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Newsletter

A publication of the Controlled Release Society



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From the Editor

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As is the norm, this issue of the newsletter has a wealth of information relating to the upcoming Annual Meeting, and once you have seen what is on offer you should not require any additional encouragement to make the journey to National Harbor. By all accounts, this 38th meeting is likely to be of great value from a scientific, regulatory, business, workshop, and networking perspective. Plan your travel dates now to hear eminent speakers such as Gordon Amidon, Henry Brem, Adam Heller, Gordon Muirhead, and Walt Orenstein talk about their research in drug delivery science. Attend a pre-conference workshop in which unmet medical needs are being discussed, and be inspired at Innovation Sunday. Time is running out for early registration for the meeting, and if the scientific and social program details are anything to go by, this meeting will be best one yet.

This newsletter is packed with interesting scientific articles and a fascinating interview with Steven Giannos, the Industrial Editor of the CRS Newsletter, in which he shares some of his wisdom in establishing an active career in various industries associated with drug delivery. In addition, you can learn about nanoencapsulation, the use of phospholipids for the screening of oral drug candidates, and the use of cyclodextrins in improving an anaesthetic formulation. You can also catch up with the Consumer & Diversified Products arena and the industry news in this edition.

The report on the 4th Annual Meeting of the AUS-CRS chapter in the Chapter News section is a clear indication that the global village of the CRS is alive and well and that, if necessary, local chapters can provide a useful platform for young scientists to gain insight from prominent researchers in the field. There is also a report on the 14th Industrial Symposium and 5th Trade Fair on Microencapsulation, which was the first time the CRS, the Bio-Encapsulation Research Group, and the Southwest Research Institute collaborated on a project. It seems this workshop was a great success and may provide a framework for other collaborative and focused or niche workshops in the future.

Voting for various positions in the CRS has already commenced and I urge you to make your voice heard by ensuring you have paid your annual membership and by voting for candidates to fill the positions that are vacant. One of the key positions under consideration is that of CRS Vice-President, so make your mark and ensure the future of the society is in good hands. Also be on the lookout for information relating to the governance and bylaws of the CRS so that you too can have a say in how we make our society stronger.

Finally, I would like for all of us to take a few moments to reflect on the recent natural disasters that have occurred around the world and specifically in New Zealand, Japan, Australia, Brazil, South Africa, and earlier this week, the USA. Nature is wonderful, powerful, and also devastating. Remember that nature created the bodies we are trying to find cures for. We are going to have to be innovative and think out of the box to be able to find the treatment and cures to overcome the myriad of conditions that may be thrown at us. Finally, we should all take time to wish those in the affected areas the strength and courage to overcome the disasters that have hit them.

Travel safely, be well, and see you in Maryland.



Mark A. Tracy Alnylam Inc. Cambridge, MA, U.S.A.

We are in an exciting time for CRS. Our annual meeting is fast approaching. The CRS election has just been held. Also, I am happy to announce that new, amended bylaws have been approved by the Board of Directors and will be sent to CRS members in a few weeks for approval. Please read the rest of this column for more information on each of these points.

Before you know it, July will be upon us and it will be time for us all to gather together in National Harbor, Maryland (just outside of Washington, D.C.), one of my favorite areas, for the 2011 Annual Meeting and Exposition of the CRS. I want to personally invite each and every one of you to join me for what will be a must-attend event for the latest advances in delivery science and technology. Plan to attend and get your best dose of delivery science all year!

I am particularly excited about this meeting. Let me tell you why.

- 1. The strength of the scientific program. The core objective of the meeting is to bring you the latest delivery science. I have taken a peek at the draft program book. So I can say we will more than accomplish that objective for you at the 2011 Annual Meeting thanks to program chairs Jamileh Lakkis, Marilyn Martinez, Ramesh Panchagnula, Mark Prausnitz, Dody Reimer, Arzu Selen, Ron Versic, CRS staff members Leah Barna and Linda Schmitt, and Scientific Secretary Ijeoma Uchegbu. No meeting offers the breadth and depth of delivery science like the CRS Annual Meeting. This year we have sessions on our core areas of new materials, novel delivery formulations and technologies, routes of delivery, and delivery of different types of actives. In addition, we have focused on unmet clinical needs in cancer and the CNS and emerging areas of delivery science including intracellular delivery, regenerative medicine, and low cost delivery solutions. We will also have programs specifically for our young scientists. We are very fortunate to have a distinguished group of plenary speakers including two CRS Fellows and distinguished leaders from the pharmaceutical industry and global health field. Check out the latest meeting information on our website.
- 2. The strength of our product development, regulatory science, and industry-oriented program. This has been one of the priority areas for us this year: to take advantage of our meeting location close to the FDA and other key governmental and industrial labs in the Baltimore-Washington, DC area and along the east coast of North America. We have two different workshops offered this year on translational development and regulatory issues, one on delivery to the CNS and one on delivery of nanoparticle agents. As a part of CRS Innovation Sunday, we will also hold our first Nanomedicine Product Development Summit, which is a series of panel discussions on issues and paths

forward to turn nanoparticle delivery systems into novel medicines. This will be a special opportunity to learn from and engage leaders in a dialog on the development of these products. An important regulatory science mini-symposium is planned to discuss quality-by-design as applied to pediatric drug development. Thought-leaders are coming together through this symposium to develop a guidance document in this important area. A session on regulations for microencapsulated products is also planned. Make sure you plan to come to the meeting early to attend these events, many of which fall on Saturday and Sunday, July 30 and 31.

- **3. Special opportunities to establish new collaborations and partnerships in delivery.** Building on the success of last year's CRS Innovation Sunday activities, we are again planning the traditional Soapbox Sessions and Releasing Technology Workshops, a panel discussion on the Business of Delivery and CRS Partnering, and, of course, the CRS Exposition Opening and Welcome Reception to help you make the connections you need to advance your delivery technologies.
- **4. Building a dialog around public policy issues relating to delivery science and technology at CRS meetings.** We are holding a session in collaboration with the American Institute for Medical and Biological Engineering (AIMBE) to discuss bottlenecks in translational research and for FDA-approved products.
- **5.** Rich networking and social opportunities to meet colleagues, build relationships, and have fun. Encouraging networking is another priority of our meetings. Personally, many relationships I established at the Annual Party and other networking and social events over the years have been invaluable to me. Many of my CRS colleagues have become close friends. To this end, we are planning the Welcome Reception as well as our second annual Women in Science Luncheon, the Young Scientists Networking Event, the First Timers Meeting, the Vet Get-Together, and also (of course), the Annual Party. This year the Annual Party will be a "Party with a Purpose" fundraiser for the first time – for students in delivery science. It will be so much fun, so plan to be there.

All of this is just minutes from some of the United States' iconic symbols like the White House and the Capitol, historic sites like Mount Vernon and Old Town Alexandria, and world class museums including the Smithsonian museums. So register now and make your travel plans to be at the Gaylord Hotel from July 30–August 3, 2011. Make sure to catch the workshops and Innovation Sunday activities on July 30–31. Also add a few days to your trip to enjoy the Washington, DC area. I look forward to seeing you at the meeting and welcoming you at our new Opening Session.

Interview with Steven A. Giannos—Industrial Editor; CRS Newsletter The Man Behind "In the News"

Brian Kilfoyle and Bozena Michniak-Kohn, Ph.D. Ernest Mario School of Pharmacy, Rutgers-The State University of New Jersey, Piscataway, NJ, U.S.A.



Steven Giannos is a senior executive with expertise in developing noninvasive and pulsatile drug delivery technologies, transdermal drug permeation technologies, peptide and protein delivery technologies, and chronotherapeutics. He is currently at Chrono Therapeutics Inc. in Trenton, NJ where he has served as the Vice President of New Product Development (2006–Present) and as the

Director of New Product Development (2004-2006). Chrono Therapeutics is a start-up company developing the ChronoDose[™] system: a pulsatile, transdermal, drug delivery device, which can be pre-programmed to administer drug doses automatically, at different times of the day, and with varying dose sizes. Throughout his long and distinguished career, Steven has worked at numerous additional prominent pharmaceutical and medical device companies including: Sontra Medical Corp. (now Echo Therapeutics, Inc.) in Cambridge, MA (1999-2003) where he assisted in the development of an ultrasound-based skin permeation device; Lavipharm Laboratories in Piscataway, NJ (1998–1999); Novartis (formerly Ciba-Geigy) in Ardsley, NY and Suffern, NY (1992–1998); University of Lowell in Lowell, MA (1988–1991); Wyeth (formerly Genetics Institute) in Andover, MA (1991); the US Army Natick R&D and Engineering Center in Natick, MA (1989–1991); Massachusetts Institute of Technology in Cambridge, MA (1986-1990); Boston Scientific (formerly Microvasive, Inc.) in Milford, MA (1985–1986); Haskon Corp. in Tauton, MA (1985); Interplas Ltd., Consulting Engineering in Franklin, MA (1985); and U.S.C. INDUSTRIES, Custom Molders in Shawnee, KS (1983-1984).

Steven has his masters in both business and chemistry, receiving his MS in Business with a concentration in Organization & Management from Capella University in Minneapolis, MN and his MS in Chemistry with a Polymer Science concentration from UMass Lowell in Lowell, MA. He received his BS in Biology and his BSET in Plastics Engineering Technology from Pittsburg State University in Pittsburg, KS and was a pharmacy student at the University of Kansas School of Pharmacy in Lawrence, KS.

Steven has been awarded patents on Biosynchronous Transdermal Drug Delivery (US Patent 7,780,981), Temporally Controlled Drug Delivery Systems (US Patent 6,068,853; WO Patent 9528144), Pure Polyanhydride from Dicarboxylic Acid & Coupling Agent (US Patent 4,916,204), One Step Preparation of Poly (Amide-Anhydride) (US Patent 4,933,431), and has additional patents pending. He has given numerous invited presentations and has written many peer reviewed manuscripts, book chapters, and invited review articles.

Steven is very active in professional societies. He has been a member of the American Association of Pharmaceutical Scientists (AAPS) since 1999, serving on numerous committees and as the Chair (2010–2012), Chair Elect (2008–2010), and Steering Committee Member of the Dermatopharmaceutics Focus group. He has been a member of the American Chemical Society (ACS) since 1987 and was a member of the Society of Plastics Engineers (SPE) in the Medical Plastics Division from 1982–2000. Steven has been a member of the Controlled Release Society since 1995, serving as a mentor in the CRS Young Scientists Mentorship Program (2008–Present) and as the Industrial Editor of the CRS Newsletter (2004–Present). We would like to thank Steven Giannos for sitting down with us for this interview and for his continued work as an editor for the CRS Newsletter.

Q. How long have you been an editor for the Newsletter?

A. I joined the Newsletter in early 2004, after having responded to an email by the Newsletter Staff, requesting applications for an Industrial Editor. I had considered becoming more involved in the CRS organization for some time and this seemed to be an excellent opportunity.

Q. What is your background?

A. My background is a unique and non-traditional mix of education, job experience and on-the-job training. Additionally, I have had to change my career directions several times in response to business and economic changes that have occurred over the last 30 years.

Q. How has your background in biology, chemistry, and plastics engineering technology led you to a career in controlled release and drug delivery systems?

A. At first my interest lay in anatomy and physiology, which I followed with the intention of pursuing a medical career. Several of my family members were physicians, as well, and served as role models.

With that in mind, I was able to take a new high school course in health careers. This course included 6-week rotations in ER, pharmacy, eye clinic, inhalation therapy, ENT clinic, and surgery at the University of Kansas Medical Center. This was a wonderful learning experience, while at the same time exposing me to life and death and what it means to be a caring doctor.

In college, I studied pre-med, and then changed to pharmacy in 1978–79 at the University of Kansas School of Pharmacy. As a first year pharmacy student, the emphasis was on retail pharmacy, not pharmaceutics. Controlled release drug delivery was still relatively new at that time and was not widely known or taught.

It was in June of 1980 when I first learned of the new field of medical plastics, i.e., implants, artificial organs, and medical devices. I was studying biology at a small school in Kansas, Pittsburg State University, and searching for a direction in my studies. My sister was studying plastics engineering technology. During that summer, I happened to read a Society of Plastics Engineers (SPE) newsletter she had received, announcing the newly formed Medical Plastics Section. I thought that this might be an ideal direction to pursue since I was beginning to get interested in biomaterials, implants, artificial organs, etc.

A letter of inquiry I wrote to the Society of Plastics Engineers (SPE) was forwarded to the section president, Mr. Harold Leeper, a Senior Engineer at ALZA Corp. and co-inventor of the Ocusert. From that contact I learned about the emerging field of controlled release drug delivery. He also suggested that I call Dr. Takeru Higuchi, which I did.

Many people at that time were entering the medical device field from all types of disciplines; mechanical engineering, chemical engineering, the plastics and rubber industries, and pharmaceuticals. Mr. Leeper even forwarded a paper by Dr. Nicholas Peppas (1980) attesting to the fact that there was a lack of structure for the education of drug delivery and controlled release scientists and therefore indicated a need for educational programming at universities.

I decided to continue in school and complete the BS in biology and the BSET in Plastics Engineering Technology. Less than two years later (1982), I took out a student loan to attend a seminar in Boston—one in which Professor Robert Langer of MIT spoke. Four years later, I was hired as a technical assistant in Professor Langer's laboratory at MIT due, in part, to attending that seminar. Over 25 years later, I'm still involved in drug delivery and pharmaceutics.

Q. Why did you decide to pursue a career in industry as opposed to academia?

A. It was common, at that time, to look forward to joining a company and working your way up the ladder. And, unfortunately at that time, I was not familiar with academic career tracks. There was no Internet, no email, no LinkedIn,

and few mentors available. Additionally, professional societies, like the CRS and the AAPS, were nonexistent then or were still small and growing.

Advice from Mr. Leeper, Dr. Higuchi, and others in 1980 suggested that I follow the course that I was pursuing. In 1980, a Ph.D. was not required for entry-level jobs in medical or drug delivery devices.

After eight years as an undergraduate, I needed to graduate, get a job, get experience, and repay student loans. I did receive a nice letter from Mr. Leeper and ALZA, saying that they would like to meet me, however they did not relocate entry-level candidates. Palo Alto, CA is a long way from Kansas City, MO and I didn't want to risk moving 1,500 miles without a job offer. The economy in 1983 was very similar to what it is today and I faced the same challenges that new graduates face now. I really empathize with today's young scientists as they seek out career opportunities and face the challenges of the current economic landscape.

Q. How has your unique background assisted you in your career?

A. In 28 years, I've gained experience developing and manufacturing consumer products, medical devices, biodegradable polymers, and controlled release systems. Traditionally, medical devices and pharmaceuticals are developed along two separate tracks with their own respective FDA regulatory pathways. However, the current trend seems to be directed towards the development of combination devices along with revised guidelines for the product development and regulatory pathways for combination drug delivery devices.

Each job along the way gave me hands-on experience, so that now, I have an understanding of the entire process from invention disclosure to clinical trials. Additionally, I have always had a QbD perspective—having a pragmatic approach to scientific research, patient centered design, application of commodity materials, and common manufacturing methods.

Q. You are currently the Vice President of New Product Development at Chrono Therapeutics. How did you get to this position?

A. While at Sontra Medical, I decided to invest in a business degree in order to round out my background. For each course, I used the concept of a pulsatile transdermal product, combined with a fictitious company. I then prepared a marketing plan, a business plan, and a full investment presentation for the entrepreneurship course. I also entered and presented at the Worcester Polytechnic Institute (WPI) Venture Forum Business Plan Contest, May 2004.

This additional degree allowed me to join Chrono Therapeutics as Director of New Product Development.

Interview with Steven A. Giannos continued from page 5

Additional work on IP, along with quick, inexpensive, and successful *in vitro* results, led to my promotion to VP of New Product Development.

Q. Our last interview was with Dr. Ron Siegel. You and Dr. Siegel share some common research interests and yet focus on different aspects. Would you please elaborate?

A. After finishing my Masters degree in the later part of 1991, I was hired by Drs. Bret Berner and Steven Dinh at Ciba-Geigy Pharmaceuticals to work on a new project called "Temporally controlled drug delivery systems." Temporally controlled drug delivery systems coupled pH oscillators with membrane diffusion in order to generate a periodic release of a drug or active ingredient transdermally, without external power sources and/or electronic controllers. The intent was to address chronotherapy (nicotine or melatonin) with a pulsatile transdermal system. The strategy was based on the observation that a drug may be rendered charged or uncharged relative to its pKa value. Since only the uncharged form of a drug can permeate across lipophilic membranes, including the skin, a periodic delivery profile may be obtained by oscillating the pH of the drug solution.

Giannos, SA, Dinh, SM, Berner, B. Temporally controlled drug delivery systems: Coupling of pH oscillators with membrane diffusion, J. Pharm. Sci. 84: 539-543 (1995).

At the same time, Drs. Ron Siegel and Colin Pitt introduced a general scheme and simplified theory for open loop, sustained oscillatory drug release that does not require periodic external activation. The strategy was inspired by chemical oscillations and biochemical reactions such as the Belousov-Zhabotinsky (BZ) reaction and the Peroxidase-Oxidase oscillator.

Siegel, RA, Pitt, CG. A strategy for oscillatory drug release: General scheme and simplified theory, J. Cont. Rel. 33: 173-188 (1995).

We both investigated the pH oscillator systems and discussed our findings while meeting at the Gordon Research Conference on Oscillations & Dynamic Instabilities in Chemical Systems in 1997 and 2000 and when we met at the CRS annual meetings. Dr. Siegel has continued his research of chemical oscillators and their application to the development of responsive gels and pulsatile gel systems for glucose sensing and insulin release.

I have become much more interested in the development of pulsatile drug delivery and biosynchronous transdermal drug delivery systems for a wide range of chronotherapy. This is due, in a large part, to my work on the temporally controlled drug delivery systems and the ChronoDose[™] system.

