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Newsletter

A publication of the Controlled Release Society





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From the Editor

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Contact dwoodard@scisoc.org for information about exhibiting, advertising or other visibility opportunities. Steven A. Giannos Chrono Therapeutics, Inc. Quincy, MA, U.S.A.



"Keep your eyes looking forward. However, now and then, glance back to see where you've come from."

A utumn has always been a time of reflection and thanksgiving for me, seeing as my birthday is late in November and here in the United States it sometimes lands on Thanksgiving. Birthday candles on a pumpkin pie are fun, and the holidays are just around the corner.

This year for the CRS has been another year of changes, both happy and sad. In this time we have increased the number of *Newsletter* issues to five, continuing categories such as Scientifically Speaking, Chapter News, Highlights from the Annual Meeting, From the Vet Group, In The News, and many more. In June, we bid a fond farewell to Dr. Jorge Heller, past president of CRS, renowned scientist, and a humble, wonderful person. In July, we held our annual meeting in Copenhagen, at which the inaugural Joseph R. Robinson Postdoctoral Fellowship was awarded, and rounded out the year with a joint AAPS workshop on the Development and Regulatory Challenges for Controlled Release formulations.

In this issue of the *Newsletter*, we have an interview with Dr. Vladimir Torchilin, Northeastern University, updates from CRS Chapters, a great Spotlight article, and a long In The News section. I am happy to be able to share that while I was assembling the In The News section, I noticed that many of the new drug delivery technologies are now making their way to the market place. Additionally, the lines separating controlled release, drug delivery, and medical devices continue to blur.

The other big news this fall was two big mergers: Pfizer/Wyeth and Merck/Schering Plough. Consolidation continues in big pharma and with it so goes a corresponding impact on our industry. The global financial crisis has affected academia and industry alike. News articles say that the job situation is the same as in 1983, the year when I started to look for a career job. A difficult time, but don't give up hope. You have many more tools to work with this time around.

Many things are different than they were in 1980, when I first learned of controlled release drug delivery. Consumer electronics have brought us e-mail, cell phones, iPhones, and BlackBerrys. Professional networking groups such as LinkedIn and others provide for quick and long-distance networking (join the CRS group on LinkedIn), and the Internet now allows us to view international meetings and attend webinars. And, I can't say enough about the CRS Young Scientist Mentorship/ Protégé Program. Again, hats off to Dr. Michael Rathbone and the program team for allowing experienced scientists to interact and give back to our younger members. Please, everybody, take advantage of these great opportunities to broaden your horizons.

As always, please feel free to send updates on CRS Chapter news, Spotlight articles, business news, and scientific articles to the *CRS Newsletter*.

Wishing you and your families Happy Holidays from the Editors at the *CRS Newsletter*!

Steven A. Giannos



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

"Coming together is a beginning. Keeping together is progress. Working together is success."—Henry Ford

I have a secret, and it's not mine alone. CRS presidents before me have known it. The Boards of Directors and CRS headquarters staff have known it too. And deep down inside, though they might not want to admit it, most CRS members know it as well. At the risk of diminishing your perception of my capable leadership, I'm going to share the secret with you. It is this: Whatever the goal, whatever the issue, whatever the question, the answer is simple—it's **you**.

Q What does it take to increase the number of CRS chapters worldwide?

A You.

- Q What does it take to remain on the cutting edge of new science?
- A You.
- Q What does it take to increase the value of CRS to its members?
- A You.
- Q Who has the power to make a difference through CRS?

A You.

And *you* are not alone. Hundreds of CRS members have discovered another secret. When you get involved in CRS, it benefits not only the Society, it benefits *you* as well.

- Q What can you do to expand your professional network?
- A Get involved.
- Q What can you do to learn valuable skills that will help you grow professionally?
- A Get involved.

Q What can you do to stay on top of the latest advances in your field?

A Get involved.

- Q What can you do to make a lasting difference?
- A Get involved.

Whether you're new to the industry or an experienced professional, whether you're an introvert or an extrovert, whether you are a team member or born leader, whatever your personality and circumstance, there is a place and a purpose for you in CRS. Volunteer to be on a committee, participate in a focus group, join the mentoring program as either a protégé or a mentor, submit an abstract for the 2010 meeting, suggest or conduct a webinar, submit an article to the *CRS Newsletter*, and attend the CRS Annual Meeting & Exposition in Portland, OR, July 10–14, 2010.

I am working diligently with the CRS Board of Directors and the CRS staff to improve communication and increase transparency within our organization. One outcome of these efforts is that it should become easier for members to learn about opportunities and get involved in our organization. Please watch this space and our website to learn more in the upcoming months.

One quick and easy way you can make a difference right now is simply to send me an e-mail. If you're interested in volunteering for a one-time, short-term project, let me know that too. If you might be interested in playing a more significant role in CRS, like serving on a committee, tell me that as well. You can also visit the CRS website, where you'll find a volunteer form under the About Us section.

CRS is about you, and it's about me, but most importantly—it's about what we can do together.

Diane J. Burgess crspresident@scisoc.org

Interview with Dr. Vladimir Torchilin

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



Dr. Vladimir Torchilin

Dr. Vladimir Torchilin is a Distinguished Professor of Pharmaceutical Sciences and director of the Center for Pharmaceutical Biotechnology and Nanomedicine at Northeastern University. From 1998 to 2008 he was the chair of the Department of Pharmaceutical Sciences. Dr. Torchilin was educated at Moscow University, where he received his M.S. degree in chemistry (1968), his Ph.D. degree in polymer

chemistry, chemical kinetics and catalysis (1971), and his D.Sc. degree in chemistry of physiologically active compounds (1981).

Prior to working at Northeastern's Bouvé College of Health Sciences, Dr. Torchilin worked at Massachusetts General Hospital and Harvard Medical School as head of the Chemistry Program at the Center for Imaging and Pharmaceutical Research and as an associate professor of radiology. Prior to that, from 1974 to 1990, he worked at the Institute of Experimental Cardiology at the Russian Cardiology Research Center as head of the Laboratory of Enzyme Engineering and, from 1968 to 1973, at the Chemical Department of Moscow State University.

Over his distinguished career, Dr. Torchilin has been recognized with many awards. In 1982 he received the Lenin Prize in Science and Technology, one of the highest awards in the former Soviet Union. He also recently received the Research Achievements Award in Pharmaceutics and Drug Delivery from the AAPS (2005), the CRS Baxter Healthcare Outstanding Parenteral Drug Delivery Award (2006), the Research Achievements Award from the World Pharmaceutical Congress (2007), Northeastern University Creativity Awards for 2001, 2003, 2004, and 2007, and the Massachusetts Technology Transfer Center Investigation Awards for 2006 and 2008. Dr. Torchilin has received the Outstanding Pharmaceutical Paper Award from the Controlled Release Society (1993), the Journal of Controlled Release Outstanding Paper Award (1993), and the 2009 AAPS Journal Manuscript Award.

Dr. Torchilin is on the Board of Directors for the International Liposome Society, is editor-in-chief for *Current Drug Discovery* Technologies, a co-editor-in-chief for Drug Delivery, and a review editor for the Journal of Controlled Release. Additionally, he serves on the editorial boards of many journals including Bioconjugate Chemistry, Advanced Drug Delivery Reviews, European Journal of Pharmaceutics and Biopharmaceutics, Journal of Drug Targeting, Journal of Microencapsulation, Journal of Bioactive and Compatible Polymers, Journal of Liposome Research, Molecular Pharmaceutics, Current Drug Delivery, Drug Discovery Today, Journal of Biomedical Nanotechnology, Expert Opinion on Drug Delivery, Current Protein and Peptide Science, International Journal of

Nanomedicine, Journal of Biopharmaceutics and Biotechnology, and Recent Patents on Drug Delivery and Formulation.

Dr. Torchilin served as the program chair for the 26th International Symposium on Controlled Release of Biologically Active Materials (1999), co-chair for the Gordon Research Conference on Drug Carriers in Biology and Medicine (2002), and president of the Controlled Release Society from 2005 to 2006. Dr. Torchilin is a Member of the European Academy of Sciences (2002), a Fellow of AIMBE (2002), and a Fellow of AAPS (2003).

We would like to sincerely thank Dr. Torchilin for taking the time out of his busy schedule to prepare this interview with us.

Q When you graduated from Moscow State University with your Ph.D. degree in chemistry, what factors played a role in your decision to stay in academia?

A Moscow State and especially its natural science departments, such as the Chemistry Department, were specifically training future researchers, so the choice of academia was in a sense pre-determined. In addition to that, the level of industrial development in the USSR [during] those years, because of a variety of reasons, was far behind the level of scientific development (especially in large centers such as Moscow, Leningrad, Novosibirsk, Kiev, and others), so very few people who graduated from Moscow State ended up in a real industry. Besides, companies in the way they exist here in the U.S. and even in Russia now did not exist in the USSR at that time. However, some research institutions working specifically to serve certain areas of the industry did exist (such as [the] institute for fertilizers, institute for polymers, etc). Unfortunately, the level of their support and (in general) the level of their researchers were not as good as in universities and institutes belonging to the system of the USSR Academy of Sciences or Academy of Medical Sciences (research only). Sure, some military-related secret institutes were well equipped and scientifically strong, but we are not talking about them here. So, I can hardly imagine myself anywhere except the university or one of academic institutes.

Q What areas of research is your lab currently working on?

A There are several topics we are currently dealing with. First, is the engineering of "smart" multifunctional pharmaceutical nanocarriers, which can switch on and switch off certain properties, depending on the properties of the physiological surrounding, such as pH or temperature. The matter is that many pathological area pH and/or temperature differ a bit from the normal ones. Now, if you can develop a system that can feel these differences and react, you could be able to



develop a really controlled delivery system, which releases, let's say, [a] certain drug only on this pathological area. Second, we are working with drug delivery systems that can penetrate target cells and specifically bring their drug load to certain intracellular organelles, such

as nuclei, lysosomes, etc. This should allow for a very precise drug targeting. Third, we are working a lot with delivery systems for "undeliverable" drugs, i.e., drugs that are very unstable or very poorly soluble. And, we are trying to make them deliverable. siRNA and some cancer drugs are good examples. There are a few other topics I am interested in, but those are the major ones.

Q What role has controlled release played in your research?

A Almost from the very beginning of my independent career, I was working with drug delivery and release. My very first paper in [an] international scientific journal (*Journal of Biomedical Material Research* as far as I remember) was on controlled release. So, I cannot even say that controlled release played a role—I was "entrapped" in this field from the very beginning.

Q Both non-targeted and targeted colloidal systems have been extensively researched in recent years. In your view, what are the pros and cons of each?

A Very serious questions. In brief, I think that the combination of non-targeted delivery and subsequent targeting will bring the best results. If non-targeted delivery, such as the passive accumulation of drugs and drug carriers via, for example, the enhanced permeability and retention (EPR) mechanism, can facilitate drug accumulation in the pathological area, targeted delivery should facilitate its subsequent internalization inside cells via various receptor-mediated targeting processes and even delivery to specific organelles inside cells. So, I wouldn't oppose these two ways of targeting; I'll better look [at] how to combine them. And, this is what we are trying to do in some of our experiments.

Q Would you discuss an example of these experiments?

A Sure. We have recently published a paper in which we have demonstrated how it can work. We made a delivery system loaded with DNA and modified with cell-penetrating peptide to better bring this DNA inside cells. Then, we grafted the whole system with polyethylene glycol–polymer, which completely covered the system, and [the] cell-penetrating peptide attached to it and made the nanoparticle longcirculating. Such a nanoparticle can now passively accumulate in areas with increased vascular permeability, such as infarcts and tumors. Inside these areas, the coating polymer detaches because we have used a pH-sensitive bond to attach it to the system, and pH in these area[s] is slightly decreased compared to normal. When this polymeric coat detaches, the cellpenetrating peptide becomes exposed and brings the whole system inside the cell, providing a more effective transfection. Thus, this is a combination of passive and active targeting, and the result is quite good.

Q What are some of the key contributions that active drug targeting has made to cancer research?

A Although many of these studies are still on the experimental level, I would say that our ability to target tumor vasculature or folate receptors on folate receptor-overexpressing tumors is of great practical significance. In addition, the combination of clinically approved anti-cancer antibodies (such as herceptin) with existing drug delivery systems looks very promising.

Q What hurdles still need to be overcome?

A In my opinion, experiment-wise scientists have done a lot. The major problem is making our results scalable and reasonably cheap. Elegant four-step processes to prepare an excellent drug delivery system working perfectly well in an experiment may be the subject of an important publication, but most probably will never make it to the clinic because of complexity and final price. Together with industry we have to develop schemes that should be reasonably easy and cheap to scale up and produce. Sometimes, we are so much involved in the beauty of our experiments that we do not think much about the real practical future of our results.

Q How has the use of colloidal delivery systems changed the field of imaging? What role will these imaging agents play in medical diagnosis/treatment?

A I cannot say it did change the field of imaging. It just helped a lot. Think about novel MRI contrasts based on superparamagnetic iron oxide nanoparticles or about gas-filled lipid bubbles for ultrasonic imaging. The use of such agents helps to get diagnostic images faster and with more information. Still, the same imaging modalities—gammascintigraphy, X-rays, NMR and ultrasound—are used; we just use the colloidal delivery systems for faster and more informative imaging.



Interview continued on page 6

Interview continued from page 5

I would like to add that colloidal delivery systems allow for what is now called theranostics—the combination of therapeutic and diagnostic properties in one nanoparticle. This should simultaneously allow us to follow a real-time biodistribution of the drug and the efficacy of therapy. This would be impossible with traditional approaches.

Q What do you think the future holds for controlled drug delivery? What role will colloidal delivery systems play?

A I think the prospects are great. The field is developing into a multibillion [dollar] industry with important products to improve human life. If today, we have in total about 40 different products on the market that are based on delivery systems and controlled release, I expect this number to grow exponentially over the next few years.

Ideally, colloidal delivery systems should result in therapeutic and diagnostic (or even theranostic) agents with simplified administration schemes, lesser toxic effects, and better specific targeting to disease areas. What else can one expect? We just have to try to make our system of medical care affordable.

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

A Hard to say. Over the years, I worked with different things, and some studies were good enough. But, if you would consider their general significance, not just the significance for myself and my career, I didn't change the world or even the field. But, what I am especially proud of is that one of my earlier studies (in the mid-70s) on the preparation of polymermodified enzymes resulted in a real, very efficient and safe thrombolytic drug—dextran-modified streptokinase—which under the trade name of Streptodekaza became one of the first (if not the first) polymeric drugs approved for clinical use and has been industrially produced and clinically used in the USSR since 1979.

Q Could you provide a reference to a scientific paper concerning the above studies?

A I had several Russian and international patents on this product, and the summary of our scientific studies in this direction were published in two papers:

Torchilin, VP, Maksimenko, AV, Mazaev, AV. Immobilized enzymes for thrombolytic therapy, Methods Enzymol. 137: 552-566 (1988).

Torchilin, VP, Maksimenko, AV, Mazaev, AV. Immobilized thrombolytic enzymes for systemic and local application, Ann. N.Y. Acad. Sci. 501:481-486 (1987).

But the real early clinical data were published in

Chazov, EI, Smirnov, VN, Suvorova, LA, Suvorov, AV, Mazaev, AV. Effect of the new Soviet thrombolytic preparation

streptodecase on the fibrinolysis system, Kardiologiia Aug. 21(8): 18-21 (1981). Russian.

The usefulness of the thrombolytic therapy in diseases of the cardiovascular system, complicated or caused by thromboses, is beyond doubt. However, the existing medicinal forms of fibrinolytic enzymes possess a number of disadvantages which limit their use. To enhance the efficacy of thrombolytic therapy a streptokinase, named streptodekase, has been created and immobilized on a watersoluble matrix. Streptodekase was tested on the haemocoagulation system in 7 patients with thrombosis of the femoral artery or the branches of the pulmonary artery. It was seen that streptodekase causes a considerable and rapid increase of fibrinolysis without unwanted disorders in the blood coagulation and other side effects. The convenience in use and simplicity (the therapeutic dose of 3,000,000 units is administered in a single injection, intravenously and immediately), the safety and high specific activity permit one to think that the drug may be widely used.

Chazov, EI, Golikov, AP. Use of streptodecase in acute myocardial infarct, Kardiologiia Dec. 21(12): 10-14 (1981). Russian.

This if the first time in the world that streptodecase has been used as a fibrinolytic drug during the first hours of clinical manifestations of myocardial infarction in 12 patients. The drug was given once, intravenously in the dose of 3,000,000 units. Favourable action of the drug on the clinical manifestations of the disease and its prolonged activating effect on the blood fibrinolysis have been established. The advantages of streptodecase over streptokinase in the treatment of acute myocardial infarction are discussed.

Q Could you explain the concept of polymer-modified enzymes in further detail?

A Many enzymes are used as drugs, such as thrombolytic enzymes to treat cardiovascular diseases or enzymes to treat cancer. Enzymes are very effective drugs, unfortunately they have some intrinsic drawbacks—low stability in biological surroundings, antigenicity, and immunogenicity. In the '60s, [a] whole science named "enzyme engineering" emerged aiming to engineer enzyme-containing systems, where "bad" properties of enzymes are eliminated, but "good" properties remain unchanged. Part of enzyme engineering was dealing with therapeutic enzymes. One of the approaches was to modify enzymes with certain biocompatible polymers, which allowed better stabilization and diminished their antigenicity. Now, this is a common approach, and there are several polymer-modified proteins on the market, but this was not the case in early '70s when I began to work with streptokinase to make this enzyme more stable and less antigenic.

Q Could you recommend a publication or two that would be of particular interest to our CRS readers?

