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Newsletter

A publication of the Controlled Release Society

Volume 26 • Number 4 • 2009

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The CRS Newsletter is the official newsletter of the Controlled Release Society. The newsletter is published five times annually providing scientific and technical information pertinent to the controlled release community and news about society and chapter activities. Members can receive the newsletter via mail. The newsletter may also be viewed online at www.controlledreleasesociety.org.

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Yvonne Perrie
Aston University, School of Life and Health Sciences,
Aston Triangle, Birmingham, U.K.

Good Science and 11 Hours of Wrestling—It's All in This Issue

Welcome to our post-meeting *CRS Newsletter*, where we bring you a roundup of all the activities over the three days of our CRS Annual Meeting in Copenhagen. CRS 09 was, as expected, an excellent conference with many interesting talks and posters. As CRS President Diane Burgess notes, the meeting was filled with the latest research in our field set in a beautiful city. Within this *Newsletter* we have lots of photos and reports of the meeting so have a look to see if you spot people you know. I myself must confess to making it into the background of one photo. I thought I had ensured I was not captured in any picture, but when the proofs came out and Steve Giannos spotted me, it was too late to remove it. So, if you are looking to fill a few moments at coffee, you can always play "Where's Wally?" I will not dwell on the meeting too much, as if you didn't manage to make it could get annoying—but just one other thing about the meeting, can I be a stereotyped Scot and say, "Gosh, the beer was expensive in Copenhagen." Whilst we are on the Scottish stereotype, I feel I must confirm that deep fried Mars Bars do not typify Scotland's diet, despite a study published in *Lancet* by Morrison and Petticrew (1) finding 22% of chip shops sell such a delicacy. I am sure times have changed; I mean where would you possibly get the funding for that research these days? However, perhaps this could be the next hot-topic in drug delivery—deep fried delivery systems for cholesterol-reducing drugs.

Whilst looking for inspiration for this editorial, I headed for Google. After searching for "writing an interesting editorial," it would appear what I need to do is provide some sort of knowledge within the article, so you don't feel you have wasted your time reading the article; already I feel I am failing. Apparently also writing an interesting article can become an enormous amount of fun (2). This has got me worried, as truth be told, I am not really having an enormous amount of fun, thus I guess I just proved this hypothesis—as those of you still reading the article are probably doing it out of politeness rather than interest. So just for you guys, here are some random interesting facts (3):

- If you spell all the numbers and try to find the letter "A," you will have to count to one thousand.
- 111,111,111 × 111,111,111 = 12,345,678,987,654,321.
- In the 1912 Olympic Games, the longest ever wrestling match was recorded. For 11 hours, two middle-weight wrestlers, Martin Klein (Estonia) and Alfred Asikainen (Russia), competed. Martin Klein eventually won, but he was so exhausted that he could not take part in the final match the next day and had to forfeit. Claes Johansson from Sweden won gold, and poor Martin went home with the silver medal.

Whilst you may find these facts mildly interesting, if you want to find some relevant and stimulating information related to controlled release and our Society, please read on, as our *Newsletter* is packed full of articles and news from our field.

Yvonne Perrie

References

1. Morrison, DS, Petticrew, M. Deep and crisp and eaten: Scotland's deep-fried Mars Bar, Lancet 364(9452): 2180 (2004).
2. http://ezinearticles.com/?Who-Will-Read-Your-Article---Writing-an-Interesting-Article.
3. http://www.interestingfacts.org/.

Diane J. Burgess, Ph.D.
Board of Trustees Distinguished Professor
School of Pharmacy, University of Connecticut, Storrs, CT, U.S.A.

I have been a member of CRS since 1986. While other aspects of my life and career have changed over the years, my interest and membership in CRS have been a constant. Through CRS, I've gained invaluable knowledge and made professional connections, as well as many friendships, that will undoubtedly last a lifetime. I was both honored and humbled when I was asked to submit my candidacy for president of CRS. To serve as CRS president is a fabulous addition to an already wonderful CRS experience. I am honored, excited, and ready to get started.

I also consider myself very lucky, as I am now leading an organization that is strong, vital, and growing. Even with the current worldwide economic climate, we had an outstanding attendance at the CRS Annual Meeting & Exposition in Copenhagen, Denmark, in July. Like Copenhagen itself, the annual meeting was exciting and stimulating beyond our expectations. From the impressive and well-received plenary presentations to the closing reception and banquet, it was an intellectual and collegial feast. Much of the thanks goes to CRS Scientific Secretary Ijeoma Uchegbu (University of London) for giving us such an outstanding program, as well as to the many member volunteers and committee members and chairs who helped make it happen.

The technical program more than achieved its goals, offering insights, new research, and thought-provoking concepts that had attendees re-examining their current thinking. The exceptional array of poster and podium topics was a strong indication of the rich and rewarding diversity of our membership and how that diversity energizes our Society. At the State of the Industry session, Chris Phelps (head of company analysis for Datamonitor) gained our appreciation and respect for providing us with an extremely well-informed and to-the-point assessment of the current state of our industry. As Phelps pointed out, these are challenging times for science and medicine.

Whatever the circumstances, CRS members have always embraced the challenge of research and discovery. This is evidenced by the reports given at the meeting by CRS committees, highlighting each committee's work over the past year and their plans for the future. There is certainly strong enthusiasm and energy within our committees.

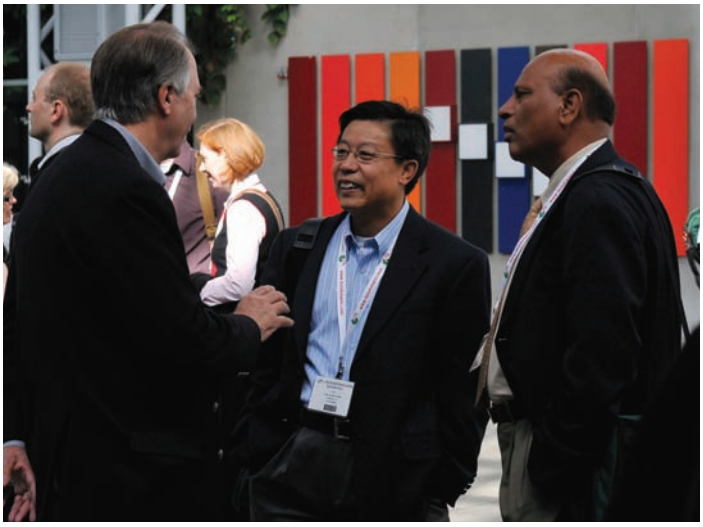
Our 21 Chapters, spread over the globe but linked and unified through CRS, are also passionate in their work. At the meeting, Chapter leaders were busy reporting, planning, and organizing for the upcoming year. Listening to their accomplishments for 2009 and their goals for 2010 left me with no doubt that we have built a worldwide network of committed, hardworking members.

Member involvement and support is critical, and it is our goal as a Society to recognize those among us whose achievements are particularly outstanding. The awards given at the CRS Annual Meeting always serve to inspire me and make me proud of my Society, which includes such gifted colleagues. I want to congratulate this year's award winners and to acknowledge the first-ever recipient of the Joseph R. Robinson Postdoctoral Fellowship, David Nguyen, a recent postdoctoral associate at MIT. The Robinson Fellowship honors past CRS President Joe Robinson and is given to an individual who demonstrates scientific excellence, scholarship, motivation, and leadership potential. The award is the CRS Foundation's first scholarship offering and was made possible by the generous support of individual and corporate donors. The CRS Foundation hopes this is the start of many more initiatives to help fund the advancement of our science, and with member support, it most certainly will be. I also want to specifically mention Past President Susan Cady who received our Distinguished Service Award and Past President Prof. Alexander T. Florence, who received our most prestigious Founders Award for outstanding research contributions. Prof. Florence was one of my mentors going back many years to my time as an undergraduate student at The University of Strathclyde, Glasgow, UK.

In 2010 we will meet again in Portland, OR, for another impressive lineup of events and programs that will continue to move us forward. In the meantime, as your president, I will focus on maintaining and growing our current level of prosperity, both financially as well as intellectually, ensuring the ongoing vitality of our publications, programs, and membership.

My door is open, and I invite you to contact me with your ideas, comments, and suggestions as we begin another year together with confidence.

Diane J. Burgess ■

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36th CRS Annual Meeting & Exposition in Review

There are various reasons people attend the CRS Annual Meeting & Exposition. Some come to meet and potentially partner with the 100 exhibitors showcasing their products and services. Others come to reconnect with colleagues and collaborate on new and continuing projects. Most come, in part, to learn about the latest research and advances in the delivery of bioactives. This year, more than 1,600 attendees found what they were looking for at the CRS Annual Meeting & Exposition, July 18–22, in Copenhagen, Denmark.

Technical Program

Plenary Presentations. An outstanding lineup of plenary speakers captivated audiences at the CRS Annual Meeting & Exposition. They presented cutting-edge research and proposed innovative ideas and techniques that got attendees thinking about how they currently do their jobs, including discussions on

- Targeting the NA+-ATPhase to Combat Metastatic and/or Multidrug-Resistant Cancers
  Robert Kiss, Belgian National Fund of Scientific Research, Belgium
- The Early History and Evolution of the Controlled Drug Delivery Field
  Allan Hoffman, University of Washington, U.S.A.
- What Is Needed to Further Improve the Health in the World?
  Mario Negri, Institute for Pharmacological Research, Italy
- Biorecognition—A Bridge from Smart Biomaterials to Drug-free Macromolecular Therapeutics
  Henry Kopeček, University of Utah, U.S.A.
- The Emergence of Innovative Transdermal-based Delivery Systems
  Gary Cleary, Corium international, Inc., U.S.A.
- Nanomedicine Research in the EU 7th Framework Program for RTD
  Heico Frima, European Commission, Belgium

Podium and Poster Topics. The core of the CRS Annual Meeting & Exposition is science and technology! When the call for papers went out in 2008, those of you with the hottest research in the industry responded! The result? A wide array of topics that covered the breadth and depth of delivery science:

- Advances in Process Technology
- Biomaterials for Medicines
- Blood-Brain Barrier
- Characterization Techniques—New Approaches
- Controlled Release for Textiles
- Evaluation of Controlled Release Products
- Gene Therapy
- Imaging Technologies for Diagnostics and Treatment
- Inhaled Medicines
- Inorganic Nanosystems
- Future Directions for Controlled Release
- Leading-Edge Device Technologies
- Liposomes and Micelles
- Membrane Transporters—Crossing Biological Barriers
- Micro- and Nanoparticles
- Nanomedicines
- Nanotechnology and Animal Models: Improving Health Outcomes
- Nasal Drug Delivery
- New Candidates for Polymer Therapeutics
- New Materials for Nanotechnology
- Oral Controlled Release Technologies
- Oral Delivery—Improving Absorption
- PEG-based Systems: Modulating Pharmacokinetics with Polymers
- Peptide and Protein Medicines
- siRNA Therapy
- Stents
- Tissue Engineering
- Transdermal
- Tumor Targeting
- Uniquely Original Delivery Systems
- Vaccines

Highlights of Student Posters. It is important to recognize the contributions of our students, the future of our science. Each year CRS selects a handful of student poster presenters who are asked to deliver their presentations in front of a panel of judges. This event recognizes the research efforts of these students, and attendees receive a concise preview of some of the best posters at the meeting. Congratulations to this year's winners!

First Place
Klaus Pollinger, University of Regensburg, Germany, for "Nanop article Delivery into Target Cells by G-Protein Coupled Receptors"

Second Place
Takunori Mozume, Kyoto Pharmaceutical University, Japan, for "Prevention of Bone Destruction in Rheumatoid Arthritis by Intrapulmonary Administration of Zoledronate, a Nitrogen Containing Bisphosphonate"

Third Place
Kate Yu Jung Lee, Emory University, U.S.A., for "Surface-Enhanced Raman Scattering (SERS)-encoded Gold Nanoparticle for Cancer Nanotherapy"

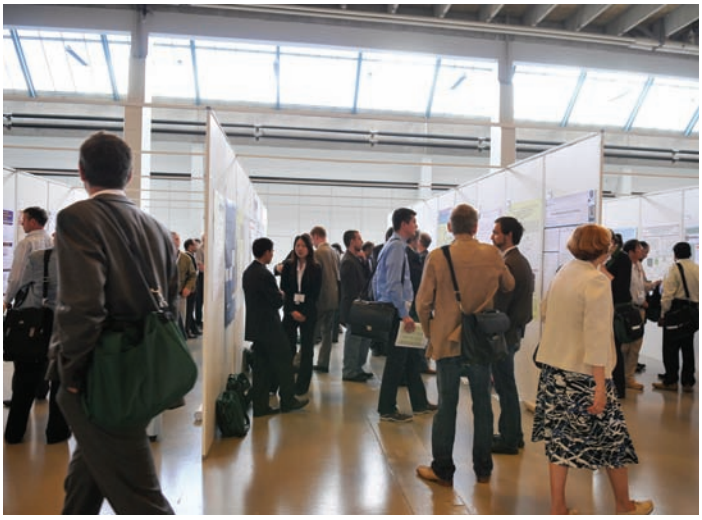
Fourth Place
Kathy Lee, Monash Institute of Pharmaceutical Sciences, Australia, for "Gastric Processing Is a Critical Determinant of the Ability of Lipid-based Formulations to Enhance the Oral Bioavailability of a Model Poorly Water-Soluble Drug"

Fifth Place
Kyung Hyun Min, Kyung Hee University, Korea, for "Synthesis, Characterization, and *In Vivo* Biodistribution of Hydrotoropic Glycol Chitosan Nanoparticles for Delivery of Paclitaxel"

Sixth Place
Odonchimeg Munkhjargal, Inje University, Korea, for "Preparation and Characterization of Porous PLGA Microparticles as a Vehicle for Protein Drug Delivery"

Mini-symposia. Attendees looking for the most complete update on the following topics made it a point to attend the Mini-symposia sessions. Each session featured a slate of invited speakers who are experts in their field:

- AIDS—Back to Basics
- Bioactive Materials & Veterinary
- Hydrogels—From Nanoparticulate Drug Carriers to Tissue Engineering Scaffold
- Innovations in Drug Delivery for Animal and Human Health Applications
- Malaria, 1 Million Deaths a Year and Still Counting!
- Neurodegeneration—Stopping the Clock
- Translocational Medicine—From the Lab to the Patient



Roundtables. Roundtables provide attendees with updated information in an informal setting that allows them to express their thoughts, ask questions, and hear about what others are doing in their discipline. Topics at the 2009 annual meeting covered

- Nanomedicine: From Material Design to Living Cells and Clinic
- Tablet Manufacturing in the 21st Century
- Young Scientist

State of the Industry Session. We are living in interesting times. Our industry is facing tough economic times in which our budgets are shrinking, demands for safety are increasing, and R&D and clinical trial times are increasing, which means that products make it to the market more slowly…if they make it at all! Chris Phelps, head of company analysis for Datamonitor, painted a picture of the current state of the industry and looked ahead at what can be expected in the future, including growth opportunities for drug delivery products.