I think future trends in personalized medicine will be the coupling of genomic diagnostics with biosynchronous drug delivery. Even though circadian rhythms have been known for 250 years, and scientifically investigated for 60 years, only

in the past 10 years has the anatomy, physiology, and the cell biology of chronobiology been revealed. I recently attended the University of California, San Diego's Center for Chronobiology 2nd annual symposium and learned more about the biology and physiology behind circadian rhythms. Other activities that I am involved with include moderating the Chronotherapy and Chronobiology networking group on LinkedIn and organizing and moderating the "Chronopharmaceutics: Optimizing Efficacy and Compliance with Alternative Dosage Forms and Modified Release" roundtable session at this years AAPS Annual Meeting.

Q. What do you regard as the most significant achievement(s) of your scientific career thus far?

A. So far, my most significant achievements have been successfully completing, publishing, and patenting two separate passive, pulsatile transdermal drug delivery systems. The first was using the pH oscillators as the internal timing mechanism. The second was achieving 3 dosings; 1 every 8 hrs over 24 hrs with the ChronoDose[™] system.

Although these have been significant achievements, I have also worked in the very early stages of several important projects such as the polyanhydrides for Gliadel[®], transdermal parathyroid peptide, transdermal camptothecin, transdermal Exelon[®], transdermal oxybutynin, and the Prelude[™] SkinPrep for skin permeation.

Q. Why is the skin such a difficult yet enticing portal for drug delivery?

A. The skin is a magnificent organ and barrier membrane. It protects us from the outside environment as well as regulating water and heat transfer. It also receives external stimuli from the environment and excretes various substances. The barrier properties of skin are most attributable to its outermost layer, the stratum corneum. The stratum corneum is effectively a 10- to 20-μm thick matrix of dehydrated, dead keratinocytes (corneocytes) embedded in a lipid matrix.

Traditionally, the most common form of drug delivery has been the oral route. While pills and tablets have the notable advantage of easy administration, they also have significant disadvantages such as poor bioavailability, due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low). Also, variations due to individual differences or food intake are additional concerns. This can lead to the need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient.

Over the past 30 years, more than 35 transdermal patch products have been approved in the U.S. and prescriptions for transdermal products have been used by approximately 12 million people worldwide for ailments ranging from bladder control to heart disease. Transdermal drug delivery systems and topical pharmaceuticals have increasingly offered key advantages over the oral route, and transdermal patches have been useful in developing new applications for existing therapeutics and for reducing first-pass drug-degradation and metabolism effects.

Q. What is it about the skin and transdermal/topical drug delivery that has captivated your attention for so long?

A. I actually became interested in pulsatile drug delivery due to a conversation with one of the post-docs at Langer Labs in 1987. It seemed to me that making a device with layers like an onion using polyanhydrides and other biodegradable polymers, having varying degradation rates, would be ideal.

Then, I joined the Basic Pharmaceutical Research Group at Ciba-Geigy and learned about transdermals. It became apparent to me that pulsatile and biosynchronous drug delivery would need to be accomplished externally in order to avoid the disadvantages from oral delivery that we just talked about. Of course, there are also limitations to transdermal delivery, but less so when the limitations such as lag period, drug half-life, PK/PD, etc. are actually taken into account and included into the design of the device. The device can also stop the delivery of the drug, or be easily removed, which an oral medication or implant cannot. Additionally, an external device is more patient-friendly and automated drug delivery should improve patient compliance, personalized medicine, and quality of life.

Q. What is the future of transdermal drug delivery? Will it begin to gain a larger share in the drug delivery market?

A. In 1997, the transdermal and topical pharmaceutical manufacturers began to align with the life science and biopharmaceutical industries to deliver large molecules, peptides, proteins, and vaccines as well as bolus dosing and on-demand dosing. And even though transdermal systems have many advantages, traditional drug-in-adhesive matrix and reservoir transdermal systems are limited by the skin barrier properties.

Since 1995, the emphasis has been to develop permeation enhancement techniques, such as abradement, electrical, mechanical, chemical, thermal, microneedles, micro-injectors, and nanotechnologies. I think ultimately, topical and transdermal drug delivery products will gain market share when they start working together and in collaboration with pharmaceutical companies. The cost for clinical trials is just too large and neither one alone can undertake such a long and expensive clinical and regulatory pathway.

Transdermals will be more effective in combination products in the sense that the transdermal device will be a combination of a permeation enhancement technology with a large drug compound or biomolecule. Skin pre-treatment is another option. Topicals will be a cream, lotion, or spray combined with a drug and nanotechnology permeation enhancers.

The most promising area is in personalized medicine. Pulsatile and biosynchronous transdermal delivery will be a useful technology. Chrono Therapeutics is developing the ChronoDose[™] system: a pulsatile, transdermal drug delivery device, which can be pre-programmed to administer drug doses automatically, at different times of the day, and with varying dose sizes. I think other improvements in skin permeation enhancement techniques such as abradement, electrical, mechanical, chemical, thermal, microneedles, micro-injectors, and nanotechnologies will also advance.

Q. Which scientists have played an important role in your scientific development?

A. Mainly I have become familiar with leading scientists through their research, publications and meeting them at conferences. Over the past 30 years, I've attended conferences and met people through CRS, AAPS, SPE, ACS, Gordon Conferences, etc. I've been fortunate to meet the CRS founders as well as leaders in chemical oscillations, chronobiology and chronotherapy, biodegradable polymers, medical devices, etc.

I've mentioned Mr. Harold Leeper. He originally was in the rubber industry and then went to ALZA. We corresponded by letter from 1980–83 and then I met him at a conference in Chicago in 1984. Then there are the people from Langer Labs 1986–1990: Robert Langer, Avi Domb, Eyal Ron, Edith Mathiowitz, Janet Tamada, and many more. While at Ciba, Bret Berner, Steven Dinh, and Ann Comfort gave me the time and freedom to develop the pH oscillators. Additionally, Dr. Prof. Vilmos Gaspar at the University of Debrecen gave me inspiration and support while working with the chemical oscillators.

I'd have to say that my major inspiration has come from one of my family members, Dr. Richard H. Sinclair, MD. Dr. Sinclair, a well-respected physician in the Kansas City area, retired several years ago from 30 years private practice in obstetrics and gynecology. Since 1982, he has focused on HRT and its affects on women's general health. Using transdermal patches and topical creams, he has gained a unique perspective on the dosing and efficacy of HRT. He now has a blog on mom2momkc.com.

Q. If you were to give advice to a recent or soon-to-be graduate, what would it be?

A. The economic and business landscape right now is very difficult and presents challenges that have not been seen in 30 years.

I strongly recommend getting involved and participating in the CRS Mentor/Protégé program. Dr. Rathbone and others have created a wonderful program that can benefit any young scientist, especially our young members. I have been a mentor for almost 3 years and I enjoy listening to my protégé's interests and goals and also being able to help them identify career opportunities, create resumes, sharpen interviewing skills, and network. I also recommend using the CRS website career page and attending the CRS Annual Meeting.

- Q. What personal attributes have allowed you to excel in your scientific career?
- **A.** I would have to say perseverance and the willingness to be open to new opportunities.

Q. You are very active in professional organizations like the CRS and AAPS. How has this influenced your career? Would you recommend others in industry to get more involved? Why?

A. Most of my career has been spent working on innovations, patents, and early feasibility projects, which by their nature must be kept secret. It is exciting to pioneer new concepts and technologies. But at the same time, it also limits my ability to meet and work freely with people.

My participation in both CRS and AAPS started relatively late in my career, so it hasn't necessarily influenced my career so much at it has enhanced it. It has allowed me the opportunity to meet and work with people from different companies and universities from all over the world. As Industrial Editor for the Newsletter, I have the opportunity to view all the recent press releases from drug delivery, life science, and medical device companies. In this sense, it gives me an overview of trends in the drug delivery world as well as the pharmaceutical and business world.

Besides the Newsletter, my greatest enjoyment has been working with young scientists and the CRS Mentor/Protégé program. I've always wanted to be able to help young scientists as they enter into professional jobs, in the same way as some of the early CRS members assisted me. So, yes, I highly recommend CRS members to get involved and participate in our organization.

Q. You have been an Editor for the CRS Newsletter since 2004. How has the newsletter changed over time? How can it continue to improve? In your estimation, what impact does it have on the CRS in general?

A. When I joined, the Newsletter was beginning a new phase of publishing. There were three issues a year and the Newsletter was smaller in the number of pages. We began to explore additional features and invited suggestions in order to expand and create a more useful Newsletter for our members. We also started to plan for six issues a year, which we accomplished last year.

In regards to being the Industrial Editor, I have standardized the formatting for the "In The News" feature, as well as try to include news items from all over the world and from all areas of controlled release, innovations, applications, and business news. I also continue to invite contributions for the "Spotlight" feature. The Newsletter has grown immensely over the past seven years – from three issues a year to six issues a year. Yvonne Perrie has been an exceptional lead editor for the Newsletter and the other editors have done an outstanding job of finding new authors and creating new features for the Newsletter. I also enjoy reading about other CRS chapter news and activities. So, from an impact standpoint, I think the Newsletter has been instrumental in leading the way and communicating the mission of the CRS and will continue to do so, along with the CRS website.

Q. Do you have any hobbies?

A. I enjoy sports such as swimming, bicycling, and general aerobic exercise and weight training. I especially enjoyed attending the 2004 CRS annual meeting in Hawaii where my girlfriend and I spent an additional week on the Big Island and stayed at a coffee farm B&B. The swimming and snorkeling were great. So were the lava flows. We also visited Lapakahi State Historical Park, a large area of ruins from an ancient Hawaiian fishing village on the Big Island of Hawaii. The park ranger told us that it was also a spiritual and health center for the early Hawaiians.

My other recent interest has been genealogy. I discovered that I am descendant from Robert Teesdale (I), who came from Scotland and became head gardener at Castle Howard, Yorkshire, England. His son, Robert Teesdale (II), also became head gardener, as well as a respected botanist, at Castle Howard and in London. His sons, John Sr. and John Jr., became coffee and tea merchants in London throughout the 1800s. My mother still has the silver tea set from Brittania, Robert's wife, dated 1805, with a letter of provenance. We also have a miniature locket with a braid of hair that could possibly be Brittania's. As a scientist myself, I find it amazing that Robert Teesdale (II) was a botanist and had the Teesdalia plant (*Teesdalia nudicaulis*, shepherd's watercress) named after him. Additionally, his son, Henry, was the famous atlas and map publisher in the 1820s and 1830s.

I also learned more about my great grandparents. They are Marian Teesdale Ellis (John Teesdale Jr.'s daughter) and husband Samuel Ellis. The Penn School (Westport, MO) was founded in 1868 by my great grandmother, in the Westport area of Kansas City, to educate the children of emancipated slaves. It was a very courageous thing to do, especially right after the Civil War.





A LEADER IN ORAL DRUG DELIVERY

Proud sponsor of the CRS Young Investigator Award

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or more than 25 years the CRS Young Investigator award has recognized a CRS member, age 40 years or younger, who has made outstanding contributions in the science of controlled release.

Eurand is committed to advancing the sciences of pharmaceutical technologies through continued support of young investigators and investment in novel research.



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CRS Annual Meeting

July 30-August 3, 2011, National Harbor, Maryland

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Make the Most of Your Time at the 38th Annual Meeting & Exposition at an Educational Workshop

National Harbor, Maryland, U.S.A.



The following premeeting workshops will be offered at the 38th Annual Meeting & Exposition of the Controlled Release Society. Separate registration is required for educational workshops. You do not need to attend the entire annual meeting in order to attend a workshop.

Interested in Attending a Workshop? Make It a Weekend!

Are you interested in a workshop but not planning to attend the entire annual meeting? When you register for any workshop on Saturday or Sunday, you can attend the original and groundbreaking programming offered at CRS Innovation Sunday for no additional charge. You'll have access to the Nanomedicine Summit and the Industry Roundtable, as well as any Releasing Technology Workshops or Soapbox Sessions that are not concurrent with your workshop. Plus, you can attend the Exposition Grand Opening/Welcome Reception and Poster Session I on Sunday evening for just \$75. You'll get to know others in the field of delivery science, have access to hundreds of posters, and meet top industry suppliers.

Educational Workshops

Educational Workshop 1: CNS Drug Delivery: From Proof of Concept to Clinical Readiness Saturday, July 30–Sunday, July 31

Chaired by Perry Calias, Shire HGT, U.S.A. Planning Committee: William Banks, University of Washington, U.S.A.; Patti Dickson, Harbor-UCLA Medical

Center, U.S.A.; David Jacobson-Kram, FDA, U.S.A.; and Anne Pariser, FDA, U.S.A.

This workshop is designed to engage you in a multidisciplinary discussion of the comprehensive strategies needed to develop drug and biological products targeted for delivery to the central nervous system (CNS), from drug discovery through to clinical evaluation. The discussion will encompass a review of existing science, determination of existing gaps in knowledge, and strategies to overcome recognized needs.

Saturday, July 30

Session 1: Targeting Delivery to the CNS Part 1: CNS Biology and Peripheral Delivery Strategies

Session Chair: Patti Dickson, University of California-Los Angeles, U.S.A.

Factors Unique to the Development of Neuraxially Delivery Drug, **Tony Yaksh,** University of California, San Diego, U.S.A.

- The Blood-brain Barrier: Challenges and Opportunities, William Banks, University of Washington, U.S.A.
- Targeting Therapeutic Carriers Across the Blood-brain Barrier, Silvia Muro, University of Maryland, U.S.A.

Session 2: Targeting Delivery to the CNS Part 2: Direct CNS Administration

Session Chair: Perry Calias, Shire HGT, U.S.A.

Intrathecal Delivery of Lysosomal Enzymes, Perry Calias, Shire HGT, U.S.A.

Nanomedicine Approaches for CNS Delivery of Polypeptides, Alexandar Kabanov, University of Nebraska, U.S.A.

Intranasal Therapeutics (drugs, biopharmaceuticals and stem cells) Bypass the Blood-brain Barrier to Treat Alzheimer's, Stroke, Parkinson's, Brain Tumors and Other CNS Disorders, William Frey, University of Minnesota, U.S.A.

Session 3: Assessing Product Delivery

Moderator: David Begley, King's College, U.K.

Strategies for CNS Drug Design and Development, Nigel Greig, National Institute on Aging, U.S.A.

- Challenges Associated with Determining Product Delivery, Mitra Azadeh, Covance Laboratories, U.S.A.
- Pharmacological Imaging: Quantitative Positron Emission Tomography, Misha Papisov, MGH, U.S.A.

Session 4: Non-Clinical Considerations for Clinical Trial Readiness

Session Chair: David Jacobson-Kram, FDA, U.S.A.

- Preclinical Study Design of Centrally Delivered Products Based on Pharmacokinetics, **Bob Boyd**, Northern Biomedical Research, U.S.A.
- Morphologic Assessment of Preclinical Safety Studies Involving Direct Delivery to the CNS, Mark Butt, Tox Path Specialists, U.S.A.

Sunday, July 31

Session 5: Considerations for Clinical Trial Readiness/ Translational Medicine Part 1: Biomarkers, PD Measures, Surrogates

Session Chair: William Banks, University of Washington, U.S.A.

CSF Biology, Proteonics, and Biomarks of Diseases, Ingolf Blasig, FMP, Germany

- Brain Imaging to Evaluate CND Drug Delivery in Animals and Humans, Satoshi Minoshima, University of Washington, U.S.A.
- Validation of CSF Biomarkers of Alzheimer's Disease: Experience in the ADNI Study, Leslie Shaw, University of Pennsylvania, U.S.A.

Session 6: Considerations for Clinical Trial Readiness/ Translational Medicine Part 2

Session Chair: Anne Pariser, FDA. U.S.A.

Presentation title TBD, Chris Austin, NHGRI, NIH TRND, U.S.A.

Biomarkers in CNS Therapeutics, Marc Walton, FDA, U.S.A.

Educational Workshop 2: Introduction to Encapsulation and Controlled Release Technologies

Saturday, July 30–Sunday, July 31

Chaired by James Oxley, Southwest Research Institute, U.S.A., and Teresa Virgallito, Microtek Laboratories, Inc., U.S.A.

This workshop will provide the attendee with a broad overview of the encapsulation and controlled release technologies available, in addition to potential applications. Newcomers to the controlled release field will use this workshop as an introduction to the field, while established members may see this as an opportunity to refresh their knowledge or find ideas outside of their specific area of interest.

Saturday, July 30

Overview of Microencapsulation, James Oxley, SwRI, U.S.A. Spray Drying, Chilling, and Prilling, Irv Jacobs, Jacobs Consulting, U.S.A.

Fluid Bed Coating, **Chuck Frey**, Coatings Place Inc., U.S.A. *Coextrusion*, **James Oxley**, SwRI, U.S.A.

Interfacial Polymerization, PUFA, **Teresa Virgallito,** Microtek Labs, Inc., U.S.A.

Coacervation, Ron Versic, RT Dogde, U.S.A.

Encapsulation Materials, Irv Jacobs, Jacobs Consulting, U.S.A.

- Nanoencapsulation, James Oxley, SwRI, U.S.A.
- *Edible Films*, **Teresa Virgallito**, Microtek Labs, Inc., U.S.A.
- Fibers, Hans Tromp, NIZO, The Netherlands

Sunday, July 31, 2011

Applications – Pharma, Buket Asku, Santa Farma, Turkey Applications – Food, Anil Gonkar, Kraft, U.S.A.

Applications – Veterinary, **Michael Rathbone**, Griffith University, Australia

Applications – Cosmetics, Teresa Virgallito, Microtek Labs, Inc., U.S.A.

Applications – Agricultural, Irv Jacobs, Jacobs Consulting, U.S.A.

Educational Workshop 3: Pharmacologic and Regulatory Issues for the Translational Development of Nanoparticle Agents

Sunday, July 31

Chaired by William Zamboni, UNC Lineberger Comprehensive Cancer Center, U.S.A., and Brian Booth, FDA/CDER/OTS/ OCP, U.S.A.

