inlet temperature 140°C, air flow rate 600l/h, outlet temperature 82°C to 100°C), and 1 w/v% chitosan solutions.[27]

Nano Spray Dryer B-90

The goal of this production was to obtain particles smaller than 3 micrometers, and possibly in the submicron range. This could be achieved by tuning the following parameters: (1) decreasing the viscosity of the chitosan solution by using a lower molecular weight (30 k and 50 k versus 67 k) and a lower concentration (0.1% versus 1%) and (2) using the Nano Spray Dryer, which allows for adjusting the spraying and drying conditions to receive powder quantities in the 100-mg scale at uniquely high yields up to 90%.

The average particle diameter was 1.1 ± 0.5 micrometers, along with a narrow size distribution (Figure 4). A large proportion of particles in the submicron size were observed. Further decrease of the particle diameter down to the nano-range could be achieved by tuning the process parameters and/or the excipient characteristics.

FIGURE 3



SEM Pictures of Chitosan Microparticles Prepared With or Without TPP (Without BSA) With the Mini Spray Dryer B-290

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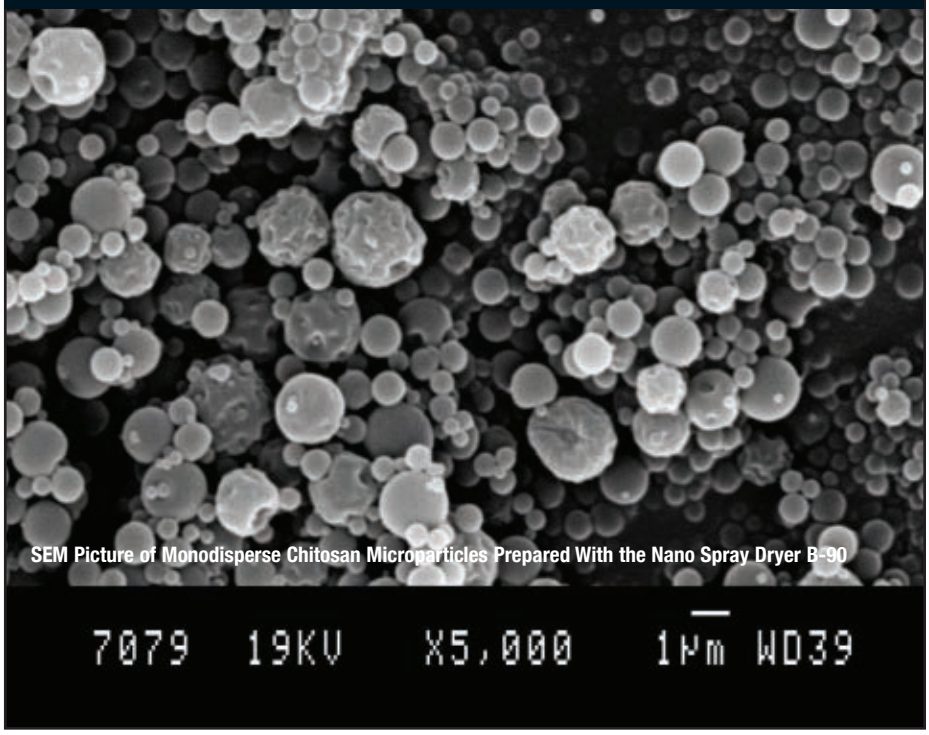
CONCLUSION

Chitosan microparticles of less than 5 micrometers and a narrow polydispersity can be produced by spray-drying using ultra-pure chitosan of non-animal origin. Interestingly, the average particle size can be finely tuned in the micron and submicron range by selecting the spray-drying technology (Mini Spray Dryer B-290 or Nano Spray Dryer B-90 from Büchi) and by adjusting the viscosity of the starting chitosan solution (by varying the concentration and/or the molecular weight of chitosan).

Such very fine chitosan microparticles with a positively charge surface are of great interest for mucosal and depot drug delivery, with remarkable bioadhesive properties and tight control of the drug-release profile. The availability of ultra-pure GMP chitosan of non-animal origin with consistent molecular features at competitive price, combined with a high-performance spray-drying process is opening new doors for tightly controlled very fine micro- and nanoparticulate drug delivery technologies.

FIGURE 4



SEM Picture of Monodisperse Chitosan Microparticles Prepared With the Nano Spray Dryer B-90

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BIOGRAPHIES

Dr. Sandrine Gautier, through her varied and international professional experience, has gained a multidisciplinary expertise in the field of polymers and polymeric biomaterials, particularly in controlled-release systems, ophthalmology, and tissue engineering. Her interest in biopolymers and the development of renewable resources led to her joining KitoZyme in June 2002 as Product Development Manager. Since April 2008, she has been managing the Business Development team, valorizing the know-how, intellectual property, and technological platform of KitoZyme into partnerships and business ventures on the four target markets of KitoZyme: nutraceuticals, cosmetics, beverage treatment, and biomedicals (drug delivery and medical devices). Dr. Gautier earned her BS in Chemical Engineering specializing Polymer Science (National Institute of Applied Sciences, Rouen, France) and her PhD in Polymer Science (Research Center on Artificial Biopolymers, University of Montpellier 1, France).

Dr. Cordin Arpagaus is Product Group Manager for laboratory-scale spray dryers at BÜCHI Labortechnik AG. His focus is on the development of new spray-drying technologies and analyzing emerging market trends in the pharmaceutical, materials, and food industry world-wide. His special interest from former occupations is in nanotechnologies and particle sciences. Dr. Arpagaus earned his MSc in Business Administration and his PhD in Process Engineering from the Swiss Federal Institute of Technology Zurich (Switzerland).

Dr. Nina Schafroth is a Product Specialist in spray-drying at BÜCHI Labortechnik AG. She has extensive international experience in spray-drying applications, especially in the field of pharmaceuticals, inhalable drugs, and nanoencapsulations. She completed several research studies in microencapsulation of APIs with biodegradable polymers for novel drug delivery systems. Dr. Schafroth earned her MSc in Chemical Technology and her PhD in the field of Chemical Engineering from Moscow University of Chemical Technology named after D. Mendeleev (Russia).

Marco Meuri, through his international occupations became a specialist in spray-drying at BÜCHI Labortechnik AG. He is experienced in the field of pharmaceuticals mainly controlled-release and respiratory drug delivery but also in food applications. He also started to gain experience in the field of nanomaterial science. From former occupations, Mr. Meuri has deep knowledge about detergents and cleaning chemicals. Mr. Meuri earned his BSc in Biochemistry, specializing in bioengineering from Zurich University of Applied Sciences (Switzerland).

Dr. Audrey Deschamps has over 10 years experience in the field of biomedical polymers with expertise in tissue engineering, drug delivery systems, and medical devices. Dr. Deschamps earned her PhD in Polymer Chemistry (Twente University, The Netherlands). After completing a post-doc at the Research Center on Artificial Biopolymers (University of Montpellier, France), she worked for 3 years as Research Scientist and Project Coordinator at Angiotech Pharmaceuticals (Vancouver, Canada), where she worked on the development of systemic and local drug-releasing formulations as well as on medical devices. In 2009, she joined KitoZyme as product development scientist and is now project manager running several internal and subsidized projects.

Dr. Véronique Maquet is Product Development Manager at KitoZyme. Her focus is on the development of new products and new applications for non-animal-derived polysaccharides like chitosan and chitin-glucan and their derivatives in different fields of applications. She has expertise in the development of innovative medical devices and drug delivery systems based on biopolymers. She also has expertise in the field of biopolymers for cell cultures and tissue engineering, processing, and characterization of biomaterials. Dr. Maquet earned her PhD in Science-Chemistry (Speciality in Biomaterials) from the University of Liège (Belgium). She joined KitoZyme in 2005.

MARKET BRIEF

Biopharmaceutical Drug Delivery: Going Beyond Injection

By: Katheryn Symank, Industry Analyst, Frost & Sullivan

INTRODUCTION

Biopharmaceuticals have been identified as one of the great breakthroughs of biotechnology and have greatly improved the treatment of several diseases that were traditionally difficult to treat, including autoimmune and inflammatory disorders, cancer, and metabolic disorders. Since the first modern biopharmaceutical, Humulin (a synthetic version of human insulin), was approved by the FDA in 1982, the demand for biopharmaceuticals has been steadily increasing. Currently, there are more than 150 biopharmaceuticals that have been approved in the US, and many more in clinical trials. According to PhRMA, in 2008, there were more than 633 biopharmaceuticals in development for more than 100 diseases ranging from cancer to infectious diseases to autoimmune disorders.

Biopharmaceuticals are medicinal products that are created using biotechnology. They are derived from or are based on living sources and may be composed of living cells, tissues, sugars, proteins, or nucleic acids. Compared to traditional, chemically synthesized drugs, biopharmaceuticals are large and complex. They range in size from 300 atoms to around 50,000 atoms and are often referred to as large molecule drugs. Considering the size and delicate nature of these products, biopharmaceuticals are difficult to get into the circulatory system. As a result, they are most commonly administered through injection or intravenous infusion. As many patients view these routes as less desirable than other options, researchers have been trying to deliver these medications through other, non-invasive, delivery methods. Various drug delivery methods present their own set of obstacles that must be first overcome. For instance, medications taken orally must contend with the potential of being broken down by the gastrointestinal system. Likewise, medications delivered through the pulmonary route must be able to survive the natural defenses of the lungs.

ORAL DELIVERY OF BIOPHARMACEUTICALS

The oral drug delivery route is generally favored by patients. However, because biopharmaceuticals are large and delicate, they are not able to be easily utilized for oral drug delivery. When taken orally, biopharmaceuticals tend to have poor bioavailability because they are either broken by the gastrointestinal tract or are unable to pass through the epithelial cells that line the tract. Several companies in the industry have come up with innovative strategies to circumvent these challenges, making oral drug delivery a potentially viable option for biopharmaceuticals.

One company making advances in this area is Unigene Laboratories (Figure 1). The company has developed an innovative solid dosage oral peptide drug delivery technology called EnteriPep that utilizes several mechanisms to ensure high bioavailability. These include an enteric coating, organic acid excipients, and absorption enhancers. The enteric coating is designed to protect the tablet or capsule from the acid in the stomach so that it can arrive in the intestines intact. Here, the enteric coating dissolves and the excipients are released. The organic acid acts as a protease inhibitor protecting the medication from degradation, while the absorption enhancer improves the solubility and transport of the biopharmaceutical. Unigene Laboratories has applied its EnteriPep oral drug delivery technology toward the development of an oral formulation of salmon calcitonin that is in Phase III clinical trials for the treatment of osteoporosis.

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AMINO ACIDS
PSEUDOPROLINES

MATERIALS AND SERVICES FOR:

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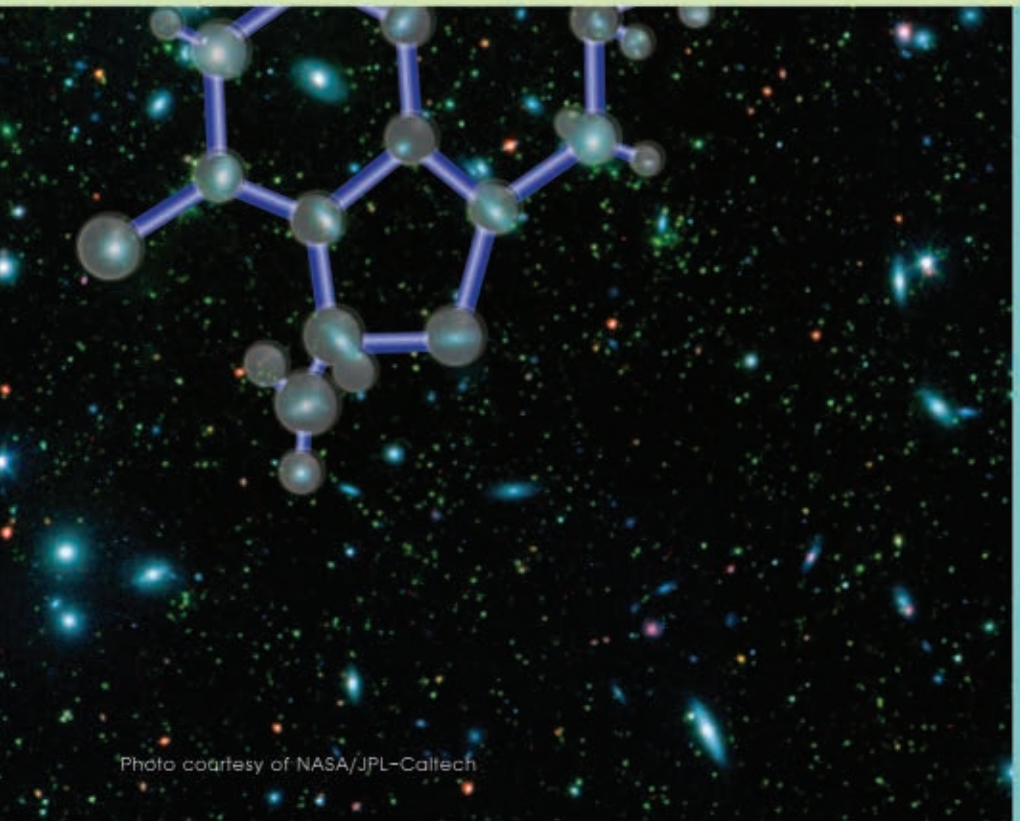
LIPOSOMAL DELIVERY

PROPRIETARY DRUG DELIVERY TECHNOLOGIES

GENZYME PHARMACEUTICALS
NAVIGATING CHEMICAL DIVERSITY



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MARKET BRIEF

TRANSDERMAL DELIVERY OF BIOPHARMACEUTICALS

Another promising drug delivery route for biopharmaceuticals is through the skin. Transdermal drug delivery is convenient and allows for a controlled release of medication. Unlike oral delivery, transdermal drug delivery bypasses the gastrointestinal tract, eliminating issues such as degradation by digestive enzymes. However, the skin itself acts as a barrier that inhibits the amount and the size of the molecules of the medications that can be delivered this way. Typically, using traditional transdermal patches, only small, lipophilic molecules can make it through the skin. Several companies have developed novel transdermal patch systems that are able to successfully deliver biopharmaceuticals.

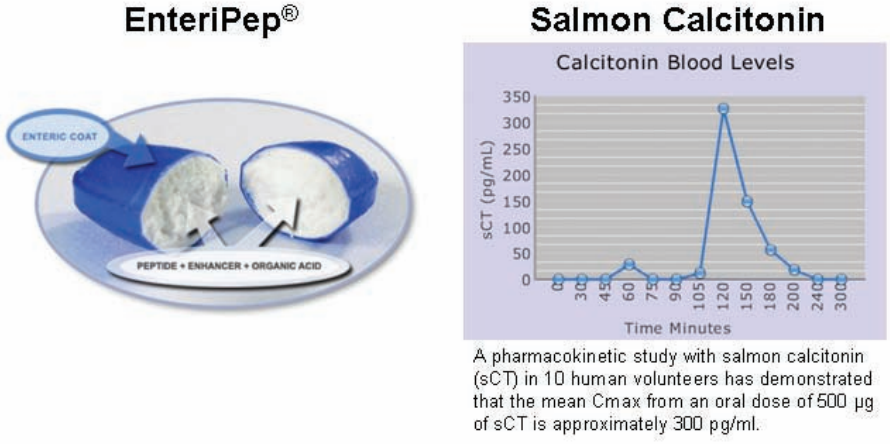
One company working in this area is Altea Therapeutics (Figure 2). The company has a proprietary technology known as the PassPort Transdermal Delivery System that is able to deliver biopharmaceuticals. The PassPort System consists of a disposable, one-use patch and a reusable applicator. The applicator uses pulses of electrical energy to create microchannels in the surface of the skin through which the biopharmaceutical can pass. Using this technology, the company is developing transdermal recombinant insulin. In addition, the company has partnered with Amylin and Eli Lilly to develop a transdermal formulation of the GLP-1 agonist, exenatide.

INTRANASAL DELIVERY OF BIOPHARMACEUTICALS

Intranasal drug delivery is another promising needle-free option for the administration of biopharmaceuticals. The nose is a great vehicle for the administration of drugs because it is highly vascularized and provides a relatively large absorption area due to transmucosal folds. In addition, it bypasses the gastrointestinal system and has relatively few enzymes. The nose allows for rapid medication absorption because drugs absorbed from the nasal cavity can pass directly into the circulatory system. Small molecule drugs are able to easily cross the nasal epithelium. However, it is much more difficult for biopharmaceuticals, which are large and polar, to pass. The result is that biopharmaceuticals delivered nasally tend to have low bioavailability. In addition, the nose also has its own defense system, the nasal mucociliary clearance system, which must be contended with.

Despite these hurdles, a few biopharmaceuticals on the market, like Fortical

FIGURE 1



Unigene's EnteriPep® Oral Drug Delivery Technology has been used to deliver to the blood significant levels of intact and biologically active peptides in animal and/or human studies for several therapeutic peptides.