Pearls of Wisdom. The Pearls of Wisdom is notorious for offering controversial topics, outrageous points-of-view, and audience participation that is often infused with humor. This year was no exception! Each session kicked off with the presentation of a motion and evidence to support the motion, followed by the opponent of the motion presenting counter evidence. Once the presenters concluded, the floor was opened to audience participation, and lively debates ensued on the following topics:

- Industry-Sponsored Academic Research: Society Benefit vs. Corporate Gain
- Nanomedicine for Cancer: More Advantages or More Risks
- Pharmacokinetics or Pharmacodynamics Research in Nanomedicines

Industrial Sessions. The Industrial sessions focus on topics of particular interest to attendees from industry. Over the course of a day-and-a-half, experts from Catalent, Patheon, PII, FDA, FMC, German Drug Regulatory Agency, and members of the

Meeting Round-up continued on page 8

Meeting Round-up continued from page 7

CRS Oral Drug Delivery Group offered their thoughts and observations about their experiences in the industry in the following areas:

- Alliance Partnership or In-house Management
- Oral Drug Delivery Around the World
- Quality by Design (QbD)

Get Up; Get Educated. Are students early risers? They were in Denmark! Students had to be up and going by 7:00 a.m. on Tuesday and Wednesday to take part in Get Up; Get Educated! Students and those new to the industry got a special early-morning treat each day—learning about non-parenteral and parenteral peptide drug delivery.

Networking

Opening Reception and Exposition. The meeting officially kicked off at the Opening Exposition and Reception Sunday evening. Friends, partners, and colleagues reunited in the exhibit hall. The event highlighted 100 exhibiting companies and more than 850 posters featuring the latest research and science.

Young Scientist Mentor/Protégé Coffee & Meet-and-Greet. The Young Scientist Mentor/Protégé Coffee & Meet-and-Greet kicked off the new CRS Mentor/Protégé program. Students and mentors had a chance to learn about the program and begin the process of being matched up. This program is designed to advance the personal and professional development of our young scientists through the establishment of meaningful relationships between them and experienced members of CRS. Protégés and mentors alike were excited to meet and get the ball rolling in Denmark.

Closing Reception and Banquet. The Closing Reception and Banquet was held at the historic D'Angleterre Hotel overlooking Kongens Nytorv (King's New Square) in the heart of Copenhagen. Attendees were dressed to impress for the ceremonial closing of the meeting. The elegant event was the backdrop for many CRS award presentations, including the announcement of the first recipient of the CRS Foundation's Joseph R. Robinson Postdoctoral Fellowship and the passing of the CRS presidential gavel from Lisbeth Illum to incoming President Diane Burgess. Please see the Recognizing Excellence section of this issue to review all the winners of this year's awards.

Recognition

CRS is synonymous with scientific excellence and exceptional advances in delivery science. The CRS Annual Meeting & Exhibition is a fitting place to come together to honor those who have contributed to our science and Society. Highlighted below are the tribute to Jorge Heller and the presentation of the inaugural Joseph R. Robinson Postdoctoral Fellowship by the CRS Foundation.

Tribute to Jorge Heller. CRS Past President Jorge Heller, who passed away in June, was honored for his dedication and commitment to the Society. At the Closing Banquet, Allen Hoffman gave a personal and pictorial remembrance of Heller, his career, family, and many contributions.

David Nguyen Presented Inaugural Joseph R. Robinson Postdoctoral Fellowship. The CRS Foundation launched its first program by awarding a $30,000 fellowship to recent MIT postdoctoral associate David Nguyen. Chosen by an impressive selection committee of CRS past presidents, Nguyen will pursue a medical degree at Stanford University, where he will continue his research on bringing controlled delivery technology to bear on critical medical problems in immunology and infectious diseases. The fellowship is named in honor of CRS Past President Joe Robinson.

Supplier Programming

Releasing Technology Workshops. The Releasing Technology Workshops provide attendees with an in-depth look at exhibiting companies, their goals, new products and services, and unique opportunities for partnerships and collaborations. The following companies provided insights and information to audiences during the 1–2 hour workshops.

- **Büchi:** Spray Drying in Laboratory Scale
- **Catalent:** Softgel Lipid-based Drug Delivery Systems
- **Elan Drug Technologies:** Platform Technologies for Clear Market Needs
- **Eurand:** Working with Insoluble Compounds: Technology Applications for NCEs and Marketed Products Including Formulation of Immediate and Extended-Release Dosages
- **Lubrizol:** Carbopol® Polymers for Oral Extended Release Dosage Forms
- **OctoPlus:** Development and Immunological Aspects of Controlled-Release Protein Formulations
- **PII:** Commercialization of Nanoparticle-based Drug Delivery Products, Challenges, and Practical Considerations

Soapbox Sessions. The fast-paced Soapbox session presentations allow technology-driven, emerging, and established businesses time to showcase their products and services in 5-minute segments. These sessions keep attendees on the edge of their seats, covering a lot of territory in a short period of time. As always the 2009 sessions gave attendees the opportunity to identify new ideas and potential collaborations.

Partnering Session. The 2009 meeting hosted the first Partnering session. Representatives from Genetech, Lilly, and Roche were available to speak about the focus of their companies, the importance of controlled release technologies for their companies, and what their companies are doing to invest in such technologies. They then discussed the specific services or skills sought by their companies and encouraged collaborations with attendees to work toward a common goal. ■

The Controlled Release Society thanks the sponsors of the 36th Annual Meeting & Exposition

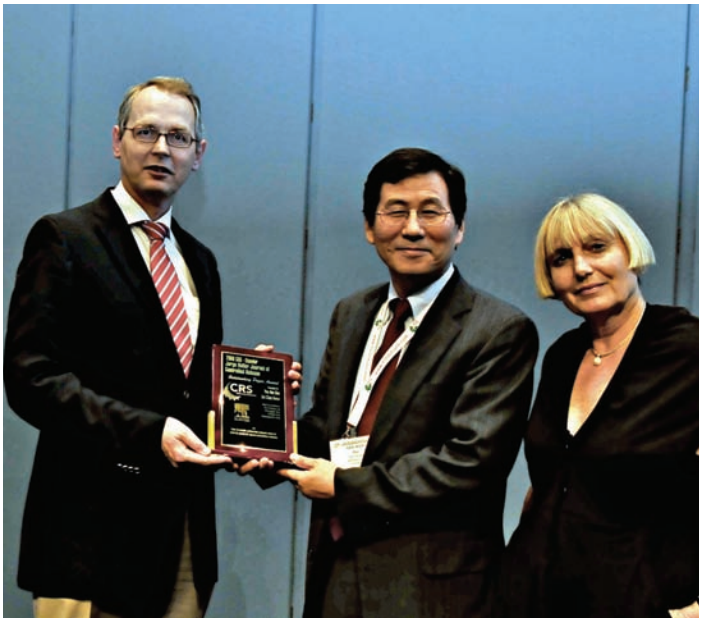
Congratulations 2008 and 2009 CRS Awardees!

The Controlled Release Society's awards ceremonies held during the 36th CRS Annual Meeting & Exposition in Copenhagen, Denmark, honored and recognized deserving scientists from around the globe. Thank you to the many sponsors who provided their time and financial support to promote the talented scientists and innovative science. ■

Lisbeth Illum with Alexander "Sandy" Florence, University of London (retired), winner of the CRS Founders' Award, and Allan Hoffman.

Tsuneji Nagai and Lisbeth Illum present Shirui Mao, Shenyang Pharmaceutical University, and Thomas Kissel (not pictured), Philipps University, with the CRS/T. Nagai Postdoctoral Research Achievement Award, co-sponsored by The Nagai Foundation Tokyo.

Stephen Perrett with Justin Hanes, Johns Hopkins University, recipient of the CRS Young Investigator's Award, co-sponsored by Eurand.



Jaap van Harten and Lisbeth Illum present You Han Bae, University of Utah, and Ick Chan Kwon (not pictured), KIST, with the CRS Jorge Heller Journal of Controlled Release *Outstanding Paper Award, co-sponsored by Elsevier.*

David Nguyen, MIT, is the first-ever recipient of the CRS Foundation's Joseph R. Robinson Postdoctoral Fellowship. The award was conferred at the Closing Reception and Banquet.

Kristy Ainslie, University of California, San Francisco, receives the CRS Outstanding Oral Drug Delivery Paper Award, co-sponsored by Banner, from Aqeel Fatmi and Lisbeth Illum.

Ann Peddle Meitz and Lisbeth Illum present Kathleen Fischer, University of California, San Francisco, with the CRS Outstanding Pharmaceutical Paper Award, co-sponsored by 3M Drug Delivery Systems.

Daniela Allhenn, University of Bonn, receives the CRS Outstanding Consumer & Diversified Products Paper Award, co-sponsored by Givaudan, from Fabio Campanile and Lisbeth Illum.

Susan Cady, Merial Ltd., receives the 2009 CRS Distinguished Service Award at the Closing Reception and Banquet.

Thank you to the Exhibitors of the 36th Annual Meeting & Exposition of the Controlled Release Society!

Exhibitors offered the latest research, technology, products, and services for controlled release and delivery at the 2009 meeting in Copenhagen, Denmark.

3M Drug Delivery Systems
ADD Technologies Ltd.
Alkermes, Inc.
Asahi Kasei Chemicals Corporation
Avanti Polar Lipids
Avestin Europe GmbH
Aveva Drug Delivery Systems Inc.
Azopharma Contract Pharmaceutical Services
Banner Pharmacaps
BASF Corporation
Bayer Technology Services GmbH
Bilcare Global Clinical Supplies (Europe)
Biocompatibles
Bio-Images Research Ltd.
Biovail Contract Research
Boehringer Ingelheim
Brabender® GmbH & Co. KG
Büchi Labortechnik AG
Caleva Process Solutions
Camurus AB
Capsulution Pharma AG
Catalent Pharma Solutions
CMA Microdialysis
Colorcon Ltd.
Dissolution Technologies
The Dow Chemical Company
Drug Delivery Technology
DSM Biomedical
DURECT Corp/LACTEL® Absorbable Polymers
Elan Drug Technologies
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OctoPlus NV
O'Hara Technologies Inc.
Oxford Instruments Magnetic Resonance
Particle Analytical
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Pharmaceutical Formulation & Quality
Pharmaceutical Manufacturing and Packing Sourcer
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Pharmaceutics International, Inc. – PII
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TeraView Ltd.
Thermo Scientific
Travel Portland
University of Copenhagen
Vector Corporation
Warwick Effect Polymers Ltd.
Wyatt Technology Europe GmbH
XSpray Microparticles

For 2010 exhibit information go to www.controlledreleasesociety.org/meeting/exposition/default.cfm or contact Debby Woodard at +1.651.994.3817 or dwoodard@scisoc.org.

Highlights from the Vet Program in Copenhagen

Raid Alany[1] and Cyril Desevaux[2]

The 36th CRS Annual Meeting & Exposition witnessed one of the most well-attended veterinary programs. Sessions were kick-started on Sunday afternoon by an intense Pearls of Wisdom debate on PK versus PD in nanomedicines research. The debaters were Prof. Ramesh Panchagnula (Pfizer, India) and Prof. Ravi Kumar (University of Strathclyde, Scotland). Both debaters made a strong case, and it was a close call, with PD edging out PK. At the end of the day the audience was entertained and enjoyed two colourful and interactive presentations.

Monday was very busy, with three successive vet sessions. The Innovations in Drug Delivery for Animal and Human Health Applications Mini-symposium was held in the morning. It attracted a record number of attendees and diverse presentations.

Invited Speaker Patrick Couvreur (University of Paris) at the Nanotechnology and Animal Models: Improving Health Outcomes session.

The first speaker, Elias Fattal (Paris-Sud University, France), discussed delivery systems for the removal of colonic residual antibiotics to reduce emergence of resistance. He shared data on the design and evaluation of pectin beads that were aimed at deactivating colonic residual antibiotics responsible for the emergence of resistance in cattle.

This was followed by one of the day's highlights, a presentation by Mike Roberts (University of Queensland, Australia). His presentation was entitled "Enhancement Strategies in Skin Penetration of Solutes and Nanoparticles: Species Differences." Mike summarised how multiphoton tomography can be used to examine drug transport in mice, pigs, and humans. Indeed, multiphoton tomography may be of particular use in defining *in vivo* 4D (in both space and time) pharmacokinetics in various species. The following two presentations by Thierry Vandamme (University of Strasbourg, France) and Mathieu Peyrou (Novartis Animal Health, Switzerland) were also well received.

Mike Rathbone (Griffith University) and Raafat Fahmy (FDA Center for Veterinary Medicine) catch up at the Vet Get Together.

The afternoon session, Nanotechnology and Animal Models: Improving Health Outcomes, attracted 16 abstracts (4 podiums and 12 posters). Patrick Couvreur (University of Paris Sud, France) spoke on a novel drug delivery platform based on squalenoylation to improve delivery of nucleoside analogues with significant anticancer and/or antiviral properties. Jean-Christophe Leroux (University of Zurich, Switzerland) shared findings on polymer nanocomplexes with gliadin and their role in minimising some of the undesirable features of celiac disease. The following two presentations, both from New Zealand, were both industrial and academic.

Guest Speaker Sandra Klein (University of Frankfurt) at the Vet Get Together.

Invited Speaker Thierry Vandamme (University of Strasbourg) speaks on innovations in drug delivery for animal and health applications during the veterinary mini-symposium.

The Vet Get Together followed on Monday evening. This event was generously co-sponsored by Novartis Animal Health and represented a social and networking opportunity for those interested in animal health. Dr. Sandra Klein (University of Frankfurt, Germany) spoke about "Waiver of Bioequivalence for Veterinary Dosage Forms." She highlighted some important physiological and anatomical differences between the different species and related those to the expected behaviour of solid dosage forms *in vivo*.

The vet sessions were very popular, and work is already underway for the forthcoming 2010 CRS meeting in Portland. Make sure that you are there! ■

[1] School of Pharmacy, University of Auckland, New Zealand.
[2] Novatris Animal Health, Switzerland.

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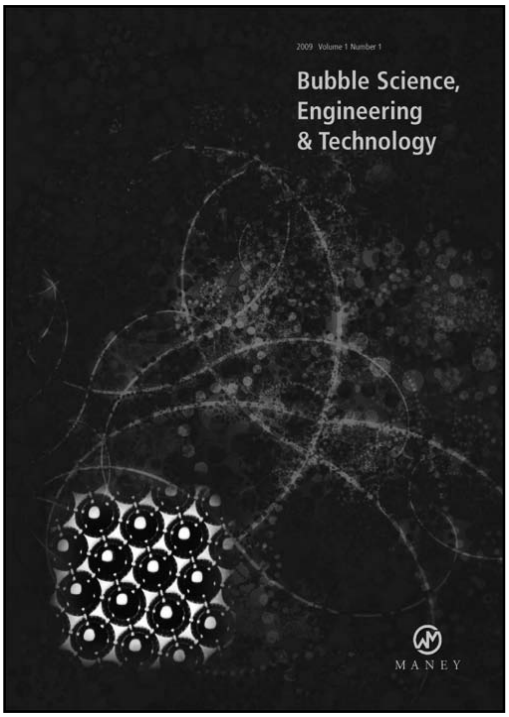

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MALDI TOF/TOF MS to Investigate Co-polymerization of D-Lys^6-GnRH in PACA Nanoparticles

Alexandra P. Kafka, Thomas Rades, and Arlene McDowell
School of Pharmacy, University of Otago, Dunedin, New Zealand

Summary
Interactions between bioactives and polymers during the polymerization process have previously been suggested using chromatographic methods such as size exclusion chromatography (1). However, such chromatographic methods detect bulk properties rather than molecular-level interactions and do not enable identification of the site of modification of the bioactive. We applied matrix-assisted laser desorption/ionization tandem time-of-flight mass spectrometry (MALDI TOF/TOF MS) to gain further insight at the molecular level into the peptide–polymer interactions during the *in situ* polymerization of D-Lys^6-GnRH in poly(alkylcyanoacrylate) (PACA) nanoparticles.