This workshop features a comprehensive overview of the ongoing investigations and important issues facing nanoparticle drug development. Sessions will summarize the pharmacodynamics and pharmacokinetics of nanoparticle agents. Significance of size and shape and the overall effects on PK-PD will be detailed. Presentations also will feature insights from preclinical studies in animal models and patients, evaluations of animal models for pharmacologic and toxicologic studies, and profiles of preclinical tumor models for nanoparticle drug development. Analysis concerning tumor-targeting approaches via ligand and antibody labeled carriers will be discussed. Finally, regulatory issues will be addressed by representatives of the FDA.

Session 1: Formulation Issues

How Formulation Issues Affect PK-PD of Nanoparticle Agents, Anil Patri, National Cancer Institute, U.S.A.

How Size, Shape, and Modulus Affect Pk-Pd of Nanoparticle Agents, Kevin Herlihy, University of North Carolina, U.S.A.

Regulatory Issues for Nanoparticle Formulations, Olen Stephans, FDA, U.S.A.

Session 2: Preclinical Models for Nanoparticle Drug Development

Factors Affecting the PK and PD of Nanoparticle Agents in Preclinical Animal Models and in Patients, William C.
Zamboni, University of North Carolina Eshelman School of Pharmacy, Lineberger Comprehensive Cancer Center, U.S.A.

Targeted Therapeutics Development Using The BIND Medicinal Nanoengineering Platform, Jeff Hrkach, BIND Biosciences, Inc., U.S.A.

Regulatory Issues on the PK and PD of Nanoparticle Agents, Abimbola Adebowale, FDA, U.S.A.

Session 3: Preclinical Models for Nanoparticle Drug Development

Evaluation of Animal models for Pharmacologic and Toxicologic Studies of Nanoparticles, **Stephan Stern**, Nanotechnology Characterization Laboratory, National Cancer Institute, U.S.A.

Regulatory Issues for Nonclinical Pharmacologic and Toxicologic Studies of Nanoparticles, Nakissa Sadrieh, FDA, U.S.A.

CRS Innovation Sunday

Turning Emerging Delivery Science into New Products Science • Partnering • Development • Commercialization

Build your networks for success during the second annual CRS Innovation Sunday! Partnering, technology, innovation, big pharma, entrepreneurs, research, development, regulatory approval, commercialization. You will find all of these elements in the fast-paced programming focused on taking innovative science through development and into the commercial sector. By attending, you will have the opportunity to network with players from multiple areas of controlled release and delivery. CRS Partnering also begins on Sunday!

Releasing Technology Workshops

Hosted by individual companies, these 1- and 2-hour workshops focus on in-depth facets of products and services supporting research and development in controlled release technologies. Releasing Technology Workshops (RTWs) are open to all registered attendees.

Soapbox Sessions

The Soapbox Sessions introduce the latest, most novel technologies, products, and services for controlled delivery in bioactive materials, consumer and diversified products, and animal health. Identify new ideas and potential collaborations in these fast-paced presentations and during the one-on-one sessions following the presentations.

Industry Roundtable: Delivery Needs in the Age of Mergers, Acquisitions, and Out Licensing

This interactive roundtable focuses on the needs of multinational biopharmaceutical companies and the various types of mergers and deals they are entering into to pursue their commercialization paths. Presenters will be senior industry executives who have been responsible for securing major agreements and integrating subsequent R&D functions with international partners. Why do executives choose particular agreements? What do these organizations need from the drug delivery community? How have the M&A activities altered their pipelines? What lessons did they experience along the way? Learn about the paths these companies have chosen and understand the impact on future requirements of controlled release and delivery technologies toward commercial success.



NEW! Nanomedicine Product Development Summit

Turning Nanoparticle Delivery Systems into Innovative Medicines

Chairs: **Rogério Gaspar**, University of Lisbon, Portugal, and **Mark Tracy**, Alnylam, Inc., U.S.A.

Come and participate in panel discussions with leaders in the development , regulatory review and commercialization of nanoparticle-based systems for the delivery of small molecules and siRNA to share experiences and discuss the latest science, challenges, and paths forward in developing new medicines based on nanoparticle delivery technologies. Be a part of the dialogue to facilitate advancement of these products through the clinic and regulatory approval process.

Panel Discussion 1: Formulation and Characterization of Nanoparticle Delivery Systems for siRNA and Small Molecules

Pieter Cullis, University of British Columbia, Canada **Scott McNeil**, National Cancer Institute, U.S.A. **William Zamboni**, University of North Carolina, U.S.A.

Panel Discussion 2: Development and Regulatory Considerations for Nanoparticle-based Medicines

Neil Desai, Celgene, Inc., U.S.A. Lawrence Mayer, Celator Pharmaceuticals, U.S.A. Sara Nochur, Alnylam Pharmaceuticals, Inc. U.S.A Nikissa Sadrieh, CDER, FDA, U.S.A. Beatriz Lima, Infarmed, University of Lisbon, Portugal

Exposition Grand Opening and Welcome Reception

CRS Innovation Sunday culminates in the Exposition Hall with the Exposition Grand Opening and Welcome Reception. Join 100+ exhibiting companies and more than 1,600 attendees where products, services, and innovations can be discussed one-on-one.

CRS 2011 Exposition

The CRS Exposition Grand Opening and Welcome Reception takes place on Sunday evening, July 31, and the Exposition remains open until midday Wednesday. Join 100+ companies and more than 1,600 attendees where thousands of products, services, and innovations still to be developed can be discussed one-on-one.

2011 CRS Exhibitors*

3M Drug Delivery Systems AC Compacting LLC Adhesives Research Agere Pharmaceuticals Agilent Technologies Akina Inc. Analytical Solutions, Inc. Aptuit, Inc. Asahi Kasei Chemicals Corp. Ashland Aqualon Functional Ingredients Avanti Polar Lipids Aveva Drug Delivery Systems Inc. Bachem Americas, Inc. Banner Pharmacaps Inc. BASF Corp. Bend Research Inc. **BioActs Bio-Images Research** Brightwell Technologies Inc. **Buchi** Corporation Catalent Pharma Solutions Celanese EVA Performance Colorcon, Inc. Corden Pharma Croda Inc. Delta Industrial Services Inc. Depomed, Inc. **Dissolution** Technologies Dow Chemical Drug Delivery Technology

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*As of press time. For updates go to www.controlledrelease.org/meeting.

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CRS LinkedIn Group Tops 1,000 Members



The CRS LinkedIn group was founded by the CRS Membership Committee as an "easy way to get the CRS

community talking to each other all year long," explains LinkedIn group manager and Membership Committee member Andy Lewis. In just over a year, it has done just that and more. While last March the CRS LinkedIn group had around 450 members, this February it celebrated its 1,000th member. The group continues to grow beyond the 1,000 mark, and as new scientists join, new connections are made that are beneficial to all members of the group.

LinkedIn is the professional version of social media outlets like Facebook, allowing like-minded individuals to create discussions and view each other's professional networks. The CRS LinkedIn group allows group members to keep up with the latest developments in the field of delivery science and creates quick connections to other scientists and pertinent businesses around the world. So far discussions have "ranged from recommendations for publications surrounding a particular technology and requests for help with a research problem, to whether you should wear a tie for job interviews and what age the cut off should be for the Young Scientists sub-group (it was decided anyone young at heart could join!)." As a social network, LinkedIn allows members to comment on posts and create a true discussion, developing new knowledge. Meetings of interest to the field are posted, as well as jobs for many career levels. "I know students looking for postdoctoral positions have used the group to make first contact with world-leading academics," said Andy Lewis. The latest CRS news and important deadlines are also available.

The group is open to everyone and has attracted a strong following of non-CRS members. This is an excellent opportunity to share the value of CRS and the research CRS members are producing. "It will serve its members best if it is shaped by the CRS community," commented Andy Lewis, "so please join and post up anything you think will be of interest to other members."

From the President continued from page 3

I want to thank all members who voted in the CRS election. You elected candidates for CRS Vice-President and for the Board of Scientific Advisors (BSA). The winner of the election for Vice-President will serve as President-elect in 2012–13 and President in 2013–14. Winners will be announced soon!

Coming Soon - New Bylaws for CRS!

Finally, as I mentioned to you in the last edition of the CRS Newsletter, one of the priorities of the CRS Board this year is to review the Society's governance structure and update our bylaws. I wanted to update you on our progress. It has been about 10 years since the CRS bylaws and governance structure were last extensively reviewed. It is typical for associations like ours to review and update the bylaws every 5-10 years. With our goal to prepare the CRS for the new decade, make us more nimble to react to opportunities and challenges, and provide a strengthened foundation to support growth in member benefits, we as a Board decided that we should undertake a review of our bylaws this year. Immediately after our meeting in Portland, the Board appointed the Bylaws and Governance Task Force with former Treasurer Arthur J. Tipton as chairperson. Task force members include former Board Member-at-Large Ian Tucker, Distinguished Service Award winner David Friend, Treasurer Debbie Bingham, President-elect Martyn Davies, and Executive Director Susan Kohn. The task force's work is supported by Stephen C. Carey Ph.D., CAE, Lead Governance Strategist with Association Management + Marketing Resources, an association management consulting firm. The Board provided the task force the charge to review and recommend updates to our bylaws and governance structure considering best practices in association governance and provide an updated set of bylaws to the Board for review and approval in early 2011. The task force completed a number of conference calls since last fall and formally submitted a first draft proposal to the Board for comments in January and an updated draft in March. At our last Board meeting in April, the Board approved an updated set of bylaws to be sent to the membership for approval. So very shortly, CRS members will receive information with the new bylaws and voting instructions. This is a special opportunity for you to help strengthen your Society as we prepare for the new decade. When you receive your voting instructions and ballot in a few weeks, please vote to approve these new bylaws so that we can update our governance and prepare for an exciting future!

Mark A. Tracy

38th Annual Meeting & Exposition of the Controlled Release Society

July 30 – August 3, 2011 Gaylord National Hotel & Convention Center National Harbor, Maryland, U.S.A.

Innovative and Low-Cost Technologies for Healthcare and Consumer Products



Gordon Amidon Professor of Pharmacy, University of Michigan, U.S.A.



Henry Brem Chair of Neurosurgery, Johns Hopkins Hospital, U.S.A.

Featured Plenary Speakers



Adam Heller Research Professor, University of Texas, Austin, U.S.A.



Gordon Muirhead Vice President and Dose Form Leader, GlaxoSmithKline, United Kingdom



Walt Orenstein Deputy Director for Vaccine-Preventable Diseases, Gates Foundation, U.S.A.

Register by May 2 to receive the lowest rates! Plus, stay in the center of the action when you book your room at the Gaylord National Hotel.



www.controlledreleasesociety.org

CRS Website Committee: Bringing a Vision to Reality

When CRS decided to launch a new website, the society knew it would have to develop a site that would be the premier resource to search for information on active delivery and create a welcome place to connect with other delivery scientists throughout the world. The Website Design Ad Hoc Committee, led by Chair Andy Lewis, envisions that the new CRS site will be the first website you go to when you need to learn about the field, find an expert, or make contacts.

The new website will contain new, easy-to-follow navigation and new information. There will also be two major additions that will be valuable resources for CRS members. Launching with the new website will be a library of peer-reviewed webinars spanning four categories: educational, research papers, industrial, and presentations from annual meetings. By watching the webinars, CRS members will be able to learn from leaders in the field, keep up to date on issues affecting their industry, and see presentations they missed at the annual meeting. As they will be peer reviewed, we aim to keep the standards high. A peer review process will ensure high-quality presentations and the webinars will be an ever-expanding resource. The Webinar Committee, chaired by David Brayden, is currently accepting presentations. The second major addition will be LATTE - Linking Academic Technologies and Techniques to Everyone. This will be a unique database allowing members to search for experts. With this new feature, CRS members will be able to easily identify individuals for collaboration, consultation, or expert opinion.

These are just two of the features of the new website that CRS members are busy bringing to reality. There will be many more to come. The website will be launched with the 2011 Annual Meeting & Exposition, July 30–August 3. More details will come in advance of the launch – watch this space!

Website Design Ad Hoc Committee

Chair: Andrew L. Lewis, Critical Pharmaceuticals Member: Jake E. Barralet, McGill University Member: David J. Brayden, University College Dublin Member: Biana Godin Vilentchouk, The Methodist Hospital Research Institute Member: Karl Malcolm, Queen's University Belfast Member: Xiaoming Xu, University of Connecticut Ex-Officio: Diane J. Burgess, University of Connecticut

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Editor in Chief Professor Kinam Park

A Novel W/O/O Double-Emulsion Solvent Removal Method for the Nanoencapsulation of Doxycycline

RS Patel, DY Cho, C Tian, A Chang, DM Decoteau, JR Morgan, and E Mathiowitz Center for Biomedical Engineering, Brown University, Providence, RI

Introduction

Although solvent evaporation is one of the oldest and most commonly used methods of microsphere preparation, its use for the encapsulation of hydrophilic therapeutic agents is plagued by significant drug loss to the aqueous phase during the solvent evaporation process. Thus, the encapsulation of hydrophilic drugs within polymer microspheres using solvent evaporation for drug delivery applications yields poor encapsulation efficiencies, requiring higher theoretical drug loadings to achieve therapeutically relevant release kinetics (1,2).

We present a modified nanoencapsulation technique based on the solvent removal process, a method originally developed for the microencapsulation of drugs within polyanhydrides due to the rapid hydrolysis of the anhydride bonds in the presence of water (3) and later used for the encapsulation of proteins in biodegradable polyesters (4). Based on our work with the encapsulation of doxycycline (DOX) in PLGA nanospheres, we propose that this technique can be adapted for a wide range of hydrophilic drugs for a variety of applications.

Experimental Methods

DOX-loaded nanospheres were fabricated by a modified water/ oil/oil (W/O/O) solvent removal method (4). A W/O emulsion was first created by emulsifying an aqueous DOX solution (with or without the addition of NaCl) in a solution of PLGA (50:50, RG502) in methylene chloride using probe-sonication. This emulsion was then added to a 20% v/v methylene chloride/ silicon oil solution and further probe-sonicated to create the W/O/O double emulsion. Solvent removal was induced by adding the double emulsion to petroleum ether, resulting in the formation of nanospheres. The spheres were washed with additional petroleum ether to remove residual silicon oil and lyophilized for further characterization. Unloaded nanospheres served as a negative control.

DOX encapsulation efficiency and release kinetics were determined using UV spectrophotometry at 255 nm. Particle

Tabl	e 1. F	orm	ilatio	ons o	fDO	X-lo	aded	PLC	GA na	anos	pheres.

Formulation	% DOX	% NaCl	% Encapsulation efficiency	TG (°C)
A	10		51 ± 5.0	35.51
В	10	1	39 ± 5.4	35.30
C	5		70 ± 3.3	36.46
D	5	1	74 ± 3.7	36.97
E	1		70 ± 1.1	36.57
F	1	1	74 ± 9.2	34.76
G	0.1		67 ± 2.6	37.84
H	0.1	1	56 ± 2.6	38.48

DOX TM = 168.533°C, PLGA TG = 46.10°C

diameters were quantified using Coulter particle sizing techniques. Surface morphology was examined using scanning electron microscopy (SEM). Differential scanning calorimetry was used to evaluate the thermal properties of bulk PLGA, bulk DOX, unloaded nanospheres, and DOX-loaded nanospheres as well as the interaction and incorporation of DOX within the PLGA.

Results and Discussion

Eight formulations of DOX-loaded nanospheres were fabricated using the W/O/O solvent removal technique (Table 1). Loadings ranged from 0–10% (w/w), and each formulation was fabricated with and without the addition of 1% NaCl which served as an osmotic agent to alter the release kinetics of the DOX from the spheres. With the exception of nanospheres containing 10% DOX with salt, encapsulation efficiencies for all formulations were above 50%, with efficiencies increasing with respect to increasing drug loading. Efficiencies were nearly 2-fold higher than those achieved for the encapsulation of DOX within PLGA microspheres using W/O/W double emulsion solvent evaporation methods described in the literature where significant loss of the hydrophilic drug into the aqueous bath occurs during the evaporation process (1,2).

With respect to particle diameters, laser particle sizing revealed a mean particle diameter of 600 nm for all formulations, with microscopy further confirming these results (Figure 1). Nanoscale particle formation using W/O/O double emulsion solvent removal as demonstrated in this work has not been achieved by prior studies utilizing this



Figure 1. SEM of DOX-loaded PLGA nanospheres.

encapsulation method (4). The smaller particle sizes achieved can be attributed to the incorporation of significantly higher shear rates by sonication during the formation of the primary and secondary emulsions to produce smaller droplets of the drug and polymer within the continuous secondary oil phase.

Analysis of the release kinetics from DOX-loaded PLGA nanospheres revealed sustained, continuous release of the hydrophilic drug over the course of 85 days. Higher loading formulations (1–10%) followed the classic biphasic PLGA release profiles with an initial burst due to hydrolysis of the outer shell of the spheres followed by a lag phase and a subsequent, secondary burst due to the bulk degradation of the polymeric



Figure 2. DOX release profiles for 1–10% loaded formulations.

observed, one following the classic biphasic PLGA release and the other following continuous release kinetics (Figure 3). In this formulation, the addition of salt resulted in a more modulated burst release.

No thermal activity consistent with the melting of DOX was observed in the formulations indicating a molecular dispersion of the drug within the matrix. The decrease in the



two release

profiles were

e Figure 3. DOX release profiles for 0.1% loaded formulation.

glass transition temperatures (T_{c}) seen for the formulations with respect to that of the bulk polymer suggests an increase in the amorphous regions of the polymer in the nanospheres as a result of the encapsulation process. We are currently evaluating this more in depth.

Conclusion

A novel method was developed for the nanoencapsulation of hydrophilic drugs without the use of an aqueous non-solvent phase. Based on a solvent removal method with the incorporation of a water/oil/oil (W/O/O) double emulsion with significantly higher shear rates, PLGA nanospheres containing DOX, a model hydrophilic drug, were fabricated with enhanced encapsulation efficiency and minimal drug loss. Despite the high surface area to volume ratio in nanoparticles and the resulting increase in the amount of polymer exposed to hydrolysis, drug release rates and subsequent degradation rates for the DOXloaded nanospheres were sustained for up to 85 days. Higher loading formulations yielded classic biphasic PLGA release profiles, while lower loadings yielded more continuous release. The versatility of this method allows for use in the nanoencapsulation of other small, hydrophilic therapeutic molecules for drug delivery applications.

