

Volume 25 • Number 4 • 2008

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Seasons Greetings from Sunny South Africa

As I sat under an acacia thorn tree on a farm about 30 km (approximately 19 miles) from Grahamstown watching my 5-year-old daughter participate in the annual nativity play in glorious sunshine this last weekend, I wondered what had happened to the year.

It certainly seems to have flown past at a rapid rate, bringing new meaning to "time flies," and that it was only a few days ago that it was January and the start of a New Year, which as usual promised many opportunities, challenges, and the hint of change. The latter has certainly been the case in CRS, with a new layout for the newsletter, a new scientific secretary, a mentoring programme for young scientists, a new leadership approach, a new look for the website, a new CRS logo and tagline, and the launch of the CRS Foundation, amongst others. All this change takes up time, and I can at least account for some of where the year went and during the break recharge the batteries for the 2009 onslaught.

Of course, there has also been unpredicted change, such as the global economic meltdown, which we hope will not have a significant effect on the 2009 CRS Annual Meeting attendance in Copenhagen and for which the deadline for abstract submission is fast approaching. We encourage you all to consider attending the meeting next year.

Since the year has flown by and as we approach the end of the academic year for some of us in the Southern Hemisphere, I am looking forward to a break and certainly to spending a wonderful Christmas with my family. Christmas is a little different down here in South Africa, with blue skies, children swimming in the sea, and temperatures in the region of 30–35°C (86–94°F), and we normally take some time to sit under the trees to enjoy our lunch or dinner. We may need to rethink the song about a "white Christmas" down here!

In closing, enjoy reading this edition of the newsletter and consider supporting or taking advantage of the many initiatives, workshops, and other exciting events and opportunities offered from CRS and its different committees. I wish you and yours a peaceful and blessed Christmas surrounded by your loved ones wherever you are in the world.

Happy Holidays, Merry Christmas, and best wishes for a happy, productive, and prosperous 2009 from South Africa.

Roderick B. Walker ■



Lisbeth Illum
IDentity, Nottingham, U.K.

The expression “credit crunch” in the last few months has become the buzzword of the day. With American and European mortgage markets in meltdown, house prices falling worldwide, price indices increasing, banks experiencing insolvency and take overs by states and countries, companies folding, interest rates increasing, the stock market crashing every second day, and currencies devaluating or increasing in value faster than ever seen before, what can I say in this column to keep your interest captured? We need your support to avoid any effect on the economy of the CRS.

How does the “credit crunch” influence the CRS and its members? As mentioned in my column in the last issue of the *CRS Newsletter*, the CRS is a non-profit organization dedicated to promoting the science, technology, and innovation of delivery of bioactives for the benefit of the global population. However, the Society needs to be run on a strong business footing to provide increased value, maintain and improve the quality of the science, and increase access to scientific meetings and workshops worldwide for all members. Presently, we are still highly dependent on the CRS Annual Meeting & Exposition as the main income source (presently 75%) for the Society. The CRS is, therefore, vulnerable to any effects of the “credit crunch” on the budgets of pharmaceutical, biotech, food and flavour companies, and other institutions that may have less money available for their employees to participate in scientific meetings. The only good news in this respect I received from my banker yesterday, who said that the companies who have suffered the least in terms of decreasing stock value are in the healthcare sector.

The CRS urges you to think about signing up to participate in the CRS Annual Meeting & Exposition in Copenhagen in July 2009. Our aim this year is to surpass the success of last year in New York. Access to submit abstracts opened November 3, 2008, and early bird registration, opening soon, will be available through May 4, 2009. Make the decision now to join the meeting, budget for the costs, and put the dates July 18–22, 2009, in your diary.

The meeting is set to present the newest and most exciting science in delivery of bioactives and other functional materials, with involvement from pharmaceutical companies, other companies, and universities from around the world. It is our goal to make this the most successful CRS European meeting ever! We have already signed up some very exciting plenary speakers, including a Nobel Prize winner. The Workshop Committee has received some very exciting proposals for workshops in Copenhagen in novel, cutting-edge research areas, and these shall be announced soon. The dollar is on its way up against the euro, so the shopping in Copenhagen should also be very attractive!

It has been a very busy time for the CRS BOD and the many CRS committees since the annual meeting in New York. One of the major goals for the BOD this autumn has been to put in place an extended strategic plan for the future of the CRS that also spells out metrics of achievement for individual goals. This work will be finalised in November. We have also set up a China Initiative Subcommittee that is charged with starting up a CRS presence in China to include, if appropriate, a Chinese Chapter and the running of satellite meetings and workshops in close collaboration with Chinese scientists in the field of delivery of bioactives. A lot of time has also been dedicated to moving the CRS Foundation forward, with generous help from a group of CRS past presidents. It is our hope that we shall be able to grant the first scholarship at the CRS Annual Meeting & Exposition in Copenhagen in honour of the late Joe Robinson. The CRS book publishing program is also progressing along the timelines set by the BOD, with the first four titles signed up.

Last but not least, I urge you to renew your membership in the CRS and also to make a donation to the CRS Foundation. The weather has turned in Europe, with snow coming in from the North and very cold winds. But, it is with a warm heart I wish you all a happy and productive autumn season.

Lisbeth Illum ■

Does What We Release Define Us?

Ian Tucker¹ and Charles Frey²



Ian Tucker

The CRS recently introduced a new logo with the tagline “Delivering Bioactives.” Although the tagline adequately represents a majority of controlled release interests, a wide variety of “non-bioactive” CRS current or potential interests are not clearly within this scope. It is arguably in the best interest of CRS and these “non-bioactive” application areas to embody the full scope of CRS in the logo and tagline. Let us consider this in more detail.



Charles Frey

The noun “bioactivity” was coined in 1970–1975. Dictionary.Com defines it as “any effect on, interaction with, or response from living tissue.” *The American Heritage® Dictionary of the English Language* (4th edition, Houghton Mifflin, 2006) defines the adjective “bioactive” as “of or relating to a substance that has an effect on living tissue.” *The American*

Heritage® Science Dictionary (Houghton Mifflin, 2002) defines “bioactive” as “relating to a substance that has an effect on living tissue.”

There is little question regarding the applicability of these definitions to the CRS bioactive materials track and, to a large extent, the CRS veterinary track; however, many applications falling within the CRS consumer and diversified products (C&DP) track are not adequately addressed with the phrase “Delivering Bioactives.” Consider the following list of C&DP controlled release possibilities:

- Color in a food product
- A lubricant additive in an industrial process or mechanical system
- An oxidizer in a tertiary oil-recovery process
- A polymerization initiator in a synthesis process
- A coolant stabilizer in an engine-cooling system
- A deposition inhibitor in a boiler system
- Genetically modified organisms into a biosystem
- Non-release of a controlled substance neutralizer that would prevent drug abuse
- Odors and flavors in ingested or masticated products
- Odor or perspiration control components
- Cleaning agents in detergents and soaps
- Ripening agents in food packaging or storage
- Increased shelf stability of stocked products
- Sunscreen agents and skin medicines

- Failure indicators in paints and coatings
- Self-healing systems for paints and coatings
- Membrane porosity measurement systems
- Textile color control, cleaning aids, odor controls, or insect repellent systems

Several of these can be linked to “Delivering Bioactives” in some way; however, many (and I anticipate numerous others that are not listed and have not yet graced the annals of CRS) do not clearly fall within this definition. This concern raises pertinent CRS goal and mission questions:

- Does the term “Delivering Bioactives” intentionally or unintentionally restrict scientific contributions to the CRS?
- Does the CRS miss out on cutting-edge CR technology due to a narrowed mission presentation?
- Is it prudent to define CRS with the term “bioactive” or should that be restricted to the “bioactive materials” track of CRS?

Regardless of how we choose to define or label CRS, the most important question may be “Does CRS miss out on scientific contributions because of a labeling concern?” The following question may best clarify this point:

Would a food, cosmetic, textile, or consumer product scientist look to the CRS or the CRS website for expertise or interest when researching controlled release work for non-bioactives (or materials perceived as non-bioactive) if the tagline is “Delivering Bioactives”?

Yes, a philosophical heart may find the bioactive connection in some way with almost anything, but what about those who may not immediately see a connection? Will they and the CRS both lose out because of a failure to realize that the CRS represents their interest? The “Delivering Bioactives” tagline may best address a majority of CRS interests, and we may not want to risk any loss of that energy and spirit; however, we must maximize societal benefits for individual members and the CRS as a whole by encompassing all interests in our general tagline and mission. Potential contributors in C&DP areas, whom have been personally directed to the CRS website, have stepped away due to a first impression that it is a pharmaceutical organization. This suggests that we are losing out on the participation and interest of many with similar interests and in similar situations. “Delivering Bioactives” has strong pharmaceutical connotations. If we continue with this tagline, we may attract only the fringes of some technologies and application areas—those innovative individuals who come to CRS to take back to their own niches. Their ability to contribute may depend on our ability to adequately embrace their niche.

An alternative tagline or another means of differentiation or identification should be considered to address the expressed

¹ CRS Member-at-Large

² Chair of C&DP Committee

concerns. The “Where the Tracks Lead” links on the new CRS website should help overcome this “first impression” concern, but a tagline with a broader scope would go further in this regard. The “Delivering Bioactives” tagline was likely considered from many available perspectives and based on a suitable set of goals. Nevertheless, an appropriate change to the tagline would most clearly and directly address the issue. A quick brainstorm can provide many alternative tagline ideas. The words “Controlled” and “Release” and/or “Delivery” should probably be included; however, is the “released” or “delivered” entity required? If so, how is the broad scope of what we release or deliver best embodied in a few words without introducing some level of restriction?

CRS is a premier global, multidisciplinary society dedicated to controlled release or delivery. Delayed, sustained, pH-triggered,

temperature-triggered, complete non-release, hyper-release, and other patterns and mechanisms are all forms of controlled release. Does what we deliver define us? If so, is “Delivering Bioactives” the best definition? Regardless of how we address the issue, we should not let a limited perspective or vocabulary restrict the CRS scope without reason.