Introduction
Previously, the analysis of larger biomolecules was complicated because ionization methods such as electron ionization, chemical ionization, or fast atom bombardment were destructive, required analyte modifications, or had low sensitivity. The development of two soft ionization methods, electrospray ionization (ESI) and MALDI, established new possibilities for measuring large intact biomolecules and polymers. Moreover, contemporary mass spectrometers are equipped with technology that allows controlled ion fragmentation in the instrument, such as collision-induced dissociation (CID). The combination of intact mass measurement, ion fragmentation, and measurement of fragment ions reveals detailed structural information about molecules and is widely used for unambiguous identification of compounds, sequencing of peptides, characterization of peptide/protein modifications, etc. In the following, we give an overview of the basics of MALDI TOF MS used in this study.

A mass spectrometer measures the ratio of mass to number of ionic charges (*m/z*) of ionised molecules and, therefore, requires a method to generate ions from uncharged sample molecules. Here we only discuss one method for the ionisation of molecules that we have used for peptide/PACA co-polymer analysis—MALDI.

In MALDI samples are co-crystallized with excess matrix, a compound that is activated upon absorption of laser energy (2). A mixture of activated matrix and analyte is vaporized and released into the vacuum of the ion source (desorption) (2). In the gas phase the activated matrix transfers (or accepts) protons to (or from) the analyte (Figure 1). Mainly singly charged ions ($z = 1$) of analytes are generated, minimizing the spectral complexity (3).

The separation of ionized species in mass spectrometry can be achieved using different types of mass analyzers, such as TOF, quadrupole ion trap, and high-resolution ion cyclotron resonance mass spectrometry. Here, we discuss mass spectroscopic analysis using a TOF analyzer. In TOF mass spectrometry, all ionized species are accelerated in an electric field (usually 15–35 kV). The same force is applied to all ionized species. The separation of analytes occurs according to their mass to number of charge ratio. The ions with the smallest molecular mass will gain the most velocity and take the shortest time to reach the detector (Newton's second law) (Figure 2A). In MALDI MS, *m/z* values can be directly converted into molecular mass with great precision, even separating C^{13}-isotopes.

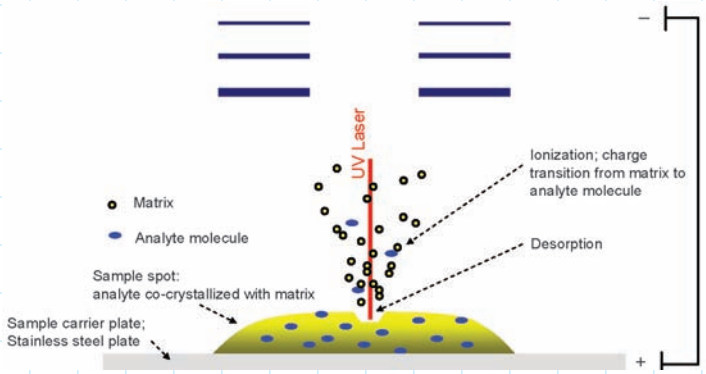

Figure 1. *Transition of sample co-crystallized with matrix from solid phase into gas phase and consecutive charge transfer from ionized matrix molecule to analyte molecule.*

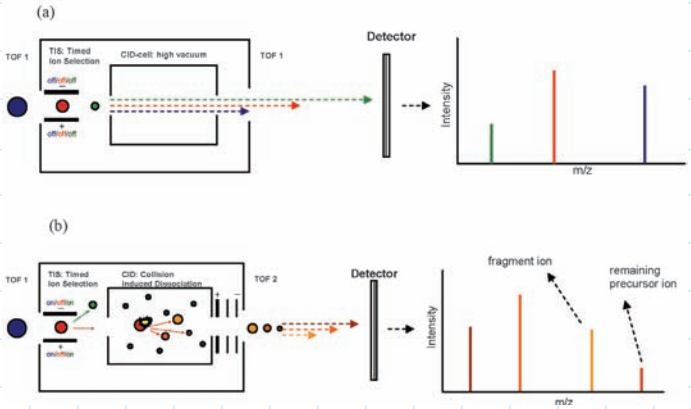

Figure 2. ***a,*** *Acquisition of full mass spectrum (precursor ion spectrum). Intact, ionized analytes (precursor ions) pass by the inactivated CID cell.* ***b,*** *Acquisition of an MS/MS spectrum (fragment ion spectrum). Only molecules matching the specified mass (precursor) will be selected to pass the CID cell and be fragmented.*

Scientifically Speaking continued on page 16

Scientifically Speaking continued from page 15

The activation of a CID cell enables ionized molecules to be fragmented upon collision with gas molecules under high pressure (Figure 2B). Prior to entry of the CID chamber, one molecular species can be selected and will pass the cell (precursor ion), whilst all de-selected molecular species will be deflected. The resulting fragment ions give a unique "mass fingerprint" of the precursor molecule, providing the potential to identify sites of modifications within the molecule.

PACA nanoparticles are well established as potential delivery systems for the peroral delivery of protein and peptide bioactives. PACA nanoparticles enclose the bioactive, thus protecting against gastric degradation, and are appealing because of their ease of preparation, biodegradability, and biocompatibility. They can be produced by a one-step *in situ* polymerization process, where all ingredients are contained in a W/O-microemulsion template prior to polymerization (4).

The decapeptide gonadotropin-releasing hormone (GnRH) is considered the master hormone controlling mammalian reproductive physiology, and its analogues and derivatives have applications in both cancer therapy and fertility control in animals. In this study the analogue D-Lys^6-GnRH (pGlu-His-Trp-Ser-Tyr-Lys-Leu-Arg-Pro-Gly-NH_2) was used as a model peptide and *in situ* polymerized with ethylcyanoacrylate to form poly(ethylcyanoacrylate) (PECA) nanoparticles. The resulting particles were characterized in terms of size, zeta potential, entrapment efficiency, and release profile (Table 1). Noteworthy is the high entrapment efficiency of D-Lys^6-GnRH (95 ± 4%).

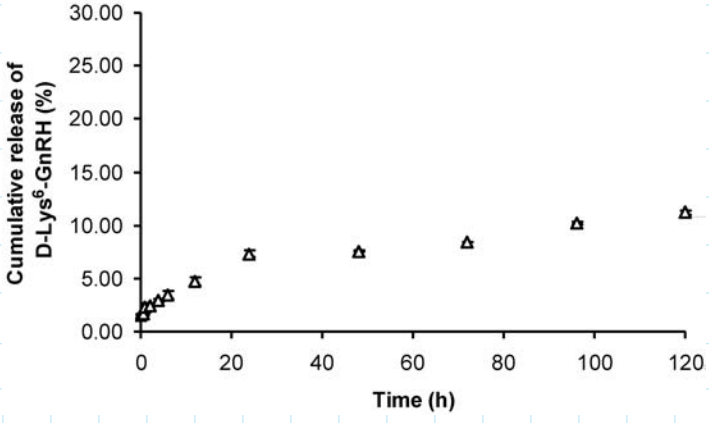

Figure 3. *Release profile of PECA nanoparticles loaded with* D*-Lys^6-GnRH in water over 5 days. Peptide was quantified using reversed-phase high-performance liquid chromatography (RP-HPLC) at a detection wavelength of 220 nm and a flow rate of 1 mL/min. A gradient of 10–35% CH_3CN containing 0.1% TFA eluted the peptide over 12 min (5). Data points are means ± SD (*n = *3).*

In a release study in water at pH 7.4, only about 10% D-Lys^6-GnRH was released from the loaded PECA nanoparticles after 5 days (Figure 3), posing questions about the remaining 90%.

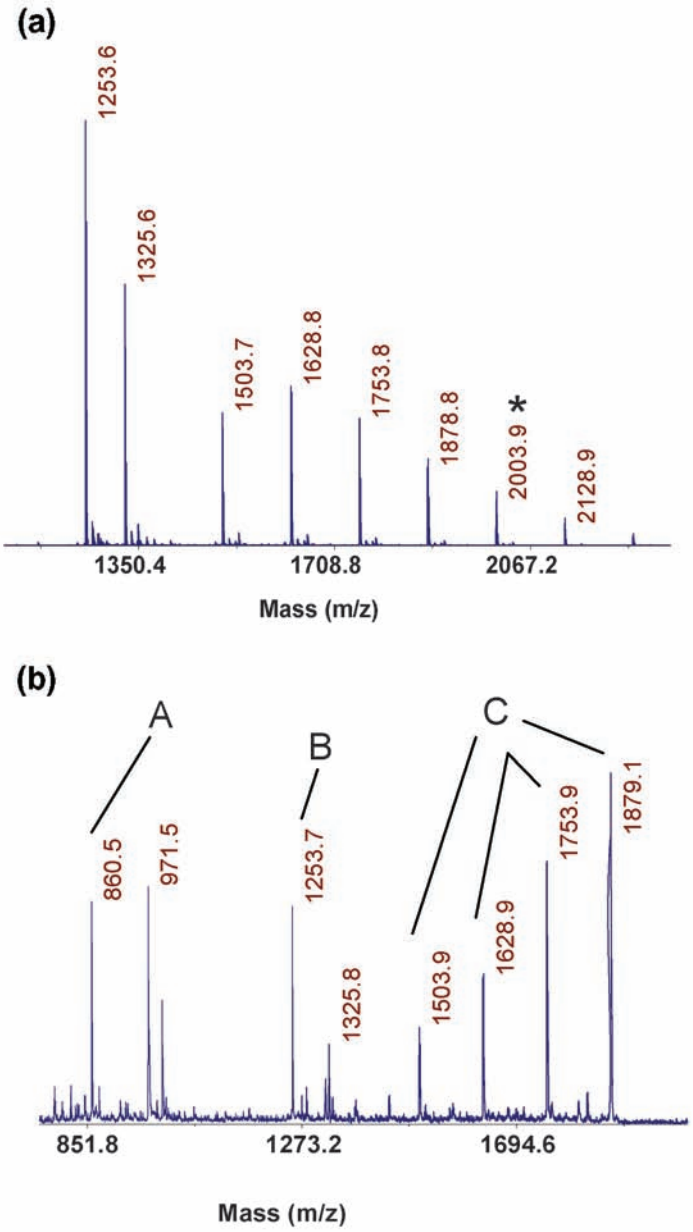

Figure 4. ***a,*** *Mass spectrum of PECA nanoparticles co-polymerized with* D*-Lys^6-GnRH. Parent mass* m/z *1253.6 corresponds to the free peptide;* m/z *1503.7, 1628.8, 1753.8, 1878.8 and 2003.9* refer to co-polymers, with peptide associated with 2, 3, 4, 5, and 6 monomer subunits. (* Peptide associated with six ECA subunits selected as precursor ion.)* ***b,*** *CID MS/MS spectrum of the precursor ion (*m/z *2003.8*). Peak A: histidine immonium ion plus six monomer subunits. Peak B: free* D*-Lys^6-GnRH peptide. Peaks C: increments of* m/z *125 of the precursor ion*, with losses of 1* (m/z *1879.0), 2* (m/z *21753.9), 3* (m/z *1628.9), and 4* (m/z *1503.9) monomer subunits.*

Table 1. Properties of PECA nanoparticles prepared by *in situ* polymerization and loaded with the peptide bioactive D-Lys^6-GnRH

Nanoparticle	Size ± SD (nm)	Zeta Potential (mV)	Entrapment Efficiency (%)
Empty	191 ± 23	–27.5	n/a
D-Lys^6-GnRH loaded	220 ± 32	–3	95 ± 4

Results and discussion

In our study, isolated D-Lys6-GnRH loaded PECA nanoparticles were analyzed on a 4800 MALDI TOF/TOF analyzer (Applied Biosystems, MA, USA). In Figure 4A, the free peptide gives a signal at *m/z* 1253.6. However, a significant proportion of the peptide is also covalently associated with monomer subunits, resulting in mass shifts of 125 mass units compared with the parent mass of *m/z* 1253.6.

To identify the reactive site within the D-Lys6-GnRH peptide molecule, the co-polymer* (*m/z* 2003.9) was fragmented by CID MS/MS (Figure 4B). The key signal at *m/z* 860.5 (peak A) refers to the histidine immonium ion (*m/z* 110.5) associated with six monomer subunits (*m/z* 6× 125). Immonium ions are internal cleavage products, which results in a mass loss of 45 mass units compared to the original mass. Since no other amino acid fragments have experienced a mass shift, histidine is the reactive site in the D-Lys6-GnRH molecule.

Conclusions

The combination of RP-HPLC and MALDI TOF/TOF MS is a powerful tool in the characterization of interactions between protein bioactives polymers on a new molecular level. *In situ* polymerization of PACA nanoparticles in the presence of D-Lys6-GnRH has the potential for direct peptide interference in the polymerization process via a histidine residue. Co-polymerization can be used an approach to design controlled release delivery systems based on the assumption that bioerosion of nanoparticles releases the bioactive over time (1). However, many questions remain unanswered. Most importantly, studies are needed to identify whether the peptide/polymer conjugates are bioactive and to clarify whether a sufficient amount of bioactive can be made available over an appropriate time frame to have the desired therapeutic effect.

Acknowledgements

We thank Dr. Torsten Kleffmann, Centre of Protein Research, Department of Biochemistry, University of Otago, for advice on mass spectrometry measurements and support.

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CRS Delivering Bioactives

CRS Illinois Student Chapter Hosts Symposium

Stephanie Drake
Illinois Student Chapter Secretary

On May 29, the CRS Illinois Student Chapter hosted a one-day symposium titled "Recent Advances in Parenteral Drug Delivery." The symposium was held as a way to foster and enhance the exchange of ideas among students and scientists who are interested in the broad area of controlled drug release and related fields. With more than 50 students, post-docs, faculty, and industry representatives in attendance, it was successful in providing in-depth knowledge of controlled release research and promoting networking in research between academia and industry. The symposium brought together people with an interest in drug delivery from Clemson University, the Illinois Institute of Technology, Loyola University, the University of Illinois at Chicago, and the University of Michigan Ann Arbor, as well as attendees from APP Pharmaceuticals, Argonne National Laboratory, Baxter Healthcare, BD Biosciences Discovery Labware, Biopharmaceutical & Drug Delivery Consulting, Covidien, and Millipore.

The symposium consisted of several speakers, lunch, and a poster session. The keynote speaker was Dr. Theodore Roseman, retired vice president of global R&D medication delivery at Baxter Healthcare and former CRS president. His presentation was titled "Heparin Contamination: Unraveling the Mystery." To further showcase research in parenteral drug delivery, other distinguished presenters spoke on a broad assortment of topics. Dr. Barrett Rabinow of Baxter Healthcare, a Baxter distinguished scientist and director of strategic development, spoke on "Nanoparticles: Impact on PK and Distribution." Dr. Joseph Wong of Baxter Healthcare, principal scientist, spoke on "Product Development Considerations with Injectable Nanosuspension." Dr. Lonnie Shea, associate professor of chemical and biological engineering at Northwestern University, spoke on "Tunable Microenvironments for Regenerative Medicine." Dr. Michael Kaminski of Argonne National Laboratory, principal materials engineer, Chemical Sciences and Engineering Division, spoke on "Magnetic Drug Delivery." Last, Dr. Jennifer J. Kang Derwent, Department of Biomedical Engineering, Illinois Institute of Technology, spoke on behalf of Dr. William Mieler, professor of ophthalmology and visual sciences at the University of Illinois at Chicago and vice chair and director of ocular oncology, on "Drug Delivery to the Posterior Segment via Thermo-responsive Hydrogels."