FIGURE 2

Altea's PassPort® Transdermal Delivery System

(calcitonin-salmon), Miacalcin (calcitonin-salmon), DDVAP (desmopressin), and Synarel (nafarelin), have been able to successfully be administered intranasally. Research indicates that a larger variety of biopharmaceuticals may be able to utilize this delivery route. For instance, OptiNose is developing innovative nasal drug delivery devices that are able to target specific areas of the nasal cavity like the olfactory region. Because there are localized insulin receptors in the olfactory bulb, the company believes that intranasal insulin delivered with the OptiNose dry powder inhaler may provide a promising drug delivery option.

PULMONARY DELIVERY OF BIOPHARMACEUTICALS

For biopharmaceuticals, pulmonary drug delivery offers an exceptional alternative to injection or intravenous infusion. The lungs have several innate characteristics that are accommodating to drug delivery, including a large surface area that maybe used for drug absorption and a rich blood supply. As with most other drug delivery routes, there are some hurdles to the successful pulmonary delivery of biopharmaceuticals. For instance, as a defense mechanism, the lungs are lined with thick mucus that traps and prevents large molecules from entering further into the lungs. Another deterrent to the pulmonary delivery of biopharmaceuticals are macrophages, which seek out and destroy foreign particles. Despite these hurdles, some companies have been able to successfully deliver biopharmaceuticals via the pulmonary route.

One such company is Baxter BioPharma Solutions, which has developed an innovative drug delivery technology called PROMAXX® Microspheres. This versatile technology uses water-soluble polymers to combine the biopharmaceutical into a bioerodible protein microsphere that can be inhaled deep into the lungs using a standard dry powder inhaler. The company has successfully applied this technology to the development of inhaled insulin referred to as recombinant human insulin inhalation powder (RHIIP). In Phase I clinical trials, RHIIP was found to be well tolerated and to have a faster onset of action than insulin administered subcutaneously. In addition, RHIIP was shown to have excellent bioavailability. The PROMAXX Microspheres formulation technology can be applied to a wide variety of other biopharmaceuticals, such as monoclonal antibodies and nucleic acid-based therapeutics.

SUMMARY

Biopharmaceuticals have almost exclusively been delivered via parenteral administration. As the demand for these products increases, so does interest in utilizing more convenient, non-invasive delivery routes. However, as biopharmaceuticals are delicate and easily altered, achieving this goal has not been an easy task. With advancing technology and new innovations, some of the hurdles preventing the delivery of biopharmaceuticals through alternative routes have been overcome, ultimately making alternative drug options like oral, nasal, transdermal, and pulmonary a solid option for biopharmaceuticals.

An in-depth report on this and other related topics can be obtained by contacting Frost & Sullivan at www.frost.com.

BIOGRAPHY

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

Dendrimers: An Emerging Therapy for Cancer

By: Hitesh Patel, MPharm; Jayvadan Patel, PhD; Ravi Patel, MPharm; Kalpesh Patel, MPharm

INTRODUCTION

The word *dendrimer* originated from two words: the Greek word dendron (meaning tree), and meros (meaning part). Dendrimer chemistry was first introduced in 1978 by Fritz Vogtle and co-workers. He synthesized the first cascade molecules, today known as dendritic molecules. In 1985, Donald A. Tomalia, working in the field of polymer chemistry, synthesized the first family of dendrimers.[1] These contributions to the field have paved the way for continuing research in this promising area. The term dendrimer refers only to an architectural motif and not a particular compound. To date, more than 160 various polymers with dendritic structures are reported in literature. The surface groups of dendrimers are amenable to modification and can be tailored for specific applications. The dendrimer architecture therefore permits control over various properties, such as shape, size, density, polarity, reactivity, and solubility. They are produced in an iterative sequence of reaction steps, in which each reaction results in a new so-called generation. Dendrimer density functions and starburst limits can be easily modeled mathematically. These features are related to core multiplicity, the branching multiplicity of the monomer units, and the branch lengths, as well as the core and branch volumes.[2] Due to their multivalent and monodisperse character, dendrimers have stimulated wide interest in the field of chemistry and biology, especially in applications such as drug delivery, gene therapy, and chemotherapy.

DENDRIMERS IN CANCER DIAGNOSIS & TREATMENT

Cancer epitomizes the challenges faced during drug delivery: an anti-cancer drug must be able to seek out subtle changes that distinguish a transformed cell from the other 200 or so healthy types of cells found in the body and then provide a sufficiently high dose of a toxic agent to selectively kill the cell while not harming its healthy neighbors. Therefore, even though dendrimers can be endowed with many favorable properties for drug delivery, an ultimate challenge - ergo, a real-world' test of these versatile nano-devices will be whether they can successfully meet the formidable tasks of diagnosing and treating malignant disease.

To begin the discussion of properties that make dendrimers attractive vehicles for cancer treatment, we revisit the concept that encapsulation or covalent linkage of small molecule drug candidates to a dendrimer enhances the pharmacological properties of the drug. In cancer chemotherapy, these desirable size-based features are reinforced by the enhanced permeability and retention (EPR) effect that improves the delivery of macromolecules to tumors. The EPR effect is based on unique pathophysiological features of a solid tumor, such as extensive angiogenesis resulting in hyper-vascularization, limited lymphatic drainage, and increased permeability to lipids and macromolecules. These features, which help ensure adequate nutrient supply to meet the metabolic requirements of rapidly growing tumors, can be turned to the tumor's disadvantage by the use of nano-sized therapeutic agents.[5,6] The EPR effect was discovered when selective accumulation of the SMANCS conjugate (styrene-maleic anhydride-neocarzinostatin) was observed at the site of tumors, while similar accumulation was not seen with neocarzinostatin alone.[7,8] The EPR response was subsequently demonstrated for similarly-sized liposomes, thereby establishing that this

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effect was largely a function of particle size and did not solely depend on the chemical or biophysical properties of the macromolecule. In one study, optimal tumor delivery occurred for liposomes having a size distribution between 70 and 200 nm in diameter.[9] An independent study showed efficacy for liposomes loaded with daunorubicin in the same size range; specifically, those at ~142 nm in diameter exhibited an inhibitory effect against Yoshida sarcoma, whereas smaller (57 to 58 nm) and larger (~ 272 nm) liposomes had weaker or no effect. Over time, cautionary notes were raised that tempered initial enthusiasm for exploiting the EPR effect for cancer treatment. For example, the porosity of the vasculature in tumors can be highly variable even with a single vessel that can be leaky to one size of particle in one region but not in another.[11] Experimentally addressing this issue was complicated by the size polydispersity of traditional nanoparticles used to exploit the EPR effect, which were typically lipids or conventional polymers that rendered a significant proportion of intended drug inactive. Fortunately, this issue, the ability to match exact and uniform sizes needed to target an individual tumor, is highly tractable with dendrimers because selection of an exactly sized entity is possible (Table 1) compared with the large size distributions that plague liposome and most polymeric materials.[12]

The ability to construct monodisperse populations of dendrimers in the size range needed to exploit the EPR effect is an encouraging step toward the passive exploitation of tumor properties. When the basic issue of size was resolved, however, secondary challenges (and opportunities) arose from observations that the chemical properties of the nano-sized particle can play significant roles in modulating the EPR effect. By way of a specific example, conventional polymeric materials showed efficacy at a smaller size range, occurring at 60 nm for both water-soluble and hydrogel forms of poly (vinyl alcohol) (PVA), whereas almost identically sized 57-nm egg phosphatidylcholine (EPC)-liposomes were ineffective.[13] As reported earlier, liposomes about twice this size showed maximal efficacy, so it was not unexpected that the EPC-liposomes were ineffective. Interestingly, however, hydrogenated egg phosphatidylcholine (HEPC)-liposomes in this size range (specifically, 58 nm) were active, illustrating that the exact chemical properties of the material is a critical design parameter. In this respect, the many options for dendrimer building blocks, as well as the ability to further tune surface properties provide many opportunities to endow dendrimers with favorable passive properties for tumor targeting.

MULTIFUNCTIONAL DENDRIMERS CAN SELECTIVELY TARGET BIOMARKERS FOUND ON CANCER CELLS

As previously discussed, dendrimers can achieve passive EPR-mediated targeting to a tumor simply by control of their size and physico-chemical properties. Passive targeting, which localizes the nanoparticle in close vicinity of a cancer cell, can be immediately useful for diagnostic purposes or for the delivery of radioisotopes capable of killing any cell within a defined radius. In general, however, most delivery strategies require that the anticancer agent be directly attached to, or be taken up by, the target cell. The ability to append more than one type of functionality to a dendrimer allows the inclusion of ligands intended to bind specifically to cancer cells in the design of a multifunctional drug delivery nanodevices. Although a wide range of targeting ligands have been considered (including natural biopolymers such as oligopeptides, oligosaccharides, and polysaccharides, such as hyaluronic acid, or polyunsaturated fatty acids) discussion here is limited to folate, which is an exemplary small molecule tumor-targeting agent, as well as monoclonal antibodies directed against tumor-associated antigens (TAAs).[14]

TARGETING BY FOLATE, A SMALL MOLECULE LIGAND

Folate is an attractive small molecule for use as a tumor-targeting ligand because the membrane-bound folate receptor (FR) is over-expressed on a wide range of human cancers, including those originating in ovary, lung,

TABLE 1

Generation by generation specifications for PAMAM (Polyamidoamine) Starburst dendrimers.

Generation	Physical or structural parameter			
	Molecular weight (Daltons)	Diameter (Å)	Surface groups ($-NH_2$)	Radius of gyration (Å)
G0	517	15	4	4.93
G1	1430	22	8	7.46
G2	3256	29	16	9.17
G3	6909	36	32	11.2
G4	14215	45	64	14.5
G5	28826	54	128	18.3
G6	58048	67	256	22.4
G7	116493	81	512	29.1
G8	233383	97	1024	36.4
G9	467162	114	2048	46.0
G10	934720	135	4096	55.2
G11	1869780	167	8192	68.3

breast, endometrium, kidney, and brain.[15] As a small molecule, it is presumed to be non-immunogenic; has good solubility; and binds to its receptor with high affinity when conjugated to a wide array of conjugates, including protein toxins, radioactive imaging agents, MRI contrast agents, liposomes, gene transfer vectors, antisense oligonucleotides, ribozymes, antibodies, and even activated T-cells.[16,17] Upon binding to the folate receptor, folate-conjugated drug conjugates are shuttled into the cell via an endocytic mechanism, resulting in major enhancements in cancer cell specificity and selectivity over their non-targeted formulation counterparts. Recently, folate has been enlisted in an innovative dendrimer-based targeting schemes.[18]

TARGETING BY MONOCLONAL ANTIBODIES

Of the many strategies devised to selectively direct drugs to cancer cells, perhaps the most elegant (and demanding) is the use of monoclonal antibodies that recognize and selectively bind to TAAs.[19-22] TAA-targeting monoclonal antibodies have been exploited as delivery agents for conjugated 'payloads, such as small molecule drugs and prodrugs, radioisotopes, and cytokines.[23-24] The field of immuno-therapy envisioned almost a hundred years ago, and given renewed impetus a quarter century ago by the development of monoclonal antibody technologies, has nonetheless progressed erratically throughout the past 2 decades as many pitfalls have been encountered. Current prospects remain mixed but hopeful and optimistic, with progress marked by commercial interest with companies providing their immuno-therapeutic drug candidates with flashy trademarked names, such as Armed Antibodies™.[25] Similarly, the rosy opinion that this field is on the verge of clinical fruition has been published recently.[26] Perhaps, more realistically, one recent synopsis holds out hope for a major clinical impact for this strategy within the next 10 years. Although a detailed discussion of the many pitfalls encountered in immuno-therapy efforts is beyond the scope of this chapter, one key issue readily addressed by dendrimers, is the requirement that an extremely potent cytotoxic drug be used in targeted antibody therapy. This point is illustrated by the fact the greatest progress in this field has occurred for immuno-toxins, which are antibody-toxin chimeric molecules that kill cancer cells via binding to a surface antigen, internalization, and delivery of the toxin moiety to the cell cytosol. In the cytosol, protein toxins, such as those from diphtheria or pseudomonas, catalytically inhibit a critical cell function and cause cell death.[27] The high potency of immunotoxins for killing cancer cells is significantly illustrated by ricin, where the catalytic activity of this ribosome-inactivating enzyme allows a single immuno-toxin conjugate to kill a cell upon successful uptake and trafficking to the site of action.[28,29] A drawback of immuno-toxins is their significant immuno-genicity, which limits repeated use. From a broader perspective, their repeated use is made necessary by difficulties in providing a sufficiently high drug load to eradicate all cancer cells despite the high potency of conjugated toxin. An alternative approach of radio immuno-therapy, where high energy radio nuclides are conjugated to TAA-targeting antibodies, also shows promise but suffers from indiscriminate toxicity (the surrounding healthy tissues as well as off-target tissues become irradiated in addition to the target cancer cells).[30] A third possible approach for immuno-therapy, the conjugation of commonly used small molecule drugs to TAAs, is hindered by the relatively low potency of most low molecular weight therapeutics. To illustrate this point, ~ 10,000 TAAs occur on a typical cancer cell, making this number the upper limit for the number of targeting antibodies that can bind to the cell.[31] The widely used anti-cancer drug cisplatin, to give one example, requires internalization of at least 50 times this level of drug molecules for therapeutic efficacy.

A numerical analysis of the aforementioned cisplatin example indicates that each tumor-targeting antibody would have to be modified with a large number of small molecules to be effective as an anti-cancer drug (in this case, roughly 50 cisplatin molecules upon superficial analysis). Modification of an antibody with multiple radioisotopes, toxins, or even small molecules to increase the efficacy of cell killing, however, diminishes or eliminates the inherent specific antigen-binding affinity of an antibody. Therefore, to maximize drug loading while minimizing the deleterious effects on the biological integrity of the host antibody, an attractive approach is to use a linker molecule, such as a dendrimer, that can be highly conjugated (or internally loaded) with drug while modifying only a single site on the surface of the antibody.[32] Methodology to covalently attach antibodies to dendrimers that preserve the activity of the antigen-antibody binding site, eg, by chemical modification of their carbohydrates and subsequent linkage to PAMAM, has opened the door for the inclusion of dendrimers in immunotherapy, thereby enhancing the future prospects of this chronically 'almost-there' strategy.[33-37]

DENDRIMERS IN CANCER DIAGNOSIS & IMAGING

The synthetic ability to attach both a tumor-targeting antibody and a potent payload of anti-cancer drugs to the same dendritic molecule provides a platform for multifunctional nano-scale drug delivery devices. Before this technology can be applied in the clinic, however, its safety and efficacy must be demonstrated. Toward this end, fluorescently modified dendritic conjugates have been used extensively to characterize cell targeting, surface binding, uptake and internalization, and even sub-cellular

localization.[38] The radio-labeled counterparts appropriate for animal studies have allowed detailed examination of the biodistribution of dendrimers. Several radio-isotopes have been conjugated to dendrimers, including ^{3}H, ^{14}C, ^{88}Y, ^{111}In, and ^{125}I.[39-46] These studies have established that the chemical and physical properties of dendrimers can be tuned to favor distribution to or away from specific organs and, ultimately, to achieve favorable biodistribution to tumors. The methods used in these experiments, however, typically requiring post-administration dissection of the host animal to allow the analysis of organ sequestration and tissue distribution of the radioisotope, are clearly not applicable to clinical practice. Instead, they have served as an important stepping stone along the path toward non- or minimally invasive diagnostic procedures, which are proceeding mainly by the development of MRI contrast agents.[47-55]

STEPS TOWARD CLINICAL REALIZATION OF DENDRIMER-BASED CANCER THERAPIES

The use of dendrimers for cancer treatment is still in its infancy with few, if any, applications successfully translated to the clinic. Consequently, their use as diagnostic agents constitutes both an important goal in and of itself, and also a valuable baby step toward the ultimate goal of curing cancer. As discussed, the process of actual killing cancer cells entails the complicated process of drug uptake followed by release of the drug into the cytoplasm or nucleus and is clearly a more demanding process than cell surface labeling, or even localization to the vicinity of the tumor, sufficient for diagnostic purposes. Nonetheless, in some cases, the transition from imaging to therapy will be closely linked, as evidenced by efforts now underway to combine antibody-targeted MR imaging nanoparticles with the delivery of anti-angiogenic genes intended to inhibit the vascularization to the V2 carcinoma model in rabbits.[56] Another promising strategy (boron neutron capture therapy) has undergone impressive development throughout the past decade and is presented next as a successful demonstration of the promise of dendrimer-based cancer therapies.

