CRS Delivering Bioactives

Newsletter

A publication of the Controlled Release Society

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Steven Giannos
Editor

Bozena Michniak-Kohn
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Editor

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CRS Newsletter

Delivering Bioactives

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The CRS Newsletter is the official newsletter of the Controlled Release Society. The newsletter is published four 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.

Controlled Release Society
3340 Pilot Knob Road
St. Paul, MN 55121 U.S.A.

Telephone: +1.651.454.7250
Facsimile: +1.651.454.0766

Visit www.controlledreleasesociety.org or e-mail crs@scisoc.org on questions about membership, meetings, publications, and services.

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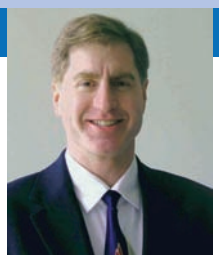
From the Editor



Steven Giannos
Chrono Therapeutics, Inc.
Trenton, NJ, U.S.A.

Big Week in the Big Apple

Wow, if you weren't able to attend this year's CRS Annual Meeting, you missed a great one. If you were there, I hope the week was as busy and enjoyable for you as it was for me. Inside this issue of the *CRS Newsletter*, you will find highlights and pictures from the annual meeting, as well as Chapter News and other regular *Newsletter* features.

The 2008 CRS Annual Meeting & Exposition was an inspiring and informative week celebrating 35 years with the largest attendance yet. Thanks to the exceptional program that Ijeoma Uchegbu, scientific secretary and former *Newsletter* editor, and the program chairs put together, the conference in New York City was just the place to combine business and science, as well as the All-Star baseball game and pregame Red Carpet Parade that ran just outside the Hilton Hotel.

This past year has been a period of transition and revitalization for the Controlled Release Society. A special thanks goes to Susan Cady for leading the Society through a year of change, rebirth, and renewed excitement for our industry. As seen in the new CRS logo, *CRS Newsletter* format, and CRS website design, this momentum is now growing and will continue through the efforts of our incoming President Lisbeth Illum and backed by the new members of the Board of Directors and Board of Scientific Advisors.

Starting with workshops on Saturday and ending with poster take down on Wednesday afternoon, the week had something for everybody. Sunday began with the ever-popular soapbox sessions, moderated by Eyal Ron. This year also saw industrial sessions in which Todd James (Trout Group, LLC) gave a Wall Street perspective of our business. Additionally, a "state of the industry" presentation by Debra Bingham (Valeo Partners) and Tim Howard (Stonecraft Capital, LLC) reviewed the historical and current impacts controlled release has had and is having on the global pharmaceutical industry.

The Closing Reception and Banquet Tuesday evening offered an opportunity to hear from Past Presidents Robert Langer and Kinam Park. As always, Bob Langer gave a great presentation that reviewed the history of controlled release and the many innovations and possibilities for controlled release technologies in the future. Kinam Park gave a retrospective of Past President Joe Robinson, encouraged contributions to the CRS Foundation, and also announced the new Joseph R. Robinson Postdoctoral Fellowship. Susan Cady presented several awards before handing over the CRS gavel to Lisbeth Illum.

In the areas of education and career development, Michael Rathbone is leading another exciting program for our members—the Young Scientists Mentorship Program. The organizing committee quickly matched mentors with protégés at the conference and provided a guide and outline for the mentor/protégé partnership. Mentors are available from industry, government, and academia, so there is a wealth of experience to draw from. I'm really excited to be a part of this effort with Michael and have the opportunity to help our younger scientists pursue a career in controlled release and drug delivery.

From the Editor continued on page 19

Lisbeth Illum
Identity, Nottingham, U.K.

The 35th CRS Annual Meeting & Exposition in New York was not only a celebration of the existence of the Controlled Release Society for 35 years, but also proof of how far the Society has come since its early beginnings in 1973. The CRS Annual Meeting in New York was our most successful meeting ever, with nearly 2,000 attendees from all disciplines within the delivery of bioactives and from many countries around the world. It was a truly international event. Scientific Secretary Ijeoma Uchegbu, with the help of the Program Committee, put an outstanding scientific program together, with plenary talks by international experts on topics such as cancer therapies, therapies for Parkinson's disease, nanostructures, counterfeit medicines, and gene regulation. There were more than 40 oral sessions (including 31 podium sessions, 6 mini-symposia, and 5 industry sessions), nearly 1,000 posters, pre-meeting workshops, soapbox sessions, pearls of wisdom discussions, and much more. The whole place was hustling and bustling throughout the day, from early morning with "Get Up; Get Educated" for the young scientists to later in the day with visits to the exhibits and various parties. It was a truly exceptional and enjoyable meeting. It was also a delight for me to see so many past presidents participating very actively in the meeting and making it an awesome experience for many young scientists. So, a big thank you to all of you who were there!

I cannot write my first column as president of the CRS, however, without mentioning our problem session during the annual meeting: the CRS Awards Ceremony and Member Meeting, which this year again took place Monday morning straight after the first plenary speaker. The room was filled with at least 1,800 people, and I was looking forward to presenting and to hearing short presentations on the strategies, budgets, and achievements of the CRS. However, as usual, within five minutes of the meeting starting we were left with 20–30 people in the huge auditorium. This meeting is for YOU, the members of the CRS. It is in this forum that you can have your say, ask questions, and talk directly to the BOD. Next year we may consider locking the doors!

The CRS Foundation has now been launched. Its first goal is to build up enough funds to set up a scholarship in recognition of Joe Robinson and from there to build up funds to provide a durable source of financial support for the advancement of educational and organizational activities that will enrich and extend the research and development of CR-associated technologies.

The CRS is a non-profit organization and the premier multidisciplinary Society dedicated to promoting the science, technology, and innovation of delivery of bioactives for the benefit of the world's population. However, the Society needs to be run on a strong business-like footing to provide increased value for our members, to maintain and improve the quality of the science, to increase access to scientific meetings and workshops worldwide for all members, and to become the #1 scientific society in our field. Last year the BOD produced a strategic plan that we will build upon in the coming years. As an organization, we need to be more independent of the CRS Annual Meeting & Exposition as the main income source (presently 75%) for the Society, which places us in a very vulnerable situation. In addition, it is of utmost importance that the CRS brings the science to you. We shall strive to change our financial independence from the annual meeting to 50% over the coming years by increasing the number of satellite meetings and educational workshops and by developing a successful CRS book publishing house. CRS needs to be on the cutting edge of new science and, hence, intends to sponsor workshops in new and exciting areas of research. In the coming year the CRS will also aim to increase communication with our members by creating more chapters and becoming more visible. You probably have already seen our much improved website, which will in the coming year become more and more interactive and contain many new and exciting features, such as webinars. Finally, our aim is to increase the number of members in the Society through active marketing, by increasing CRS's profile in the scientific and economic world spheres, and by truly becoming a centre of excellence.

CRS has also in the past year changed its logo to stress new beginnings but has not changed its basis. CRS is a truly international organization that serves 2,000 members from more than 45 countries. Two-thirds of the CRS membership represents industry, and one-third represents academia and government. Controlled release is the field of scientific activity concerned with the control in time and space of the biological effects of therapeutic agents in human and animal health and of other active agents in environmental, consumer, and industrial applications. Controlled release draws on the expertise of many disciplines: chemistry, chemical engineering, pharmaceutics, physics, materials science, and biological sciences—biochemistry, biophysics, molecular biology, physiology, cell biology, medicine, etc. Newer approaches, such as gene therapy, are being addressed as other forms of controlled release. The science of controlled release has become a research discipline whose future depends on a thorough understanding of the interactions between the delivery system and the biological or environmental barriers to delivery of active substances.

Lisbeth Illum ■


Exposition!


EXIT


ERCURY
ALLROOM


EXIT

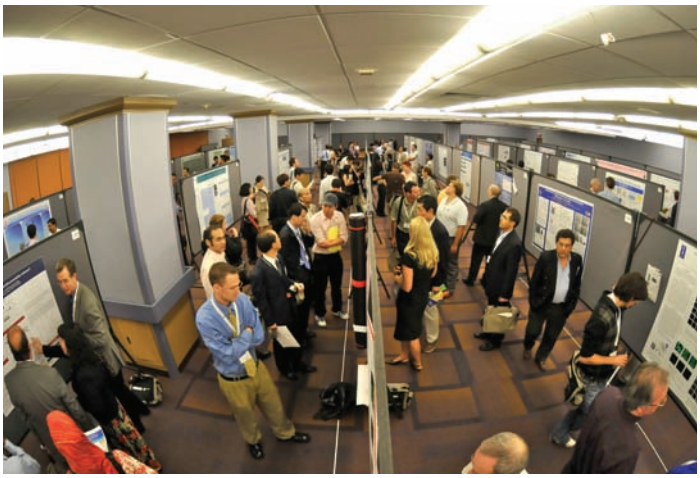

How do I get involved as a Protégé? .....
1. Complete a Protégé Application Form
2. Turn up here again at 9-30 am
3. Committee will assign you a Mentor
4. You will be introduced to your Mentor
5. You will be given the opportunity to get to know your Mentor and make plans
Get involved!!!


Delivery

Midtown Manhattan was the perfect setting for the record number of attendees and their energy at the 35th CRS Annual Meeting & Exposition in New York City. The incredible science and exhibiting companies inside the Hilton New York kept everyone on the edge of their seats and walking the exhibit halls.

CRS New York had a tremendously successful beginning with three educational workshops on Saturday. The crowds in the Delivery of Biologics with Novel Polymeric Constructs (chaired by David Brayden); Oral Drug Delivery: Challenging Patient Groups (chaired by Daniel Bar-Shalom, Brigitte Skalsky, and Clive Wilson); and Strategies to Advance the Bioavailability of Low Solubility Drugs (chaired by Yvonne Perrie and Thomas Rades) Educational Workshops filled their rooms with outstanding presentations and Q&A sessions that continued long after the closing bells rang. The presentations caused Wall Street to stand up and take notice.

Farid Dorkoosh and Rod Walker chaired a one-day Young Scientist Workshop focused on the regulatory aspects of pharmaceutical sciences. The room was packed with young, and not so young, scientists eager to hear about the drug approval process in the United States, IND applications, the FDA perspective on analytical validation and NDA trends, and managing innovation in pharmaceutical sciences.



Raid Alany, Terry Bowersock, and Sevda Senel of the CRS Veterinary Committee had a young, captivated audience on hand at the Sunday morning Young Scientist Workshop to learn about the world of veterinary drug delivery. This workshop focused on drug delivery in veterinary medicine and the growing need for novel drug delivery systems in animal health.

The companies presenting the Releasing Technology Workshops opened up their informational files on Sunday afternoon to enthralled audiences. Whether you attended ChemImage's "Dynamic Hyperspectral Imaging Solutions for Controlled-Release Systems," OctoPlus' "Controlled Release Technologies for the Delivery of Protein Therapeutics," Buchi's "Spray Drying

in Laboratory Scale," Lubrizol's "Oral Extended Release Dosage Forms with Carbopol® Polymers," Lipoid's "Lecithins and Phospholipids for Advanced Drug Delivery," Kendle and SOLIQS' "Drug Tampering and Abuse Deterrence: What You Need to Know and What Drug Abusers Don't Want You to Know," or Genzyme's "Cerense…Like Counting Cars on the Brooklyn Bridge: The Delivery to, and Assessment of, Potential Therapeutics into the CNS," you came away with knowledge you could only acquire by being there at that time.

The Sunday Soapbox Session was standing-room-only for good reason. From the 40+ submissions received, Chairs Philippe Dor and Eyal Ron once again selected a great mix of presenters and topics for the fast-paced, 5-minute pitches. One good thing led to another on Sunday afternoon when Industrial Session I played to a packed audience. This outstanding session was immediately followed by the first ever State of the Industry presentation at the CRS. Sarah Terry of Datamonitor Healthcare in New York City was the keynote speaker, and she delivered a strong and encouraging message. The Sunday afternoon Highlights of Student Posters Session was chaired by Doug Dale of Genencor and Kurt Fegely of Colorcon. These two companies have been involved with the student highlights for years as chairs and sponsors, and the session they created from the 70+ potential student poster presenters was a great thing to witness. Nine students were selected from among 72 who applied. If you happened to miss this dynamic session, be sure to look for Pooja Chandna, Esha Desai, Takeshi Kasuya, Jong Oh Kim, Yuki

Murase, Aristarchos Papagiannaros, Duangkamon Sakloetsakun, Milin Shah, and Anja Vetter's award-winning posters in the CRS Annual Meeting & Exposition's *Transactions* CD. Esha Desai received the top prize.

The bulls and bears were speaking their minds at the Pearls of Wisdom debates on Sunday afternoon. Thanks to Carla Carmella for keeping track of it all so successfully in her first year as chair of the debates. The bioactive materials topic, "Pulmonary Delivery of Proteins," was quite lively, with John Patton stating inhaling proteins can be a great approach depending on the proteins, and Lex Adjei saying inhalation delivery of biotherapeutics is a failing technology and a losing proposition. The C&DP topic, "Sunscreen Actives: Friends or Foes?," played to a packed room long after the closing bell rang. Robert Sayre peaked everyone's interest with his interesting theories, and Chuck Frey ably stepped into the role of the pro speaker at the very last minute, with the aid of originally scheduled presenter Ratan Chaudhuri's slides and research provided by moderator Teresa Virgallito. The Vet topic, "Veterinary Sustained Release Formulations Are More Complex Than Human Formulations: Women, Men, Pigs, Cats, and Chickens—Is There a Difference?—Challenges for CR Dosage Forms," let everyone know they were in for quite a show from Todd Foster and Ian Tucker.

There was another first for the CRS, the First-Timers' Greeting. Attendees who were new to the CRS and the CRS Board of Directors met informally to introduce themselves to each other. Who better to tell you about the CRS than a member of the Board!

The rush was on Sunday evening to get to the Opening Exposition and Reception in the exhibit halls. Plenty of nibbles and bits were consumed and exhibitors visited. The exhibit halls remained a popular venue throughout the annual meeting.

The Young Scientist Workshop Chairs Farid Dorkoosh and Rod Walker must not mind getting an early start to their day, along with a few of their closest 100 or so friends, because the Get Up; Get Educated sessions on Monday and Tuesday mornings were very successful. On Monday, Hamid Ghandehari discussed "Non-viral Gene Delivery"; and on Tuesday, Arash Hatefi spoke

on "Recent Advances and Potential Problems with the Use of Viral Vectors for Gene Therapy."

The grand Awards Ceremony was held Monday morning, followed by the CRS Member Meeting. CRS is honored to be the premiere Society dedicated to promoting the science, technology, and innovation of delivery of bioactives for the benefit of the world's population, and this was clearly evident at the Awards Ceremony. Winning one of the highly competitive CRS abstract-based and nominated awards is quite an achievement due to the quality and quantity of abstracts and nominees reviewed. CRS and the award sponsors congratulate all of the winners and thank all of the committee members who made the difficult decisions.

The CRS Member Meeting provided a clear picture of where the Society is headed scientifically and the message that all is well financially. The meeting was full of goodbyes and thank yous as BOD member Randy Mrsny, along with Board of Scientific Advisors members Terry Bowersock, Ralph Niven, and Thomas Rades, completed their terms of office.

Rakesh Jain of Massachusetts General Hospital and Harvard University was the first plenary speaker in New York. Dr. Jain's

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Meeting Round-up continued from page 7

presentation, "Normalization of Tumor Vasculature and Microenvironment by Antiangiogenic Therapies: From the Bench to the Bedside and Back," held everyone's attention. Plenary Speaker Dr. Raymond Bartus of Ceregene kept everyone's attention during his presentation, "The Development of AAV-Neurturin (CERE-120) as a Novel Neurorestorative Therapy for Advanced Parkinson's Disease: From Concept to Clinical Trials and Beyond." Monday was truly a scientifically outstanding day at the CRS meeting.

The Industrial Sessions continued on Monday and Tuesday and were as popular as ever, playing to standing-room-only crowds. Watch for Industrial Session Chair Ted Broman's innovative ideas for Copenhagen.

The Vet Get Together is a tradition for those involved in the many veterinary and related fields. This year's gathering featured Ramesh Panchagnula as the keynote speaker. Plenty of liquid refreshment was enjoyed by all, and it certainly got interesting discussions going and tall tales told.

Attendees were inspired on Tuesday morning by Jackie Ying's plenary presentation, "Nanostructure Processing of Advanced Biomaterials and Biosystems." Scientists, clinicians, physicians, researchers, and academicians involved in the delivery of bioactives are making a difference in lives, and Dr. Ying shared her successes with an enthralled audience. Tuesday afternoon's plenary session given by Dora Akunyili on "Combating Counterfeit Medicines in Nigeria" was outstanding. For the CRS attendees, Dr. Akunyili's trip from Nigeria to New York was well worth her time and theirs.

The Hilton New York's Trianon Ballroom was the setting for the CRS Closing Reception and Banquet. CRS President Susan Cady welcomed the gathering of friends and colleagues and introduced Bob Langer, who gave a colorful, informative, and delightful picture of controlled release in the past, present, and future. Following Bob was Kinam Park, who presented a tribute to CRS pioneer Joe Robinson. Kinam concluded his presentation by encouraging all in attendance to contribute to the CRS Foundation and the Joe Robinson Fellowship. Before dessert was served, Susan Cady ceremoniously presented the Distinguished Service Award to Martyn Davies, the Founders Award to Kazunori Kataoka, and the Young Investigator Award to Samir Mitragotri. There was one more piece of official business that took place before the night ended—witnessing Susan Cady hand the CRS gavel to incoming President Lisbeth Illum. It was a delightful way to conclude a lovely evening.

In the past, after enjoying a CRS banquet on a Tuesday night, there have been some attendees who have not quite made it to the plenary presentation the following morning. This was definitely not the case this year. Dr. Thomas Tuschl spoke to an alert and involved group. His presentation on "Mechanisms of Mammalian Small-RNA-Mediated Gene Regulation" had everyone ready for the full day ahead. As Wednesday afternoon came around, you could feel the anticipation of the final plenary presentation of the meeting. Mark Davis' presentation, "Nanoparticle Cancer Therapeutics: From Concept to Clinic," met everyone's expectations. The time Dr. Davis devoted to answering questions was truly appreciated.

A CRS Annual Meeting & Exposition wouldn't be complete without the outstanding science, exhibitors you need to talk with, committee meetings to attend, catching up with old friends and making new friends, developing plans to complete ongoing projects and new ideas, and just having a grand time. It's with these thoughts in mind that the door closes on New York City and opens wide to Copenhagen! See you there. ■

The Controlled Release Society thanks the sponsors of the 35th Annual Meeting & Exposition

Congratulations 2007 and 2008 CRS Awardees!