Symposium coordinators (from left to right): Suhair Sunoqrot, Misuk Bae, Stephanie Drake, Amrita Banerjee, Ramana Vishnubhotla, and Kristin Thomas.

A poster session was held during which awards were given for the first, second, and third best posters presented at the symposium. Yen-Ling Lin of the University of Michigan was awarded first place for her poster, "Development of 'Smart' Particles for Enhanced Intracellular Delivery of Therapeutic Nucleic Acids." She received $1,000 to be used to attend the 37th CRS Annual Meeting & Exposition, July 10–14, 2010, in Portland, OR. Scott Medina of the University of Michigan was awarded second place for his poster and received $150. Sok Bee Lim and Deepali Vartak, both of the University of Illinois at Chicago, were awarded third place and received $50.

With the success of this symposium we are looking forward to organizing a symposium in 2010. ■

Development and Regulatory Challenges for Controlled Release Formulation

CRS/AAPS Workshop • November 7–8, 2009
Los Angeles Convention Center • Los Angeles, California U.S.A.

Workshop Chairs

Ron Ortiz, Upsher-Smith Labs, U.S.A.
Dody Reimer, Northern Lipids, Inc., Canada
Louise Rosenmayr-Templeton, Tower Pharma Consulting, Austria
Avinash Thombre, Pfizer, Inc., U.S.A.

Educational Objectives

- To provide an understanding of the developmental and regulatory challenges for controlled release formulations utilizing mature and evolving new technologies in Europe and North America
- To provide a venue for young and/or established scientists to informally meet with other scientists and regulatory authorities
- To share and discuss fundamental science and experiences that may be of value to individuals dealing with various CR technologies
- To gain an understanding of the differences between the regulatory bodies of the E.U. and the FDA
- To increase an individual's knowledge about a variety of controlled release technologies that may not be found in the literature through shared experiences and panel discussions
- To apply newly acquired knowledge and a suitable approach to the potential design of the attendees own pharmaceutical products

Topics

Carrying out Early Phase Clinical Trials in the European Union on Non EU Produced Investigational Medicinal Products: Importation and Qualified Person Certification Challenges
Controlled Release and Immunogenicity—A Vaccine Perspective
Development and Regulatory Challenges Associated with the Transdermal Delivery of Small Molecules
Development of Orally Disintegrating Tablets
Developmental and Regulatory Challenges with Interferon Microparticles—Locteron
Developmental and Regulatory Challenges with Liposomes
Developmental and Regulatory Challenges with RNAi Therapeutics
Technical and Regulatory Challenges Associated with Diffucaps Drug Delivery Systems
The Development History of NanoCrystal® Products: A 10 Year Perspective
The Regulatory Challenges during the Development of Risperdal Consta—A Long Acting Injectable
The Science and Regulatory Perspectives of Controlled Release Products with Emerging Technologies

Invited Speakers

Richard Green, Pfizer, U.K.
Kevin Harper, Sanofi-Pasteur, Canada
Michael Horstmann, LTS, Germany
Elaine Liversidge, Elan Pharmaceuticals, U.S.A.
Aidan Madden, FivePharma, Ireland
Patrick Marroum, FDA, U.S.A.
Sara Nochur, Alnylam, U.S.A.
Michael Palmieri, Alkermes, U.S.A.
Tom Redelmeier, Northern Lipids Inc., Canada
Laurens van Pinxteren, OctoPlus, The Netherlands
Gopi Venkatesh, Eurand, U.S.A.

Workshop Registration

CRS members can register at the AAPS member rates at www.aapspharmaceutica.com/annualmeeting.

Registration rates include two days of programming, with coffee breaks and two lunches. The registration fee does not include breakfast.

Generously Sponsored by: 3M Drug Delivery Systems • Northern Lipids Inc.

Photo courtesy of Tom & Michele Grimm.

CRS Foundation Chooses David Nguyen for Inaugural Joseph R. Robinson Postdoctoral Fellowship

The CRS Foundation had much to celebrate at the 36th CRS Annual Meeting & Exposition in Copenhagen. David Nguyen, outstanding recent MIT postdoctoral associate and current Stanford medical school student, was introduced at the first plenary session, awarded the prestigious $30,000 Joseph R. Robinson Postdoctoral Fellowship at the Closing Banquet, and presented his research, "Using Drug Delivery to Control RNA Function," in the poster program.

One Goal, Hundreds of Participants
With a mission to financially support advanced research in the delivery of bioactives, the CRS Foundation's goal for 2009 was to launch its first program, the Joseph R. Robinson Postdoctoral Fellowship. Designed to honor past CRS President Joe Robinson by cultivating future leaders, the award is given to a CRS postdoctoral member who demonstrates scientific excellence, scholarship, motivation, and leadership.

CRS Foundation Leadership
The CRS Foundation Board of Directors is composed of Past Presidents Susan Cady (chair), Kinam Park, and Randall Mrsny; past CRS Treasurer Arthur Tipton recently joined the board. The board has worked since 2007 to develop the Foundation's structure, while envisioning programs that will result when funding goals are met. Cady remarks, "Not every organization would choose the economic conditions of 2008–2009 to launch a foundation and a fundraising campaign, but we are a mix of scientists, business people, and entrepreneurs. Working together as a society and in our professional lives, we know that breakthroughs emerge from single ideas that are further expanded and accomplished when many people become involved."

Selection Committee of CRS Past Presidents
Chaired by Kinam Park, the Selection Committee was composed of Past Presidents Susan Cady, Alexander Florence, Richard Guy, Jorge Heller, Robert Langer, Vincent Lee, Randall Mrsny, and Tsuneji Nagai. All accepted Park's invitation to review dozens of application packages and to determine the candidate who best met the selection criteria for the fellowship.

Outstanding Candidates, Dedicated References
More than 50 candidates prepared extensive applications that included educational background, research focus, patents, publications, and goals. As evidenced by the credentials of these young postdoctoral applicants, there is a strong future ahead for CRS and the science of the delivery of bioactives. For each candidate, there was also a postdoctoral advisor who gave time and thoughtful insight to introduce their candidate to the committee and to recommend them for their outstanding accomplishments and futures.

Generous Donors
None of this could have been accomplished without a generous grassroots response to the request for funding. Special thanks to the individuals and corporations listed on the next page for the contributions that made the first CRS Foundation's vision a reality.

The Future
The slate of candidates for the Joseph R. Robinson Postdoctoral Fellowship was extraordinary. One exceptional person was selected, and there are many more of the Society's best and brightest who will benefit from the support that the CRS Foundation will supply. Your support is needed and valued. ■

David Nguyen
David Nguyen, a recent post-doctoral associate at MIT, worked in the laboratory of MIT Prof. Robert Langer on ways to combine gene therapy and drug delivery to develop novel antiviral and immunotherapeutic strategies. Says Langer, "I'm personally thrilled to see David Nguyen, who has been one of my top students and postdocs, become the first recipient of this award."

Nguyen earned B.S. degrees in biology and chemical engineering from MIT in 2002. He then completed a Ph.D. degree in materials science and medical engineering through the MIT-Harvard Division of Health Sciences and Technology and the MIT Department of Materials Science. Nguyen's thesis work explored the role that drug delivery plays in controlling the function of RNA molecules, particularly with respect to innate immune responses and RNA interference.

Nguyen's work on RNA delivery has been published in *Nature Biotechnology*, *Biotechnology and Bioengineering*, and *Molecular Therapy* and has led to one patent application. His research interests also include polymeric micro- and nanoparticle delivery systems for DNA vaccines. He has co-authored papers on this subject that have been published in *Nature Materials*, *Biomaterials*, and *Advanced Materials*. Nguyen has also dedicated himself to teaching undergraduates in the community, classroom, and laboratory. In 2008 he received MIT's Outstanding Graduate Student UROP Mentor Award for his commitment to advising more than a dozen undergraduate researchers.

In fall 2009, Nguyen will pursue a medical degree at Stanford University, where he will continue his research on bringing controlled delivery technology to bear on critical medical problems in immunology and infectious diseases.

Joseph R. Robinson
The Joseph R. Robinson Postdoctoral Fellowship honors Joe Robinson's lifelong passion for teaching and his commitment to the Controlled Release Society. An outstanding professor at the University of Wisconsin, Robinson prepared his students for meaningful careers in drug delivery science, bridged academia and industry in his consulting work, served as president of CRS, and was a founding member of the *Journal of Controlled Release*.

Thank You, CRS Foundation Donors

Special thanks to the following individuals and corporations for their contributions to support programs that advance research and education in the delivery of bioactives.

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Consumer and Diversified Products

Rajarajeswari Sivalenka, Ph.D.
CRS Newsletter Editorial Board, C&DP

This report describes notable patents in the area of controlled release applications for consumer and diversified products. It covers patents granted, published, or filed in the areas of food and beverage, flavor, agricultural, and cosmetic industries in the first half of 2009.

Delivery and Controlled Release of Encapsulated Lipophilic Nutrients (PepsiCo, Inc., U.S.A.) US20090061048

This invention describes a system to deliver lipophilic nutrients in an acidic aqueous system pertaining to food and beverage products. The nutrients that can be encapsulated include, for example, omega-3 fatty acids and fish oil. This encapsulation system provides such nutrients protection from oxidation and prevents negative effects such as hydrolysis, off-flavor, unpleasant aroma, etc. The system is composed of a complex coacervate delivery system that upon ingestion substantially releases the lipophilic nutrient in the lower gastrointestinal tract in a pH-controlled manner. The controlled release of encapsulated lipophilic nutrients reduces aftertaste and enhances the bioavailability and overall physiological efficacy of the lipophilic nutrient.

Compositions Containing Cationically Surface-Modified Microparticulate Carrier for Benefit Agents (AMCOL International Corporation, U.S.A.) US20090162408

This patent describes a technology for delivery of a benefit agent in a microparticulate carrier coated with a cationic polymer. The technology is applicable to flavors, fragrances, insect repellents, silicone oils, fabric-softening agents, anti-static agents, anti-wrinkle agents, stain-resistant agents, emollients, moisturizing agents, waxes, ultraviolet (UV) ray absorbers, antimicrobial agents, antioxidants, pigments, film-forming agents, skincare agents, hair-care agents, scalp-care agents, anti-dandruff agents, hair-coloring agents, hair-conditioning agents, and combinations of these products. The methods disclosed provide compositions with improved characteristics and use of much lower amounts of cationic polymer(s) than previously employed, making the compositions more commercially and industrially applicable.

Indicia-bearing Package for Delivery Systems for Managing Release of Flavors in an Edible Composition (Cadbury Adams USA LLC, U.S.A.) US20090162418

This patent discloses a package assembly to support a delivery system for inclusion in an edible composition. The package is characterized by a release profile that is influenced by a variety of factors upon ingestion. The factors are, for example, chewing rate, chewing intensity, amount of the ingredient in the edible composition, the form of the ingredient added to the edible composition (e.g., encapsulated in a delivery system, un-encapsulated, pretreated), how the edible composition is mixed or otherwise prepared, when or how the ingredient is added to other ingredients in the edible composition, the ratio of the amount of the ingredient to the amount(s) of one or more other ingredients in the edible composition, the ratio of the amount of the ingredient to the amount of one or more other ingredients in a delivery system that is included in the edible composition, etc. Actives that could be influenced in such systems, besides medicaments, are nutrients, nutraceuticals, herbals, nutritional supplements, and/or their combinations.

Resin-Encapsulated Food Acid (Gumlink A/S) US20090098241

This invention relates to an encapsulated delivery system for confectionary compositions containing food acids and natural resins for their modified release. It reveals methods for preparation of such a system and the components of the confectionary compositions. It is a chewable composition with increased stability.

Cosmetic Delivery System and Process for the Manufacture Thereof (Unilever, U.S.A.) US20090041685

This invention details a delivery system for use in cosmetic or cleansing products for enhanced stability of the benefit agent. The release of the benefit agent upon application of the product to human skin is induced by shear-sensitive globules upon rubbing. The system disclosed comprises a polysaccharide-zein complex, benefit agent, and plasticizer. The benefit agents that could be delivered are, for example, oils, extracts, powders, flavors, perfumes, moisturizers, emollients, herbal oils, skin-lightening agents, sunscreen agents, or mixtures of such. The process for the manufacture of the delivery system and examples of such formulations are also described.

Antipruritic Cosmetic and Dermatological Preparations (Beiersdorf AG, Germany) US20090110649

A non-ionic O/W emulsion for topical delivery of cosmetic and dermatological preparations is described in this patent. This system, comprising one or more oil phases in water, PEG 12 cetearylether and/or PEG 40 monostearate, polidocanol, menthol, and one or more O/W emulsifiers or co-emulsifiers, is claimed to be effective in treating pruritic (itchy skin) conditions. The formulation further possesses a lasting skincare effect, is moisturizing, and provides protection against the harmful effects of UV rays. Examples of such formulations are listed that when applied to irritated skin were shown to have the immediate effect of reducing or eliminating itching. Furthermore, these preparations are claimed to possess increased ease of application and are pleasantly spreadable.

Amine-based and Imine-based Polymers, Uses and Preparation Thereof (Bereskin and Parr, Canada) US20090076168

This patent discloses a process for preparation and use of a modified polysaccharide for release of bioactive agents in cosmetic, pharmaceutical, and food products. The modified polysaccharide has hydrophobic functional groups attached and is a result of

reaction between 1) a polysaccharide comprising a plurality of monosaccharide subunits having at least one primary amino group, and 2) a hydrophobic aldehyde. The polysaccharide is obtained from reaction between agarose, alginate, pectin, or cellulose and a derivatizing agent with the formula $X–W–NH_2$, wherein X is a leaving group, W is C_{1-10} alkyl, and the aldehyde and amino group form together an imine group. Although various such polymers have been described previously, they are relatively expensive to manufacture. This invention proposes a matrix for delivery of various active agents that can be produced at a low cost using natural polymer as a starting material. The bioactive agents that can benefit from this invention include drugs, enzymes, antibacterial agents, antifungal agents, antioxidants, preservatives, peptides, proteins, vitamins, minerals, bacteria, or cells.

Temperature-Responsive Delivery Systems (Kimberly-Clark Worldwide, Inc., U.S.A.) US20090117075

This technology provides a new aqueous temperature-responsive delivery system that is useful in delivering moisturizers or pharmaceutically active agents to the user in a controlled release manner through the tissues in a body cavity. It is made with a temperature-responsive polymer and an intrinsically cationic bio-adhesive. The proposed deliverable actives could comprise an effective amount of treating agent, such as moisturizers and other cosmetic actives. Compared to the preexisting polymeric technology systems, which are limited in ease of use and tissue coverage, this application is proposed to provide enhanced performance and biocompatibility through tissues. This bioadhesive polymer system is in a liquid state when applied but becomes a semi-solid gel in the body cavity through thermo-gellation. The *in situ* gellation of bioadhesive polymers is induced by body temperature, referred to as "thermo-gellation." The positively charged bioadhesives in this invention are proposed to adhere well to negatively charged tissue surfaces and mucosal membranes.