BORON NEUTRON CAPTURE THERAPY

Cisplatin-based therapies illustrate the need for multiple conjugations of small molecules (estimated at 50 for this platinum drug) to a targeting antibody. While some efforts are underway to use dendrimeric strategies for platinum drug delivery, an even more demanding situation (where thousands of ligands are required per targeting antibody) is provided by boron neutron capture therapy (BNCT).[57] Accordingly, BNCT will be discussed here as an illustrative example of how dendrimers can help overcome high hurdles in the development of innovative cancer therapies. As a brief background, BNCT is based on the nuclear reaction that occurs when boron-10, a stable isotope, is irradiated with low energy (≤ 0.025 eV) or thermal neutrons to yield alpha particles and recoiling lithium-7 nuclei. A major requirement for the success of BNCT is the selective delivery of a sufficient number of boron atoms (~ 109) to individual cancer cells to sustain a lethal ^{10}B (n, alpha)$\rightarrow{}^{7}Li$ capture reaction.[58,59] Considering that the maximal number of antigenic sites per tumor cell is in the range of 100 000, and more commonly only one-tenth that level, an a priori calculation suggests that each targeting antibody must be linked to at least 2000, but preferably closer to 5000, boron atoms. Clearly, a single TAA-targeting antibody cannot be directly conjugated at this level and conventional polymers - eg, polylysine conjugated with ~ 1700 boron derivatives and linked to a targeting antibody - caused the antibody to lose in vivo tumor localizing properties.[60] By contrast, when a PAMAM dendrimer was used for polyvalent boron conjugation, the linked antibody maintained immuno-recognition, although in vivo tumor targeting remained problematic because the conjugated dendrimer had a strong propensity to mislocalize in the spleen and liver. Throughout the decade, since these pioneering efforts were first reported, continued progress has been made to solve problems, such as off-target tissue localization, which was traced to the size of the dendrimer and presence of a large number of amine groups on the surface of PAMAM, by exploiting the versatility of dendrimer chemistry. In short, the re-design of boronated, antibody-targeted dendrimers has culminated in the successful treatment of gliomas in the rat and laid the foundation for translation of this technology into clinical tests in the foreseeable future.

SUMMARY

Dendrimers, chemically defined entities with tunable biological properties, have advanced throughout the past two decades to the point at which they stand on the cusp of major contributions to the treatment of cancer in a meaningful way. Although, as has been apparent by the many instances cited throughout this chapter where gaps in knowledge still remain and that must be plugged before dendrimers are ready for wide clinical use, their extreme versatility combined with extensive research efforts now underway are sure to add sophistication to drugs already in use as well as spur the development of entirely new classes of anticancer therapies.

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Nuchal Topical Neuro-Affective Therapy: A Novel Treatment for Parkinson's Disease Using Apomorphine

By: Ronald Aung-Din, MD

INTRODUCTION

Approved medical therapy for Parkinson's disease (PD) in the US is limited to oral and subcutaneous (sub-Q) injection. The tablet, in ordinary or oral-dissolving form (ODT), is used to deliver levodopa (L-Dopa) to the central nervous system (CNS) in combination with carbidopa (Sinemet and Parcopa) or with a COMT (Catechol-O-Methyl-Transferase) inhibitor (with Comtan as Stalevo). The dopamine (DA) agonists, MAO (Mono-Amine Oxidase) inhibitors, COMT inhibitors, and the anti-cholinergic agents for PD (Artane, Cogentin), are all also in pill form.[1] The DA agonist apomorphine (Apo) is approved as a rescue sub-Q injection (Apokyn) for the acute treatment of episodes of hypomobility/off-periods associated with later stages of PD. Apo injection is also administered by continuous infusion pump.[2]

All current PD treatment modalities are considered systemic in that therapeutic effect relies on drug reaching target sites in CNS through blood flow. Drug first enters the systemic circulation after absorption through the gastrointestinal (GI) tract (with oral preparations) or through subcutaneous vessels (with sub-Q injection or transdermal patch); then, by cardiac output and cerebral blood flow, to intended target areas. The transdermal DA agonist (rotigotine) patch, Neupro, although applied to the skin, requires active drug absorption into sub-Q blood vessels for eventual delivery to the CNS. Neupro was taken off the US market after technical problems with crystallization within the patch matrix. It remains available in Europe with efforts underway to reintroduce it in the US.

With reliance on blood flow for therapeutic effect, idiosyncrasies of the cardiovascular and cerebrovascular systems are important considerations with systemic delivery. Heart disease and cerebral atherosclerosis, common in elderly PD patients, can impact blood flow, influencing drugs reaching the CNS. With oral PD drugs, GI issues affecting GI transit, absorption, and hepatic metabolism present concerns.[3]

SYSTEMIC PD DRUG THERAPY: SIDE EFFECTS & MOTOR COMPLICATIONS

The widespread presence of active drug in systemic and cerebral blood is likely the primary source of side effects associated with PD drugs. As stimulation of DA receptors and other neuro-chemical effects occur at regions other than intended, unwanted drug effects occur. Common side effects include lethargy, nausea, fatigue, orthostatic blood pressure changes, hallucinations, and other behavioral changes. With DA agonists, like pramipexole (Mirapex), obsessive-compulsive behaviors in the form of pathologic gambling and hypersexuality may occur. Episodes of suddenly falling asleep during activities of daily living have also been reported, contributing to auto accidents.[4]

Systemic PD drugs also raise the concern of non-physiologic effects as drug is delivered to downstream neuro-anatomical structures before those upstream. Within the DA system, the sequence of neuro-chemical flow and

TABLE 1

Patient	Sex	Age	Duration PD (Years)	Current PD Medications	UPDRS Motor Pre, Post, Diff
EB	F	86	8	Stalevo (Sinemet & Comtan)	51, 32, 19
GV	M	87	12	Stalevo	38, 18, 20
EK	F	75	6	Sinemet & Mirapex	36, 19, 17
WH	M	88	11	Sinemet & Mirapex	51, 31, 20
SK	F	89	5	Sinemet	66, 52, 14
IR	M	64	10	Sinemet, Mirapex & Amantatine	57, 34, 23

* Expanded UPDRS motor score of 27 items: 0 (nl) to 108 (27x4) range 1.0 mg of apomorphine in Lipoderm except 0.5 mg in patient EK.

Topical Apomorphine Therapy in Off-State Parkinson's Patients: Changes In UPDRS Motor Scores*

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effect begins in the brainstem substantia nigra pars compacta, where DA is produced, then to the striatum (caudate and putamen) via ascending nigra-striatal pathways. From the striatum, additional DA effects occur through connections to cortical and sub-cortical motor areas and other structures.[5-7]

The cardinal clinical signs and symptoms of PD (tremor, rigidity, postural instability, and bradykinesia) are thought to occur when DA production in substantia nigra is reduced by 60% to 70% through loss of DA-producing neurons. PD is considered a neuro-chemical disorder resulting primarily from the loss of DA function in the CNS. Recent reports suggest other neuro-transmitters, specifically serotonin (5-HT) and norepinephrine (NE), may also play important roles.[7-9] These other neuro-transmitters may contribute to the non-motor aspects of PD: anxiety, depression, restlessness, sleep disturbance, muscle aches and pains, bowel dysfunction, and loss of smell and appetite with associated weight loss.

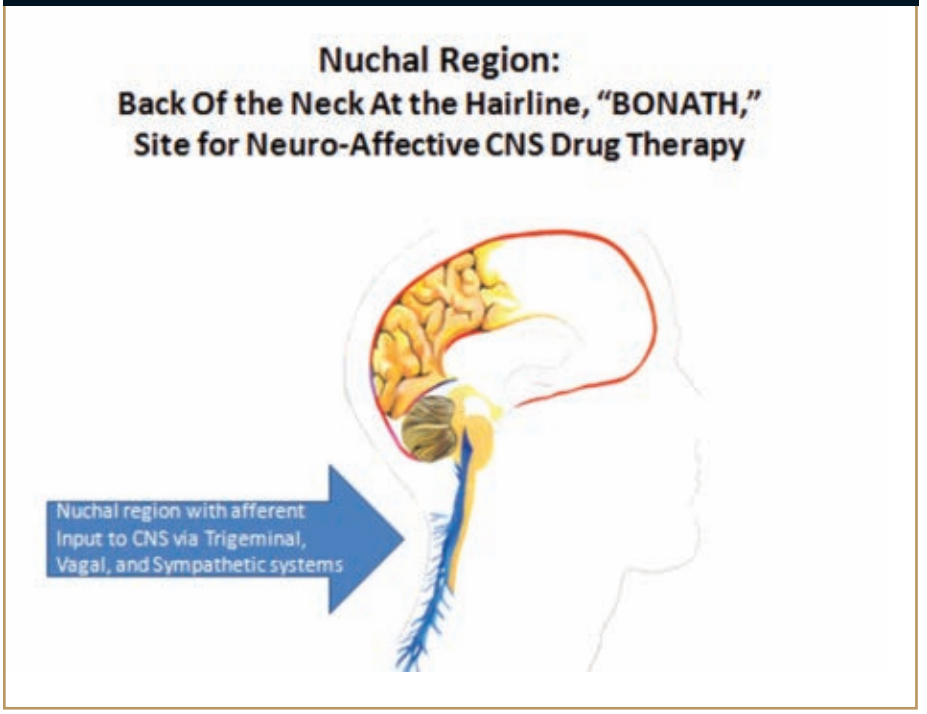
Current PD drug therapy is aimed at providing DA to affected pathways and receptors deficient in the neuro-chemical. This is achieved by boosting the brain's endogenous DA function or by providing exogenous DA as L-Dopa. The function of DA produced in the CNS (endogenous DA) may be enhanced by DA agonists and drugs that reduce DA metabolism and breakdown, allowing a more prolonged DA effect. COMT and MAO-B inhibitors are in this latter category of drugs.[1,2,5,6]

However, there eventually comes time in the clinical course of PD when endogenous DA is incapable of supporting the DA requirements of the patient and alleviating the progression of symptoms. It is at this point exogenous DA is added to the drug regimen. In addition, when clinical symptoms are already significant at the time of diagnosis, exogenous DA is often started early. It is still unclear whether the motor complications of late-stage PD are the result of receptor hypersensitivity from prolonged and fluctuating exogenous DA exposure or part of the natural course of disease, or both. Further, long-term exogenous DA effect at downstream DA receptors (in the striatum and subcortical/cortical structures) could conceivably produce negative feedback inhibition of DA synthesis in the substantia nigra. Whether this potential for suppressing endogenous DA accelerates PD progression needs consideration.[5-8]

The recognized disadvantages of exogenous DA therapy as L-dopa include its short half-life, inducing pulsatile stimulation of DA receptors; its decrease in effectiveness over time; and the emergence of dyskinesias and motor (and non-motor) fluctuations after prolonged use.

It would seem PD drug therapy is best realized when DA effect follows the normal physiologic sequence: brainstem to striatum to subcortex and cortex. This may particularly be true for the DA precursor, L-Dopa, and DA agonists. As discussed, the long-term exogenous DA effects of receptor hypersensitivity (motor complications and on-off phenomena) may result from the persistent, fluctuating, non-physiologic downstream DA receptor stimulation of these drugs.

FIGURE 1

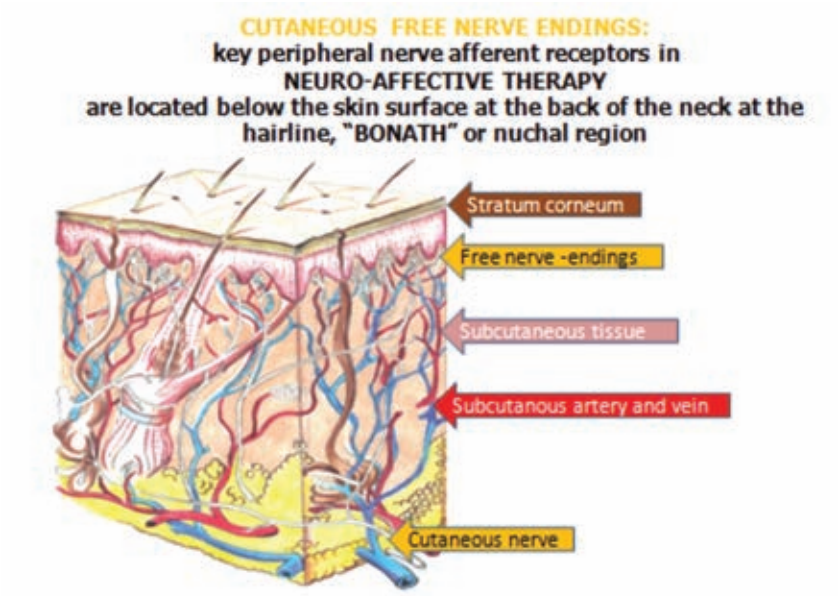


UNIQUE & REVOLUTIONARY NATURE OF NUCHAL TOPICAL APOMORPHINE NEURO-AFFECTIVE THERAPY

Nuchal Apo therapy for PD operates through free nerve endings below the skin surface (stratum corneum) at the upper posterior cervical or nuchal region: back of the neck at the hairline (BONATH). These have direct afferent connections through cervical nerves and nerve roots to afferent components of the Trigeminal Nerve System (the Trigemino-Cervical Complex), the Cervical Sympathetics, and Vagus Nerve that input to the brainstem and the CNS. At no other location is there neural circuitry to this extent between cutaneous free nerve endings and CNS through afferent networks as at the nuchal region or BONATH (Figures 1, 2, and 3).[3]

Afferent impulses are those from the body (skin, muscle, and internal organs) to CNS, and efferent impulses originate in the CNS and flow out to the body. Exposed, un-myelinated free nerve-endings at the nuchal region function as peripheral nerve afferent receptors. When affected by certain topically applied CNS-active drugs, they influence

FIGURE 2



CNS efferent outflow to modulate/reduce clinical symptoms. The cutaneous free nerve endings are easily accessible to drugs compounded in an appropriate dermal penetration-enhancing medium and applied to the skin.

In the instance of nuchal Apo, the compounded Apo cream (1.0 mg/0.5 ml Lipoderm) is gently rubbed into the skin at BONATH over an approximate 15- to 20-sq-cm area at both sides of midline. Roughly estimated, there are in the order of hundreds of thousands to millions of free nerve endings in this area of topical drug application providing afferent feedback to CNS through extensive neural connections.

REGARDING OTHER POSSIBLE MECHANISMS

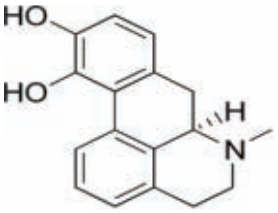
The possibility that nuchal Apo clinical effect is through topical drug entering sub-Q vessels and working through the vascular system is unlikely in consideration of the observed times of therapeutic effect, generally 5 to 10 minutes. The time to therapeutic benefit is too short to account for drug diffusion across concentration gradients in the subcutaneous tissue and absorption into the vascular system. Cardiac output and cerebral blood flow factors also need to be considered. Therapeutic blood levels must be achieved for clinical effect in systemic drug delivery. Doses of Apo used in nuchal therapy (1 to 2 mg applied topically) would be insufficient to provide therapeutic drug concentrations in consideration of dilution in systemic and cerebral blood.

Systemic delivery by transdermal patch is analogous to filling a reservoir to achieve a therapeutic drug level in blood. In contrast, topical neuro-affective therapy at the nuchal region may be viewed as the discharge of an electrical capacitor that results in neural impulse formation and propagation - following cutaneous free nerve ending effect by active drug. In this respect, the significant disparity in time to clinical effect comparing nuchal topical therapy to systemic drug delivery by transdermal patch or oral means makes sense.

The possibility that nuchal Apo effect is on the basis of up-take of drug via a neuronal process (of free nerve endings) with retrograde axonal transport to CNS is likewise unlikely. Again, the relatively short times to clinical effect and the low drug concentrations used in nuchal Apo are against this mechanism.

An additional question is whether application of compounded topical Apo cream at sites other than the nuchal region or BONATH, for instance, the arm or leg, would work in treating PD. I believe the answer to be no, not very likely. The distance from the cutaneous free nerve endings and peripheral nerves at these locations to the spinal cord and CNS is relatively much greater. Further, the extensive afferent neural network with Trigeminal, Sympathetic, and Vagal systems, essential to the CNS effects of nuchal therapy, does not exist at these other areas.[3]

TABLE 2



Formula	$C_{17}H_{17}NO_2$
Mol. mass	267.322 g/mol

Apomorphine (Apokyn, Ixense, Spontane, Uprima) is a non-selective dopamine agonist which activates D1-like and D2-like receptors. It is a morphine decomposition product, hence the -morphine suffix. Apomorphine does not contain morphine or bind to opioid receptors. It is a potent emetic (ie, it induces vomiting) and should not be administered without an antiemetic. It is used to induce therapeutic emesis in veterinary medicine. Pharmacology: Apomorphine affinity for receptors:

Dopamine	Serotonin	Norepinephrine
D_1 (K_i = 372 nM)	5-HT_{1A} (K_i = 117 nM)	α_{1B}-adrenergic (K_i = 676 nM)
D_{2S} (K_i = 35 nM)	5-HT_{2A} (K_i = 120 nM)	α_{1D}-adrenergic (K_i = 65 nM)
D_{2L} (K_i = 83 nM)	5-HT_{2B} (K_i = 132 nM)	α_{2A}-adrenergic (K_i = 141 nM)
D_3 (K_i = 26 nM)	5-HT_{2C} (K_i = 102 nM)	α_{2B}-adrenergic (K_i = 66 nM)
D_4 (K_i = 4.4 nM)		α_{2C}-adrenergic (K_i = 36 nM)
D_5 (K_i = 15 nM)		

Apomorphine Data

THE ADVANTAGE OF NUCHAL APO THERAPY

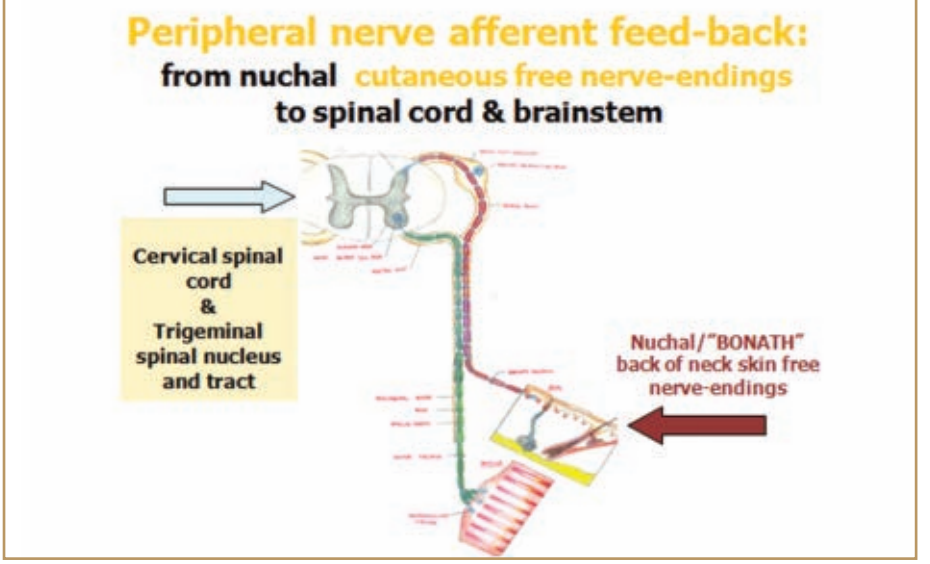
The therapeutic benefit of nuchal Apo in PD is achieved by its effect on cutaneous free nerve endings at the back of the neck. Commercially available Apo powder is formulated in a proprietary manner in a compounding medium (Lipoderm) to allow dermal penetration of active drug to the nerve endings.