Acknowledgments

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The Phospholipid Vesicle-Based Barrier for Screening of the **Oral Absorption Properties of Drug Candidates**

Gøril Eide Flaten¹, Kristina Luthman² and Martin Brandl³

Oral Bioavailability

Oral administration of drugs is preferred over any other administration route due to the convenience for the patients and the resulting good compliance. An important property of a drug is its bioavailability, and for an orally administered drug the bioavailability is mainly limited by its solubility and/or permeability through the intestinal epithelia. Within drug discovery and early development it is thus an issue to employ methods suitable for rapid screening of the permeability properties of large numbers of new drug candidates. Today the most often used methods are the Caco-2 cell model and the PAMPA models. However, there are still needs for new, rapid and efficient methods for permeability screening. Since most NCEs (new chemical entities) developed today are large lipophilic poorly soluble compounds, screening of drug formulations rather than compound permeability is of increasing importance.

What is the Phospholipid Vesicle-Based Barrier?

The phospholipid vesicle-based barrier is a novel model that has been developed in our research group at the University of Tromsø, Norway. The barrier consists of a tight layer of liposomes on a filter support which is made by first depositing smaller liposomes within the pores and then larger liposomes on top of the filter, by use of centrifugation. Freeze-thaw cycling is then used to promote liposome fusion to generate a tight barrier (see Figure 1). The barriers have been shown to be stable for two weeks of storage. This grants the opportunity to produce a large

batch of barriers and just collect the number of barriers needed from the freezer every time experiments should be run. The characterization of the barrier structure showed that the pores of the filter are filled with liposomes and that there is a layer of liposomes on top of the filter. There are oligo- and multilamellar structures and most probably also unilamellar structures in the barrier. A schematic cross sectional drawing of the barrier is shown in Figure 2(1).

Correlation with In Vivo Data and Other Permeation Models

The permeability values obtained from the phospholipid vesiclebased model for a diverse set of compounds correlate well with literature data on *in vivo* absorption of the drugs in humans. By using the common classification system for permeability properties, 17 out of 22 compounds were correctly classified, whereas the remaining five compounds were assigned to a class next to the correct one (see Figure 3). These studies showed that our approach appears to model the *in vivo* absorption equally well or even better than the DS-PAMPA model and equally well as the Caco-2 cell model. In addition, it is a lot easier to handle than the cell based assays (2).

What Can this New Model Handle of Relevant Test **Conditions?**

The barriers have shown to maintain their integrity in a pH range from 2.0 to 8.0. The permeability of ionogenic compounds was also shown to decrease with increasing ionisation according to the pH partition hypothesis. This renders the model suitable for studies of segmental absorption in the gastrointestinal tract. The model has also shown to be compatible with relevant



Figure 1. Flow chart for the preparation of the liposome barriers.

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Figure 2. A schematic illustration of the structure of the phospholipid vesiclebased barrier. The pink area is the filter support while the blue represent the liposomes found both inside the pores and in a layer on top of the filter.

solubility enhancing agents. Some solubilizers led to an increased flux of lipophilic drugs, which is a promising start for further development of the model into a suitable approach for permeability testing of drugs with poor water solubility as well as drug formulations containing solubility enhancing agents (1,3).

Increased Throughput with Automation?

Attempts to increase the throughput of the phospholipid vesicle-based model by automation of filter insert production, use of pre-fabricated barriers as well as adaptation of the permeation experiments to a robotic system have proven promising. Manufacturing of the filter supports by fusion of the filters to bare inserts has successfully been automated by using specially constructed heat-sealing machines, resulting in a much faster and less error prone filter insert production process. Furthermore, the permeability assay has successfully been transferred to the robotic system, Tecan Genesis RSP 150 workstation from Tecan, Crailsheim, Germany. It could be shown that transferring the assay to an automated system does not affect the outcome of the permeability testing. The most time-consuming steps of the permeability assay were thus shown to be eligible for automation (4).

Can the Model be Used in the "Real World"?

The phospholipid vesicle-based model has recently also been used in testing of the permeability of both novel active substances as well as drugs in complex formulations. The oral permeability of novel antibacterial peptides has been predicted and the model proved to be appropriate for this purpose (5). The phospholipid vesicle-based barrier also appears to be suitable for

IN VIVO

Fraction absorbed in humans after oral administration Excellent Moderate Poor

Timolol Chloramphenicol Alprenolol Metoprolol Testosterone Acetylsalicylic acid Caffeine	Amiloride Tranexamic acid Sulpiride	
Salicylic acid	Nadolol Ranitidine Atenolol Acebutolol Cimetidine Enalapril Hydrochlorothiazide Terbutaline Naproxen	Sulphasalazine
		Chlorothiazide

LIPOSOME MODEL

Figure 3. Diagram showing the correlation of permeability classes according to in vivo data on percent absorbed in human and the permeability values obtained from the present model. White = perfect classification; light gray = slight discrepancy; dark gray = incorrect classification.

investigating the passive transport of APIs (active pharmaceutical ingredients) from various complex formulations like solid dispersions and may thus represent a useful extension of the permeability screening toolbox, especially in comparison to the Caco-2 model and in cases where a differentiation between passive and active transport is desired (6).

Take Home Message

The phospholipid vesicle-based permeability assay, suitable for automation, represents an interesting addition to the tool-box of *in vitro* permeability assays running in a medium- to highthroughput format. This permeability assay is very feasible due to its easiness to use, its transferability to other laboratories and its good correlation with *in vivo* data on the fraction absorbed of drugs in humans.

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Can Cyclodextrins Improve the Formulation of the Anaesthetic Tribromoethanol?

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Anaesthesia and analgesia are important components for a range of *in vivo* procedures involving animals. This may be to immobilise the animal for manipulation or to prevent pain and suffering in the test animal for welfare reasons. Pain is known to affect normal behaviour and physiological responses, and this may compromise research if not minimised.

Tribromoethanol is an anaesthetic used in laboratory rodents, especially for the production of transgenic mice, and is typically given by the intraperitoneal (IP) route. It has minimal effects on embryonic development and reproductive performance, with pregnancy rates similar to natural pregnancy (1). Tribromoethanol is reported to produce good surgical anaesthesia with rapid induction and recovery (2). This agent has been available as the brand Avertin in the past (a 66.7% solution of tribromoethanol in tert. amyl alcohol), but this is no longer manufactured, so the researcher must formulate their own solution.

Problems with tribromoethanol in rodents have been identified when the extemporaneous preparation is used. The storage conditions of the formulation vary between institutions. For example, one protocol in use calls for the solution to be stored for two months before use. Tribromoethanol is known to degrade to dibromoacetaldehyde and hydrobromic acid, both of which are irritant substances (3). As well as the potential for injecting irritating compounds into the animal's peritoneum, one cannot be sure of the final concentration of the solution after two months of storage. Tribromoethanol is also known for variation in response between different species and strains, as is the case with many other anaesthetics in animals. This makes it difficult to determine a dose rate that will result in reproducible surgical anaesthesia. Of particular concern are the reports of high rates of morbidity and mortality with the use of tribromoethanol. Some researchers have found unacceptable rates of post-anaesthesia mortality, peritonitis, intestinal ileus and abdominal adhesions



Figure 1. Structure of β -cyclodextrin and the proposed shape of the cyclodextrin molecule (6).

(4), whereas others have used this agent for years with minimal problems (2). These issues could be related to storage and degradation of tribromoethanol, concentration and dosage used, or the placement of the IP injection itself.

Cyclodextrins are composed of a number dextrose units joined by 1-4 glycosidic bonds in a cyclic structure. The arrangement of these molecules creates a hydrophilic exterior and relatively hydrophobic interior cavity (Figure 1), comparable to the lipophilicity of ethanol (5). Formation of an inclusion complex can occur in an aqueous solution, where the hydrophilic water molecules drive inclusion of a hydrophobic molecule or moiety (such as a drug molecule) within the cyclodextrin cavity. This results in a dynamic equilibrium between the free drug, free cyclodextrin and drug:cyclodextrin complex. The use of cyclodextrins in the formulation of tribromoethanol may increase aqueous solubility of the drug, eliminating the need for the organic solvent (tert. amyl alcohol) which itself can cause irritation. The cyclodextrin may also increase stability of tribromoethanol, reducing the degradation to dibromoacetaldehyde and hydrobromic acid, which could reduce direct irritation from the drug.

The aims of this study were to investigate an alternative formulation of tribromoethanol with hydroxypropyl- β -cyclodextrin (HP- β -CD) for improved solubility and to determine the anaesthetic response following intraperitoneal injection.

Methods

The water content of the HP- β -CD was determined by Karl Fischer titration, giving a value of 8.37% w/w. The approximate solubility of tribromoethanol at room temperature was 4% w/v in 0.035 M HP- β -CD. The cyclodextrin formulation was made by dissolving tribromoethanol at a concentration of 1.25% w/v in 0.035M HP- β -CD. Once fully dissolved, the solution was filtered (0.2 µm) and stored at 4°C with protection from light. The standard formulation was produced by dissolving the tribromoethanol in tert. amyl alcohol (0.625%) then diluting with NaCl 0.9%, to 1.25% w/v. Dilution of the tert. amyl alcohol solution produced a precipitate which re-dissolved with stirring. Again, the final solution was filtered (0.2 µm) and stored at 4°C with protection from light.

A dose trial was undertaken in female balb/c, adult mice to determine the dose required to produce surgical anaesthesia in this species. This was initiated in 3 mice with the standard tribromoethanol solution at 125 mg/kg and gradually increased to 260 mg/kg. At the dose of 260 mg/kg there was good surgical anaesthesia; however, there was also some evidence of respiratory

depression in the mice (i.e., vocalisations, laboured breathing). Consequently, atropine was administered 30 minutes prior to anaesthesia at 0.05 mg/kg by subcutaneous injection. The inclusion of atropine improved the anaesthesia and reduced respiratory depression.

Anaesthetic efficacy was assessed by observing the loss of several reflexes in the mice. The righting reflex is the animals reflex to roll onto its front when placed on its back, and this is lost quickly after anaesthetic administration. The tail pinch reflex is assessed by pinching the tail of the mouse to elicit a pain response, and the reaction will depend on the level of pain felt. The pedal withdrawal reflex occurs when the interdigital skin on the fore and hind feet is pinched, and again, a reaction will be given depending on the level of pain. The tail and pedal withdrawal responses were scored on a scale of 0-3 (0 = no response through to 3 = strong response as per normal), and were added for each time point to give a combined reflex score (CRS) of 0-9 (0 = surgical anaesthesia, 9 = fully responsive) (7).

The cyclodextrin tribromoethanol formulation and the standard tribromoethanol solution were compared using the dose regimen of 260 mg/kg tribromoethanol IP with 0.05 mg/kg atropine SC in balb/c adult female mice (n = 6 per group). Parameters observed were depth of anaesthesia, righting reflex loss/gain and respiratory rate. A necropsy was undertaken 14 days after administration of the anaesthetic, where tissue samples were taken for histological examination.

Statistical analysis was completed using the software SPSS (IBM, Version 19). Significance value was set at p < 0.05 for all analyses. The comparison between respiratory rate with standard



Figure 2. Influence of anaesthetic formulation on combined reflex score (CRS) for mice treated with standard tribromoethanol (Std) and cyclodextrin tribromoethanol (CD) (Data points are mean \pm SD, n = 6). Dose of tribromoethanol was 260 mg/kg + atropine 0.05 mg/kg. CRS 0 = surgical anaesthesia and 9 = fully responsive.

Table 1. Comparison of times to loss and gain of righting reflexbetween the standard formulation and cyclodextrin formulation.

Average time to:	Standard	Cyclodextrin	Significance
Loss of righting			
reflex (min ± SD)	1.01 ± 0.12	1.52 ± 0.28	p ≤ 0.006
Regain righting			-
reflex (min ± SD)	34.2 ± 12.8	22.5 ± 9.5	p ≤ 0.104

and cyclodextrin tribromoethanol formulations was undertaken by repeated measures analysis of variance model. The time to loss and gain of righting reflex was compared between the two treatment groups using an independent samples t-test.

Results

A comparison of anaesthesia between the two formulations (Figure 2) shows the trend for the standard formulation to produce a deeper level of anaesthesia; however, this was not able to be confirmed statistically. Neither formulation consistently produced surgical anaesthesia, which was seen in the dose trial. Results from observation of the righting reflex (Table 1) show that this reflex is lost approximately 30 seconds faster with the standard formulation (p = 0.006) and it appears to take longer to return, although this result was not significant.

Respiratory rate was assessed in the mice by visual observation, and the rates followed different trends, with the standard formulation the respiration seemed more rapid (Figure 3).

The animals were monitored daily for 14 days after administration of the anaesthetic for clinical signs of illness, i.e., weight loss, reduction in water intake, abnormal behaviour. At day 14 the mice were euthanised by cervical dislocation and a necropsy was undertaken. No gross lesions were identified in the abdominal cavity of the animals. Tissue samples were taken from the spleen, kidney, bowel and liver for histological examination. No inflammation was found in any of the tissues examined and there was no difference between the two tribromoethanol formulations investigated (Figure 4).



Figure 3. Comparison of respiratory rate (breaths per minute) between the standard (Std) and cyclodextrin (CD) tribromoethanol formulations (mean \pm SD, n = 6).



Figure 4. Bowel section from mice treated with standard tribromoethanol formulation (a) and cyclodextrin formulation (b).

From the Vet Group continued from page 23

Discussion

The solubility of tribromoethanol in water is reported to be 1 in 40 (2.5% w/v) at 40°C (3). We estimated it at room temperature to be about 2% w/v (data not shown), which is lower than the 1.25% (12.5 mg/mL) used as an anaesthetic. Therefore, we do not expect the tribromoethanol to precipitate following intraperitoneal injection at the concentration used in this study. The major difference between formulations was that tribromoethanol could be readily dissolved directly in the cyclodextrin solution prior to use, whereas for the standard formulation tribromoethanol required dissolution in an organic solvent followed by dilution with normal saline. When the organic solution was diluted, tribromoethanol precipitation was noted and time was required to allow this to re-dissolve prior to use. The binding constant between tribromoethanol and HP-β-CD was not determined in this work; however, the ease of preparation of the HP- β -CD solution without the need for an organic solvent suggested it may be a suitable alternative formulation for tribromoethanol.

A high level of variation in response to anaesthesia regardless of formulation, even between animals of the same inbred strain, age, sex and approximate weight. Circadian rhythm was taken into account by performing the procedures at the same time of day, and the same researchers completed all experiments.

The standard tribromoethanol formulation appeared to produce deeper anaesthesia than the cyclodextrin formulation, with a minimum CRS of 1.8 compared to 5.2. This may be due to the presence of the organic solvent (concentration = 0.625% in the injected solution), which is known to cause depression and ataxia on its own. This could also be evidence of complexation of tribromoethanol in the cyclodextrin cavity, as this binding would result in reduced levels of free anaesthetic. The loss and gain of righting reflex reflects the level of anaesthesia reached with the two formulations. Differences in the respiratory rate may be related to the quality of anaesthesia, or could be due to the difficulty in visually assessing the breathing rate of mice. A more accurate form of measurement should be used in the future. No pathology was seen in either group of mice. This may be due to the relatively low concentration of solution and dose used, as studies have illustrated an increase in inflammation as these factors increase (8). The post mortem was undertaken 14 days after anaesthetic administration and the inflammation may have resolved by this time (9).

Conclusions

This study has identified the value in using atropine in addition to tribromoethanol for anaesthesia. Because of the concerns of anaesthetics resulting in respiratory and cardiac depression, it could be a recommendation to use this anticholinergic more frequently with other anaesthetics. tribromoethanol could be formulated as a 1.25% w/v solution 0.035M HP- β -CD in a single step without a need for organic solvent. The reduced anaesthetic effect may have been due to tribromoethanol complexation with the cyclodextrin so that a dose response study

is needed to determine the appropriate anaesthetic dose for this formulation. No evidence of peritonitis or abdominal adhesions were observed with either formulation, suggesting that freshly prepared tribromoethanol solutions (reference or HP- β -CD) at a concentration of 1.25% were not significantly irritant.

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Consumer and Diversified Products

Charles Frey Coating Place, Inc., Verona, WI, U.S.A.

This Patent Watch covers the time period from July 1, 2010 to December 31, 2010. It includes selected patents from the U.S. Patent Database that involve controlled release or a related aspect of controlled release. Patent selections were based on Consumer and Diversified Product interests and are presented in random order. The actual patents can be found on the U.S. Patent Website at http://patft.uspto.gov/.

Viscosity Modifiers in Controlled Release Lubricant Additive Gels (The Lubrizol Corporation, Wickliffe, OH); U.S. Patent 7,833,955

This invention involves the use of viscosity modifiers in a control release additive gel for sustained delivery of additives in lubricants to extend service life. It extends current controlled release gel technology in this area to gel-breaking lubricants. It is targeted for controlled release of viscosity modifier(s), friction modifier(s), ashless detergent(s), cloud point depressant(s), pour point depressant(s), demulsifier(s), flow improver(s), anti-static agent(s), ashless antioxidant(s), antifoam(s), corrosion/rust inhibitor(s), extreme pressure/antiwear agent(s), seal swell agent(s), lubricity aid(s), antimisting agent(s), a low viscosity material, and gel-breaking surfactants. Lubricant applications include gasoline engines, diesel engines, lubricating systems, and a wide variety of machinery.

System for Manufacturing Controlled Release Dosage Forms, such as Zero-Order Release Profile Dosage Form Manufactured by Three-Dimensional Printing (Massachusetts Institute of Technology, Cambridge, MA); U.S. Patent 7,820,201

This invention involves the use of print technology to form cylindrical delivery matricies that can be tailored to provide zero order, escalating, or decreasing release profiles. A key element of this technology is three-dimensionally printed radially-nested regions that are in contact with and axially extend to the cylinder ends. It also claims the ability to tailor the design to prisms and other shapes and to be able to compress these dosage forms into a larger dosing platform after printing.