Preparations for Topical Application and Methods of Delivering an Active Agent to a Substrate (Dow Corning Corporation and Genencor International, Inc., U.S.A.) EP1680097B1

A multilayer dressing-based controlled release application and its composition are disclosed in this patent. It comprises an oil-in-water emulsion containing the active component intended for topical application. The active agent, a protein, is incorporated into the hydrophilic phase of the emulsion, which is made up of a silicone component. The technology taps the beneficial properties of silicone and aids in controlled release. An adhesive layer is adjacent to the controlled release layer to adhere the dressing to the substrate. The composition is capable of delivering performance properties such as adhesion, controlled tack, controlled lubrication, shear reduction, cushioning, water resistance, barrier properties, maintenance or provision of a moist wound environment, and scar reduction. The patent also references various examples that demonstrate the effectiveness of this sustained release technology.

Controlled Release Fertilizers and Methods of Manufacture (Cellulosetek, LLC, U.S.A.) US20090044582

This patent describes a procedure for the manufacture of encapsulated fertilizers in two polymer films. Optimizing the release of fertilizer is important to avoid its leaching excessively into the ground, which may result in environmental damage. Further, it is essential to control rapid dissolution of a fertilizer into the moisture in soil, which can prevent its use by plants. Although polymer-coated fertilizers are used extensively, most of them have the disadvantage of uneven coating, and the procedures for making them are also relatively more expensive. Using various polymer films that have varying moisture-barrier properties and varying layers of thickness of each polymer, this invention proposes to optimize the controlled release rate of fertilizers much more effectively.

Topical Delivery System for Antiaging and Skin-Whitening Agents (Bioderm Research, U.S.A.) US20090074691

This application discloses the use of a "hydroxyaryl" group of compounds in the treatment of enzyme malfunctions that result in skin and hair discoloration. It relates to certain hydroxyaryl alkanols, alkyl amines, alkyl amino acids, alkyl amino alkanols; their organic and inorganic acid or alkali salts, and metal complexes. These compounds are also claimed to be useful for enzyme modulation, such as phenylalanine hydroxylase, tyrosine transaminase, phenylalanine transaminase, tyrosinases, various MMP (matrix metalloproteases), superoxide dismutases, 5-alpha reductase, and citrate lyase. The patent also illustrates methods for preparation of these compounds and provides examples of certain formulations for specific applications.

Compositions for Controlled Release of Pest Control Products in Aquatic Environments (Pestalto Environmental Products, Canada) US7563453

The present invention discloses compositions for treatment of water columns in catch basins. The compositions described comprise an admixture of pest control products with water-soluble and -insoluble waxes. Examples and the method for development of formulation are provided. This controlled release technology is particularly intended to release pest control products into aquatic environments.

Polymeric Antioxidants (University of Massachusetts Lowell and the United States of America, as represented by the Secretary of the Army, U.S.A.) US7507454

This patent describes methods for preparing and using antioxidant polymeric systems. The method for preventing oxidation of the incorporated substance uses polymers such as substituted benzene antioxidant. Because they are largely unabsorbed by the skin, they are expected to be non-toxic to animals. They are more potent than small-molecule antioxidants and thermally stable. They have added advantages over small-molecule antioxidants in that when they are blended into another polymeric material they diffuse relatively slowly. The method described here to manufacture such polymers is also environmentally safe. ■

In the News

Compiled by Steven Giannos
Industrial Editor

August 2009

Nutra Pharma Subsidiary, ReceptoPharm, Files Patent Application for Oral Delivery of Cobra Venom for Treatment of Pain

Business Wire: August 13, 2009 – BOCA RATON, FL – Nutra Pharma Corp. (OTCBB: NPHC), a biotechnology company that is developing treatments for adrenomyeloneuropathy (AMN), HIV, and multiple sclerosis (MS), has announced that its wholly owned drug discovery subsidiary, ReceptoPharm, has filed a patent for a novel composition and method for oral delivery of cobra venom for the treatment of pain.

"While the clinical use of cobra venom for treating pain has been well documented for the past 75 years, our recent research using one of our lead drug candidates, RPI-78, as an analgesic has allowed us to perfect a novel oral formulation and oral delivery method using cobra venom as a pain reliever," commented Dr. Paul Reid, CEO of ReceptoPharm. "With our in-depth knowledge of cobra venom and our comprehensive clinical data using cobra venom as an analgesic, we believe that filing this patent is one of the final required steps before introducing a new type of pain reliever developed from cobra venom for treating moderate to severe pain," he added.

"Filing this patent application provides ReceptoPharm with the opportunity to immediately commercialize a revolutionary new analgesic that we believe will compete effectively with current pain relievers, including those that contain opioids and acetaminophen, but without the negative side effects," explained Rik J. Deitsch, chair and CEO of Nutra Pharma. "We plan to release additional details as we move these products closer to market," he concluded.

In June, ReceptoPharm announced the completion of a clinical study that examined its leading drug candidate for the treatment of pain, RPI-78. The study showed that the pain-reducing effects of RPI-78 lasted four-times as long as morphine, without the negative side effects associated with opioid-based pain relievers.

BioSante Pharmaceuticals Reports Positive LibiGel® Safety Data in Phase III Program

Business Wire: August 13, 2009 – LINCOLNSHIRE, IL – BioSante Pharmaceuticals, Inc. (NASDAQ: BPAX) has announced positive safety data in its ongoing LibiGel® Phase III clinical development program. BioSante reported that with over 1,250 women enrolled and almost 825 years of exposure in its LibiGel® Phase III clinical development program, there have been no deaths and only five cardiovascular events. This analysis of blinded data indicates a very low cardiovascular event rate has occurred thus far. Therefore, in view of the excellent LibiGel® safety profile, BioSante's LibiGel® Phase III development program will continue as planned. BioSante targets submission to the FDA of a new drug application (NDA) by mid-2011.

"The cardiovascular safety data indicate that LibiGel, to date, has been shown to be safe," said Stephen M. Simes, BioSante president and CEO. "We are happy to see that LibiGel continues to show its safety in healthy women, and also in those women with at least two cardiac risk factors enrolled in our cardiovascular and breast cancer safety study. We will continue to analyze blinded cardiac event data on a regular basis. LibiGel remains the only pharmaceutical product in the U.S. in active development for the treatment of hypoactive sexual desire disorder (HSDD) in menopausal women. We continue to believe that LibiGel can be the first product approved by the FDA for this common and unmet medical need also referred to as female sexual dysfunction (FSD)."

In addition to the Phase III cardiovascular and breast cancer safety study, BioSante is conducting two LibiGel® Phase III efficacy trials. The Phase III efficacy trials of LibiGel® in the treatment of FSD are double-blind, placebo-controlled trials that will enroll up to approximately 500 surgically menopausal women, each for a six-month clinical trial. The efficacy trials are being conducted under an FDA-approved SPA (special protocol assessment agreement).

NuPathe Reports Positive Phase III Results for Zelrix™, a Novel Transdermal Patch for Acute Migraine

Business Wire: August 11, 2009 – CONSHOHOCKEN, PA – NuPathe Inc., a specialty pharmaceutical company developing innovative products for the treatment of neurological and psychiatric diseases, has announced top-line results from the pivotal Phase III clinical trial of Zelrix™, a novel transdermal patch in clinical development for the treatment of acute migraine. In this multi-center, randomized, parallel group, double-blind, placebo-controlled trial, the efficacy and tolerability of Zelrix™ were compared with placebo in a total of 530 adults.

The Zelrix™ patch combines NuPathe's proprietary SmartRelief™ iontophoretic transdermal technology with sumatriptan, the most prescribed treatment for acute migraine in the United States. "Zelrix was designed to overcome key barriers to successful treatment of migraine: treatment-altering nausea, treatment-limiting side effects, and inconsistent drug absorption," said Jane Hollingsworth, chief executive officer of NuPathe.

According to the National Headache Foundation, 55% of migraine sufferers frequently experience nausea as part of their migraine attacks, commonly resulting in patients delaying, modifying, or skipping treatment. Concerns about treatment-

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related side effects also lead patients to delay, modify, or skip treatment in over one-third of migraine attacks. Moreover, many patients experience inconsistent relief, which experts attribute, in part, to substantial variation in oral drug absorption.

Zelrix™ was well-tolerated in the trial. Skin tolerability was typical of other transdermal products, with mild to moderate erythema present upon patch removal. The incidence of triptan-specific adverse events was very low. The most common adverse events were itching, pain, and tingling at the application site. The majority of adverse events were reported as mild and transient.

"The pivotal Phase III results confirm that Zelrix provides clear clinical benefits for patients. Zelrix demonstrated efficacy consistently across all symptoms of acute migraine combined with a very low incidence of triptan adverse events," said Mark Pierce, M.D., Ph.D., chief scientific officer at NuPathe. "Patients need a migraine treatment that can deliver effective relief in a well-tolerated manner without being undermined by the treatment-altering nausea, vomiting, or other gastric symptoms associated with migraine. This milestone brings NuPathe one step closer to bringing the first and only migraine patch to the market. We look forward to submitting an NDA for Zelrix in 2010." NuPathe plans to present a comprehensive summary of the data from this trial at the upcoming 14th Congress of the International Headache Society being held in Philadelphia, PA, September 10–13, 2009.

Javelin Pharmaceuticals Reports Ereska (Intranasal Ketamine) Phase III Trial Results for Postoperative Orthopedic Pain

Business Wire: August 11, 2009 – CAMBRIDGE, MA – Javelin Pharmaceuticals, Inc. (NYSE Amex: JAV – News) has described its initial review of top-line results from a Phase III study of Ereska™ (intranasal ketamine, 30 mg). This randomized, multicenter, double-blind, 1:1 placebo-controlled study assessed the safety and analgesic efficacy of repeated doses of Ereska™ over 6 hr in 259 patients with acute moderate-to-severe pain following orthopedic surgery.

The predefined primary outcome measure for this trial was the summary of pain intensity differences over a 6-hr period after initial drug dosing (SPID-6). The baseline- and site-adjusted means (plus or minus standard errors) for SPID-6 were 78.2 ± 12.4 for the Ereska™ group and 47.9 ± 12.3 for the placebo group, yielding a borderline *P* value of 0.053. (The standard for statistical significance in pivotal clinical trials is a *P* value of 0.05 or less.) Having had only a brief period of time to review select data from the trial, our initial assessment is that a high degree of intersubject variability likely impacted the *P* value of the primary endpoint. In addition, certain clinically relevant secondary endpoints that we have been able to review so far, including patient global evaluations, were statistically significant in favor of Ereska™.

Ereska™ was generally well tolerated in the trial. Of particular note, incidences of psychological side effects were ≤3% in subjects given Ereska™ and were typically mild and transient. The company will thoroughly examine all aspects of this trial. In a recent interaction with the FDA, prior to the availability of this trial's initial data, the division offered to review the results of this study. "Low, subanesthetic doses of ketamine are increasingly described by pain specialists as a useful alternative for pain control. The present trial provides additional valuable experience with intranasal ketamine for pain control. My colleagues and I will carefully review this data and the results of our earlier trials of Ereska as we proceed with the development of this novel product candidate," stated Javelin Chief Medical Officer Daniel B. Carr, MD.

AlphaRx Receives Chinese Patent for Its Drug Delivery Platform

PRNewswire-FirstCall: August 10, 2009 – MARKHAM, ON, Canada – AlphaRx Inc. (OTC BB: ALRX.OB – News), an emerging biopharmaceutical company utilizing proprietary drug delivery technology to develop novel formulations of drugs, has announced that it has been granted a comprehensive patent in China for its topical platform technology, titled "Vehicle for Topical Delivery of Anti-inflammatory Compounds." The platform is an integral part of the company's clinical stage product candidate Indaflex™.

"China represents a major opportunity for AlphaRx because of its huge and growing market for innovative therapeutics products," said AlphaRx President and CEO Michael Lee. "The granting of this patent from the Chinese government intellectual property authority helps protect our innovative drug delivery technology and further endorses our competitive position in China."

In April 2006, AlphaRx licensed the global rights (with the exception of Asia and Mexico) for Indaflex™ to Proprius Pharmaceuticals, Inc. Under the terms of the agreement, AlphaRx is eligible to receive milestone payments of up to $116 million for the successful development and commercialization of Indaflex™, as well as double-digit royalties on sales. Proprius was acquired by Cypress Bioscience Inc. in March 2008.

Tiny Cup Attached to Eye Improves Drug Delivery for Retinal Diseases

PRNewswire-USNewswire: August 7, 2009 – LOS ANGELES, CA – A new drug delivery system that uses a tiny silicone cup filled with any drug and sealed to the outer surface (episclera) of the eyeball may offer a more effective method for the sustained delivery of medicines for retinal and vitreous diseases, according to a new report by A. Linn Murphree, M.D, director of the Retinoblastoma Program in The Vision Center at Children's Hospital Los Angeles. Dr. Murphree is also professor of ophthalmology and pediatrics at the Keck School of Medicine at the University of Southern California and attending physician at the Doheny Eye Institute.

In his invited presentation, made July 30, 2009, at the Association for Research in Vision and Ophthalmology (ARVO) Summer Eye Research Conference on Ophthalmic Drug Delivery Systems in Bethesda, MD, Dr. Murphree said the

device, called an episcleral drug reservoir, holds the potential to fundamentally change how we deliver medications to the eye for diseases like macular degeneration, diabetic retinopathy, uveitis, endophthalmitis, and retinoblastoma. Working much like an organ-specific transdermal skin patch, the tiny cup isolates the medication targeted to the eye from being absorbed into the blood stream. This new delivery system is a safe and non-invasive way to deliver effective doses of medications to the interior of the eye over long periods of time (weeks to months). Currently drops, periocular injections, and intraocular injections are used to deliver medications to the eye but generally only for short periods of time.

Alnylam and Tekmira Participate in New Research Collaboration Focused on Discovery of Novel Cationic Lipids for Systemic Delivery of RNAi Therapeutics

Business Wire: August 6, 2009 – CAMBRIDGE, MA, and VANCOUVER, BC, Canada – Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), a leading RNAi therapeutics company, and Tekmira Pharmaceuticals Corporation (TSX: TKM), have announced that they will jointly participate in a new research collaboration focused on the discovery of novel cationic lipids and lipid nanoparticles for the systemic delivery of RNAi therapeutics.

Under the terms of the two-year research collaboration, Alnylam will receive exclusive rights to all new inventions, as well as rights to sublicense any resulting intellectual property to Alnylam's current and future partners. Tekmira receives rights to use new inventions for their own RNAi therapeutic programs licensed under Alnylam intellectual property through its InterfeRx™ program.

"We are excited to participate with Tekmira to support research efforts that will focus on the discovery of novel lipids for nanoparticle-based formulations of RNAi therapeutics that we believe will have the potential to push the frontiers of systemic delivery to further improve potency and broaden biodistribution," said Barry Greene, president and chief operating officer of Alnylam.

The research collaboration will be funded by Alnylam, and the work will be conducted by scientists at The University of British Columbia (UBC) and at a newly formed company called AlCana Technologies, Inc. UBC, and AlCana will focus on generating novel cationic lipids to be evaluated in lipid nanoparticles for the systemic delivery of RNAi drugs.

"We're pleased to continue our successful relationship with Alnylam and UBC in this new collaboration," said Dr. Mark J. Murray, Tekmira president and chief executive officer. "In the new effort, Alnylam and Tekmira will share in the development of new intellectual property that we believe will further extend our industry leadership position in the delivery of RNAi therapeutics."