In operating through neural mechanisms rather than blood flow, systemic and cerebral side effects are minimized or avoided. Therapeutic effect is also more rapid than with pill or transdermal patch, as concentration gradients within subcutaneous tissues for drug absorption into blood vessels are unnecessary. While sub-Q Apo injection (Apokyn) is fairly rapid in onset (15 to 30 minutes), there exists the potential for a bolus effect with exaggerated side effects and wash-out of therapeutic drug effect. Further, to counter the very possible side effects of nausea and vomiting with Apokyn, a 3-day pre-treatment regimen with the anti-emetic trimethobenzamide (Tigan) is recommended. An initial dose determination process under the supervision of a healthcare provider is also required. Finally, this form of PD drug therapy is considered invasive and unacceptable to individuals who are needle phobic.[2]

As discussed, therapeutic drug effect with nuchal Apo therapy follows physiologic lines as it begins at the cutaneous free nerve endings; continues by peripheral nerves to cervical nerve roots and spinal cord; then, from brainstem structures (substantia nigra), via ascending nigra-striatal pathways, to striatum and other downstream structures. With systemic delivery, active drug is haphazardly delivered to neural structures by blood flow, contrary to physiologic neuro-anatomical sequence. As such, active drug affects areas not specifically targeted, causing unwanted side effects, such as the significant nausea encountered with Apo sub-Q injection.

FIGURE 3

RELATION OF CERVICAL FREE NERVE ENDINGS, PERIPHERAL NERVES, AND NERVE ROOTS TO CERVICAL CORD



CLINICAL EXPERIENCE WITH NUCHAL APO IN PD

To date, my associate, Bridget Keller, MD, and I have treated more than 60 PD patients with nuchal Apo through our neurology practice in Sarasota, Florida. Our observations indicate nuchal Apo alleviates clinical symptoms of PD in a measurable way more than 85% of the time when patients are treated in a relative off-state, exhibiting symptoms of tremor, rigidity, postural instability, and reduced spontaneity. Symptom improvement after topical application of 1 mg/0.5 ml compounded Apo to the back of the neck was generally clinically obvious within 15 minutes. Except for a few patients who developed slight localized skin irritation, no significant side effects have been noted. In these individuals, changes in the compounding formula were made. Clinical benefit on average lasted 4 hours, with some patients reporting longer.

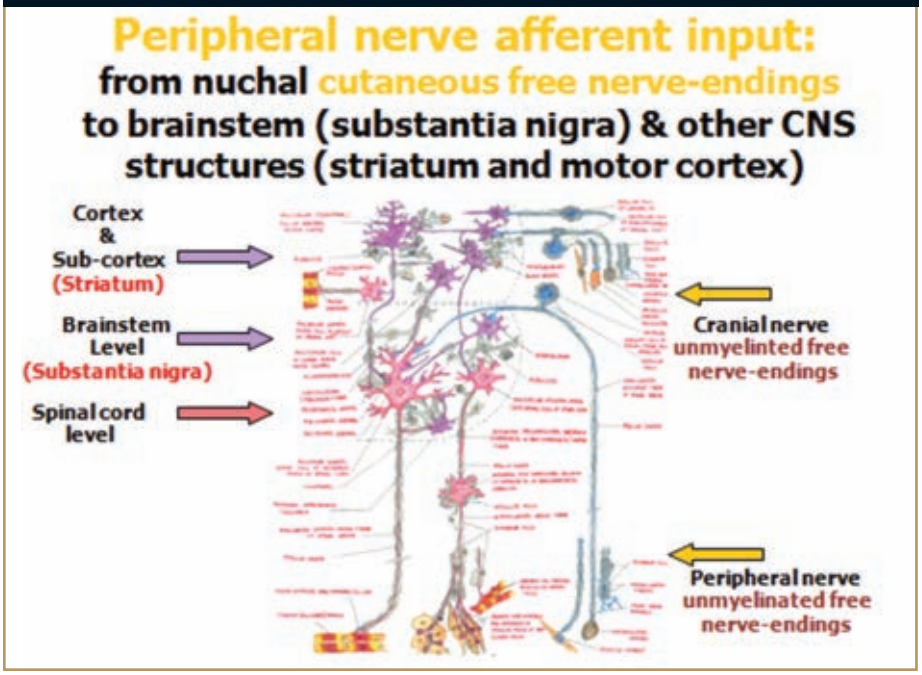
Of the aforementioned patients, two have passed the 1-year mark for continuous twice-daily use of nuchal Apo for PD. There have been no significant side effects with chronic use or the need to increase dose to maintain therapeutic benefit. On the contrary, after a period of several weeks to

TABLE 3

Potential Benefits of Nuchal Apo In PD

- Quick onset of action, 10-15 minutes, with duration of effect up to 3-4 hours.
- Demonstrates efficacy in reducing tremor and rigidity; improves psychological affect/sense of well-being in patients in the off-state at different stages of PD, from mild to severe.
- Use of nuchal Apo can reduce use of other PD medications, simplifying therapy and eliminating side effects associated with concomitant medications, of particular importance in the elderly.
- Nuchal Apo is easily administered and without significant side-effects.
- May preserve DA neuronal function, minimize motor complications, and delay disease progression and need for exogenous DA in PD by facilitating endogenous DA: neuro-protective.
- Allows use of a clinically proven drug for PD (apomorphine) in a novel and more convenient manner.
- Bypasses the Blood-Brain-Barrier.

FIGURE 4



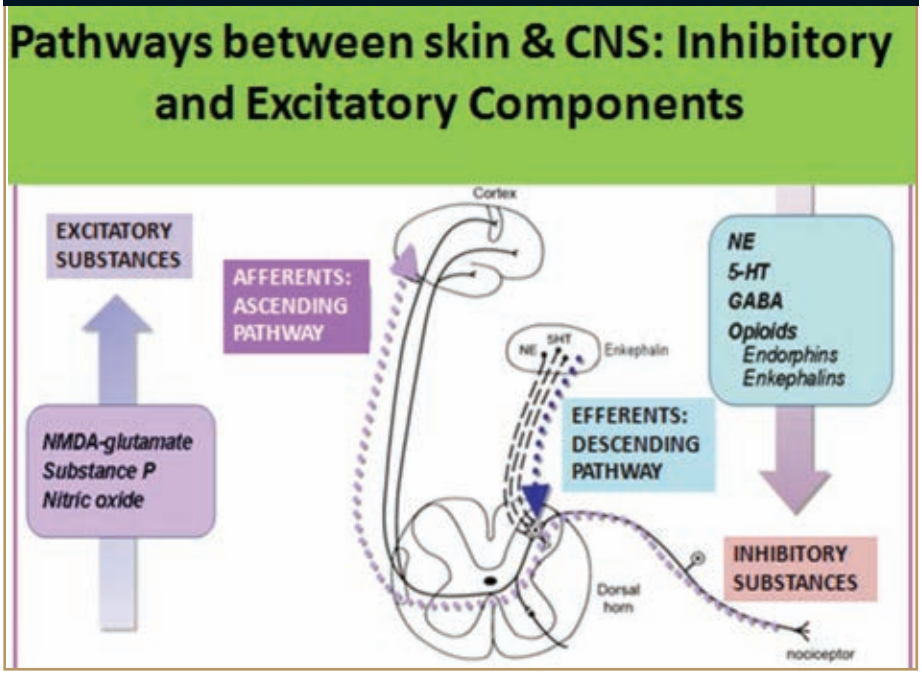
months, some patients were able to reduce their dose of nuchal Apo and concomitant PD drugs.

Table 1 outlines the results of nuchal Apo in six established PD patients. These results exemplify those observed in other treated patients. The expanded Unified Parkinson's Disease Rating Scale (UPDRS) was used to objectively assess the functional states of patients pre- and post-treatment. Twenty-seven (27) components of the clinical neurological exam are rated on a 0 to 4 scale in regard to severity: 0 = normal and 4 = severe, thus giving a range of 0 to 108.6

As can be appreciated by the UPDRS scores, these six patients were significantly affected by PD. The average pre-treatment score in their relative off-state was 50. Within 15 to 30 minutes of topical application of compounded Apo (0.5 to 1.0 mg), all six patients were improved, as reflected by reductions in their UPDRS scores. The average UPDRS score post-treatment was 31, indicating an average improvement for the group of 19 points.

The duration of clinical motor function improvement in these patients was reported at 2.5 to 26 hours (with average of 4 hours), representing the period patients felt they were able to function off their usual PD medications. This was attributed to the therapeutic benefit of nuchal Apo. After treatment with nuchal Apo, patients returned to their previous PD drug regimen, consisting of taking medications 3 to 4 times per day. By their own accounts, and of their caretakers, their current PD therapy was considered sub-optimal. The only side effects expressed were transient fatigue and dizziness, in patients EK and SK. The relationship of these symptoms to nuchal Apo was unclear. As additional documentation, patients were videotaped pre- and post-nuchal Apo treatment.

FIGURE 5



NON-MOTOR EFFECTS OF NUCHAL APO & YET TO BE DETERMINED MECHANISMS

In addition to the significant improvement in motor function as reflected by the post-treatment reduction in UPDRS scores, patients also expressed an improved sense of well-being after nuchal Apo. Some noted an overall decrease in perceived muscle tone that was accompanied by a relaxed feeling.

Anxiety and psychological tension are common non-motor manifestations of PD. These may pre-date motor symptoms by several years. The observed improvement in non-motor function may be attributed to the alpha-adrenergic and serotonergic effects of Apo when administered as nuchal Apo. Apo is thought to function primarily as a DA agonist in the clinical setting. However, it has recognized effects on norepinephrine and serotonin receptors, some quite significant in vitro. It is possible the potential non-motor

effects of Apo in PD are generally masked by the more significant and overriding symptoms of nausea and other systemic effects seen with traditional Apo therapy as sub-Q injection, Apokyn (Vernalis/Ipsen).[15-17]

Recall therapy with sub-Q Apo for PD requires a 3-day pre-treatment regimen with an oral anti-emetic; this may need to be continued throughout therapy. The potent emetic (nausea inducing) property of Apo is used to advantage in treating ingestion of poisons and other toxic substances in man and animals in which therapeutic emesis is required. These side-effects, on the other hand, have not been noted with nuchal Apo as there is presumed negligible to no systemic Apo effect (Table 2).[15]

Dopmine, norepinephrine, and serotonin pathways from brainstem to frontal cortex and limbic structures influence mood and pleasure as well as alertness and focus. These likely play a role in the non-motor symptoms of PD and other neuro-chemical disorders of the brain (Figures 4, 5, and 6).[7]

The exact mechanisms by which a topically applied agonist drug, like Apo, affects cutaneous free nerve endings at the nuchal region to modulate inhibitory and excitatory influences on the ascending and descending neural pathways to produce clinical effect has yet to be fully determined. Additional studies with other agonist and antagonist agents may help shed light on this phenomenon (Figures 5 and 7).

CONCLUSIONS & FUTURE IMPLICATIONS

These preliminary open-label findings in an outpatient office setting suggest potential utility for nuchal Apo therapy in the management of PD. This form of Apo has also been used in other movement disorders, such as benign essential tremor and tremor associated with multiple sclerosis (MS), stroke, and cerebellar degeneration, with similar efficacy. Plans are underway for a formal double-blind, placebo-controlled, parallel-group crossover study to confirm these preliminary results and establish proof-of-concept.

There is strong neuro-physiological logic to suggest nuchal Apo may help preserve DA function in the striatum, minimizing motor complications and delaying disease progression in PD. This may occur as nuchal Apo augments endogenous DA function by utilizing established neural pathways, as opposed to haphazard, non-physiologic stimulation of DA receptors that occurs with drug delivery through blood flow. Accordingly, nuchal Apo would act to enhance endogenous DA production and utilization. The potential for negative feedback inhibition of DA production in substantia nigra, as may occur with prolonged exogenous DA therapy, is likewise avoided.

FIGURE 6

Dopamine, serotonin, and norepinephrine producing areas of the brainstem and effect on "higher cortical functions": attention, mood, and pleasure.

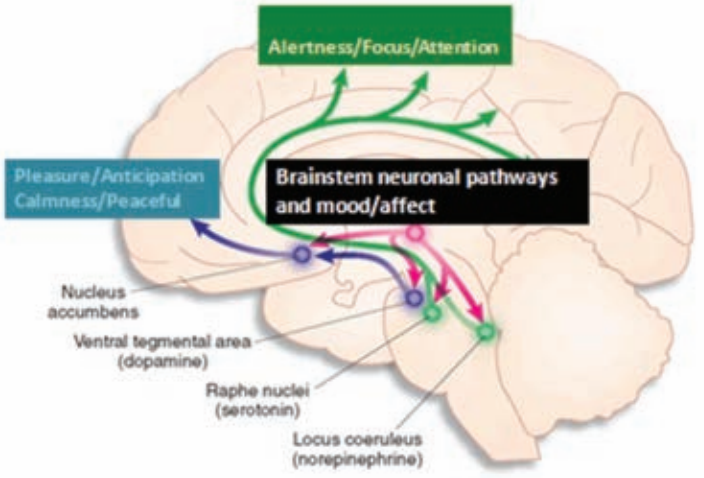
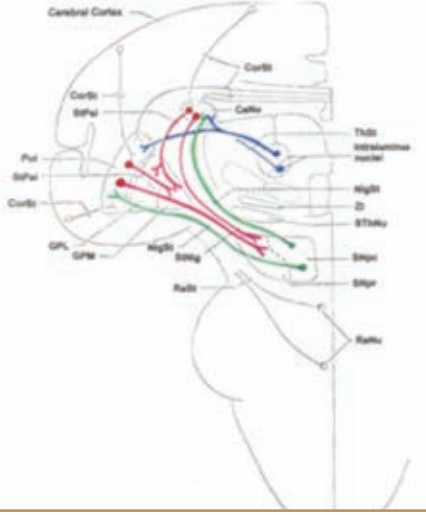


FIGURE 7

Striatal Connections:

Afferent fibers to caudate and putamen originate from cortex, thalamus, substantia nigra pars compacta, and raphe nuclei



Abbreviations:

CaNu	Caudate nucleus
CorSt	Cortico-striate fibers
GPL	Globus pallidus, lateral
GPM	Globus pallidus, medial
NigSt	Nigro-striatal fibers
Put	Putamen
RaNu	Raphe nuclei
RaSt	Raphe-striatal fibers
SNpc	Substantia nigra pars com.
SNpr	Substantia nigra pars retic.
StNig	Striato-nigral fibers
StPal	Striato-pallidal fibers
SThNu	Subthalamic nucleus
ThSt	Thalamo-striate fibers
ZI	Zona incerta

ACKNOWLEDGEMENTS

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BIOGRAPHY

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LC/MS METHOD DEVELOPMENT

Fast LC/MS/MS Methods Using Restricted Access Media (RAM) Guard Columns & Switching Valves

By: Venkata Boppana, MPharm

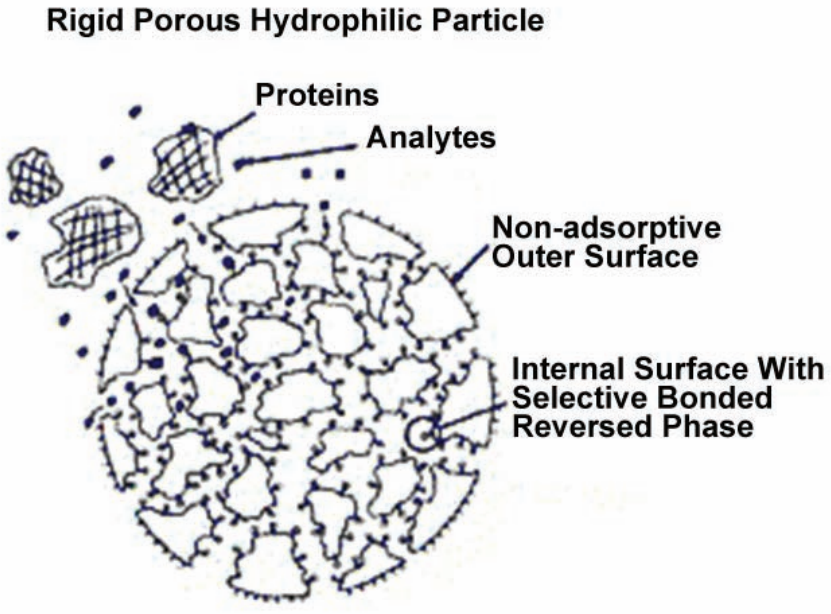
ABSTRACT

On-line solid phase extraction (SPE) coupled with liquid chromatography and mass spectrometer (LC-MS-MS) offers a convenient and elegant approach to analyze drugs and their metabolites in biological samples with high sensitivity and minimal sample preparation. The on-line automated sample enrichment technique eliminates multiple sample pre-treatment steps, reduces chemical and biological waste, and lowers the costs. The on-line system can be easily assembled and adopted for any acidic, basic, and neutral compounds to enrich the analyte and thereby enhance the assay sensitivity. The method involves direct injection of plasma or other biological fluid onto a Restricted Access Media (RAM) guard column, washing the proteins or the endogenous components to waste with aqueous acetonitrile, and back-flushing the analytes onto an analytical column using switching valves. The separated analytes are quantitated with a tandem mass spectrometer operated in selected reaction monitoring (SRM) mode using electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI). Use of two RAM guard columns in parallel configuration allows alternate injections of plasma samples on these columns for sample enrichment, shortening the column equilibration and LC-MS-MS analysis times, thereby increasing the sample throughput. The total run time, including both sample enrichment and chromatography, can be reduced to as little as 5 minutes. Several bioanalytical methods have been developed and validated using this approach. The automated on-line method described here was simple, reliable, and economical and can be assembled with commercially available components.