The Controlled Release Society's awards ceremonies held during the 35th CRS Annual Meeting & Exposition in New York City were special times that honored and recognized deserving scientists from around the globe. CRS is grateful to the many sponsors who provided their time and financial support to promote the talented scientists and innovative science. Congratulations to all! ■

Kenneth Ofokansi receives the 2008 CRS Outstanding Consumer & Diversified Products Paper Award, co-sponsored by Givaudan, from Chris Soper of Givaudan.

Naoki Okada receives the Jorge Heller Journal of Controlled Release *Outstanding Paper Award for 2007, co-sponsored by Elsevier, from Jaap van Harten of Elsevier; Jorge Heller, the award's namesake; and CRS President Susan Cady.*

Esha Desai, 2008 CRS Highlights of Student Posters Grand Prize winner. The award is co-sponsored by Colorcon and Genencor International, Inc.

Martyn Davies receives the 2008 CRS Distinguished Service Award from CRS President Susan Cady.

On behalf of Felix Theeuwes, John Gibson accepts the 2008 CRS Industrial Award, co-sponsored by Eurand, from CRS President Susan Cady and Erin O'Brien of Eurand.

Samir Mitragotri receives the 2008 CRS Young Investigator Award, co-sponsored by Capsugel, from CRS President Susan Cady and Dennis Murachanian of Capsugel.

Khaled Greish receives the 2008 CRS/T. Nagai Postdoctoral Research Achievement Award, co-sponsored by the Nagai Foundation Tokyo, from Tsuneji Nagai of the Nagai Foundation Tokyo and CRS President Susan Cady. Award recipient Hiroshi Maeda was unable to attend, and Kazunori Kataoka (left) accepted on his behalf.

Kazunori Kataoka receives the 2008 CRS Founders Award from CRS President Susan Cady.

CRS President Susan Cady thanks Stephen Perrett of Eurand for co-sponsoring the 2008 CRS Industrial Award.

Seema Betigeri receives the 2008 CRS Outstanding Pharmaceutical Paper Award, co-sponsored by 3M Drug Delivery Systems, from John Simons of 3M Drug Delivery Systems and CRS President Susan Cady.

Vincent Malaterre receives the 2008 CRS Outstanding Oral Drug Delivery Paper Award, co-sponsored by Banner, from Aqeel A. Fatmi of Banner and CRS President Susan Cady.

Thank you to the Exhibitors of the 35th Annual Meeting & Exposition of the Controlled Release Society!

More than 100 exhibiting companies offered the latest research, technology, products, and services for controlled release and delivery at the New York City, New York, meeting.

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Magnetic Resonance Imaging (MRI) Applications of Novel Polymeric Contrast Agents

Steven MacLellan,[1,2] I. F. Uchegbu,[2] W. M. Holmes,[3] T. J. R. Evans,[4] B. Condon,[5] and A. G. Schätzlein[2]

Introduction

Magnetic resonance imaging (MRI) is an extremely powerful non-invasive imaging technique that is used extensively in diagnosis and characterisation of diseases of the central nervous system such as multiple sclerosis. In addition MRI and, in particular, dynamic contrast-enhanced MRI (DCE-MRI) have revolutionised cancer imaging. DCE-MRI involves serial imaging in conjunction with the administration of a contrast agent; subsequent analysis of the contrast agent "wash-in" and "wash out" characteristics allows for tumour delineation and staging and its use is commonplace in analysis of breast, head and neck, prostrate, and adrenal gland tumours. A number of low molecular weight gadolinium chelates are available for use as contrast agents, of which Magnevist (MW > 1 kDa) was the first licensed and is still the most commonly used (1,2).

Despite the widespread satisfactory use of Magnevist in these applications, the opportunity exists to develop contrast agents that address its limitations, such as the rapid clearance that limits possible imaging time and produces poor tissue specificity. The term "blood pool" contrast agents covers those that offer greater plasma residence time and the potential for more detailed vascular imaging. We have developed two such agents that are based on a polymeric backbone with gadolinium imaging moieties as pendant groups; these agents have molecular weights of approximately 20 and 75 kDa and have been tested in both brain and tumour imaging.

Imaging Details

All imaging was performed on nude mice using a Bruker BioSpin 7T system. Tumour studies of A431 flank xenografts used a custom-built surface coil that allowed extremely high resolution imaging (100 μm^3) (3). All contrast agents were given at a dose of 0.1 mmol gadolinium/kg of body weight, and data were analysed using in-house–generated routines in IDL.

Brain Imaging with Novel Polymeric Contrast Agent

The higher molecular weight polymeric agent (MW ≈ 75 kDa) was used to image the mouse brain. The diffuse enhancement in Figure 1A shows the lack of specificity of the low molecular weight agent Magnevist and is the result of leakage of contrast material into the tissues that surround the brain. Conversely the polymeric agent remained confined to the blood pool, giving clear enhancement of the brain vasculature (Figure 1B). We feel that this approach offers advantages in vascular visualisation over the traditional magnetic resonance angiography (MRA) technique, as it is less susceptible to the direction and speed of flow (4), as well as having a shorter scan time. There are a number of potential applications of this contrast agent in the field of stroke, such as experimental evaluation of novel therapies and ultimately clinically in diagnosis and monitoring.

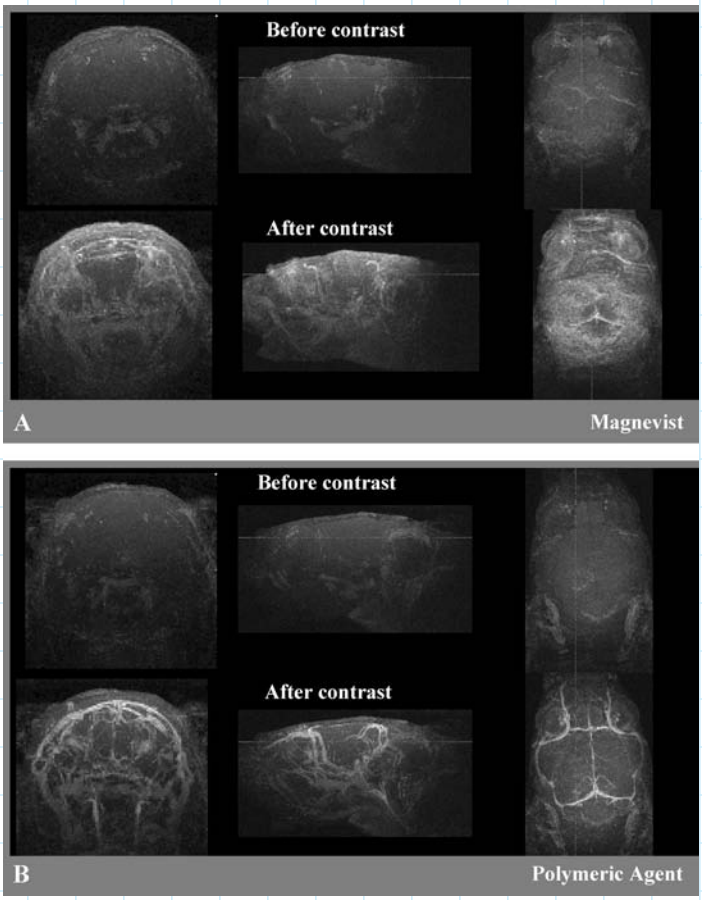

Figure 1. *Maximum intensity projections from T_1-weighted MRI: (A) before (top row) and 3 minutes after (bottom row) administration of Magnevist; (B) the results for the novel polymeric agent.*

Tumour Usage of Novel Polymeric Contrast Agent

Two potential applications of the lower molecular weight polymeric agent (MW ≈ 20 kDa) were investigated: vascular imaging and as a surrogate for modelling the delivery of macromolecular cancer therapeutics.

Solid tumours require blood vessels for growth; consequently, there are a number of established and emerging anti-angiogenic

[1] Medical Devices Doctoral Training Centre, Bioengineering Unit, University of Strathclyde, Glasgow, G4 0NW, Scotland.
[2] The School of Pharmacy, University of London, London, WC1N 1AX, England.
[3] 7T MR Facility, Wellcome Surgical Institute, University of Glasgow, Glasgow, G61 1QH, Scotland.
[4] Centre for Oncology and Applied Oncology, University of Glasgow, Glasgow, G61 1QH, Scotland.
[5] Department of Clinical Physics and Bioengineering, Southern General Hospital, Glasgow, G51 4TF, Scotland.

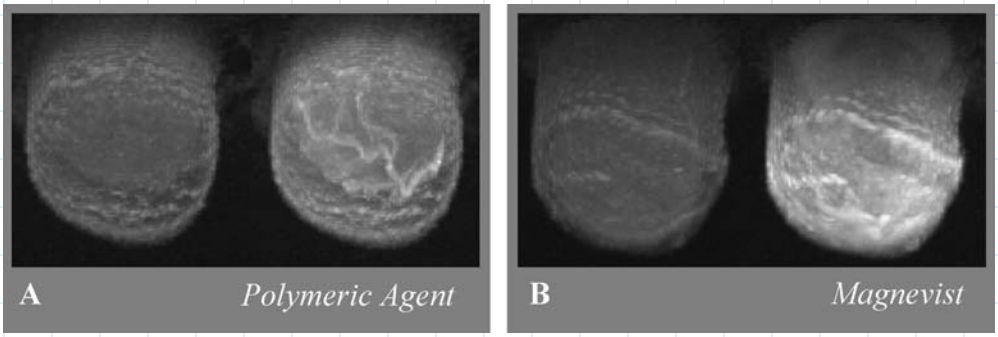

Figure 2. *Maximum intensity projections of T_1-weighted tumour MRI: (A) before (left) and three minutes after (right) the administration of a novel polymeric contrast agent (MW ≈ 20 kDa); (B) the same experiment using Magnevist (MW < 1 kDa).*

therapies that aim to treat the tumour by destroying blood vessels and depriving the tumour of oxygen and nutrients. Jain (5) and co-workers have revolutionised how these treatments are viewed with their concept of vascular normalisation. They offer evidence of a time window following anti-angiogenic therapy in which the tumour vasculature has been normalised (gained more of the structural and functional characteristics of normal vasculature), allowing more efficient drug delivery. Figure 2 shows how the polymeric contrast agent can be used to visualise the tumour vasculature. This technique offers the chance to non-invasively serially monitor the effects of therapies on the structure of the larger vessels of the tumour to gain further understanding of the ideal window for chemotherapy delivery following anti-angiogenic treatment.

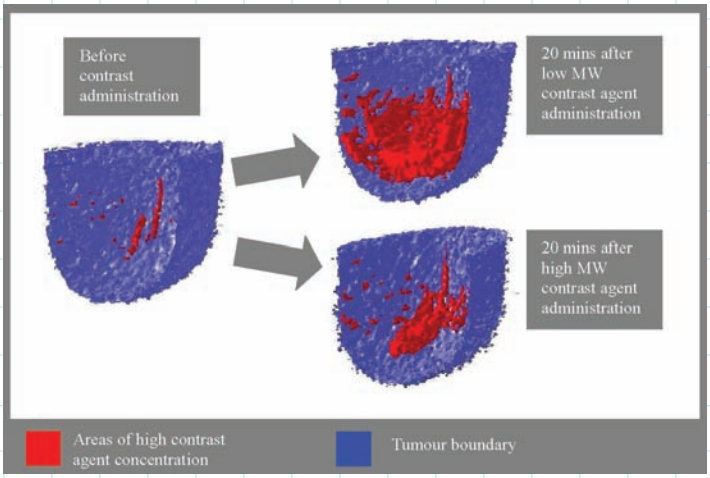

Figure 3. *Tumour MRI data manipulated to show regions of high signal intensity (high contrast agent concentration) following administration of two different molecular weight contrast agents. Images shown are before (left) and 20 minutes after administration of low molecular weight (top right) and high molecular weight (bottom right) contrast agents.*

The abnormal "leakiness" of tumour vasculature allows macromolecules to extravasate, a phenomenon known as the enhanced permeability and retention (EPR) effect. It is via EPR that a number of therapeutics are targeted passively to tumours; however, the tumour offers several barriers to this process and subsequent interstitial transport. These barriers are of particular relevance for emerging macromolecular therapies such as monoclonal antibodies and gene therapy. To investigate the effect of molecular weight on extravastation and interstitial transport, low (<1 kDa) and high (20 kDa) molecular weight contrasts were administered sequentially, and their distributions monitored with time. Figure 3 shows how the low molecular weight agent achieved a far more homogenous distribution at 20 minutes post-administration, whereas the high molecular weight agent remained more localised.

The advantage of using such a polymeric contrast agent in this context as a surrogate for drug transport is that the molecular weight can be tailored in the synthesis process to replicate the drug molecule of interest.

Conclusions

This article gave a brief overview of the plethora of information that can be derived using MRI in conjunction with polymeric contrast agents. We have shown how these contrast agents can be used to image the vasculature of the brain and solid tumours and as drug surrogates in tumour transport studies. Contrast-enhanced MRI allows for the evaluation of the optimum conditions for drug delivery to solid tumours and should support the pre-clinical and clinical development of novel therapies.

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Development of Metoclopramide Microparticles Using VarioSol® Technology

L. Segale,[1] L. Giovannelli,[1] H. Danan,[2] L. Galli,[3] P. Esposito,[2,4] and F. Pattarino[1]

VarioSol® is based on an innovative spray-cooling, solvent-free, near-critical fluid technology developed by Messer (1,2). VarioSol® equipment is able to produce fine powders or microspheres from solid or liquid materials, using near-critical CO_2 as the spraying and cooling agent (3). The material to be processed is introduced into a feeding vessel, and if not already in a liquid or semi-solid state, the material can be melted and brought to the desired temperature by a heater. The melted material is then sprayed, under controlled pressure, into a spraying tower, where it comes in contact with expanding near critical CO_2. The expanding fluid atomizes the sprayed material into microscopic particles, while simultaneously cooling it. The direct contact of the coolant with the sprayed product ensures good heat transfer and optimum utilization of the cold energy in the gas. The size and shape of the resulting microparticles can be influenced by formulation characteristics and nozzle geometry and dimensions.

The aim of the present work was to develop formulations of a model drug in lipid microparticles using VarioSol® technology. In particular, the objective was to produce metoclopramide (MCP)-loaded microparticles for oral administration that are able to yield a taste-masking effect of the active molecule in a formulation able to control and modulate the drug release rate.

Experimental Methods

Five formulations containing MCP as the active principal and cetearyl alcohol (Ce) alone or mixtures of cetearyl alcohol and Compritol 888 ATO (Co) as excipients were subjected to the VarioSol® process (Table 1).

Optical evaluation was used to investigate the size and shape of the microparticles. The average diameter of the microparticles was determined using a laser diffraction particle size analyzer (Malvern, MasterSizer). *In vitro* drug release tests were carried out, in triplicate, at 37°C in 500 mL of hydrochloric acid at pH 1.0 and in phosphate buffer at pH 6.8, using USP apparatus II (AT7 Smart, Sotax) operating at 100 rpm. Samples (5 mL) were withdrawn at predefined time intervals, using a syringe equipped with a glass-fibre filter, and analysed as is by UV spectrophotometer at 274 nm.

Table 1. *Percent composition of formulations subjected to the VarioSol® process.*

	Metoclopramide	Cetearyl Alcohol 888	Compritol ATO
MCP-Ce	15.00	85.00	–
MCP-CeCo5	15.00	80.75	4.25
MCP-CeCo10	15.00	76.50	8.50
MCP-CeCo25	15.00	63.75	21.25
MCP-CeCo50	15.00	42.50	42.50

Results and Discussion

In all the tested formulations, the VarioSol® process produced fine powders of microparticles ranging in diameter between 20 and 100 µm (Table 2). The average diameter increased as the percentage of Co in the formulation increased. Stereomicroscope images show that the microparticles were spherical in shape and had homogeneous and non-porous surfaces (Fig. 1). Furthermore, elimination of the bitter taste typical of MCP was evidenced in an informal test performed by the authors. Table 2 also shows that drug loading reproducibly approached the theoretical value (15%), with an entrapment efficiency of more than 90%.

Table 2. *Average diameter and Metoclopramide content of microparticles (values are means of three determinations).*

	Average Diameter (µm)	Drug Content
MCP-Ce	20.23 ± 0.01	13.21 ± 1.53
MCP-CeCo5	20.99 ± 0.38	13.39 ± 0.47
MCP-CeCo10	26.66 ± 0.04	13.82 ± 0.71
MCP-CeCo25	36.02 ± 2.02	13.95 ± 0.62
MCP-CeCo50	100.14 ± 4.03	13.13 ± 0.70

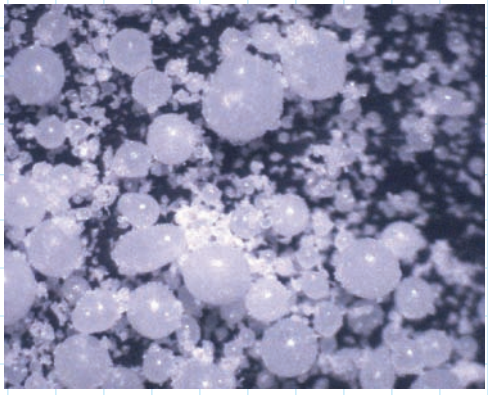

Figure 1. *Stereomicroscope image of MCP-CeCo50 VarioSol® microparticles.*

The results of *in vitro* drug release tests carried out at pH 1.0 are reported in Figure 2. For all the tested formulations, except for the one containing the highest Co amount, the drug was released completely a few minutes after the beginning of the test, and there were no significant differences between the release profiles of MCP from the microparticles and the dissolution curve of MCP alone. However, in the case of MCP-CeCo50 microspheres, MCP was released at a much slower rate than in

[1] DISCAFF, Università del Piemonte Orientale, Via Bovio 6, 28100 Novara, Italy.
[2] SiTec Consulting, Bioindustry Park, Via Ribes 5, 10010 Colleretto Giacosa (TO), Italy.
[3] Messer Italia, Via Vittorio Sassi 23, 10093 Collegno (TO), Italy.
[4] Present address: Esteve, Polígono Industrial, 08107 Martorelles, Spain.

the other formulations, and it took about 5 hr to release the drug completely.