What are your thoughts?

Share your opinion on this by visiting the CRS website at www.controlledreleasesociety.org/customer/source/communities/communityHomePage.cfm?section=Home&CmtyId=5 ■

Look to the Future with CRS!

Oral Multi-Particulate Drug Delivery Systems: Challenges and Opportunities

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38th Annual Meeting & Exposition of CRS

July 30-August 3, 2011
Gaylord National Resort and Convention Center
National Harbor, Maryland, U.S.A.



Probing Nanoscale Structures by Small-Angle Neutron Scattering—Characterisation of Microemulsions for Drug Delivery

Chien-Ming Hsieh,¹ Cécile A. Dreiss,¹ Jayne Lawrence,¹ and Richard Heenan²

Why Choose an Oil-in-Water Microemulsion as a Drug Delivery Vehicle?

It is estimated that ~40% of all new drug candidates have very poor water solubility and, as a consequence, cannot be developed as a formulation suitable for human use. Unless a way of successfully formulating such molecules is found, large numbers of potential drug candidates will continue to be discarded, costing the pharmaceutical industry vast amounts of money and, more importantly, costing the lives of patients.

Our research group at King's has been investigating a range of drug delivery systems to increase the apparent aqueous solubility of poorly water-soluble drugs, including vesicles (1), nanosuspensions (2), micelles, and microemulsions (3). The system that shows the most promise in terms of drug-loading capacity and stability is the oil-in-water (o/w) microemulsion (Figure 1a). Figure 1 also shows two other commonly encountered microemulsion structures, namely a bicontinuous microemulsion (channels of oil and water separated by a surfactant monolayer) (Figure 1b) and a water-in-oil microemulsion (Figure 1c). Regardless of their precise microstructure, microemulsions are clear, spontaneously forming nano-sized dispersions of oil and water stabilised by a surfactant or surfactants. Microemulsions possess an advantage over micelles with respect to their drug-solubilising capacity, as they contain a core of oil in which the poorly water-soluble drug may additionally dissolve.

To formulate microemulsions suitable for use as drug delivery vehicles, we have embarked on a programme to understand their physico-chemical behaviour. In this study, we report on the

formation and physico-chemical properties of o/w microemulsions containing a pharmaceutically acceptable oil, either ethyl butyrate (EB) or ethyl caprylate (EC), and stabilised by the zwitterionic surfactant 3-(*N,N*-dimethyldodecylammonio)-propanesulfonate (DDAPS). The study focuses on establishing how the location of oil and lipophilic drug, namely testosterone propionate (TP), varies with microemulsion composition.

Phase Behaviour

Initial studies determined the phase behaviour of the o/w DDAPS microemulsions (Figure 2). The results show that the oil with the longer acyl chain length and, therefore, the larger molecular volume, namely EC, forms microemulsions over a smaller range of compositions than the shorter acyl chain length oil, EB. As the densities and, therefore, the volumes of the two oils are comparable, the only way to explain the observed difference in phase behaviour is by the fact that the two oils are incorporated into the microemulsion droplets in different ways, rather than them both forming a core of oil in the centre of the droplet.

Drug Solubilisation Capacity

Originally, our expectation was that microemulsions containing the oil with the greatest drug-solubilising capacity would solubilise the larger amount of drug. Surprisingly, however, this was found not to be true, as it was the microemulsions containing the oil that dissolved relatively small amounts of drug (here TP) that tended to exhibit the highest drug loading (Figure 3).

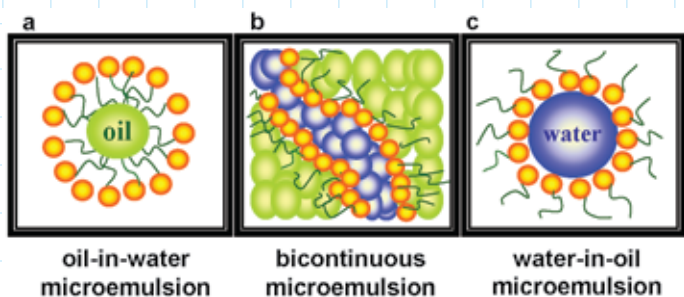


Figure 1. Schematic representation of the three most commonly encountered microemulsion microstructures: (a) oil-in-water, (b) bicontinuous, and (c) water-in-oil.

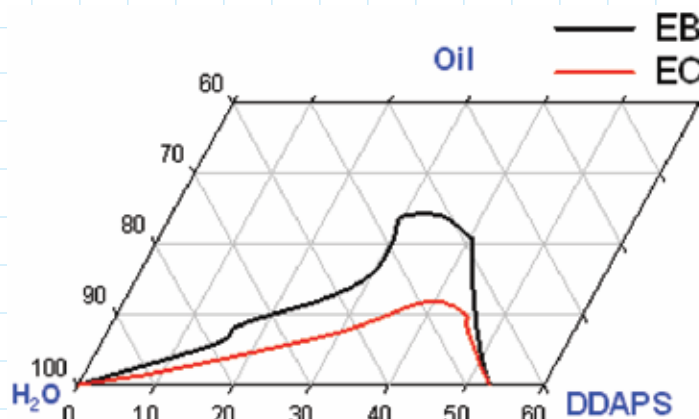


Figure 2. Partial phase diagram of o/w DDAPS microemulsions containing EB or EC.

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² ISIS Facility, Rutherford Appleton Laboratory, U.K.

Small-Angle Neutron-Scattering Studies

To understand the phase behaviour and solubilisation results, small-angle neutron-scattering (SANS) studies were performed. SANS is comparable to X-ray and light-scattering techniques but uses neutrons instead of X-rays or light as the probe (Figure 4). The very short wavelength of neutrons makes it possible to probe size, shape, and in some instances the internal structure of materials on the nanometer to micrometer scale (4).

One very powerful feature of neutron scattering is that it is possible to “highlight” or “hide” different parts of the system using a technique called “contrast-matching.” This technique relies on the fact that hydrogen has a scattering power or “scattering length” (analogous to refractive index for light) very different from that of deuterium, and thus, by selectively deuterating some components of the system it is possible to determine information about the internal structure. Figure 5 shows the three microemulsion systems prepared using different hydrogenated (h-) and deuterated (d-) materials for each composition. The “shell contrast,” prepared using d-oil and D₂O, provided information about the thickness of the surfactant shell; the “core contrast,” using d-oil and h-DDAPS and H₂O, provided information about the distribution of oil in the microemulsion. The use of h-oil and h-DDAPS in D₂O yielded

information about the size and shape of the droplet (“droplet contrast”). Each of the contrasts was prepared both in the presence and absence of protonated TP. All three sets of scattering data obtained for each composition were simultaneously analysed to derive a self-consistent model, thereby giving a high level of confidence in the results. The SANS data were best fitted using monodisperse ellipsoidal structures. Figure 6 shows the results of simultaneously fitting the three contrast sets for 2 wt% DDAPS microemulsions containing 0.5 wt% EC. The results show that the microemulsion droplets containing EC were larger than those containing EB (Figure 7). In addition, EB penetrated into the tails of the surfactant, while (at least some of the) EC formed a core in the microemulsion (Figure 7). The presence of TP did not alter the distribution of oil.

Our SANS studies explained the inverse correlation between the ability of an oil to dissolve a drug and its molecular volume. Furthermore, we unambiguously established, for the first time, that a smaller molecular volume oil did not form a core but was dispersed throughout the droplet, while in contrast the larger molecular volume oil formed a distinct core, thereby providing an extra locus for drug solubilisation, explaining its better drug-loading capacity.

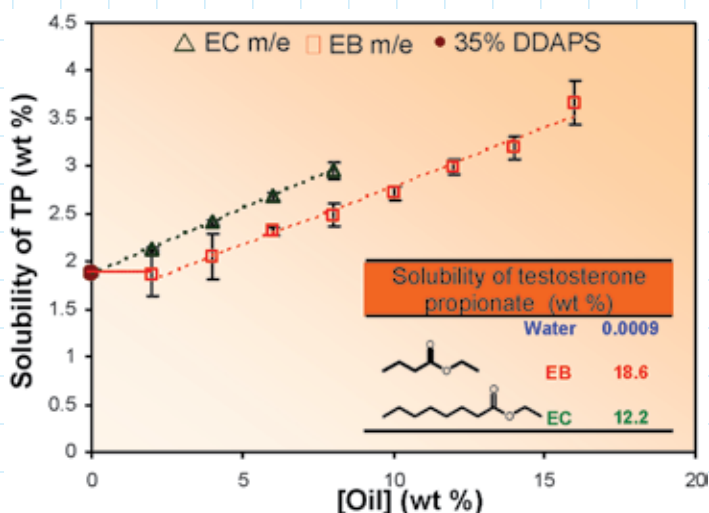


Figure 3. Comparison of the solubility of TP in micelles and microemulsions containing increasing amounts of EB or EC.

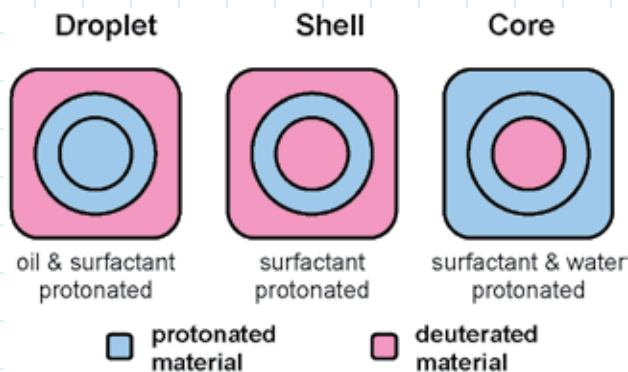


Figure 5. Schematic representation of the contrast variation experiment on o/w microemulsions.