INTRODUCTION

Quantitative analysis of drugs and their metabolites in preclinical and clinical biological samples by various analytical techniques is a vital function in drug discovery and development. Typically, these analytical methods involve extraction of drugs and their metabolites from a biological matrix (such as plasma, serum, or urine), separation most often by high-pressure liquid chromatography (HPLC), and detection using one of several readily available detectors, such as ultraviolet absorbance, fluorescence, electrochemical, or mass spectrometric detectors. Although advances have been made in automation of

FIGURE 1



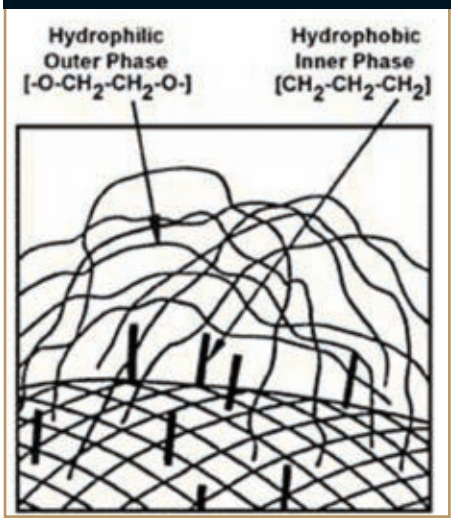
Semi-Permeable Surface (SPS) Guard Columns

HPLC systems, sample preparation procedures, which greatly impact method development, sample analysis time, and overall sample throughput, are frequently performed manually using traditional isolation methods.

The effect of sample preparation times on method development and sample analysis have become more pronounced since the introduction of LC-MS-MS for routine quantitative analysis. This technique has greatly increased the number of samples that can be analyzed in a day by reducing the analysis cycle time (frequently < 5 mins) and decreased the time required for method development through its inherently high sensitivity and specificity. In order to use LC-MS-MS optimally, large numbers of samples are prepared for analysis using one of several traditional sample preparation techniques, which are amenable to LC-MS-MS analysis, including solid-phase extraction (SPE), liquid-liquid extraction, and protein precipitation. Precipitation of proteins from biological samples prior to LC-MS-MS analysis is a quick procedure, but the samples become diluted in the process and still contain abundant endogenous interferences, causing ionic suppression and introducing particulate impurities into the mass spectrometer. As a result, this method is not amenable to methods requiring very high sensitivity. Liquid-liquid extraction is also typically faster than SPE approaches and is useful for high sensitivity assays, but is not readily automated and is not applicable to more polar analytes. Of all of these sample preparation methods, SPE approaches, which readily concentrate analytes, offer the broadest range of applicability in terms of fulfilling high sensitivity requirements on a wide range of chemical structures. Robotic equipment for automating SPE is commercially available, but is very expensive, slow in processing samples, and generally requires human intervention at various stages of sample preparation. On-line sample preparation techniques require little or no sample manipulation, eliminate the disadvantages associated with off-line SPE sample preparation methods, and are compatible with LC-MS-MS systems.

Commercially available RAM columns, are compatible with direct injection of plasma samples without prior sample preparation, but have not received general application.[1-9] Porous silica supports contain a directly accessible external surface as well as internal pores accessible only to molecules with an approximate molecular weight of less than 12,000 Daltons. In contrast to conventional HPLC phases, in which both external surface and the inner pores have homogenous stationary phase, the RAM phases are prepared by unique bonding processes that result in distinct inner and outer surfaces. A dual surface configuration is especially important because the majority of the silica's surface area is in the pores. This dual phase system allows for the separation of analytes through a combination of size exclusion and conventional phase partitioning. The outer surface employs both size exclusion and hydrophilic interaction to prevent large biomolecules from accessing the inner layer. As a result, proteins in plasma samples are excluded by the outer hydrophilic phase from entering the inner hydrophobic phase of the RAM column and pass through the column without clogging, while the small analyte molecules penetrate through to the inner surface of the pores where they are retained and separated by the underlying hydrophobic support. After washing the RAM column to remove proteins and other endogenous compounds, the analytes can be transferred onto a

FIGURE 2



reversed-phase analytical column with the help of a column-switching device, for further separation and quantitation by mass spectrometry. This combination of short RAM guard column for plasma protein removal and column-switching devices for analyte transfer offer a simple on-line sample preparation system that could be easily interfaced with an LC-MS-MS system to develop fast high sensitivity assays. This on-line process can result in excellent clean-up and enrichment of analytes of interest and is particularly well suited for ultra-high sensitivity LC-MS-MS applications.

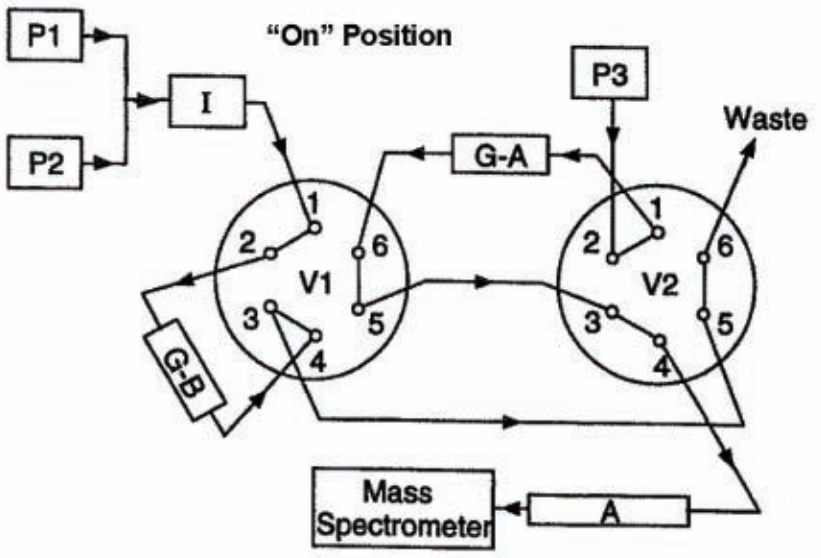
TYPES OF RAM GUARD COLUMNS

Two types of RAM columns, internal surface reverse phase (ISRP) and semi-permeable surface (SPS), are commercially available.

ISRP Guard Columns

The ISRP packing (Figure 1) has an outer surface of glycine and inner surface of tripeptide, Glycine-Phenylalanine-Phenylalanine (GFF). GFF tripeptide was bonded to the silica surface through a monofunctional glycidoxypropyl linkage.

FIGURE 3



Column-Switching Configuration - "ON" Position

The tripeptide is bonded so as to leave a free carboxylic acid group, and is therefore a hydrophobic weak cation exchanger.

The pH range of the column is between 2.5 and 7.5; however, within the optimal pH range of 6.0 to 7.5, both the proteins and the glycine outer surface take on a negative charge. As a result, negatively charged proteins are repelled by the outer phase and pass quickly through the column.

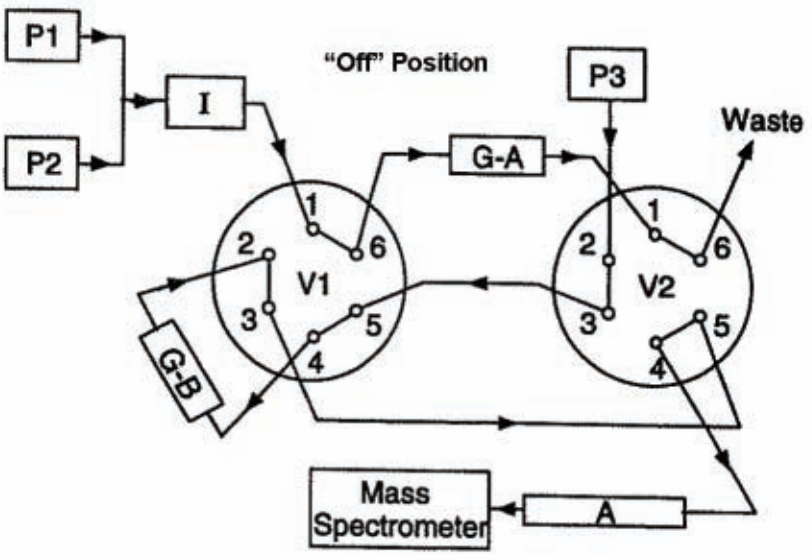
SPS Guard Columns

Similar to the ISRP phase, the SPS phases consist of both hydrophilic outer and hydrophobic inner surfaces. The distinct difference is that the inner and outer surfaces of the SPS are bonded separately, allowing each to be varied independently. The SPS structure includes a hydrophobic inner phase, such as octadecyl silica (ODS), and a hydrophilic outer phase of polyethylene glycol (Figure 2). The outer phase provides size exclusion and hydrophilic shielding, which repels large biomolecules. The various inner phases allow for separation of small analytes.

The retention mechanism of these SPS phases involves hydrogen bonding by the outer phase and hydrophobic interaction by the inner phase. Polar solutes interact primarily with the outer phase and show little discrimination among the various inner phases. Conversely, the non-polar solutes interact primarily with the inner phase.

The SPS columns offer increased durability, selectivity (by changing the inner phase to one of octyl, ODS and phenyl phases), and allows use of buffered, normal-phase, and reversed-phase eluents. The actual composition is limited only by the pH and organic modifier parameters dictated by the proteins contained within the sample.

FIGURE 4



Column-Switching Configuration – "OFF" Position

REAL-WORLD EXAMPLE

Sample Preparation

Plasma samples (100 µL) from clinical or preclinical studies were transferred to autosampler vials and centrifuged at 2000 g for 5 mins. For the analysis of acidic analytes, 20 µL of 1.0 M citric acid was added to 100 µL plasma and centrifuged at 2000 g for 5 mins.

Column-Switching Configuration

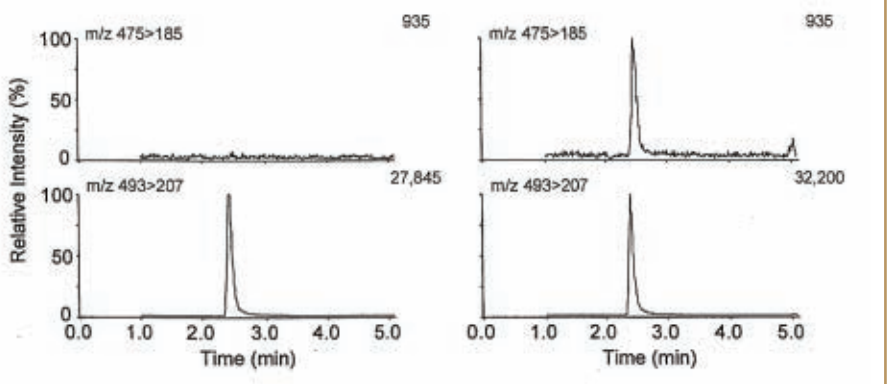
The heart of the column-switching device consisted of two six-port Rheodyne valves (V1 and V2), which could be individually switched between on (Figure 3) and off (Figure 4) positions. Two 10-mm x 3.0-mm ID Internal Surface Reversed-Phase

(ISRP GFF II, G-A, and G-B) guard columns and one analytical column were connected through the two valves of the column-switching device as shown in Figures 3 and 4. The high-pressure solvent gradient system (pumps P1 and P2) was connected to switching valve V1 through the injector (I) and was used to load plasma samples onto ISRP guard columns A or B as well as to wash and re-equilibrate the ISRP columns. The initial loading solvent, composed of water-acetonitrile (95:5, v/v) was pumped at a rate of 1.0 mL/min. An additional isocratic pump (P3) was connected to valve V2 of the switching device. Pump P3 supplied the chromatographic mobile phase, which back flushed the analytes from the guard columns onto the analytical column (A) and eluted the analytes into the mass spectrometer.

Automated Sample Enrichment & Chromatography Using a Column-Switching Device

The main feature of the present system was the alternating pre-column enrichment technique, which significantly reduced the cycle time.[10] Initially, both valves V1 and V2 were set to the ON position (Figure 3), such that guard column G-B was vented to waste. With the valves set to this position, G-B was conditioned with loading solvent (water: acetonitrile, 95:5 v/v) from the gradient solvent system (P1 and P2) in preparation for the autosampler to inject the plasma sample. Also during this stage, the mobile phase from pump P3 flowed into the mass spectrometer through guard column G-A and analytical column. In a typical chromatographic run, the auto-sampler injects the plasma sample onto the guard column G-B while activating the gradient and timed events of the gradient pump

FIGURE 5

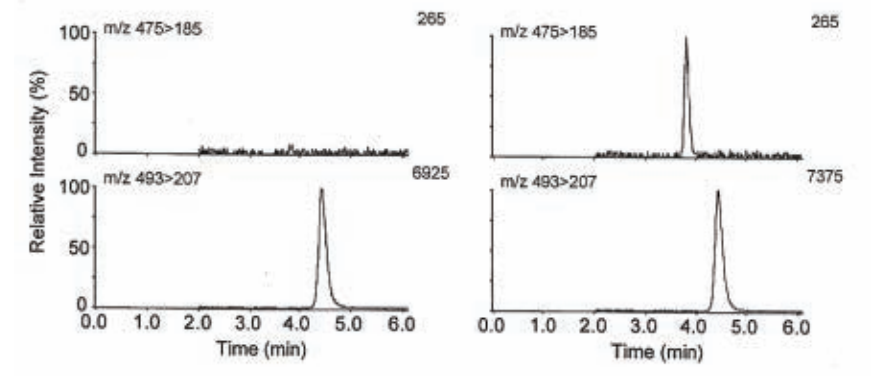


Ion chromatograms from APCI analysis of dog plasmas: LHS: blank (top) and spiked with IS (bottom), and RHS: plasma containing 2 ng/mL API (top) and IS (bottom). Injection volume - 25 µL plasma, Analytical column - 50 x 4.6 mm ID 5 micron octyl silica (inertsil), mobile phase - 50 mM ammonium acetate pH 5.0:acetonitrile (60:40 v/v), flow - 1 .0 mL/min.

system. The timed events from the gradient system controlled the column-switching device and, thereby, the flow path of the entire on-line sample preparation system. Valves V1 and V2 remained at this position (ON) for 1 min, during which the plasma proteins were vented to waste from the G-B column. At the end of the 1-min period, both valves V1 and V2 were switched to the OFF position (Figure 4), allowing the elution mobile phase from pump P3 to back flush the analytes from the G-B guard column. The analytes were separated on the analytical column and detected by the mass spectrometer. Also during this OFF stage, the G-A guard column was washed and re-equilibrated in preparation for the next sample. The concentration of acetonitrile from the gradient pumps was increased to 20% in order to wash the G-A guard column and was then cycled back to the loading solvent conditions. The valves remained in this position while the next sample was injected onto the G-A guard column, and the cycle was repeated.

Typical ion chromatograms obtained using APCI for drug-free dog plasma and plasma spiked with compound A (API) and

FIGURE 6



Ion chromatograms from ESI analysis of dog plasmas: LHS: blank (top) and spiked with IS (bottom), and RHS: plasma containing 2 ng/mL API (top) and IS (bottom). Injection volume - 25 µL plasma, Analytical column - 50 x 4.6 mm ID 5 micron octyl silica (inertsil), mobile phase - 0.1% aqueous formic acid:acetonitrile:methanol (55:35:10 v/v), flow - 0.2 mL/min.

internal standard (IS) are shown in Figure 5. Similar ion chromatograms obtained using electro-spray ionization are shown in Figure 6.