Alnylam and Tekmira have each advanced a systemic RNAi therapeutic program to the clinic using Tekmira's stable nucleic acid lipid particle (SNALP) technology. Alnylam has an ongoing Phase I multi-center, open-label, dose-escalation trial to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of ALN-VSP in patients with advanced solid tumors with liver involvement, including hepatocellular carcinoma (HCC). Tekmira has initiated a Phase I human clinical trial for ApoB SNALP, which is being developed as a treatment for patients with high LDL cholesterol, or "bad" cholesterol. Tekmira expects to complete the Phase I trial in early 2010.

Aradigm Receives Orphan Drug Designation in Europe for Inhaled Liposomal Ciprofloxacin to Treat Cystic Fibrosis

Business Wire: August 5, 2009 – HAYWARD, CA – Aradigm Corporation (OTCBB: ARDM – News) has announced that the European Medicines Agency (EMEA) granted orphan drug designation to the company's inhaled liposomal ciprofloxacin drug product candidate for the treatment of lung infections associated with cystic fibrosis (CF).

Under European guidelines, the orphan medicinal product designation provides 10 years of potential market exclusivity if the product candidate is the first product candidate for the indication approved for marketing in the European Union. The orphan drug designation also allows the candidate's sponsor to seek assistance from the EMEA in optimizing the candidate's clinical development through participation in designing the clinical protocol and preparing the marketing application. Additionally, a drug candidate designated by the European Commission as an orphan medicinal product may qualify for a reduction in regulatory fees as well as a European Union-funded research grant.

"We are very pleased that the EMEA granted our liposomal ciprofloxacin Orphan Drug Designation for the treatment of cystic fibrosis," said Dr. Igor Gonda, Aradigm Corporation CEO and president. "This designation is an important step in our development of a new chronic treatment for management of respiratory infections commonly experienced by CF patients. Our once-a-day dosing has the potential to significantly decrease the burden of therapy for these patients."

Ciprofloxacin is a widely prescribed antibiotic in the form of oral and intravenous formulations to treat acute exacerbations of infections of the lung frequently experienced by CF patients. It is often preferred because of its broad-spectrum anti-bacterial action. The company's once-a-day novel inhaled formulation of ciprofloxacin delivered in liposomes is to be used for chronic maintenance therapy, as it is expected to achieve high antibiotic concentration for efficacy at the site of infection and relatively low systemic antibiotic concentrations to minimize side effects.

The company was granted previously orphan drug designations by the U.S. Food and Drug Administration for inhaled liposomal ciprofloxacin for the management of CF and for non-CF bronchiectasis. The company is also developing inhaled liposomal ciprofloxacin as a potential treatment for prevention and treatment of bioterrorism infections such as inhaled anthrax.

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First Human Demonstration of Significant, Persistent Antibody Response Using Electroporation-delivered DNA Vaccine Published in *Human Gene Therapy*

Business Wire: August 5, 2009 – SAN DIEGO, CA – Inovio Biomedical Corporation (NYSE Amex: INO), a leader in DNA vaccine design, development, and delivery, has announced new data representing what Inovio believes to be the first demonstration of a significantly increased and persistent level of antibody response generated by a DNA vaccine delivered using electroporation.

The results, generated in a clinical study conducted by Inovio's collaborators, the University of Southampton and The Institute of Cancer Research in the United Kingdom, were published in the medical journal *Human Gene Therapy*, July 20, 2009, in a paper titled, "DNA Vaccination with Electroporation Induces Increased Antibody Responses in Patients with Prostate Cancer." The DNA vaccine is designed to induce a strong helper T-cell response, with the aim of enhancing induction of a cytotoxic T-cell response against tumor cells. Measuring antibody (humoral) responses against the helper sequence in the vaccine may help judge the vaccine's potential performance. It may also allow predictions of vaccine performance in other settings, e.g., against viral and bacterial diseases, where strong antibody responses are imperative in providing protection.

This open-label Phase I/II, two-arm, dose-escalation trial is evaluating a novel DNA vaccine based on a prostate-specific membrane antigen (PSMA) fused to a tetanus toxin (DOM). The PSMA antigen is designed to induce a CD8+ T-cell response capable of killing tumor cells; the DOM element is designed to help enhance the immune response to PSMA. The study is also evaluating delivery of this DNA vaccine with and without Inovio's proprietary electroporation delivery technology. In each arm, five patients were treated at each of three dose levels. The protocol included three vaccinations at 4-week intervals followed by booster doses at 24 and 48 weeks.

The published data complete the reporting of antibody responses in the 30 patients vaccinated in this study. The data indicate that the use of electroporation yielded significantly enhanced antibody responses to DOM, while the absence of electroporation resulted in low anti-DOM antibody responses (25-fold mean increase over baseline compared with a 1.5-fold mean increase, respectively). Importantly, the level of antibody response further increased following additional boosts of DNA vaccine delivery via electroporation at later time points. Furthermore, antibody responses persisted out to 18 months of follow-up, a significant result that would be useful in the context of a practical vaccine regimen. As reported in prior releases, this vaccine was found to be safe and well tolerated. Analyses of T-cell immune responses to the PSMA antigen are ongoing.

Dr. Christian Ottensmeier of the University of Southampton, principal investigator on the study, commented, "We are pleased to publish these data indicating a notably higher induction of antibodies to the tetanus toxoid component upon DNA vaccination with electroporation. The antibody levels appear to be in a range comparable to traditional protein-based vaccination or injection of attenuated or inactivated pathogen. With the advantageous safety profile of electroporation-delivered DNA plasmids indicated by human data to date, this data supports optimism for use of this next-generation vaccine modality as a strategy against infections and cancer."

Dr. J. Joseph Kim, Inovio CEO, said, "We have demonstrated in different human trials that Inovio's electroporation devices are safe and well-tolerated. This longer-duration data further validates the importance of our electroporation technology in achieving the primary goal of scientists in this field, which is to improve the immunogenicity of DNA vaccines in humans. These results bode well for our programs in development."

The development of this DNA vaccine was supported by the U.K. cancer charities the Leukemia Research Fund (www.lrf.org.uk) and Cancer Research UK (www.cancerresearchuk.org), and rights to the vaccine are owned by Cancer Research Technology Limited (www.cancertechnology.com). The study was supported by Cancer Research UK funding, the Allan Willett Foundation, Inovio Biomedical Corporation, and the Experimental Cancer Medicine Centre in Southampton. The clinical study is a collaborative project between the University of Southampton (www.southampton.ac.uk), with Southampton University Hospitals NHS Trust, and the Institute of Cancer Research, with the Royal Marsden NHS Foundation Trust, Sutton, Surrey, U.K.

Elan Drug Technologies Announces First Approval of a Long-acting Injectable Formulation Using NanoCrystal® Technology

Business Wire: August 4, 2009 – DUBLIN, Ireland – Elan Drug Technologies, a business unit of Elan Corporation, plc (NYSE: ELN), has announced the first approval of a long-acting injectable formulation using its proprietary NanoCrystal® technology. Janssen, a division of Ortho-McNeil-Janssen Pharmaceuticals, announced the approval of INVEGA® SUSTENNA™, the first once monthly atypical antipsychotic injection, by the U.S. Food and Drug Administration.

"The approval of INVEGA® SUSTENNA™, is an important milestone for our NanoCrystal® technology as it marks the first long-acting injectable product approved by regulatory authorities using the technology," announced Shane Cooke, executive vice president and head of Elan Drug Technologies. "Our versatile NanoCrystal® technology in this instance, allowed for a stable, low viscosity, high drug-loaded formulation in a small injection volume, to be developed."

The NanoCrystal® technology, a technology enabling the formulation of poorly water-soluble compounds for all routes of administration, allows for a ready-to-use one-month duration intramuscular depot formulation of paliperidone palmitate that can be administered by healthcare professionals. The

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

Dicerna Pharmaceuticals Scientific Founder to Present Data Demonstrating Dual Inhibitory Function of Aptamer-Dicer Substrate siRNA Conjugates at Oligonucleotide Therapeutics Conference

Business Wire: August 3, 2009 – WATERTOWN, MA – Dicerna Pharmaceuticals, Inc., a second-generation RNA interference (RNAi) company developing novel therapeutics utilizing its proprietary Dicer Substrate Technology™ and dicer substrate RNA (DsiRNA) molecules, has announced the presentation of data at the Oligonucleotide Therapeutics—From Concept to Implementation conference, as part of IBC USA's Drug Discovery & Development Week in Boston, August 3–6, 2009. On August 4, a presentation titled "A Novel Dual Inhibitory Function Anti-HIV Envelop Aptamer-siRNA Chimera," was presented by John J. Rossi, Ph.D., Lidow Family Research chair and professor in the Division of Molecular Biology, dean of the Graduate School of Biological Sciences at City of Hope's Beckman Research Institute, and scientific co-founder of Dicerna.

Dr. Rossi discussed RNA interference (RNAi) as a powerful mechanism that can be used to inhibit replication of the human immunodeficiency virus (HIV). He will highlight dual inhibitory function aptamer-siRNA chimeras, developed such that both the aptamer and the DsiRNA have potent and long-lasting anti-HIV activity. Dr. Rossi will also introduce a modular aptamer-DsiRNA strategy, allowing "mixing and matching" of different DsiRNAs with a given aptamer.

"These data are relevant to Dicerna, as they speak to the adaptability of our Dicer Substrate Technology and also support our 'double hit' rationale for maximizing the therapeutic potential of our proprietary oligonucleotide drug candidates. While HIV is not a disease area we intend to pursue internally, the data is important; first – to showcase the ability of DsiRNA molecules to achieve superior potency and duration of action against specific disease targets; and second – to demonstrate cell-specific targeting and intracellular uptake of DsiRNA molecules conjugated to highly selective targeting moieties such as aptamers," said James C. Jenson, Ph.D., chief executive officer and co-founder of Dicerna. He added, "Per our recently announced collaboration with Archemix, we are further exploring the therapeutic advantages of DsiRNA-aptamer conjugates against important cellular targets."

July 2009

Emisphere's SNAC Carrier Achieves GRAS Status for Use with Nutrients Added to Foods and Dietary Supplements

Business Wire: July 28, 2009 – CEDAR KNOLLS, NJ – Emisphere Technologies, Inc. (OTC BB: EMIS) has announced that, concurrent with the publication of two papers in the July/August issue of the peer-reviewed *International Journal of Toxicology*, which describes the toxicology of its sodium *N*-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC) carrier, SNAC has achieved generally recognized as safe (GRAS) status for its intended use in combination with nutrients added to food and dietary supplements.

Commenting on the news, Michael V. Novinski, president and chief executive officer of Emisphere, stated, "The publication of our two papers in the *International Journal of Toxicology* was the final, necessary step in the process of obtaining GRAS status for our SNAC carrier, and we are very pleased to have achieved this goal."

Allergan Receives FDA Approval for ACUVAIL™ Ophthalmic Solution for Treatment of Pain and Inflammation Following Cataract Surgery

Business Wire: July 23, 2009 – IRVINE, CA – Allergan, Inc. (NYSE: AGN) has announced that the U.S. Food and Drug Administration (FDA) has approved ACUVAIL™ (ketorolac tromethamine ophthalmic solution, 0.45%), an advanced, preservative-free formulation of ketorolac, a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of pain and inflammation following cataract surgery. Cataracts are a leading cause of blindness among older adults, and cataract surgery is the most frequently performed surgical procedure in the United States, with more than 3 million procedures performed each year.

ACUVAIL™ is formulated at pH 6.8, enabling deionized drug delivery on the corneal surface. ACUVAIL™ contains carboxymethylcellulose (CMC), a viscous molecule also found in Allergan's REFRESH® Brand Tears, that enables the drug to adhere to the ocular surface and enhances patient comfort. With ACUVAIL™, patients benefit from the drug's comprehensive inhibition of the COX-1 and COX-2 enzymes. Studies show that these enzymes should be blocked to inhibit the development of prostaglandins, which are considered the primary sources of pain and inflammation following cataract surgery.

"Building on Allergan's 60-year expertise in eye care, we are pleased to provide physicians and their patients with an advanced and effective NSAID option for the treatment of pain and inflammation following cataract surgery," said Scott Whitcup, M.D., Allergan executive vice president, research and development and chief scientific officer. "With its preservative-free formulation, optimized tolerability and twice-daily dosing convenience, we anticipate that ACUVAIL™ will be a valuable addition to the overall management of cataract surgery patients."

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The efficacy of ACUVAIL™ ophthalmic solution was assessed in two multi-center, randomized, double-masked, parallel group-comparison studies involving more than 500 patients receiving either ACUVAIL™ or a vehicle. In the clinical studies, the efficacy of ACUVAIL™ was defined as complete clearance of anterior chamber inflammation measured by a summed inflammation score (SOIS) and ocular pain relief following cataract extraction with posterior chamber intraocular lens (IOL) implantation. Results of these studies demonstrated that at day 7, nearly twice as many patients receiving ACUVAIL™ solution had an SOIS score of zero compared with patients treated with a vehicle (32% versus 17%). In addition, patients were shown to have a significantly higher incidence of clearing of anterior chamber inflammation at day 14 versus patients receiving a vehicle (53% versus 26%). ACUVAIL™ was also shown to be significantly superior to the vehicle in resolving ocular pain post-cataract surgery. On day 1 post-cataract surgery, the percentage of ACUVAIL™ patients with pain scores of zero was 72% compared with 40% for patients in the vehicle group.

"As an ophthalmic surgeon, I rely on effective therapies that provide my patients with an optimal experience and improve visual outcomes," said Eric Donnenfeld, M.D., F.A.C.S., Ophthalmic Consultants of Long Island. "ACUVAIL™ is an enhanced ketorolac compound and the first preservative-free, twice-daily ophthalmic NSAID that demonstrates complete elimination of inflammation for patients undergoing cataract surgery." ACUVAIL™ is expected to be available to physicians and patients in the United States in September 2009.

Gore Receives FDA Approval for Next Generation of Large-Diameter GORE VIABAHN® Endoprosthesis with Heparin Bioactive Surface

Business Wire: July 21, 2009 – FLAGSTAFF, AZ – W. L. Gore & Associates announced that it has received approval from the U.S. Food and Drug Administration (FDA) to market the most up-to-date design for the GORE VIABAHN® Endoprosthesis for device diameters 9–13 mm. The next generation of the large-diameter product enables streamlined deployment on the same 0.035-in. guidewire and TIP to HUB direction as the 5–8 mm sizes. Additional modifications to the large-diameter GORE VIABAHN® Endoprosthesis include radial device expansion, a contoured proximal edge, and a lower profile that is now available for most sizes.

"The self-expanding, covered, GORE VIABAHN Endoprosthesis offers elegant and versatile endovascular solutions to difficult vascular problems," said Michael B. Silva, Jr., MD, professor of vascular surgery, professor of radiology, and director of the Texas Vascular Center, University of Texas Medical Branch. "The latest improvements to the GORE VIABAHN Endoprosthesis with Heparin Bioactive Surface, including smaller delivery profile and 0.035″ wire compatibility for the larger diameter endografts, will allow us to easily deliver the larger devices to more locations. Treating difficult vascular problems requires good skills and good equipment. We just got some cool new enhancements to our toys."