Porous Organo-Metallic Skeleton Material Containing an Additional Polymer (BASF Aktiengesellschaft, Ludwigshafen, DE); U.S. Patent 7,815,716

The invention involves formation of a polymer in a porous metal-organic framework material for uptake of substances such gases or liquids. The framework material is composed of at least a bidentate organic compound bound by coordination to metal ions and creates pores for the polymer, which is selected for adsorption of the gas or liquid. Absorption may be selective and absorbed materials may include hydrogen, alkanes, carbon monoxide, carbon dioxide, nitrogen oxides, oxygen, sulfur oxides, halogens, noble gases, odor substances such as perfumes and fragrances, or organic solvents or liquids. The invention includes the framework production method, a method for taking up at least one substance by the framework material, and the use of the framework material for the storage, separation, controlled release, or chemical reaction of a substance that would be absorbed.

Terpolymers for Controlled Release of Bioactive Agents from Implantable Medical Devices (Medtronic Vascular, Inc., Santa Rosa, CA); U.S. Patent 7,815,927

This patent discloses the use of acrylate and/or vinyl terpolymers to overcome shortcomings of mixed polymer systems used for controlled release in implantable devices such as vascular stents, stent grafts, urethral stents, bile duct stents, catheters, guide wires, pacemaker leads, bone screws, sutures, and prosthetic heart valves.

Algae Resistant Roofing Granules with Controlled Algaecide Leaching Rates, Algae Resistant Shingles, and Process for Producing Same (CertainTeed Corporation, Valley Forge, PA); U.S. Patent 7,811,630

This patent involves the incorporation of copper oxide or zinc oxide into pores of roofing granules structured for sustained release. The algaecides are first incorporated in a soluble precursor form, which is subsequently heat treated to form the oxide.

Slow and Controlled-Release Polymeric Fertilizer with Multiple Nutrients, Preparing Process for the Same and the Use Method of the Same (Yaqing Liu, Taiyuan, Shanxi Province, CN); U.S. Patent 7,753,984

This invention involves slow and controlled-release polymeric fertilizers composed of multiple nutrients. Potassium, phosphorous, nitrogen, and micronutrient levels are controlled through the addition of appropriate amounts of potassium chloride, phosphoric acid, carbamide, formaldehyde, and micronutrient salt to form a polymeric matrix of balanced composition for the target application. Granules produced provide a sustained release mechanism with minimal environmental strain.

Bioactive Agent Release Coating and Controlled Humidity Method (Surmodics, Inc., Eden Prairie, MN); U.S. Patent 7,833,548

This patent describes coating compositions and the method of applying the compositions under conditions of controlled humidity to tailor the release profile of bioactive agents under physiological conditions. The coating composition is a combination of the bioactive agent along with poly-acrylate and poly-(ethylene-co-vinyl acetate) mixed polymer systems designed for use with medical devices such as stents and catheters. Control of bioactive agent release is achieved with both polymer composition and control of relative humidity during the coating process. Humidity is controlled through process air moisture content and/or the addition of water to the coating vehicle. API release rate from coated products increases with increasing process humidity.

Controlled Release Materials (Akzo Nobel N.V., Arnhem, NL); U.S. Patent 7,799,421

This invention relates to polymers whose water solubility may be triggered by changes in pH, salt concentration, surfactant concentration. The polymers are a copolymer or terpolymer containing an amine functionality that has been neutralized with a fixed acid. Films from these polymers are insoluble in a deprotonated form at a higher pH and at high salt or surfactant concentrations. The films become soluble upon protonation at a lower pH and at lower salt concentrations. The polymers can be used to coat or encapsulate active ingredients that are released based on changes in the environment, such as in the rinse cycle of a dishwasher or laundry washing machine.

Lignin-Based Microparticles for the Controlled Release of Agricultural Actives (Monsanto Technology LLC, St. Louis, MO); U.S. Patent 7,771,749

A method of producing lignin-based matrix micro-particles for the controlled release of agricultural actives such as pesticides, herbicides, and plant growth regulators is described. The process involves formation of an emulsion of an organic solution in an aqueous solution with a lignin derivative and the agricultural active. Upon removal of the organic solvent, controlled release micro-particles of the active in a lignin derivative matrix are produced.

Granular Pesticide Preparation (Kumiai Chemical Industry Co., Ltd., Tokyo, JP); U.S. Patent 7,829,499

This invention aims at providing a granular controlled release product of size and shape to provide optimum controlled-release of herbicides, plant growth regulators, fungicides, or insecticides. Granules are formed by various processes and are designed with a 30 minute disintegration time in water.

Encapsulation of Readily Oxidizable Components (General Mills IP Holdings II, LLC., Minneapolis, MN); U.S. Patents 7,803,413 and 7,803,414

These similar patents disclose a means of encapsulating oxidizable components such as omega-3 fatty acids for incorporation into particles, pellets, and formidable mixtures such as doughs. A plasticizer is used to solubilize an acidic antioxidant allowing antioxidant mobilization to scavenge oxygen and malodorous amines.

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For more information, contact Debby Woodard, CRS Business Development, at dwoodard@scisoc.org or +1.651.994.3817.

Drug Delivery and Translational Research

DDTR Highlights

Members are Invited to Publish in and Access *DDTR* Online for FREE

The all new *Drug Delivery and Translational Research* (*DDTR*) is an official member journal of CRS providing a unique forum for publication of high-quality research that focuses exclusively on translational aspects of drug delivery. It is available online to CRS members as a benefit at no additional charge. Join the leading scientists who are publishing their work in *DDTR*. All research is published before print immediately after peer-review and edit. To view *DDTR* articles, CRS members must login to the CRS website first, then select the menu tab, "Journal Access," and then click the link to *DDTR* online.

DDTR Editor's Picks

Two *DDTR* Articles Demonstrate Progress in Vaccine Delivery Technology

Vaccination is the most cost-effective means to prevent the spread of infectious diseases. However, the development of delivery technologies that can effectively induce a protective immune response and conveniently be used in mass populations remains a challenge. New articles published in the *DDTR* highlight these issues. A review article by Jain et al. describes various novel vaccine delivery technologies and challenges. A research highlight article by Kim and Prausnitz describes a microneedle-based skin patch for vaccination that can potentially be used without requiring hospital visits.

Coming Next Month!!

A *DDTR* Special Focus Issue on "Advances in Vaginal Drug Delivery," with David R. Friend as Guest Editor

Vaginal drug delivery systems are gaining widespread interest because they allow the local administration of drugs to prevent transmission of sexually transmitted diseases such as HIV-1 and



HSV-2. These systems may also apply for contraception. This special issue describes various "multipurpose" drug delivery technologies for drugs of different physicochemical properties including peptides and vaccines, either alone or in combination, for a number of indications. Since sexually transmitted diseases are on the rise worldwide, an effective vaginal drug delivery technology could have global implications.

Videos Coming to DDTR Online!

CRS is pleased to announce the launch of video enhancements to *DDTR* articles available through Springer.com. This allows authors and readers to interact with *DDTR* in a unique way. Although anyone can upload an original video, this new submission feature will

be especially useful for *DDTR* authors who wish to augment their papers in innovative ways. Video submissions will undergo an editorial review process to check for suitability, conflict of interest, and other review criteria before posting. Learn more... http://videos.springer.com/

CRS and Springer will Combine to Reward *DDTR* Outstanding Paper Recipient

The scientist who receives the *DDTR* Outstanding Paper Award will receive recognition from the Society along with valuable prizes from Springer publishing and CRS, according to *DDTR* Editor-in-Chief, Vinod Labhasetwar. The awardee will receive the following:

- \$500 Book Award Choice of more than 37,000 titles published by Springer
- Complimentary CRS Annual Meeting and Exposition Registration
- Certificate of Recognition
- Award Winner to Give Presentation at the 39th CRS Annual Meeting in 2012



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Report on the 4th Annual Meeting of AUS-CRS, Australian Chapter of the Controlled Release Society 2010

Written by Ben Boyd (President AUS-CRS)

The 4th Annual Meeting of the Australian Chapter of the Controlled Release Society (AUS-CRS 2010) was held on Thursday and Friday the 25th and 26th of November 2010 at Monash Institute of Pharmaceutical Sciences in Melbourne. This was an important landmark event for the Chapter as it was the first meeting held independently of other associations, the first time the program had run over two days, and the first time we had had contributed papers as podium presentations. The conference was generously sponsored by **Sotax, Davies Collison Cave, and Hospira,** represented by Jean Louis Raton, Paula DeBruyn, and Leab Sek, respectively.

The AUS-CRS 2010 was opened by an introductory talk by Ben Boyd (current president of AUS-CRS). Diane Burgess was the invited Plenary Speaker (Immediate Past President of CRS, University of Connecticut, USA) who provided an outstanding plenary lecture entitled 'Control at Interfaces.'

The program continued on the first day with lectures from national and international invited (Istvan Toth (past Aus-CRS President), Martina Stenzel, Joselito Razal, and Kim Chan) and contributed papers (Marius Skwarczynski, Chantelle Driever, Paul White, Anthony Day, Hui Xin Ong, and David Morton). The afternoon was punctuated by an entertaining 'double-act' contributed paper by Peter Stewart and Paul Young where they gave a competitive debate-style presentation on their differing theories around the mechanism and importance of particle deagglomeration in respiratory delivery! The conference dinner on the Thursday night was held at the nearby Melbourne Zoo, with attendees entertained by the Cheek to Cheek Trio, a great time had by all! **Davies Collison Cave** provided a random door prize of an outstanding bottle of Penfolds Grange gladly accepted by Paul Young from University of Sydney.

The Friday program again featured invited (Tak Kee, Colin Pouton, Michael O'Donoghue, Maree Smith, Paul Gavin, and Xavier Mulet) and contributed presentations (David Owen, Andrea O'Connor, and Angel Tan). The standard of the contributed talks was outstanding and we thank these speakers especially for their participation.





Plenary speaker, Prof. Diane Burgess (Immediate Past President of CRS) is introduced to open the conference by Ben Boyd, current President of AUS-CRS.

Photos by Josephine Chong (Monash University)

AUS-CRS attendees enjoy lunch below the magnificent Cossar Hall mural.



Prof. Istvan Toth (inaugural President AUS-CRS) presents his lecture on vaccine delivery (left); Jean Louis Raton (Sotax) expounds the virtues of USP Apparatus 4 to Des Williams (University of South Australia) at right.

The AUS-CRS conference has strongly supported students in past years with 2× \$1,000 travel bursaries to the CRS Annual Meeting as prizes for the two best posters presented at the conference. Student poster presentations (23) were on display throughout the 2010 conference during the breaks and were judged by committee members and session chairs. This year the winners were:

1st prizes: Pegah Varamini, The University of Queensland and Wye-Khay Fong, Monash Institute of Pharmaceutical Sciences each awarded \$1,000 contribution towards attending CRS Washington, U.S.A. 2011. Pegah's poster was entitled "*In vivo* pharmacological assessment of two lipid conjugated endomorphin-1 analogues," while Wye-Khay's poster was entitled "Light responsive nanostructured matrices for pulsatile delivery."



Photos from the conference dinner, clockwise from top left: Paul Young (University of Sydney) receives his bottle of Penfolds Grange from Paula DeBruyn (Davies Collison Cave); Jean Louis Raton (Sotax), Diane Burgess (U. Conn.), and Chantelle Driever (University of Melbourne) enjoy a predinner drink; Pavla Simerska (Scientific Secretary, AUS-CRS seated right) with colleagues Pegah Varamini and Fredericke Mansfield from University of Queensland, Clive Prestidge from University of South Australia and Dani Traini University of Sydney (Secretary – AUS-CRS); attendees enjoy the music and dancing (shall remain nameless!).



Clockwise from top left: Ben Boyd presenting the 1st poster prizes to Pegah Varamini and Wye-Khay Fong and 2nd prize to Daryn Goodwin and 3rd prize to Thilaga Yuvaraj.

2nd and 3rd prizes (\$100 book voucher): Daryn Goodwin (University of Queensland) and Thilaga Yuvaraj (University of South Australia).

We thank CRS for in part funding for Diane Burgess's travel costs, and we are particularly grateful to our generous sponsors Sotax, Davies Collison Cave, and Hospira, without whom this highly successful event would not be possible.

AUS-CRS Annual General Meeting

At the conclusion of conference proceedings, the Annual General Meeting of AUS-CRS was held. The committee elected for AUS-CRS in 2011 were as follows:

- 1. Ben Boyd was re-elected as the President of AUS-CRS
- 2. Michael Rathbone was re-elected as the Vice-President
- 3. Pavla Simerska was re-elected as Scientific Secretary
- 4. Daniela Traini was elected the new Secretary
- 5. Leab Sek was elected as Treasurer

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People in the News

Compiled by Steven Giannos Industrial Editor

NAE Elects 68 Members and Nine Foreign Associates

February 8, 2011 – WASHINGTON – The National Academy of Engineering (NAE) has elected 68 new members and nine foreign associates, announced NAE President Charles M. Vest today. This brings the total U.S. membership to 2,290 and the number of foreign associates to 202.

Election to the National Academy of Engineering is among the highest professional distinctions accorded to an engineer. Academy membership honors those who have made outstanding contributions to "engineering research, practice, or education, including, where appropriate, significant contributions to the engineering literature," and to the "pioneering of new and developing fields of technology, making major advancements in traditional fields of engineering, or developing/implementing innovative approaches to engineering education."

A select list of the newly elected members and foreign associates follows, with their primary affiliations at the time of election and a brief statement of their principal engineering accomplishments.

New Members

Nadine N. Aubry, Raymond J. Lane Distinguished Professor and head of the mechanical engineering department, Carnegie Mellon University, Pittsburgh. For contributions to lowdimensional models of turbulence and microfluidic devices, and for leadership in engineering education.

Michael J. Cima, Sumitomo Electric Industries Professor of Engineering, department of materials science and engineering, Massachusetts Institute of Technology, Cambridge. For innovations in rapid prototyping, high-temperature superconductors, and biomedical device technology.

James Joseph Collins, professor of biomedical engineering and co-director, Center for BioDynamics, Boston University, Boston. For contributions to synthetic biology and engineered gene networks.

Stuart L. Cooper, University Scholar Professor and chair, department of chemical and biomolecular engineering, Ohio State University, Columbus. For contributions to polymer chemistry, biomedical polyurethanes, blood compatibility, and academic administration.

Linda G. Griffith, professor of biological and mechanical engineering and director, Biotechnology Process Engineering Center, Massachusetts Institute of Technology, Cambridge. For contributions to 3D functional biomaterials, engineered hepatic tissues, and cell transplant devices. Mark S. Humayun, professor of ophthalmology, biomedical engineering, and cell and neurobiology, University of Southern California, Los Angeles. For contributions to development and clinical implementation of the visual prosthesis for restoration of sight.

Keith P. Johnston, M.C. (Bud) and Mary Beth Baird Endowed Chair and Professor of Chemical Engineering, University of Texas, Austin. For advances in science and technology of particles and colloids used in drug delivery, biomedical imaging/ therapy, microelectronics, and energy applications.

Jindrich Kopecek, Distinguished Professor of Pharmaceutics and Pharmaceutical Chemistry and Distinguished Professor of Bioengineering, University of Utah, Salt Lake City. For contributions to the design of hydrogel biomaterials and polymeric drug delivery systems.

Cato T. Laurencin, Van Dusen Endowed Chair in Academic Medicine; Distinguished Professor of Orthopaedic Surgery and Chemical, Materials, and Biomolecular Engineering; dean, School of Medicine; and vice president for health affairs, University of Connecticut, Farmington. For biomaterial science, drug delivery, and tissue engineering involving musculoskeletal systems, and for academic leadership.

Joseph C. Salamone, chief scientific officer, Rochal Industries LLP, San Antonio. For advances in ophthalmological devices and wound healing therapies and for distinguished academic and professional service.

Dr. Abraham Abuchowski of Prolong Pharmaceuticals Honored With Inaugural Tibbetts Award by the U.S. Small Business Administration

PRNewswire: February 17, 2011 – SOUTH PLAINFIELD, NJ – Dr. Abraham Abuchowski, CEO and Scientific Founder of Prolong Pharmaceuticals, was honored by the U.S. Small Business Administration on February 15 with their inaugural Tibbetts Award for leadership in innovation and job creation. Dr. Abuchowski was one of eight individuals recognized, and the only honoree in the pharmaceutical/biopharmaceutical industry.

Dr. Abuchowski was the originator of the PEGylation technology, now the most widely-used protein drug delivery system in the world. Prior to being one of the founders of Prolong Pharmaceuticals, Dr. Abuchowski founded Enzon Pharmaceuticals, now a fully integrated, publicly-traded company. During his time as CEO, Enzon successfully introduced the PEGylation technology and brought three new protein-based drugs to market with FDA approval. PEGylated drugs have garnered sales in the tens of billions of dollars around the world.

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The Tibbetts Award winners were honored for the critical role they play in research and development for the government and for their success in driving innovation and creating new jobs. "Winning the future requires redoubling our commitment to supporting innovative entrepreneurs like those we honor with Tibbetts Awards," said Karen Mills, SBA administrator. "Their stories illustrate the promise of the new generation of innovative entrepreneurs and remind us all how central the success of one high growth small business can be to our competitiveness as a nation."

Pharmaceutics International Inc. (Pii) Announces Appointment of Rampurna Prasad Gullapalli, Ph.D. as Vice President of Drug Delivery Technologies

PRNewswire: March 17, 2011 – HUNT VALLEY, MD – Pharmaceutics International Inc. (Pii), a leading contract development and manufacturing organization, today announced the appointment of Rampurna Prasad Gullapalli as vice president of Drug Delivery Technologies. Dr. Gullapalli is responsible for providing strategic scientific and technical leadership in areas of softgel, liquid-filled hard capsules, and novel drug delivery technologies for Pii's contract development and manufacturing business.