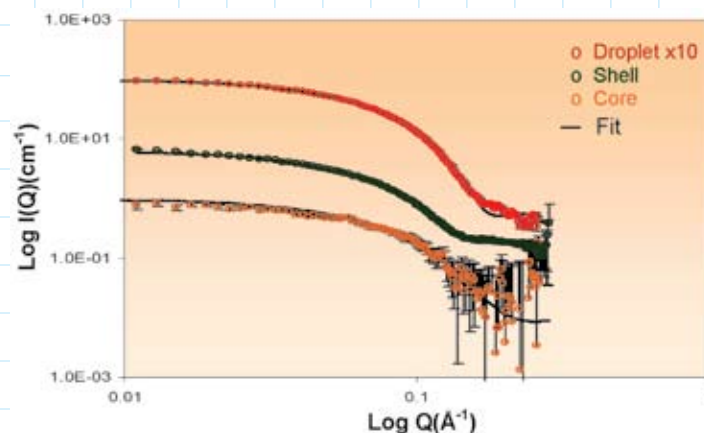


Figure 6. Simultaneous fit of the three contrasts, namely core, drop, and shell, prepared for 2 wt% DDAPS microemulsions containing 0.5 wt% EC.

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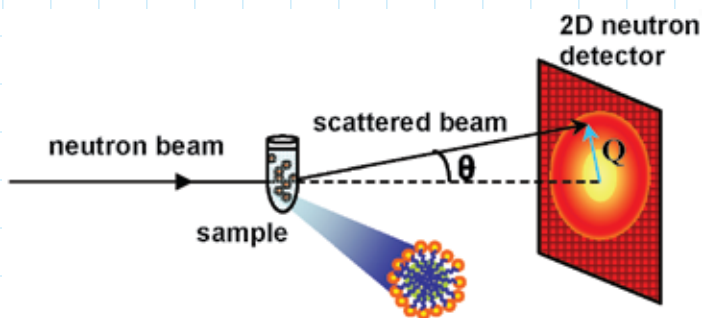


Figure 4. Schematic representation of a SANS experiment.

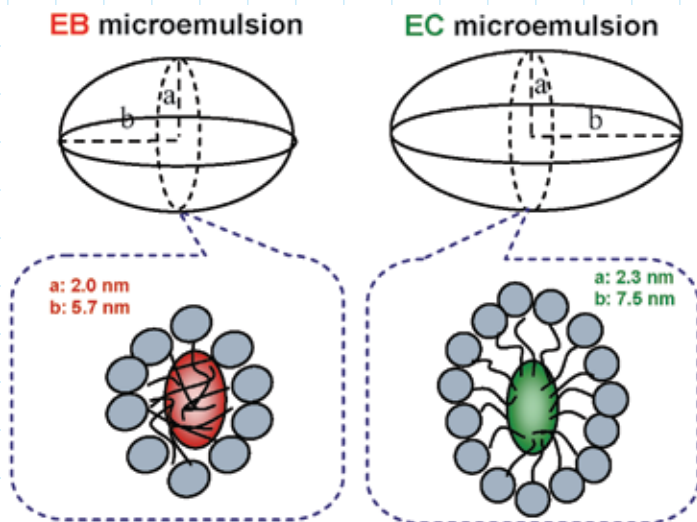


Figure 7. Schematic representation of microemulsions of the same composition containing EB and EC.

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News

from CMA Microdialysis

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Multistage Mesoporous Silicon-based Nanocarriers: Biocompatibility with Immune Cells and Controlled Degradation in Physiological Fluids

Biana Godin,¹ Jianhua Gu,¹ Rita E. Serda,¹ Silvia Ferrati,¹ Xuewu Liu,¹ Ciro Chiappini,¹ Takemi Tanaka,¹ Paolo Decuzzi,^{2,3} and Mauro Ferrari^{1,4,5}

Introduction

During the last decades, the advancements in micro- and nanotechnology have brought tremendous encouragement to the current biomedical research. Porous silicon (pSi) has many interesting properties that are being investigated for diverse biomedical applications, including biomolecular screening, optical biosensing, drug delivery through injectable carriers and implantable devices, and orally administered medications with improved bioavailability (1,2). There are already several FDA-approved and marketed products based on pSi technology that have found a niche in ophthalmology and another product, based on radioactive ³²P-doped pSi, is currently in clinical trials, as a potential new brachytherapy treatment for inoperable liver cancer.

Targeted delivery could offer significant toxicity reduction in adjuvant or neo-adjuvant cancer therapies. Our research group has designed and developed a multistage nanocarrier based on the pSi technology, with the potential to overcome the multiple biological barriers encountered in the circulation and efficiently deliver therapeutics to the tumor site (3). Hemispherical disk-shaped particles with a diameter of 1–3 μm have been chosen to enhance the specific recognition and adhesion to vascular targets based on the theory of Decuzzi et al. (4) and Sakamoto et al. (5). Also, the pSi particle (first stage) has been shown to effectively load multiple types of smaller nanoparticles (second stage), such as quantum dots and single-wall carbon nanotubes, thus originating a multistage delivery system (3). The mechanism of action of the multistage system is schematically presented in Figure 1 (3).

Biocompatibility and biodegradability are the key requirements for any drug delivery carrier. Moreover, in the multistage system biodegradation plays an important role in delivering second-stage nanoparticles to the target site. In the present study we aimed at evaluating how surface modifications of the multistage pSi nanovectors affect these critical parameters.

Methods

Fabrication and Surface Modification of the Particles. pSi particles were fabricated from P⁺⁺-doped wafers with a resistivity of 0.0008–0.005 Ohm-CM by electrical-chemical etching, as previ-

ously described (3). The physical dimensions and pore sizes of the particles were verified by high-resolution SEM, and the surfaces were oxidized in a piranha solution, resulting in oxidized particles. The positively charged particles were produced by the introduction of amine groups on the surface by silanization with 0.5% (vol/vol) 3-aminopropyltriethoxysilane (APTES) in isopropanol at room temperature. PEG-NHS with different lengths was further conjugated to the APTES-modified particles.

Biodegradation Study. Mesoporous silicon particles with different pore sizes and surface modifications were tested. The particles were incubated in PBS (pH 7.4) or fetal bovine serum (FBS) for up to 72 hr. The samples were collected at various time points and processed for ICP-AES analysis of silicic acid, which is the degradation product of pSi in the medium, and for SEM analysis of particle morphology.

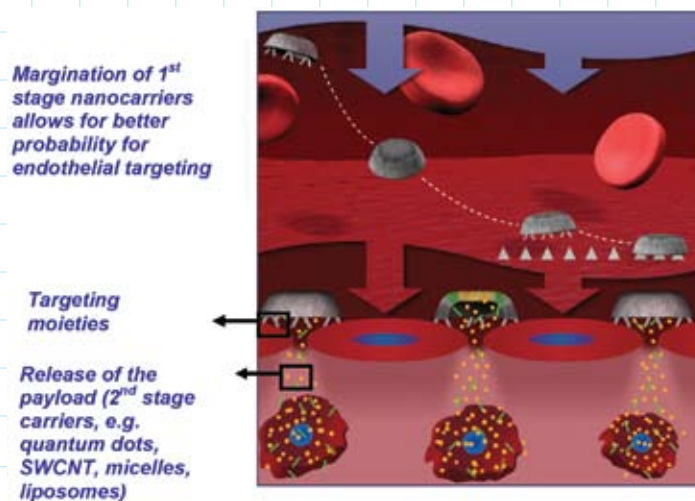


Figure 1. Schematic presentation of the mechanism of action of multistage pSi nanovectors (3). The multistage delivery system is assembled by loading second-stage nanoparticles (Q-dots and SWNTs, micelles, liposomes, etc.) into the pores of mesoporous silicon microparticles. After intravenous injection, the rationally designed multistage system travels through the blood stream and, as a result of its unique size, shape, and chemical modifications, avoids RES uptake, interaction with red blood cells, and finally, migrates to the vessel wall (margination), where it adheres to the target endothelium. Multistage microparticles release their payload, which penetrates through the fenestrations of the target vasculature and eventually diffuses into the tissue surrounding the vessel. Second-stage nanoparticles are then taken up by the cells, where they accomplish their tasks.

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Biocompatibility Evaluation. THP-1 human monocytes, J774 murine macrophages, and human umbilical vein endothelial cells (HUVEC) were purchased from ATCC and Lonza. THP-1 monocytes were differentiated into macrophages in 24-well dishes for 48–96 hr with 5–80 ng/mL of phorbol ester PMA. The cells were washed and incubated with oxidized, APTES-modified, and PEGylated particles for up to 48 hr. Zymosan particles were used as a positive control of cytokine production. The cell culture supernatant samples were collected at 1, 4, 8, 24, and 48 hr. Production of pro-inflammatory cytokines, IL-6 and IL-8, in the supernatants were determined by commercial ELISA kits. Phagocytosis of the particles with various surface modifications was evaluated using J774 macrophages for 4 hr, followed by processing and SEM analysis.

Whole mouse blood, collected following a cardiac puncture, was used to evaluate the compatibility of the systems with erythrocytes. The 10^7 – 10^8 particles/mL of blood were incubated at 37°C, using a rotary shaker for up to 5 hr. The blood was then centrifuged, and the plasma was collected and analyzed for iron content, using ICP-AES as an indicator of hemolysis.