The GORE VIABAHN® Endoprosthesis family of devices is constructed with a durable, reinforced, biocompatible, expanded polytetrafluoroethylene (ePTFE) liner attached to an external nitinol stent structure. The product's flexibility enables it to traverse tortuous areas and to conform to the complex anatomy of the artery.

"The recent modifications to the GORE VIABAHN Endoprosthesis device underscores our commitment to continually provide our customers with next-generation, innovative products for the treatment of Peripheral Arterial Disease (PAD) in the iliac artery," said Erin Hutchinson, Gore Peripheral Vascular Business. "Gore strives to be at the forefront of technology innovation and we're pleased to provide interventionalists with an improved version of the large diameter devices that will allow more patients to receive safe and effective interventional therapies for the treatment of PAD in iliac arteries."

The original device configuration in 6–8 mm sizes was initially approved by the FDA in 2005 for treating PAD in the superficial femoral artery (SFA). In 2007, Gore added a 5 mm size and made modifications to the device, including reducing its profile and adding a heparin bioactive surface. In 2008, Gore received approval for large diameters of the GORE VIABAHN® Endoprosthesis, 9–13 mm, to improve blood flow in patients with symptomatic peripheral artery disease in iliac artery lesions. In June, Gore announced that the FDA approved a manufacturing change to the device to remove excess material at the device margin, resulting in a contoured edge at the proximal end. The device is the only stent-graft approved by the FDA for the treatment of patients suffering from PAD in superficial femoral and iliac artery lesions.

A Drug-dispensing Contact Lens

PRNewswire-USNewswire: July 21, 2009 – BOSTON, MA – Taking eye drops multiple times a day can be difficult for patients to do, and because of blinking and tearing, as little as 1–7% of the dose is actually absorbed by the eye. Now, researchers led by Daniel Kohane, MD, PhD, director of the Laboratory for Biomaterials and Drug Delivery at Children's Hospital Boston, have developed special contact lenses that can gradually dispense a constant amount of medication to the eye, at adjustable rates. They describe their prototype lens in the July issue of *Investigative Ophthalmology and Visual Science*.

Although other groups have developed drug-releasing contact lenses, none have been able to achieve a constant, steady release of substantial amounts of drug; typically, a burst of drug is delivered in the first few hours, followed by rapidly dwindling amounts that are too low to be therapeutic. Kohane, collaborator Joseph Ciolino, MD, of the Massachusetts Eye and Ear Infirmary, and colleagues at the Department of Chemical Engineering at the Massachusetts Institute of Technology (MIT) created a two-layer contact lens with an inner drug-bearing biodegradable polymer film known as PLGA. Both PLGA and pHEMA (used for the coating) have been well

studied and are already approved for ocular use by the Food and Drug Administration.

In laboratory testing, the prototype lenses dispensed ciprofloxacin (an antibiotic often used in eye drops) for 30 days, the longest duration for which contact lenses are currently approved by the FDA; in some tests, the lenses continued releasing drug for up to 100 days. The amounts dispensed were sufficient to kill pathogens in a laboratory assay.

Kohane and Ciolino see applications in conditions such as glaucoma and dry-eye that require frequent daily eye drops. They have begun to test the lens in animals and plan to begin human testing as soon as possible. The technology recently won the Life Sciences track in MIT's 100K Entrepreneurship Competition.

The study was supported by the National Institute of General Medical Sciences at the National Institutes of Health, a Fight for Sight Grant-in-Aid, a Center for Integration of Medicine and Innovative Technology/Johnson & Johnson Young Investigator Award, and the Boston KPro Fund, Massachusetts Eye and Ear Infirmary. Ciolino and colleagues published their study in *Investigative Ophthalmology and Visual Science* (Invest. Ophthalmol. Vis. Sci., 2009; 50:3346-3352).

Archemix and Dicerna to Collaborate on Conjugated Aptamer-Dicer Substrate RNAi Therapeutics

Business Wire: July 21, 2009 – CAMBRIDGE, MA, and WATERTOWN, MA – Archemix Corp., a biotechnology company focused on discovering, developing, and commercializing aptamer therapeutics, and Dicerna Pharmaceuticals, Inc., a second-generation RNA interference (RNAi) company developing novel therapeutics utilizing its proprietary Dicer Substrate Technology™ and dicer substrate RNA (DsiRNA) molecules, announced that the two companies have entered into an agreement to collaborate on aptamer-DsiRNA therapeutics that leverage both the intracellular delivery capabilities of Archemix's aptamers and the potent gene silencing of Dicerna's DsiRNA molecules. Both companies are making an investment of resources to develop the aptamer-DsiRNA therapeutics and will work collaboratively on the R&D activities. The agreement includes an option for Dicerna to obtain exclusive rights to further develop and commercialize aptamer-DsiRNA therapeutics generated during the collaboration. Additional terms of the agreement were not disclosed.

A.P. Pharma Announces FDA Acceptance of the New Drug Application for APF530 for Chemotherapy-induced Nausea and Vomiting

Business Wire: July 20, 2009 – REDWOOD CITY, CA – A.P. Pharma, Inc. (Nasdaq: APPA), a specialty pharmaceutical company, has announced that the U.S. Food and Drug Administration (FDA) has accepted for review the new drug application (NDA) for APF530 for the potential treatment of chemotherapy-induced nausea and vomiting (CINV). APF530 is a long-acting formulation of granisetron that utilizes the company's proprietary Biochronomer™ drug delivery system. Based on the Prescription Drug User Fee Act (PDUFA), the FDA has issued an action date of March 18, 2010.

"The acceptance of the APF530 NDA represents another important step towards providing physicians and patients with a potential new long-acting therapeutic agent to combat chemotherapy-induced nausea and vomiting," said Ronald J. Prentki, A.P. Pharma president and chief executive officer. "Our team recognizes the important role APF530 could play in cancer care, and we are dedicated to working with the FDA as it reviews our NDA submission."

The NDA was submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, whereby the company can rely upon the FDA's prior safety and efficacy findings for APF530's active ingredient, granisetron.

Alnylam and Cubist Announce Complete Data from Phase II Study of ALN-RSV01 in Lung Transplant Patients Naturally Infected with Respiratory Syncytial Virus

Business Wire: July 20, 2009 – CAMBRIDGE, MA, and LEXINGTON, MA – Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), a leading RNAi therapeutics company, and Cubist Pharmaceuticals, Inc. (Nasdaq: CBST), an acute care-focused therapeutics company, has reported complete data from their Phase II study of ALN-RSV01, an RNAi therapeutic for the treatment of respiratory syncytial virus (RSV) infection. Data were presented at the BIT Life Science's 2nd Annual Summit of Antivirals held in Beijing, China, July 18–25, 2009. The Phase II study was a randomized, double-blind study of inhaled ALN-RSV01 or placebo in adult lung transplant patients naturally infected with RSV. Clinical evaluations at 90 days confirmed that the primary objective of safety and tolerability was achieved.

In the Phase II study, conducted at 11 sites in 4 countries, 24 lung transplant patients with confirmed RSV infection were randomized to receive inhaled ALN-RSV01 ($N = 16$) or placebo ($N = 8$) once daily for three consecutive days. Overall, the study achieved its primary objective of demonstrating the safety and tolerability of ALN-RSV01. In particular, there were no drug-related serious adverse events or discontinuations, and there were no clinically significant differences in the overall adverse event profile between ALN-RSV01 and placebo. Importantly, there was no evidence of disease exacerbation related to ALN-RSV01 treatment. At the 90-day endpoint, all patients survived, and the incidence of intubation, new respiratory infection, or acute rejection was comparable across ALN-RSV01 and placebo groups.

"We are very pleased with the outcome of this study, which demonstrated for the first time the safety and tolerability of inhaled ALN-RSV01 in naturally infected patients," said Akshay Vaishnaw, M.D., Ph.D., Alnylam senior vice president, clinical research. "As such, these data provide important de-risking for the advancement of our overall ALN-RSV program. While the

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study was not powered for efficacy and is too small to make firm conclusions, we are encouraged by the 90 day clinical endpoint data, including improvement in lung function and a statistically significant reduction in new or progressive BOS in patients receiving ALN-RSV01 as compared with placebo."

"We are encouraged by these important safety results and other findings in this program in support of the continued advancement of our overall ALN-RSV program," said Steven C. Gilman, Ph.D., senior vice president, chief scientific officer, for Cubist Pharmaceuticals. "We are in the process of reviewing data from these and other studies related to specific plans for the advancement of our RSV program and look forward to providing further guidance on our specific plans later this year."

The companies plan to evaluate these and additional data from the broader ALN-RSV program, including its second-generation compounds, to determine the optimal development strategy and specific plans for all RSV indications.

Zogenix Obtains Approval in United States for Sumavel™ DosePro™; Aradigm to Earn $4 Million Milestone Payment upon Commercial Launch and Royalties on Sales

Business Wire: July 17, 2009 – HAYWARD, CA – Aradigm Corporation (OTC BB: ARDM.OB) has announced that Zogenix, Inc. was granted approval of the Sumavel™ DosePro™ (sumatriptan injection) needle-free delivery system that enables subcutaneous delivery of sumatriptan without a needle for the treatment of acute migraine. Aradigm is entitled to a $4 million milestone payment upon first commercial sale and royalty payments upon any sales of products in the United States and other areas, including the European Union, which may be developed and sold using the DosePro™ technology.

Sumavel™ DosePro™ uses the novel, proprietary DosePro™ drug delivery system to subcutaneously administer sumatriptan, a medication that has been used to treat migraines effectively and safely for over 15 years, without many of the issues associated with needle delivery. Sumavel™ DosePro™ has the potential to offer migraine relief beginning in as little as 10 min, in a system sufferers can self-administer in three easy steps. Given the unique attributes of Sumavel™ DosePro™, Zogenix believes it has the potential to be used as a replacement for needle-based injectable forms of sumatriptan, as well as to replace tablet and nasal spray triptans for challenging migraine episodes. Migraine affects approximately 30 million people in the United States. Patients suffer with extreme pain, nausea, vomiting, and sensitivity to light and sound, making it difficult to undertake work or other activities. Because of this, speed of relief is a key attribute identified by migraine patients when choosing a medication.

In August 2006, Aradigm sold all of its assets related to the Intraject™ needle-free injector technology platform and products, including 12 U.S. patents along with foreign counterparts, to Zogenix, Inc., a private company. Zogenix is responsible for development and commercialization efforts of Intraject™ (now rebranded under the name DosePro™).

BioDelivery Sciences and Meda Announce FDA Approval of ONSOLIS; BDSI to Receive $27 Million in Milestone Payments

Business Wire: July 16, 2009 – RALEIGH, NC – BioDelivery Sciences International, Inc. (Nasdaq: BDSI) and Meda AB have announced approval from the U.S. Food and Drug Administration (FDA) to market ONSOLIS™ (fentanyl buccal soluble film), formerly referred to as BEMA™ fentanyl, for the management of breakthrough pain (BTP) in patients with cancer, 18 years of age and older, who are already receiving and who are tolerant of opioid therapy for their underlying persistent cancer pain. ONSOLIS™ is the first product to utilize the company's proprietary bioerodible mucoadhesive (BEMA™) drug delivery technology, which consists of a small dissolvable polymer film for application to the buccal mucosa (inner lining of the cheek).

"The approval of ONSOLIS is a landmark and transformational event for BDSI and represents the culmination of an extraordinary and focused effort by a determined group of BDSI and Meda employees," said Dr. Mark A. Sirgo, president and chief executive officer of BioDelivery Sciences. "All of us at BDSI, along with our partner Meda, are very pleased to provide healthcare practitioners and their patients suffering from breakthrough cancer pain with a new treatment option for this serious and debilitating condition."

"Importantly, with the approval of ONSOLIS, we have validated the utility of the BEMA drug delivery technology and demonstrated our ability to move a product through clinical development and the regulatory requirements set by FDA," said Dr. Andrew Finn, executive vice president of product development. "We now look forward to replicating our performance and regulatory achievements as we progress our pipeline."

"Having worked on the clinical development of ONSOLIS, it is exciting to see it reach approval," said Dr. Richard L. Rauck, executive director of the Carolinas Pain Institute and of the Center for Clinical Research, a site that participated in the Phase III trials for ONSOLIS™. "Many patients with cancer suffer from these sharp spikes in pain referred to as breakthrough pain. These patients can benefit from a product like ONSOLIS with its onset of action and oral tolerability profile. We look forward to having this important option available for our patients with cancer breakthrough pain."

ONSOLIS™ is anticipated to be available in the fourth quarter of 2009 and will be commercialized in the United States by Meda Pharmaceuticals, the U.S. subsidiary of Meda AB. Meda is the company's commercialization partner for the product worldwide, with the exception of Taiwan and South Korea, the rights to which remain with BDSI. "We are very excited to launch ONSOLIS in the U.S. and make this product available to patients and healthcare providers," said Anders Lonner, chief executive officer of Meda AB. "The introduction of ONSOLIS has high priority for us, and we are well positioned to be successful."

AMS 700® with INHIBIZONE® Approved by FDA as Only Inflatable Penile Prosthesis Proven to Reduce Infection

Business Wire: July 16, 2009 – MINNEAPOLIS, MN – American Medical Systems, Inc. (AMS) (NASDAQ: AMMD), a trusted provider of medical solutions for restoring men's and women's pelvic health, announced that its AMS 700® with INHIBIZONE® has been approved by the U.S. Food and Drug Administration (FDA) as the only inflatable penile prosthesis with clinical evidence showing a significant reduction in the rate of revision surgery due to infection.

Based on nearly seven years of post-market study data from more than 40,000 patients implanted with the AMS 700® devices, the FDA agreed that the use of INHIBIZONE®-treated inflatable penile prosthesis resulted in a significant reduction in the rate of revisions due to infection in patients receiving both a first-time AMS 700® implant or an AMS 700® revision implant.

For diabetic patients, who by the nature of their condition are at an increased risk of infection, the post-market study also concluded that the use of INHIBIZONE®-treated penile prosthesis resulted in a significant reduction in the rate of revisions due to infection in those receiving a first-time AMS 700® implant.

"The risk of infection is one of the most serious complications of penile implant surgery, and it's one that urologists routinely take great care to guard against," said Whitney Erickson, vice president and general manager for men's health at AMS. "We hope the fact that the AMS 700 is the only inflatable penile prosthesis on the market clinically proven to reduce the rate of revision surgery due to infection will give both doctors and patients greater confidence in this device as a treatment option for chronic erectile dysfunction."

The AMS 700® with INHIBIZONE® is the gold standard for innovative penile implant technology and the only antibiotic-impregnated penile prosthesis on the market. The external silicone surfaces of the device's dual cylinders are impregnated with a proprietary combination of minocycline hydrochloride and rifampin, which elute from the surface when implanted.

"Managing post-op infection can be quite challenging and extremely expensive for the practitioner. It is quite painful for the patient, and the only way to remedy it is to endure a second surgery to resolve device-related infection," stated Dr. Culley Carson, Rhodes Distinguished Professor of Urology and chief of urology, University of North Carolina Hospitals, Chapel Hill. "The AMS 700 with INHIBIZONE significantly reduces the risk of revision, even in diabetic patients, helping to ensure a higher degree of both doctor and patient satisfaction." For more information about American Medical Systems and the AMS 700®, visit www.americanmedicalsystems.com.