CONCLUSION

The automated on-line sample preparation system can be successfully coupled to an LC-MS-MS to develop and validate high-sensitivity analytical methods for diverse analytes in a very short time. The system can be built easily using inexpensive, commercially available components. The system is robust and performs extremely well over time, saving money in consumables (SPE cartridges vs. reusable RAM guard columns) and has been used extensively in developing several analytical methods. The system can be easily adopted in the analysis of drugs; their metabolites and degradation products in plant and tissue extracts, food and beverages; formulations; and environmental samples using conventional HPLC instrumentation.

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BIOGRAPHY

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Technology Infrastructure to Promote Product Licensing Exchange

By: Joel Finkle

INTRODUCTION

About 10 years ago, G.D. Searle and Company and Pharmacia & Upjohn merged to become Pharmacia. As the dust settled, it became obvious that to become more than just the sum of the parts, various systems - such as clinical data management, regulatory submission content management, and submission publishing - needed to be combined. This provided gains not only due to reduced costs of maintaining multiple computer systems and multiple sets of standard operating procedures (SOPs), but in creating an environment that would simplify the exchange of information with other companies when products were acquired or licensed out. As a matter of fact, one of the primary goals of the project for the combined content management system was to make it easier for the next merger. This proved to be prophetic, as a mere 4 years later, Pharmacia was acquired by Pfizer, Inc.

Since that time, the biopharmaceutical industry has invested a lot of effort in developing standards and models for representation of data, content management, and packaging collections of documents for regulatory submission. With development partnerships and in-licensing of products serving as major drivers of revenue for Tier-1 companies, efficient delivery of data and documents is critical for moving a new product into the pipeline. Conformance with standards should be a key part of the due diligence done before entering into such deals; the costs of integrating the regulatory and product knowledge around a medicinal product should be considered in the price of the product acquisition.

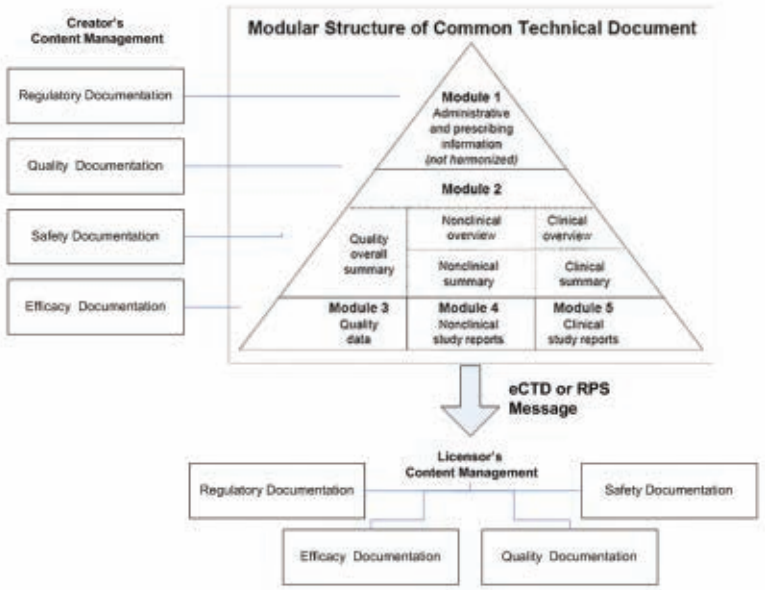
The following will discuss the established standards of Clinical Data Interchange Standards Consortium (CDISC) data, structured product labeling (SPL) for product data, and the Electronic Common Technical Document (eCTD) submission format, as well as other technologies still under development: CDISC Protocol Representation, the Drug Information Association (DIA) Electronic Document Reference Model, and Health Level 7's (HL7) Regulated Product Submissions (RPS), the successor to eCTD. While all of these were developed with the goal of streamlining regulatory submissions, they also provide a fulcrum on which product information can be leveraged between product sponsor companies.

MOVING DAY - SUBMISSION PACKAGING

At the highest level, there is always a challenge for exchanging the relevant information to partners or acquiring companies - information needs to be sent in such a way that all the relevant data about a document can be easily exchanged without a lot of manual labor.

The same techniques that are state-of-the-art for submission to regulatory agencies provide an excellent mechanism for exchanging documents. The Electronic Common Technical Document, or eCTD (Figure 1), was defined by the International Conference on Harmonisation (ICH) in 2003, incorporating requirements by the health agencies and pharmaceutical companies of the European Union, the US,

FIGURE 1



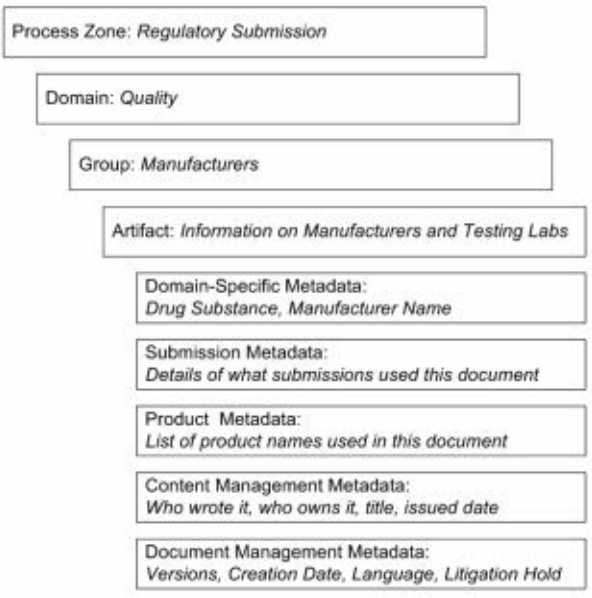
and Japan, with participation today by Australia, Switzerland, and Canada. It provides detailed information about a submission, including the classification of every document being sent, and substantial information about the studies, the product, excipients, etc.

The eCTD is an XML "backbone" or "envelope" that describes the documents being submitted. The documents themselves are sent using the industry standard Portable Document Format (PDF) - familiar to most people as the format used by Adobe Acrobat.

The beauty of the eCTD format is that it has a place for everything, and everything has its place…to a point. It covers all aspects of submission data for drugs and biologics approvals and follow-ups, but certain parts of a product portfolio, such as the trial master file, or other supporting documentation, have no official slot in which to be placed. Tools for creating eCTD packages should have a capability of creating node extensions - a means of specifying additional categories for documents not specified by the ICH standard. These are commonly used in European submissions - and forbidden by US FDA submissions. This certainly gives companies the ability to provide the categorization for any kind of document, but requires an agreement between the parties ahead of time as to how each item should be labeled.

In 2007, the FDA began a project with HL7, an ANSI-accredited standards body, to create a successor to the eCTD that would support all products they regulated. In addition to drugs and biologics, it should also support medical devices, food additives, radiological products, and veterinary medicines. This standard is called Regulated Product Submissions (RPS), and its first release was approved in 2008. In early 2010, the ICH identified RPS as the "next major version" of the eCTD, assuming it could meet a set of enhanced requirements. RPS is not currently in use by any agencies. The FDA's Center for Drugs anticipates implementing the third release of RPS in 2013, currently in development, while the most likely early adopter would be the Center for Food Safety and Nutrition. The rest of the ICH participants would likely follow closely after the FDA's implementation.

FIGURE 2



RPS is taking a somewhat different approach to designing the "envelope" that encloses all the documents (and does not change the documents at all). Rather than the eCTD's fixed set of hierarchical categories that resemble a table of contents at the front of a book, an RPS message is just a list of the files being sent, and the categories they belong to - more like the index at the back of a book. The categories can be more detailed and granular than the eCTD, and categories can be drawn from multiple predefined lists. It's also designed for communication not just from manufacturers to agencies, but back from the agencies to the sponsors, and between companies to handle exactly these kinds of tasks. Except for the limitation that there are few tools for creating RPS messages, this can be used today to incorporate a wider variety of document types.

At its heart, RPS is really just a computer protocol for synchronization of a piece of a content management system. That's a big step for companies needing to swallow and digest the knowledge base of a product that's been acquired, licensed, or partnered, and there is still the challenge of how to deal with those received files.

THE CORPORATE KNOWLEDGE BASE – CONTENT MANAGEMENT

At this point, we have a collection of documentation that is well described and

packaged up using the eCTD or RPS standards. Finding an easy way to map from those categories of documents back into the existing content management system used by the acquiring company is still troublesome. There are no standards or regulation around content management. The only area of FDA regulations that impact such systems are in the Code of Federal Regulations title 21, part 11 (ie, 21 CFR Part 11), which covers the reliability of electronic records. Its impact on these systems is primarily in the areas of audit trails and document retention. How content is categorized, organized, searched for, and retrieved is not something that government agencies are going to control - beyond their need to request them on an audit.

Combined with the fact there are many content management vendors and many systems that must interface with them (eg submission assembly, component-based authoring, report publishing, etc), there is a need to standardize the ways of talking to content management. To this end, the DIA formed a team to develop the Electronic Document Management Reference Model (EDM RM), which is less of a standard than it is a set of user requirements that any content management system vendor should be able to provide.

The biggest part of the Reference Model is the organization of all the document types needed for submission documents (and now, Trial and Drug Substance Master Files). This is organized hierarchically, with the top level being Process Zone (Regulatory Submission or Master File). Within the Regulatory Submission zone are the subject Domains of Administrative Information/Regulatory, Prescribing Information (in development), Pharmacovigilence (in development), Quality, Non-Clinical, and Clinical. Within each Domain are Groups, smaller collections of associated documents. At the bottom are Artifacts, which are the primary categorization of each kind of document.

For documents in each Domain, there are specific metadata items. For instance, clinical documents may have Indications, Study Numbers, and in the case of patient records, the Site and Subject Identifiers. Not all Artifacts will require all metadata. For example, a Summary of Clinical Efficacy would have none of the clinical items previously mentioned. Figure 2 is an example of a Manufacturing Document.

Several vendors now deliver versions of their systems that follow, or are equivalent to, the Reference Model. In the short run, equivalence will provide good value - these are after all, a set of good user requirements. The real value will be in reduced costs in implementing systems related to content management, which can with less configuration effort take advantage of the metadata for submission assembly, report publication, regulatory tracking, and others. For now, though, the reference model should provide a well-known platform for document exchange, where each partner will know what the other is talking about when referring to a kind of document.

DRILLING DOWN TO THE DETAILS – DATA STANDARDS

The aforementioned processes are like building a library and shelving the books, but are of limited value in absorbing the knowledge within those books. The data in the clinical trials, animal safety studies, and stability are critical for preparing for manufacturing and marketing. From the first guidance provided by the FDA on electronic submissions, data was to be sent in the SAS Transport format, an open standard. However, this didn't provide any rules for the structure or organization of data - it was often sent as direct dumps of clinical data systems and could use different names for observations across multiple studies for the same drug.

Clinical Data Interchange Standards Consortium (CDISC) has created a set of standards to assist with that, called SDTM (Study Data Tabulation Model), ADaM (Analysis Data Model), LAB (Laboratory Data Model), and SEND (Standard for Exchange of Nonclinical Data). Except for LAB, all of these use the existing SAS Transport format for the data exchange, but they provide the required structure. For instance, take a simple field such as the patient's sex. In older studies, the sex of a man in a study may have been found in a column named "SEX", "GENDER", "PTSEX", "PATIENTSEX", and so on, with values of "MALE", "M", "1", etc. The CDISC standards insist that it be called "SEX" and has values of "M", "F", or "U" (for unknown observations), and it is placed only in the "DM" (Demographics) data set. The SDTM rules provide all of the common values for safety and major efficacy categories as well as guidelines on how to present additional information to ensure consistency across studies and submitters.

The descriptions of the actual fields used are sent to the FDA (data files are not typically required elsewhere) in an XML file format called CRT-DDS (Case Report Tabulation Data Definition Specification), also known as Define.XML - the name of the file as it is sent. The ADaM and SEND formats are similar in nature to the SDTM standards. LAB, on the other hand, uses XML to carry

both the data and its description, and is designed for interchange of laboratory data from independent labs to drug sponsors. Stability data is also provided in an XML standard, which was developed by HL7, targeted for implementation in 2010 by the FDA. There are also standards being designed to move from the SAS Transport format into an all-XML model in the future.

By using such standards for transmission of data, it should take minimal effort to accurately incorporate the original research data into an acquiring company's clinical and toxicology data systems.

X(ML) MARKS THE SPOT - LABELS

The product label is the culmination of the product approval process. It contains the key safety issues, treatment permitted, and the physical characteristics of the product down to where components are manufactured. The SPL standard, based on XML and created by HL7, is required by the FDA (the only document that must be sent in electronic form) and includes not only the text of the label folded into the medication box, but also indexing data covering manufacturing registrations and drug listings. These data portions of the standard provide a great deal of knowledge about the product that should be critical to incorporating a product into a company's portfolio. Although it is only required by the FDA, there are few products that are developed only for markets beyond the US, meaning that these files should be available for nearly all products. Mining these data for product knowledge should be simple for an acquiring company.

In the European Union, the EMEA announced in September 2009 that the PIM (Product Information Management) standard is finally leaving its pilot phase for implementation over the next 2 years. However, PIM does not include the same level of product management detail that SPL does - its complexity comes more from the management of the text across the 28 languages of the EU.

SUMMARY

Swallowing the product portfolio of another company is enough to give a corporation serious indigestion. However, use of state-of-the-art (not even bleeding edge) technology standards can be the spoon full of sugar that helps the new medicines in your organization go down easily. The costs of implementing standards may have up-front costs in systems implementation, but the return on investment is magnified when companies realize that it's not just their own systems that need to be in alignment, but any company that has the potential to be a partner or acquisition. Especially when the time to bring a product to market must be reduced to a minimum to beat competition or maximize value, existing systems and their legacy processes must adapt swiftly.

In the aftermath of the Pfizer acquisition of Pharmacia, one regulatory director went on to lead a project at Pfizer that reduced their content management environment in R&D from 50 disparate systems down to 3 (one each for legacy documentation, current documents, and an open collaborative space), proof that a good idea can overcome bureaucratic inertia.

BIOGRAPHY

Joel Finkle is ISI's Director of Regulatory Informatics. In addition to architecting their content authoring and PDF Rendering systems ISIWriter™ and ISIRender™, he serves on project teams with HL7 as well as Special Interest Action Committees of the DIA.

DRUG DELIVERY Executive

DisperSol TECHNOLOGIES

DISPERSOL TECHNOLOGIES: ACHIEVING IMPROVED DRUG SOLUBILITY USING SOLID DISPERSION

Yaniv Gershon, PhD
CEO & President

DisperSol Technologies, LLC

"We are currently working with several pharmaceutical and chemical companies to develop dissolution-enhanced oral dosage forms with BCS class II compounds using specific carrier materials. We have been able to not only demonstrate an increase in solubility and dissolution rates of these compounds that exceeds results from other known technologies, but due to the very short processing times at elevated temperatures, we have also demonstrated superior stabilities for thermally labile compounds."

It is estimated that 25% to 30% of newly developed drug substances exhibit poor solubility characteristics, resulting in poor dissolution performance and low bioavailability. The development of processing methods to enhance the dissolution rate and degree of supersaturation achieved with these compounds has become a major focus in the pharmaceutical industry. For many, the solution has been to either use spray-drying or hot-melt extrusion to turn the active into a powder formulation. While these may prove successful strategies for some compounds, solubility does not change significantly for others. Solid dispersion has emerged as an inexpensive and effective method for improving these characteristics in that they provide enhanced dissolution properties through a combination of particle size diminution and reduced crystallinity. Yaniv Gershon, PhD, MBA, CEO and President of Austin, Texas-based DisperSol Technologies, LLC, recently spoke with Drug Delivery Technology about the advantages that KinetiSol® Solid Dispersion (KSD), a high-energy manufacturing process for the production of pharmaceutical solid dispersions, brings to the drug delivery market.

Q: What is the main research focus of your company?

A: DisperSol Technologies provides solutions for companies that are developing drug substances with poor water-solubility characteristics. Our clear niche is on thermally sensitive components that have low solubility. The formation of amorphous solid dispersions is well known to enhance the bioavailability of these compounds. Our technology is a novel manufacturing technique to rapidly form these systems and would be used when other manufacturing techniques are found to be unacceptable.

Q: What are the major advantages of KinetiSol Solid Dispersion over other manufacturing techniques for the formulation of poorly water-soluble drug substances?

A: Solid dispersions can be prepared by solvent or fusion-based techniques. Solvent-based techniques such as spray-drying are not ideal for a variety of reasons. This technique often requires toxic solvents that must be properly disposed of as well as expensive drying steps to ensure that residual solvents fall below a threshold amount. Fusion-based techniques such as hot-melt extrusion are well suited for many drug substances. However, these processes often result in residence times

extending beyond 2 minutes in hot temperature environment and in many cases require plasticization. Due to the high shear rates inherent to the patent-based KinetiSol Dispersing process, compositions are subjected to high temperatures for only a few seconds (3 to 10) without the need for plasticization. This allows the preparation of amorphous solid dispersions of thermally labile drug substances that are more physically stable than those requiring plasticization. This technique has also been shown to effectively render compositions amorphous that could not be rendered amorphous by hot-melt extrusion.

Q: How does the KinetiSol technology compete with other drug delivery technologies today?