Results and Discussion

Two independent methods, ICP-AES and SEM analysis, have shown that surface modifications, as well as the porosity of the particle, affect the rate of degradation and, as a result, the amount of silicon deposited in solution in both physiological solutes (Figure 2). The degradation is complete when the concentration of silicon in the solution, as analyzed by ICP-AES, reaches a pla-

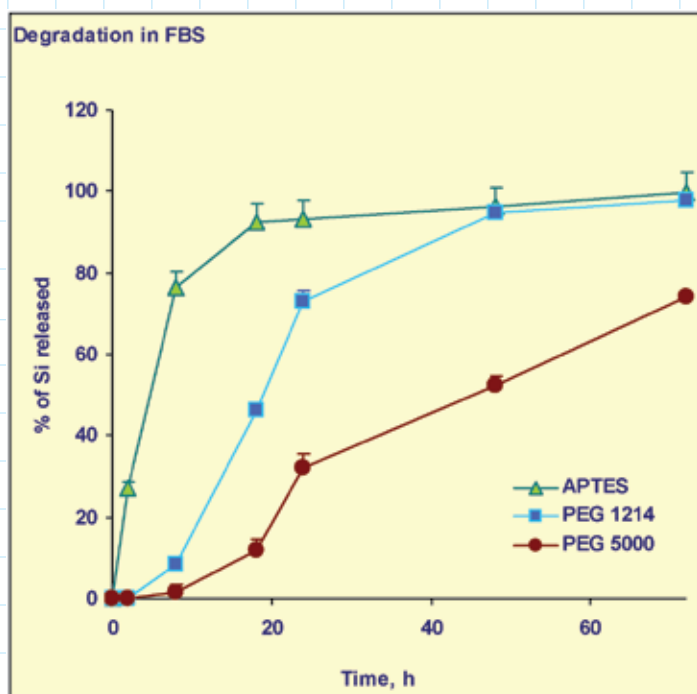


Figure 2. Degradation of pSi particles with different surface modifications over time: quantification of the particle degradation product, silicic acid, released to the degradation medium by ICP-AES.

teau. The particles conjugated to higher molecular weight PEGs and having small pore sizes exhibit degradation kinetics at a much slower rate.

Fine control of the degradation, which impacts the release kinetics of nanoparticles and drugs from the mesoporous silicon structures, is of fundamental importance in the development of multistage and multifunctional delivery systems. pSi microcarriers can be administered systemically and used to deliver a payload of a different nature (therapeutic, imaging, or both). The size of the pores and surface chemistry of the pSi structure can be controlled during the fabrication process and thereafter. Our data point toward the possibility to control degradation of mesoporous silicon microparticles and devices by means of particle morphology, porosity, and PEGylation and may have important clinical implications.

Internalization of the pSi multistage particles by murine and human immune cells can be controlled by means of particle surface modifications (Figure 3). PEGylation prevents particles from being internalized by macrophages. No significant release of pro-inflammatory cytokines were observed when the immune and endothelial cells were incubated with mesoporous silicon multistage carriers, as can be seen in Figure 4 for release of IL-6 from HUVEC and THP1 cells. Similar results were obtained for various other cytokines in THP-1, HL60 (differentiated human neutrophils), J774 (murine macrophages), Jurkat (T cells), and HUVEC cells.

The results of incubation of the carrier with whole blood show that the particles did not induce erythrocyte lysis, since plasma content of iron was not different from the untreated control.

Conclusions

The results of this study show that 1) the multistage delivery carrier is biocompatible with immune cells, endothelial cells, and erythrocytes; and 2) the degradation profile of pSi structures could be modulated as a function of morphology and surface modifications. This unique multistage system, composed of mesoporous silicon particles able to carry a payload of various nanoparticles, is currently being investigated for

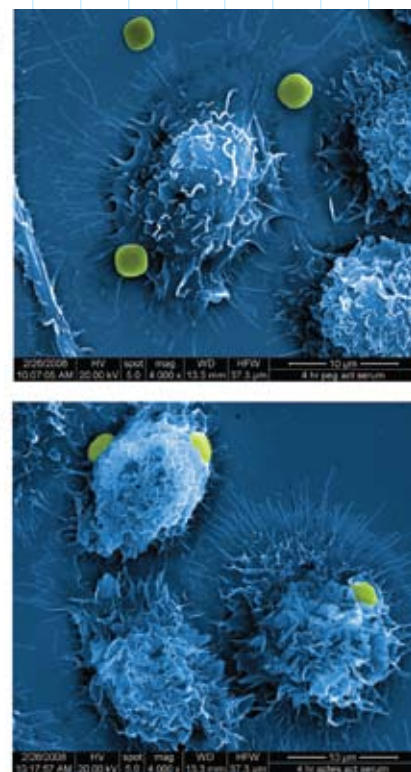


Figure 3. Internalization of (A) PEGylated (PEG M_w 5,000 Da) and (B) APTES pSi particles by J774 murine macrophages following 4 hr of incubation.

targeted delivery of therapeutics and imaging agents to the tumor site.

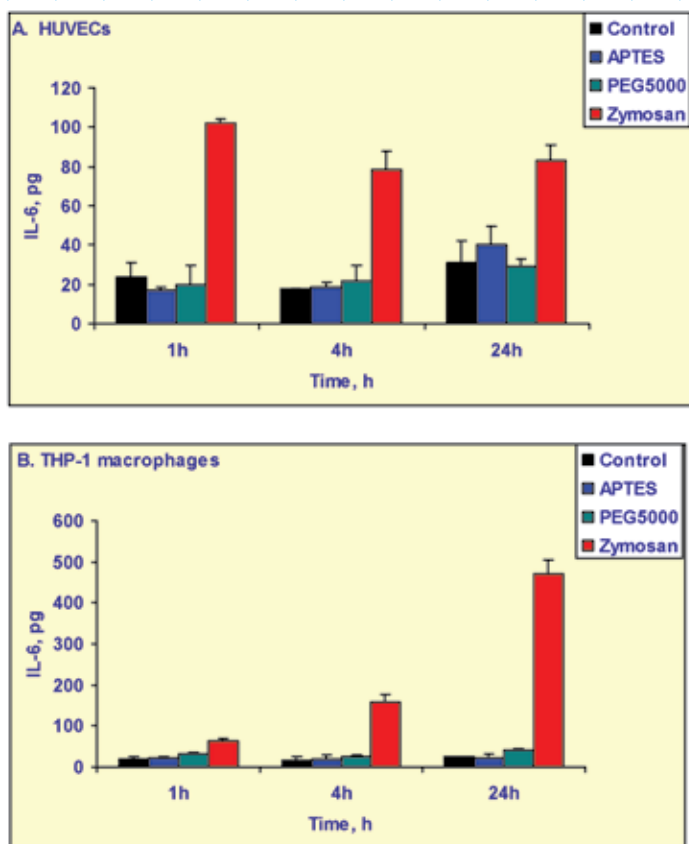


Figure 4. Release of IL-6, a proinflammatory cytokine, by endothelial HUVEC cells and THP-1 human macrophages following incubation with PEGylated and non-PEGylated multistage pSi particles compared with untreated cells (control) and a positive control, zymosan particles that induce cytokine release.

Acknowledgments

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Critical Pharmaceuticals Ltd.

Faron Jordan, Lisbeth Illum, and Andrew Lewis

Introduction

Critical Pharmaceuticals is a drug delivery company with unique sustained release technologies based on supercritical fluid (SCF) processing. SCF processing enables encapsulation of active pharmaceutical ingredients (APIs), such as small molecular weight drugs, peptides and proteins, and vaccines in polymer matrices, creating microparticles, fibres, or implants/monoliths formulations, with selected drug release regimes from weeks to months. Critical Pharmaceuticals technologies (CriticalMix[®] and NanoMix[®]) are covered by strong patents. When gases such as carbon dioxide (scCO₂) reach a certain temperature and pressure (the critical point) they become “supercritical” and take on both gas- and liquid-like properties and are able to penetrate and liquefy certain polymers. This can be exploited to mix thermally labile or solvent-sensitive drugs into polymers in the dry state. The key advantages of SCF technology are that it operates at near ambient temperatures and in the absence of solvents, permitting very effective encapsulation of labile drugs without adversely affecting their activity. Studies on 30 different proteins and peptides have shown no effect of the production process for the primary, secondary, or tertiary structure, as well as fully maintained biological activity.

The CriticalMix[®] Process

Encapsulation of an API within a polymer matrix, which slowly releases the drug, is an attractive alternative to derivatisation of a drug to increase serum half-life, since no chemical modification

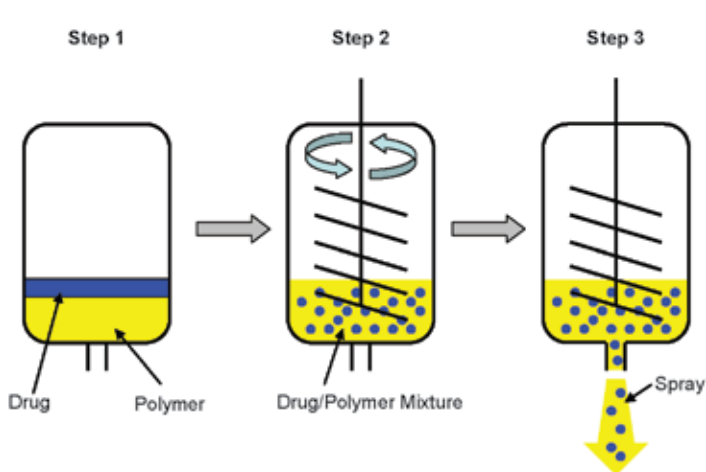


Figure 1. Preparation of drug-loaded polymers. The drug and polymer are loaded into a pressure vessel that is then pressurised with CO₂ and heated (step 1). The liquefied polymer and drug are mixed (step 2), and the mixture is then sprayed through a nozzle, creating the drug-loaded microparticles (step 3).

of the drug is involved. Hence, generics can be taken through clinical development via an abbreviated FDA (ANDA) process. The manufacturing processes used by other groups for the production of sustained release formulations are known to denature proteins to different degrees, causing loss of activity. Furthermore, emulsification processes are associated with the economic and environmental costs of solvent disposal.

The CriticalMix[®] technology uses a simple, one-step process, whereby polymer and API in the dry state are added into a pressure vessel that is sealed, pressurised with CO₂, and heated to approximately 32°C. The supercritical CO₂ penetrates and liquefies the polymer, allowing effective mixing with the dry API. The polymer/API mixture is then sprayed through a nozzle, and microparticles containing the drug are collected (Figure 1). Through control of the process, the size and distribution of the microparticles can be controlled, and by variation of the process, fibres and implants with differing morphologies can easily be manufactured (Figure 2).