A Are you asking about general publication in the field, or about publications I'm personally involved in? If in general, those are too numerous to be listed. We have a good dozen new books on drug delivery, nanomedicine, etc. published each year, and



many dozens of good review papers. If about my own, I would name the books on nanoparticulates as pharmaceutical carriers, which I have edited for Imperial College Press in 2006, and on multifunctional pharmaceutical nanocarriers, which I have edited for Springer in 2008, and a couple of recent reviews:

Torchilin, VP. Recent approaches to intracellular delivery of drugs and DNA and organelle targeting, Annu. Rev. Biomed. Eng. 8: 343-375 (2006)

Torchilin, VP. Multifunctional and stimuli-sensitive pharmaceutical nanocarriers, Eur. J. Pharm. Biopharm. 71: 431-444 (2009).

Q What personal attributes have allowed you to be so successful?

A I don't know to [what] extent I am really successful. There are a lot of good scientists in our field, including those who, in my opinion, are better and more successful than I am. Still, I always liked what I was doing, and I always was eager to learn. Fairly, I hope I still am.

Q How has working in Boston, a major hub of scientific thought and activity, impacted your career?

A I think the possibility of direct communication and interaction with your peers from other institutions is extremely important. And, certainly Boston provides many opportunities for that. My lab actively collaborates with such institutions as Harvard Medical School, Massachusetts General Hospital, Beth Israel, Tufts University, and Boston University. We have joint grants and joint publications. Certainly, it is very stimulating. In addition to that, we can visit multiple lectures and scientific seminars in the area, and this is also very useful.

I have to add, however, that with the development of novel communication technologies, it has become much easier to collaborate even with rather distant institutes not located in Boston. We have very interesting joint projects with Auburn University and with Louisiana Tech right now. Still, science and colleagues in Boston are just great.

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

A There are several names of key importance in my scientific life. My first teacher, who eventually became a very dear friend, Professor Victor Kabanov from the Moscow State. Unfortunately, he is no longer with us, but I still am trying to follow [the] advice he gave me years back. Professor Evgenii Chazov from the Russian Cardiology Research Center, who was the first to put medicine-related task[s] in front of me and explain how important these tasks are. After that, my whole scientific life became medically oriented. Professor Edgar Haber-stellar scientist and physician-who passed away a few years back. He was the one who invited me to collaborate with his lab in Mass General when I was still in Moscow and eventually was my guide through American science and American life. And, Professor Gerry Wolf, who invited me to work in his Center at MGH after I emigrated to the U.S. and created absolutely magnificent conditions for my research. I was lucky to meet and work with such people.

Q Outside of your scientific endeavors and rooting for the Boston Red Sox, what other hobbies do you enjoy?

A Not an easy question. First of all, I have to admit that though I certainly follow the Red Sox, I didn't become a real fan, and sometimes still prefer to watch soccer. Regarding other hobbies, my problem is that I have far too many of those, which probably negatively influenced my scientific outcome over the years. But, what can I do? It is stronger than I am. I am a crazy collector-I have a very big library of a few thousand books, with many of them antiquarian books. I also collect art, mainly Russian, but also some international art too. So, I experience a great wall space shortage in my house. I like music, and even with my library of approximately 1,000 CDs, I still try to go to the Boston Symphony every other week. And, on top of that, I am also an author, who [has] published already four books of short stories in Russian and numerous stories in Russian language literary magazines both in Russia and [the] U.S. So, the life is pretty busy...

Q Would you mind sharing a couple of these references for the reader who may be interested in more than you scientific writings?

A Only if those people can read Russian. There are two options go to the site http://magazines.russ.ru and print my name in a search box. It will show quite a few of my publications in various literary magazines. The other option—go to Amazon. com; they still could have some of my books—Vladimir Torchilin. Povezlo (The Lucky One), or Vremya Mezhdu (Time in Between), or Kruzok Druzei Avtandila (The Circle of Avtandil's Friends). ■

Portland 2010

Ijeoma F. Uchegbu Professor of Pharmaceutical Nanoscience CRS Scientific Secretary



Ijeoma F. Uchegbu

Members, members, the world is emerging from recession, stocks are up, and Portland is eagerly waiting for your data! "Personalised Medicines and Products for the Next Generation" is our theme for 2010, and your programme chairs have been busy, very busy. Working really hard since last spring, Dave Putnam, Ick Chan Kwon, Leila Zarif, Christophe Barbe, James Oxley, Mike Rathbone, and Jim

Riviere have put together a programme like no other. Highlights include Mauro Ferrari from the University of Texas, who has done some really super work on smart nanomedicines and who will share with us his expertise in the area of biomarkers in cancer chemotherapy. Additionally, Ramin Najafi of NovaBay Pharma will lecture on the secrets of commercialisation. Over the past 12 months, commercialising the fruits of scientific discovery has risen to the top of the agenda; especially now that we know that we cannot rely on banks to create wealth! Now more than ever the world needs the knowledge economy to come to its aid and create real and tangible prosperity, prosperity you can rely on, and no I did not lose money in the bank crash!

In Portland we are going to be experimental and bring on board some unfamiliar topics, such as a session on theranostics, and to celebrate the fact that you can now do well-funded stem cell research in the United States, we have a "Stem Cells, Yes



Portland Skyline with Gov. Tom McCall Waterfront Park and Hawthorne Bridge, by Robert Reynolds.



Peninsula Park Rose Garden, courtesy of Travel Portland/Steve Terrill.

We Can!" session. In our desire to embrace the new, however, we will not be forgetting the warm and familiar, and so there will be your normal meeting favourites, such as sessions on peptide and protein delivery, hydrogels, and of course the ubiquitous oral controlled release. A CRS meeting is never complete without a sell-out oral and controlled release session!

Wanting more already? Well simply get involved! Submit your abstracts online at www.controlledreleasesociety.org before January 31, 2010. This year there are so many topics to choose from there must be one for you. Topics include "Nanoparticles and Fibres for Controlled Release," "New Chemistries for Drug Delivery," "siRNA and MicroRNA Therapies," "Pulmonary Delivery," and then some. The best abstracts will be given a podium slot, so there is a real incentive to do a thorough job of it.

As usual, I shall end by saying something friendly but inconsequential, so please do wrap up warm if you live in the north, wear sunblock (if you need to) and live in the south, and do come to our meeting if you live on the equator.

I look forward to reading your abstract.





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New Focus Groups Welcome

Ijeoma Uchegbu Chair in Pharmaceutical Nanoscience CRS Scientific Secretary

Have you ever wanted to listen to a talk on a particular topic or a talk by your most admired scientist? Have you ever wanted to just sit down and have a chat about the latest scientific discoveries, because they impact your work? Well, now you can get together with like-minded people, discuss your science, and showcase it to CRS members. How? Via a Focus Group!



Hamid Ghandehari



Claus Michael Lehr

In 2008, the first three Focus Groups were born: Nanomedicines (led by Hamid Ghandehari and Claus Michael Lehr), Tablet Manufacture (led by Claudia Leopold and Gino Martini), and Oral Drug Delivery (led by Ali Rajabi-Siahboomi). The Nanomedicines and Tablet Manufacture Focus Groups successfully held their first scientific discussion sessions in Copenhagen last summer, and the Oral Delivery Focus Group ran a really successful satellite meeting in Vienna last spring. These three Focus Groups have been so successful that we want more. Additional Focus Groups can only lead to a more vibrant and interactive society.

thr If your appetite is whetted for one of the existing Focus Groups, all you have to do is

attend their meeting at the forthcoming CRS annual meeting in

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Prediction of Plasma Drug Concentration After Oral Administration of Cyclindrical Matrices

M. Grassi,^{1,2} A. Dal Col,¹ R. Lapasin,¹ G. Grassi,³ B. Perissutti,⁴ and D. Voinovich⁴

Introduction

The practical importance of the "mathematical modeling" approach in the controlled delivery field has been recognized for many years, and numerous publications on this topic have been published (1). In particular, the attention of many researchers has been devoted to the mathematical modeling of drug release and absorption following oral administration. Indeed, the oral dosage form represents the most common route for drug administration into the human body, because it leads to better patient compliance and it is very versatile where dosing conditions are concerned. Thus, the possibility of predicting plasma drug concentration following oral administration or of determining some important pharmacokinetic parameters from experimental knowledge of the plasma drug concentration is very useful from both scientific and industrial points of view.

Unfortunately, however, absorption is intrinsically a complex process (2), as it depends on many factors, such as physiological conditions, patient-specific characteristics, and drug/carrier properties. Accordingly, a powerful mathematical model, in principle, should be able to account for drug properties (solubility, Log P, pK, or pK_1 , for example) on one hand and for drug release and absorption on the other hand. In addition, this model should be able to simultaneously account for drug release and absorption, since, in general, these two aspects are correlated as they can influence each other. This last issue is not trivial, as, in this case, the model numerical solution (i.e., the predicted drug plasma concentration) can be very hard in terms of computation. When the release stage must be modeled as a three-dimensional problem (e.g., think about drug release from a nonuniformly drug-loaded cylindrical matrix), the numerical solution can take hours on modern workstations. The usual strategy employed to overcome this problem is to build up a model mainly based on the drug release aspect or, conversely, mainly based on the absorption aspect. The aim of this work is to provide an example of how the drug release and absorption steps can be simultaneously considered once the drug properties are known.

Mathematical Modeling

The proposed mathematical model relies on the assumptions that the gastrointestinal (GI) tract is a well-stirred environment

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(uniform drug concentration in its liquid volume) and that drug permeability is constant along the GI tract. In addition, drug solubility in the release environment is assumed to be pH independent, and matrices undergo neither significant swelling nor erosion in the GI tract (Figure 1). While solid drug dissolution follows an ordinary first-order law, drug diffusion inside the matrix obeys Fick's law. Finally, drug pharmacokinetics can be represented by a one- or two-compartment model with first-order elimination. On the basis of these hypotheses, the model can be applied to polymeric matrices undergoing a rapidswelling process, to already swollen polymeric matrices, or to matrices produced by melt extrusion of hydrophilic and hydrophobic substances. In this last case, in order to simplify the analysis it is assumed that the dissolution of hydrophilic excipients is very rapid compared with the drug, so that drug release occurs from a porous matrix. Regardless of its nature, we suppose that matrix characteristics (such as density, porosity, mesh size, drug concentration) can be different in the four zones indicated in Figure 2 $(h_1, h_2, e_1, and e_2)$. Obviously, inside each zone, matrix uniformity is assumed.

Results and Discussion

Although this model relies on the severe approximation of a "homogeneous" GI tract volume, it can provide interesting information about the dependence of the plasma drug concentration on one important engineering parameter—the shape of the cylindrical matrix. For this purpose, four particular configurations of the cylindrical matrix are considered (Figure 2): uniform, hole, clove, and lock. In each configuration, the black zone is characterized by a higher drug diffusion coefficient $(D_{\rm h})$



Figure 1. Schematic representation of the release-absorption-exchangeelimination process.

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with respect to that characterizing the yellow zone (D_l) . The volume occupied by the black zone is the same in the three configurations (hole, clove, and lock), and the drug amount contained in each configuration (uniform, hole, clove, and lock) is always the same. Simulations are led assuming PK data referring to theophylline (3) (one-compartment model). In particular we set distribution volume = 7,500 cm³, solid drug dissolution constant = 0.1 sec⁻¹; drug solubility = 12.495 mg/ cm³; elimination constant = 2.5×10^{-5} sec⁻¹; absorption constant = 8.0×10^{-5} sec⁻¹; initial drug concentration in the matrix = 600 mg/cm³; $D_h = 6 \times 10^{-5}$ cm²/sec = $10 \times D_i$; matrix height = 0.5 cm; and matrix radius = 0.35 cm. The volume fraction characterized by a higher diffusion coefficient (black zone; Figure 2) has the same value in the clove, hole, and lock

matrices and is equal to one-half of the total matrix volume. Figure 3 shows that when a high diffusion coefficient zone is introduced, plasma drug concentration $(C_{\rm h})$ is neatly increased with respect to the uniform matrix regardless of the matrix configuration considered (hole, clove, or lock). At the same time, the $C_{\rm b}$ trend is heavily influenced by the geometry of the high diffusion coefficient zone, being equal to its extension. Accordingly, appropriate changes in the drug diffusion coefficient and the initial drug concentration in the four zones $(h_1, h_2, e_1, and$ e_2) lead to marked modifications in the plasma concentration trend. Figure 4 illustrates the drug concentration (C) time course taking place in the GI tract environment. An initial C_r increase is followed by a marked decrease due to drug absorption by GI mucosa. Also, in this case, matrix geometry affects the $C_{\rm c}$ time course. Finally, Figure 5 illustrates the amount of drug eliminated $(M_{\rm el})$ (metabolized). In this case, minor differences arise between



Figure 2. Cylindrical matrix composed by four zones $(h_p, h_2, e_p, and e_2)$ differing in density, porosity, mesh size, and drug concentration. Four matrix configurations are considered: uniform, hole, clove, and lock. Black zone indicates a higher drug diffusion coefficient (D_p) with respect to that of the yellow zone (D_p) .



Figure 3. Predicted drug concentration in the blood (C_b) for the four matrix conditions considered (uniform, hole, clove, and lock).



Figure 4. Predicted GI drug concentration (C₂) trend for the four matrix conditions considered (uniform, hole, clove, and lock).



Figure 5. Predicted amount of drug eliminated (M_{tr}) for the four matrix conditions considered (uniform, hole, clove, and lock).

the three configurations (hole, clove, and lock). On the other hand, all of them detach from the uniform configuration that is characterized by a lower (on average) drug diffusion coefficient.

Conclusions

The novelty of this model lies in the possibility of taking into account the mutual influence of drug release, absorption, and metabolism in the presence of a three-dimensional release process. Thus, this model allows the establishment of a rational and theoretical link between *in vitro* and *in vivo* tests. There is a fundamental need to perform a proper design of the delivery system, once drug PK characteristics are known.

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Sokol Blosser Vineyard with Pinot Noir sign courtesy of Doreen Wynja.

Dexamethasone-loaded Nanoengineered Alginate Microspheres as Drug Delivery Carriers for Localized Inflammation Control: Toward Development of an Implantable Glucose Sensor¹

R. D. Jayant² and R. Srivastava School of Biosciences and Bioengineering, IIT Bombay, Mumbai, India

Summary

Even though implantable glucose sensors were developed a few decades ago, there is still no glucose sensor that can work for a long period of time after implantation. This loss of function in vivo is caused by events that affect the sensor itself, i.e., inflammation and biofouling, as well as by changes in the tissue surrounding the sensor, i.e. fibrous capsule deposition. Therefore, in order to develop a consistent implantable glucose sensor that will remain efficient for a long time *in vivo*, it is critical to study and control the effects of the biological surroundings on the sensor itself, as well as to manage tissue reactions to the sensor. A novel approach was developed for co-immobilization of immunomodulating drug and glucose-sensing chemistry inside alginate microspheres for continuous glucose sensing. A layerby-layer self-assembly technique was used to achieve controlled release of encapsulated drug, which will aid in improving sensor functionality and longevity.

Background

Non-invasive and minimally invasive methods for continuous monitoring of glucose have opened new avenues in diabetes care. Commercially available, minimally invasive *in vivo* glucose sensors based on subcutaneously implanted amperometric enzyme electrodes or reverse iontophoresis (1) suffer from several problems, including inaccurate results, low precision, and frequent calibration. Newer, fluorescence-based "smart tattoo" glucose sensors are sought as an alternative solution. The sensor will be implanted under the skin (2,3). Interstitial glucose level changes will be monitored by the sensor and correlated with blood glucose levels. Sensing will be done using simple optical instrumentation; a schematic representation is shown in Figure 1.

The major issue with such sensor implants is the inflammation due to immune response that leads to fibrous encapsulation, calcification, and protein biofouling around the sensor, leading to sensor failure (4,5). Novel nanoengineered alginate microspheres are used as drug delivery carriers to control localized inflammation at the sensor/tissue interface, improving the functionality and longevity of the smart tattoo glucose sensor, which is schematically represented in Figure 2.

- ¹ Previously published as a research paper in the *Journal of Drug Delivery* (16(6): 331-340, 2009).
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Results and Discussion

Uniformly sized alginate microspheres ($60 \pm 10 \mu m$) were prepared using a commercially available droplet generator. The encapsulation efficiency of dexamethasone-loaded alginate microspheres was 77 ± 8%. Polyelectrolyte coating was used to control the burst release. The effect of different nanoengineered coatings on *in vitro* drug release was than studied (Figure 3A). A significant difference (P < 0.05) in cumulative release was obtained.

To achieve 100% drug release in 30 days, a hypothesis was laid out to modulate release kinetics in the desired fashion by mixing appropriate proportions of one or two different types of microspheres. Thus, a mixture of (PAH/PSS)₁-coated and



(A) Implantation (B) Interrogation (C) Readout **Figure 1.** Illustration of "smart tattoo" glucose sensor (McShane, MJ. Topic in fluorescence, Glucose Sensing, Vol. 10).



Figure 2. Schematic representation of components of a "smart tattoo" glucose sensor.





Figure 3. *A*, *Cumulative release profile of uncoated and different* polyelectrolyte-coated alginate microspheres. *B*, *Cumulative release* profile of uncoated and different combinations of uncoated and (PAH/ PASS)₁-coated alginate microspheres.

uncoated microspheres in various ratios was studied for release (Figure 3B). A biphasic release profile constituting an initial burst release and a zero-order release thereafter, which is a characteristic of matrix diffusion kinetics, was observed. Data were fitted to various kinetic model equations and proved to follow the zero-release kinetics. Dexamethasone released at a steady rate of $k = 4.83 \,\mu\text{g/day}$, which is sufficient to combat localized inflammation (5). Cytotoxicity studies were done using the L929 cell line on uncoated and polyelectrolyte-coated microspheres; the results showed excellent (>82%) cell viability.