At pH 6.8, the formulation without Co (MCP-Ce) released a curve very similar to the dissolution curve of the active alone. Where the formulations in which the excipient was a mixture of Ce and Co, there was a relationship between the drug release rate and Co amount. The drug release rate decreased as the percentage of Co in the formulation increased (Fig. 3).

The release data obtained at pH 6.8 from all the VarioSol® formulations that contained Co were analysed by the Weibull function (4) to acquire general information about the MCP release kinetics. Values of the *b* parameter <1 were obtained (Table 3): in all cases, the shape of the release curves was parabolic in the initial tract and then became exponential, suggesting drug release was governed by more than one mechanism.

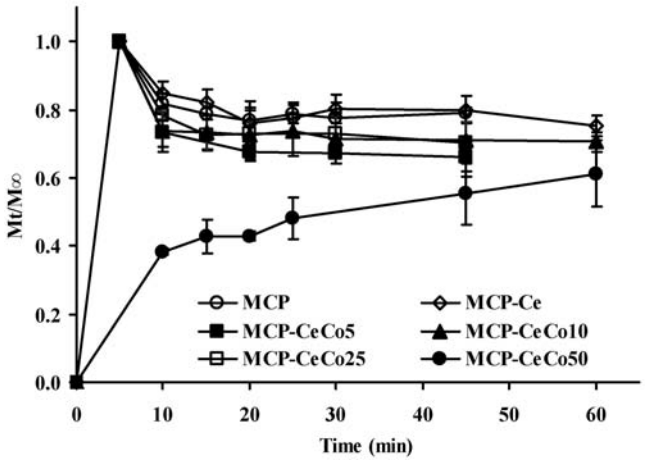

Figure 2. *Metoclopramide release profiles of microparticles in hydrochloric acid at pH 1.0.*

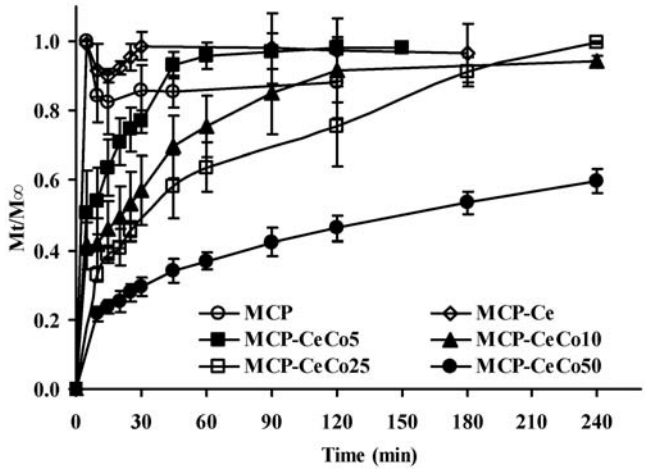

Figure 3. *Metoclopramide release profiles of microparticles in phosphate buffer at pH 6.8.*

Table 3. *Weibull model parameters for drug release from microparticles produced by the VarioSol® process.*

	b	*a*	R^2
MCP-CeCo5	0.57	4.25	0.932
MCP-CeCo10	0.40	4.54	0.960
MCP-CeCo25	0.53	8.40	0.916
MCP-CeCo50	0.44	12.20	0.960

Table 4. *Time required for the release of 10, 25, and 50% of metoclopramide from microparticles.*

	t 10%	t 25%	t 50%
MCP	34"	1' 26"	2' 51"
MCP-Ce	43"	1' 46"	3' 33"
MCP-CeCo5	1' 13"	3' 02"	13' 46"
MCP-CeCo10	1'44"	4' 19"	48' 18"
MCP-CeCo25	1' 41"	4' 12"	58' 36"
MCP-CeCo50	2' 22"	30' 54"	237'

The values for t 10%, t 25%, and t 50% confirm the results of the Weibull model: all the formulations, except MCP-CeCo50, showed an initial burst effect, as confirmed by the short time necessary to release 10 and 25% of the loaded drug (Table 4). On the other hand, the higher the Co percentage in the formulation was, the longer the time required to release 50% of the loaded drug.

Conclusions

VarioSol® technology can produce microparticles characterized by regular shape, small size, and high drug content. The nature and properties of the selected excipients and the specific operating conditions allow the manufacture of controlled release microparticles or microparticle formulations with a taste-masking effect. In this particular case, the MCP-Ce formulation may represent a taste-masking, immediate-release formulation, while the MCP-CeCo50 formulation may represent a satisfactory controlled release micronized drug delivery system.

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Interspecies Differences Influencing Interspecies Extrapolations Part III of III: Interspecies Differences in Metabolism and Toxicology

Marilyn N. Martinez, Ph.D.
FDA Center for Veterinary Medicine, Rockville, MD, U.S.A.

There are numerous examples of substances that are safe for use in one animal species but are toxic when administered to another species:

- A 100–150 mg/kg piece of pure chocolate is toxic to dogs. This toxicity is related to the poisonous effect of the theobromine contained in chocolate (www.kc.net/~wolf2dog/chocolate.htm).
- Onions and garlic cause hemolytic anemia in dogs and cats because of the presence of thiosulfate (www.petalia.com.au/Templates/StoryTemplate_Process.cfm?specie=Dogs&story_no=257#ct-4).
- A single regular-strength tablet of acetaminophen is toxic and potentially lethal to cats. Compared with dogs, cats tend to be much more sensitive to the toxic effects of acetaminophen (www.petplace.com/cats/acetaminophen-toxicity-in-cats/page1.aspx#pt3).
- An IV injection of a relatively low dose of doxycycline can cause cardiac arrhythmias, and ultimately cardiac arrest and death, in horses (www.elephantcare.org/Drugs/doxycycl.htm).
- Tilmicosin, which is safe for use in cattle and sheep can be fatal if accidentally injected into humans, swine, and horses (www.elephantcare.org/Drugs/tilmicos.htm).

Benzidine is an example of differences in drug metabolism that lead to species-specific toxic reactions (1). In dogs, hepatic N1-glucuronidation of benzidine forms an acid-labile conjugate that is transported in the blood while bound to plasma proteins. Upon being filtered by the kidney, the drug accumulates in the urine, whereupon acid hydrolysis releases the amine. The amine is subsequently activated by bladder enzymes, thereby initiating the carcinogenic process. In rats, liver rather than bladder cancer is the endpoint, presumably due to the low capacity of rat liver UGT to conjugate benzidine.

The Laboratory of Clinical Pharmacology of the U.S. Food and Drug Administration (FDA) provides other examples, demonstrating the importance of understanding interspecies differences in drug metabolism when assessing preclinical study data (2):

- In humans, the primary mechanism of paclitaxel elimination is via CYP2C8. However, negligible amounts of this enzyme are present in rat microsomes. Therefore, rats cannot be used to examine drug–drug interactions in humans.
- With iododeoxydoxorubicin, in rats the parent drug is the predominant circulating moiety. Conversely in humans, there is a 10-fold greater exposure to metabolites compared with the parent compound.

Furthermore, certain metabolic reactions appear to be negligible or even totally lacking in certain animal species. For example (3),

- Rats have a deficiency in the N-hydroxylation of aliphatic amines.
- Dog are unable to acetylate compounds.
- Guinea pigs have a deficiency in N-acetylation cysteines.
- Cats have a deficiency in glucuronidation reactions.
- Pigs have a deficiency in most sulfation reactions.
- N-Glucuronidation of sulfadimethoxine and other methoxysulfonamides is limited to humans and certain primates.
- Metabolic idiosyncrasies can be correlated with animal diet: herbivores tend to be far more efficient than other species with regard to oxidative reactions.

The cytochrome P450 family has been implicated in the carcinogenic activation of numerous xenobiotics (4), and caffeine is often used as a metabolic probe for this family of enzymes. Using hepatic microsomes from humans, monkeys (*Macaca fascicularis*), rats, rabbits, and mice, three dimethylxanthines resulting from N-demethylation (theobromine, paraxanthine, and theophylline) and one compound resulting from oxidation at the C-8 position(trimethyloric acid) were formed (5). Despite qualitative similarities, the relative proportion of the metabolites was markedly different across animal species. Moreover, unlike that seen in the other species, rats and mice exhibited dose-dependent *in vivo* caffeine metabolism. In humans, mice, rabbits, and rats, the CYP1A2 isoform predominated over CYP1A1, although the ratios of these enzymes differed across these species. In monkeys, no CYP1A isoform was detected. These findings are consistent with the substantial discrepancy noted in the major P450 enzymes across the four major toxicological test species: dog, rat, rabbit, and mouse (6).

In addition to differences in enzyme systems, differences in protein binding and biliary secretion can lead to other important interspecies differences in drug disposition. In general, the extent

of biliary excretion tends to be much higher in dogs and rats compared with pigs, monkeys, and humans. The mouse falls somewhere in between these two groups (95). With regard to protein binding, the differences between dogs and rats resulted in species-specific differences in pranoprofen enantiomer disposition (7).

Differences in gut bacterial flora can also lead to marked differences in drug toxicity. For example, chenodeoxycholate, a compound used to facilitate the dissolution of gallstones in humans, is toxic in rats, hamsters, rabbits, dogs, rhesus monkeys, and baboons but is not toxic in the squirrel monkey, chimpanzee, or humans. This species-specific sensitivity was correlated with the ability of the respective intestinal flora to produce a toxic metabolite of chenodeoxycholate (8,9).

Preclinical evaluation of excipients is important, as these components are not inert and can themselves result in both adverse reactions and altered bioavailability. In several instances, these excipient effects appear to be species specific. For example (10),

- Methanol exhibits a sensitization reaction in guinea pigs, although very infrequent allergic reactions are noted in humans.
- Polyethylene glycol (low molecular weight) is associated with teratogenic effects in mice but is not teratogenic in humans.
- Propylene glycol toxicosis in llamas results from administration of propylene glycol gels formulated and labeled for use in cattle. The resulting ketosis reflects the toxic nature of the excipient to llama stomach gut flora.
- Chlorofluorocarbons induce cardiac arrhythmias in dogs but appear to have a wide margin of safety in humans.
- Diethyl phthalate produces slight to moderate dermal irritation in rabbits, rats, and guinea pigs, but there is no evidence of similar irritation in humans.

Recognizing the importance of interspecies differences in drug product development, the CRS Veterinary Committee, in conjunction with the American Association of Pharmaceutical Scientists, is developing a database of journal citations. We ask that relevant Pubmed citations be forwarded to marilyn.martinez@fda.hhs.gov. We will keep CRS members updated on the progress of this initiative.

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From the Editor continued from page 2

Additionally, please be sure to read "From The President" by Lisbeth Illum. She is fired up and already putting a lot of effort into maintaining the momentum generated by Susan Cady and growing the membership of the CRS. She is also concerned about the lack of participation during this conference's CRS Member Meeting. I have to agree. I attended the meeting Monday morning and was also struck by the lack of attendance. This was much different than the Awards and Member meetings that I attended in 2004 in Honolulu or 2005 in Miami. It is your organization, and I hope that a majority of members not only want to know what is happening within the CRS but also would like to see, hear, and meet their officers. Those of you who left also missed a personal invitation by Lisbeth to attend next year's 36th CRS Annual Meeting & Exposition in Copenhagen, her hometown.

Next year, we will be increasing the number of *Newsletter* issues to five. So, as always, we encourage you to submit Spotlight and Scientifically Speaking articles, news items, and back-to-basics articles. Additionally, besides the "In the News" section, we have added a new "People in the News" section. We welcome any announcements of major awards, entrepreneurial endeavors, or honors received by our members who would like to share their news.

Best wishes,

Steven ■

Defining the Critical Quality Attributes of Modified Release Parenteral Dosage Forms: Opportunities for Ongoing Dialogue

Marilyn Martinez,[1] Mai Huynh,[1] Diane Burgess,[2] and Michael Rathbone[3]

Parenteral modified release (MR) formulations have the potential to maintain therapeutic levels of systemic drug concentrations for a period of weeks to months, ensuring user compliance and enabling the therapeutic needs of human or veterinary patients to be met. The engineering of sustained release characteristics for parenteral products can be accomplished through a wide variety of approaches, such as microspheres, liposomes, *in situ* forming gels, suspensions, implants, lipophilic solutions, and drug-eluting stents. This list represents a wide array of formulation types, manufacturing techniques, and release mechanisms, all of which are associated with unique challenges with respect to the development of meaningful *in vitro* drug release methodologies and specifications.

When establishing *in vitro* drug release specifications for MR parenteral dosage forms, it is important to know the variables that can influence *in vivo* drug release and absorption and the *in vivo* variables that can lead to undesirable interactions with product excipients. These specifications can be used both to ensure batch-to-batch uniformity of product quality and performance and the consistency of *in vivo* product performance during the minor manufacturing changes that can occur over the product lifetime. In addition, when drug release is intended to occur over a period of months or years, these *in vitro* specifications need to be linked to an expiry date that will ensure that the product will perform in a manner identical to that of a fresh lot if it is administered at the expiry date.

Ensuring appropriate *in vivo* release of the therapeutic moiety is a fundamental concern for patient welfare. Therefore, understanding the critical manufacturing variables and establishing appropriate manufacturing specifications are essential. However, the development of *in vitro* drug release test methods that predict the *in vivo* performance of these products is encumbered by the lack of standard methods, the need to accelerate the *in vitro* drug release rate relative to that occurring *in vivo*, the instability of the dosage form or drug, and the failure to accurately reproduce the *in vivo* environment.

[1] U.S. Food and Drug Administration Center for Veterinary Medicine, Office of New Animal Drug Evaluation, Rockville, MD.
[2] Department of Pharmaceutical Sciences, University of Connecticut, Storrs, CT 06268.
[3] InterAg, 558 Te Rapa Road, P.O. Box 20055, Hamilton, New Zealand.

In vitro tests are also generally unable to accurately predict the effect of host–product interactions that can negatively influence product performance or are responsible for the targeted and/or prolonged duration of action. In addition, there are factors that may affect *in vivo* performance but which may not be readily identified from either the *in vitro* release data or the *in vivo* blood concentration versus time profile. For example, blood level data may not be able of identify those changes in formulation that will lead to a slow "trickle release" from the injection site. When this occurs in a preparation intended for use in food-producing animals, such characteristics can influence human food safety without affecting target animal safety or effectiveness. Similarly, *in vitro* release tests alone may not adequately identify long-term host reactions to residual product (e.g., ghosted or loaded microspheres or implants) that could potentially accumulate over years of repeated administrations. All these factors make the development of a meaningful *in vitro* test problematic, and these factors often need to be addressed on a case-by-case basis.

In an effort to explore some of these issues, the Controlled Release Society (CRS) hosted a 2007 educational workshop titled Sustained Release Parenteral Products: *In Vitro* and *In Vivo* Considerations that was co-chaired by the authors of this article. This workshop provided the opportunity to engage pharmaceutical scientists and pharmacologists in discussions regarding the critical variables impacting the development of novel parenteral sustained or MR formulations. The speakers included scientists representing government, academia, and industry. A summary report from the workshop has been published in the *Journal of Controlled Release* (1).

The information exchanged during the workshop helped elevate the current state of knowledge in this arena. Furthermore, by identifying the diverse sets of conditions for which the various MR parenteral formulations are being applied (both in human and veterinary medicine), the workshop further underscored the importance of understanding the product quality attributes that may impact *in vivo* conditions: whether one can develop a risk-based approach, similar to that being applied for solid oral dosage forms, where the critical process parameters or attributes are assessed for their risk for product quality, and, of equal importance to the factors that can be monitored on a production line and identified, the need to have *in vitro* methods that can be

used as prognostic tools for conditions that may alter *in vivo* drug release.

Ultimately, the question is whether we as a scientific community can identify novel methods for predicting product *in vivo* performance and identifying and controlling the critical manufacturing variables associated with each of the innovative parenteral technologies. An example of how such challenges can be addressed was demonstrated in a research article published in *Vaccine* (2). In this work, Streefland et al. (2) showed how a microarray scanner could be used to explore the applicability of process analytical technology (PAT) to the cultivation of *Bordetella pertussis* bacteria as part of the manufacture of a vaccine against whooping cough disease. These investigators identified marker genes for product quality, providing the means to quantitatively assess product quality. Based on their work, these investigators were able to conclude that the monitoring of disturbances in mRNA expression levels of specific genes, combined with an on-line monitoring tool (such as near infrared or Raman spectroscopy), would make PAT application on this process feasible for the development of a vaccine against whooping cough. This same high level of innovation is needed from all scientists who are involved in the development and regulation of MR parenteral pharmaceutical formulations.

Despite the wealth of information presented at the CRS-hosted educational workshop, the scientific and regulatory communities are still left with many unanswered questions, including

1. What variables associated with the formulation and manufacture of *in situ* forming gels can influence their *in vivo* product release?
2. Can *in vitro* release characteristics predict the *in vivo* performance of long-acting lipophilic solutions?
3. When setting the expiry date for a long-acting parenteral product intended to continue releasing for months upon administration, how does one ensure that the product will perform in a manner comparable to a fresh product if administered at the expiry date?
4. Despite the possibility of unique formulations that will require variations in standard test methods, is it feasible to develop standardized *in vitro* test methods that can be applied to the different types of MR parenteral formulations? Or, will different mechanisms of release necessitate, or allow for, the use of different test methods?
5. What unique challenges will be faced when attempting to develop/demonstrate the *in vivo* bioequivalence of the various categories of parenteral MR products?

The co-chairs of the 2007 workshop decided that these issues should be the subject of a continuing dialogue. Therefore, to stimulate further discussion in this regard, they are spearheading a three-pronged approach to address the five questions listed above (and any other critical questions that may be raised by experts in this field):

1. CRS is hosting a web-based discussion forum where individuals can provide their thoughts on the five questions listed above, or raise additional questions for discussion. This website will be monitored by the authors of this article; interactions between CRS members are encouraged. Access to the discussion forum can be reached via the "Communities" button on the CRS home page.
2. A collaborative American Association of Pharmaceutical Scientists (AAPS)/CRS workshop is scheduled to occur November 15–16 just prior to the 2008 AAPS Annual Meeting in Atlanta, GA, November 16–20. For further details visit www.aapspharmaceutic.org/. This workshop will include two breakout sessions where these questions, along with issues raised in our CRS website exchange and during workshop discussions, will be considered.
3. A white paper will be developed based on the website exchange and the AAPS/CRS workshop results. In addition, the 2010 AAPS Arden House is devoted to controlled release parenterals and a follow-up session from the Atlanta conference will be held at this Arden House.