A: There are several unique combinations of low solubility, thermally labile drug substances that could not be processed by other methods. We believe KinetiSol processing would have a competitive advantage over hot-melt extrusion and spray-drying. Additionally, even in less-extreme conditions, there are other advantages our technology provides, such as enhanced mixing and rapid processing, which contribute to potentially higher thermal stability and enhanced shelf-life.
Initial findings of several tested compounds had demonstrated a significant increase in potential bioavailability compared with existing technologies. This implies that these compounds could be produced with a significantly lower dosage of the API. Not only is this potentially better for the patient and less expensive, but could also potentially extend the life of the drug beyond its patent life if the dosage cannot be duplicated using other methods.

While the actual processing of the API with the excipients is conducted using our patented equipment, further processing utilizes standard pharmaceutical industry equipment.

Q: Can you describe the equipment used for KinetiSol Dispersing?

A: A custom-built compounder was designed by DisperSol. The unit consists of a product containment vessel containing a rotating shaft with processing blades extending outward from the shaft. During operation, the blades rotate at a high rotational velocity, rapidly processing the material through the development of heat generated by shear and frictional motion of product within the vessel. No external heat input is required during production. Operational temperatures and processing speeds are monitored through a computer-regulated control system, and the material is automatically discharged upon reaching the target temperature. Upon discharge, the material is quench-pressed between two chilled plates and ground using an impact mill. Power is further comminuted using a glass mortar and pestle.

Q: We all know many technologies work well in a lab environment, but have issues with scale-up. Will this be an issue for KinetiSol Dispersing?

A: The technology has been utilized in the polymer manufacturing industry for over a decade. One facility's production line manufactures product at a rate of 6,000 pounds per hour. Initial feasibility studies to determine if the technology would work to create solid dispersions were conducted on full-scale production equipment. With the success of the feasibility testing, a scaled down, lab-sized unit was designed and built for further testing. While many technologies struggle with scale-up, we will be simply returning to the scale we started with.

Q: At this point, what interest have you received from pharmaceutical companies?

A: We are currently working with several pharmaceutical and chemical companies to develop dissolution-enhanced oral dosage forms with BCS class II compounds using specific carrier materials. We have been able to not only demonstrate an increase in solubility and dissolution rates of these compounds that exceeds results from other known technologies, but due to the very short processing times at elevated temperatures, we have also demonstrated superior stabilities for thermally labile compounds. With such a large number of NCEs having solubility challenges, we are very excited about the potential for KinetiSol technology to help solve these issues.

Q: What are your plans for commercializing the technology in the future?

A: Currently, we are continuing the on-going effort demonstrating the strength of KinetiSol to several pharma companies, as well as expanding the research in additional directions and applications. The immediate objective is to work with various pharma companies under license on specific compounds, and support all phases of FDA approval. We currently have GMP equipment capable of producing products for clinical testing. It is important to further develop all aspects of this processing technology, and not focus on the first commercially available narrow aspect, as well as further enhancing the existing analytical basis of the technology.

Additionally, we are planning to collaborate with experienced equipment manufacturers to support the manufacturing of our specialized processing stations for high-volume production. The long-term goal is to provide multiple licenses for high-volume production of drug products as well as support continued research for NCEs benefiting the most from the unique characteristics of our technology.

DisperSol Technologies is currently self-funded by its existing shareholders. Depending on the rate of growth, funding from external sources will be sought.

Q: What challenges do you face as a young company?

A: The main challenge with a new technology, especially in the pharmaceutical industry, is gaining acceptance and recognition. Many start-ups are bringing their ideas to the market, hoping they have value and generate enough interest. While we, at DisperSol and UT Austin, are convinced KinetiSol has more than a niche in processing compounds for oral delivery, we understand that recognition and acceptance will come with more development projects with large pharma companies as well as continued publications in professional journals along with participation at scientific conferences.

Q: What mistakes must you avoid as you move forward?

A: At DisperSol, we all share the conviction that KinetiSol has a great future both financially as well as delivering a significant benefit to patients. If we could convert some drugs currently administered via injection to oral delivery, it will reach more patients, with less risks and less pain. We recognize the fact we are experts in material processing and know a little less about the pharmaceutical industry. Our collaboration with The University of Texas at Austin, College of Pharmacy brings credibility to the table, and we will continue working with these experts to be sure the technology gets the attention it deserves. I believe we will be strong enough to make sure this opportunity is not wasted at the expense of short-term gains. ◆

Technology Showcase

Nasal Spray Device

Latitude® is a novel patented side-actuated nasal spray device designed by Aptar Pharma Prescription Division to enhance ergonomics and hygiene in the hands of patients. To make Latitude easy to use, comfortable, and convenient, allergic rhinitis patients were placed at the center of the development process from the start of the project (Design for User approach). The compact-shaped device provides intuitive-to-use handling due to an optimum hand grip on the lateral trigger and a very low force to operate to guarantee a soft actuation. An optimized motionless nasal nozzle was created, and a clear level indicator window has been integrated to allow patients to easily manage medication replacement. Latitude is easy to customize and has been designed for large-volume manufacture, including easy filling and packaging operations. For more information, visit Aptar Pharma at **www.aptar.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.**

Solubility/Bioavailability Enhancement

Soluplus® is a graft copolymer composed of polyethylene glycol, polyvinylcaprolactam, and polyvinylacetate. It is designed to solubilize poorly soluble drugs and increase their bioavailability. It is ideally suited for preparation of solid solutions or solid dispersions by hot melt extrusion, spray drying, melt granulation, and co-precipitation processes. Soluplus is highly soluble in water at low and high pH and organic solvents. It is significantly less hygroscopic than many other polymers. Its low glass transition temperature (70°C) allows it to be extruded over a wide temperature range without the need for plasticizers. For more information, contact BASF at (800) 443-0627 or visit **www.soluplus.com**

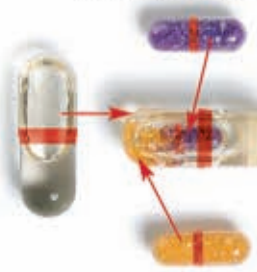
Prefillable Delivery Systems

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**.

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:

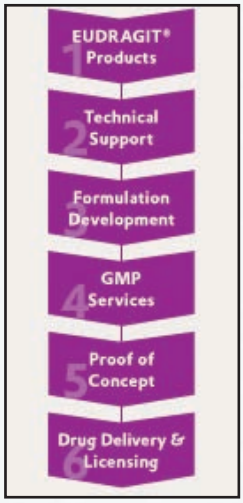
INNERCAP® TECHNOLOGIES, INC

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

9216 Palm River Road, Suite 203 • Tampa, FL 33619 USA • (813) 837-0796 • www.innercap.com • busdevelopment@innercap.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.**

Aerosol Expertise

exemplar
Aerosol Expertise

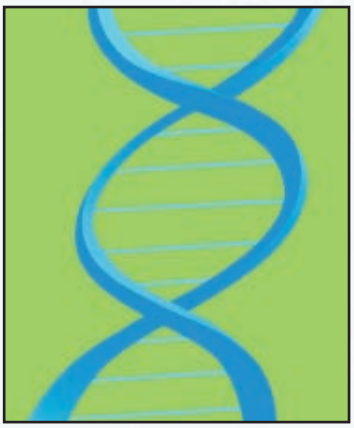
Exemplar Pharma is missioned to support pharmaceutical companies with the development and commercialization of respiratory therapeutics for lung, nasal, and buccal delivery. These CMS-related activities are performed in two subsidiary operations: Exemplar Pharmaceuticals and Exemplar Laboratories. The scientific team at Exemplar Laboratories focuses on the development of formulations, dosage forms, analytical method development/validation, stability, and product characterization studies related to metered dose inhalers (MDIs), dry powder inhalers (DPIs), nebules, and nasal sprays. At Exemplar Pharmaceuticals, the process development and production team has the ability to provide development, clinical, and commercial scale batches of MDIs, DPIs, and Nasal Sprays in a modern cGMP facility. During the past 7 years, Exemplar has successfully supported several companies with products approved through NDA and ANDA pathways. For more information, contact Exemplar Pharma (Charles R. Eck, PhD, at 508-676-6726 or 508-324-1481) or visit **www.xemplarpharm.com**.

Analytical Testing Services

Gateway ANALYTICAL

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

Oligonucleotide-Based Therapeutics Tools



Due to the many challenges facing the delivery of RNA and DNA derivatives into cells, Genzyme Pharmaceuticals provides value-added solutions for delivering these oligonucleotide-based therapeutic actives using a unique combination of products, services, and technologies. Products: readily available products such as synthetic phospholipids, cationic lipids, sphingolipids, and helper lipids, can be used in liposomal and other lipid-based delivery systems. Custom Manufacturing Services: through an integrated resource of custom manufacturing expertise with core competencies in lipids, peptides, polymers, carbohydrates, lipo-peptides, and other small molecules, we provide high-quality GMP excipients needed for cutting-edge oligonucleotide-based delivery systems. Technologies: LipoBridge® and LipoMask™ are two proprietary drug delivery technologies that may be considered for oligonucleotide delivery. For more information visit Genzyme Pharmaceuticals at www.genzymepharmaceuticals.com or email at **pharmaceuticals@genzyme.com**.

Technology Showcase

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**.

Excipients & Technology

MEGGLE
EXCIPIENTS & TECHNOLOGY

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

Oral & Inhalation Products

SkyePharma
Making good drugs better

SkyePharma is a specialist drug delivery company developing oral and inhalation products. With a wide range of patented and proven technologies, SkyePharma helps to make good drugs better. SkyePharma's proprietary drug delivery technologies enable the development of new formulations of existing products as well as new chemical entities to provide a clinical benefit to patients. Geomatrix™ and Geoclock™ technologies enable controlled- or timed-release versions of immediate-release products to be developed, providing advantages to both partner companies and patients. The Group's inhalation technologies include formulation as well as device technologies and encompass metered dose inhalers and dry powder inhalers. With R&D facilities in Switzerland and manufacturing in France, SkyePharma offers a comprehensive range of services from feasibility through to commercial-scale manufacture. For more information, visit SkyePharma at **www.skyepharma.com**.

Taste-Masked Actives

SPI Pharma plans to introduce a line of taste-masked actives under the Actimask™ tradename, using SPI's proprietary Tasteshield™ technology for use in patient-friendly dosage forms, such as Orally Disintegrating Tablets (ODTs), Chewable Tablets, and Orally Dispersible Powders (ODPs). SPI's Tasteshield technology can be applied to a broad range of physical and chemical forms of actives, including liquid solutions/suspensions, as well as solid active cores/particles. A special feature of Tasteshield technology is the ability to taste-mask micronized actives as individuals or on a multicore basis. Actimask systems can be designed for an acidic, basic, or non-ionized active structure. Tasteshield technology is a new addition to SPI Pharma's ongoing Pharmasolutions program. Patient-friendly therapy is especially critical for pediatric and geriatric populations in which pleasant taste, good mouthfeel, and ease of administration drives compliance. For more information, visit SPI Pharma at **www.spipharma.com**.

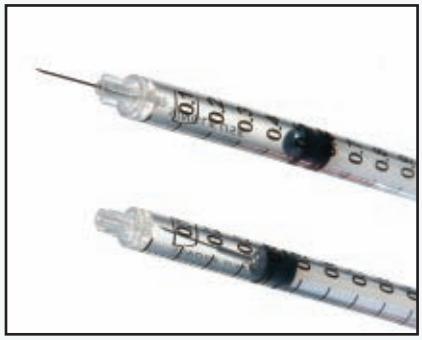
Technology Showcase

Performance Excipients

Stepan

Pharmaceutical excipients produced by Stepan Company feature outstanding performance characteristics for use in the development of medical delivery systems including topical formulations. NEOBEE® Medium Chain Triglycerides are odorless, colorless, and naturally derived. Their low viscosity and polar nature facilitates handling under low-temperature processing conditions and promotes improved dispersibility, spreading, and dissolution of actives. ONAMER® M (Polyquaternium-1) exhibits unique antimicrobial activity, is extremely mild, and exhibits very low toxicity to host cells, allowing ONAMER® M to function in a wide range of medical device applications, including surgical scrubs, surgical preps, and other topical formulations requiring a broad spectrum of antimicrobial efficacy. For more information, contact Stepan at (201) 712-7642 or visit **www.stepan.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**.

Intranasal Vaccine Device

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

Drug Development

Xcelience® Formulation Development

Xcelience is the premier source for unsurpassed quality in drug development services. The company brings together the industry's most experienced and talented scientists, consistently and efficiently moving compounds through the research and development continuum to regulatory approval. Since 1997, the Tampa-based laboratory has been developing formulations for clients throughout the pharmaceutical industry. Xcelience's unique corporate structure creates project teams that work intensively with each client, bringing an extension of their own organization into the Xcelience lab. The lab uses only state-of-the-art equipment, highlighted by the patented Xcelodose®, which fills API directly to capsules (Xcelodose is a registered trademark of Capsugel BVBA). This and other technologies give Xcelience unparalleled speed to market without compromising its absolute commitment to quality. For more information, contact Xcelience at (608) 643-4444 or visit **www.xcelience.com**.

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2011 KEYNOTE SPEAKERS

The Emotion Behind Invention

Dean Kamen
Inventor, Entrepeneur, Advocate & Founder,
DEKA RESEARCH

The Decision Tree

Thomas Goetz
*Author, "**The Decision Tree: Taking Control of Your Health in the New Era of Personalized Medicine**" Executive Editor,*
WIRED MAGAZINE

Insights From Inside the Beltway on Health Reform

Tom Daschle
Former Senate Majority Leader,
UNITED STATES SENATE, *and Author, **"Getting It Done: How Obama and Congress Finally Broke The Stalemate to Make Way for Health Care Reform"***

BREAKTHROUGH INSIGHTS ON DRUG DELIVERY INNOVATION

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Visit the DDP website for details on how to make a nomination for the 2011 awards.

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www. drugdeliverypartnerships.com

Executive Summary

David Exline
Senior Vice President, Gateway Analytical
Gateway ANALYTICAL

Gateway Analytical: Conventional & Novel Analytical Testing Services for Drug Development

A wholly owned subsidiary of ChemImage Corporation, Gateway Analytical is a newly formed company with a diverse expertise in pharmaceutical laboratory analysis, offering various customized analytical technologies to meet drug developer needs. Scientists at Gateway Analytical have more than a decade of experience advising clients in regulatory procedures and conventional USP testing methodologies, as well as more innovative methods like chemical imaging.

At Gateway Analytical, understanding specific drug developer needs, as well as the most efficient means to satisfy them, is of top priority. Routine testing methods that are frequently used in the drug development marketplace provide only a basic scientific understanding. Some cases, however, require the use of complementary analytical methods and creative thinking to gain a better understanding of a drug product's quality and performance in the long-term. What differentiates Gateway's analytical laboratory from others of its kind is its ability to combine mainstream methods with innovative technology, using different combinations of techniques to perform the most complete level of sample characterization available to solve complex client problems.

Recently, *Specialty Pharma* spent some time with David Exline, Senior Vice President of Gateway Analytical, to discuss the company's launch, the needs its services address in the marketplace, as well as its role in drug development.

Q: ***What prompted ChemImage to launch Gateway Analytical?***

A: As a company specializing in the research and development of chemical imaging technology, ChemImage has long known the value its contract services can bring to drug developers as an innovative characterization method. Given the varying nature of challenges drug developers face, focusing solely on one type of technology limited the strategic solutions ChemImage could provide. In an effort to expand the company's chemical imaging contract service offerings, Gateway Analytical was launched to create a platform where this technology could be utilized as a complementary method to other more traditional testing methods.

In many cases, the methodologies that are required to solve complex problems or elicit the most beneficial results have evolved from analytical testing knowledge across several scientific disciplines due to the technology transfer of instrumental analysis and specialized sample interrogation. This evolution has led to advancements in product development testing, including content uniformity testing, layer and coating identification in controlled release technologies, polymorph analysis, particle sizing, as well as areas that directly affect the drug formulation process, such as Quality by Design (QbD) guidance and non-conformance investigations.

These advanced methodologies and expertise can be found at Gateway. Our scientists are dedicated to providing the regulatory guidance and support needed to ensure that drug developers receive the greatest return on investment, while increasing the safety and quality of

laboratory services. One of our strengths is our ability to adapt and combine different analytical testing techniques based on individual client needs.

Q: ***ChemImage Contract Services focused primarily on chemical imaging technology. Does Gateway Analytical utilize the same technology?***

A: Gateway Analytical utilizes a diverse set of analytical testing methods to solve some of the biggest problems facing today's drug developers. Although our scientific staff has extensive expertise in the application of chemical imaging for drug development characterization, it is method that will only be utilized when that level of sample interrogation is required. Common chemical imaging services we provide include the following:

- Content uniformity testing: displays characterization of sample composition, distribution, and morphology of oral drug tablets; semi-solid creams and gels; and medical or transdermal drug devices
- Layer and coating identification: facilitates a better understanding of a controlled release drug's formulation design through the identification of layers, coatings, and coating thickness of multi-layered beads, tablets, or medical devices
- Ingredient-specific particle sizing: determines the chemical identity and particle size distribution (PSD) of micronized drug substances in aqueous suspension nasal sprays, metered-dose inhalers, dry powder inhalers, semi-solids, and transdermals
- Polymorph analysis: detects spatially variable changes and evaluates polymorphic transformations in nasal spray suspensions, metered-dose inhalers, dry powder inhalers, semi-solids, solids, oral drug tablets, and transdermals

Aside from having expertise in chemical imaging, our scientific staff is composed of forensic scientists, chemists, and materials scientists who work in concert to provide the best solution strategy. In addition, our expertise in various USP testing methods, optical microscopy, scanning electron microscopy, Raman and FTIR spectroscopy, and other chemical methods allow us to develop a full suite of testing services to provide a complete level of sample characterization.