Conclusions

By altering different combinations of coated and uncoated microspheres, 100% drug release at a steady rate of 4.83 μ g/day was achieved. LBL coatings helped reduce the burst release and prolong the period of drug release. The drug release mechanism was confirmed to be diffusion controlled by the application of mathematical models, and the corresponding drug diffusions were also calculated for all of the polyelectrolyte coatings. Thus, these findings imply that nanoengineered alginate microspheres shows promise as release systems to improve biocompatibility and prolong the life span of implantable smart tattoo glucose sensors.

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Accu-Break[™] Offers a Solution to Lack of Dose Flexibility in Controlled Release Products

Geoff A. Green, Carolyn Berg, and Norma Valdez Accu-Break Pharmaceuticals Inc., Plantation, FL

Accu-Break Pharmaceuticals, Inc. (ABP) is on a mission to develop innovative pharmaceutical tablet technologies to fulfill the unmet medical need for accurate, customizable solid oral dosing. The idea behind Accu-Break Technologies is simple: create tablets that can be swallowed whole or, if desired, easily subdivided by hand into exact smaller doses. The unprecedented functionality enables patients and caregivers to safely split tablets, including controlled release tablets, to achieve inbetween or lower than marketed doses—an important feature for medications that frequently undergo titration and/or dose adjustment.

Like the idea, the technology is simple. The company has rearranged the inactive ingredients to create a multilayer tablet that contains both a drug-free layer, and an active drug layer(s). The drug-free layer, comprised of excipients, serves as a break region, and partial doses are obtained by splitting the tablet through this layer. The tablet structure enables risk-free tablet splitting, avoiding inaccurate doses, loss of mass, and product waste. The technologies can be applied to immediate release (IR) and controlled release (CR) formulations, as well as combinations of medications and different formulations. This has important implications for CR medications, as most current CR dosage forms are available as either capsules or unscored tablets that are unsuitable for splitting due to potential changes in the release kinetics when the dosage form is modified.

Data first reported at the 2009 Controlled Release Society meeting in Copenhagen suggest that for all of the conveniences offered by oral CR medications, there exists a significant lack of dose flexibility, making dose adjustments a potentially costly problem (1). A review of all FDA-approved prescription, solid oral CR medications on the U.S. market as of December 31, 2008, revealed a total of 73 branded products (CR products). According to the labeled dosing instructions, a staggering 70% (51) of the CR products had some form of titration or dose adjustment recommended as part of the labeled dosing instructions. Of these, 55% were unscored tablets, 35% were



Figure 1. Accu-T Technology uses a drug-free break layer within each tablet to segregate the dose into precise halves, so CR tablets may be subdivided by hand into half doses without compromising the release kinetics. (U.S. patents 7,318,935 and 7,329,418; U.S. patent pending 10/598,355)

capsules, and just 10% were scored tablets. Of the five scored CR products, four were suitable for subdividing, according to the manufacturer's instructions: Isoptin SR (verapamil HCl); Sinemet CR (carbidopa/levodopa), Toprol XL (metoprolol succinate), and Isosorbide mononitrate ER. In other words, 47 of 51 (92%) of the CR products for which titration is recommended, per the labeled dosing instructions, were supplied in a dosage form that was unsuitable for splitting.

It is easy to conclude that for most products with a CR formulation, managing dose adjustments per the manufacturer's instructions would necessitate either a new prescription or having to administer multiple doses. Maintaining therapeutic blood levels with CR medications is a trial-and-error process for most individuals due to the reported lack of *in vitro-in vivo* correlation (2). Ideally, it would be beneficial for patients and caregivers to have the option of splitting CR products into accurate smaller doses without changing the release profile.

Accu-Break Technologies: Tablets Made to Be Broken

The Accu-T Technology (Figure 1) integrates the drug-free layer in the middle of two active drug layers at each end of the tablet. Using this technology, controlled-release formulations are layered onto either end of the tablet, separated by an immediate-release, drug-free break layer. The CR tablet may be swallowed whole or split through the drug-free layer to obtain a precise half dose. Since the break occurs away from the CR formulation layer and



Figure 2. Accu–B Technology combines two layers within the tablet: an active layer containing the drug and a drug-free layer. The active layer is pre-divided into smaller doses and scored such that the break occurs through the drug-free layer.

no additional surface area is exposed, the release kinetics of the CR tablet are not altered as a result of tablet splitting. Accu-T tablets can also be used to create combination drug tablets with a different active on either end of the tablet or combinations of IR and CR formulations.

In the Accu-B Technology (Figure 2), a drug layer is pre-divided during the manufacturing process into exact smaller doses, such as halves, thirds, of quarters, depending on the scoring pattern. The drug layer is backed by a drug-free layer, and tablet subdivision occurs through this drug-free layer. Accu-B Technology can be used for single-agent, combination, and CR products and is suitable for medications that are frequently titrated or dose-adjusted, commonly prescribed to the elderly or children and are dose-dependent for safety and efficacy.

Scoring High Marks

Besides the obvious medical advantages, Accu-Break Technologies offer economic and convenience advantages. Physicians and patients have the convenience of multiple prescriptions in one and the flexibility of dose-adjustable tablets with 100% accuracy. Tablets are easily split into exact smaller doses, minimizing wasted tablets. Physicians can dose adjust without the added burden of the cost and inconvenience to the patient of obtaining a new prescription. Caregivers and patients can adjust the dose with confidence that they are obtaining the intended dose, rather than an unpredictable one.

From a technical perspective, implementing this technology is simple. Accu-Break tablets are manufactured on commercially available multilayer compression equipment, making it low cost and low risk. Manufacturers benefit through a patented technology (issued patents extending until at least 2025), which creates a barrier to entry for counterfeiters. More importantly, the technology grants competitive advantages derived from its valueadded features for physicians, payers, and patients.

From a product development standpoint, the technologies can be used to develop new dosage strengths and treatment options for narrow therapeutic medications and unique combination products with compatible and/or incompatible active ingredients or formulations.

Innovation in Action

Accu-Break Technologies were invented at Accu-Break Pharmaceuticals, Inc. in 2004 by members of the medical community and pharmaceutical industry. Since then, ABP has actively pursued its vision of improving patient care and the practice of medicine through individualized dosing.

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Recent Research in the Area of Veterinary Controlled Release

Arlene McDowell University of Otago, Dunedin, New Zealand

For our final issue of the *CRS Newsletter* for 2009, I was interested in looking back on what has been published in the past year in the area of controlled release for animal health applications. Based on recently published papers, controlled release technology has been embraced by researchers working with animals. It is also evident that there is scope for researchers with expertise in the area of controlled release to collaborate on projects to solve problems for animal patients. The literature in this area is diverse and encompasses a range of animal species with corresponding differences in anatomy and physiology, as well as a range of reasons for administration of pharmaceuticals. The list below is a just a selection of the diverse research that has been published recently.

Mike Rathbone and David Brayden are well known and respected researchers in the veterinary controlled release community. In a recent article, they highlight the fundamentals in research in the animal health arena and also discuss different approaches for scientists working in the field of veterinary pharmaceutics. This article is well worth a read.

Rathbone, MJ, Brayden DJ. Controlled release drug delivery in farmed animals: Commercial challenges and academic opportunities, Curr. Drug Delivery 6: 383–390 (2009).

The ability to effectively synchronize estrus is animals is considered to be something of a Holy Grail in production animal research. Estrus synchronization is a management tool that is used to shorten the breeding season and maximize pregnancies in production animals. A CIDR (controlled internal drug release) vaginal implant was developed by Mike Rathbone and colleagues at InterAg in New Zealand for coordinating estrus. CIDR technology enables delivery of reproductive hormones in a physiological manner over an extended period of time. Two recent research articles utilize the CIDR implants for delivery to beef cattle and buffalo.

Leitman, NR, Busch, DC, Mallory, DA, Wilson, DJ, Ellersieck, MR, Smith, MF, Patterson, DJ. Comparison of long-term CIDR-based protocols to synchronize estrus in beef heifers, Anim. Reprod. Sci. 114: 345-355 (2009).

Murugavel, K, Antoine, D, Raju, MS, Lopez-Gatius, F. The effect of addition of equine chorionic gonadotropin to a progesterone-based estrous synchronization protocol in buffaloes (Bubalus bubalis) under tropical conditions, Theriogenology 71: 1120-1126 (2009). Improving the reproductive performance in pigs using controlled release technology has also been highlighted in an article by Vigo et al. The bioactive in this case was semen, and the goal was to improve preserve spermatozoa.

Vigo, D, Faustini, M, Villani, S, Orsini, F, Bucco, M, Chlapanidas, T, Conte, U, Ellis, K, Torre, ML. Semen controlled-release capsules allow a single artificial insemination in sows, Theriogenology 72(4): 439-444 (2009).

Nanoscience was also featured this year in the field of animal health, and an example is the use of solid lipid nanoparticles for administration of tilmicosin, an antibiotic used for the treatment and prevention of pneumonia in livestock.

Han, C, Qi, CM, Zhao, BK, Cao, J, Xie, SY, Wang, SL, Zhou, WZ. Hydrogenated castor oil nanoparticles as carriers for the subcutaneous administration of tilmicosin: In vitro and in vivo studies, J. Vet. Pharmacol. Ther. 32: 116–123 (2009).

Research on drug delivery for production animals dominated the area of veterinary pharmaceutics and is evidenced by the greater number of publications in this area in 2009 compared to other groups of animal patients. However, companion animals are the other main group of animals treated by veterinary pharmaceutics. Optimal delivery of anesthetics and analgesics is a recurring theme in literature involving companion animals, and Aragon et al. compare the delivery of morphine to dogs administered as immediate and extended release formulations.

Aragon, CL, Read, MR, Gaynor, JS, Barnhart, MD, Wilson, D, Papich, MG. Pharmacokinetics of an immediate and extended release oral morphine formulation utilizing the spheroidal oral drug absorption system in dogs, J. Vet. Pharmacol. Ther. 32: 129–136 (2009).

Something to look for in coming months in the area of animal pharmacology is a new title in the excellent *Handbook of Experimental Pharmacology* series by David Brayden and colleagues.

Brayden, DJ, Oudot, EM, Baird AW. Drug delivery systems in domestic animals. In: Handbook of Experimental Pharmacology: Comparative and Veterinary Pharmacology. F. Cunningham, J. Elliott, P. Lees, eds. Springer Publications. In Press. (Due to be released April 2010).

Happy reading!



Controlled Release Education Articles on Technology, Original Research, and Science.

Back to Basics: Dissolution Testing 2: The Rotating Basket Method (Apparatus 1)

G. Bryan Crist¹ and R. B. Walker²

This is the fourth in a series of articles introducing the basics of aspects of research techniques that may be required for the development and evaluation of controlled release technologies.

Introduction

This is the second in a series of articles covering the basic principles of operations required for various dissolution apparatus configurations. The rotating basket method, commonly called "Apparatus 1," is the topic of this article, which focuses on the proper execution of the dissolution test to ensure accurate, reproducible, and reliable results are generated.

As mentioned in the first article, the dissolution test consists of two primary components: 1) sample preparation on the dissolution apparatus; and 2) analytical finish performed primarily with spectrophotometric or liquid chromatographic analytical instrumentation. This article concentrates on the basket dissolution apparatus, evolution and compendial requirements of the rotating basket apparatus, testing procedure, and performance qualification and calibration.

Until the 1960s the disintegration test was used to ensure that dosage forms would reduce to small particles rapidly when immersed in simulated gastric fluid. It was felt at the time that disintegration indicated that a drug was available for absorption in the GI tract and, therefore, reflected bioavailability. However, continuing studies proved that disintegration had very little to do with bioavailability, and the need for a dissolution test became apparent. During the 1950s and 1960s, a number of basket and stirring devices were developed, and numerous papers were published on the benefits of dissolution testing. Eventually, the rotating basket method for dissolution, generally credited to M. Pernarowski in 1968 (1), became widely accepted as a suitable apparatus for dosage form evaluation.

The rotating basket was incorporated in USP XVIII in 1970 as the first official dissolution test. Notably, this early apparatus had a concave vessel bottom that later evolved into the hemispheric bottom vessel that is used today. The basket apparatus was useful for submerging floating dosage forms such as encapsulated products. Other typical products tested with the rotating basket include swelling dosage forms, bead formulations, coated and uncoated tablets, suppositories, and a variety of immediate and modified release formulations.

The Rotating Basket Apparatus

The rotating basket apparatus consists of a 316 stainless steel shaft and basket and a 1,000 mL glass vessel (Figure 1). The basket is attached to the shaft by three retention clips. Other means of attachment, including O-rings, have been used, but they do not meet USP requirements, and they have demonstrated lower results (2). Therefore, validation should be conducted to show that an O-ring attachment is equivalent to the official clip attachment on a product-by-product basis.

The basket apparatus was harmonized between the European (2.9.3), Japanese (15), and U.S. (<711>) Pharmacopeias. The International Conference on Harmonisation (ICH) produced common technical documents to standardize dissolution methods



Figure 1. USP basket stirring element.

 Scientific Affairs Manager–Pharma, Varian, Inc., Cary, North Carolina, U.S.A.
 Head and Dean, Faculty of Pharmacy, Rhodes University,

Grahamstown, South Africa.

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and procedures, providing a simplified and consistent process for the submission and approval of drug standards throughout the world. However, we must be mindful that the various pharmacopeias have different specifications for the mesh dimensions of the basket. A single harmonized specification exists today that encompasses two different basket mesh sizes, specifically the 40-mesh basket from the EP and USP and the 36-mesh basket from the JP. The mesh number reflects the number of openings per linear inch (25.4 mm) of woven screen. In the opinion of these authors, the baskets are not equivalent and should be properly validated within the regions of their use. If a difference in results is observed between the baskets, the dimensions of the basket should be included in the dissolution procedure. Preliminary studies indicate slightly lower test results for USP Prednisone Tablets with the 36-mesh baskets (3).

The baskets are quite fragile and require proper handling and care. Baskets should be rinsed immediately after use, dried, and stored properly. They should not be allowed to roll around in a drawer where they may be dented or misshapen. Baskets should always be attached and detached from the shaft by holding the upper rim of the basket. Otherwise, improper handling will damage the basket, and it will not maintain its cylindrical shape. To ensure consistent dissolution performance, a damaged or corroded basket must never be used.

Additional baskets designs have been developed and justified for special dosage forms that have shown performance issues when tested with the standard compendial baskets. These include variations in mesh number from 10-µm to 10-mesh, slotted baskets for suppository testing, large baskets to handle veterinary bolus tablets, and mini-baskets for use with 200-mL vessels.

The Rotating Basket Procedure

When executing the rotating basket dissolution test, a series of steps should be routinely performed during each test. These steps may be included in a general dissolution standard operating procedure (SOP), as they are often not included in a specific test method for a particular product.

• Prior to the start of the test, the analyst should evaluate the dissolution apparatus, vessels, baskets, and shafts to ensure that they are clean and dry.

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- The analyst is responsible for the verification of physical parameters prior to the start of a test, especially if the vessel, shaft, or basket components have been moved or exchanged.
- Media must be properly prepared according to the method and thoroughly deaerated. Dissolved gasses that have not been removed will form bubbles in the mesh of the basket during the test, which will change the performance of the basket. Lower profiles or test results may be observed due to blocked apertures in the wire cloth of the basket.
- Media must be delivered to the vessel while maintaining a volumetric accuracy of ±1%. For a typical dissolution test with 900 mL and a required volumetric accuracy of ±9 mL, appropriate Class A volumetric glassware is required, which may exclude most graduated cylinders.
- The media must reach 37.0°C in each vessel prior to the start of the test. If the media is barely within the lower range, 36.5°C, the temperature will drop below the range when the cold steel shafts and baskets are lowered into the media.
- Media temperature must be measured and recorded for each vessel at a minimum before and at the end of each dissolution test to verify that the temperature of the media has been maintained properly (Figure 2).



Figure 2. Temperature measurement.

	ICH Harmonized		
Parameter	Specifications (USP, EP, JP) (5)	FDA (DPA-LOP.002) (6)	ASTM (E2503-07) (7)
Basket/paddle depth	25 ± 2 mm	25 ± 2 mm	25 ± 2 mm (or within 8% of desired height)
Rotational speed	±4% of specified rate	±2 rpm of target	Within 2% or ±2 rpm of stated rate (use larger)
Shaft wobble	No significant wobble	≤1.0 mm total runout	≤1.0 mm total runout
Shaft verticality	Not measured	≤0.5° from vertical	Within bubble
Basket wobble	±1 mm	≤1.0 mm total runout	≤1.0 mm total runout
Vessel/shaft centering	NMT 2 mm from center axis	≤1.0 mm from center line	≤1.0 mm from center line
Vessel verticality	Not measured	≤1.0° from vertical from	≤1.0° from vertical from
		2 positions 90° apart	2 positions 90° apart
Vessel plate level	Not measured	Not measured	Not measured
Performance			
verification test	USP Prednisone Tablets RS	Not measured	Not measured

Table 1. Dissolution apparatus specifications

- Prepare all sampling materials if sampling manually or automatically, including fresh filters and measuring equipment that is clean and dry. Prepare fresh, clean, dry, and properly labeled vials or test tubes for each sample time point.
- Handle all dosage units with gloved hands or protective tweezers that will not scratch or crack capsules or the coating on tablets. Moisture and oils on the skin will affect the performance of many dosage forms prior to the start of the dissolution test.
- If weights are required for documentation, expose the dosage forms to as little humidity as possible.
- Do not place dosage units in the basket until you are ready to begin the test (Figure 3). Suspending the dosage units in the basket above the dissolution apparatus for a lengthy period prior to the test could expose the dosage unit to high humidity levels, which may alter the performance of the dosage unit.
- Have all documentation materials nearby to record temperatures and times and to note visual observations taken during the test.
- Record the times at which the baskets are lowered into the media and when each of the samples is pulled from the vessel.
- Visually inspect the baskets for bubble formation. There should not be a bubble under the basket, which may occur when starting the test with wet or dirty baskets. While many capsules may be seen floating in the top of the basket, tablets should not be trapped in the top of the basket with an air bubble, which may delay the dissolution of the tablet coating.
- Samples should be pulled within 2% of the time that the test begins. In other words, samples must be pulled for a 30-min time point within ±36 sec of the 30-min time point. If all six samples are started at the same time, then all six samples must be pulled and filtered within this window of time. Automated sampling equipment is often used to obtain, filter, and document sampling accuracy.