Case Study 1—Controlled Release hGH

Human growth hormone (hGH) is secreted by the pituitary gland and is responsible for a variety of physiological processes, including bone and muscle development. hGH deficiency in children results in stunted growth and delayed muscle development and in adults results in diminished lean body mass and poor bone density, as well as a number of physical and

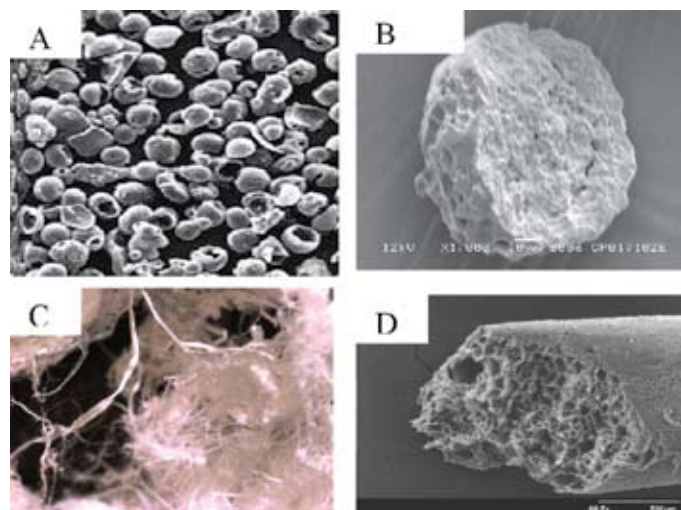


Figure 2. Products prepared using Critical Pharmaceuticals SCF technology: (A) microparticles, (B) a fractured microparticle, (C) fibrous material, and (D) a porous monolith/implant.

psychological symptoms, including poor memory, social withdrawal, and depression. The market for hGH products is currently worth an estimated \$2.7 billion annually.

Patients suffering from hGH deficiency are currently treated with a once-daily injection of hGH. This treatment regimen has a considerable impact upon patients' lives and affects patient compliance. A sustained release hGH formulation, therefore, is highly desirable. The target is a product to be injected once every 2 weeks instead of the present once-a-day product, with sustained hGH plasma profiles and similar growth pattern. Nutropin Depot, a controlled release microparticulate formulation of hGH manufactured using a proprietary emulsion process, successfully reached the market in 1999. However, the product was withdrawn from the market for several reasons, e.g., the high manufacturing costs associated with organic solvent disposal and the labour-intensive production process. Additionally, children receiving Nutropin Depot showed less growth compared to those on once-a-day injections, and incidences of local intolerance at the injection site were also reported. The CriticalMix® hGH sustained release microparticle formulation is an ideal alternative to Nutropin Depot. The one-step production process is fast, with a maximal production time of one day, and organic solvents are not used. The hGH bioactivity is maintained throughout the production process, and no change to the primary, secondary, or tertiary structure of hGH has been shown. Importantly, the formulations comfortably pass the limits for protein aggregation and degradation set by the European Pharmacopoeia.

By selecting the composition of the polymer matrix encapsulating the hGH, both the initial burst release and the subsequent hGH release rate can be controlled (Figure 3a). A pharmacokinetic/pharmacodynamic study was performed in primates to predict plasma profiles in humans. A single injection of two different sustained release formulations manufactured using CriticalMix® were compared to the same total dose of hGH solution injected as seven daily doses (Figure 3b). Both sustained release formulations resulted in nearly constant plasma levels above the target serum levels (1 ng/mL) throughout the study, as opposed to the control daily injected hGH formulation,

where the plasma levels varied from day to day due to rapid clearance. Additionally, a similar IGF-1 response was seen for a single injection with CriticalMix™ hGH microparticles compared with seven daily injections with soluble hGH, indicating the formulations should be as effective as the current marketed formulations.

Case Study 2—Controlled Release Vaccines

While vaccination continues to be the most successful interventionist health policy to date, infectious diseases remain a significant cause of death worldwide. The World Health Organization estimates that more than 2 million people (50% of which are children under 5 years of age) die each year from diseases for which immunization is routinely recommended, including measles, diphtheria, pertussis, and tetanus. A primary reason for the less than optimal immunogenicity of vaccines is the lack of appropriate adjuvants capable of initiating the desired immune response. Despite years of evaluation, the only adjuvants currently approved by the U.S. FDA are aluminium-based mineral salts (generically referred to as alum). Whilst alum has a good safety record, it is a weak adjuvant for antibody induction to protein subunits and a poor adjuvant for cell-mediated immunity. Additionally, alum adjuvants have been associated with allergic reactions in some human subjects. Generally, such vaccines need at least two booster vaccinations to induce a sufficient and lasting immune response.

Polymer microparticles have a significant potential as adjuvants for vaccines, and single-dose vaccines can result from the controlled release of the antigen. A single-dose vaccine would vastly improve the effectiveness of vaccinations, particularly in the developing world. The Nanomix® technology is an ideal alternative to other microparticle formulations, since production is a simple two-step process that first involves freeze-drying the protein/antigen onto the polymer, followed by the CriticalMix® processing step.

As a model vaccine, tetanus toxoid (TT) was encapsulated in PLA microparticles and administered to mice as a single-dose vaccine. Additionally, mice were administered alum formulations on day 0 and two further booster vaccinations on days 28 and 56.

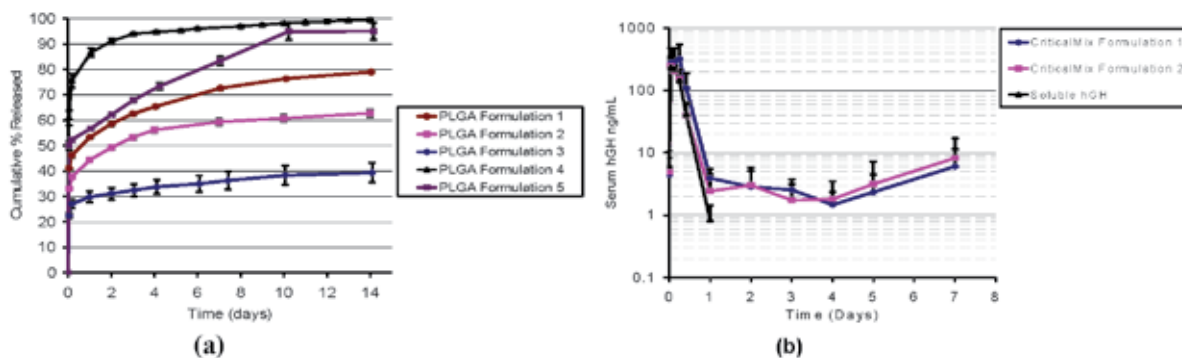


Figure 3. (a) In vitro hGH release rates from CriticalMix® microparticle formulations and (b) serum hGH Levels in primates following a single subcutaneous injection of two different formulations manufactured by CriticalMix® and a daily dose with soluble hGH.

TT-specific IgG titres were determined for up to 154 days following the day 0 vaccination. The single-dose microparticle TT formulation produced a similar or better immune response compared with the “three dose” alum formulation injected on three separate occasions. The immune response was maintained for at least 22 weeks after injection (Figure 4). No immune response was detected in the placebo group.

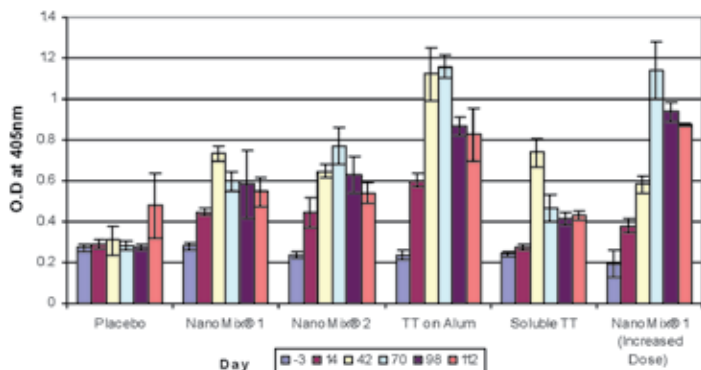


Figure 4. Tetanus toxoid specific IgG titres determined from 0 weeks up to 22 weeks after vaccination.

The Nanomix[®] vaccine delivery system allows successful immunisation based on a single-dose injection of a vaccine without the need for boosters. Such a single-dose vaccine will provide invaluable benefits, particularly in developing countries. Additionally, the NanoMix[®] vaccine delivery system is produced by a simple non-expensive procedure that preserves the bioactivity of the antigen.

At Critical Pharmaceuticals, we are experts in drug delivery and are developing a number of groundbreaking products to treat diseases as diverse as growth hormone deficiency and schizophrenia, apart from single-dose vaccines. We welcome partners interested in co-developing these products. Alternatively, if pharmaceutical/biotechnology companies have molecules that are difficult to deliver or are close to patent expiration and need a lifecycle management strategy, we will work closely with the company to design a rapid development program for an improved formulation of the drug using our technology.

For further information, please contact Critical Pharmaceuticals, BioCity Nottingham, Pennyfoot Street, Nottingham, U.K. NG1 1GF. Website: www.criticalpharmaceuticals.com; E-mail: info@criticalpharmaceuticals.com; Tel: +44 (0)115 8820 100. ■



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Bio-Images Research Ltd.

Sarah Connolly, Ph.D.

Bio-Images Research Ltd., a leader and at the forefront of innovation in gamma scintigraphy, undertakes early-phase clinical studies to streamline drug development processes and assists decision-making. Founded in 2000 by Professor Howard Stevens and Professor Clive Wilson, Bio-Images Research Ltd. (Glasgow, U.K.) is a spin-out company from the University of Strathclyde. The company, based within Glasgow Royal Infirmary, undertakes early-phase clinical studies in volunteers and patient groups, specialising in gamma scintigraphy.