Q: ***What needs do your services address in the marketplace?***

A: The needs of the pharmaceutical industry are vast. Gateway Analytical is uniquely positioned to administer services that maximize our experience and expertise in several key areas of the marketplace. Our scientists have worked closely with industry experts to offer support in many facets of the drug development lifecycle.

As products are developed, we can offer assistance using standardized USP methods, as well as the testing of raw materials, to ensure product quality.

In the areas of research and development, we provide expert services to support product and process development, including drug substance characterization and identification, particle characterization, analysis of blend and content uniformity, as well as layered and controlled release materials.

In addition, our forensic experts have more than a decade of experience working with the pharmaceutical industry to support non-conformance investigations of foreign particulate matter and product investigations of drug delivery devices.

The focus of our consulting services is to supply Quality by Design (QbD) guidance and patent infringement support, while assisting with novel characterization methods that facilitate intellectual property development.

Q: ***What are some of the key drug delivery strengths that your services offer?***

A: Our scientific approach has several key strengths that increase the quality and efficiency of results for our clients. Areas such as particle sizing and polymorphism affect a formulation's bioavailability, directly influencing the activity of the drug. The pairing of basic testing methods with novel techniques, as well as our expertise in this area, is an integral component to the drug delivery process. This combination of chemical imaging technology with more basic testing methodologies, such as optical microscopy, scanning electron microscopy, and routine USP methodologies, has proven to be a reinforcement to scientific data, adding greater confidence to results.

Gateway Analytical cGMP testing services focus in several drug delivery areas. Orally Inhaled and Nasal Drug Products (OINDPs) have become a focal point of analytical testing due to the inherent strengths of chemical imaging in this specific area. OINDPs face significant scrutiny in all aspects of the drug development lifecycle, including materials used, environmental conditions, and processes in which they are developed and used. Our testing capabilities address these issues relative to nasal spray suspensions, aerosol products,

metered-dose inhalers, and dry powder inhalers.

There are many benefits to using a multi-analytical approach to drug delivery services. Take particle sizing, for example. Routine particle sizing analysis is a necessary step in the testing process, but often lacks the specificity needed for meaningful evaluation of the data. Our multi-analytical approach to sample interrogation provides our clients not only with the baseline data required in the industry, but also yields information that aids in the decision-making process throughout each phase of drug development.

Another key service strength deals with contaminants in drug products. Often, trace contaminants or crystallization forms occur and must be investigated. Understanding if a contaminant originated from the process environment, packaging, or chemical interactions in the sample is critical. Our integrated approach to problem-solving supplies a platform to identify these issues and expand investigations into more complex areas. Overall, our cGMP-compliant laboratory capabilities and expertise in evaluating challenging samples can give drug developers the information they need to expedite a product's time to market.

Q: ***You touched on Gateway's QbD and cGMP expertise, but how important is it to have quality control procedures in place?***

A: Quality control procedures should be viewed as one of the most important aspects of evaluating a contract laboratory, as the lab acts as an extension of the customer and should be held to the same standard. Demonstrating that analytical data and test procedures are consistent, reliable, and accurate should be the core of a contract laboratory's quality system. Inadequate quality oversight and management can lead to inaccurate measurements causing product recalls, harmful contaminants entering the environment, and trace impurities in the drug product, which can be harmful to a person's health.

With that said, Gateway takes great care to ensure the reporting reliability and production of accurate data within our laboratory quality system. In addition, our qualification and validation of processes and instrumentation are designed to not only meet the expectations of auditing bodies and customers, but to exceed them.

Q: ***There are a number of CROs out there today. Describe what makes Gateway Analytical unique.***

A: At Gateway Analytical, our commitment to providing outstanding customer service is what sets us apart. Our approach to client interaction and service is simple - we provide customizable, cutting-edge solutions that utilize a mixture of basic and novel analytical testing techniques. In that sense, we take a forensic approach to analytical testing and create an environment in which the customer is integrated into the entire analytical testing process.

Our staff is another differentiator in the marketplace. We provide more than just testing results - we provide our expertise. With extensive knowledge of multiple testing methods spanning different industries, as well as current regulatory standards, our scientists are best positioned to advise developers on how to achieve optimal solutions. In addition, they have a great deal of experience working directly with pharmaceutical companies on their most challenging problems, as well as assisting in the development of novel methodologies such as chemical imaging.

Q: ***How does Gateway Analytical work with drug developers?***

A: Gateway Analytical works with pharmaceutical companies in several aspects of the drug development process. First and foremost, drug developers rely on scientific experts to provide high-quality analytical data and guidance on the methodologies used to expand on the information received from existing test data. To that end, the information provided by Gateway Analytical experts can help drug developers gauge the deliverable drug load, respirable fraction, and the overall quality of the drug product. In some cases, we can provide testing methodologies to better understand foreign particulate and contamination issues. Whether Gateway Analytical is administering nondestructive testing services on a controlled release bead's ingredient blend uniformity or providing support in the creation of a (QbD) drug formulation program, Gateway strives to be a part of the drug developer's overall success.

Q: ***What are some of the challenges pharmaceutical developers face? How do you help to address them?***

A: Generally, pharmaceutical developers find it challenging to locate fast, efficient, analytical testing methods that provide a clear result. Many testing methodologies are non-specific to a drug's API and excipient components in the final product. For example, test methods exist for the sizing of particles in an aerosolized nasal spray, but the specificity of each component is not defendable. In such cases, Gateway Analytical utilizes novel characterization methods like chemical imaging to discriminate between API particles and those of an excipient or a surfactant. In more extreme cases, trace contaminants can also contribute to making interpretation more difficult. To help reduce any issues that may arise during the drug development process, we combine step-by-step analytical protocols to characterize materials, adding other analytical methods to identify foreign particulates. ■

Oncolytic Viruses: The Future of Cancer Therapy?

By: Douglas W. Loe, Ph.D, MBA

Introduction

Chemotherapy, as any cancer patient will tell you, is not for the faint of heart, but it can kill many forms of cancer. Some form of chemotherapy, originally discovered as a cancer treatment almost 70 years ago, is still routinely prescribed for most types of the disease. The treatment works by targeting fast-growing cells, like those typically found in rapidly growing tumors. But while chemotherapy can shrink tumors, they often grow back and become resistant, or refractory to the treatment.

To combat this resistance, chemotherapy is now often used in combination with other treatments that have different mechanisms for attacking and killing cancer cells. Doctors must be cautious when combining treatments to ensure the regimen does not become too toxic for patients to tolerate. The goal is to introduce drugs that can be used synergistically with chemotherapy to not only extend life, but improve quality of life while undergoing treatment.

The Potential of Oncolytic Viruses

One approach that has proven quite promising is known as oncolytic virotherapeutics. Here, viruses are harnessed to infect, multiply within, and subsequently lyse cancer cells; the virus targets tumors without affecting normal tissue.

Several types of oncolytic viruses have been developed to date. These include the adenovirus, which is a non-enveloped virus with a double-stranded, linear DNA genome that forms particles that are 70 to 90 nm in size. There are multiple engineered versions of this virus in clinical trials, including Onyx-015 and H101. The latter has been approved in China and is sold by Shanghai Sunway Biotech.

A second form of oncolytic virus is Newcastle disease virus (NDV). This is an enveloped virus with a single-stranded, negative-sense RNA genome that forms pleiomorphic particles ranging from 150 to 300 nm. Naturally attenuated versions, such as PV701, are in clinical development. Although still in Phase I testing, slow virus infusion rather than injection seems to mitigate side effects. The Maryland-based private firm Wellstate Biologics has two Phase I open-label PV701 cancer trials ongoing.

Poxviruses are a family of enveloped viruses that contain a double-stranded, linear DNA genome and form particles that are 200 nm in diameter and 300 nm in length. Myxoma and vaccinia are family members that are under therapeutic development. Among several candidates, the most advanced is probably Jennerex's JX-594, which is entering a Phase II liver cancer trial.

It may come as a surprise to some that the herpes simplex virus is also under consideration as an oncolytic virus. This is an enveloped virus with a double-stranded, linear DNA genome that forms particles that are 150 to 200 nm. Many engineered versions are in clinical trials for the treatment of patients with cancer, such as OncoVEXGM-CSF, G207, HSV-1716, and NV1020. The most advanced

of these is OncoVEXGM-CSF, a combination of the oncolytic virus OncoVEX plus granulocyte macrophage-colony stimulating factor (GM-CSF) developed by the Massachusetts-based private firm BioVex; the combination is already well-advanced in a 360-patient Phase III advanced melanoma trial and a Phase III head and neck cancer trial design has been endorsed by the US FDA under a Special Protocol Assessment and should begin this year. G207 was developed by the German firm Medigene, which recently completed a Phase II brain cancer trial. Medigene is also developing NV1020, which is in a Phase II liver metastasis colon cancer trial. UK-based Crusade Laboratories tested HSV-1716 in a Phase I oral cancer trial; a Phase III GBM trial is being planned as are Phase I/II ovarian cancer and liver cancer trials.

Picornaviruses are a family of non-enveloped viruses with single-stranded, positive-sense RNA genomes that form particles that range from 18 to 30 nm. Members of this family that are being tested as oncolytic therapeutics include coxsackieviruses and engineered versions of poliovirus. The latter is in development at a few locations, including research institutes at Duke University and Stony Brook University, and has shown some preclinical efficacy against GBM and neuroblastoma. The firm Viralytics is developing the coxsackievirus A21 in a Phase I advanced melanoma study.

Vesicular stomatitis virus (VSV) is an enveloped virus with a single-stranded, negative-sense RNA that forms 65 to 185 nm bullet-shaped particles. This virus is still in the research stage; two constructs have recently been tested at the Mt. Sinai School of Medicine in New York.

Reoviruses: The Most Promising Option?

Finally, we come to what some consider the most promising form of oncolytic virus: the reovirus. This is a non-enveloped virus with a double-stranded, segmented RNA genome that forms particles that are 60 to 90 nm. The reovirus preferentially replicates in cancer cells that feature a common mutation known as an "activated Ras pathway," while sparing normal cells. This makes it intrinsically tumor selective without the need for any genetic manipulation.

Reovirus is a virus with no known associated disease. It replicates in the cytoplasm and therefore does not integrate into the cell's DNA. Reovirus is found everywhere in nature and has been isolated from untreated sewage, river, and stagnant waters. Exposure to reovirus is common in humans, with half of all children by the age of 12 having been exposed, and up to 100% testing positive by adulthood.

Tumors bearing an activated Ras pathway cannot activate the anti-viral response mediated by the host cellular protein, PKR. Studies have shown that reovirus actively replicates in transformed cell lines with an active Ras signaling pathway, eventually killing the host cell and freeing the viral progeny that go on to infect and kill more Ras-activated tumor cells. When normal cells are infected with reovirus, the immune system can neutralize the virus. Approximately one-third of human cancers have activating mutations in the Ras gene itself, and it is possible that more than two-thirds of cancer cells have an activated Ras-signaling pathway because of activating mutations in genes upstream or downstream of Ras.

How Reoviruses Might Help

While it has been demonstrated in animal studies that reovirus is capable of treating metastatic cancer in immunocompetent mice, it has also been shown that reovirus used in conjunction with immuno-suppressive drugs can effectively prolong animal survival. Combining IV reovirus therapy with Cyclosporine A, an immune suppressant, significantly inhibited tumor regrowth. In a model of disseminated LLC metastatic lung cancer in C57BL mice, treatment with reovirus and either Cyclosporine A or T cell depleting antibodies (anti-CD4 and anti-CD8 Ab) led to an increase in survival compared to treatment with reovirus alone.

The aforementioned results supported the development of clinical protocols in which immune-suppressive drugs could be combined with a systemically administered reovirus in the treatment of cancer. The combination of reovirus with various chemotherapies in human colorectal cancer cell lines demonstrated synergistic cytotoxic activity. In addition to modulating the immune response, the use of chemotherapies along with

reovirus treatment may enhance intratumoral spread of the virus.

Calgary-based Oncolytics Biotech Inc. has developed a biologic agent, Reolysin, from naturally occurring reovirus. The virus has demonstrated impressive results in clinical trials on its own, but particularly in combination with certain chemotherapeutics. In preclinical studies in a wide variety of cancer cell lines, investigators found that when used together, reovirus and chemotherapy resulted in more efficient and synergistic anti-cancer activity than when each agent was used on its own.

Summary

These combinations are showing extremely good results in human trials, particularly in refractory head and neck cancer patients. Many head and neck cancer patients treated with a combination of Reolysin and chemotherapy to date have experienced significant and prolonged tumor shrinkage, without increasing adverse side effects. Non-small cell lung cancer (NSCLC) is another potential target for this treatment combination. The Cancer Therapy & Research Center at the University of Texas Health Science Center - a big proponent of oncolytic viruses - has committed to funding up to five Phase II clinical trials using Reolysin in combination with chemotherapy against a variety of advanced cancers.

It is difficult to provide a crystal clear economic forecast for oncolytic viruses as a whole, but an indicator of their potential future sales earnings can be derived from examining two recently launched anti-cancer therapies already on the market. One of these is Tarceva, developed by OSI Pharmaceuticals and launched in 2004. An oral small molecule tyrosine kinase inhibitor drug that is prescribed for patients with advanced stage non-small cell lung cancer, it earned $20 million in 2004, $387 million in 2005, and $813 million in 2006. Sales reached $1.215 billion in 2008. Another is the immuno-modulatory and anti-angiogenic drug Thalomid, developed by Celgene and launched in 2003 for treating multiple myeloma, which enjoyed sales of $224 million that first year and reached $505 million by 2008. And a third is Revlimid, a drug structurally related to Thalomid that generated even more robust sales growth after its launch in 2006, achieving blockbuster sales in 2008 of $1.3 billion that grew to $1.7 billion last year. The year-over-year, steadily increasing demand for these two drugs provides supporting evidence that demand for new and effective agents in oncology remains strong, giving us confidence that Reolysin could be similarly embraced if it performs well in Phase III testing.

There are a number of oncolytic viruses that have shown potential use in cancer treatment, and demand for more effective agents is strong. Future research studies will give us an even clearer perspective on which, if any, of these viruses offer the most effective route toward a reliable and commercially viable complement to chemotherapy for oncologists and their patients. ◆

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Do Not Burrow Down Into Obscurity!

By: Dan Marino, MSc

"A man who stops advertising to save money is like a man who stops the clock to save time." As a business-to-business publishing professional for most of my career, this quote by the great entrepreneur Henry Ford seems to say it all. I know it can be difficult, especially in these economic times, but advertising efforts in any form should never be shelved entirely. I am not saying companies should not review and reallocate marketing dollars or practice fiduciary responsibility, I am simply saying do not burrow down into obscurity!

Let me tell you a true story. I was working for a Medical Education company in the late 90s, and my department was working on an exciting and innovative technology that would change the way we were currently executing some of our initiatives. Times were good for the company. We were a boutique agency, and there was plenty of work for us that the big guys just didn't find worth their while. My team spent a lot of time, money, and effort making sure this new offering would not over-promise and under-deliver. We were going to compete with the big guys. After 12 long months, we finally achieved all of our goals and objectives. Raises and bonuses for everyone, right? Wrong!

Although we had done everything right (evaluating market potential, needs assessment, perfecting the technology, focus groups for end-users, etc.), something was missing. Remember, I said earlier this was a boutique agency, which by definition means limited resources. The company still had its current day-to-day operations to execute, and all of the associated manpower and finances that went along with it were finely tuned and allocated. My team was told not too long after we lit our celebratory cigars that there wasn't a significant amount of money left for marketing. In fact, there was no money left for advertising. Now what?

We did what any other type of business does in our situation. We relied 100% on our business development employee to magically create awareness and sell our new technology to all of the potential clients in our industry. I cannot believe to this day she was not able to call 3000 people and tell them all about our masterpiece to secure my raise and bonus! She did make some sales, and the future looked pretty good. However, a few other agencies were doing the same exact thing. How did we know this? They were marketing it all over the place. I also cannot believe someone else had the same idea we had!

Sales at the company for the new initiative remained respectable for a year, but not too long afterward, our business development professional was looking for a new job. Companies came out of the woodwork offering the same, and we never made a statement with our presence. We were a boutique agency, and it was extremely obvious to our clients.

Looking back, the President of the company actually admitted that with some very careful planning, he did have the ability to roll out a progressive marketing initiative that increased with our projected sales. However, he wanted to save money and was not willing to risk the investment. That's his right, after all, it was his company. I don't blame him, we were people who educated physicians, not marketing professionals.

All of our readers out there are made up of people working on new services and technologies and people looking for new services and technologies. Times are tough right now I understand, but they will not be tough forever. Get out there and generate awareness. Your clients may not need you today or next week, but they may need you next month. And where will you be when they do? In their face? Or burrowed down in obscurity? ◆

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