Figure 3. Placing the basket on the shaft.

- The filter stops the dissolution process and clarifies the sample for analytical measurement. Only validated filters should be used that remove all undissolved particles from the sample and do not bind the drug substance after conditioning with a specified amount of sample-containing medium.
- The dissolution samples are ready for analytical measurement once they have cooled to room temperature.

Qualification: Chemical vs. Mechanical

All dissolution apparatus used for testing within a cGMP environment should be properly qualified. The dissolution test is a test of the performance of the drug product, and therefore, qualification testing should include a periodic performance qualification (PQ) in addition to the standard installation and operational qualifications (IQ and OQ). The USP prescribes the use of the Performance Verification Test with USP Prednisone Tablets RS, but this is not a requirement of the harmonized dissolution chapters.

Mechanical qualification of the dissolution apparatus has been proposed by the U.S. Food and Drug Administration (FDA) in a draft Guidance for Industry. This proposal suggests an alternative approach to the use of USP Performance Tablets in calibrating a dissolution apparatus (4). Table 1 contains the specifications that the dissolution apparatus must maintain to meet mechanical calibration standards. The frequency of measurement and documentation of these parameters will be the responsibility of laboratories choosing mechanical qualification practices.

If the mechanical calibration procedure is used, additional documentation is required to verify the dimensions for each individual vessel, basket, and basket shaft used in the laboratory. Additional operational checks must also be documented at the time of each test for baskets to ensure that they are not corroded misshapen, deformed, or frayed and are free from residue. Vessels must be documented to ensure they are free from residue, cracks, scratches, and pits. Vessel temperature must be taken, and vibration must be evaluated.

In the next "Back to Basics" article the paddle apparatus, "Apparatus 2", will be discussed.

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CRS New Jersey Student Chapter Events Update

Bozena Michniak-Kohn, Ph.D.,¹ and Robert Falcone²

The CRS New Jersey Student Chapter (NJCRS) was formed in May 2008 and began hosting events in fall 2008. Dr. Bozena Michniak-Kohn is the chapter faculty advisor, and Robert Falcone is the student president. Our membership presently consists of seven members, because most of our regular members have completed their studies and become regular CRS members. The chapter co-sponsored and sponsored two workshops in 2008 and two workshops and one seminar in 2009.

In September 2008, NJCRS co-sponsored, along with the Laboratory for Drug Delivery, New Jersey Center for Biomaterials and Hill Top Research, the Second Annual Skin Workshop, which was devoted to "New Developments in Dermaceuticals and Wound Care." This workshop invited speakers from industry and academia to discuss and share topics such as the "Role of Peptides in Wound Care, Current & Future Skin Permeation Technologies for Drug Delivery" and "Ultrasonic Drug Delivery" (for further details, see www. njbiomaterials.org/web/index.php?p=industry&s=99524). The main role of NJCRS was to sponsor a student poster competition. There were 17 posters submitted from industry and academia, and the winners of the competition were

1st Place: Human Skin Equivalent (HSE) for *In Vitro* Permeation Testing of Formulations

Priya Batheja, Ernest Mario School of Pharmacy, Rutgers University, NJ; and *Yifan Song*, Department of Pharmacology and Physiology, UMDNJ-New Jersey Medical School, NJ

2nd Place: Making Human Skin Equivalents for *In Vitro* Applications Using Polymer Scaffolds and Skin Derived Cells *Prafulla Chandra*, The New Jersey Center for Biomaterials, Rutgers University, NJ; *Vishwas Rai*, Ernest Mario School of Pharmacy, Rutgers University, NJ; *Joachim Kohn*, The New Jersey Center for Biomaterials, Rutgers University, NJ; and *Bozena Michniak-Kohn*, The New Jersey Center for Biomaterials and Ernest Mario School of Pharmacy, Rutgers University, NJ

3rd Place: Effect of Solvent Systems on Skin Delivery of DEET in Presence of Penetration Modifiers

Yasmin Poustchi, BA/MD Program, Rutgers/UMDNJ-RWJMS, and Ernest Mario School of Pharmacy & New Jersey Center for Biomaterials, Rutgers University, NJ; *Diksha Kaushik*, Ernest Mario School of Pharmacy & New Jersey Center for Biomaterials, Rutgers University, NJ; and *Bozena Michniak-Kohn*, Ernest Mario School of Pharmacy & New Jersey Center for Biomaterials, Rutgers University, NJ

- ¹ Ernest Mario School of Pharmacy, Rutgers-The State University of New Jersey, Piscataway, NJ.
- ² Medical Device Concept Laboratory, New Jersey Institute of Technology, Newark, NJ.

For further details, see www.njbiomaterials.org/web/index. php?p=industry&s=29139.

In November 2008, NJCRS was asked to sponsor a workshop with the New York Chapter of the Society of Cosmetic Chemists. Robert Falcone prepared and delivered a workshop titled Project Management for Product Development. This workshop was attended by 42 members from both societies. In June 2009, NJCRS along with the Laboratory for Drug Delivery ran a workshop on New Approaches and Technologies in Oral Drug Delivery at the New Jersey Center for Biomaterials, Rutgers University. This workshop presented a review of new concepts presently explored in academia and industry for new oral drug delivery systems (for further details see www.njbiomaterials.org/ web/index.php?p=industry&s=73287). Part of this workshop was a poster session with 10 entries from academia and industry; the winners were

1st Place: Nanospheric Chemotherapeutic and Chemoprotective Agents

Larisa Sheihet, Rutgers University and the New Jersey Center for Biomaterials, NJ

2nd Place: Control of the Spreading of Drug-Solvent Mixture onto Edible Substrates and Design of Drop On Demand System with Real Time Gravimetric Control

Marlena Brown, Engineering Research Center for Structured Organic Particulate Systems, Rutgers University, NJ

3rd Place: A Human Skin Equivalent (HSE) for *In Vitro* Permeation Testing of Formulations—New Developments *Priya Batheja*, Ernest Mario School of Pharmacy, Rutgers University, NJ; and *Yifan Song*, Department of Pharmacology and Physiology, UMDNJ-New Jersey Medical School, NJ



Oral Delivery Workshop Student Poster Winners. Left to right: Priya Batheja, Marlena Brown, Robert Falcone, Dr. Bozena Michniak-Kohn, Dr. David Hauss, and Larisa Sheihet.



Robert Falcone, NJCRS Student Chapter president, and Dr. Bozena Michniak-Kohn, NJCRS Student Chapter faculty advisor.

Future Events

For further details, see www.njbiomaterials.org/ web/index.php?p=industry &s=51238.

In September 2009, NJCRS co-sponsored a seminar with the New Chapter of the Society of Cosmetic Chemists on the use of nanotechnology in skin-care products and the legislation surrounding this topic in the United States.

NJCRS will be assisting NYSCC to run its Fall 2009 Workshop set for November. Moreover, the chapter has been asked to cohost the NYSCC Spring 2010 Workshop (date and topic to be determined), and plans are in place to run a late spring/summer seminar with the New Jersey Center for Biomaterials and the Medical Device Concept Laboratory of the New Jersey Institute of Technology, as well as to co-sponsor the 3rd Annual Skin Workshop. Dates and topics will be made available soon. Elections for a new president will be held this coming December, because Robert Falcone will be completing his studies and can



Second Skin Workshop Student Poster Competition 2nd Place winners Prafulla Chandra (left) and Vishwas Rai (right) with Robert Falcone.

no longer serve as chapter president in accordance with CRS guidelines.

For further information or membership information, please contact Marie Pavelchak (Dr. Michniak-Kohn's assistant) at CBMMil@Biology.Rutgers.Edu.

CRS Nordic Chapter News

Bente Steffansen¹ and Jouni Hirvonen²

During the CRS Annual Meeting in Copenhagen, the CRS Nordic Chapter arranged a highly successful networking event on Monday evening, July 20, 2009, at The University of Copenhagen in Munkekælderen. The program and networking evening were initiated and arranged by the CRS Nordic Chapter Board Chair Prof. Jouni Hirvonen, University of Helsinki; Assoc. Prof. Bente Steffansen, University of Copenhagen; Prof. Kristiina Järvinen, University of Kuopio; Prof. Marjo Yliperttule, University of Helsinki; Prof. Anette Larsson, Chalmers University of Technology; Prof. Martin Brandl, University of Southern Denmark; Prof. Thorstein Loftsson, University of Iceland Reykjavik; Dr. Torkel Gren, Astra Zeneca; Dr. Flemming Seir Nielsen, Novo Nordisk A/S; Dr. Ole Hjelstuen, GE Healthcare AS; Prof. Ingunn Tho, University of Tromsø; and Assoc. Prof. Christel Bergström, Uppsala University.

At the networking event Prof. Jouni Hirvonen welcomed the approximately 70 participants and told them about the previous,

- ¹ Associate Professor, Ph.D., University of Copenhagen, Faculty of Pharmaceutical Sciences, and CRS Nordic Chapter Board member.
- ² Professor, Ph.D., University of Helsinki, Faculty of Pharmacy, and CRS Nordic Chapter Board chair



Daniel Bar-Shalom (left) and Jouni Hirvonen (right).

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current, and future activities of the Controlled Release Society and, especially, the CRS Nordic Chapter. During the event, 10 Nordic Chapter graduate students were given US\$150 awards each based on the high quality of their oral or poster presentations during the CRS Annual Meeting in Copenhagen. Funding for the Awards was provided by the CRS. The award winners were

Podium Presentations

Tiina Heikkilä, University of Helsinki, Finland Miia Kilpeläinen, University of Kuopio, Finland Ebbe J. B. Nielsen, iNANO and University of Århus, Denmark



Attendees at the CRS Nordic Chapter networking event.

Poster Presentations

Carina Dahlberg, YKI Institute for Surface Chemistry, Sweden Tove Evjen, University of Tromsö and Epitarget AS, Norway Ulrik Rahbek, iNANO and University of Århus, Denmark Jessica Rosenholm, Åbo Akademi University, Finland Tina Skjörringe, Kennedy Center, Denmark Mladen Stojanov, Aalborg University, Denmark Anna Viridén, Chalmers University of Technology, Sweden

Next, Assoc. Prof. Daniel Bar-Shalom, University of Copenhagen, Faculty of Pharmaceutical Sciences, presented, in a very lively and attention-catching manner, his recent research activities and new applications of the erosion-based oral drug delivery concept. Finally, Prof. Dr. Flemming Steen Jørgensen entertained the audience with information on the graduate programs in the Faculty of Pharmaceutical Sciences, University of Copenhagen. An excellent buffet and drinks, sponsored by the Faculty of Pharmaceutical Sciences and the Drug Research Academy, University of Copenhagen, and Novo Nordisk A/S, were served during the event.

The next CRS Nordic Chapter event will be held June 28–29, 2010, at the Astra-Zeneca facilities in Mölndal, Sweden. It will include four parallel sessions: Challenges with Poorly Soluble Drugs; Processes for Solid Dosage Forms; Drug Transporters and Delivery; and Biomolecular Delivery. For further information, please visit www.swepharm.se.

UKICRS Summer Programme

Over the summer, UKICRS has been busy with various c onferences.

August 2009 – Irish Drug Delivery Network (IDDN) Conference with UKICRS: Optimising Drug Delivery

The "Optimising Drug Delivery" conference, co-hosted by the IDDN and UKICRS, was held at University College Dublin (UCD) on the August 19. The UCD-funded meeting was attended by over 70 attendees from Ireland and the United Kingdom, and it provided a platform for discussion on a range of topics encompassing the broad drug delivery area. The meeting was also attended by members of the Irish government science-funding agencies, Science Foundation Ireland (SFI), Enterprise Ireland, and the Irish Development Agency, as well as by attendees from national and international pharma companies, so it was an ideal forum for developing interactions. The invited speakers provided a lot of novel data, and each presentation was informative and provoked lively discussions. The opening address to the meeting was from Dr. Stephen Simpson, director of life sciences at SFI, who gave some insight into the synergies that can come out of multi-disciplinary collaborations.

The first presentation was provided by Prof. David Brayden (University College Dublin), director of the IDDN, who discussed his team's work on "Epithelial Tight Junctions and Oral Peptide Delivery." The focus was on how the oral absorption enhancer sodium caprate has gone right through over a 30-year period from mechanistic cell- and tissue-based work into rat studies and, finally, to current human clinical studies being carried out by Merrion Pharmaceuticals (Dublin) as a solid-dosage form to enhance the poorly permeable bisphosphonate zoledronic acid. In "Physiological Aspects of the Gut: Impact on Delivery" by Prof. Clive Wilson (University of Strathclyde), the audience was given a very entertaining talk on individual variation in many aspects of gut physiology, in which it seems that inter-individual differences in pH, motility, and metabolism are more the norm than the exception, and this provides extreme challenges for targeted formulations. UKICRS President Prof. Yvonne Perrie (Aston University) then discussed "Particulate Adjuvants-Exploiting Cationic Lipids," in which she presented oral mouse immunology data with stable liposomes containing hepatitis B antigens. She also showed how badgers could potentially be vaccinated with bait containing the BCG vaccine in an attempt to halt transmission to cattle, a very controversial topic in the United Kingdom and Ireland.



Left to right: Vitaliy Khutoryanskiy, Woei Ping Cheng, Afzal Mohammed, and Talia Buggins.

In the second session, "Cyclodextrins and siRNA Delivery," was given by Prof. Caitriona O'Driscoll (University College Cork). Caitriona described a range of novel neutral cyclodextrins vesicles that the IDDN is using to deliver siRNA into cells in proof-ofconcept studies. She showed that these structures are very different from typical cyclodextrins and are constructed differently than competitor technologies. The final presentation of the morning was "Gene Delivery Vectors: Update and Assessment", which was given by the leading gene therapy scientist Dr. Catherine O'Riordan (Genzyme). Catherine described how Genzyme has evolved its gene delivery programme from adenoviruses in cystic fibrosis research in the early 1990s to its current focus on adenovirus-associated vectors for local gene delivery to the eye (for macular degeneration) and brain (for Parkinson's disease). She showed some very encouraging clinical data from both programmes, which included some remarkable brain imaging technology readouts.

First up after lunch was Raymond Schiffelers (University of Utrecht), who discussed "siRNA as a Drug: Shift from Drug Discovery to Delivery." Raymond described a range of novel particulates based on PEG-PEI that are being used to silence RNA by systemic administration. Many of these are targeted with RGD ligands for integrins on cancers grafted onto mice. Photochemical internalisation seemed to assist in overcoming the significant hurdle of endosomal escape. The second speaker of the afternoon, Dr. Carsten Ehrhardt (Trinity College Dublin), presented "The Use of In Vitro Epithelial Cell Culture Models for Pulmonary Delivery." Carsten described the advantages and disadvantages of using airway cell lines for predicting drug transport and provided evidence that human primary airway cultures grown on filters may have superior properties with respect to drug transporters and metabolism. It seems that the received wisdom that human pulmonary alveolar epithelia lacks the metabolic capacity to break down peptides may not be so accurate after all. Prof. David Woolfson (Queen's University Belfast) described some of his work on "Vaginal Delivery of HIV Microbicides and Mucosal Vaccines." This was a very practical illustration of how controlled release of microbicides can be tailored into the design of intravaginal rings. In addition, David gave an elegant description of how HIV mucosal vaccines can be entrapped and released from newly designed rings, and this may eventually have significant potential for the developing world.

After the break, Dr. James Birchall (University of Cardiff) led the final session, with "Microneedle Approaches for Achieving Efficacious Transdermal Delivery." This was a very entertaining and informative talk on how microneedles are incorporated into skin patches to yield very good immune responses. He described how fresh human skin biopsies seem to be the best in vitro model to assess many parameters of microneedles and provided histological evidence of the lack of damage caused by such systems. The final speaker of the day was Prof. Cormac Taylor (University College Dublin). His talk was on "Novel Targeted Therapeutics for Inflammatory Bowel Disease," in which he showed how novel hydroxylase inhibitors may have the potential for local topical treatment of inflammatory bowel disease. The principle was that a dysregulated hypoxia pathway can be exploited for therapeutic benefit and that drug delivery technologies such as the liquid emulsion drug delivery system being developed by Sigmoid Biotechnologies are required for colonic delivery. The research exploited a range of knock-out mice to examine aspects of the hypoxia pathway and then showed that an hydroxylase inhibitor could repair the gut inflammation in the dextran mouse model of colitis. UKICRS and IDDN are very grateful for their contributions to what was a great first collaborative meeting.