"Prasad's extensive background in oral dosage form development adds to Pii's leadership position as a foremost provider of oral dosage form development and GMP manufacturing services to the pharmaceutical industry," said Steve King, senior vice president of Pii. "We look forward to him helping us continually grow our oral formulation development capabilities."

Prior to joining Pii, Dr. Gullapalli served as an associate director of Elan Pharmaceuticals, where he was responsible for preformulation and oral dosage form development. He also served in various scientific positions with increasing responsibilities at Chiron Corporation, Purdue Pharma, Banner Pharmacaps and R.P. Scherer (now Catalent). During his career, Dr. Gullapalli has had extensive experience in the development and manufacturing of a broad range of dosage forms including softgels, liquid-filled hard capsules, nanosuspensions, suspensions, solutions, and controlled release tablets and capsules for highly insoluble and soluble compounds.

Dr. Gullapalli holds a Ph.D. in Pharmaceutics form the University of Tennessee, Memphis and a Masters in Pharmacy in Phamracology from Andhra University (India). He holds Regulatory Affairs Certification (RAC-US) and is experienced in the FDA and EMA CMC regulatory submissions. Dr. Gullapalli is an invited guest lecturer at the University of California at Davis and authored/co-authored several publications in professional journals and presentations at national conferences. He is also an inventor/co-inventor of several patents and patent applications.

Spotlight on the

38th Annual Meeting & Exposition of the Controlled Release Society Host City

National Harbor, Maryland, U.S.A.



National Harbor is just 11 miles south of Washington, DC, and a scenic water taxi ride across the Potomac to historic Old Town Alexandria, Virginia.

- National Harbor, Maryland. Familiar U.S. retailers and unique local boutiques line this bustling urban town center, filled with pedestrian-friendly plazas, tree-lined walkways, and colorful streetscapes. National Harbor's waterfront and marina backdrop completes the perfect setting for dinner cruises, water taxi rides, outdoor dining, and entertainment opportunities.
- Washington, DC—The U.S. Capital. Washington, DC's Metro is one of the world's best public transportation systems providing a quick, convenient, and affordable way to get around the city. Many of Washington, DC's major attractions are open to the public, free-of-charge, including the National Zoo, National Portrait Gallery, Library of Congress, the U.S. Supreme Court, Ford's Theatre, the Smithsonian Institution museums, and the national monuments and memorials located on or near the National Mall.
- Historic Old Town Alexandria, Virginia. Alexandria, Virginia, is located just 5 miles away from National Harbor and is the third oldest district in the United States. The free King Street Trolley will take you to the numerous restaurants, antique shops, and art galleries that line the cobblestone streets of this neighborhood once home to George Washington and Robert E. Lee.

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Photo courtesy of National Harbor.

14th Industrial Symposium and 5th Trade Fair on Microencapsulation

James Oxley, Ph.D.

Recently, 120 scientists from 19 countries gathered in downtown San Antonio, TX for the 14th Industrial Symposium and 5th Trade Fair on Microencapsulation. The event was a collaborative effort between the Bioencapsulation Research Group (BRG), Controlled Release Society (CRS), and the Southwest Research Institute (SwRI). Started 20 years ago by Denis Poncelet, the BRG has an established history of organizing industrial symposia and conferences multiple times a year at various locations around the world. The BRG teamed with the CRS Consumer and Diversified Products committee to help bring an industrial symposium to the United States, choosing San Antonio and SwRI to help host and organize the event.

Over the course of three days, attendees listened to 10 presentations by leading professionals, interacted with 14 exhibit booths, participated in over 500 one-on-one meetings, and spent an afternoon at SwRI observing process demonstrations and touring the R&D facilities. The most unique and successful component of this symposium were the one-on-one meetings. Upon registering for the meeting, attendees were required to fill out a profile to summarize their company, business, and reason for attending the conference. Attendees were then granted access to the profiles of all attendees to rank who they would like meet during the conference. Immediately prior to the meeting, all of the requests were processed and printed into individual personalized schedules that contained up to 20 pre-arranged



one-on-one meetings. The meetings were scheduled for 40 minutes apiece and provided a scheduled structured environment to promote discussions between attendees, which might not occur in a more casual or traditional conference setting. Feedback for this format was extremely positive and participation was very high.



The conference concluded with a half-day visit to SwRI. Approximately 75 of the conference attendees were bused to SwRI and split into groups for observation of process demonstrations and a tour of the SwRI facilities. The four processes demonstrated were spray drying, fluid bed coating, coextrusion, and emulsion encapsulation processes. The 25 minute demonstrations were led by top scientists in each of the fields, accompanied by a SwRI technician to aid equipment operation and support.

This inaugural collaborative event between CRS, BRG, and SwRI was a great success. Downtown San Antonio and the nearby Riverwalk, combined with excellent weather, provided a wonderful setting for the 14th Industrial Symposium and 5th Trade Fair on Microencapsulation. The CRS was well represented by seven members from the Consumer & Diversified Products group. And, based on the success of this meeting, plans are underway to repeat this event in the near future.

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In the News

Compiled by Steven Giannos Industrial Editor

March 2011

Localized Delivery of an Anti-Cancer Drug by Remotecontrolled Microcarriers

PRNewswire: March 16, 2011 – MONTREAL, CA – Soon, drug delivery that precisely targets cancerous cells without exposing the healthy surrounding tissue to the medication's toxic effects will no longer be an oncologist's dream but a medical reality, thanks to the work of Professor Sylvain Martel, Director of the Nanorobotics Laboratory at Polytechnique Montréal.

Known for being the world's first researcher to have guided a magnetic sphere through a living artery, Professor Martel is announcing a spectacular new breakthrough in the field of nanomedicine. Using a magnetic resonance imaging (MRI) system, his team successfully guided microcarriers loaded with a dose of anti-cancer drug through the bloodstream of a living rabbit, right up to a targeted area in the liver, where the drug was successfully administered. This is a medical first that will help improve chemoembolization, a current treatment for liver cancer.

The therapeutic magnetic microcarriers (TMMCs) were developed by Pierre Pouponneau, a Ph.D. candidate, under the joint direction of Professors Jean-Christophe Leroux and Martel. These tiny drug-delivery agents, made from biodegradable polymer and measuring 50 micrometers in diameter-just under the breadth of a hair—encapsulate a dose of a therapeutic agent (in this case, doxorubicin) as well as magnetic nanoparticles. Essentially tiny magnets, the nanoparticles are what allow the upgraded MRI system to guide the microcarriers through the blood vessels to the targeted organ. During the experiments, the TMMCs injected into the bloodstream were guided through the hepatic artery to the targeted part of the liver where the drug was progressively released. The results of these in-vivo experiments have recently been published in the prestigious journal Biomaterials and the patent describing this technology has just been issued in the United States.

The Nanorobotics Laboratory, which aims to develop new platforms for medical intervention, works closely with interventional radiologist Dr. Gilles Soulez and his team of the Imaging Research Platform at the Centre hospitalier de l'Université de Montréal Research Centre to develop medical protocols adapted for future use on humans.

Dr. Martel and his team receive financial support from the Canadian Institutes of Health Research (CIHR), the Canada Research Chair (CRC), the Canada Foundation for Innovation (CFI), the Natural Sciences and Engineering Research Council of Canada (NSERC), the Fonds québécois de la recherche sur la nature et les technologies (FQRNT) and the Fonds de la recherche en santé du Québec (FRSQ). Reference: Pouponneau, P., Leroux, J.-C., Soulez, G., Gaboury, L. and Martel, S. (2011). Co-encapsulation of magnetic nanoparticles and doxorubicin into biodegradable microcarriers for deep tissue targeting by vascular MRI navigation. Biomaterials. Volume 32, Issue 13, May 2011, Pages 3481-3486. (DOI: 10.1016/j.biomaterials.2010.12.059)

Gold Nanoparticles Use DNA to Deliver DOX Anti-Cancer Drug

PRNewswire: March 16, 2011 – SYRACUSE, NY – Scientists in Syracuse University's Chemistry Department have created a new drug delivery system expected to advance the effectiveness of cancer-killing drugs. It uses gold nanoparticles with attached DNA that binds to a proven anti-cancer drug, Doxorubicin or DOX.

Preliminary tests indicate this delivery device has the potential to significantly improve the results of cancer chemotherapy. DOX is currently used against cancers of the breast, bone marrow, thyroid, bladder, ovary, small cell lung and several others.

"The possibilities of this new system are really exciting," says SU Professor James C. Dabrowiak. "For example, it would be easy to add to the device molecules that have the ability to target cancer cells. Another possibility is using light excitation to release high concentrations of an anti-tumor drug directly within the tumor."

These and other upgrades could enable clinics to focus chemotherapy more tightly on cancer cells and reduce negative side effects on healthy cells in other parts of the body.

A key element of the new system is that the DNA attached to the gold particles is engineered specifically to bind to the DOX antitumor drug. Studies show that the DOX can be transferred by diffusion to a receptor DNA molecule.

The gold nanoparticles have an average diameter of only 15.5 nanometers or a few billionths of a meter. A single nanoparticle presents more than 100 DOX sites and that, when multiplied by millions of the particles, could create a massive and deadly assault on a tumor.

"We believe this work can bring significant gains in the effectiveness of chemotherapy treatments," says Mathew M. Maye, SU Assistant Professor of Chemistry and co-inventor of the delivery system. "We still have work to do but this advance opens a promising new field of investigation that can lead to important new clinical tools."

The anti-tumor drug, DOX, already accepted by the FDA, is a key advantage of the new system. Other such drugs may be

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In the News continued from page 35

deployed using this system simply by engineering the DNA to bind to a different drug molecule. The Syracuse laboratory is continuing investigations to check the toxicity of the system. They will also explore "smart" particles capable of attaching to cancer cells and responding to triggers that will activate drug release. Prior discoveries demonstrate that such nano-delivery systems may be within reach and could help deliver large payloads of anti-tumor drugs where needed.

Depomed Licenses Acuform[®] Technology and Glumetza[®] Data to Boehringer Ingelheim

Fiercedrugdelivery.com: March 15, 2011 - MENLO PARK, CA - Depomed, Inc. (NASDAQ: DEPO) today announced that Boehringer Ingelheim has licensed worldwide rights to Depomed's Acuform[®] gastric retentive drug delivery technology to develop and commercialize certain fixed dose combination product(s) which include extended release metformin and proprietary Boehringer Ingelheim compound(s) in development for type 2 diabetes. Boehringer Ingelheim has also been granted a right of reference to the Glumetza® (extended release metformin hydrochloride tablets) NDA and associated data for use in potential regulatory submission processes. "We are pleased to have closed our third licensing deal for our extended release metformin technology. The upfront and future milestone payments will strengthen our balance sheet, while the potential royalties will add to our revenue build-up as a specialty pharmaceutical company," said Carl A. Pelzel, president and chief executive officer of Depomed.

Under the terms of the agreement, Boehringer Ingelheim is responsible for development and commercialization of the product(s). Depomed will receive a \$12.5 million license fee, \$10 million of which is payable upfront, with an additional \$2.5 million payable upon delivery of experimental batches of prototype formulations. Depomed is also eligible to receive additional milestone payments based on regulatory filing and approval events, and royalties on worldwide net sales of product(s). Further details of the agreement were not disclosed.

"We are pleased to contribute the value of Glumetza's dossier and our metformin extended release technology to Boehringer Ingelheim's type 2 diabetes compound(s)," said Thadd Vargas, Depomed's senior vice president, Business Development. "This exciting new partnership adds an important new aspect to our unique metformin franchise strategy," he added. Additional information about Depomed may be found on its website, http:// www.depomed.com.

Inovio Pharmaceuticals' Partner ChronTech Initiates Phase II Clinical Trial of Hepatitis C Virus DNA Vaccine Using Inovio's Electroporation Delivery Technology

PRNewswire: March 14, 2011 – BLUE BELL, PA – Inovio Pharmaceuticals, Inc. (NYSE Amex: INO), a leader in the development of therapeutic and preventive vaccines against cancers and infectious diseases, announced today that its partner, ChronTech Pharma AB (formerly Tripep AB), has initiated a Phase IIb clinical study of its ChronVac-C[®] DNA vaccine for hepatitis C virus (HCV), delivered by Inovio's proprietary electroporation DNA vaccine delivery technology, in combination with standard of care.

In a Phase I clinical trial of ChronVac-C using Inovio's MedPulser[®] electroporation device, the therapy resulted in a robust increase in T-cell immune responses against HCV and was safe and well tolerated. Post-study observation of subjects who completed the protocol and then entered into standard of care (SOC) treatment using interferon and ribavirin showed a complete and rapid viral response (four weeks) in 70% of those participants (5 of 7 patients). More significantly, 83% of the participants (5 of 6 patients) who were monitored for an extended period of time continued to be free of the virus six months after they completed SOC. SOC treatment alone usually results in about 40–50% of patients reaching undetectable virus levels after six months of treatment.

This Phase II follow-on trial is an open-label, single-dose, randomized trial of 32 patients to further explore the effect of the ChronVac-C[®] DNA vaccine administered by Inovio's MedPulser[®] electroporation delivery device. The therapy will be given two times, with four weeks in between, followed by SOC treatment after the final vaccine dose in treatment-naïve chronic HCV infected genotype-1 subjects. This trial will assess the level of immune responses, levels of HCV viral load, and further assess the response to the delivery technology. Twenty patients will receive ChronVac-C[®] vaccine delivered with Inovio's electroporation device; the 12-patient comparison group will receive standard-of-care treatment alone. The study has received approval from the Swedish Medical Products Agency and local ethical committee.

"If we can repeat the Phase I results in this phase IIb study there is certainly a possibility that vaccination with ChronVac-C[®] before drug therapy could become a part of the standard of care therapy for patients with chronic hepatitis C-virus infection. In particular, we hope that vaccination with this novel therapy will result in a considerable shortening of the duration of interferon and ribavirin treatment," said Anders Vahlne, CEO of ChronTech Pharma AB.

Dr. J. Joseph Kim, Inovio's president and CEO, said: "We are encouraged by the phase I results showing the improved cure rate in patients who received the HCV vaccine followed by a SOC drug therapy. Any improvement to the HCV standard of care response rates would be well received by HCV patients and practitioners. We are pleased to collaborate in this advancement of ChronVac-C[®], using Inovio's innovative delivery technology, into Phase II."

Inovio's electroporation-based DNA delivery systems can increase the cellular uptake of an agent by 1,000 times or more. When used to deliver DNA vaccines, Inovio's systems can increase levels of gene expression (i.e., production of the coded protein) and immune responses by 100 times or more compared to plasmid DNA delivered without other delivery enhancements. Inovio has recently reported best-in-class immune responses with DNA vaccines for cervical dysplasias/cancers and HIV. Inovio has also shown the safety and tolerability of its electroporation devices in many hundreds of patients and continues to advance device innovations to further enhance the utility of these devices for mass vaccinations.

Inovio is developing a new generation of vaccines, called DNA vaccines, to treat and prevent cancers and infectious diseases. These SynCon[™] vaccines are designed to provide broad crossstrain protection against known as well as newly emergent strains of pathogens such as influenza. These vaccines, in combination with Inovio's proprietary electroporation delivery devices, have been shown to be safe and generate significant immune responses. Inovio's clinical programs include HPV/ cervical dysplasia and cancer (therapeutic), avian flu (preventive), and HIV vaccines (both preventive and therapeutic). Inovio is developing universal influenza and other vaccines in collaboration with scientists from the University of Pennsylvania. Other partners and collaborators include Merck, National Cancer Institute, U.S. Military HIV Research Program, NIH, HIV Vaccines Trial Network, University of Southampton, and PATH Malaria Vaccine Initiative. More information is available at www.inovio.com.

IPX066 Demonstrates Efficacy and Safety in ADVANCE-PD

Business Wire: March 14, 2011 – HAYWARD, CA – Impax Pharmaceuticals, the branded products division of Impax Laboratories, Inc. (NASDAQ: IPXL), today announced statistically significant, positive, top-line results of the ADVANCE-Parkinson's Disease (PD) Phase III clinical study of the safety and efficacy of IPX066 versus immediate-release (IR) carbidopa-levodopa (CD-LD) in advanced PD patients experiencing motor fluctuations. IPX066 is an investigational extended release (ER) CD-LD product. The ADVANCE-PD results demonstrated that IPX066 produced significantly improved control of motor symptoms as compared to IR CD-LD in multiple clinical measures in subjects with advanced PD.

The primary endpoint of this comparison study of IPX066 to IR CD-LD was the percentage of "off time" during waking hours. IPX066 demonstrated a 37% improvement from baseline for IPX066 vs. a 17% improvement from baseline for IR CD-LD (p<0.0001). "Off time" is the functional state when patients' medication effect has worn off and there is a return of Parkinson's symptoms.

The study enrolled 471 subjects on a stable regimen of IR CD-LD who were first entered into a dose-adjustment phase of their IR CD-LD, followed by a conversion to IPX066, after which they were then randomized to either IPX066 or IR CD-LD. Subjects converted to IPX066 experienced a reduction from baseline of more than 2 hours in total "off time" during waking hours, and this effect was maintained in the group then randomized to IPX066 during the blinded study portion. While the group treated with IR CD-LD achieved similar improvement during conversion to IPX066, "off time" worsened by 1.0 hours during double blind treatment with IR CD-LD (p<0.0001). In addition, during double-blind treatment, subjects experienced similar results in "on time" without troublesome dyskinesia with an increase of 1.9 hours for IPX066 compared to an increase of 0.8 hours for IR CD-LD as measured from study entry (p<0.001).

Additional clinical and patient-reported outcome measures in the study consistently demonstrate the improved IPX066 efficacy profile when compared to IR CD-LD. This includes the Unified Parkinson's Disease Rating Scale (UPDRS), Clinician Global Impression of Change (CGI) and Patient Global Impression of Change (PGI), which also demonstrated significant improvements in treatment with IPX066 compared to IR CD-LD (p<0.0001 for all comparisons). In quality-of-life (QOL) measures, IPX066 demonstrated significant improvement over IR CD-LD as measured by PDQ-39 (p<0.035) and modified Rankin Test (p<0.006).