LATITUDE Pharmaceuticals Initiates Two New Collaboration Studies for Its PG Depot

Business Wire: July 16, 2009 – SAN DIEGO, CA – LATITUDE Pharmaceuticals, Inc. (LPI), a San Diego-based drug formulation developer, announced that it has initiated two new collaboration programs for its phospholipid gel (pg) depot drug delivery platform. The programs are designed to provide prolonged and peak-free pharmacokinetic profiles for 3 and 7 days following a subcutaneous injection with an antibiotic and a protein drug, respectively. The new studies bring the total to seven feasibility/license agreements that are applying the PG depot to deliver small molecules, peptides, and proteins for pain, metabolic disease, anti-bacterial, and cardiovascular applications.

Andrew Chen, PhD, LPI president, noted, "Our newest feasibility studies represent a growing validation of our PG Depot technology. Like our ongoing collaborations, the new programs aim to transform a cumbersome routine of multiple injections each day into a convenient once-daily or once-weekly format. Both pharma and biotech companies definitely see high value in simplifying parenteral drug administration and extending or resurrecting IP protection through novel delivery technology. The protein-friendly nature of the PG Depot will create many opportunities to convert biologics from daily to weekly injections."

Noven and Hisamitsu Enter into Definitive Merger Agreement

Business Wire: July 14, 2009 – MIAMI, FL, and TOSU, Japan – Noven Pharmaceuticals, Inc. (NASDAQ: NOVN – News) and Hisamitsu Pharmaceutical Co., Inc. (TSE: 4530 – News) jointly announced that they have entered into a definitive merger agreement pursuant to which Hisamitsu has proposed to acquire Noven for a total cash consideration of approximately $428 million, or $16.50 per share, in an all-cash tender offer for 100% of the outstanding shares of Noven.

The acquisition is expected to be effected through a cash-tender offer by a wholly owned subsidiary of Hisamitsu for the outstanding shares of Noven. The tender offer, if successful, would be followed by the merger of the Hisamitsu subsidiary with and into Noven, with Noven surviving as a wholly owned subsidiary of Hisamitsu. The companies expect that Noven will continue as a standalone business unit, operating at its current locations in Miami and New York with its existing work force.

Peter Brandt, Noven president, CEO, and board member, said, "Today is a great day for Noven, our shareholders, our employees and all Noven constituents. The proposed acquisition by Hisamitsu—a company Noven has come to know, respect and trust over the course of several years—provides substantial value to Noven shareholders, while positioning Noven as the U.S. growth platform of a global company with significant resources and a vision aligned with our own. It brings together two industry leaders in complementary geographic markets that share a joint commitment to the development, manufacture and

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commercialization of transdermal and other therapies. With our combined capabilities and shared vision, we expect to accelerate the achievement of the Noven mission—to develop and commercialize products and technologies that meaningfully benefit patients, our customers and our industry partners—and to achieve that mission on a grander scale than we could alone."

Commenting on the transaction, Hirotaka Nakatomi, president of Hisamitsu, said, "In Noven, we believe we have found the ideal catalyst to accelerate Hisamitsu's strategic objective of increasing our U.S. presence. The transaction presents the opportunity to build upon Noven's impressive capabilities in transdermal drug development, clinical/regulatory affairs, manufacturing, and product commercialization. In addition, we believe products incorporating Noven's technologies have the potential to supplement Hisamitsu's development efforts in Japan and elsewhere, thereby advancing our vision of serving patients globally with new transdermal therapies that improve the quality of life."

Following the transaction, Jeffrey F. Eisenberg, currently Noven's executive vice president and president of the Novogyne joint venture, will be named Noven's president and chief executive officer. He will assume the responsibilities of Peter Brandt, who will leave Noven after a transition period.

Purdue Researchers Create Prostate Cancer "Homing Device" for Drug Delivery

July 6, 2009 – WEST LAFAYETTE, IN – A new prostate cancer "homing device" could improve detection and allow for the first targeted treatment of the disease. A team of Purdue University researchers has synthesized a molecule that finds and penetrates prostate cancer cells and has created imaging agents and therapeutic drugs that can link to the molecule and be carried with it as cargo. A radioimaging application used for body scans is expected to enter clinical trials this fall, and an optical imaging application used to measure prostate cancer cells in blood samples is already in clinical trials.

According to Philip Low, the Ralph C. Corley Distinguished Professor of Biochemistry who led the team, a targeted treatment could be much more effective in treating cancer and would greatly reduce the harmful side effects associated with current treatments. "Currently none of the drugs available to treat prostate cancer are targeted, which means they go everywhere in the body as opposed to only the tumor, and so are quite toxic for the patient," said Low, a member of the Purdue Cancer Center. "By being able to target only the cancer cells, we could eliminate toxic side effects of treatments. In addition, the ability to target only the cancer cells can greatly improve imaging of the cancer to diagnose the disease, determine if it has spread or is responding to treatment."

A clinical trial of the radioimaging application is expected to begin at the Indiana University Medical Center in the fall through a collaboration between the Purdue Cancer Center and the Indiana University Cancer Center with additional support from Endocyte Inc.

There is currently only one radioimaging agent for prostate cancer approved by the Food and Drug Administration. "The current imaging capabilities available for prostate cancer are very poor," Low said. "The existing imaging agent is limited because of its large size, which is difficult to get into a solid tumor. Also it seeks out a target located inside the cancer cell and is only able to mark injured cells that are falling apart as opposed to actively growing cancer cells."

The targeting molecule and radioimaging agent combination designed by Low's group is more than 150 times smaller than the existing agent and can much more easily penetrate through a solid tumor to reach all of the cells inside. It also has the advantage of targeting an area of PSMA exposed on the outside of cancer cells.

June 2009

Flamel Technologies Announces New Feasibility Projects and Technology Access Fee

Business Wire: June 22, 2009 – LYON, France – Flamel Technologies, SA (Nasdaq: FLML – News) has announced that it has entered into agreements with a leading global healthcare provider to assess the applicability of the Medusa® platform for controlled release formulations of therapeutic proteins. The company will receive technology access fees totaling €2.5 million pursuant to these agreements, plus full development costs for the program.

Stephen H. Willard, chief executive officer of Flamel Technologies, said, "We are very pleased to add a new partner for multiple molecules using our Medusa technology. We are gratified that our technology has achieved the recognition which justifies upfront payments as well as the usual license fees, development fees, milestones, and royalties. We look forward to announcing additional details of our collaboration in the month to come."

Flamel Technologies, S.A. is a biopharmaceutical company principally engaged in the development of two unique polymer-based delivery technologies for medical applications. Micropump® is a controlled release and taste-masking technology for the oral administration of small-molecule drugs. Flamel's Medusa® technology is designed to deliver controlled-release formulations of therapeutic proteins and peptides, as well as small-molecule drugs.

Access Pharmaceuticals Announces Initiation of Two New Cobalamin™ Oral Insulin Drug Delivery Collaborations

PRNewswire-FirstCall: June 17, 2009 – DALLAS, TX – Access Pharmaceuticals, Inc. (OTC Bulletin Board: ACCP) has announced that the company has signed evaluation agreements with two biopharmaceutical companies for its Cobalamin™ oral drug delivery technology. Under the terms of the agreements, both companies plan to evaluate Access' oral insulin product in preclinical models as a prerequisite to entering licensing discussions.

Access announced previously that it had an agreement with a large pharmaceutical company for the evaluation of Cobalamin™ oral drug delivery formulations of human growth hormone (hGH).

"While all of the products and technologies which we chose to showcase at the recent BIO 2009 conference in Atlanta attracted a great deal of interest, it was clear that the Cobalamin oral drug delivery technology generated the most interest," commented Phillip Wise, Access vice president of business development and strategy. "We are delighted that two companies have decided to take a closer look at the Cobalamin oral drug delivery technology. Meanwhile, we have several ongoing discussions with other companies regarding the application of our oral drug delivery options for their promising new drugs."

The proprietary Cobalamin™ technology utilizes the body's natural vitamin B_{12} oral uptake mechanism to facilitate oral absorption of pharmaceuticals by a "Trojan horse" mechanism. Since presenting promising results at a scientific conference in mid-2008, Access has made substantial improvements to the formulation technology. A new Cobalamin™-coated insulin-containing nanoparticle formulation delivered orally provided a pharmacological response (lowering of blood glucose levels in an animal model of diabetes) equivalent to 90% of that achieved by insulin delivered subcutaneously. This represents substantial oral bioavailability, indicating that this formulation has potential for clinical development and ultimate commercialization. Adaptation of this technology has provided a Cobalamin™ HGH formulation that has demonstrated good efficacy, represented by more than 25% improvement in weight gain, when given orally in an established animal model. Access continues to move both products toward clinical development and plans to submit an additional patent application to protect their improvements to the technology.

"While Access' focus has been on the oral delivery of peptides, the technology is sufficiently flexible to allow us to deliver a wide range of actives," commented David P. Nowotnik, Ph.D., Access senior vice president of R&D. "In addition to peptide delivery, we have received inquiries recently about the potential of this technology to deliver actives ranging from small molecules to siRNA to monoclonal antibodies. As siRNA needs to be delivered intracellularly to be effective as a therapeutic, the Cobalamin technology may be particularly beneficial as an intracellular delivery technology, as the demand for vitamin B_{12} increases in many disease states." For additional information on Access Pharmaceuticals, please visit our website at www.accesspharma.com.

Matrixx Initiatives Voluntarily Withdraws Zicam Cold Remedy Swabs and Zicam Cold Remedy Nasal Gel

PRNewswire-FirstCall: June 16, 2009 – SCOTTSDALE, AZ – Matrixx Initiatives, Inc. (Nasdaq: MTXX – News) has confirmed that it received a warning letter from the U.S. Food and Drug Administration about 2 of its 19 existing Zicam products, specifically Zicam Cold Remedy Nasal Gel and Zicam Cold Remedy Swabs. The warning letter cited consumer reports that the use of these products could cause a temporary or permanent loss of smell, known as anosmia. Zicam Cold Remedy oral products and other products in the Zicam cold, allergy, and sinus lines were not included in the letter. The company has announced it will comply with the FDA's requirements but will seek a meeting with the FDA to vigorously defend its scientific data developed during more than 10 years of experience with the products, demonstrating their safety.

Consumer safety is and has always been the company's top priority. While Matrixx Initiatives believes that the FDA action was unwarranted, it is voluntarily withdrawing Zicam Cold Remedy Swabs and Zicam Cold Remedy Gel from the market. Based on the FDA's recommendation, consumers should discard any unused product or contact Zicam at +1.877.942.2626 or visit www.zicam.com to request a refund.

Since Zicam Cold Remedy intranasal cold remedy products were first introduced in the market in 1999, more than 35 million retail units, representing over 1 billion doses, have been sold, and the cumulative body of scientific and medical evidence compiled over those years has demonstrated both the safety and efficacy of Zicam intranasal cold remedy products under conditions of ordinary use. Zicam Cold Remedy products have alleviated countless numbers of colds for millions of satisfied consumers.

"Matrixx Initiatives stands behind the science of its products and its belief that there is no causal link between its Zicam Cold Remedy intranasal gel products and anosmia," said William J. Hemelt, Matrixx Initiatives acting president. "It is well understood in the medical and scientific communities that the most common cause of anosmia is the common cold, which Zicam Cold Remedy intranasal gel products are taken to treat. Given the enormous number of doses sold and colds treated, there is no reason to believe the number of complaints of anosmia received is more than the number that would be expected in the general population. There is no reliable scientific evidence that Zicam causes anosmia."

Commenting on the FDA action, Hemelt continued, "We were surprised that the FDA decided to take this action without notifying us first, given our cooperative relationship with the FDA since we launched our first product in 1999. Had we had the opportunity to sit down with the FDA beforehand, we are confident that the FDA would have agreed that the scientific data clearly demonstrated the safety of our products."

Matrixx Initiatives, Inc. is engaged in the development and marketing of over-the-counter healthcare products that utilize innovative drug delivery systems. Zicam, LLC, its wholly owned subsidiary, markets and sells Zicam products in the cough and cold category. For more information regarding Matrixx products, go to www.zicam.com. To find out more about Matrixx Initiatives, Inc. (NASDAQ: MTXX – News), visit our website at www.matrixxinc.com.

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Researchers Uncover How Nanoparticles May Damage Lungs

Reuters: June 12, 2009 – HONG KONG, China – Researchers in China appear to have uncovered how nanoparticles used in medicine for diagnosis and delivering drugs may cause lung damage. Nanotechnology, or the science of the extremely tiny, is an important industry. One nanometer is one-billionth of a meter. Apart from medicine, nanotechnology is used in products like sporting goods, cosmetics, tires, and electronics and has a projected annual market of around US$1 trillion by 2015.

However, concerns are growing that nanoparticles may have toxic effects, particularly to the lungs. But, it has never been clear how the damage is caused. In an article published in the *Journal of Molecular Cell Biology*, Chinese experts said a class of nanoparticles used in medicine, ploy amidoamine dendrimers (PAMAMs), may cause lung damage by triggering a type of programmed cell death known as autophagic cell death.

In experiments, they observed how several types of PAMAMs killed human lung cells but found no evidence that the cells were dying by apoptosis, a natural and common type of cell death. In a subsequent experiment in mice, they injected an autophagy inhibitor in mice and later exposed the rodents to nanoparticles and found that it "significantly ameliorated the lung damage and improved survival rates."

"This provides us with a promising lead for developing strategies to prevent lung damage caused by nanoparticles," said the leader of the team, Chengyu Jiang, a molecular biologist at the Chinese Academy of Medical Sciences in Beijing.

Exenatide Once Weekly Provides Sustained Improvements in Glycemic Control with Weight Loss Over Two Years

Business Wire: June 7, 2009 – NEW ORLEANS, LA – Amylin Pharmaceuticals, Inc. (Nasdaq: AMLN – News), Eli Lilly and Company (NYSE: LLY – News), and Alkermes, Inc. (Nasdaq: ALKS – News) have announced long-term, interim results from their DURATION-1 study, which showed sustained glucose control with weight loss, as well as improvements in systolic blood pressure and triglycerides, through 2 years of treatment with exenatide once weekly, an investigational therapy for type 2 diabetes. These findings were presented at the 69th Annual Scientific Sessions of the American Diabetes Association (ADA) in New Orleans. A new drug application (NDA) for exenatide once weekly was recently submitted to the U.S. Food and Drug Administration.

In the controlled portion of the open-label study, patients received exenatide once weekly or BYETTA® (exenatide) injection for 30 weeks, followed by 74 weeks of treatment with exenatide once weekly for all patients during an open-ended assessment period. Significant reductions in A1C of 1.7% and fasting plasma glucose (FPG) of 40 mg/dL were maintained after 2 years of treatment. Sixty-five percent of patients achieved an A1C of 7% or less. (A1C of <7% is the target for good glucose control as recommended by the ADA.) Body weight was significantly reduced, with patients losing an average of 5.8 lb. Serum lipid profiles were significantly improved, and there was a significant reduction in systolic blood pressure (SBP).

"These two-year DURATION-1 data showed that maintenance of steady state concentrations of exenatide may result in sustained improvements in glycemic control, with potential weight loss," said Orville G. Kolterman, M.D., senior vice president of research and development at Amylin. "In DURATION-1, exenatide once weekly has been shown to provide superior glycemic control, with weight loss, compared to BYETTA. If approved, this therapy could fill an important unmet need for treating patients with type 2 diabetes with just one dose per week." ■

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www.nanodds.org/

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www.icrc2009.ir

10th International Symposium on Polymers for Advanced Technologies
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www.pat2009.com

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