September 2009 – British Pharmaceutical Conference

Within the annual BPC, UKICRS hosted two sessions. In our first session, on Monday, September 7, we looked at "Oral Drug Delivery." Dr. Vitaliy Khutoryanskiy (University of Reading) chaired the session, which opened with Dr. Afzal Mohammed (Aston University) discussing his work on the development of "Novel Zero-Order-Saccharide Fast Disintegrating Tablets." Dr. Mohammed's group investigated the feasibility of using a range of amino acids as novel matrix-forming agents in the formulation of rapidly disintegrating tablets by studying the effect of these amino acids on tablet properties. His work identified a range of formulations that offer potentially improved rapidly disintegrating tablets.

Next, Dr. Talia Buggins (AstraZeneca) discussed combinations of dissolution and clinical studies to understand product quality for a BCS class 4 compound. Dr. Buggins noted that for class 1 and 3 compounds, the link between dissolution in simple aqueous buffers and *in-vivo* performance is already well established. However, for BCS class 4 compounds, this relationship needs to be explored and understood on a compound-specific basis. With class 4 compounds, it is thought that there is a higher biopharmaceutical risk, and their *in vivo* performance is more sensitive to process and formulation changes than other compounds. However,



Left to right: Cameron Alexander, Barbara Conway, and Yvonne Perrie.

Dr. Buggins showed that with a case study compound, process and formulation changes had no significant impact on bioequivalence. Dr. Buggins reported that this allowed a "safe space" dissolution window to be defined, within which dissolution could be altered without impacting bioequivalence.

The final speaker of the session, Dr. Woei Ping Cheng (University of Hertfordshire), discussed the use of polymeric self-assemblies as emerging nano-carriers for the oral delivery of proteins and hydrophobic drugs. Using insulin as a model protein, Dr. Cheng and her colleagues demonstrated the ability of amphiphilic polyallylamine (PAA) to form nano-complexes with insulin. These nano-complexes were shown to protect insulin from in vitro enzymatic degradation by trypin, chemotrypsin, and pepsin at varying degrees. The difference in the protective effect was dependent on the polymer architecture. Using a CaCo, cell model, she showed that these nano-complexes were able to open a tight junction, as well as promote cellular uptake of insulin. The potential of these nano-carriers was also extended to solubilising a range of hydrophobic drugs and promoting earlier cellular uptake of a novel hydrophobic anticancer agent. Our second session, "Delivering Anti-infectives," on Tuesday, September 8, was chaired by Prof. Yvonne Perrie (Aston University), and we opened the session with Dr. Barbara Conway (Aston University), who discussed chlorohexidine skin antisepsis and penetration. Since micro-organisms reside not only on external skin surfaces but also inhabit hair follicles and sites beneath the skin surface, such organisms can cause infection when the protective skin barrier is breached. Dr. Conway and colleagues looked to develop skin antisepsis to prevent infections associated with invasive procedures and to provide an efficient and rapid permeation of the applied antiseptic agent into the deeper layers of the skin. The most widely used antimicrobial for skin antisepsis is chlorohexidine (2%, w/w), and this was used by the group. Using a Franz diffusion cell model, skin permeation studies were carried out to determine the penetration of chlorohexidine using fullthickness human skin. They found synergistic antimicrobial activity of chlorohexidine and essential oils, including eucalyptus oil against Staphylococcus epidermidis. Also, using the same human

skin model, it was shown that the combination of eucalyptus oil and chlorohexidine applied at the skin surface increased both the rate and extent of delivery of chlorohexidine within the deeper skin layers. This may prevent infection and microbial recolonisation of the skin in clinical practice following invasive procedures.

Next, Dr. Carl Alving (Walter Reed Army Institute of Research) discussed a novel approach to target HIV-1 with the use of liposomes. HIV-1 is relatively unstable, and many clades exist that make the production of monoclonal antibodies against the principle vaccine targets, glycoproteins gp120 and gp41, unsuccessful. One of the mains aims, therefore, is to develop a broadly neutralising antibody similar to that found in persons whom are immune to HIV-1. The observation that the epitope of these neutralising antibodies lies both on the virus and the host's membrane lipid rafts has resulted in a possible vaccine strategy: develop a liposome combining synthetic gp41 peptides and lipid A to which the host will produce antibodies (the use of lipid A is due to its inherent immunogenicity *in vivo*).

Our last speaker of the session, Dr. Cameron Alexander (University of Nottingham), discussed polymers used for and against cell attachment. Biological recognition at surfaces is important, and polymers can be used for bacterial recognition, whereby bacterial attachment at surfaces takes place as an artificial material enters a biological environment. Polymers can also control such interfacial phenomenon, allowing cell interactions to be switched on or off. Probe cell attachments can occur via switchable bioadhesion pat-

terns at a nano-scale via adjustment of polymer brushes to achieve a hydrophilic or hydrophobic brush. As a result, control of the cell's behaviour to spread out or line up is dependent on the temperature, which influences short-term cell interactions. Particular interactions are controllable via surface modifications with glycopolymers, achieving specific cell attachments. Bacterial infections continue to be a worldwide health problem, and new meth-



Carl Alving chatting after his presentation.

ods of detecting bacteria are required. Therefore, there is a necessity to design new disease control modalities, and one such approach is the use of polymer cell interactions in suspension. Polymers can be prepared to controllably bind cells at surfaces, and these polymers exhibit the potential for specific cell detection, which would make targeted delivery achievable.

Many thanks to Dr. Graham Armstrong (University College Dublin), Randip Kaur, Malou Henriksen, and Jubair Hussain (Aston University) for contributing to this article.

CRS Committee Action Plans

The CRS Board of Directors (BOD) utilizes the CRS Strategic Plan as the Society's compass, ensuring that CRS activities are focused in the direction needed to accomplish the Society's longterm goals. This translates through to the annual action plans developed by all of the CRS committees. These plans were reviewed recently at the BOD meeting held in London, October 5–6, 2009.

The proposed committee plans underscore the vitality that drives CRS forward. Some things to look forward to in the coming year include

Awards – A new College of Fellows program is being developed to honor members who have made significant contributions to the Society. A Chapters Award will also be unveiled to spotlight an outstanding Chapter.

Board of Scientific Advisors – The BSA will prepare a State of the Field report that will be an invaluable tool in planning for the future.

Consumer & Diversified Products – The committee is hard at work developing sessions for the CRS annual meeting in Portland, as well as looking at possible C&DP topic-focused satellite meetings for the future.

Chapters – The Chapters Committee is focused on developing new chapters and creating new forms, website resources, and budgets that support these efforts.

China Initiative – The committee is working to create a CRS presence in China through meetings and other opportunities.

Finance – In order to maintain CRS's strong financial position, the Finance Committee will be refining the CRS Financial Strategic Plan and Priorities, as well as reviewing the individual business centers.

Foundation – The Foundation had an extremely successful year with the granting of the first Joseph R. Robinson Fellowship and is now looking to 2010 as a way to connect with more individual members and companies.

Marketing – The committee's focus for 2010 is the development of the new Innovation Sunday, which will debut in Portland.

Meeting – The Meeting Committee is focused on delivering an outstanding annual meeting for 2010 in Portland, as well as formulating new satellite meetings to enhance member value.

Membership – The committee's main focus in the coming year is membership development and retention. The committee will also be working with staff to develop an "After Party" for Portland.

Mentoring – The CRS mentoring program has experienced rapid growth, with more than 25 pairs active in 2009. In 2010, the goal is to develop 40 active mentor/protégé pairs.

Publications: Books – The editors of the first four CRS books are hard at work preparing to submit first drafts of their manuscripts by the end of 2009. Look for these new titles in 2011.

Publications: Newsletter – The committee will be producing six issues of the *CRS Newsletter* in 2010.

Webinar – The first set of educational webinars from the Copenhagen meeting are being reviewed and will soon make their way to the CRS webpage. If you are interested in recording a webinar, please contact Todd Quiram at tquiram@scisoc.org.

Young Scientist Committee – This is a very active committee. For the Portland meeting the committee is looking at ways to increase attendance at the Get Up, Get Educated sessions, as well as looking at offering a workshop on how to review articles.

Veterinary – The Veterinary Committee is working to publish a special issue of the *Journal of Controlled Release* and will be developing focus groups in 2010.

If any of these activities interest you and you would like to get involved with a committee, please let us know!

LEVERAGE DRUG DELIVERY TECHNOLOGY TO MAXIMIZE VALUE



CRS Education Committee Satellite Workshop in Conjunction with the 14th annual Drug Delivery Partnerships with the

Full Day Workshop: 9:00am to 4:00pm Development and Regulatory Challenges for Controlled Release Formulations

The workshop includes a combination of FDA and European regulatory perspectives on developing controlled release formulations, and newly emerging technologies to help individuals understand the challenges in developing the technology of controlled release formulations as well as the regulatory hurdles that these technologies may face. There will case studies discussing mature technologies and the associated developmental and regulatory challenges that were encountered along the road to success. We encourage and expect a lively discussion among the attendees, speakers, and regulatory officials that can shed some light on what is expected when working to get a controlled release product to market. Visit **www.drugdeliverypartnerships.com** for workshop faculty updates and complete workshop details.



January 25-27th, 2010 • The Omni Orlando Resort at ChampionsGate, Orlando, FL • www.drugdeliverypartnerships.com

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In the News

Compiled by Steven Giannos Industrial Editor

October 2009

NovaDel Licenses Its NitroMist[®] Lingual Spray to Mist Acquisition

Business Wire: October 27, 2009 – FLEMINGTON, NJ – NovaDel Pharma Inc. (NYSE AMEX: NVD) has entered into a licensing agreement with privately held Mist Acquisition, LLC to manufacture and commercialize the NitroMist[®] lingual spray version of nitroglycerine, a widely prescribed and leading shortacting nitrate for the treatment of angina pectoris. Under the terms of the agreement, Mist will pay NovaDel a \$1,000,000 licensing fee upon execution of the agreement, milestone payments totaling an additional \$1,000,000 over the next 12 months, and ongoing performance payments of 17% of net sales.

Through a separate license agreement with Mist, Akrimax Pharmaceuticals, LLC will receive the exclusive right to manufacture, distribute, market, and sell NitroMist[®] in North America. NitroMist[®] provides acute relief of an attack or acute prophylaxis of angina pectoris due to coronary artery disease. The lingual spray form of the drug is conveniently administered and rapidly absorbed into the bloodstream via the oral mucosa, providing patients a fast and tolerable treatment option for the prevention or relief of pain associated with such attacks.

"Akrimax's focus on metabolic diseases and its leadership's proven experience launching successful products and companies makes it an ideal partner to launch this innovative therapy," said Steven B. Ratoff, NovaDel chair and interim CEO. "We're delighted to have Akrimax leveraging its manufacturing expertise and progressive commercial platform to optimize the value of NitroMist[®]," he added.

"NitroMist[®] offers an important practical innovation in the delivery of a life support medicine for cardiovascular patients suffering from angina," stated Alan L. Rubino, CEO and president of Akrimax. "We are extremely enthusiastic to be introducing and commercializing NitroMist[®] as this new product is an excellent complement to our developing cardiovascular and metabolic portfolio."

Endocyte Awarded Patent for Vitamin Receptor-binding Drug Delivery Conjugates

Business Wire: October 27, 2009 – WEST LAFAYETTE, IN – Officials at Endocyte Inc., a cancer drug discovery and development company, have announced that the company has been awarded a patent from the U.S. Patent and Trademark Office covering vitamin receptor-binding anti-cancer agents.

The patent, "Vitamin Receptor Binding Drug Delivery Conjugates" (U.S. patent 7,601,332), covers novel conjugation linkages and anti-cancer agents, including Endocyte's EC145, which is currently in development as a potential treatment for ovarian and non-small cell lung cancers.

The patent represents years of research into Endocyte's groundbreaking technology that links potent anti-cancer agents to receptor-binding moieties on the surfaces of cells. The technology utilizes a proprietary "linker" technology that connects the anti-cancer agent to the appropriate receptor-binding moiety to form a conjugate. The moiety enables the conjugate to remain stable while in circulation and be delivered selectively into cancer cells. The novel "linker" causes the anti-cancer agent to be released in its intact and fully active form within the cells. This patented combination of targeting moiety-linker drug conjugates describes a number of Endocyte conjugates, including its lead drug candidate, EC145, which uses the vitamin folate as the targeting moiety and which is currently in Phase II clinical trials.

Impax Pharmaceuticals Initiates Second Phase III Trial of IPX066 in Parkinson's Disease Patients

Business Wire: October 27, 2009 – HAYWARD, CA – Impax Pharmaceuticals, the brand products division of Impax Laboratories, Inc. (NASDAQ: IPXL) has announced that it has initiated a multinational Phase III trial of its late-stage drug candidate IPX066 in advanced Parkinson's disease (PD) patients. IPX066 is an investigational extended release carbidopa-levodopa product intended to rapidly achieve and then sustain effective blood concentrations of levodopa, potentially improving PD clinical symptom management. This is the second of two Phase III studies designed to support marketing approval of IPX066 for Parkinson's disease. Impax Pharmaceuticals previously reported in June the initiation of the first Phase III study of IPX066 in naïve PD patients.

Michael Nestor, divisional president of Impax Pharmaceuticals said, "We are extremely pleased to start the second Phase III study for IPX066. This trial in patients with advanced PD includes significant input from the FDA into the study design." He added, "Impax Pharmaceuticals looks forward to the successful development of IPX066 and bringing its potential benefits to physicians who treat Parkinson's and their patients as quickly as possible."

Depomed Announces Delivery of First Formulation to Covidien and Receipt of \$500,000 Milestone Payment

Business Wire: October 22, 2009 – MENLO PARK, CA – Depomed, Inc. (NASDAQ: DEPO) has delivered the first formulation under its worldwide license agreement with Covidien, focusing on the exclusive development of four products utilizing Depomed's Acuform[®] gastric retentive drug delivery

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technology. The delivery of the first formulation to Covidien triggered a \$500,000 milestone payment.

"We are pleased to complete our work on the initial formulation and have already made significant progress on the second formulation. We believe that these products have the potential to provide meaningful clinical advantages to patients and look forward to continuing our collaboration with Covidien. Both companies have evolved a strong working relationship over the time period of the projects," said Dr. Mike Sweeney, Depomed vice president, research and development.

The active ingredients in the products that are being developed with Covidien utilizing Depomed's Acuform[®] delivery technology include acetaminophen in combination with opioid analgesics.

Bleeding Is Rare in IVF Patients Who Become Pregnant When Treated with a Combination of Vaginal Progesterone Gel and Oral Estrogen

Business Wire: October 22, 2009 – LIVINGSTON, NJ, and ATLANTA, GA – A prospective, multi-center study demonstrated that in IVF (*in vitro* fertilization) cycles supplemented with once-daily dosing of Crinone vaginal progesterone gel and Estrace oral estrogen, vaginal bleeding is rare in patients who become pregnant. Bleeding does occur in approximately one-quarter of patients who do not become pregnant. These data were presented at the American Society for Reproductive Medicine (ASRM) Annual Meeting in Atlanta, GA.

Vaginal bleeding is reported in some IVF cycles during the luteal phase (the end of a woman's menstrual cycle, when progesterone levels are significantly higher) and can be a major concern for women undergoing infertility treatment. This study, including 66 patients who became clinically pregnant and 53 patients who did not conceive, evaluated the effectiveness of the combination of Crinone with estrogen on luteal-phase bleeding.

James P. Toner, MD, PhD, Atlanta Center for Reproductive Medicine, demonstrated that 36% of patients had spotting or bleeding associated with egg retrieval. No more than two (5%) of the pregnant patients bled on any day past egg retrieval. The combination of vaginal progesterone gel and oral estrogen appears to reduce the incidence of bleeding in IVF patients who become pregnant.

"By treating IVF patients with a combination of Crinone and Estrace, we may succeed in eliminating bleeding in those who achieve pregnancy and reduce the level of stress and concern for patients during this stage of their treatment cycle," stated Toner. "We are continuing to collect data, including data from other centers that use either intramuscular progesterone or do not supplement their Crinone cycles with estradiol, to determine if bleeding rates are different with these other strategies for luteal support."The study was supported by a grant from Columbia Laboratories (Nasdaq: CBRX).

Novel Oral PTH Formulation Using Emisphere's Eligen® Technology Shows Potential Therapeutic Advantages to Available Injectable PTH in Postmenopausal Osteoporotic Women

Business Wire: October 20, 2009 – CEDAR KNOLLS, NJ – Emisphere Technologies, Inc. (OTC BB: EMIS) has announced study results demonstrating that a single dose of the novel oral parathyroid hormone PTH1-34, which utilizes Emisphere's proprietary Eligen[®] drug delivery technology and absorptionenhancer carrier molecule 5-CNAC, achieved potentially therapeutically relevant exposure and safety profiles similar to those of the currently available injectable formulation in healthy postmenopausal women. The results, from a single-center, partially blinded, incomplete cross-over study conducted by Emisphere's partner Novartis Pharma AG, were presented at the 73rd Annual Scientific Meeting of the American College of Rheumatology in Philadelphia.

Emisphere's Eligen[®] technology makes it possible to orally deliver a therapeutic molecule without altering its chemical form or biological integrity. Eligen[®] delivery agents, or "carriers," such as the absorption-enhancer 5-CNAC, facilitate or enable the transport of therapeutic molecules across the mucous membranes of the gastrointestinal tract to reach the tissues of the body where they can exert their intended pharmacological effect.