The effort to increase our understanding and foster progress in this area is highly dependent on your input and willingness to share your thoughts and experiences. Therefore, we are depending on your participation in these efforts, so please visit the CRS home page and access the discussion forum via the "Communities" button! If you have any questions or comments, please feel free to contact Marilyn Martinez by e-mail (marilyn.martinez@fda.hhs.gov) or phone (+1.240.276.8357).

We look forward to hearing your thoughts and receiving your contributions.

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CRS-Chicago Student Chapter Holds First Seminar

The Controlled Release Society (CRS)-Chicago Student Chapter held its first seminar event on May 23, 2008, at the College of Pharmacy, University of Illinois at Chicago. The chapter has been affiliated with the CRS as one of its student chapters since fall 2007. The Chicago Student Chapter was set up with the goal of enhancing networking among graduate students in the Chicago area who are interested in controlled release-related science and technologies.

As its first seminar speaker, Dr. Mahesh Chaubal, director of global R&D medication delivery at Baxter Healthcare and chair of the CRS Chapter Committee, was invited to give a talk on "Use of Controlled Release Technologies in Parenteral Drug Delivery." Approximately 25 students, 1 post-doc, and 3 professors attended the seminar. The attending students came from various departments within the University of Illinois, including Biopharmaceutical Sciences, Medicinal Chemistry, Bioengineering, and Mechanical and Industrial Engineering, as well as the College of Dentistry. Following the seminar, there was a lunch/discussion session to allow for more in-depth discussion between the seminar speaker and students about his presentation and pharmaceutical career development strategy.

From left to right: Ashwini Pai, Mahesh Chaubal, Misuk Bae, and Sok Bee Lim.

The CRS-Chicago Student Chapter currently has 17 members, including 4 board members: Misuk Bae (president), Sok Bee Lim (vice president), Ashwini Pai (secretary), and Ramana Vishnubhotla (treasurer). Dr. Richard A. Gemeinhart is the faculty advisor to the chapter. ■

CRS Italian Chapter Holds 2008 Meeting in Collaboration with AFI

As a tradition, the 2008 Meeting of the CRS Italian Chapter was organized in collaboration with AFI, the Italian Association of Pharmaceutical Industry. The CRS symposium was held on Thursday, June 12 as a satellite symposium of the 48th AFI Congress held in Rimini, Italy, June 11–13. The organization of a AFI/CRS Italian Chapter joint symposium offers an excellent opportunity to gather Italian scientists and product developers working in the field of drug delivery, exchange information, and promote possible cooperation among universities and industries. The CRS Italian Chapter traditionally has organized the one-day scientific session on drug delivery that this year was dedicated to biotechnological drugs: Biotechnologies: Research and Production. The session attracted a large number of attendees.

Dr. Lorena Segale, Ph.D. student at University of Novara, receives an award from Prof. Paolo Caliceti, CRS Italian Chapter President, for the best scientific contribution at the joint AFI/CRS Italian Chapter congress.

At the opening, the Chairs Prof. C. Caramella and Dr. Vingiani welcomed the attendees and briefly introduced the ongoing session and then the floor was opened to six oral contributions that were in the forefront of biotech drug discovery and delivery. The session continued in the afternoon, chaired by Drs. Tajana and Garavani, with the presentation of short scientific contributions either from universities or industries, covering a wide spectrum of scientific topics from bioconjugation to nanoparticles, innovation in local delivery to mucoadhesion, polysaccharide hydrogels to scaffolds for tissue engineering. During the 10-minute presentations, the speakers described the main results and perspectives of their research projects.

The symposium highlighted the collaboration between public institutions, namely universities, and industry. As an example, the University of Milan and Bouty (Milan) presented joint research on skin permeation with patches containing PEG-sterates; the University of Pisa and Opocrin (Modena) presented a study on modified lenses for ocular delivery; and the University of Pavia and Antarespharma (Switzerland) presented data on penetration enhancers for oral delivery.

A scientific committee composed of industry and university members was in charge of selecting the best presentation to receive the CRS Italian Chapter prize. Although there were many interesting presentations, there was a toss-up with two of them because of their originality, innovation, and industrial applications: "Use of VarioSol Process for the Preparation of Metoclopramide Loaded Microspheres," by a collaboration between the University of Piemonte Orientale (Novara) and Messer (Turin), and "Drug Permeation Study Through Human Infected Nails; Development of an Experimental Model and Relationship with Bovine Hoof Slices," by a collaboration between the University of Pisa and Polichem (Lugano, Switzerland). The first was selected at the end of the session.

After the first morning session, during the assembly of the CRS Italian Chapter, CRS Italian Chapter President Prof. Paolo Caliceti updated members on the formal steps needed to obtain the official status of the association. He introduced the new directive council and the recently elected advisory board, while Treasurer Prof. Maria Edvige Sangalli informed members about the economic standing of the chapter. The president also informed members about the CRS activities that have been planned for 2008. He reported on the two workshops held in Porto Conte (Sardinia), co-sponsored with Tefarco, PortoConteRicerche, and the University of Sassari: Technology Transfer of Biosimilars and New Delivery Challenges: Nanocarriers for the Delivery of siRNA and Vaccines. He also presented the upcoming activities organized with contributions from the CRS Italian Chapter: Nanosystems for Drug Delivery (Novara June 20) and Biosimilar Products: Challenges and Opportunities (Pavia, September 2008). In autumn, a workshop titled Tumour Targeting will be organized in Padua.

Plenary session of the joint AFI/CRS Italian Chapter Symposium held in Rimini June 12, 2008.

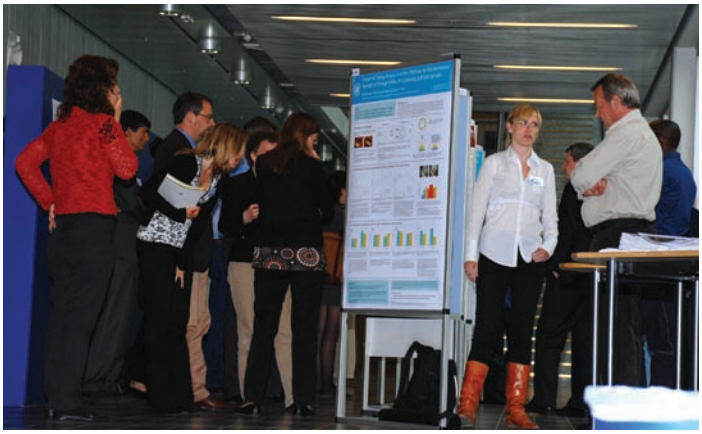
The assembly actively discussed the new activities of the association to make it as efficient as possible in conjunction with national and international initiatives, in accordance with its mission. In particular, the assembly agreed that the organization of a thematic workshop fully managed by the local CRS is essential to involve scientists interested in controlled release. Particular effort is required to involve industrial partners. New formulas will be investigated to contribute to the next AFI symposium. As the involvement of all delegates is paramount to the association, the delegates were invited to make proposals for scientific activities that will be supported fully by the chapter. Finally, the discussion focused on the chapter's possible contribution to the 2009 CRS Annual Meeting, which was initially planned in Milan and then suddenly moved to Copenhagen. The attendees advised the president to collect proposals that would be reported to the organizing committee at the CRS Annual Meeting in New York. ■

2nd Midnight Sun Meeting Held on Drug Transport and Drug Delivery

Martin Brandl
University of Tromsø, Institute of Pharmacy, Tromsø, Norway

The Midnight Sun Meeting on Drug Transport & Delivery was held June 25–27, 2008, for the second time since 2004 on the island of Tromsø, located 69° north, where the sun literally never sets during the summer months. The meeting was co-organised by the Drug Transport & Delivery Research Group of Tromsø University on the occasion of its 10th anniversary and by the Controlled Release Society Nordic Chapter.

The meeting, attended by more than 80 delegates from across Europe, showcased recent advances in drug transport through biological barriers, solid-state pharmaceuticals, and nano-particulate drug delivery. The meeting was held as a single-session event, giving delegates the opportunity to listen to all of the presentations. There was a small poster and exhibitor display, and the meeting attracted several sponsors: Polypure AS, Lipoid GmbH, Clavis Pharma AS, Epitarget AS, Ratiopharm, Soliqs, and SpareBank 1 Nord-Norge. The primary aim of the meeting



The poster session draws attendees.

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was to provide a small intimate forum for pharmaceutical science delegates to exchange data and broaden their education. The meeting also provided an arena for research groups in Nordic countries to document their research interests. The program included 25 lectures and 24 scientific posters. Delegates, drawn from academia, small biotechnology companies, and intermediate-sized pharmaceutical industry organizations, included a mix of young and more experienced scientists. The meeting covered a variety of aspects of delivery and transport, proving that the chosen set up works to bring scientists together, even when their interests are diverse, as they inevitably will be in a multidisciplinary subject area such as the pharmaceutical sciences. The small size of the meeting allowed ample opportunities to question speakers and poster presenters. Sessions were liberally sprinkled with coffee and tea breaks, and these breakout sessions enabled delegates to discuss papers and initiate collaborations.

Scientific Highlights

In the solid-state session there were a total of seven lectures, the CRS-sponsored invited lecture given by Henning Gjelstrup Kristensen, emeritus professor of Copenhagen University, and seven short communications. Kristensen's lecture illustrated his 50 years of experience in pharmaceutical technology and emphasized the change in comprehension from pure constituents or "inactive" ingredients to functional additives. The late afternoon was devoted to poster and industry exhibit presentations. The scientific poster presentations and industry exhibits found lively interest among the delegates, and the scientific discussions and networking stretched into the informal welcome reception on the premises.

On day two, lectures focussing on drug transport continued. Invited speaker Christel Bergström from Uppsala University opened the session with an overview of the Pharmaceutical Screening and Informatics Group's approach to early identification of poorly soluble drug candidates. Anna-Lena Ungell from AstraZeneca R&D, Mölndal, Sweden, shared her experience in optimising the output of experimental *in vitro* studies for prediction of drug absorption in humans with the audience. Matthias Brandsch from Biozentrum, Martin-Luther University, Halle, Germany, the third invited speaker, presented an illustrated overview of the transporters of the solute carrier (SLC) superfamily, including their potential for drug delivery. The session also included a total of six selected short communications.

Finally, there were nine presentations given in the drug delivery session. The session primarily covered aspects of nano-particulate drug delivery. The first speaker on Friday was Heike Bunjes from the University of Braunschweig, Germany, who was invited by CRS to give an overview of drug delivery by nano-carriers.

CRS Nordic Chapter invited speakers Profs. Henning G. Kristensen (left) and Heike Bunjes (right).

From the submitted presentations, Christopher Bachran's (Freie Universität Berlin) talk "Combined Application of Saponins and Chimeric Toxins for Tumor Treatment in Mice" and Avi Schröder's (Hebrew and Ben Gurion University of Massuout Yithak, Israel) poster "Controlled Release of Drugs from Liopsomes by Low-Frequency Ultrasound: Effect of PEGylation" were selected as the best oral and poster presentations, respectively.

Networking

The program also included a variety of social events, the most memorable of which was the conference dinner at a traditional fish restaurant, where delicacies from the arctic sea were served to delegates as they discussed aspects of science and networking late into the night, witnessing broad and blazing day light in the middle of the night! Many participants perceived the meeting as very informative with a relaxed atmosphere. Unfortunately, the midnight sun did not show its face during the meeting. Only those who stayed over the weekend were rewarded with its beautiful sight.

In summary, the 2nd Midnight Sun Meeting on Drug Transport & Delivery contained numerous high-quality presentations, and there was a friendly atmosphere at all times, particularly during heated debates. The CRS Nordic Chapter is encouraged by the feedback from many attendants on the small meeting model, since it is quite effective for discussion and debate and allows for meaningful interaction among the delegates. The CRS Nordic Chapter is looking forward with enthusiasm to the 36th CRS Annual Meeting in 2009, which will be held in Copenhagen, Denmark. We encourage all our colleagues to attend and participate in the numerous functions of that meeting. ■

CRS/AAPS Joint Workshop at the AAPS Annual Meeting

Be sure to join CRS members Diane Burgess, Mai Huynh, Marilyn Martinez, and Mike Rathbone November 15–16, 2008, at the Critical Variables in the *In Vitro* and *In Vivo* Performance of Parenteral Sustained Release Products Workshop. The workshop will be held in conjunction with the 2008 AAPS Annual Meeting in Atlanta, GA, and will offer a full two days of expert speakers discussing the topics you want to hear more about. CRS members receive the AAPS member discounted rate when registering for the workshop, so take advantage of this CRS member benefit and register today!

Complex parenteral formulations present an increasingly important mechanism for the delivery of small and large molecules. Because these products generally contain large amounts of drug (to allow for sustained release over days, weeks, or months), it is essential that we understand the critical manufacturing and formulation variables influencing product performance. However, development of manufacturing specifications (and the use of design space concepts) is far more difficult than what generally is encountered with oral dosage forms. Furthermore, unlike immediate-release dosage forms, where traditional methods of setting expiry dates can assure safe and effective *in vivo* product performance, it is unclear how such test methods need to be modified for products that are intended to release a drug for weeks or months after injection. Through the continuation of discussions begun in 2007 (presentations and breakout sessions), it is our hope that we can further refine our understanding of the critical variables influencing the performance of parenteral sustained release products.

The workshop chairs are pleased to bring CRS and AAPS together to offer this outstanding two-day workshop. To whet your appetite, below are a few of the speakers you'll hear and the topics they will discuss:

Application of Design Space Concepts to Parenteral Products
Kristen Anderson and Greg Hunter, FDA/CVM, U.S.A.

Host Response to Biomaterials and *Challenges in* In Vitro *Release Testing for Parenteral Products*
Diane Burgess, University of Connecticut, U.S.A.

Explant Approaches for Estimating In Vivo *Drug Release*
John Dooley, Cordis Corporation, U.S.A.

Implants
Sanjay Goskonda and Huey-Ching Su, DURECT Corporation, U.S.A.

Developing Performance Specifications and Design Space
Stephen Hoag, University of Maryland, U.S.A.

Stability and Expiry Dating
Mai Huynh, FDA/CVM, U.S.A.

Describing Design Space Concept
Mansoor Khan, FDA/CDER, U.S.A.

Microspheres
Rajesh Kumar, Alkermes, Inc., U.S.A.

Folate-Targeted Drug Delivery: From Animals to Humans
June Lu, Endocyte, Inc., U.S.A.

Use of Animal Models in Defining In Vitro *Specifications*
Marilyn Martinez, FDA/CVM, U.S.A.

In Situ *Forming Gels, LA Parenteral Suspensions*
Franklin Okumu, DURECT Corporation, U.S.A.

Registration is open. Visit www.aapspharmaceutica.com/crs to sign up now. ■

CRS Board Members—Adding New Faces and Saying Goodbye

With the passing of the gavel at the Hilton New York Trianon Ballroom, one CRS member took his new office on the CRS Board of Directors (BOD). Mark Tracy (Alnylam, Inc.) became the new CRS Vice President. Mark's term of office will take him from vice president all the way through to immediate past president, serving as president-elect and president along the way.

At the Awards Ceremony, CRS was pleased to honor retiring BOD member Randy Mrsny (University of Bath). Having fulfilled their three-year terms on the Board of Scientific Advisors (BSA), Kazunori Kataoka (University of Tokyo), Ralph Niven (APT Pharmaceuticals, Inc.), and Thomas Rades (University of Otago) were all recognized during the New York Awards Ceremony. Their contributions to the CRS are appreciated.

The BSA welcomed new members at their meeting on Sunday, July 13: Russell Potts (Russ Potts Consulting LLC), Frank Szoka (University of California-San Francisco), and Francisco Veronese (University of Padua). As always, rotating new members onto the BSA helps to keep the hot topics at the forefront for the Society and the discussions lively.

2008–2009 CRS Board of Directors
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Vice President – Mark Tracy, Alnylam, Inc., U.S.A.
Immediate Past President – Susan Cady, Intervet/Schering-Plough Animal Health, U.S.A.
Treasurer – Arthur Tipton, Brookwood Pharmaceuticals, Inc., U.S.A.
Scientific Secretary – Ijeoma Uchegbu, University of London, U.K.
Member-at-Large – Elka Touitou, Hebrew University of Jerusalem, Israel
Member-at-Large – Ian Tucker, University of Otago, New Zealand ■

CRS Board of Scientific Advisors

The CRS Board of Scientific Advisors (BSA) is the largest committee within CRS. Under the able leadership and direction of Chair Ron Smith, BSA members have contributed to the success of the redesign of the CRS website, reviewed abstracts for the annual meeting, chaired sessions at the annual meeting, and continued to keep up with the new frontiers in the delivery of bioactives, etc.

The BSA and CRS Board of Directors (BOD) met in New York to discuss new projects for the BSA. One of the action items that came together during the New York meeting was the formation of the BSA/Webinar project. BSA member David Brayden and former CRS Lunch with the Experts Chair Chun Wang will join forces to showcase leaders in the fields of controlled release and delivery through webinars. Watch the CRS website for more news on these exciting presentations.

BSA Chair Ron Smith and member Rod Walker have accepted the task of drafting the BSA charge and its responsibilities for all BSA members to review and discuss. BSA will be involved with suggesting book topics, continue to look into the future of the many disciplines in which CRS members are involved, reach out to CRS Chapters, provide leadership to the CRS Foundation, continue its involvement with the annual meeting through the review of abstracts and chair sessions, and keep the dialogue flowing between itself and other CRS committees.

As you can see, the BSA is a vital link to members, the BOD, other CRS committees, and the future of the CRS. If you're interested in becoming more involved with CRS and the BSA peaks your interest, contact a BSA member today.

2008–2009 Board of Scientific Advisors

Joke Bouwstra
David Brayden
Marcus Brewster
Igor Gonda
Claudia Leopold
Karsten Mader
Betina Martinez
Mariko Morishita
Russell Potts
Sevda Senel
Patrick Sinko
Ron Smith
Frank Szoka
Francisco Veronese
Rod Walker ■

Consumer and Diversified Products

Jamileh Lakkis, Ph.D.

The following report highlights notable patents in the areas of food and consumer and diversified products. It covers patents filed or granted in the first six months of 2008.

Functional Chitosan Derivatives (Nestec, S.A.) EP 1,152,013 B1

This invention claims a method for enhancing the functionality of chitins or chitosans by increasing their solubility and, thus, enhancing their compatibility with biological tissues. The functionalization method consists essentially of deacetylating the chitin molecule to form the poly-N-acetylglucosamine species followed by binding with a photoreactive group and a carbohydrate molecule with a reduced terminal. The resulting polymer is claimed to be highly soluble, with enhanced hydrogel-forming properties and without the need for any chemical cross-linking agents, such as isothiocyanates or aldehydes, that may compromise its safe application, in particular for wound healing.