Professor Wilson, together with colleagues at Queen's Medical Centre, Nottingham, U.K., was one of the pioneers in the application of scintigraphic imaging techniques in drug research. Gamma scintigraphy allows non-invasive visualisation of drug formulations and body systems. A gamma emitting radiopharmaceutical, typically ^{99m}Tc or ^{111}In , is incorporated into the formulation before administration to the volunteer or patient, allowing images to be acquired at precise intervals over a period of time. The emitted radiation is captured by the gamma camera to produce scintigraphic images.

Analysis of these images provides qualitative and quantitative information on formulation behaviour *in vivo*. By drawing a region of interest (ROI), for example around the stomach in an oral drug delivery study (Figure 1), it is possible to transform scintigraphic images into radioactive counts, which can be used to determine *in vivo* kinetic behaviour of a formulation, such as the creation of gastric emptying curves (Figure 2) (1). Dual isotope studies can also be performed that would allow, for example, evaluation of a tablet formulation containing both immediate release and controlled release technologies.

Applications of this technology in the field of oral drug delivery include the evaluation of buccal drug delivery systems, oesophageal transit studies, analysis of gastroretentive dosage forms,

gastric emptying studies, gastrointestinal transit, food effects, intra- and inter-subject variability, and site of delivery, such as the investigation of formulations designed to target the colon.

A recent study by Ghimire et al. (2) illustrates the use of gamma scintigraphy to determine the erosion behaviour of a controlled release matrix tablet. During *in vitro* studies, the addition of ^{99m}Tc -labelled charcoal to a wax matrix tablet allowed erosion to be monitored using the gamma camera (Figure 3). Following a clinical study in volunteers, *in vivo* erosion behaviour was determined using the scintigraphic images acquired (Figure 4). This

allowed an *in vitro-in vivo* comparison to be made for the controlled release tablet (Figure 5).

It is particularly informative when a scintigraphic study is coupled with blood

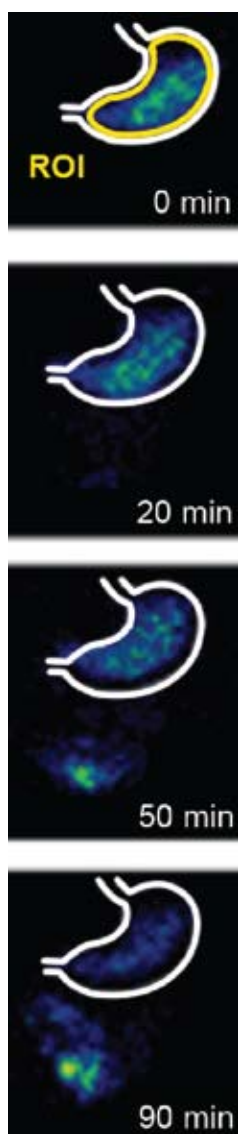


Figure 1. Gastric emptying.

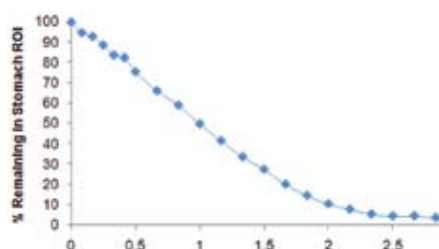


Figure 2. Gastric emptying curve.

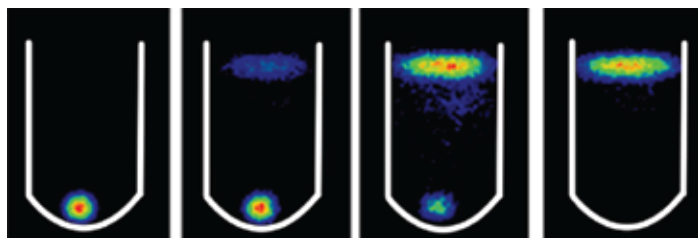


Figure 3. In vitro erosion.

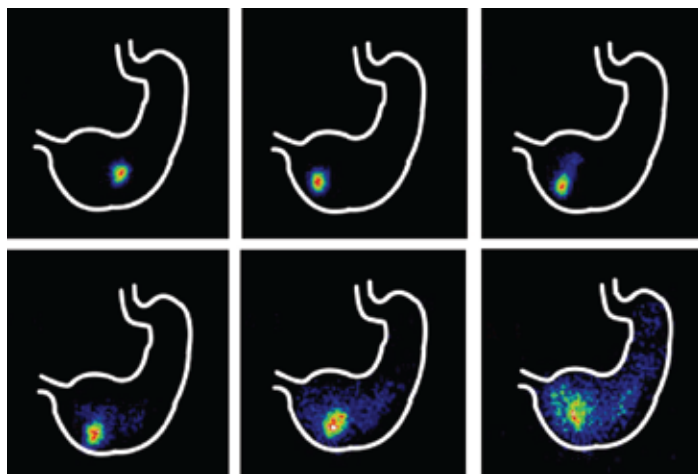


Figure 4. Typical images in vivo.

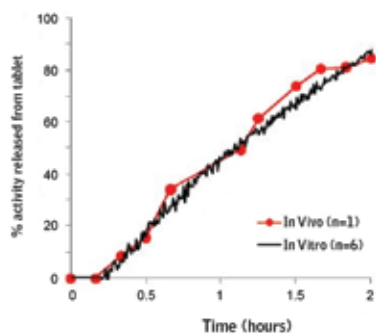


Figure 5. In vitro-in vivo comparison.

containing the model drug theophylline (3). Accurate scintigraphic information, both alone and in combination with pharmacokinetics, will assist in drug development decision-making, including the development of new formulations, re-formulation of existing products, and marketing.

In addition to applications for oral drug delivery systems, gamma scintigraphy is also routinely used to investigate nasal, ophthalmic, and pulmonary formulations. Studies can be conducted, for example, to assess the residence of bioadhesive nasal or ophthalmic formulations, determine the clearance of these preparations (4), assess absorption enhancers, quantify lung deposition, and correlate inhalation performance with PK data. Bio-Images has extensive experience in designing suitable labelling techniques for new formulations and delivery systems.

Bio-Images recently acquired the breakthrough technology, the imaGIT[®] capsule. ImaGIT[®], licensed from Casper Associates, is an ingestible, radio-controlled device used to evaluate regional drug absorption.

Employing Bio-Images' leading non-invasive gamma scintigraphic imaging techniques, imaGIT[®] is tracked through the digestive tract following oral administration, and on arrival at the

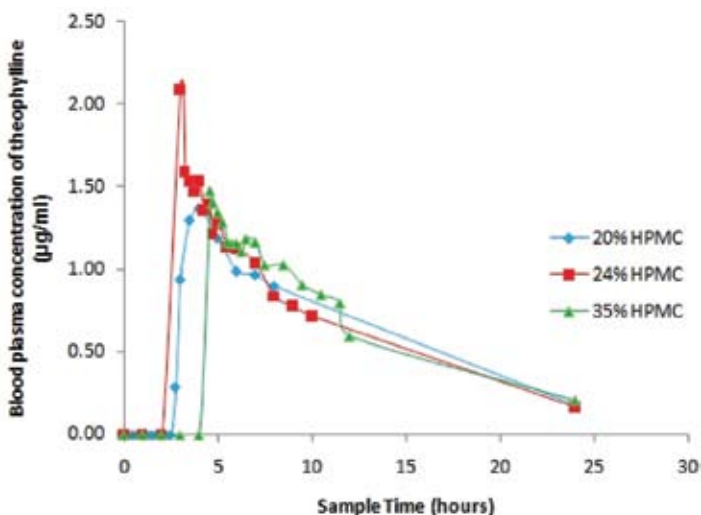


Figure 6. Pharmacokinetic profile for three time-delayed formulations in subject 001.

sampling, permitting drug pharmacokinetic parameters to be determined. The PK data can be interpreted more fully when accompanied by evidence of where the dosage form was located at a given moment and whether it underwent any physical change. Figure 6 shows a pharmacokinetic profile for three time-delayed capsule formulations

desired target site, release of the contained drug is triggered by an external radio signal. Blood sampling following drug release allows assessment of bioavailability, the results of which assist pharmaceutical companies to rationalise their formulation development strategies. The imaGIT[®] capsule reduces development time and costs through identification of drug absorption sites, rationalises development of modified release preparations, and permits a targeted dosage form to be developed for regions of maximum absorption.

Preclinical studies are also conducted in a purpose-designed facility equipped with a gamma camera, enabling a full range of scintigraphic studies to be undertaken. Preclinical gamma scintigraphy offers the possibility of conducting such studies at an earlier stage than might be possible in humans, and pharmacokinetic studies can also be performed (5).

Bio-Images has secured numerous blue-chip customers in Europe, the United States, and Japan and has delivered six steady years of top-line growth and profitability. The recent announcement of its strategic partnerships in the United States and Japan will enable Bio-Images to expand its expertise and customer base. These alliances will allow new customers access to the range of Bio-Images' clinical services, including

- A hospital base that allows access to defined patient groups and specialist medical support
- Connections with world-renowned experts
- University links that provide access to new technologies
- A proven track record for innovative radiolabelling techniques
Experienced staff dedicated to quality of service
- Competitive costs

The company have also completed validation of a fully compliant cGMP manufacturing facility at their clinical research unit in Glasgow. The manufacturing authorisation is a major event in the company's evolution, bringing manufacturing operations in-house and providing streamlined service to clients.