BioSante Pharmaceuticals Reports Positive LibiGel Safety Data in Phase III Program

Business Wire: October 20, 2009 – LINCOLNSHIRE, IL – BioSante Pharmaceuticals, Inc. (NASDAQ: BPAX) has announced positive safety data in its ongoing LibiGel Phase III clinical development program. For the first time, unblinded data have been reviewed by the independent DMC of the LibiGel Cardiovascular and Breast Cancer Safety Study. Based on this review of unblinded data, the DMC unanimously recommended continuation of the study as described in the study protocol, with no modifications.

BioSante reported that the DMC reviewed all unblinded adverse events in the safety study, including all "serious adverse events" and all "adverse cardiovascular and breast cancer events" in 1,055 women with 883 women-years of exposure. To date, there have been no deaths, one myocardial infarction, and only three breast cancers reported. Therefore, in view of the DMC recommendation, the BioSante LibiGel Phase III development program will continue as planned. BioSante targets submission to the FDA of a new drug application (NDA) by mid-2011.

The LibiGel safety study is tracking a predefined list of cardiovascular events, in agreement with the FDA, including cardiovascular death, myocardial infarction, and stroke, in women 50 years of age or older and suffering from at least two cardiovascular risk factors, including hypertension and diabetes. The objective of the safety study is to show the relative safety of testosterone compared to placebo in the number of cardiovascular events. The incidence of breast cancer also will be tracked over the course of the study.

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In addition to the Phase III Cardiovascular and Breast Cancer Safety Study, BioSante is conducting two LibiGel Phase III efficacy trials. The Phase III efficacy trials of LibiGel in the treatment of FSD are double-blind, placebo-controlled trials that will enroll up to approximately 500 surgically menopausal women, each for a 6-month clinical trial. The efficacy trials are being conducted under an FDA-approved SPA (special protocol assessment) agreement.

Dainippon Sumitomo Pharma Co., Ltd. Completes Acquisition of Sepracor Inc.

Business Wire: October 20, 2009 – OSAKA, Japan, and MARLBOROUGH, MA – Dainippon Sumitomo Pharma Co., Ltd. (DSP) and Sepracor Inc. (NASDAQ: SEPR) have announced the successful completion of DSP's acquisition of Sepracor for US\$23.00 per share in cash. DSP completed the acquisition through a cash tender offer and by exercising an option to acquire additional shares directly from Sepracor followed by a short-form merger of an indirect wholly owned subsidiary of DSP with and into Sepracor on October 20, 2009. Sepracor is now an indirect wholly owned subsidiary of DSP. Additional information about Sepracor is available through its corporate website at www.sepracor.com.

Frost & Sullivan Recognizes Agile Therapeutics for Its Innovative Weekly Low-Dose Contraceptive Patch

PRNewswire: October 16, 2009 – MOUNTAIN VIEW, CA – Based on its annual assessment of companies making innovative contributions in healthcare, Frost & Sullivan has recognized Agile Therapeutics, Inc. with the 2009 North American Pharmaceuticals & Biotechnology Healthcare Innovation of the Year Award for its outstanding achievements in drug development. Agile's lead product, AG200-15 with SKINFUSION[™], offers great potential as a convenient contraceptive option. Not only does this once-per-week contraceptive patch offer maximized patient comfort, it also provides a safe and effective method of birth control.

Of the estimated 62 million women of reproductive age in the United States, approximately 60% are currently using a contraceptive method to prevent pregnancy, according to the National Survey of Family Growth (NSFG). The Centers for Disease Control identifies oral contraceptives as the most popular form of birth control—used by an estimated 11.6 million American women. However, patient compliance is typically characterized as low for oral birth control pills, with 19–47% of patients missing one or more pills per cycle.

"Missed doses result in decreased efficacy and may result in unwanted pregnancies," says Frost & Sullivan Research Analyst Katheryn Symank. "One way to ensure proper patient use is through the use of contraceptives with less frequent or novel dosing, which highlights the strong market opportunity for contraceptives that increase patient convenience."

Agile's AG200-15 utilizes the company's proprietary transdermal drug delivery technology, SKINFUSION[™], in an innovative

low-dose contraceptive patch that administers the proven hormonal combination of levonorgestrel and ethyinyl estradiol, with its established safety profile in oral contraceptives for over 30 years. Agile's transdermal patch combines a patented peripheral and active adhesive system to offer a soft, flexible transdermal patch that looks good and is comfortable to wear for 7 days. Moreover, AG200-15 with SKINFUSION[™] technology allows for stable drug delivery and dependable adhesion over 7 days. AG200-15 is a 28-day regimen, with a patch worn once weekly for 3 weeks, with the fourth week off.

Inovio Biomedical Announces Initiation of HIV Clinical Trial for DNA Vaccine Delivered Using Electroporation

Business Wire: October 15, 2009 – SAN DIEGO, CA – Inovio Biomedical Corporation (NYSE Amex: INO), a leader in DNA vaccine design, development, and delivery, and the HIV Vaccine Trials Network (HVTN) has announced the initiation of a Phase I clinical study of Inovio's PENNVAX[™]-B preventive DNA vaccine delivered using its proprietary electroporation technology. The multi-center study will be conducted at several HVTN clinical sites under a protocol designated HVTN-080.

The study will enroll healthy volunteers to assess the safety of and immune responses to this DNA-based vaccine delivered via *in vivo* electroporation. Inovio previously reported data from nonhuman primates demonstrating up to a 100-fold enhancement in immune responses resulting from the vaccine when delivered via *in vivo* electroporation compared with syringe injection without electroporation. PENNVAX[™]-B is currently in a clinical study being conducted under the HVTN-070 protocol by the same group of collaborators to test the safety and immunogenicity of the vaccine delivered via intramuscular syringe injection without electroporation. The HVTN-080 follow-on study is sponsored by the National Institute of Allergy and Infectious Diseases (NI-AID), an NIH agency.

Dr. J. Joseph Kim, Inovio president and CEO, said, "We are pleased to collaborate with the NIH and HVTN to test the SynCon™ PENNVAX™-B HIV vaccine delivered via electroporation. With our recently announced positive interim immunogenicity data from our clinical trial for our human papillomavirus/ cervical cancer DNA vaccine using a similar technology approach, we are optimistic that electroporation delivery of PENNVAX™-B vaccine will demonstrate similar levels of safety and immunogenicity in this trial." More information about the HVTN-080 trial can be found at www.clinicaltrials.gov.

Critical Pharmaceuticals Secures £1.5 Million from Wellcome Trust to Develop hGH Nasal Spray

Business Wire: October 14, 2009 – NOTTINGHAM, Great Britain – Critical Pharmaceuticals, the specialty pharmaceuticals company, has secured a £1.5 million translation award from the Wellcome Trust to develop a nasal spray of human growth hormone (hGH) using its proprietary CriticalSorb[™] technology as an alternative to injection. hGH, a leading biological drug for the treatment of growth disorders, had global sales of \$2.8 billion in 2007.

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Lisbeth Illum, chief executive officer of Critical Pharmaceuticals, said the hGH market represented a major opportunity for Critical: "This project addresses a large unmet medical need. Biologics continue to grow in importance, representing 30% of new drugs. However, 98% of these are administered by frequent injection, which can cause problems with patient compliance. Human growth hormone is a prime example. Current therapies require daily injections and are strongly disliked by patients and their carers. We believe Critical Pharmaceuticals' CriticalSorb[™] technology has the potential to enable the non-invasive delivery of not just human growth hormone but many other biological drugs with at least equivalent efficacy."

CriticalSorb[™] is an absorption promoter that has been shown to enable the delivery of biological drugs in preclinical studies with exceptional bioavailabilities. It is a GRAS (generally regarded as safe) material that is already marketed in various drug products for intravenous and oral administration.

The Wellcome Trust funding will support the development of a nasal hGH product through a Phase I proof of concept study in human volunteers and determine the long-term nasal tolerability of CriticalSorb[™]. Richard Seabrook, head of business development, Technology Transfer Division, at the Wellcome Trust added, "Technologies for non-injectable administration of complex drugs like human growth hormone are desperately needed. We are very pleased to be funding this application of CriticalSorb[™] which may avoid patient discomfort and improve eventual outcomes for this patient population. We look forward to Critical's results."

Depomed Reports Results from Two Phase III Clinical Trials Evaluating Non-hormonal Therapy for Menopausal Hot Flashes

Business Wire: October 12, 2009 – MENLO PARK, CA – Depomed, Inc. (NASDAQ: DEPO) has announced top-line results from the BREEZE 1 and 2 Phase III clinical trials evaluating the safety and efficacy of Serada[™], an investigational non-hormonal extended-release formulation of gabapentin for the treatment of menopausal hot flashes.

In the higher dose treatment arm of the two doses evaluated, the 1,800-mg dose achieved positive results at 4 weeks. All four coprimary endpoints of the 1,800-mg dose at 4 weeks demonstrated significant reductions in frequency and severity in both clinical trials (*P* values ranged from 0.0001 to 0.004). Of the other four co-primary endpoints of the 1,800-mg dose at 12 weeks, one endpoint was positive (*P* = 0.0026), while the other three endpoints did not achieve statistical significance.

In the lower dose treatment arm, the 1,200-mg dose at 4 weeks achieved statistical significance in three of the four co-primary endpoints. Frequency was significantly reduced in both clinical trials (*P* values of 0.0024 and 0.0117) at 4 weeks. Severity was significantly reduced in only one trial (P = 0.0016). Of the other four co-primary endpoints of the 1,200-mg dose at 12 weeks, one endpoint was positive (P = 0.0024), while the other three endpoints did not achieve statistical significance.

The primary endpoints in the studies were a statistically significant reduction in the frequency and severity of menopausal hot flashes relative to placebo after 4 and 12 weeks of stable treatment. Both patients' and clinicians' impression of overall improvement in the higher dose treatment arm was highly statistically significant relative to placebo in both studies.

BioDelivery Sciences and Meda Launch ONSOLIS (Fentanyl Buccal-Soluble Film)

Business Wire: October 8, 2009 – RALEIGH, NC – BioDelivery Sciences International, Inc. (Nasdaq: BDSI) has announced that its commercial partner Meda will launch the FDA-approved ONSOLIS (fentanyl buccal-soluble film) for the management of breakthrough pain (BTP) in patients with cancer, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

ONSOLIS will be commercialized by Meda Pharmaceuticals, the U.S. subsidiary of Meda, a leading international specialty pharmaceutical company. Meda has initiated a national sales campaign, with a full sales force effort specifically targeting pain management physicians, oncologists, and other healthcare professionals who treat cancer BTP. ONSOLIS will be promoted through a highly experienced and well-trained specialty sales force. BDSI will receive double-digit royalties on the sales of ONSOLIS, as well as milestone payments of up to an additional \$30 million upon reaching specified sales thresholds.

ONSOLIS is the first product to utilize BDSI's patented BioErodible MucoAdhesive (BEMA) drug delivery technology, which consists of a small, dissolvable, polymer film for application to the buccal mucosa (inner lining of the cheek). ONSOLIS utilizes the BEMA technology to deliver the opioid fentanyl. ONSOLIS has been demonstrated in clinical trials to provide rapid plasma concentrations of fentanyl and effective relief of BTP in a novel and easy to use buccal-soluble film formulation. For additional information on BDSI, visit www.biodeliverysciences.com.

Emisphere Technologies Introduces Its First Commercially Available Product, Oral Eligen[®] B₁₂

Business Wire: October 8, 2009 – CEDAR KNOLLS, NJ – Emisphere Technologies, Inc. (OTC BB: EMIS – News) has announced that the company is introducing and launching its first commercially available product, oral Eligen[®] B₁₂ (100 µg). Oral Eligen[®] B₁₂ (100 µg) has been specifically developed to help improve vitamin B₁₂ absorption and bioavailability with a patented formulation.

"We are very excited that our first product introduction will help to advance the field of nutrition by offering a superior oral formulation to improve Vitamin B_{12} absorption and bioavailability," stated Michael V. Novinski, president and chief executive officer, Emisphere Technologies. "By partnering with Life Extension, a highly respected company in the nutrient and supplement field, we are confident that we will have the proper marketing and sales infrastructure to allow oral Eligen[®] B_{12} (100 mcg) to be successful."

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Emisphere is also working on a high-dose medical food Eligen[®] B_{12} product (1,000 µg) to compete directly with the standard high-dose B_{12} injection currently administered to millions of individuals under medical supervision for B_{12} deficiency. It is estimated that between 30 and 40 million high-dose injections of B_{12} are given each year in the United States alone, and over 250 million such injections are given worldwide. Emisphere is currently conducting a clinical study with Eligen[®] B_{12} (1,000 µg), which is expected to be completed in 2010.

Particle Sciences, Inc. and Dow Corning Corporation Cooperate to Develop New Product Technology

PRNewswire: October 6, 2009 - BETHLEHEM, PA - Particle Sciences has announced that it have been engaged by Dow Corning to develop technology for a key Dow Corning product development project. Bruce Frank, director of project management for Particle Sciences remarked, "This is a little outside our normal focus of pharmaceutical development but the technological approach is perfectly analogous. We expect to provide a novel and robust solution that allows Dow Corning to develop a product that will benefit its customers." Andrew Loxley, director, new technologies for Particle Sciences added, "Particle Sciences is leveraging its extensive experience and expertise to evaluate a number of technologies deemed suitable for the complex performance characteristics of this particular product. Developing a suitable approach will lead directly to a fast-track scale-up and technology transfer program to commercialize this product." Additional terms of the agreement have not been released.

Transdel Pharmaceuticals Announces Positive Phase III Study Results for Lead Topical Pain Drug Ketotransdel®

PRNewswire-FirstCall: October 6, 2009 – LA JOLLA, CA – Transdel Pharmaceuticals, Inc. (OTC Bulletin Board: TDLP), a specialty pharmaceutical company focused on developing topically administered products using its proprietary transdermal delivery platform, has announced positive top-line clinical results for its lead pain drug Ketotransdel[®] in a Phase III trial that evaluated the efficacy and safety of the drug in acute soft-tissue injuries of the upper and lower extremities. Ketotransdel[®] is composed of a transdermal formulation of ketoprofen, an NSAID (non-steroidal anti-inflammatory drug), and the company's innovative proprietary Transdel[™] drug delivery system.

Further detailed analyses are currently ongoing, and the company intends to present the clinical trial results at upcoming medical conferences and in peer-reviewed journals. The company expects that Ketotransdel[®], if and when approved by the U.S. Food and Drug Administration (FDA), could become the first topical NSAID cream product available by prescription in the United States for acute pain management. Transdel is seeking a commercial partner for Ketotransdel[®] and is actively pursuing discussions with U.S.- and foreign-based potential partners with sales and marketing infrastructures.

Depomed, Inc. Announces Positive Top-Line Results from Phase III Clinical Trial of DM-1796 in Postherpetic Neuralgia

Business Wire: October 5, 2009 – MENLO PARK, CA – Depomed, Inc. (NASDAQ: DEPO) has announced top-line results from a Phase III clinical trial demonstrating that DM-1796 (also referred to as gabapentin ER) achieved a statistically significant reduction in pain associated with postherpetic neuralgia (PHN) versus placebo using the baseline observation carried forward (BOCF) method required by the FDA. The primary endpoint measured pain scores from baseline to the end of a 10-week treatment period using the numerical Likert pain scale.

DM-1796 is an investigational extended-release, once-daily tablet formulation of gabapentin for the treatment of PHN. Depomed has licensed DM-1796 to Solvay Pharmaceuticals, Inc. in the United States, Canada, and Mexico for the treatment of pain.

"This study demonstrates the effectiveness of our proprietary drug delivery technology in producing meaningful clinical benefits for PHN patients. We look forward to working with our strong and committed partner, Solvay Pharmaceuticals, through the regulatory process and making DM-1796 a commercial success," said Carl A. Pelzel, president and chief executive officer of Depomed.

Titan Announces Award of NIH Grant for Probuphine Clinical Development

Business Wire: October 1, 2009 - SOUTH SAN FRANCISCO, CA - Titan Pharmaceuticals, Inc. (Pink Sheets: TTNP) has announced that the National Institutes of Health (NIH) has awarded a Research and Research Infrastructure Grand Opportunities grant to the company through the American Reinvestment and Recovery Act of 2009 (ARRA). The two-year grant for Probuphine clinical development is expected to provide approximately \$7.6 million, with a first-year award of approximately \$5.6 million now made available to Titan by the NIH. This grant will be administered by the National Institute on Drug Abuse (NIDA). These funds will directly support a substantial part of the second Phase III clinical study to confirm the safety and efficacy of Probuphine for the treatment of opioid addiction. Probuphine is an innovative, long-term, implantable formulation of buprenorphine that is designed to provide a constant, low level of drug for 6 months following a single treatment. It has the potential to address the key issues of treatment non-compliance and illicit diversion often reported with the currently available sublingual pill formulation.

Probuphine has been shown to be safe and effective in the three Phase III studies that have been completed to date, including a 6-month, double-blind, placebo-controlled safety and efficacy trial; 6-month, open-label re-treatment safety trial; and pharmacokinetic safety study. In the News continued from page 33

Halozyme Presents Phase II Results for Regular Insulin-PH20 Confirming Faster Insulin Absorption and Superior Glucose Control

Business Wire: October 1, 2009 – SAN DIEGO, CA – Halozyme Therapeutics, Inc. (Nasdaq: HALO) has announced additional Phase II results that demonstrated faster insulin absorption and increased peak insulin concentrations in type 1 diabetic patients after co-administration of its recombinant hyaluronidase enzyme (rHuPH20 or PH20) with Humulin[®] R (regular human insulin), a mealtime insulin. In addition, study results also showed a significant reduction in postprandial blood glucose levels following administration of a standardized test meal and less hypoglycemia compared with Humulin R alone. These results provide additional confirmation in type 1 diabetes patients of the effects observed in a Phase I study conducted in healthy volunteers. The company presented these results at the European Association for the Study of Diabetes in Vienna.