Plant Ethylene Response Inhibition Complexes (Agrofresh, Inc.) EP 1,584,234 B1

An encapsulation method and composition for extending the shelf life of plants, cut flowers, fruits, and vegetables by inhibiting ethylene response is described. Unlike traditional treatments such as carbon dioxide flushing, which is short-lived; ethylene synthesis inhibitors, which are effective in maintaining the viability of live plants but not during storage and transportation; or blocking of plant receptor sites by silver thiosulfate (SILFOR), which is highly undesirable due to environmental regulations and disposal limitations, this patent describes the complexing of ethylene response inhibitors such as cyclopropene gases with cyclodextrins to reduce their susceptibility to oxidation. Release of the active gases is triggered by dissolving the complex in water and subsequent spreading of the cyclopentene in the immediate environment of the plants or flowers upon storage or transportation.

Polysaccharide Double-Layer Microcapsules as Carriers for a Biologically Active Substance for Oral Administration (Fondazione Carlo e Dirce Callerio Onlus) EP 1,152,013 B1

Microcapsules of gelled chitosan and alginate that have been stabilized by divalent ions are described. The composition and process are mainly directed for applications in therapeutic veterinary and fish vaccinations. Advantages of the process include the ability to generate extremely small capsules (<10 μm), an important requirement, especially when the biological active is an antigen administered to induce an immune response. The double-layered design, i.e., the entrapment of the active substance in an alginate/HPMC matrix and the further application of a chitosan outer layer, are claimed to provide excellent structural stability for the microcapsule.

Long-Lasting Absorption of Flavonoids (Nestec, S.A.) EP 1,891,967 A1

Long-term sustained release of orally administered flavonoids, especially rhamnose-containing flavonoids, in the GIT is claimed. Flavonoids are natural components of many plants and are believed to have many important biological functions, in particular their effect on the skin and hair of animals. The natural conjugation of flavonoids with glucosides such as flavonoid rutinoside, however, results in their slow and delayed bioabsorption due to the lack of alpha-rhamnosidase in the small intestine. This application describes a composition whereby the enzyme can be bioencapsulated in lactobacilli or other suitable bacterial cell walls, where it is maintained in a dormant stage. The encapsulated enzyme can be co-administered with the flavonoid, and its release is designed to be triggered upon ingestion, a result of the pH prevailing in the GIT of the animal.

Process for the Production of Compounds That Are Starch-Containing Particles Coated, Embedded, or Encapsulated by at Least One Bioploymer (Unilever) EP 1,905,311 A1

Production of starch particles with controlled digestibility for reduction of the release of glucose mainly in the lower intestines is claimed. In the stomach, digestibility of starch can be adjusted by manipulating the type and amount of food ingested but little can be done about its hydrolysis in the small intestine, where most of the starch degradation takes place within 2 hr before it moves into the colon and is absorbed. This application describes a composition for encapsulating starch particles by entrapment in food-grade biopolymers such as alginates via an emulsification. The process involves the formation of an aqueous solution of alginates and starch followed by addition of oil and emulsification and further hardening of the alginate gels using calcium ions. The oil can be removed further from the encapsulating matrix by repetitive washing with calcium solutions. Data included in this application show a significant impact of starchy material encapsulation on its degradation in alpha-amylase–containing media. Methods for optimizing particle size to provide the required release profile without impacting mouthfeel are also discussed.

Oxidative Stabilization of Omega-3 Fatty Acids in Low Linoleic Acid-Containing Peanut Butter (GFA Brands, Inc.) US 7,344,747 B2

A formulation-based approach to inhibiting the oxidation of omega-3 fatty acids without the need for encapsulation is claimed. Incorporation of omega-3 fatty acids into a low linoleic system such as peanut butter is claimed to provide a high level of protection compared with other vegetable oils or even aqueous media such as milk and yogurt.

Glassy Matrices for the Stabilization of Coffee Aroma (Nestec, S.A.) US 2008/0038421 A1

An inert glassy matrix for the entrapment of specific components in aqueous coffee extracts is described. The application further claims a method that meets the strict limitations on designation of "soluble coffee," where only water-soluble components from roasted coffee may be present in the final product and which currently limits the application of other techniques for sustaining aroma stability. The process involves mixing aqueous coffee extracts with food-grade PVP, which forms a glassy matrix that can entrap the coffee aromas while the undesirable degradation products can be removed further by ultrafiltration.

Protecting Bioactive Ingredients Using Microorganisms with Reduced Metabolizing Capacity (Comapgne Gervais Danone) US 2008/0050354 A1

This patent application discloses an approach for restricting the metabolism of milk peptides by live microorganisms in yogurt, while preserving the fermented product's sensory attributes. Specific milk peptides such as α_s[91-100] are favored in a variety of dairy products for their health benefits. Such benefits, however, cannot be realized in fermented products containing live cultures due to the preference of the microorganisms to feed on such peptides. Thus, by using "decoy" food ingredients that are deliberately delivered to the live microorganism, the desired peptides can be preserved intact, even if added before fermentation, without any major loss in peptide activity.

Protection of Bioactive Ingredients by Means of Encapsulation (Comapgne Gervais Danone) US 2008/0050355 A1

An alternative approach for protecting beneficial peptides from live microorganisms is disclosed. Encapsulation of the peptide via fat coating (using low melting fat such as palm oil, 37°C) and the subsequent formation of an emulsion is claimed to help prevent the metabolism of active peptides by the live microorganisms in yogurt. The emulsion can be added further to the fermented dairy mass with no detectable effect on the product's functional and/or sensory attributes.

Aldehyde-Conjugated Flavonoid Preparations (Agency for Science, Technology and Research) US 2008/0102052 A1

A method and composition for enhancing the bioavailability of high molecular weight flavonoids is described. The invented delivery system comprises a flavonoid that has been conjugated at the C6/C8 positions of its A-ring. Examples provided include using aldehyde-treated PEG or hyaluronic acid derivatized with an aldehyde group containing a highly concentrated flavonoid core. The assembly is claimed to provide enhanced bioavailability of the flavonoid polymer.

Natural Water-Insoluble Encapsulation Compositions and Processes for Preparing Same (Colarome, Inc.) US 2008/0160084 A1

A dry water-insoluble coloring composition that could provide a natural alternative to lake colors and is free of aluminum or other metals is claimed. The dry particulates of a water-insoluble matrix of proteins and a desired coloring material can be prepared via extrusion, so when the matrix is wetted in a clear, colorless aqueous solution or mineral oil it has a lightness value of $L^* > 40$, color vividness or chroma of $C^* < 33$, and a hue angle between 70 and 90°.

Reactive Chemistries for Warming Personal Care Products (Kimberly-Clarke Worldwide, Inc.) US 2008/0145437 A1

This application describes a reactive chemistry-based composition for the generation of a unique sensation, mainly warming. Applications of the technology are described as mainly in personal care products such as wet wipes. The warming sensation is a result of a redox reaction in which an oxidizing agent, such as an aqueous solution of peroxide, comes in contact with a reducing agent, such as sodium ascorbate, in the presence of a catalyst mineral, such as iron. By encapsulating one or both redox actives, the reaction and sensory impact can be controlled adequately.

Chewing Gum Containing Hydroxyapatite (Gumlink) US 2008/037252 A1

A chewing gum system with rod-shaped apatite crystals with a length to width ratio >5 for reduced teeth sensitivity is claimed. Hydroxyapatite in the form of $Ca_{10}(PO_4)_6(OH)_2$ is chemically similar to the mineral component of bones and teeth and is routinely administered to help fill the pores and spaces of teeth surfaces by forming a light solid film on the surfaces of the teeth. The claimed rod-shaped packed film can locate itself on top of the tubules in the dentin enamel, thus blocking it from external stimuli and reducing its sensitivity. ■

People in the News

Compiled by Steven Giannos
Industrial Editor

Nicholas Peppas, Sc.D., Leads New Biopharma Company, Appian Labs, LLC

Blood Weekly via NewsEdge (NewsRx.com): July 3, 2008 – Appian Labs, LLC, a biopharmaceutical company specializing in advanced therapeutic design has announced its launch as a new company focused on providing comprehensive and strategic drug delivery and design solutions for biotech, pharmaceutical, and life science companies worldwide. The company provides solutions for a number of drug delivery problems, including poor bioavailability or solubility, dose timing, toxicity, and many others. Appian Labs is funded and managed by venture firm Emergent Technologies, Inc. (ETI).

Appian's laboratory is led by Chief Scientist Nicholas Peppas, Sc.D., a pioneer in the field of drug delivery and controlled release chemistry over the last three decades. Dr. Peppas has published more than 1,050 peer-reviewed articles and 33 books, covering drug delivery, hydrogels, and related controlled release. He has made life-changing contributions to drug delivery and biomaterial applications using his recognized expertise in biomedical engineering and polymer chemistry.

Aptly named for the great, innovative feat of human engineering, the Appian Way, the leading delivery route of the ancient world, Appian Labs' industry-leading scientist laid the foundation of the science and mathematical formulas used broadly in the modern drug delivery industry today. Now, employing the latest innovations in drug design and delivery, Appian Labs' technologies will be utilized to design tailor-made solutions to current drug delivery problems, as well as develop innovative formulations for the next generation of pharmaceuticals for safer and improved healthcare.

Brian Windsor, Ph.D., president of Appian Labs, stated, "Building on the drug delivery leadership of our scientific team, we can design delivery solutions tailored to pharma companies' drugs and that improve bioavailability, dosing, or timing of a drug. Our breadth of expertise and technologies enables us to match virtually any kinetic profile desired." The company's first marketing initiative to potential pharmaceutical partners is an invitation to "Draw your own profile," and Appian Labs will design a custom drug delivery system to match. Windsor added, "Having worked with pharmaceutical companies for several decades to solve drug delivery problems, our scientific team knows both the common needs and the far-reaching goals of drug manufacturers."

Dr. Nicolas Peppas has received numerous awards for his multidisciplinary research in drug delivery, biomedical engineering, and polymer chemistry. Recognized internationally as a leading scientist, he is a member of both the National Academy of Engineering and the French Academy of Pharmacy and is an honorary member of the Controlled Release Society. In addition to serving as chief scientist of Appian Labs, Peppas will remain as the Fletcher Stuckey Pratt Chair in Engineering in the Departments of Chemical and Biomedical Engineering and professor in the College of Pharmacy at the University of Texas at Austin. ■

Take Your Stand

at the 36th Annual Meeting & Exposition of the Controlled Release Society

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Contact Debby Woodard today for more details.

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Silvia Arpicco
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Jun Seok Hwang
Jun Inoue
Kenneth Israel
Naveen K. Jain
Rachna Jain
Ratnesh Jain
Shih-Fan Jang
Sun Woo Jang
Keith D. Jensen
Seonoh Jeong
Jun-Ichiro Jo
Myeong Jo
Vijay John
Michael J. W. Johnston
Jacqueline A. Jones
Moham Kabadi
Lev Kalontarov
Madan Mohan Kamila
Felix Karim
Glenn Kazo
Molinda Kearns
Dave Kerns
Chulhee Kim
Hyun Jin Kim
In-San Kim
Ju-Young Kim
Sung Tae Kim
Sun-Kyoung Kim
Tae-il Kim
Yong-Hee Kim
Young Hoon Kim, Sr.
Samuel Knight
Fifa Konradsdottir
Aristides P. Koutrouvelis
Edward R. Kraft
Martin Kratzel
Laila Kudsiova
Mahesh Kulkarni
Shirishkumar B. Kulkarni
Hemant Kumar
Rajesh Kumar
Saran K. Kumar
Sasank Kunadharaju
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Shunichi Kuroda
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Fan Lee
Jeong-Min Lee
K. Daniel Lee
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Kyung-Dall Lee
Sang Min Lee
SungHoon Lee
Leonora Ethleen Leigh
Stephanie Lemoult
Jing Li
Xiaohong Li
Zhengmao Li
Florencia Lim
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Richard Lu
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Marzia Massignani
Takashi Matsuzaki
Victoria L. McArdle
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Arikha Moses
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Tiziana Musacchio
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Ngoc B. Nguyen
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Onajite Okoh
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Godfried G. Owusu-Ababio
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Yesha N. Patel
Rajesh R. Patil
Maireadh Pedersen
Samuel Perreault
Regine Peschka-Suess
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Adchara Pongpeerapat
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Adeline Siew
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Dmitry Zimnitsky

In the News

Compiled by Steven Giannos
Industrial Editor

AUGUST 2008

CPEX Pharmaceuticals and Serenity Pharmaceuticals Announce Collaboration on Drug Candidate for Urology Indication

Business Wire: August 4, 2008 – EXETER, N.H. – CPEX Pharmaceuticals, Inc. (NASDAQ: CPEX) and privately held Serenity Pharmaceuticals have announced that they are collaborating on an intranasal drug candidate for a urology indication. New York-based Serenity's drug candidate will be delivered using CPEX's patented drug delivery technology. Serenity believes the drug targets a potential worldwide market of $2–3 billion.

"We are delighted to be working with Serenity in a truly collaborative manner," said John Sedor, CPEX Pharmaceuticals' president and chief executive officer. "CPEX provided access to its intellectual property, developed the formulations, produced a pilot scale manufacturing process and prepared clinical and stability supplies. Our expertise in product and process development and Serenity's clinical expertise in specialty areas have quickly proven to be a complementary fit."

Dr. Samuel Herschkowitz, Serenity Pharmaceuticals' CEO, said, "We have been consistently impressed with CPEX's platform technology, its expertise and its infrastructure. From the beginning, we found CPEX to be an excellent partner, and we have made progress in advancing our drug from concept into Phase I development with their assistance. Based on the profile of their delivery platform and our current R&D pipeline, we are hopeful that we can collaborate with CPEX on additional drug candidates in the future."

Sedor said, "Including the launch of Serenity's Phase I trial, our CPE-215® drug delivery platform has formed the basis for the filing of three separate INDs, all of which represent diverse therapeutic areas: testosterone replacement, diabetes and urology. This diversity speaks to the broad applicability of our technology and its potential to effectively deliver pharmaceutically active peptides, peptidomimetics and proteins across a variety of membranes."

"Today's announcement also demonstrates how we can capitalize on the value of our technology in ways that can increase our shareholder value," Sedor continued. "We received a patent in late July 2007 that extended the coverage for our intranasal drug delivery technology utilizing CPE-215® beyond insulin. We signed an agreement to begin working with Serenity less than three months later. We believe this partnership is indicative of how our platform can generate opportunities for future potential revenue streams." For more information about CPEX, please visit www.cpexpharm.com.

Frost & Sullivan Honors TransPharma Medical for its Innovative ViaDerm Drug Delivery System

Business Wire: August 2, 2008 – LONDON, U.K. – The 2008 Frost & Sullivan European Transdermal Drug Delivery Product Innovation Award has been conferred on Israel-based TransPharma Medical Ltd. in recognition of its innovative ViaDerm drug delivery system. The company's two flagship drug product development programs—ViaDerm-hPTH(1-34) for the treatment of osteoporosis and ViaDerm-hGH for the treatment of human growth hormone deficiency—both in Phase II of clinical development.

The unique ViaDerm system solution allows for low-cost, patient friendly transdermal delivery of a wide variety of drugs from a patch. Suitable for home use, the ViaDerm system employs a re-usable battery-operated handheld electronic device in combination with a patch containing the drug.

"The basis of the ViaDerm device is TransPharma's proprietary RF-MicroChannel technology which is applied to create an array of microscopic pores in the outer skin surface, facilitating the systemic delivery of drugs," explained Frost & Sullivan Research Analyst Sylvia Miriyam Findlay. "The pores are created rapidly with no pain or trauma to the skin. The device can be applied to all skin types and is fully controlled by a unique feedback mechanism that ensures precise and reproducible drug delivery."

The RF-MicroChannels are large enough to enable the delivery of high molecular weight molecules and are open up to 24 hr, allowing prolonged systemic delivery of a wide range of drug molecules, including biologics, which currently are available primarily by injection. The ViaDerm system offers patients an administration method that avoids the need for injections, thereby increasing compliance and safety.

TransPharma Medical aims to deliver the best solutions for unmet needs in transdermal drug delivery. It has attempted to meet the challenge of delivering large peptide and proteins by introducing a dry printed patch to complement its innovative RF-MicroChannel technology. The printed patch uses the dry form of the drug, thereby increasing stability and shelf life at room temperature.

"TransPharma Medical has constantly worked to spread its novel technology for transdermal drug delivery in therapeutic areas such as endocrine, pain, osteoporosis and diabetes," stated Findlay. "Its application can cover a wide range of therapeutic molecules like hPTH, hGH, GLP-1 analogues, Granisetron, Calcitonine, Testosterone, Diclofenac, and more."

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The company has sought to forge productive partnerships with pharmaceutical and biotechnology companies, which will maximize the synergy between its innovative technology and pharmaceutical company pipelines. Accordingly, TransPharma Medical has a strategic collaboration with Elli Lilly for the development and commercialization of ViaDerm-hPTH(1-34) for the treatment of osteoporosis. The product, currently in Phase II testing, is administered transdermally and, thus, can enable patients to manage their disease while eliminating the need for daily painful injections.

JULY 2008

Tumor Targeting Docetaxel Abstract Presented at the 11th Liposome Research Days Conference

Business Wire: July 29, 2008 – COLUMBIA, Md. – Celsion Corporation (NASDAQ: CLSN) has announced the presentation of its docetaxel thermosensitive liposome preclinical study results at the 11th Liposome Research Days Conference during the poster session on July 22, 2008.

The presentation provided detailed preclinical results regarding the use of Celsion's temperature-sensitive liposome formulation with docetaxel. This novel, patent-pending encapsulation of a well-known chemotherapeutic agent demonstrates improved anti-tumor effect *in vivo*. In the presented study, mice were tumored with a Lewis lung cell line in the leg and then treated in three cohorts: with free docetaxel only; docetaxel encapsulated in non–temperature-sensitive liposomes; or with Celsion's proprietary temperature-sensitive liposomes containing docetaxel. Each of the three cohorts was treated by intravenous injection every other day, followed by the application of heat to the tumored leg. After treatment, the tumor volumes were monitored for 2 weeks. Results indicated that the reduction in tumor volume generated by the heat-activated liposomal formulation was statistically superior to both the free docetaxel and the non–temperature-sensitive liposomal formulation. Docetaxel is marketed worldwide under the name Taxotere®.