"Impax Pharmaceuticals is excited to report these positive results for the ADVANCE-PD trial demonstrating the clinical benefits of IPX066 over IR CD-LD, which is the gold standard in treating advanced PD," stated Dr. Suneel Gupta, Impax Pharmaceuticals' Chief Scientific Officer. "Consistent with our Phase II findings, these data show IPX066 provides a robust level of efficacy across a range of PD clinical and QOL measures, which represents a potentially significant improvement over existing treatment options. With the successful completion of this ADVANCE-PD trial and the APEX-PD trial in patients with early PD, we have completed the two required Phase III trials for a New Drug Application (NDA) as agreed with the Food and Drug Administration. We are working diligently to file an NDA in the fourth quarter of 2011."

IPX066 was generally well tolerated, and during the doubleblind portion of the trial had an adverse event (AE) rate of 43% compared to 40% for IR CD-LD. The most common AEs reported for IPX066 included: insomnia, nausea, fall, dizziness, and dyskinesia (no event was associated with a greater than 3.5% overall incidence). The rate of related serious AEs was comparable, with one subject in each treatment arm reporting serious treatment-related AEs in the double-blind treatment phase.

According to Robert A. Hauser, MD, Professor of Neurology, Molecular Pharmacology, and Physiology and Director of the Parkinson's Disease & Movement Disorders Center at the University of South Florida and an ADVANCE-PD study investigator, "There is a major unmet need in patients with advanced PD for a therapy that can consistently extend and improve motor symptom control through the day and enhance quality of life." Dr. Hauser added, "In the ADVANCE-PD study, daily 'off time' was reduced without worsening of dyskinesia, and both patients and clinicians reported overall improvement. The magnitude of benefit observed with IPX066 was clinically

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significant and results indicate that PD patients should be able to enjoy improved control of their motor symptoms and a better quality of life."

InVivo Therapeutics Announces Data on Novel Hydrogel Technology in Spinal Cord Injury and Neurosurgical Applications

Business Wire: March 9, 2011 – CAMBRIDGE, MA – InVivo Therapeutics (OTCBB: NVIV), a company focused on the development of groundbreaking technologies for the treatment of spinal cord injuries (SCI), today announced that a poster highlighting data from a laboratory investigation of the company's injectable hydrogel technology for local, controlledrelease drug delivery, is being presented at the 2011 Annual Meeting of the American Association of Neurological Surgeons (AANS)/Central Nervous System (CNS) Section on Disorders of the Spine and Peripheral Nerves, which is being held March 9–12 in Phoenix, Arizona.

The laboratory investigation, titled "An injectable thiol-acrylate poly(ethylene glycol) hydrogel for sustained release of methylprednisolone sodium succinate for treatment of spinal cord injury and in neurosurgical applications," was designed to evaluate the potential of the rationally designed hydrogel to overcome limitations associated with systemic administration of high-dose methylprednisolone (MP), a steroid that is commonly used in the treatment of SCI. Current limitations include increased risk of infection, delayed wound healing, pneumonia, and sepsis.

"Biomaterials have the potential to enable more localized and controlled delivery of MP, reducing many of the safety risks associated with conventional delivery methods while exerting an anti-inflammatory effect directly on the site of injury," said Eric J. Woodard, MD, Chief of Neurosurgery, New England Baptist Hospital, who co-authored the study and will be representing the poster at the meeting.

Dr. Woodard continued: "Our findings indicate that the injectable, polyethylene-glycol-based hydrogel used in the study is a potential candidate for local controlled release of MP in the intraparenchymal and peridural spaces of the spinal cord. Drug dosage for local administration could be individually tailored without affecting the release time-period or hydrogel volume. Its demonstration of syneresis may ensure that no pressure is exerted by the hydrogel upon equilibration to avoid compression of neural elements, making it a potentially useful candidate in neurosurgical applications."

Along with its biocompatible polymer scaffold device, which the company plans to move into a clinical study in the second half of this year, InVivo is developing its novel hydrogel technology as a treatment for SCI. Both technologies focus on protection of the spinal cord and prevention of secondary injury, an approach, which unlike any currently available treatment, is designed to address the underlying pathology of a SCI.

InVivo Therapeutics Holdings Corp. is a Cambridge, MA medical device company focused on utilizing polymers as a platform technology to develop treatments to improve function in individuals paralyzed as a result of traumatic spinal cord injury. The company was founded in 2005 on the basis of proprietary technology co-invented by Robert Langer, ScD, Professor at Massachusetts Institute of Technology, and Joseph P. Vacanti, MD, who is affiliated with Massachusetts General Hospital in Boston.

Elan Announces First European Commission Approval of Injectable Treatment Using Elan's NanoCrystal[®] Technology

Business Wire: March 9, 2011 – DUBLIN, IRELAND – Elan Drug Technologies (EDT), the drug delivery unit of Elan Corporation, plc (NYSE: ELN), today announced that the first injectable product using EDT's NanoCrystal[®] technology has been approved by the European Commission. XEPLION[®], Janssen-Cilag International NV's long-acting injectable treatment for patients with schizophrenia which uses EDT's NanoCrystal[®] technology, was approved by the European Commission earlier today.

"The versatility of our NanoCrystal[®] technology enabled the development of a long-acting injectable antipsychotic which is designed to help patients maintain continual treatment, reduce the likelihood of relapse and thereby potentially improve their overall quality of life."

"The European approval of XEPLION[®] is an important milestone for our NanoCrystal[®] technology as it marks the first long-acting injectable product approved by the European regulatory authorities using this technology," said Shane Cooke, Executive Vice President and Chief Financial Officer of Elan and Head of EDT. "The versatility of our NanoCrystal[®] technology enabled the development of a long-acting injectable antipsychotic which is designed to help patients maintain continual treatment, reduce the likelihood of relapse and thereby potentially improve their overall quality of life."

On March 9, 2011, Janssen-Cilag International NV, one of the Janssen Pharmaceutical Companies, announced the approval of XEPLION[®], a once monthly atypical antipsychotic injection, by the European Commission. XEPLION[®] is indicated for maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone. In selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, XEPLION[®] may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed.

EDT's NanoCrystal[®] technology enables the formulation of poorly water-soluble compounds for all routes of administration. The technology allows for a ready-to-use, one-month duration, intramuscular injection formulation of paliperidone palmitate which can be administered by healthcare professionals. The

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intramuscular injection is administered using a small bore needle and small volume syringe, thereby negating the need for a power injector. By applying the NanoCrystal[®] technology to paliperidone palmitate, healthcare professionals will be able to provide patients with consistent medication coverage for one month, potentially allowing them to improve compliance for patients with schizophrenia.

NanoCrystal[®] technology is a proprietary technology developed by EDT through Elan Pharma International Limited and other Elan affiliates. XEPLION[®] is the fourth licensed product using Elan's NanoCrystal[®] technology that has been approved by the EMA.

3M Skin & Wound Care Launches Soothing Antifungal Cream

Business Wire: March 8, 2011 – ST. PAUL, MN – 3M Skin & Wound Care has introduced new 3M[™] Cavilon[™] Antifungal Cream, an easy-to-apply cream that effectively relieves skin discomforts due to fungal infections. Addressing the needs of incontinence caregivers and patients, this new cream offers a soothing solution to relieve redness, irritation, scaling, itching, and burning associated with fungal infections. The new product is available in convenient two-ounce and five-ounce tubes.

Cavilon Antifungal Cream has been enriched with waterrepelling ingredients, critically important for protecting vulnerable skin and ideal for helping caregivers working in incontinence settings. The cream has been formulated with twopercent Miconazole Nitrate, an active ingredient that has been clinically proven to treat tinea corporis (ringworm), tinea pedis (athlete's foot), and tinea cruris (jock itch). The product is also approved for use on fungal infections caused by *Candida albicans*.

"This product addresses skin fungal infections with a barrier property that resists washing off. I plan to use this product for incontinence care in my practice, and it can be used by and for patients in all types of settings, from hospitals to long-term care facilities," said JoAnn Ermer-Seltun, RN, a Wound Ostomy Continence Nurse and Family Nurse Practitioner at Mercy Medical Center in North Iowa.

"Cavilon Antifungal Cream fills a significant need for clinicians and their patients, and by launching this new product, 3M is reinforcing its strong commitment to skin care," said Marcello Napol, global business director, 3M Skin & Wound Care. "It also bolsters our Cavilon brand by meeting clinical needs for all types of skin applications."

Cavilon Antifungal Cream is the latest product extension of the Cavilon professional skin care line, which offers healthcare professionals, home caregivers, and patients a full range of products to simplify skin care regimens, maintain and support skin integrity, and provide comfort and convenience. In fall 2010, the entire Cavilon brand was updated with new, innovative packaging to help caregivers easily identify the right product for a specific need. Later this year 3M will be adding enhanced product formulations, sizes, and new patient-friendly delivery systems to the Cavilon line.

All Cavilon products come with easy-to-read packaging, and 3M also offers training and product support for caregivers and health professionals. 3M invites professional and non-professional caregivers and patients to visit www.3M.com/Cavilon, which provides information and support. In addition, a dedicated toll-free helpline, 1-800-228-3957 has been established. For more information on 3M Skin & Wound Care, visit www.3M.com/ SkinHealth.

Alliqua Successfully Completes Next Milestone in Transdermal Pain Patch Development

Business Wire: March 7, 2011 – NEW YORK, NY – Alliqua, Inc. (OTCBB: ALQA) (FWB: HL1) ("Alliqua"), an advanced biomedical products company focused on the development and manufacturing of proprietary drug delivery and liver health technologies, announced today the successful completion of its initial *in vitro* permeation study for its transdermal pain patch project. These results represent an important milestone in the development of a transdermal pain patch. Alliqua previously announced the successful completion of its dissolution study.

In the comparative in vitro permeation study, the Alliqua patch demonstrated mean cumulative drug permeation that was competitive with the market leading product for the treatment of pain associated with post-herpetic neuralgia ('PHN") or shingles, a rising medical problem in the United States and around the world as countries continue to struggle with increasingly elderly populations. In the in vitro permeation study, multiple formulations were evaluated, with some achieving mean cumulative drug permeation amounts much higher than the market leading product, indicating the potential for an improvement over the existing product. Alliqua believes that the results provide it with options to pursue a 505(b)(2) type of a New Drug Application (NDA), along with a generic route for an Abbreviated New Drug Application (ANDA). Based on the positive results, Alliqua will proceed to the next stage of its developmental program.

"The continued success of our developmental efforts further validates our delivery platform and our belief in the ultimate success in our specialized transdermal pain patch," said Richard Rosenblum, President and Director of Alliqua. "Utilizing our proprietary hydrogel technology and our existing facilities, we believe Alliqua can become a high quality, low cost producer of this next generation transdermal pain patch, with the possibility for significant market share." Alliqua also intends to continue pursuing a generic version of an existing pain management patch for the treatment of PHN.

Management estimates that the total U.S. market for pain management pharmaceuticals, exclusive of over-the-counter (OTC) products, totaled in excess of \$20 billion in 2009, with the market for existing prescription pain patches in excess of \$1

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billion in the U.S. alone. According to the Centers for Disease Control, approximately 1 million cases of shingles occur in the United States annually, and approximately 20% of shingles cases result in PHN. Alliqua's patch technology enables the delivery of drugs and active ingredients directly through the stratum corneum, avoiding "first pass" of the digestive system and the liver.

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

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

Echo Therapeutics Receives Frost & Sullivan's 2011 Technology Innovation Award

PRNewswire: March 1, 2011 – FRANKLIN, MA – Echo Therapeutics, Inc. (OTC Bulletin Board: ECTE), a company developing the Symphony[™] tCGM System as a non-invasive, wireless, transdermal continuous glucose monitoring (tCGM) system and the Prelude[™] SkinPrep System for transdermal drug delivery, today announced that it won the prestigious 2011 North American Frost & Sullivan Technology Innovation Award in Pharmaceuticals and Biotechnology. Echo received this award in recognition of the Prelude SkinPrep System's breakthrough technology.

The Prelude SkinPrep System uses a needle-free, painless technology that removes the outermost layer of skin, the stratum corneum, to permit topical drug delivery or needle-free analyte analysis. For its initial use, Echo's partner, Ferndale Pharma Group, has applied to the U.S. Food and Drug Administration for permission to market the Prelude SkinPrep System to enhance the delivery of topical 4% lidocaine.

Echo is now accelerating the final Prelude manufacturing validation and scale-up in order to prepare for commercial launch and it expects marketing efforts of the Prelude SkinPrep System to commence in the third quarter of this year, pending FDA approval. The FDA 510(k) submission was supported by clinical data from a study that demonstrated skin anesthesia with 4% lidocaine was achieved within five minutes following use of the Prelude System, compared to the customary 30- to 60-minute wait.

"We are pleased that Frost & Sullivan has recognized the significance of Echo's Prelude SkinPrep technology in drug delivery," said Echo's Chairman and CEO Patrick T. Mooney, M.D. "We believe that 2011 will be a transformative year for Echo and our shareholders and we feel that this recognition is well-deserved and demonstrates the value of our technology."

The Frost & Sullivan Award for Technology Innovation of the Year is given for the development and introduction of a new technology, a well-designed product family as well as significant product performance contributions. Frost & Sullivan found Echo's performance superior to its key competitors, based on analytical tools that integrate both quantitative and qualitative metrics.

"Prelude SkinPrep overcomes the primary obstacle to achieving therapeutic drug levels via the transdermal route – the brick-andmortar-like stratum corneum – making it possible to transdermally deliver a compound in a manner that preserves the integrity of the skin, reduces the risk of infection, and improves the quality of care," concluded Frost & Sullivan Research Analyst, Misty Hughes. "Echo Therapeutics' innovative platform technology goes beyond the function and capabilities of traditional passive transdermal technologies, and has the potential to greatly expand the range of molecules that can be delivered and extracted transdermally."

Valeritas Receives FDA 510(k) Clearance for the V-Go™ Disposable Insulin Delivery Device for Use with NovoLog[®]

PRNewswire: March 1, 2011 – BRIDGEWATER, NJ – Valeritas, Inc., a medical technology company committed to the development and commercialization of innovative drug delivery solutions, announced today that the U.S. Food and Drug Administration has cleared the company's V-Go Disposable Insulin Delivery Device for use with Novo Nordisk's NovoLog[®] for the continuous subcutaneous delivery of insulin in preset basal rates and with on-demand bolus dosing for adult patients requiring insulin. In December 2010, Valeritas received FDA clearance for the V-Go's use with Eli Lilly's Humalog[®].

"With the addition of NovoLog[®] to the V-Go label, we have demonstrated that the two most widely prescribed fast acting insulins in the United States can be used safely with the V-Go and thereby have increased healthcare professional and patient insulin options available for use with the V-Go Disposable Insulin Delivery Device," said Valeritas CEO Kristine Peterson.

February 2011

Pfizer Completes Acquisition Of King Pharmaceuticals, Inc.

Business Wire: February 28, 2011 – NEW YORK, NY – Pfizer Inc. (NYSE: PFE) today announced that it has combined operations with King Pharmaceuticals, Inc. On February 28, 2011, Pfizer completed its acquisition of King through the merger

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of its wholly owned subsidiary, Parker Tennessee Corp., with and into King. King is now a wholly owned subsidiary of Pfizer. Under the terms of the transaction, each outstanding share of King common stock has been converted into the right to receive \$14.25, net in cash (without interest and less any required holding taxes). Prior to the merger, Parker Tennessee Corp. acquired approximately 92.5% of the outstanding King shares through a tender offer. Effective as of the close of trading yesterday, King common stock ceased trading on the New York Stock Exchange.

"With the addition of King's talented colleagues and innovative products and technology, Pfizer will offer patients who are in need of pain relief and pain management a broader spectrum of treatment options," said Ian Read, Pfizer president and chief executive officer. "Pfizer's expanded portfolio also includes King's Meridian auto-injector business for emergency drug delivery, which develops and manufactures the EpiPen[®], and its Alpharma animal health business, both of which are complementary to and aligned with Pfizer's existing businesses."

"We believe we are in a position to quickly capitalize on the benefits offered by the combination with King, including a strengthened portfolio, immediate incremental revenues, and an anticipated contribution to steady earnings growth and shareholder value."

Pfizer continues to expect the transaction to be accretive to its adjusted diluted earnings per share(1) by approximately \$0.02 annually in 2011(2) and 2012(2), and approximately \$0.03-\$0.04 annually from 2013 through 2015, and to yield initial cost savings from operating expenses of at least \$200 million, which are expected to be fully realized by the end of 2013.

Pfizer has appointed American Stock Transfer & Trust Company, LLC as paying agent for payment of the merger consideration. Additional information will be mailed to King registered shareholders outlining the steps to be taken to obtain the merger consideration. Shareholders do not need to take any action regarding their shares until contacted by the paying agent. For additional information, King shareholders can contact American Stock Transfer & Trust Company at 877-248-6417 or 718-921-8317.

Noven Files Patent Infringement Lawsuit Against Mylan Technologies

Business Wire: February 22, 2011 – MIAMI, FL – Noven Pharmaceuticals, Inc. announced today that it has filed a lawsuit in the U.S. District Court for the Southern District of New York against Mylan Technologies Inc. ("Mylan") claiming infringement of certain Noven patents (the "Patents") by Mylan.

The lawsuit was filed as a result of an Abbreviated New Drug Application (ANDA) submission by Mylan seeking FDA approval to market and sell a generic version of Vivelle-Dot[®] (estradiol transdermal system) prior to the scheduled expiration of the Patents in 2014. The lawsuit reflects Noven's commitment to vigorously defending its intellectual property rights against infringement. Under the Hatch-Waxman Act, because Noven filed this patent infringement lawsuit within 45 days of receiving a Paragraph IV notification letter from Mylan, the FDA must refrain from approving Mylan's ANDA for 30 months (until June 2013), or until a district court decision declaring that the Patents are invalid or not infringed, whichever occurs earlier. For more information about Noven, visit www.noven.com. For information about Hisamitsu, visit www.hisamitsu.co.jp/english.