Onset Therapeutics Launches BenzEFoam[™] Emollient Foam for Body Acne

Business Wire: October 1, 2009 – CUMBERLAND, RI – Onset Therapeutics, a specialty pharmaceutical company focused on dermatology, has announced the commercial availability of BenzEFoam[™] (benzoyl peroxide) 5.3% emollient foam, the first prescription foam formulation of benzoyl peroxide. BenzEFoam[™] emollient foam is indicated for the topical treatment of mild to moderate *Acne vulgaris*. BenzEFoam[™] emollient foam is currently available through all major drug wholesalers. For more information, visit www.BenzEFoam.com.

Nanotherapeutics Acquires Assets of DelSite

Business Wire: October 1, 2009 – ALACHUA, FL – Nanotherapeutics, Inc., a privately held specialty biopharmaceutical company, has acquired certain assets from DelSite (formerly Carrington Laboratories, Inc.) out of Chapter 7 bankruptcy proceedings in the U.S. Bankruptcy Court for the Northern District of Texas, Dallas Division.

Before the bankruptcy, DelSite was headquartered in Irving. TX, and had manufacturing facilities in Irving and Costa Rica and a research lab in College Station, TX. The DelSite assets acquired include the patented, naturally derived, biocompatible, resorbable biopolymer GelSite[®], the GelVac[™] nasal powder platform technology, lab equipment, intellectual property, and other related products. The GelSite[®] polymer has been tested in various vaccine formulations for administration by the nasal route and injection.

Nanotherapeutics also acquired the *in situ* gelling nasal powder influenza vaccine Phase I clinical program based on the novel GelVac[™] powder formulation that incorporates the GelSite[®] polymer. GelSite[®] provides mucoadhesion and sustained antigen release within the nasal cavity for enhancement of the immune response. This vaccine possesses distinct potential advantages, including induction of both mucosal and systemic immunity, room-temperature stability, prolonged shelf life, cold-chain–free distribution, and needle-free administration that can be particularly valuable in meeting the needs for pandemic preparation and stockpiling.

September 2009

DOR BioPharma Announces Corporate Name Change to Soligenix and Begins Trading Under New Ticker Symbol SNGX

PRNewswire-FirstCall: September 30, 2009 – PRINCETON, NJ – DOR BioPharma, Inc. (OTC Bulletin Board: SNGX), a late-stage biotechnology company, has completed a corporate name change from DOR BioPharma, Inc. to Soligenix, Inc. As a result of the name change, the company's shares of common stock will immediately begin trading under the new ticker symbol SNGX.

"We are pleased to announce the name change of our company to Soligenix," stated Christopher J. Schaber, Ph.D., president and CEO of Soligenix. "The name 'Soligenix' is derived in part from the Latin word 'Solis,' meaning sun. The name change heralds the new corporate stability and direction that we have worked hard to establish over the last several years."

Dr. Schaber continued, "We are also looking forward to the imminent initiation of our confirmatory Phase 3 clinical trial of orBec[®] in GI GVHD under a Special Protocol Assessment (SPA) with the FDA. In connection with the initiation of the trial, we expect to receive a \$1 million milestone payment from Sigma-Tau in accordance with our collaboration agreement." Soligenix's address and contact numbers will also remain the same. Soligenix's new web address is www.soligenix.com.

NIAID to Fund Development of Emergent BioSolutions' Advanced Anthrax Vaccine Candidate

Business Wire: September 30, 2009 – ROCKVILLE, MD – Emergent BioSolutions Inc. (NYSE: EBS) has announced that it was awarded a cooperative agreement from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, to further the development of one of Emergent's advanced anthrax vaccine candidates, dmPA7909. The novel vaccine candidate is designed to have characteristics that will make it ideal to meet the U.S. government's needs for an advanced anthrax vaccine, such as the potential to confer a rapid immune response following only two doses, long-term stability to enable ambient storage in the Strategic National Stockpile, and the potential to be distributed in a national emergency without the need for cold-chain storage conditions.

The anthrax vaccine candidate is composed of the double-mutant recombinant protective antigen (dmPA), which has been genetically engineered for improved stability. dmPA is adsorbed to Alhydrogel[®], combined with the immunostimulatory compound CPG 7909 (VaxImmune[™]), and formulated as a dry powder. Emergent is employing proven stabilizing technologies for each of the components in the vaccine formulation, seeking to maximize vaccine stability even at elevated temperatures and to extend shelf life.

LifeCycle Pharma Announces Positive Results from a 12-Month Extension Phase of the Phase II Clinical Study of LCP-Tacro Once Daily in Stable Liver Transplant Patients

Business Wire: September 29, 2009 – HØRSHOLM, Denmark – LifeCycle Pharma A/S (CSE: LCP) has announced positive results from a completed 12-month extension phase of the Phase II clinical study of LCP-Tacro tablets in stable liver transplant patients. LCP-Tacro is a once-daily immunosuppression drug to prevent rejection after organ transplantation. These new data demonstrate that LCP-Tacro tablets for stable liver patients continues in the extension phase of the study to have a potential best-in-class profile compared with the currently marketed twice-daily tacrolimus capsule, Prograf[®]. Maintaining the once-daily administration improved bioavailability by approximately 30%, leading to a 70% dosing compared with Prograf[®] in the initial part of the study and reduced variability (peak/trough ratio), with a 30% reduced peak.

According to LCP, the positive data from the 12-month extension phase of the Phase II study in stable liver transplant patients provide confirmation of the proposed dosing regimen. With these latest results, as well as the results announced in August 2009 from the clinical Phase IIb pharmacokinetic studies, LCP can now initiate discussions with the FDA regarding the design and timing of the Phase III program for liver transplant patients. For further information, visit www.lcpharma.com.

Acrux Announces Successful AXIRON[™] Phase III Trial Results

Business Wire: September 29, 2009 – NEW YORK, NY – Australian company, Acrux, has announced positive results from a Phase III trial evaluating the safety and efficacy of AXIRON[™] in 155 men with testosterone deficiency (hypogonadism), across 26 sites in 6 countries, in which the primary endpoint of 84% exceeded the benchmark requirement of 75%.

AXIRON[™] is applied to the underarm using a unique "no-touch" applicator. Upon approval, AXIRON[™] would be the first and only pharmaceutical product applied to the armpit (in much the same way as an antiperspirant). As well as existing patents that protect AXIRON[™] to 2017, Acrux has a new patent that, when granted, will extend protection of this novel, class-leading feature until 2026.

In 2008 Acrux published results from market research conducted with both patients and physicians in the United States, in which two-thirds of patients confirmed that they would prefer AXIRON[™] to their existing gel treatment and 87% of physicians said that they would offer AXIRON[™] to their patients who currently use gels. Importantly, 94% of patients who tried AXIRON[™] rated it better than testosterone gels in its ability to reduce the risk of transference of testosterone to others. In addition, 92% of physicians surveyed who prescribe gels as firstline therapy rated AXIRON[™] as very good or excellent in its ability to reduce the risk of transference to others compared with gels. "We are excited by the AXIRON[™] Phase III trial results and are now well positioned to submit our NDA by the end of 2009," said Dr. Richard Treagus, CEO and managing director of Acrux. "These results, along with our recent meeting with the FDA, place us in a strong position as we initiate a process to select marketing partners for what is a unique testosterone delivery system that we believe will be a patient preferred treatment for hypogonadal men," he said.

pSivida Reports Safety and Efficacy Results from 18-Month Interim Readout of Human PK Iluvien Study

Business Wire: September 29, 2009 – WATERTOWN, MA – pSivida Corp (NASDAQ: PSDV) (ASX: PVA), a leading drug delivery company that has developed two of the only three products approved by the FDA for the long-term, sustained release delivery of drugs to treat chronic back of the eye disease, has reported the interim 18-month safety and efficacy results from the first human pharmacokinetic study (PK study) of Iluvien. The PK trial is being conducted by Alimera Sciences, the licensee for Iluvien.

Dr. Paul Ashton, CEO of pSivida, said: "We are encouraged with the results we see from this small, 37-patient PK study, particularly as it relates to the safety profile. The lower incidence of elevated IOP with Iluvien in the PK study compared to the higher incidence shown in the data for studies of Retisert[®] (one of our FDA-approved, surgically inserted products which uses the same steroid), is very promising. In this PK study, we see an increase in efficacy in the high dose group and a decrease in efficacy in the low dose group in the results at 18 months as compared to 12 months. While the efficacy data is encouraging, these are very small patient numbers. Data from the almost 1,000 patient Phase III FAME[™] trial is due at the end of the year, which will give us a clearer picture of the relative efficacy of Iluvien dosages."

This 36-month, open-label, Phase II study is designed primarily to assess systemic exposure of the corticosteroid fluocinolone acetonide (FA), after administration of Iluvien in patients with DME. Secondarily, the PK study is designed to provide information on the safety and efficacy of Iluvien in a DME patient population. A total of 37 subjects were enrolled in the PK study: 20 patients on the low dose of Iluvien (approximate 0.23 μ g/day dose), and 17 patients on the high dose of Iluvien (approximate 0.45 μ g/day dose).

Iluvien is an investigative, extended release intravitreal insert currently under development for the treatment of diabetic macular edema (DME). Each Iluvien insert is designed to provide a sustained therapeutic effect of up to 36 months for the low-dose Iluvien and up to 24 months for the high-dose Iluvien. Iluvien is inserted into the patient's eye with a 25-gauge needle, which allows for a self-sealing wound. This insertion is very similar to an intravitreal injection, a procedure commonly employed by retinal specialists. An NDA for Iluvien is expected to be filed with the FDA early in 2010 by Alimera.

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Halozyme Begins Clinical Trial to Compare Three Insulin Analogs and Provides Update on Ultrafast Insulin Program

Business Wire: September 28, 2009 – SAN DIEGO, CA – Halozyme Therapeutics, Inc. (Nasdaq: HALO) has announced the commencement of a Phase I clinical study that will assess the effects of three approved prandial (mealtime) insulin analogs administered with its proprietary rHuPH20 (PH20) hyaluronidase enzyme compared with each of the analogs alone. This randomized, three-way cross-over design, euglycemic clamp study will compare the postprandial pharmacokinetics (PK) and glucodynamics (GD) of the insulin analogs. Previous studies conducted by Halozyme have demonstrated that the combination of insulin lispro (Humalog[®]) with PH20 yielded faster systemic insulin absorption, increased peak insulin concentrations, and improved glycemic control that better mimicked the normal metabolic response to physiologic insulin release compared with insulin lispro alone.

"This clinical study is designed to investigate and compare the pharmacokinetic and glucodynamic effects of our PH20 enzyme administered with each of the three commercially available insulin analogs," stated Doug Muchmore, M.D., Halozyme vice president of clinical development for endocrinology. "To our knowledge, this is the first study that will compare all three analogs in a head-to-head study of this type. It will broaden our experience with additional analogs and provide insight regarding how our enzyme may influence their effects." Additional information about this study can be found at clinicaltrials.gov using the identifier NCT00979875. Results of this study should be available by 2010. For more information, visit www.halozyme.com.

Pieris AG Enters into Anticalin Collaboration with Allergan, Inc.

PRNewswire: September 15, 2009 – FREISING-WEIHEN-STEPHAN, Germany – Pieris AG has entered into a collaboration agreement with Allergan, Inc. (NYSE: AGN) that combines Pieris' proprietary Anticalin technology with Allergan's expertise in drug delivery and ophthalmic drug development, with a goal of developing agents for the treatment of serious ocular disorders.

Under the terms of the collaboration, Pieris will work with Allergan to optimize existing lead Anticalins and design novel Anticalins. Allergan will be solely responsible for all discovery, development, and commercialization costs and will be responsible for clinical development and related activities and commercialization. Pieris has granted Allergan a worldwide and exclusive license to Allergan for specific Anticalins to be used in the field and in return will receive an upfront payment of \$10,000,000. Further financial terms were not disclosed.

Pieris is developing Anticalins for the treatment of a variety of disorders. Anticalins are a novel class of biologic drugs that are engineered to bind disease-relevant targets with high affinity and specificity. They are based on naturally occurring proteins called lipocalins, which are present in human plasma and body fluids, where they bind, store, and transport various small molecules, including lipids and hormones. Anticalins possess multiple distinguishing features, including an inherently high degree of stability, a property that lends itself to depot formulation strategies. Anticalins benefit from their small size (20 kDa) and are produced in micro-organisms, thus conferring a significant cost advantage to the production of the therapeutic agent.

"Allergan has world class expertise in ophthalmology, and we look forward to working together to develop Anticalins as important medicines for the treatment of a number of ocular diseases. This collaboration further validates the potential for Anticalins as a new drug-class," said Claus Schalper, interim CEO of Pieris.

Alexza Announces Preliminary Results from Its AZ-104 (Staccato Loxapine) Phase IIb Trial in Patients with Migraine Headache

PRNewswire-FirstCall: September 14, 2009 – MOUNTAIN VIEW, CA – Alexza Pharmaceuticals, Inc. (Nasdaq: ALXA) has announced the preliminary results from its Phase IIb clinical trial of AZ-104 (Staccato loxapine) in 366 patients with migraine headache. Both AZ-104 dose groups trended toward statistical significance, but the study did not meet its primary endpoint, which was defined as pain relief at the 2-hr time point, compared with placebo. There were no serious adverse events in the clinical trial, and AZ-104 was generally safe and well tolerated in this patient population.

"The failure to reach statistical significance on the primary endpoint is disappointing, as we were not able to reproduce the positive clinical findings from our AZ-104 Phase 2a proof-ofconcept clinical trial," said James V. Cassella, Ph.D., senior vice president, research and development at Alexza. "Loxapine is a drug that had not been previously studied in migraine patients, except for our earlier proof-of-concept study. As part of our collaboration with Symphony Allegro, we initiated this migraine program in 2007 to investigate whether loxapine might be a viable product candidate for migraine, due to the scientific rationale that loxapine's primary mechanism of action (dopamine antagonism) has shown effectiveness in treating migraine."

"We continue to be impressed with Staccato's ability to safely and very accurately deliver a portfolio of drugs in a simple, one-breath, patient-controlled inhalation," said Thomas B. King, president and CEO of Alexza. "The uniqueness of our Staccato technology allows us to examine medicines for both known and new indications, and we will continue to do so in a patient setting. Not every clinical trial will necessarily have positive findings. However, there is much value we can bring to patients through our Staccato technology, as evidenced by our late-stage, pre-NDA program with AZ-004 (Staccato loxapine, high dose) for the acute treatment of agitation."

Mpex Pharmaceuticals Announces Positive Phase IIb Clinical Trial Results with Aeroquin (MP-376) Treatment in Cystic Fibrosis Patients

PRNewswire: September 10, 2009 – SAN DIEGO, CA – Mpex Pharmaceuticals, Inc. has announced positive data from its Phase IIb clinical trial with Aeroquin (a novel aerosol formulation of levofloxacin [MP-376]) in cystic fibrosis (CF) patients. Trial results showed that nebulized Aeroquin met the primary endpoint of reducing bacterial counts of *Pseudomonas aeruginosa* in sputum after 28 days of dosing versus placebo. Clinically and statistically significant improvements versus placebo were also seen in a number of important clinical endpoints, including FEV1, percent predicted FEV1, FEF25-75 (all measures of respiratory function), and time to need for anti-pseudomonal antibiotics (a measure of exacerbations). Both once- and twicedaily dosing of Aeroquin showed activity in this trial, with higher doses showing improved responses. Aeroquin was well tolerated, and no significant change in antibiotic resistance was observed in this study. Detailed results will be presented at a major respiratory meeting in the near future.

UCSB Researchers Develop Drug Delivery System Using Nanoparticles and Lasers

Eurekalert: September 9, 2009 – SANTA BARBARA, CA – Researchers at UC Santa Barbara have developed a new way to deliver drugs into cancer cells by exposing them briefly to a nonharmful laser. Their results were published in a recent article in *ACS Nano*, a journal of the American Chemical Society.

"This entirely novel tool will allow biologists to investigate how genes function by providing them with temporal and spatial control over when a gene is turned on or off," explained Norbert Reich, senior author and a professor in the Department of Chemistry and Biochemistry at UCSB. "In a nutshell, what we describe is the ability to control genes in cells and we are working on doing this in animals simply by briefly exposing them to a non-harmful laser."

The scientists used cancer cells from mice, and grew them in culture. They then introduced gold nanoshells with a peptidelipid coating that encapsulated silencing ribonucleic acid (siRNA), which was the drug that was taken up by the cells. Next, they exposed the cells to a non-harmful infrared laser.

"A major technical hurdle is how to combine multiple biochemical components into a compact nanoparticle which may be taken up by cells and exist stably until the release is desired," said Gary Braun, first author and a graduate student in UCSB's Department of Chemistry and Biochemistry. "Laser-controlled release is a convenient and powerful tool, allowing precise dosing of particular cells within a group. The use of biologically friendly tissue penetration with near-infrared light is the ideal for extending this capability into larger biological systems such as tissues and animals."

The authors demonstrated, for the first time, the delivery of a potent siRNA cargo inside mammalian cancer cells, which were released by exposing the internalized nanoparticles for several seconds to a pulsed near-infrared laser tuned for peak absorption with a specific spatial pattern. The technique can be expanded to deliver numerous drug molecules against diverse biological targets.