Mr. Michael Tardugno, Celsion president and chief executive officer, commented, "Celsion's elegant; tumor targeting, liposomal technology continues to demonstrate its significant potential. Our objective this year is to replicate these results in a variety of xenograft human tumor models and to initiate toxicological studies. Celsion will finalize a clinical development strategy and devise a regulatory pathway with the FDA following the successful outcome of these studies." Copies of the abstract and poster can be found on the company's website at www.Celsion.com.

West's MixJect System Selected by Watson for Use in Treatment of Prostate Cancer

Women's Health Weekly via NewsEdge (NewsRx.com): July 24, 2008 – West (NYSE: WST), the world's premier manufacturer of components and systems for injectable drug delivery, has announced that Watson Pharma, Inc., a subsidiary of Watson Pharmaceuticals, Inc., has selected MixJect as the new delivery system for TRELSTAR (triptorelin pamoate for injectable suspension), a palliative treatment for advanced prostate cancer. The MixJect system, developed and manufactured by West's subsidiary Medimop Medical Projects Ltd., is a patented reconstitution device that ensures the safe and easy delivery of lyophilized drugs. West provides the reconstitution system in a kit, also containing the diluent syringe.

As more and more pharmaceuticals enter the market in lyophilized form, reconstitution at the point of use is becoming increasingly prevalent. The MixJect system is one of West's safe administration products that streamline this process. The delivery system allows for needle-less reconstitution prior to injection and is equipped with a 21-gauge needle that can be covered by a shield both before and after the drug is administered, making administration of TRELSTAR and disposal of the used syringe and vials significantly easier and safer for patients and caregivers alike.

"Convenience and safety are of the utmost importance for the patients and healthcare providers using West's products; our reconstitution systems address both of these issues simultaneously," said Graham Reynolds, West vice president, safety and administrations systems. "The MixJect system is an excellent delivery system for TRELSTAR and an example of our continued commitment to developing innovative products that meet the needs of pharmaceutical and biopharmaceutical customers and the patient populations they serve. Our partnership with Watson is proof that leading drug manufacturers continue to view West as a trusted resource for drug administration options."

Vyteris, Inc. Receives $2.5 Million Loan from Ferring Pharmaceuticals, Inc.

Business Wire: July 21, 2008 – FAIR LAWN, N.J. – Vyteris, Inc. (OTC BB: VYTR), manufacturer of the first FDA-approved active patch transdermal drug delivery system, received a $2.5 million principal amount of financing effective July 9, 2008, from Ferring Pharmaceuticals, Inc., which represents an advance on a potential milestone payment for a Phase II clinical trial of a product for female fertility treatment.

The $2.5 million was advanced in the form of a loan and bears interest at the rate of 10% per annum. If Ferring elects to proceed with the Phase II trial, the principal amount of the loan will be paid off through application of the Phase II payment, which would otherwise be due under the license agreement between Vyteris and Ferring. "This advance payment represents our productive working relationship with Ferring," said Haro Hartounian, president of Vyteris, Inc. "We feel that Ferring's advance of the milestone to us, through the loan, is further indication of our progress in our joint clinical development efforts." The possible Phase II clinical trials would be significant in scope and are designed to establish proof of principle. Phase I trials successfully demonstrated the first transdermal delivery of a peptide molecule.

"This financial support validates Ferring's commitment to this project. This funding will be used in part to cover the projected

costs of a Phase II clinical trial," said Donald Farley, executive chair of Vyteris, Inc. "While we continue to explore other avenues to raise capital needed for further operations, we continue our efforts in controlling costs and expenditures while focusing on our development and licensing initiatives."

The product under development by Vyteris and Ferring employs Vyteris' patented Smart Patch drug delivery technology. The technology is designed to provide a safe and effective method of delivering a peptide hormone from a patch automatically using a low-level electrical current, allowing continuous pulsatile delivery of a peptide in a painless, convenient manner. This precise dose control is an essential characteristic in the delivery of therapeutics for the treatment of female infertility. The Smart Patch technology system is needle-free and convenient to use, minimizing concerns about patient compliance.

New Patient and Physician Voice of the Customer for U.S. Drug Delivery

Business Wire: July 21, 2008 – PALO ALTO, Calif. – Following successful work in the areas of diabetes, chronic pain, inflammation, and neurological disorders, Frost & Sullivan is seeking partner companies for a new end-user study on preferences and drivers of adoption for various drug delivery technologies in the U.S. pharmaceutical market. Through interviews with both physicians and patients, Frost & Sullivan aims to identify key drivers and obstacles to adoption and utilization of various drug delivery technologies. Additionally, patient feedback will be obtained in terms of awareness, usage, and desired improvements of specific brands as determined by clients.

Frost & Sullivan seeks feedback on areas of interest to the industry for an in-depth look at these issues from respondents. Various new therapeutic areas and treatment settings are being evaluated. The final decision for this new project will be based on market demand and shaped to meet the needs of the industry. If you are interested in partnering with Frost & Sullivan, shaping, or obtaining the research for the study U.S. Drug Delivery Voice of the Customer 2008, please send an e-mail to Johanna Haynes, Corporate Communications, at johanna.haynes@frost.com with the following information: your full name, company name, title, telephone number, e-mail address, city, state, and country.

"Understanding how patients and prescribers view drug delivery methods as part of treatment is vital to drug developers throughout the industry," notes Frost & Sullivan Industry Manager Daniel Ruppar. "Especially as companies evaluate new delivery opportunities, understanding how different technologies are viewed may lead to new product pathways not previously considered."

While there are numerous types of drug delivery technologies available in terms of approved drugs for a disease, physician and patient decision factors are often the primary determinant of drug choice. This especially can impact drugs using device-driven delivery or the success of new first-in-class products with novel delivery approaches. "Developers that can better understand the drivers and obstacles of adoption and utilization preferences for pharmaceutical drug delivery can develop and refine their technologies to best serve patients and the medical community," stated Ruppar. "This can also drive decision factors for both lifecycle management activities and R&D programs."

U.S. Drug Delivery Voice of the Customer 2008 is part of ongoing research conducted within the Pharmaceutical and Biotechnology Subscription, which also includes research in the following markets: contract research & manufacturing, biopharmaceuticals, specialty pharmaceuticals, vaccines and drug delivery. All research included in subscriptions provide detailed market opportunities and industry trends that have been evaluated following extensive interviews with market participants. Interviews are available to the press.

Head-to-Head Study Demonstrates Focalin® XR Offers Faster and Better Symptom Control than Concerta® in Early Part of ADHD Patients' Day

Drug Week via NewsEdge (NewsRx.com): July 17, 2008 – A head-to-head study, published in the June *Journal of Child and Adolescent Psychopharmacology*, confirms that Focalin® XR (dexmethylphenidate HCl) extended-release capsules offer greater improvements in managing symptoms of attention deficit/hyperactivity disorder (ADHD) compared with Concerta® (d,l-methylphenidate HCl) extended-release tablets at 2 hr post-dose, the primary study endpoint.

Focalin® XR 20 mg and 30 mg also demonstrated better symptom control versus Concerta® 36 mg and 54 mg, respectively, from 30 min to 6 hr. Symptom control was demonstrated as early as 30 min post-dose with Focalin® XR 20 mg and 30 mg versus placebo. Neither dose of Concerta® was effective versus placebo at 30 min. Novartis is seeking revised labeling to reflect the 30-min onset of action.

"There are many things to consider when determining which treatment is best for a patient, including lifestyle implications," said Alice Mao, M.D., associate professor of psychiatry at the Baylor College of Medicine. "The results of this study demonstrate the benefits of Focalin XR during the early part of the day, which may be better for children who need their medication to begin working before they leave for school and continue working throughout the day."

ADHD affects approximately 3–7% of children in the United States, and its symptoms—inattention, hyperactivity, and impulsivity—can significantly impact a child's ability to focus and learn in an educational setting. The study included children between the ages of 6 and 12 and examined their response to Focalin® XR compared to Concerta®, as well as placebo, in a classroom setting.

Similar efficacy was observed between Focalin® XR and Concerta® at 8 hr post-dose. Only at 10–12 hr and 11–12 hr post-dose did Concerta® 36 mg and 54 mg demonstrate

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symptom improvement over Focalin® XR 20 mg and 30 mg, respectively. "Focalin XR helps children with ADHD optimize their natural cycle of the day because its drug delivery system allows for a quick onset in the morning, effective symptom management during the day, and then tapers off in the evening," said Rafael Muniz, MD, senior medical director, Novartis Pharmaceuticals Corporation.

Focalin® XR uses the proprietary SODAS® (spheroidal oral drug absorption system) technology developed by Elan Corporation, where 50% of the dose is released immediately, and the remaining 50% is released after approximately 4 hr, resulting in a maximum peak at about 1.5 hr and a second peak at about 6.5 hr. Concerta® is formulated to release 22% of the drug initially, with the remainder released through a controlled osmotic process.

In addition, Focalin® XR and Concerta® have chemical differences. Focalin® XR isolates the active d-isomer of d,l-methylphenidate. Therefore, only half the dose of methylphenidate is required. Concerta® is a d,l-methylphenidate.

Collegium Pharmaceutical Inc. Announces U.S. Patent Issued Covering Its DETERx™ Abuse Deterrent Sustained Release Technology

Business Wire: July 16, 2008 – CUMBERLAND, R.I. – Collegium Pharmaceutical, Inc., a specialty pharmaceutical company, has announced that a new patent has been issued by the U.S. Patent and Trademark Office (USPTO) relating to its tamper resistant, abuse-deterrent formulation platform. U.S. Patent 7,399,488 contains claims that cover orally administrable compositions comprising Collegium's proprietary micro-particle formulations. The formulations are designed to be more resistant to physical methods of tampering than are currently available sustained-release dosage forms. The patent will provide protection for DETERx™ and products incorporating the DETERx™ technology into the year 2025.

The patent will provide broad coverage for Collegium's abuse-deterrent, sustained-release, orally administered DETERx™ formulation platform. The DETERx™ platform consists of a multi-particulate matrix formulation in a capsule. While developed primarily to provide tamper-resistant properties, the multi-particulate design potentially allows patients with difficulty swallowing to open the capsule and administer the contents on food or with water, while maintaining the sustained-release properties of the product.

Collegium's lead DETERx™ product candidate, COL-003, a formulation of sustained release oxycodone, will be covered by the patent. As previously reported, COL-003 is currently under clinical development pursuant to an active investigational new drug application on file with the U.S. Food and Drug Administration (FDA). Based on *in vitro* testing and previously reported pharmacokinetic results, COL-003 is expected to provide adequate plasma concentrations to effectively treat pain over a 12-hr period. The abuse-deterrent properties of DETERx™ are the result of the formulation itself, which protects the drug from dose dumping, as demonstrated in a variety of laboratory tampering simulations, without relying on aversive agents or pharmacological approaches that could have harmful effects in legitimate patients. The product ahs received Fast Track Designation from the FDA.

"We are pleased to announce the issuance of the first patent that broadly covers our DETERx™ technology. Since the claims cover the DETERx™ technology, we are not limited to one specific drug candidate. This patent will protect a variety of active ingredients incorporated into DETERx™, in addition to our lead product COL-003. We intend to continue to prosecute additional patents that will strengthen our intellectual property for this technology," said Michael Heffernan, president and CEO, Collegium Pharmaceutical.

SurModics and Brookwood License Nanotechnology Drug Delivery System

Business Wire: July 14, 2008 – EDEN PRAIRIE, Minn. – SurModics, Inc. (Nasdaq:SRDX), a leading provider of surface modification and drug delivery technologies to the healthcare industry, has announced that its Brookwood Pharmaceuticals subsidiary has licensed lipid nanoparticle technology from PharmaSol GmbH of Berlin, Germany. Under the agreement, Brookwood has exclusive rights to all pharmaceutical applications of the technology.

The PharmaSol technology can be used to formulate drugs into nanostructured lipid carriers (NLCs), which offer a number of advantages over other drug delivery nanotechnologies, such as liposomes, emulsions, and solid-lipid nanoparticles. These advantages include increased drug loading, improved drug incorporation, and the ability to produce suspensions of higher solids content, allowing for decreased dose size and products with a longer shelf life. NLC formulations of drugs can be administered orally, as well as through intravenous or subcutaneous injection. Brookwood is currently offering this technology to potential customers, while also generating additional data to accelerate product development of the NLC drug delivery platform.

"This license further broadens the drug delivery technology offerings of SurModics and Brookwood and complements our existing portfolio," said Arthur J. Tipton, Ph.D., president of Brookwood. "Our microparticle technology has demonstrated multi-day to multi-month delivery; incorporating this NLC technology can enable shorter-duration injectable delivery, targeted delivery and high value oral applications for nearly all therapeutic areas. The license agreement with PharmaSol demonstrates our commitment to offering leading-edge proprietary technologies to our customers."

Professor R. H. Müller, Ph.D., the inventor of the technology and founder of PharmaSol, is a recognized leader in the field of lipid nanotechnology. Dr. Müller stated, "I am delighted we have executed this license agreement. Brookwood has exceptional capabilities in particle technology, including scale-up and

manufacturing. With this collaboration, we can accelerate the development of NLC lipid technology and expand its use into a broad range of clinical applications including oncology, central nervous system (CNS) and cardiovascular."

"NLC technology broadens the nanotechnologies that we can offer to customers in need of drug delivery solutions," stated Thomas R. Tice, Ph.D., vice president of research of Brookwood. "Many promising drug candidates do not reach commercialization because they will not dissolve in the stomach or intestinal tract. NLCs are designed to increase solubility of poorly soluble drugs, thus improving oral bioavailability. Additionally, injectable NLC formulations can time release drugs for up to 7 days."

ELADUR™ Development Update: DURECT Receives Orphan Drug Designation for Bupivacaine for Post-herpetic Neuralgia

Medical Letter on the CDC & FDA via NewsEdge (NewsRx.com): July 10, 2008 – DURECT Corporation (NASDAQ: DRRX) has announced that the U.S. Food and Drug Administration (FDA) has granted to DURECT orphan drug designation for bupivacaine for relief of persistent pain associated with post-herpetic neuralgia (PHN). Bupivacaine is the active pharmaceutical ingredient in ELADUR™, DURECT's investigational transdermal drug patch. If ELADUR™ is the first bupivacaine product approved for PHN, under the 1983 Orphan Drug Act ELADUR™ will receive seven years of market exclusivity following the approval of the product by the FDA.

"The receipt of orphan drug status enhances the product opportunity for ELADUR, including providing a more favorable development pathway," stated James E. Brown, DVM, president, and CEO of DURECT. "We are continuing to develop ELADUR as a potentially best in class transdermal product for those suffering from PHN."

ELADUR™ is an investigational transdermal drug patch intended to deliver bupivacaine for up to 3 days from a single application, as compared to a wearing time limited to 12 hr with currently available anesthetic patches (e.g., Lidoderm®, an FDA-approved lidocaine patch for post-herpetic neuralgia pain management). Bupivacaine, the active agent in ELADUR™, is a potent, FDA-approved long-acting local anesthetic used in regional anesthesia for local tissue infiltration, nerve block, and epidural and intrathecal anesthesia. DURECT currently retains full commercial rights to this product candidate.

DURECT previously has announced positive results for ELADUR™ from a 60-patient Phase IIa clinical trial of patients suffering from post-herpetic neuralgia. In this study, ELADUR™ showed improved pain control versus placebo during the 3-day continuous treatment period. In addition, ELADUR™ appeared to be well tolerated overall, and patients treated with ELADUR™ and placebo exhibited similar safety profiles. A poster describing this study was presented at the 27th Annual Scientific Meeting of the American Pain Society and is accessible online at www.durect.com/wt/durect/page_name/Publications.

Anesiva Launches Needle-free Zingo™ to Reduce Pain from IV Starts and Blood Draws in Children

Pain & Central Nervous System Week via NewsEdge (NewsRx.com): July 10, 2008 – Anesiva, Inc. (NASDAQ: ANSV) has announced that it has launched its first commercial product, Zingo™ (lidocaine hydrochloride monohydrate) powder intradermal injection system. Zingo™ is an easy-to-administer, single-use, needle-free system that reduces the pain associated with peripheral intravenous (IV) line placements and blood draws in children 3–18 years of age. Zingo™ works quickly, within 1–3 min, to relieve pain at the needle insertion site.

"Zingo is the first easy-to-administer, fast-acting local anesthetic that could lead to a paradigm shift in the approach to venous access procedures such as drawing blood and placing IV lines in children," said William T. Zempsky, M.D., associate professor, Department of Pediatrics, University of Connecticut; associate director, Pain Relief Program, Connecticut Children's Medical Center, Hartford, who led the pediatric trials of Zingo™. "Because available topical anesthetic creams can take up to 30 to 60 minutes to work, healthcare providers have had to sacrifice patient comfort when performing the numerous peripheral venous access procedures that occur each day. Zingo will be a source of relief to both them and the children and parents they deal with every day."

"The commercial launch of Zingo is a major milestone that is notable both for our company and for patients. We are fully committed to driving successful market introduction for this exciting new product," said Michael L. Kranda, Anesiva president and chief executive officer.

"We are initially focusing our efforts on the children's hospitals and academic medical centers with large pediatric units which facilitate the majority of acute and chronic pediatric care. Many of the patients served in these hospitals undergo peripheral venous access procedures repeatedly, and are undertreated, indicating a significant unmet medical need," said Nancy E. Donahue, senior vice president, sales and marketing. Anesiva estimates that approximately 18 million pediatric peripheral venous access procedures are performed annually in U.S. hospitals.

Anesiva and its co-promotion partner Sagent Pharmaceuticals, Inc. are working in tandem to educate caregivers about the importance of addressing peripheral venous access pain in children and to ensure Zingo™ availability through hospital pharmacies. Anesiva's seasoned team of 15 hospital-based regional account managers with an average of 14 years' industry experience, led by two directors who have a combined 30 years of experience, will drive the launch of this product in the United States. Sagent has assigned 15 field representatives, all of whom have an average of more than 18 years of hospital selling

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experience and whose national account representatives have an average of 25 years of hospital sales experience.

Zingo™ currently is manufactured with established, approved processes. Anesiva continues to pursue Zingo™ manufacturing scale-up to reduce cost of goods and meet anticipated increasing market demand.

Access Pharmaceuticals Signs Merger Agreement to Acquire MacroChem Corp.