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A Learning Opportunity for Those Interested in Delivery Technology and Who Want to Look Across Borders

Dr. Erwin Mombarg¹ and Dr. Arlene McDowell²

At the 2008 Controlled Release Society Annual Meeting & Exposition in New York City, numerous new technologies were presented. As a scientist I like to test relevant technologies as soon as possible, and attending the Young Scientist Workshop 2, The World of Veterinary Drug Delivery, helped me to select the most interesting ideas to evaluate. Sevda Senel (Hacettepe University) gave an excellent introduction to veterinary delivery systems for the large group of young scientists, who also enjoyed an excellent breakfast as part of the workshop. We gratefully acknowledge the sponsorship of the Young Scientist Workshop provided by Pfizer Animal Health.

Treatment of brain cancer was one of the topics of the presentation given by Simon Wheeler (Novartis). Brain tumors are twice as common in dogs as in humans; however, oral delivery systems in animals are not as easily controlled as in humans. A system that guarantees the uptake of the appropriate amount of API, therefore, is very interesting. Avanash Thombre (Pfizer Inc.) develops mixtures of pet food and API with a target shelf life of 2 years. The addition of flavors (yeast and artificial beef) makes it more appetizing to the pet. Delivery via the skin was discussed by Jim Riviere (University of North Carolina). In the skin the blood flow is 100 times higher than is needed to keep cells alive. The Langerhans cells may make the skin a valuable place for vaccine administration. David Brayden (University College Dublin) showed that Ivermectin



Dr. Ramesh Panchagnula, co-chair of the Veterinary Committee and guest speaker at the 2008 Vet Get Together.

transportation in cell membranes differs between species and, in extreme examples, can lead to mortality. Gas-producing batteries and osmotic pumps are used in the device presented by Michael Rathbone (InterAg New Zealand). The increased pressure in the device is used to move a plunger that forces the formulation through a small orifice to achieve drug delivery. Terry Bowersock (Pfizer Animal Health, USA) focused on alternative delivery methods for vaccines. The main challenges are broken needles and vaccine remains. The properties of Artigel (liquid at room temperature and solid at body temperature) can be used for a slow release formulation. Vaginal vaccination of cows lined up in the stable is an interesting thought. Todd Foster presented the Revelor XS formulation with four uncontrolled and six controlled releasing parts, which releases for up to 200 days. Raid Alany (University of Auckland) presented a cutting-edge formulation. His formulation consists of a hydrophilic polymer in oil. Absorption of water after injection results in a strong increase in viscosity due to a phase transfer.

The Vet Get Together was a very pleasant social event with a light, humorous, but interesting, talk given by Ramesh Panchagnula (Pfizer India) while everyone enjoyed drinks and snacks. We extend sincere thanks to Pfizer Animal Health, our co-sponsor for this event.



Todd Foster (Pfizer Inc., USA) engages in a discussion with participants at the Young Scientist Workshop, The World of Veterinary Drug Delivery.

¹Intervet Schering-Plough Animal Health, The Netherlands.

²School of Pharmacy, University of Otago, New Zealand.

Attendees were also treated to a series of excellent podium presentations as part of the Veterinary Mini-symposium, Enhancing Drug Delivery Using Novel Animal Models. The need for more information about animal patients for *in silico*

modeling was a message from Kinam Park, who opened the mini-symposium as an invited speaker. Jim Riviere provided a nice summary of inter-species differences when considering the transdermal route of drug administration. One interesting piece of information was that hairless animals have hair follicles, just no hair, so the follicular route still needs to be considered. Lucila Garcia-Contreras presented an interesting talk on aerosol delivery and the importance of considering anatomy and physiology in species choice. Rodents are typically used for pulmonary delivery studies because only a small amount of the test drug is needed; however, there are inter-species differences in lung structure and airflow that can lead to differences in bioavailability. Florence Delie discussed a very interesting novel animal model for assessing toxicity and biodistribution of drugs using chick embryos and the chorioallantoic membrane (CAM) either *ex ovo* or *in ovo*.

In the A Veterinary Delivery Odyssey session, speakers discussed a range of topics that highlighted the diversity of topics within the area of veterinary delivery and animal health. Carsten Schmidt opened the session with a discussion of IVIVC as it relates to release-form biodegradable implants. Neslihan Gursoy then spoke about chitosan formulations for the treatment of foot and mouth disease using guinea pigs as the model species. Dogs were used as the model species in an interesting talk given by Lee Ann Hodges to investigate gastric emptying and prokinetic agents. Judy Chan presented her work on the production of



Todd Foster (Pfizer Inc., USA; left) and Ian Tucker (University of Otago, New Zealand; right) provide a lively debate as speakers in the veterinary segment of the Pearls of Wisdom.

controlled released granules for anticoagulants used to control pest animals. Yvonne Perrie closed the session with an excellent presentation highlighting the challenges (and fun) of working with wild animals. Vaccination of badgers for Tb using flavored baits was the challenge for this study, and this was the first talk I have attended at a CRS conference that included night footage of animals. A number of posters were also presented on the topic of veterinary drug delivery, but it would be great to see even more in Copenhagen.

The veterinary segment of the Pearls of Wisdom is a much-anticipated event at CRS conferences, where speakers take the opportunity to stimulate discussion in an informal atmosphere. In 2008 the format for discussion was a debate between Ian Tucker (con speaker) and Todd Foster (pro speaker) on the topic, “Veterinary Sustained Release Formulations Are More Complex Than Human Formulations.” The moderator for the session was Terry Bowersock. Both speakers provided insightful and compelling arguments, and the winner of the debate was decided by a vote of the audience.

The Vet Group also holds its annual general meeting at the CRS Conference and is open for anyone with an interest in veterinary delivery and animal health to attend. The Veterinary Committee for 2008–2009 is

Chair: Dr. Arlene McDowell (University of Otago, New Zealand)

Co-chair: Dr. Ramesh Panchagnula (Pfizer Animal Health, India)

Committee Members:

Dr. Erwin Mombarg (Intervet Schering-Plough Animal Health, The Netherlands)

Dr. Marilyn Martinez (FDA, Center for Veterinary Medicine, USA)

Dr. Keith Ellis (CSIRO Consultant, Australia)

Programme Chairs:

Dr. Raid Alany (University of Auckland, New Zealand)

Dr. Cyril Desevaux (Novartis Animal Health, Switzerland)

We would be very interested to hear from anyone who would like to become involved with the activities of the Vet Group. Please contact Arlene McDowell by e-mail at arlene.mcdowell@stonebow.otago.ac.nz. ■



Young Scientists Mentorship Program... Today's Leadership Helping Tomorrow's Leaders

Michael Rathbone, Ozgen Ozer, Teresa Virgallito, and Sudip Das

New York provided the location, and the Young Scientists Mentorship Committee provided the opportunity for 27 young scientists to become involved one-on-one in a year-long partnership with an established member of the CRS for the purpose of developing their personal and professional growth.

Preceding the launch of the Young Scientists Mentorship Program, a 9-month pilot program was organized and run by the Industry Initiatives Subcommittee of the CRS Education Committee, which aimed to evaluate the value and worth of the initiative. Throughout the pilot program, activities were critically monitored by the Industry Initiatives Subcommittee, and detailed records were kept of experiences. These, combined with 6-month reports that were submitted by both the mentors and protégés, were used to evaluate the initiative. The pilot program provided a valued and fulfilling experience for the mentors and proved to be an invaluable opportunity for the protégés. The pilot program was deemed a success, and the decision was made to expand it into a full program (called the Young Scientists Mentorship Program) with the aim of involving 20 mentor and protégé pairs during 2008–2009.

Young Scientists Mentorship Program... *Helping CRS Plan for the Future by Providing Young Scientists the Opportunity to Profit from the Past*

The Young Scientists Mentorship Program was launched at the 2008 CRS Annual Meeting & Exposition in New York City during the Young Scientists Mentorship Program Breakfast, where Dr. Michael Rathbone provided an overview of the program and highlighted the benefits of the program to the CRS, mentors, and protégés alike. Personal reflections were given



The Young Scientists Mentorship Program Subcommittee (left to right) Sudip Das, Teresa Virgallito, Michael Rathbone (chair), and Ozgen Ozer.

by four of the participants in the pilot program (Prof. Randy Mrnsy, Dr. Sally-Anne Cryan, Dr. Gino Martini, and Dr. Irene Papanicolaou). Randy Mrnsy said, "I found this mentorship program a great way to give back to the CRS some of what I have received over the years from the Society through my interactions with its scientific leadership. While those interactions were very helpful to me, the mentorship program provided a more formal mechanism to find people who can share information regarding specific professional/career concerns and questions posed by younger CRS members."

Professor Mrsny's protégé, Dr. Sally-Ann Cryan, said, "As a junior pharmacy faculty member I was not short of opportunities to practice my mentoring skills with undergraduate, post-graduate, and post-doctoral students, but at this critical and challenging stage of my career, accessing a suitable senior academic mentor for myself was proving difficult. The CRS Mentorship Program offered me a unique opportunity to be mentored by a world-renowned scientist who acted as both an impartial sounding board and as a guide to me over the last year. The mentorship sessions with Professor Mrsny helped me to reflect upon, and to define, my long-term career goals, from which day-to-day administration can so often distract us. Professor Mrsny provided practical tips and action points on leading and managing my research team that I have since implemented to great professional and personal benefit. The Mentorship Program also provided me with an opportunity to get more actively involved with the Society, and overall, I would congratulate CRS on the initiative and look forward to its continuation and hopefully acting as a mentor myself in the program in years to come."



Randy Mrnsy provides an inspiring talk, reflecting on his experiences in the pilot Mentorship Program.

Dr. Gino Martini commented that he personally found the Mentorship Program to be of great value, as it allowed him the opportunity to pass on what he has learned from his mistakes to up-and-coming key talent, such as his protégé Irene Papanicolaou. He thought that John Crosby summed up the whole program when he said, “Mentoring is a brain to pick, an ear to listen, and a push in the right direction.”