Oramed Pharmaceuticals Commences Human Clinical Trials of an Oral GLP-1 Analog

PRNewswire-FirstCall: September 9, 2009 – JERUSALEM, Israel – Oramed Pharmaceticals, Inc. (OTCBB: ORMP.OB), a developer of oral drug delivery systems, has received approval from the Institutional Review Board (IRB) to commence human clinical trials of an oral GLP-1 analog. This approval was granted after successful preclinical results were reported. The trials will be conducted on healthy volunteers at Hadassah University Medical Center in Jerusalem.

Currently, GLP-1 analogs are only available in injection form. The oral administration of GLP-1 analogs may convey physiological advantages for diabetic patients, as the hormone mimics the physiological route of incretin absorption. GLP-1 analogs belong to the incretin family of drugs, which have pleiotropic effects desirable in the management of diabetes. Among the more important effects are the insulinotropic effects and resultant reduction in blood glucose levels, inhibition of glucagon secretion, and restoration of β -cell mass. GLP-1 analogs are also associated with weight loss, which is very desirable in patients with diabetes.

"The move from preclinical trials to human clinical trials of ORMD-0901 marks a strategic milestone for the company. We have expanded our platform technology and will now have the opportunity to demonstrate its effectiveness in another important family of polypeptide drugs for diabetes, which is currently only available in injection form," said Oramed, CEO Nadav Kidron.

Oramed is currently conducting Phase IIb clinical trials of its flagship product, ORMD-0801, an oral insulin capsule. For more information, visit http://www.oramed.com.

Wilmington Pharmaceuticals Receives FDA Approval for Orally Disintegrating Metoclopramide Tablet

PRNewswire: September 9, 2009 – WILMINGTON, NC – Wilmington Pharmaceuticals has announced that the U.S. Food and Drug Administration (FDA) has granted marketing approval for METOZOLV ODT (metoclopramide HCl), an orally disintegrating formulation of metoclopramide for the treatment of gastroesophageal reflux disease (GERD) and diabetic gastroparesis. Wilmington has licensed METOZOLV ODT to Salix Pharmaceuticals, Inc., a specialty pharmaceutical company with a focus on gastrointestinal disorders.

Wilmington Pharmaceuticals designed METOZOLV ODT to improve the delivery mode for patients who have difficulty swallowing pills or liquids due to their disease state. Orally disintegrating METOZOLV ODT tablets rapidly melt on the tongue, thereby eliminating the need for swallowing pills with water, according to Eugene Haley, founder and CEO of Wilmington Pharmaceuticals.

"We are extremely pleased to have achieved a significant milestone, the approval of a patient-friendly formulation of an

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established drug that addresses the needs of patients who cannot swallow traditional tablets," Haley said. "As developers of rapiddissolve formulations for proven drugs, we provide our industry partners with significant potential for commercial gain without typical risks, costs, and time commitments associated with new drug development."

Salix Pharmaceuticals will market METOZOLV ODT under a licensing agreement with Wilmington Pharmaceuticals. METOZOLV ODT is indicated for relieving symptoms in adults with acute and recurrent diabetic gastroparesis and for short-term therapy (4–12 weeks) in adults with symptomatic, documented GERD that fails to respond to conventional therapy.

Hovione's TwinCaps[®] Inhaler Delivers Successfully in Phase III Clinical Trials for Influenza

PRNewswire: September 8, 2009 – LOURES, Portugal – Hovione is pleased to announce that its TwinCaps[®] inhaler licensees Daiichi Sankyo Co. Ltd. (Tokyo, Japan) and Biota Holdings Ltd. (Victoria, Australia) have both announced successful Phase III trials for CS-8958, a new long-acting neuraminidase inhibitor for treatment of influenza (known as a prodrug of laninamivir).

CS-8958, co-owned by Daiichi Sankyo and Biota, is delivered by TwinCaps[®], a patented dry-powder inhaler that Hovione specifically designed for the treatment and prevention of influenza infections in both seasonal and pandemics situations. The device was designed to be used across a broad range of patient inspiratory flow rates and requires a single priming action prior to use.

In the Phase III trials conducted by Daiichi Sankyo, a single inhaled dose of CS-8958 was shown to be as effective as oseltamivir (Tamiflu®) administered orally twice daily for 5 days (total of 10 doses). A parallel Phase II/III trial of CS-8958 in pediatric patients also met the primary and secondary endpoints compared with oseltamivir.

CS-8958 is an important new treatment against influenza, as current neuraminidase inhibitors for influenza require daily or more frequent dosing, whereas CS-8958 requires one dose for treatment and possibly once-weekly dosing for prophylaxis. The ability to dose patients on a weekly, or even less frequent, basis offers numerous benefits. First, the volume of product stored in stockpile reserves may be smaller, and second, a single-dose treatment offers better patient compliance and convenience.

TwinCaps[®], for which patent applications were filed worldwide in 2006, is an innovative inhaler, delivering a significant dose of drug to the lungs, in a simple device comprising only two plastic components. Daiichi Sankyo and Biota have a worldwide exclusive license to use TwinCaps[®] for the treatment and prevention of influenza infections. TwinCaps[®] is available for licensing for use in other indications, including antibiotic and vaccine delivery. Hovione is now planning for large-scale manufacturing of the TwinCaps[®] devices. Daiichi Sankyo intends to submit its market authorization application for Japan by March 2010, while Biota continues to advance the clinical development program required to support registration in the United States and United Kingdom.

New Gel Technology Reaches Hidden Areas of the Mouth

PRNewswire: September 8, 2009 – PITTSBURGH, PA – The makers of Aquafresh[®] and Sensodyne[®] have introduced a breakthrough technology in toothpaste—new Iso-active[®] foaming gel. Iso-active[®] has a revolutionary delivery system that disperses active ingredients quickly, penetrating hard-to-reach areas of the mouth.

According to a recent survey, 68% of adults do not realize how much of their tooth surface is actually hidden between the teeth. Generating twice the foam volume as ordinary toothpaste, Isoactive[®] spreads active ingredients around the mouth, reaching the surfaces between the teeth to provide a whole mouth clean.

"With 40 percent of the tooth surface in between the teeth, it is important that we are getting in those hidden areas of the mouth to achieve overall oral health," says Dr. Kourosh Maddahi, a nationally recognized dentist. "The unique foaming action and advanced delivery of Iso-active ensure my patients are getting in to those hard-to-reach areas for a deeper clean."

Iso-active[®] is a first-of-its-kind toothpaste that is delivered in a novel canister format with a gel-to-foam action. The toothpaste is dispersed from the canister as a gel and turns to foam in the mouth as a result of the ingredient isopentane. Isopentane responds to increases in temperature caused by the warmth of the mouth. This relatively small increase in temperature causes the isopentane to evaporate, which stimulates the enhanced foaming action of the product.

Both Sensodyne[®] and Aquafresh[®] Iso-active[®] are available at most drug, grocery, and mass merchandise retail outlets in the United States. For information, visit www.Aquafresh.com or www.Sensodyne.com.

August 2009

Hisamitsu Pharmaceutical Completes Acquisition of Noven Pharmaceuticals

PRNewswire-FirstCall: August 27, 2009 – TOSU, Japan, and MIAMI, FL – Hisamitsu Pharmaceutical Co., Inc. (TSE: 4530) and Hisamitsu U.S., Inc. have announced the completion of their acquisition of Noven Pharmaceuticals, Inc. pursuant to a shortform merger of Northstar Merger Sub, Inc., a wholly owned subsidiary of Hisamitsu U.S., Inc., with and into Noven. Pursuant to the Agreement and Plan of Merger among the companies, at the effective time of the merger all remaining outstanding shares of Noven's common stock, other than those held by stockholders who properly perfect appraisal rights under Delaware law, were converted into the right to receive \$16.50 per share in cash. As a result of the transaction, Noven has become a wholly owned subsidiary of Hisamitsu U.S., Inc. Hisamitsu

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expects Noven to continue as a stand-alone business unit under the Noven name, operating at its current locations in Miami and New York and with its existing workforce.

Endo Pharmaceuticals to Partner with ProStrakan to Commercialize FORTESTA™ in the United States

PRNewswire-FirstCall: August 26, 2009 – CHADDS FORD, PA – Endo Pharmaceuticals (Nasdaq: ENDP) has signed an agreement with U.K.-based ProStrakan Group plc (LSE: PSK) for the exclusive right to commercialize FORTESTA[™] (testosterone gel) 2% in the United States.

FORTESTA[™], a patented 2% testosterone transdermal gel for testosterone replacement therapy in male hypogonadism, utilizes a metered dose delivery system designed to permit accurate dose adjustment to individual patient requirements. This product is registered in the United States, where the Food and Drug Administration (FDA) is currently reviewing ProStrakan's New Drug Application submission.

"We are committed to advancing men's health with effective new medicines. Being in a position to potentially offer this treatment, alongside our new long-acting injectable testosterone product, will help fill an important gap in testosterone replacement," said David Holveck, president and chief executive officer of Endo Pharmaceuticals. "This treatment option is synergistic with our recent therapeutic expansion and strengthens our portfolio in urology and endocrinology."

Frost & Sullivan Honors Oramed Pharmaceuticals with the 2009 European Oral Drug Delivery Technology Innovation Award

PRNewswire-FirstCall: August 25, 2009 – JERUSALEM, Israel – Oramed Pharmaceuticals Inc. (OTCBB: ORMP.OB) (www.oramed.com), a developer of oral delivery systems, has announced that it is the recipient of the 2009 Frost & Sullivan European Oral Drug Delivery Technology Innovation Award.

Oramed Pharmaceuticals is developing a platform technology to create oral delivery systems for drugs and vaccines delivered via injection. Oramed focuses on the treatment of diabetes through its proprietary flagship product, an oral insulin capsule that is currently in Phase IIb clinical trials. Oramed's research pipeline also includes other product candidates, such as an oral GLP-1 analog capsule.

"We are honored to receive the 2009 European Oral Drug Delivery Technology Innovation Award," said Nadav Kidron, Esq., Oramed CEO. "Being recognized for our leadership position in the oral drug delivery field by Frost & Sullivan is an encouraging validation of our progress.

Health Canada Approves Abbott's XIENCE V Drug-eluting Stent

PRNewswire-FirstCall: August 24, 2009 – ABBOTT PARK, IL – Abbott (NYSE: ABT) has received approval from Health Canada for the XIENCE V everolimus-eluting coronary stent system for the treatment of coronary artery disease (CAD). XIENCE V is the only drug-eluting stent to have demonstrated superiority over the TAXUS paclitaxel-eluting coronary stent system in the primary endpoints of two randomized, pivotal (Phase III) clinical trials. Abbott will launch XIENCE V in Canada immediately.

"XIENCE V is an important next-generation treatment option combining impressive deliverability with demonstrated efficacy and safety," said Guy Leclerc, M.D., FRCPC, FACC, interventional cardiologist and associate professor of research, Centre Hospitalier de l'Universite de Montreal. "With strong, long-term data supporting it, XIENCE V is a welcome addition for treating patients with coronary artery disease."

The XIENCE V drug-coated stent is used to treat CAD by propping open a narrowed or blocked artery and releasing the drug, everolimus, in a controlled manner over time to help prevent the artery from becoming blocked again following the stent procedure.

PCI Biotech Commences Phase I/II Trials of Amphinex®

PRNewswire-FirstCall: August 24, 2009 – OSLO, Norway – PCI Biotech Holding ASA, the Norwegian drug delivery company focusing on effective delivery of cancer therapeutics, has announced that the first patient has received treatment in the Phase I/II trial with the lead candidate Amphinex[®], which uses a new approach called photochemical internalization. The patient was treated at the University College Hospital (UCH) in London. PCI's proprietary photosensitizer Amphinex[®] is in this study combined with the therapeutic agent bleomycin. When activated by light, Amphinex[®] promotes effective delivery of large therapeutic molecules such as bleomycin through triggered endosomal release. The trial will investigate a broadly representative spectrum of cancers, including head, neck, and breast, to demonstrate the safety and potential of this new approach.

The primary objective of this study is to assess the maximum tolerated dose of Amphinex[®] in PCI treatment with bleomycin. Secondary objectives include determination of the antitumor activity of Amphinex[®] when used in combination with bleomycin, as well as its pharmacokinetics.

Colin Hopper, principal investigator at UCH, said: "At UCH we are dedicated to high quality patient care and we have extensive experience in the use of photodynamic therapy to treat cancer patients. PCI is a very exciting new approach in photodynamic medicine that has shown great promise in preclinical studies. We are very proud of being the first centre to move this new technology into the clinic."

Per Walday, CEO of PCI Biotech, said: "This first in human trials is an important step forward for the company. We are confident that our approach addresses one major challenge in oncology how to deliver therapeutics with large enough loads to effectively

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destroy tumours while at the same time reducing the risk of damaging healthy cells. Bleomycin is ideal for demonstrating this—there is no doubt about its therapeutic potential, but until now delivery problems and associated toxicity have prevented the realisation of its full potential. We expect to have the first preliminary results of the trial early in 2010."

"In addition, whilst our main initial focus is cancer, we strongly believe the PCI technology also has potential to improve the effect of emerging treatments such as gene therapy and therapies based on nanotechnology or on biotechnological principles. In particular, we are looking at siRNA through projects funded by EU and by the Norwegian Research Council."

XSpray Launches GMP Production Facility

PRNewswire: August 20, 2009 – STOCKHOLM, Sweden – XSpray Microparticles AB, a life science technology company, has launched its new GMP production facility in Malmo, Sweden. In addition to offering particle development and characterization services, XSpray can now provide customers with high-quality drug particles and powders for use in their clinical studies.

XSpray's RightSize particle manufacturing technology, a groundbreaking solution for pharmaceutical particle development and production is based on supercritical fluid technology. Overcoming many of the drawbacks of traditional micronization, it is well suited to demanding applications, such as inhaled compounds, sparingly soluble compounds, and biopharmaceuticals. Offering all the advantages of earlier supercritical fluid technologies, it is also fully scalable.

The new GMP facility has been developed in collaboration with Galenica AB, an established Swedish CRO focused on pharmaceutical formulation. Manufacturing will be carried out by Galenica at the company's state-of-the-art GMP suites in Malmo, Sweden.

XSpray CEO Per Andersson said, "We are extremely pleased to have this facility in place, we can now satisfy our customers' needs for GMP material. This also proves the technology can be scaledup, an important step towards developing full pharmaceutical manufacturing capabilities."

FDA Accepts Drug Application for Miconazole Lauriad® to Treat Oropharyngeal Candidiasis

PRNewswire-FirstCall: August 19, 2009 – WOODCLIFF LAKE, NJ – Strativa Pharmaceuticals, the proprietary products division of a wholly owned subsidiary of Par Pharmaceutical Companies, Inc. (NYSE: PRX), has announced that the U.S. Food and Drug Administration (FDA) has accepted the new drug application (NDA) for miconazole Lauriad[®] mucoadhesive buccal tablets (MBT) to treat oropharyngeal candidiasis (OPC). Miconazole MBT delivers the antifungal miconazole via a mucoadhesive buccal tablet that is designed to enable once-daily dosing of the active ingredient at the site of infection.

The NDA submission was based primarily on data from a Phase III study demonstrating noninferiority to Mycelex[®] troche (clotrimazole) in the complete resolution of signs and symptoms of OPC. The randomized, double-blind, double-dummy study was conducted in 577 HIV-positive patients in 40 sites in the United States, Canada, and South Africa.

"The NDA acceptance of miconazole MBT represents a significant milestone for Strativa Pharmaceuticals as this would be the first oral miconazole therapy available in the U.S. and would provide healthcare providers with a new option for treating OPC," said John A. MacPhee, president of Strativa Pharmaceuticals. "We believe miconazole MBT's delivery system and once-daily dosing schedule will offer an effective, convenient alternative to currently available local therapies, which require several doses per day to treat OPC." Strativa could launch miconazole MBT in the second half of 2010, if approved.

Par Pharmaceutical and Aveva Drug Delivery Systems Receive Final Approval to Market Generic Catapres TTS®

PRNewswire-FirstCall: August 18, 2009 – WOODCLIFF LAKE, NJ – Par Pharmaceutical Companies, Inc. (NYSE: PRX) has announced that its licensing partner, Aveva Drug Delivery Systems, has received final approval from the U.S. Food and Drug Administration for its Abbreviated New Drug Application for a clonidine transdermal system. Clonidine TDS is a generic version of Boehringer Ingelheim's Catapres TTS[®] and is the first generic 7-day patch indicated in the treatment of hypertension. Clonidine TDS is available in 0.1, 0.2, and 0.3 mg/day strengths. Annual U.S. sales of Catapres TTS[®] were approximately \$297 million, according to IMS Health data. Par will begin shipping clonidine TDS to the trade in the near future.

Under the terms of its agreement with Aveva, Par has exclusive rights to market, sell, and distribute Aveva's clonidine TDS in the United States. The product will be manufactured by Aveva, and the companies will share profits from sales of the product.

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Calendar of Events

2009

10th US – Japan Symposium on Drug Delivery Systems

December 16-20 Lahaina, HI, U.S.A. http://web.mit.edu/langerlab/ 9thsymposium/index.html

2010

CRS Satellite Workshop: Development and Regulatory Challenges for Controlled Release Formulations

January 25 Omni Orlando Resort at ChampionsGate Orlando, FL, U.S.A. www.drugdeliverypartnerships.com

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First World Conference on

Nanomedicine and Drug Delivery April 16-18 Kottayam, Kerala, India www.nanomedicine.macromol.in/

Chemistry, Manufacturing & Control (CMC): Quality, Regulatory and Scientific Requirements and Strategies June 21-22 Shanghai, China www.cpa.org.cn

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

FIP Pharmaceutical Sciences 2010 World Congress (in association with the AAPS Annual Meeting and Exposition)

November 14-18 New Orleans, Louisiana, U.S.A. www.pswc2010.org/

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