Kalobios Selects POTELLIGENT® CHOK1SV Cell Line for the Research, Development and Manufacture of Humaneered™ Antibodies

Business Wire: February 8, 2011 – PRINCETON, NJ and BASEL, SWITZERLAND – KaloBios Pharmaceuticals, Inc., has signed a research and commercial agreement with BioWa, Inc. and Lonza to use their POTELLIGENT[®] CHOK1SV cell line for the development and production of its Humaneered[™] antibodies.

POTELLIGENT[®] CHOK1SV is a new host cell line for manufacturing recombinant antibodies that combines the power of BioWa's engineered glycosylation POTELLIGENT[®] Technology with the advantages of Lonza's proprietary GS Gene Expression System[™], which includes the industry-leading cell line CHOK1SV.

"We are gratified by the confidence that Kalobios displays in selecting the POTELLIGENT[®] CHOK1SV cell line as its production host for its innovative treatments", said Janet White, Head of Development Services at Lonza. "We look forward to working with Kalobios to meet its manufacturing needs and to continuing our successful, long-lasting collaboration."

The POTELLIGENT[®] CHOK1SV cell line is available as one of the options in Lonza cell line construction offerings. To learn more about the benefits of POTELLIGENT[®] CHOK1SV, please contact one of our experts at +44 (0) 1753 777 000 or GSLonza@lonza.com.

Fuisz Pharma Announces Patented Communication of Analyte Information Between Microchip Containing Smart Tablet and a Body Fluid Analyzer

PRNewswire: February 7, 2011 – MIAMI, FL – Based on U.S. Patent 7,824,612 ("Body Fluid Analyzer and System including Same and Method for Programming Same"), Fuisz Pharma today announced the use of their patented technology to create a new class of microchip containing smart tablets that communicate with personal body fluid analyzers.

These tablets wirelessly inform a body fluid analyzer of acceptable analyte values for body fluids, set by the drug company so that the analyzer can provide alerts where the patient's results exceed a threshold value.

Joseph Matus Fuisz, CEO of Fuisz Pharma, states, "We are seeing extraordinarily exciting developments around the use of

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microchip enabled smart tablets that can wirelessly communicate pertinent information to receiving devices. At the same time, we are seeing further growth in the capabilities of personal body fluid analyzers and a greater appreciation for their use in drug development and personalized medicine. Thus, we see the use of our patent 7,824,612 to enable the value added connection of tablet smart chips together with personal analyzers to convey a broad spectrum of pertinent information. This enhances the function of smart tablets and analyzers alike."

Fuisz Pharma (www.fuisz.com) is a private pharmaceutical technology company originated by the Fuiszes. The Fuiszes have made substantial contributions in drug delivery including orally dissolving tablets and novel particle coating systems at Fuisz Technologies; inventing and developing thin film drug delivery technologies at Kosmos Pharma and MonoSol Rx, as well as independently developing extruded sheet technology, and have extensive experience working with big and specialty pharma.

Celtic Pharma Announces Presentation of Preclinical Data at the 69th Annual Meeting of the AAD in New Orleans

PRNewswire: February 7, 2011 – LONDON, NEW YORK, and HAMILTON, BERMUDA – Celtic Pharmaceutical Holdings L.P. ("Celtic Pharma"), the global private equity firm focused on the biotechnology and pharmaceutical industries, announced today the presentation of key *in-vitro* data at the American Academy of Dermatology (AAD) 69th annual meeting in New Orleans (4–8 February, 2011) for TDT 067, terbinafine in Transfersomes[®], for the topical treatment of onychomycosis (also known as a fungal nail infection).

The first of the two *in-vitro* studies presented by the lead investigator, Professor Mahmoud Ghannoum, Director of the Centre for Medical Mycology at Case Western Reserve University in Cleveland, Ohio, investigates the activity of TDT 067 against the common causative agents of onychomycosis as measured by minimum inhibitory and fungicidal concentrations. The data demonstrate that TDT 067 has potent inhibitory and fungicidal activity against dermatophyte strains, and that the fungicidal activity of TDT 067 is shown to be more potent than conventional terbinafine preparations.

In a second *in-vitro* study, presented by Professor Ghannoum, the morphology and ultrastructure of dermatophyte hyphae were investigated following exposure to TDT 067 using scanning electron microscopy (SEM) and transmission electron microscopy (TEM). The data show that terbinafine formulated in Transfersomes in Celtic Pharma's TDT 067 drug candidate potentiates the action of terbinafine by enabling it to penetrate more effectively to its site of action inside the fungus, where it disrupts the intracellular matrix leading to eventual death of hyphae.

Michael Earl, co-CEO of Celtic Pharma Development Services, said: "The *in-vitro* data presented at the AAD demonstrate that TDT 067 potentiates the anti-fungal effects of terbinafine and the entry of the drug into dermatophyte hyphae, which we believe will provide a significant clinical benefit for the treatment of

onychomycosis. We hope to see confirmation of this benefit through the on-going pivotal clinical trial."

TDT 067 is currently in Phase III development. A 42-center global trial is currently in progress and has fully enrolled the planned 776 patients. The study is powered to provide registrational data on the efficacy, tolerability, and safety of topically applied terbinafine delivered through the Transfersome® targeted delivery technology over 48 weeks. Transfersomes® are a transdermal drug delivery system that enables delivery of high concentrations of drug to deep tissue without significant systemic exposure to the drug, so TDT 067 is designed to obviate the hepatotoxicity issues associated with oral administration of terbafine.

Particle Sciences and HORIBA Instruments Form Strategic Relationship

February 7, 2011 – BETHLEHEM, PA – Particle Sciences, Inc., a leading pharmaceutical CRO, is pleased to announce the establishment of a strategic alliance with HORIBA Instruments of Irvine, CA, which is the U.S. sales and marketing division of HORIBA Limited of Kyoto, Japan. This alliance assures that both client bases are provided with a total solution, combining the most up-to-date physical characterization tools with operational expertise in a fully GLP/GMP compliant setting.

Under the arrangement, the full array of HORIBA characterization tools will be available at Particle Sciences. Dr. Robert Lee, Vice President of Pharmaceutical Development at Particle Sciences states, "The need for particle size analysis and physical characterization in general is growing rapidly within this highly regulated environment. Particle Sciences is a world leader in particulate formulations and drug/device combination products. We looked for a partner that shared the same commitment to quality and innovation and HORIBA fit the bill."

With this in place, HORIBA clients will have a resource that can both develop and perform characterization under cGLPs and cGMPs. According to Dr. Mike Pohl, HORIBA's Vice President, "Our client base ranges from startups to the largest multinational pharma and biotech companies. For a variety of reasons, we are often asked if we can recommend a site familiar with pharmaceutical development at which they could have work performed. We have worked with Particle Sciences for some time and have been impressed with their facility and their team. By entering into this relationship, we can ensure that our clients not only gain access to the most advanced technology, but also that the operators are highly trained to use the instruments to their fullest capability."

Dr. Lee adds, "Particle Sciences is committed to remaining one of the premier drug delivery development services providers. We offer a broad array of drug delivery technologies and routinely work on atypical dosage forms. It's critical that our analytic and characterization capabilities keep pace with our formulation expertise. Additionally, as our clients scale to clinical and ultimately commercial processes, we need to ensure the methods we develop are phase appropriate and based on readily available

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techniques. HORIBA is the world's largest instrument manufacturer with the most complete product offering and can now provide the level of security our clients deserve."

Dr. Pohl asserts, "Many pharmaceutical customers are located along the East Coast. The combination of our Edison, NJ headquarters plus the Bethlehem, PA location of Particle Sciences, Inc., gives HORIBA a strong one-two punch to support these customers. Services ranging from sample analysis, customer support, and full consulting services will now be readily accessible to our customers."

The HORIBA Group of worldwide companies provides an extensive array of instruments and systems for applications ranging from automotive R&D, process and environmental monitoring, in-vitro medical diagnostics, semiconductor manufacturing and metrology, to a broad range of scientific R&D and QC measurements. Proven quality and trustworthy performance have established widespread confidence in the HORIBA brand. Particle Sciences is an integrated provider of drug development services. Particle Sciences has deep expertise in micro- and nano-particulate drug delivery technologies and drug/ device combination products with additional specialized capabilities in topical and mucosal drug products. Through a full range of formulation, analytic, and manufacturing services, Particle Sciences provides pharmaceutical companies with a complete and seamless development solution that minimizes the time and risk between discovery and the clinic. The company was founded in 1991 and is headquartered in Bethlehem, Pennsylvania. Visit www.particlesciences.com, email info@ particlesciences.com or contact us at (610) 861-4701 for information. Contact: Maureen Cochran, mcochran@ particlesciences.com.

Hospira Announces FDA Approval of Topotecan Injection

PRNewswire: February 3, 2011 – LAKE FOREST, IL – Hospira, Inc. (NYSE: HSP), the world leader in generic injectable pharmaceuticals, today announced U.S. Food and Drug Administration (FDA) approval of Topotecan Injection, the first solution formulation of the oncology drug approved in the United States. The medication is a generic version of Hycamtin[®], which had 2010 U.S. sales of more than \$140 million.

Hospira's topotecan is indicated for treatment of small cell lung cancer (SCLC) sensitive disease after failure of first-line chemotherapy. The solution formulation of topotecan, with a concentration of 4 mg/4 ml, is designed to improve caregiver convenience and safety, and Hospira expects to launch the product by the end of February.

"Hospira's solution version of topotecan expands our portfolio of value-added generics," said Thomas Moore, president, U.S., Hospira. "We're excited to offer the medical community access to a lower-cost, more convenient version of this key oncolytic."

Hospira's specialty injectable pharmaceuticals (SIP) offering includes approximately 200 generic injectable drugs in many

dosages and formulations. In addition, many of its products are available in popular differentiated presentations, several of which are proprietary, such as ADD-Vantage[™] drug delivery system and iSecure[™] prefilled syringes. Therapeutic segments include analgesia, anesthesia, anti-infectives, cardiovascular, oncology, emergency, and other areas. Hospira also has robust pipelines of both generic and biosimilar drugs.

First Human Demonstration of Responsive, Microreservoir Drug Delivery Technology

PRNewswire: February 3, 2011 – BEDFORD, MA – MicroCHIPS, Inc., a developer of innovative drug delivery systems, is initiating the first clinical study to demonstrate precisely controlled delivery of a peptide from a multi-reservoir, programmable, implant system. The study will assess the pharmacokinetics of long-term parathyroid hormone (hPTH 1-34) delivery in women with osteoporosis.

Parathyroid hormone is a 34-amino acid peptide that is currently self-injected daily to increase bone density in women suffering from severe osteoporosis. During MicroCHIPS' first human study, in progress at a site in Denmark, participants will receive a series of precisely timed doses of PTH(1-34) over a period of months, eliminating the need for injections. The drug will be delivered automatically using wireless communication to confirm dose delivery.

"MicroCHIPS' clinical study marks an important milestone in the comprehensive research and development of a new approach to drug delivery," said Robert Langer, ScD, Institute Professor at the Massachusetts Institute of Technology and a MicroCHIPS co-founder. "MicroCHIPS' breakthrough technologies have the ability to transform therapy in numerous disease states using active and responsive drug delivery devices."

MicroCHIPS' systems are designed to achieve more effective regimens and increase control over the dose, timing and location of drug delivery. The reservoir devices can release individual doses of a drug with a range of target pharmacokinetics over an extended *in vivo* period. Therapy can be delivered on a pre-programmed basis, and the regimen can be modified as a patient's condition changes.

MicroCHIPS' miniaturized systems are adaptable to implants and catheters and can be integrated into external pumps, pens and infusion systems.

"Many of today's drug delivery products can offer only incremental improvements in efficacy and compliance," said Ajit Gill, MicroCHIPS' President and CEO. "MicroCHIPS has developed sophisticated technologies that can function as embedded or standalone delivery devices to create precise dosing regimens. The capabilities are well-suited for the delivery of proteins and peptides where current therapy is complex or cumbersome for patients and their physicians."

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January 2011

Echo Therapeutics Launches Corporate Twitter Account and Facebook Page

PRNewswire: January 25, 2011 – FRANKLIN, MA – Echo Therapeutics, Inc. (OTC Bulletin Board: ECTE), a company developing its needle-free Symphony[™] tCGM System as a noninvasive, wireless, transdermal continuous glucose monitoring system and its Prelude[™] SkinPrep System for transdermal drug delivery, today announced that the company has launched a corporate Twitter account and corporate Facebook Page. Twitter users can now follow Echo at http://www.twitter.com/echotx and Facebook users can visit Echo at http://www.facebook.com/ echotx.

Echo joins other medical device companies who are utilizing social media to provide online communities and individuals with faster and more direct access to credible health information, resources, news, and events.

"As we move toward the anticipated commercialization of our products this year Echo is eager to communicate directly with the company's investors and with physicians and patients in order to share valuable information in a timely manner," said Echo's Chairman, President and CEO Patrick T. Mooney, M.D. "We are excited to enter the social media network by incorporating Twitter and Facebook into our broader communication efforts."

Soligenix Receives FDA Orphan Drug Designation for RiVax[™] for the Prevention of Ricin Intoxication

PRNewswire: January 20, 2011 – PRINCETON, NJ – Soligenix, Inc. (OTC Bulletin Board: SNGX) (Soligenix or the Company), a late-stage biopharmaceutical company, announced today that the US Food and Drug Administration (FDA) has granted Orphan Drug Designation to RiVax[™] for the prevention of ricin intoxication. RiVax[™] is a proprietary vaccine that contains a recombinant subunit of the A chain of ricin toxin which induces ricin neutralizing antibodies in humans and animals.

The US Orphan Drug Act is intended to assist and encourage companies to develop safe and effective therapies for the treatment of rare diseases and disorders that affect fewer than 200,000 individuals within the United States. In addition to providing a seven-year term of market exclusivity for RiVaxTM upon FDA approval, Orphan Drug Designation also positions Soligenix to be able to take advantage of certain financial and regulatory benefits, including government grants for conducting clinical trials, waiver of FDA user fees for the potential submission of a Biologics License Application for RiVaxTM, and certain tax credits.

RiVax[™] induces a protective immune response in animal models of ricin exposure and is currently being evaluated in humans. A human Phase 1A clinical trial of RiVax[™] has been completed and a Phase 1B clinical trial remains ongoing. Results of the Phase 1A clinical trial of RiVax[™] indicated that the immunogen was safe and induced antibodies anticipated to protect humans from ricin exposure. The outcome of the study was published in the Proceedings of the National Academy of Sciences (Vitetta et al., 2006, PNAS, 105:2268-2273). The Phase 1B trial, sponsored by University of Texas Southwestern Medical Center in Dallas (UT Southwestern), is currently evaluating a more potent formulation of RiVaxTM. Soligenix has developed processes for large-scale manufacturing of the vaccine product and is developing the product using animal models for efficacy under the FDA animal rule. RiVax[™] was invented by Ellen Vitetta, PhD, Director of the Cancer Immunobiology Center and colleagues at UT Southwestern.

"The FDA's decision to grant RiVax[™] Orphan Drug Designation for the prevention of ricin intoxication marks another important step forward in our biodefense pipeline," stated Christopher J. Schaber, Ph.D., President and CEO of Soligenix. "Marketing exclusivity through Orphan Drug Designation adds significantly to the existing patent estate surrounding RiVax[™]. We are enthusiastic about the prospects of developing a ricin vaccine to anticipate civilian and military biodefense requirements and for potential government stockpiling."

RiVax[™] is Soligenix's proprietary vaccine developed to protect against exposure to ricin toxin and is the most advanced vaccine in the company's portfolio. RiVax[™] has been shown to induce a protective immune response in animal models of ricin exposure and in human clinical trials. The current Phase 1B clinical trial is being supported by a grant to UT Southwestern from the FDA's Office of Orphan Products. The development of RiVax[™] to date has been sponsored through a series of overlapping challenge grants (UC1) and cooperative grants (U01) from the National Institutes of Allergy and Infectious Diseases (NIAID), which were granted to Soligenix and to UT Southwestern, where the vaccine originated. Soligenix and UT Southwestern have collectively received approximately \$25 million in grant funding from the NIH for development of RiVaxTM and related vaccine technologies. For further information regarding Soligenix, Inc., please visit the Company's website at www.soligenix.com.

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DRUG DELIVERYand

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Calendar of Events

2011

2011 AAPS National Biotechnology Conference

May 16–19 Hilton San Francisco Union Square San Francisco, CA, U.S.A. www.aapspharmaceutica.com/ NationalBiotech

CLINAM - European Foundation for Clinical Nanomedicine

May 23–25 Basel, Switzerland http://www.clinam.org/

Second International Congress Immunopharmacology 2011

June 26–30 Meliá Varadero Hotel Varadero Beach, Cuba www.immunopharmacologycuba.com/ Controlled Release Society Symposium: An Overview for Empowering Controlled Release Technology Transfer in Personal Care & Cosmetics June 30

New York City, New York, U.S.A. www.hbaexpo.com

38th Annual Meeting & Exposition of the Controlled Release Society

July 30–August 3 Gaylord National Hotel and Convention Center National Harbor, MD, U.S.A. www.controlledreleasesociety.org/ main/meetings

71st FIP World Congress of Pharmacy and Pharmaceutical

Sciences September 2–8 Hyderabad, India www.fip.org/congresses

2011 AAPS Annual Meeting and Exposition

October 23–27 Washington, DC, U.S.A. www.aapspharmaceutica.com/ meetings/annualmeet/AM11

2012

9th World Biomaterials Congress

June 1–5 New International Exhibition & Convention Center Chengdu, China www.wbc2012.com

39th Annual Meeting & Exposition of the Controlled Release Society

July 14–18 Centre des Congrès de Québec Québec City, Canada www.controlledreleasesociety.org/main/ meetings