PRNewswire-FirstCall: July 10, 2008 – DALLAS, Tex. – Access Pharmaceuticals, Inc. (OTC Bulletin Board: ACCP) and MacroChem Corporation (OTC Bulletin Board: MACM) have announced that they have signed a definitive merger agreement providing for Access to acquire MacroChem through the issuance of 2.5 million shares of Access Pharmaceuticals' common stock. MacroChem's product portfolio includes two clinical-stage oncology products: 4-thio Ara-C, which is a next generation nucleoside analogue licensed from Southern Research Institute, and sodium phenylbutyrate, which is licensed from the NIH and is currently partnered with Access Pharmaceuticals. MacroChem's portfolio of late-stage clinical drug candidates includes Pexiganan, a novel topical anti-infective for the treatment of diabetic foot infection that has already completed two Phase III clinical trials; and EcoNail, a novel topical treatment for onychomycosis that is currently in a Phase II clinical trial. Macrochem also has two proprietary dermatology drug platforms: SEPA® and MacroDerm™. The acquisition is expected to close in the third quarter of 2008.

"The acquisition of MacroChem brings multiple late-stage clinical drug candidates into the Access pipeline, some of which are further along than Access' current assets," stated Jeffrey B. Davis, Access president and CEO. "We are currently active in partnering and out-licensing discussions, and MacroChem's dermatology assets will be added to that partnering effort. The oncology assets are highly synergistic with the oncology development efforts ongoing at Access, and we look forward to the opportunity to move them along and monetize those assets through additional partnering activities."

"With the precarious state of the financial markets adding further challenges for microcap biopharmaceutical companies, we believe the strategic combination with Access is a very positive step forward for the continued development of MacroChem's product candidates," stated Robert J. DeLuccia, chair of MacroChem Corporation. "We are pleased to work with Access to assure an orderly transition and believe that this is the best strategy currently available to maximize value for our shareholders."

Emisphere Announces License Agreement with Novo Nordisk to Develop Oral Formulation of GLP-1 Receptor Agonists for Diabetes

Diabetes Week via NewsEdge (NewsRx.com): July 3, 2008 – Emisphere Technologies, Inc. (NASDAQ: EMIS) and Novo Nordisk A/S (NYSE: NVO) have entered into an exclusive development and license agreement to develop and commercialize oral formulations of Novo Nordisk's proprietary GLP-1 receptor agonists, which have the potential of treating type 2 diabetes, using Emisphere's eligen® technology. The agreement includes at least $87 million in product development and sales milestone payments to Emisphere, of which $10 million will be the minimum first-year payment, as well as royalties on sales. The agreement also provides Novo Nordisk with the option to develop oral formulations of Novo Nordisk compounds other than GLP-1 receptor agonists using Emisphere's proprietary carrier technology. Further financial details of the agreement were not made public.

Under the new agreement, Novo Nordisk is responsible for the development and commercialization of the product candidates. Novo Nordisk and Emisphere have collaborated since 2007 on early-stage pre-clinical research that has preliminarily confirmed the utility of Emisphere's carriers to provide bioavailable oral formulations of GLP-1 receptor agonists.

"This partnership with Novo Nordisk is important for Emisphere for several reasons," said Michael V. Novinski, president and chief executive officer of Emisphere. "First, it couples Emisphere with Novo Nordisk, the worldwide leader in the field of diabetes research. Second, it places our technology with a treatment for diabetes that we hope will be able to improve upon the healthcare of millions of patients with this disease. Finally, it also positions our eligen® technology in such a way that helps to bring innovative solutions to the pharmaceutical development arena."

"This is an encouraging agreement on a promising technology for oral administration of proteins. It fits very well with Novo Nordisk's strategy within diabetes research," said Peter Kurtzhals, senior vice president, Diabetes Research Unit. Emisphere's broad-based drug delivery technology platform, known as eligen® technology, uses proprietary, synthetic chemical compounds, known as Emisphere delivery agents, sometimes called carriers. Emisphere's eligen® technology makes it possible to deliver a therapeutic molecule without altering its chemical form or biological integrity.

New Findings from Kaohsiung Medical University, Institute of Pharmaceutical Science in the Area of Phototherapy

Cancer Weekly via NewsEdge (NewsRx.com): July 3, 2008 – New research, "Comparison of 5-Aminolevulinic Acid-Encapsulated Liposome Versus Ethosome for Skin Delivery for Photodynamic Therapy," is the subject of a report. "Topical photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) is an alternative therapy for many non-melanoma skin cancers. The major limitation of this therapy, however, is the low permeability of ALA through the stratum corneum (SC) of the skin," investigators in Kaohsiung, Taiwan, reported.

"The objective of the present work was to characterize ethosomes containing ALA and to enhance the skin production of protoporphyrin IX (PpIX), compared to traditional liposomes.

Results showed that the average particle sizes of the ethosomes were less than those of liposomes. Moreover, the entrapment efficiency of ALA in the ethosome formulations was 8–66% depending on the surfactant added. The particle size of the ethosomes was still approximately <200 nm after 32 days of storage. An *in vivo* animal study observed the presence of PpIX in the skin by confocal laser scanning microscopy (CLSM). The results indicated that the penetration ability of ethosomes was greater than that of liposomes. The enhancements of all the formulations were ranging from 11- to 15-fold in contrast to that of control (ALA in an aqueous solution) in terms of PpIX intensity. In addition, colorimetry detected no erythema in the irradiated skin," wrote Y. P. Fang and colleagues, Kaohsiung Medical University, Institute of Pharmaceutical Science.

The researchers concluded, "The results demonstrated that the enhancement ratio of ethosome formulations did not significantly differ between the non-irradiated and irradiated groups except for PE/CH/SS, which may have been due to a photobleaching effect of the PDT-irradiation process." Fang and colleagues published their study in the *International Journal of Pharmaceutics* (International Journal of Pharmaceutics, 2008;356(1-2):144-52). For additional information, contact Y. P. Fang, Graduate Institute of Pharmaceutical Sciences, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan.

PainReform Licenses a Novel Sustained Release Formulation of Ropivacaine from Encore Therapeutics Inc.

Business Wire: July 2, 2008 – TEL AVIV, Israel and CARLSBAD, Calif. – PainReform and Encore Therapeutics have announced that the two companies have entered into a licensing and development agreement related to Encore Therapeutics' ETI-211 product for the treatment of post-surgical pain. The product, which is administered subdermally using Encore Therapeutics' proprietary Phospholipid Gel technology, is currently in pre-clinical testing.

Under the terms of the agreement, PainReform will obtain exclusive North American rights to ETI-211 and will also obtain an option to expand the agreement to other areas, including Japan and the European Union. Encore Therapeutics will receive an undisclosed upfront payment and will also receive development and sales milestones, as well as royalties on sales. PainReform will be responsible for further development activities.

"ETI-211 represents our first major licensing agreement and we look forward to working with Encore Therapeutics on the development of this exciting product," stated Dan Teleman, chief executive officer of PainReform. "ETI-211 validates our business model that is focused on identifying, licensing and developing innovative formulations of pain therapeutics. We are actively looking to expand our pipeline with additional products that offer meaningful clinical benefits."

"A single local application of ETI-211 at the surgical site has the potential to reduce or eliminate postsurgical pain for up to 72-hours. By working locally, systemic opiate or NSAID induced side effects can be greatly minimized because of the reduced need for systemic pain medication," stated Stephen Cooper, PainReform executive VP for development. "We plan to evaluate ETI-211 in a variety of postsurgical situations leading to an NDA filing."

Paul J. Marangos, chair and CEO of Encore Therapeutics commented, "The PG technology developed by Dr. Andrew X. Chen is a novel, natural and more feasible alternative to liposomes with great potential for drug delivery. We are pleased to be working with PainReform to move this important new product into the clinic. Opiate use, post surgery, not only has side effects and addiction potential but also can increase hospital stays and thereby costs to the healthcare system. ETI-211 may have favorable effects on those aspects of post-surgical pain management."

Altea Therapeutics and Hospira Enter into Development and Commercialization Agreement for Transdermal Product

Business Wire: July 2, 2008 – ATLANTA, Ga. – Altea Therapeutics has announced that it has entered into a partnership with Hospira, Inc., a global specialty pharmaceutical and medication delivery company, for the development and commercialization of an undisclosed product utilizing the company's proprietary PassPort™ transdermal delivery system.

Under the terms of the agreement, Altea Therapeutics has granted Hospira exclusive worldwide rights to develop and commercialize the product. Altea Therapeutics will fund certain Phase I clinical studies, after which Hospira will fund all further product development, manufacturing, and commercialization activities. In return, Altea Therapeutics will receive from Hospira an upfront payment, which includes an equity investment. In addition, Altea Therapeutics could receive from Hospira clinical, regulatory, commercialization, and sales performance milestone payments of up to $109 million and undisclosed royalties on sales of the product over the term of the agreement.

"This agreement further validates the development of the Altea Therapeutics transdermal patch technology for drugs that previously were administered by needle injection or infusion, including water-soluble proteins, carbohydrates, and small drugs," said Dr. Eric Tomlinson, Ph.D., D.Sc., president and CEO of Altea Therapeutics. "Based on our existing relationship with Hospira, we believe they are the ideal partner with the technological and scientific expertise, and the global commercial reach necessary to develop and commercialize this product."

JUNE 2008

NuPathe Reports Positive Phase I Results for NP101, a Novel Transdermal Patch for Acute Migraine

Business Wire: June 30, 2008 – CONSHOHOCKEN, Pa. – NuPathe Inc., a privately held specialty pharmaceutical company developing innovative products for the treatment of neurological

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and psychiatric diseases, has announced positive Phase I results for NP101, a novel drug-device patch for acute migraine in clinical development. NP101 combines NuPathe's SmartRelief™ proprietary iontophoretic transdermal technology with sumatriptan, the most widely prescribed treatment for acute migraine in the United States and the active ingredient in Imitrex®.

The study was a Phase I, single-center, single-dose, open-label, five-way crossover study to compare the pharmacokinetics of two NP101 patch formulations with three FDA-approved formulations of Imitrex® (20-mg nasal spray, 100-mg oral tablet, 6-mg subcutaneous injection) in 23 healthy volunteers. Tolerability and safety were assessed for all formulations, and skin evaluations were performed for subjects after administration of NP101. Results of the study were presented June 28, 2008, at the American Headache Society meeting in Boston, MA.

The plasma concentrations for NP101 were more consistent among subjects compared with either the 20-mg nasal spray or 100-mg oral tablet formulations. "These findings support the hypothesis that parenteral administration of sumatriptan, either through subcutaneous injection or transdermal delivery, provides a more predictable method of drug delivery by bypassing absorption through the gastrointestinal system," said Mark Pierce, M.D., Ph.D., chief scientific officer at NuPathe, who presented the results in Boston.

NP101 was well tolerated. Adverse events for NP101 generally were mild, and most resolved without treatment. The most common reported adverse event was pruritus at the patch application site. Upon patch removal, 75% of subjects had minimal or no skin erythema, and by 48 hr all subjects had minimal or no erythema. No subject withdrew from the study due to skin irritation.

No subject reported atypical sensations such as flushing or pain and pressure sensations after application of NP101. These adverse events, common with triptans, were reported for both the 6-mg subcutaneous injection and the 100-mg oral tablet at frequencies similar to previously reported data. "This absence of atypical, pain and pressure sensations with the NP101 patch may reflect the lower and more consistent peak plasma concentration levels obtained with NP101 patches when compared to the 100 mg oral tablet and 6 mg subcutaneous injection of Imitrex®," reported Dr. Pierce.

According to Jane Hollingsworth, chief executive officer of NuPathe, "Patients clearly need better options for acute migraine. Triptans, the gold standard in treatment today, can be quite efficacious, but are inadequate for many in their current forms. Many patients experience difficulty taking their medication due to nausea that accompanies their migraine and many experience troublesome side effects from current medications." Ms. Hollingsworth also said that "The results of this study are extremely exciting for patients and NuPathe as they demonstrate that NP101 delivers sumatriptan in a rapid, predictable, and consistent manner. Large Phase III clinical trials are being initiated now to evaluate the efficacy and safety of NP101 for the treatment of acute migraine."

Freedom2 Expands Market Horizons Based on Patented Particle Encapsulation Delivery System

Business Wire: June 11, 2008 – CHERRY HILL, N.J. – Freedom2 Holdings, Inc., (Freedom-2, Inc.'s holding company), pioneers in the development of safe, quality inks for the purpose of permanent but more easily removable tattoos has announced its expansion into the $250-billion worldwide skincare industry through the application of the company's patented Particle Encapsulation Delivery System (PEDS). PEDS, the result of seminal discoveries from prominent research physicians and scientists, allows the safe encapsulation of dyes, pigments, and active pharmaceuticals to the skin, through the skin, or under the skin. Freedom-2's product pipeline includes aesthetic, cosmetic, and therapeutic solutions.

Currently the company is encapsulating a highly effective ingredient for blocking UVA and UVB rays in microscopic polymer beads to produce a safer, stronger sunblock. Also under development is a facial rejuvenation product based on Clear™ microscopic beads. The company is actively exploring drug delivery systems using an erodible bead technology for time-released delivery of active pharmaceutical products. Researchers working on treatments for diseases resistant to other types of treatment, such as hepatitis and AIDS, are reviewing PEDS as a drug delivery system.

"Our research scientists and market specialists are at work refining and preparing new products," stated Martin Schmieg, president and CEO. "Including both direct and collaborative market opportunities, our annual product pipeline is projected to bring in excess of $1 billion in annual revenues." For more general company information, visit www.freedom2inc.com.

Vyteris Announces Plans to Pursue Strategy for Transdermal Drug Delivery Technology

Business Wire: June 11, 2008 – FAIR LAWN, N.J. – Vyteris, Inc. (OTCBB: VYHN), manufacturer of the first FDA-approved active patch transdermal drug delivery system, has informed its shareholders of important plans to pursue an aggressive partnership and licensing strategy for its transdermal drug delivery technology, as well as restructuring of its board, management, and capitalization.

"With the recent changes made to strengthen the company's management and strategic plan, we believe we are in a stronger position to pursue our key objectives for development of our Smart Patch technology in additional pharma product lines," said Donald F. Farley, executive chair of Vyteris, Inc. "The development program with Ferring has shown successful demonstration of peptide molecule delivery and attempts to forge partnerships with other peptide drug developers is a roadmap we will aggressively pursue." In a letter to Vyteris shareholders, which was made public by the company in an 8-K

filed with the SEC, Farley outlined the company's strategic focus moving forward in three key areas:

Basic Phase I clinical testing goals have been completed, and optimization studies to determine best dosage and related variables are in progress. Vyteris is progressing in manufacturing planning for Phase II clinical supplies and is poised to meet needs when Ferring makes the decision to initiate Phase II. Under the current agreement with Ferring, a $2.5 million milestone payment will be earned when Ferring elects to initiate Phase II clinical trials, and a $3.0 million milestone will be earned at commencement of Phase III.

Based on Vyteris' prior experience with peptide feasibility work and progress-to-date with the Ferring project, a comprehensive program is being launched to identify and secure another peptide development program in 2008, to manage a biotech outreach initiative to secure additional peptide collaborations for 2009, and, finally, to establish a licensing initiative for new peptides.

A number of biopharmaceuticals have been qualified as ideal candidates for Vyteris' Smart Patch technology. In some cases, preliminary feasibility work has already been completed. Vyteris now plans to undertake a much more active role in generating collaborative development programs in this area, including targeting pharma company's proprietary molecular candidates and seeking to engage them in a collaboration aimed at extending patent life, improving therapeutic outcomes and/or creating a generic specialty, and selecting specific generic molecules or those approaching the end of their patent lives and initiating proposals for a development program. Vyteris will take a leadership role and recruit pharma partners.

Nastech Initiates New Corporate Direction with Name Change to MDRNA, Inc. and Appointment of J. Michael French as Chief Executive Officer

Business Wire: June 10, 2008 – BOTHELL, Wash. – Nastech Pharmaceutical Company Inc. (Nasdaq: NSTK - News) has announced that having acquired shareholder approval, the company has changed its name to MDRNA, Inc. (MDRNA). MDRNA will leverage its scientific and intellectual property (IP) position surrounding the research, development, and delivery of Dicer substrates and Meroduplex (mdRNA) RNA interference (RNAi) drug candidates to build an industry-leading position in the development and commercialization of RNAi-based therapeutics. In addition to its license through the City of Hope to Dicer substrate IP, MDRNA will leverage its portfolio of delivery IP, including an issued patent on the Trp Cage phage display library for generating tissue-homing peptides.

As part of its new corporate and scientific focus, MDRNA has named J. Michael French, formerly of Sirna Therapeutics, as chief executive officer. Mr. French succeeds Steven C. Quay, M.D., Ph.D. Dr. Quay has been appointed chief scientific officer and chair of MDRNA's Scientific Advisory Board and will remain chair of the Board of Directors.

"I am thrilled to join MDRNA and be a part of this truly exciting science," stated Mr. French. "I look forward to working with this exceptional MDRNA team to establish an industry leading position in the emerging field of RNAi. With Dr. Quay leading an outstanding group of young, bright and energetic researchers, I believe we will make significant strides in the coming months to further demonstrate efficient delivery and therapeutic effectiveness of our RNAi-based therapeutics. In establishing an industry-leading position, we are aggressively pursuing partnerships with major biopharmaceutical companies while advancing a pipeline of pre-clinical product candidates. We look forward to reporting our progress over the next six months." Dr. Quay commented, "I am looking forward to focusing my attention on the further development of our core delivery technologies and the rapid advancement of our preclinical pipeline of novel MDRNAi and siRNA drug candidates toward human clinical development. This is an exciting time for me and our world-class scientific team as we continue to capitalize on the breakthroughs we have made in developing safe and effective RNAi-based therapeutics."

MDRNA is currently pursuing pre-clinical RNAi programs in influenza and rheumatoid arthritis, from which it will identify appropriate target candidates for partnering and clinical development. The company believes it has been building one of the broadest and deepest patent estates in the RNAi field, with more than 260 filed patents addressing 144 gene sequences, including numerous disease-validated targets. Concurrently, the company is seeking to monetize its legacy nasal drug delivery business through licensing, partnering, or acquisition of its Phase II intranasal programs, including its ultra-rapid–acting insulin for diabetes, peptide YY3-36 for obesity, and parathyroid hormone (PTH1-34) for osteoporosis.

Mr. French was senior vice president of corporate development at Sirna Therapeutics, one of the leading RNAi companies, from 2005 until 2007, when the company was acquired by Merck. Previously, Mr. French was chief business officer for Entelos, Inc., a pre-IPO biotechnology company, and held a variety of positions at other healthcare companies, including HealthIQ, Farma Biagini, and Bayer Pharmaceuticals. Mr. French holds a M.S. degree in physiology and biophysics from Georgetown University and a B.S. degree in aerospace engineering from the United States Military Academy.

MAY 2008

Nuvo Licenses Topical Pain Product From Paladin

CNW: May 29, 2008 – MISSISSAUGA, ON, Canada – Nuvo Research Inc. (TSX: NRI), a Canadian drug development company focused on the research and development of drug products delivered to and through the skin using its topical and transdermal drug delivery technologies, has announced that it has licensed the exclusive rights from Paladin Labs Inc. (TSX: PLB) to develop and commercialize a novel topical pain formulation with the potential to treat inflammatory and

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neuropathic pain conditions. The formulation is in the pre-clinical formulation development stage and is the subject of a pending patent application.

Nuvo will issue to Paladin 961,538 common shares having a value of $125,000 for the right to commercialize this topical pain product. As part of the transaction, Paladin may receive an additional payment of $250,000 upon achievement of a regulatory milestone and will have rights to market, distribute, and sell the product in Canada, South America, Central America, and South Africa. Nuvo will receive royalties on Paladin sales and will have exclusive rights to exploit the licensed formulation in all other territories, including the United States.

"We are pleased to expand both our relationship with Paladin and our topical analgesic drug pipeline," said John London, Nuvo vice chair. "Paladin's investment further strengthens our financial position as we continue to develop our early stage pipeline and move toward our resubmission of Pennsaid for US approval in early 2009."

"The topical pain market is growing at a rapid rate and Nuvo, with its San Diego based transdermal research centre, has established a global leadership position in terms of people, technology and infrastructure to successfully develop topical formulations and obtain regulatory approval for this promising pain product," said Jonathan Ross Goodman, president and CEO of Paladin. "We are pleased to license this technology to Nuvo and look forward to marketing and selling it in the future."

Biojector® 2000 Technology Put to the Test in CDC Flu Vaccine Study

Business Wire: May 27, 2008 – PORTLAND, Oreg. – Bioject Medical Technologies Inc. (Nasdaq: BJCT), a leading developer of needle-free injection therapy (NFIT) systems, has announced that the Biojector® 2000 (B2000) needle-free system has advanced to Phase II in a clinical study sponsored by the Centers for Disease Control and Prevention (CDC). The trial, performed in the Dominican Republic, evaluates influenza vaccine using a reduced dose delivered into the skin via an intradermal (ID) route compared with similar and standard larger doses delivered intramuscularly (IM) by conventional needle and syringe. The study is a prospective, phased, randomized, investigator, and parent-blinded controlled comparison of therapeutic activity (immunogenicity) and safety/side effects (reactogenicity) in infants and toddlers from 6 to 23 months of age.

The ID route of vaccination is of interest for influenza and other diseases for which vaccines may be in short supply in a pandemic or otherwise unaffordable in developing countries. Prior studies found that reduced doses in the skin often work just as well as full doses injected into fat or muscle. Such "dose sparing" might extend protection to more people than otherwise would be possible. The influenza pandemic preparedness plans of both the U.S. government and the World Health Organization have identified such research as a priority.

ID injection by the traditional needle method, however, is difficult and requires extra training and experience by health workers to perform correctly. An intradermal spacer on the B2000 injector provides a quick and simple method to deliver such doses. A needle-free system also eliminates other drawbacks of needle syringes, including needlestick injuries and, in many countries, improper unsterile reuse and unsafe disposal of needle waste. The CDC decided to use the B2000 because its ID spacer had the most clinical use in adult studies to justify its investigational use in children. Phase I of the still-blinded trial is now complete, and its safety results were presented in a poster presentation at the 11th Annual Conference on Vaccine Research, in Baltimore, MD, during May 2008 (www.nfid.org/pdf/conferences/vaccine08abstracts.pdf). An independent data safety monitoring board reviewed unblinded results from Phase I and deemed the study safe and ethical to proceed to its larger Phase II study, which began in April 2008.

"We are hopeful this study will determine whether intradermal vaccination by needle-free jet-injector will be of practical use in young children, who are particularly vulnerable to influenza," said Dr. Bruce G. Weniger of CDC, U.S. principal investigator and sponsor of the study. "If it works, developing country health officials would have additional options to better protect their populations against this serious disease," Dr. Weniger added.

"This study is very well designed to carefully evaluate the safety and effectiveness of our needle-free injection device for the intradermal delivery of reduced-dose influenza vaccine," said Dr. Richard Stout, MD, executive vice president and chief medical officer of Bioject. "We are delighted that the B2000 was selected to be included in this important CDC study which aims to benefit patients in the developing world, and look forward to results from the trial's ongoing Phase II," he continued.

The influenza vaccine studied is Vaxigrip®, manufactured by Sanofi Pasteur in France. Participant children who receive reduced doses will afterward get a full dose to ensure protection. All children will get a bonus dose 6 months later for the next influenza season. For more information about Bioject, visit www.bioject.com.

Osmotica Pharmaceutical Receives FDA Approval to Market Novel Forms of Extended-Release Venlafaxine HCl

Business Wire: May 23, 2008 – WILMINGTON, N.C. – Osmotica Pharmaceutical Corp. has received notice of final approval for its venlafaxine hydrochloride extended-release 37.5-, 75-, 150-, and 225-mg tablets NDA from the FDA for major depressive disorder and social anxiety disorder. The Osmotica product provides a controlled release tablet form of venlafaxine HCl, including a previously unavailable 225-mg dosage strength. Equal doses of venlafaxine HCl extended-release tablets are bioequivalent to Effexor XR® capsules, a leading product marketed by Wyeth, when administered under fed conditions. Osmotica expects to launch the new product line for the two FDA-approved indications in the near future.

Forrest Waldon, CEO of Osmotica Pharmaceutical stated, "We are excited about the approval and pending launch of this innovative product. The combination of our Osmodex® controlled release technology with the venlafaxine molecule has allowed us to bring a dosage strength not currently available to the marketplace. We are evaluating proposals from potential marketing partners and expect to make the final marketing decisions in the near future." For more information, visit www.osmotica.com.

Drug Delivery Success Rates and Development Times Defined in Report from Bionumbers, LLC

Drug Week via NewsEdge (NewsRx.com): May 15, 2008 – Bionumbers, LLC has announced the publication of the first report in its "Parameters of Performance" series: "Drug Delivery 2008 – Product Success Rates and Development/Approval Times." The report is based on an analysis of more than 430 products in development from 1993 to 2007 and evaluates the impact of multiple development parameters on success rates and development times for drug delivery products. The Bionumbers report estimates the overall success rate for drug delivery development products to be 26%. This figure was found to vary by class from 0 to 90% depending on definable parameters associated with the drug delivery product. The average time to product approval was 5.7 years, with a range of 2 to 13 years.

"This report provides the first detailed analysis of the development times and success rates for drug delivery products and will be of interest to companies developing products in this sector, their partners and investors," stated Josef Bossart, author of the report and managing director of Bionumbers, LLC. "The data provided in this report will play a critical role in refining the way companies forecast the development and approval performance of drug delivery products. The overall 26% success rate is surprising relative to the 20% success rate quoted by the Pharmaceutical Research and Manufacturers Association (PhRMA) for new chemical entity pharmaceuticals, and the sense among industry professionals that drug delivery products have a much higher success rate. The report finds that it is possible to improve the success rate to well over 50%; but only when the parameters are understood and appropriately managed."

In addition to an overall success rate, the report analyzes the impact of a wide range of variables on product approval success rates and development and approval times. Both corporate status and technology platform validation status were found to have a remarkably high impact on success rates and approval times.

The report includes an easy-to-use algorithm that permits companies to estimate their own product development and approval times based on the report findings. The report is available for $8,300 in Adobe Portable Document Format (PDF) (www.bionumbers.com).

NewLysozymes Findings from Georgia Institute of Technology

Vaccine Weekly via NewsEdge (NewsRx.com): May 15, 2008 – New research, "Dissolving Microneedles for Transdermal Drug Delivery," is the subject of a report. "Microfabrication technology has been adapted to produce micron-scale needles as a safer and painless alternative to hypodermic needle injection, especially for protein biotherapeutics and vaccines. This study presents a design that encapsulates molecules within microneedles that dissolve within the skin for bolus or sustained delivery and leave behind no biohazardous sharp medical waste," researchers in the United States report.

"A fabrication process was developed based on casting a viscous aqueous solution during centrifugation to fill a micro-fabricated mold with biocompatible carboxymethylcellulose or amylopectin formulations. This process encapsulated sulforhodamine B, bovine serum albumin, and lysozyme; lysozyme was shown to retain full enzymatic activity after encapsulation and to remain 96% active after storage for 2 months at room temperature. Microneedles were also shown to be strong enough to insert into cadaver skin and then to dissolve within minutes. Bolus delivery was achieved by encapsulating molecules just within microneedle shafts. For the first time, sustained delivery over hours to days was achieved by encapsulating molecules within the microneedle backing, which served as a controlled release reservoir that delivered molecules by a combination of swelling the backing with interstitial fluid drawn out of the skin and molecule diffusion into the skin via channels formed by dissolved microneedles," wrote J. W. Lee and colleagues, Georgia Institute of Technology.

The researchers concluded "that dissolving microneedles can be designed to gently encapsulate molecules, insert into skin, and enable bolus or sustained release delivery." Lee and colleagues published their study in *Biomaterials* (Biomaterials, 2008;29(13):2113-2124). For additional information, contact J. W. Lee, School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, 311 Ferst Drive, Atlanta, GA 30332, U.S.A.

New Drug Development Study Findings Have Been Reported by Researchers at China Pharmaceutical University

Drug Week via NewsEdge (NewsRx.com): May 15, 2008 – Investigators have published new data in the report "A Novel System for Three-Pulse Drug Release Based on 'Tablets in Capsule' Device." "The objective of the present study was to obtain programmed drug delivery from a novel system, which contains a water-soluble cap, impermeable capsule body, and two multi-layered tablets. Types of materials for the modulating barrier and its weight can significantly affect the lag time (defined as the time when drug released 8% of the single pulse dosage)," scientists reported in the *International Journal of Pharmaceutics*.

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"We chose sodium alginate and hydroxy-propyl methyl cellulose (HPMC E5) as the candidate modulating barrier material. Through adjusting [the] ratio of sodium alginate and lactose, lag time was controllable between the first two pulsatile release. [A] linear relationship was observed between the ratio and the lag time. Through adjusting the ratio of HPMC E5/lactose, lag time between the second and the third pulse can be successfully modulated. In further studies, [the] drug release rate of the second pulsatile dose can be improved by adding a separating layer between the third and the modulating barrier layer in the three-layered tablet. To evaluate [the] contribution of [the] bulking agent to drug release rate, lactose, sodium chloride, and effervescent blend were investigated. No superiority was found using sodium chloride and effervescent blend. However, lactose favored it," wrote B. Li and colleagues, China Pharmaceutical University, Department of Pharmaceutics.

The researchers concluded, "The results reveal that programmed drug delivery to achieve pulsatile drug release for three times daily can be obtained from these tablets in capsule system by systemic formulation approach."

Li and colleagues published their study in the *International Journal of Pharmaceutics* (International Journal of Pharmaceutics, 2008;352(1-2):159-164). Additional information can be obtained by contacting B. Li, School of Pharmacy, Dept. of Pharmaceutics, China Pharmaceutical University, NanJing, Jiangsu 210038, PR China.

Akela Pharma Wins Best Abstract Reward at the 11th Asia Pacific Congress of Nephrology

CNW Telbec: May 14, 2008 – MONTREAL, QC, Canada – Akela Pharma Inc. (TSX: AKL), a drug development company focused on developing therapies for the inhalation and pain markets, has announced that it won the Best Abstract Reward at the recent 11th Asia Pacific Congress of Nephrology in Kuala Lumpur in the International Abstract category for its GHRH Phase II results abstract.

"We are very proud to see the great results obtained in our GHRH Phase II trial recognized at such a prestigious event. The results which showed after only 28 days of treatment a marked improvement in the nutritional status of patients along a significant increase in fat-free mass and a significant decrease in fat mass are a testimony to the superior efficacy of our product. " said Dr. Halvor Jaeger, chief executive officer of Akela Pharma Inc.

Akela's proprietary 29 amino-acid peptide analogue of GHRH is designed to stimulate growth hormone secretion in patients. Positive results from its previous Phase I/II trial showed that after administration of AKL-0707, a rapid and very significant increase in the levels of growth hormones occurred at all dosage levels without significant adverse events.

Akela Pharma is an integrated drug development company focused on developing therapies for the growing multi-billion dollar inhalation and pain markets. Its lead product, for the treatment of breakthrough cancer pain, is a fast-acting fentanyl formulation delivered using the company's TAIFUN® dry powder inhaler platform. Its pipeline also includes therapeutics for asthma, COPD, growth hormone deficiencies, and controlled substance abuse deterrent formulations. For more information, visit www.akelapharma.com.

QLT Reports Initial Proof of Concept Data for Punctal Plug Delivery Technology

CNW: May 12, 2008 – VANCOUVER, BC, Canada – QLT Inc. (NASDAQ: QLTI; TSX: QLT) has announced results from a proof-of-concept trial conducted by QLT's wholly owned subsidiary, QLT Plug Delivery, Inc., on its punctal plug drug delivery technology. The results demonstrated that QLT's drug elution technology was effective in controlling intraocular pressure (IOP) and was well tolerated.

The proof-of-concept, open-label study was initiated to determine whether sustained administration of latanoprost using the company's punctal plug drug delivery technology could lead to a reduction in IOP over 90 days when administered using a conventional plug design. Five patients (10 eyes) with glaucoma or ocular hypertension were enrolled at a single center. The primary efficacy endpoint was measurement of IOP. At baseline, the mean IOP was 23 mmHg for the 10 eyes treated. At the 90 day follow-up, the mean IOP was reduced to 17 mmHg for the six eyes that remained. Data from two patients were excluded due to loss of plugs. No significant adverse events were reported.

"We are very pleased to report positive results from this preliminary proof of concept trial," said Bob Butchofsky, president and chief executive officer of QLT. "Although the number of patients is small, we are encouraged by the clinically meaningful reduction in IOP that was observed and sustained for approximately 90 days. We look forward to providing you with additional details from this study at our Annual General Meeting on Wednesday, May 14."

The objective of QLT's punctal plug program is to demonstrate that the company's drug elution technology leads to a statistically significant reduction in IOP for 90 days and that its proprietary punctal plug design can be retained comfortably in a high percentage of patients during that time period. The trial results are an early indication that QLT's drug elution technology has the potential to provide a meaningful therapeutic benefit. To generate proof of concept data for the company's proprietary punctal plug drug delivery system, QLT is currently enrolling patients in the CORE study, a Phase II, randomized, double-blind trial to assess the safety and efficacy of its latanoprost punctal plug delivery system for the treatment of glaucoma and ocular hypertension at three different doses (low, medium, high). The medium dose of latanoprost in the CORE study was used in the trial.

Generex Biotechnology Announces That It Has Produced MetControl, the Company's Proprietary Metformin Chewing Gum Product for Upcoming Clinical Study

Prime Newswire: May 12, 2008 – WORCESTER, Mass. – Generex Biotechnology Corporation (NasdaqCM: GNBT - News), the leader in drug delivery for metabolic diseases through the inner lining of the mouth, has announced that it has produced clinical samples of MetControl™, the company's proprietary Metformin chewing gum product. These samples have been manufactured under GMP conditions and will be used in an upcoming trial; the results from which will allow the company to proceed with additional R&D initiatives and consider regulatory agency registration applications. The protocol for the MetControl study is an open-label crossover study comparing MetControl™ and immediate release tablets in healthy volunteers. The company anticipates that approximately 36 patients will participate in the study.

Metformin is a generic drug used to regulate blood glucose levels by reducing liver glucose production and improving the insulin sensitivity of cells. Through this action, Metformin allows the insulin produced by the body to be used more effectively and ultimately reduces the amount of glucose in the blood.

Metformin is the backbone of almost all treatments for Type 2 diabetes mellitus. It has a broad range of beneficial qualities for this extremely complex disease. Despite the fact that it is the most prescribed drug for Type 2, there are still millions who do not use it because of a variety of factors, including gastrointestinal side effects, large pill size, and bitter taste (especially in the burgeoning population of children with Type 2 diabetes). The delivery of Metformin in a good tasting chewing gum format may make the drug more acceptable to these patients and, thereby, may increase compliance with the therapy.

The R&D path that leads to commercialization of this product is not anticipated to be as lengthy as a typical NCE (new chemical entity), as Metformin itself is not a new active compound. It is a well-established active that has been accepted globally for the treatment of patients with diabetes.

"We are pleased to have completed this significant milestone with respect to our medicinal chewing gum product," said Rose Perri, the company's chief operating officer. "This represents the expansion of the company's proprietary drug delivery platform as it utilizes the core science behind the company's RapidMist™ delivery system in another form and application." ■

Calendar of Events

2008

1st Asian Pharmaceutical Technologies Arden Conference

October 30-November 2
BTG Fragrant Hill Hotel
Beijing, China
www.cpa.org.cn/arden/arden.htm

CRS/AAPS Joint Workshop: Critical Variables in the *In Vitro* and *In Vivo* Performance of Parenteral Sustained Release Products

November 15-16
Georgia World Congress Center
Atlanta, Georgia, U.S.A.
www.aapspharmaceutica.com/meetings/meeting.asp?id=134

2008 AAPS Annual Meeting and Exposition

November 16-20
Georgia World Congress Center
Atlanta, Georgia, U.S.A.
www.aapspharmaceutica.com/meetings

2009

ISOPS 9th International Symposium on Pharmaceutical Sciences

June 23-26
Ankara University, Faculty of Pharmacy
Ankara, Turkey
www.pharmacy.ankara.edu.tr

36th Annual Meeting & Exposition of the Controlled Release Society

July 18-22
Bella Center
Copenhagen, Denmark
www.controlledreleasesociety.org/main/meetings

2010

37th Annual Meeting & Expostion of the Controlled Release Society

July 10-14
Oregon Convention Center
Portland, Oregon, U.S.A.
www.controlledreleasesociety.org/main/meetings

2011

38th Annual Meeting & Exposition of the Controlled Release Society

July 30-August 3
Gaylord National Resort and Convention Center
National Harbor, Maryland, U.S.A.
www.controlledreleasesociety.org/main/meetings

CRS Delivering Bioactives

Controlled Release Society
3340 Pilot Knob Road
St. Paul, MN 55121
United States of America