Dr. Irene Papanicolaou said that “Being part of the CRS Mentorship Program turned out to be a very rewarding experience. I had a very fruitful interaction with my mentor, Dr. Gino Martini. The fact that we were both based in the same organization (GSK) was critical for the success of our mentoring relationship. It was instrumental in achieving my main objective: to gain a better understanding of my organization and the wider pharmaceutical industry. In addition to better understanding what was a new environment for me (I joined the company after finishing my Ph.D.), I worked with Dr. Martini toward acquiring the skills that were necessary to fulfill my new role. He provided me with valuable insights and reading material on subjects such as the management of individuals and projects. He also supported and advised me on how best to pursue my next big challenge: studying for a MBA degree. Dr. Martini’s many years of experience in GSK and his experience as a MBA student himself were truly invaluable to me. Overall, it was a very educational experience, and I am grateful to the CRS for

initiating the Mentorship Program. I sincerely hope that this initiative becomes a permanent feature of the Society, as it has the potential to bring members closer together and benefit mentors and protégés alike.”

Young Scientists Mentorship Program... *Facilitating Today's Young Scientists to Become Tomorrow's Leaders*

These reflections proved to be inspirational and prompted 27 young scientists to enroll in the program. The Industry Initiatives Subcommittee matched up the budding protégés with mentors who had previously volunteered their time and efforts for the coming year. Protégés were then introduced to their mentors and given the opportunity to get to know them, discuss their needs, and arrange how they will interact with each other over the coming year. Based on the vibrant atmosphere and noisy discussions that echoed around the room, this meet-and-greet opportunity was well received by the protégés.

The short-term goal of the Young Scientists Mentorship Program Subcommittee was achieved: to successfully launch the program and join at least 20 mentor and protégé pairs together. The subcommittee will now focus on its role of leading and monitoring the activities of the CRS Mentorship Program, with the long-term goal of implementing new ideas that result in continuous improvement in the program. ■

The CRS Foundation

Established with a clear vision ...

to provide a durable source of financial support for the advancement of educational and organizational activities that enrich and extend the research and development of CR-associated technology platforms involved in the delivery of bioactives and other functional materials

... the CRS Foundation needs your help to positively impact the future.

To learn more about the CRS Foundation

Contact Deborah Woodard at dwoodard@scisoc.org
or +1.651.994.3817.



VIII Spanish-Portuguese Conference on Controlled Drug Delivery Held

*Manuel Guzmán Navarro
Department of Pharmacy and Pharmaceutical Technology,
University of Alcalá, Alcalá de Henares, Spain¹*

The VIII Spanish-Portuguese Conference on Controlled Drug Delivery, co-organized by the Universities of Alcalá and Complutense of Madrid, was held at the University of Alcalá, Alcalá de Henares, Spain, October 20–22, 2008. The close collaboration between researchers and teachers from the Departments of Pharmaceutical Technology of both universities allowed the conference to be jointly organized.



The main facade of the University of Alcalá (in the plateresque style) was designed by Gil de Hontañón in 1553.

The Spanish-Portuguese Local Chapter of CRS (SPLC-CRS) was formed in 1995 in Santiago de Compostela, under the auspices of Prof. Nicholas Peppas, who presented the idea in 1994. The promoters of SPLC-CRS came from research institutions and academia, including the Departments of Pharmaceutical Technology from the Universities of Santiago de Compostela, La Laguna, Coimbra, and INETI in Lisbon. The first committee was headed by Prof. María José Alonso (president) and included Dr. María Eugenia Meirinhos da Cruz (vice president), Prof. Matías Llabrés (treasurer), Prof. Dolores Torres López (secretary), and Prof. Rogelio Pinto de Sa Gaspar (vice secretary).

SPLC-CRS devotes its efforts to improving the quality of life through promotion of the advancement of science, technology, and education in the field of controlled release of drugs and biological molecules. To this end, the chapter hosts an international congress in Spain or Portugal every two years. The previous seven congresses were organized by the universities and research institutions of Santiago de Compostela (1995), La Laguna (1997), Lisbon (INETI) (1998), Vitoria (2000), Seville (2002), Coimbra (2005), and Pamplona (2006). The 2008

international congress focused on the latest research related to the search for new controlled release drug delivery systems, mainly for new biopharmaceutical products.

Controlled drug delivery is a mainstay in pharmaceutical research and development. On the one hand, new molecules of the highest therapeutic interest are expected to be developed in the coming years, due to the current growth in genomics, proteomics, and metabolomics, as well as other “-omics” fields of science and biotechnology. On the other hand, it is currently believed that having molecules with high pharmacological activity is necessary in developing a pharmaceutical dosage form that can efficiently deliver a drug into the body, because the latter plays a pivotal role in the ultimate success of the drug. With the help of controlled drug delivery systems, these new drugs (peptides, proteins, antibodies, genetic materials, etc.) could be formulated in a manner such that their administration to patients results in more feasible, safe, and effective treatments. In this way, the effectiveness and selectivity of therapeutic treatments will increase for both current and upcoming drugs.

The platform of Spanish nanotechnology includes within these release systems the complex forms that carry an active substance and release it in a selective way (e.g., liposomes, nanoparticles, dendrimers, micelles, etc.), as well as biologically active molecules that are selectively directed to their target site while at the same time remaining stable in biological fluids (e.g., conjugated to antibodies or active molecules and polymers). These ideas were the goals we focused on when organizing the agenda of this congress.



Patio of Santo Tomas de Villanueva (in the Herrerian style), the University of Alcalá.

Lecturers and Scientific Program

Congress attendees included researchers and academics, university professors and students in training, and professionals from the pharmaceutical industry. The congress program included six plenary lectures on the state of science in the most current issues related to the delivery of controlled drugs:

¹E-mail: manuel.guzman@uah.es

Dr. Paolo Caliceti, *Universidad de Padua, Italia*; “Colloidal Systems for Protein Delivery”

Dr. Florence Delie, *Universidad de Ginebra, Suiza*; “Nanoparticles for the Delivery of Photosensitizers: Improvement for Photodetection and Photodynamic Therapy”

Dr. Arto Urtti, *Universidad de Helsinki, Finlandia*; “Challenges in Drug Delivery to the Posterior Segment of the Eye”

Dr. Maria Blanco Prieto, *Universidad de Navarra, España*; “New Therapeutic Strategies in Parkinson’s Disease: Targeting and Delivery of GDNF from Biodegradable Polymeric Microparticles”

Dr. Luisa Corvo, *Instituto Nacional de Ingeniería, Tecnología e Innovación NETI, Lisboa, Portugal*; “Liposomal Formulations for Modified Protein-Delivery in Inflammation”

Dr. Véronique Pr at, *Universidad Cat olica de Lovaina B lgica*; “Oral Delivery with Polymeric Nanocarriers: A Mechanistic Approach”

Fifteen abstracts on the following open topics were selected for presentation as podium communications during the plenary sessions:

- Advanced drug delivery systems
- Polymers and biomaterials
- Nanotechnology and nanomedicines
- Peptide and protein delivery
- Gene delivery
- Targeting and site-specific delivery
- Particulate drug delivery
- Novel material for controlled release of active substances

The scientific sessions concluded on October 22 with a panel discussion dedicated to the future prospects in this field, with participation by A. Mu oz (Hospital Gregorio Maranon), M. Gaspar (INETI), J. San Roman (CSIC), and J. L. Pedraza (University of Vitoria). To encourage the participation of young researchers in training, the chapter has established an award for the best doctoral thesis presented in Spain and Portugal over the past two years. Also, awards were given for the two best presentations (oral and poster) by students attending the congress.

Dr. Robert Langer, professor at the Massachusetts Institute of Technology (MIT) and recipient of the 2008 Prince of Asturias Award for Technical and Scientific Research, was not able to participate in the congress. Nevertheless, he was able to spend some time in Madrid on his way to Oviedo to receive the Prince

of Asturias Award and give a lecture on “Advances in Drug Delivery and Tissue Engineering.” The lecture was held on October 23 at the National Royal Academy of Pharmacy (RANF) thanks to the help of Prof. Mar a Jos  Alonso and RANF Chair Prof. Mar a Teresa Miras and Secretary Prof. Antonio Doadrio. This lecture, organized by the RANF and SPLC-CRS, was transmitted directly online at www.ranf.com and www.splc-crs.org, allowing everyone to follow it. At that time Prof. Langer also received his nomination as an elected Foreign Corresponding Academician Member of the Royal

National Academy of Pharmacy.



Trilingual Patio, where university studies created by Cardinal Cisneros began in 1508.

Several sponsors provided financial support for this venue: CRS, the Universities of Alcal  and Complutense of Madrid, the government of Madrid, the Innovation Agency of Madrid, Noscira,

Lilly, Arafarma,

Normon, Ewonik, Agilen Technologies, Gatefosse, COFARES, Colegio de Farmaceuticos de Madrid, Consejo General de Colegios Oficiales de Farmac uticos, Caixa Galicia, and Asociaci n de Amigos de la Universidad de Alcal .

The City of Alcal  de Henares

The VIII Spanish-Portuguese Conference on Drug Delivery took place in Alcal  de Henares, 30 km from Madrid. It is both an ancient and modern city, blessed with a rich cultural heritage. It is known as the birthplace of Miguel de Cervantes, author of *Don Quijote de la Mancha*, and for its university, founded by Cardinal Jim nez de Cisneros in the 16th century. The conference was held during the fifth centenary of the beginning of studies at the Cisnerian University of Alcal —the world’s first planned university city designed and built solely as the seat of a university and which served as a model for other centres of learning in Europe and the Americas.

From a city where the lessons of history come alive, we would like to wish all members of the Controlled Release Society around the world the greatest success in their scientific research and personal lives.

More information is available at www.splc-crs.org/es/index.htm. ■



Oral Multi-Particulate Drug Delivery Systems: Challenges and Opportunities

March 24–25, 2009 • Hilton Vienna Danube • Vienna, Austria

Satellite Meeting Chairs

Ali Rajabi-Siahboomi, Colorcon, Inc., U.S.A.
Brigitte Skalsky, Evonik Rohm GmbH, Germany

Educational Goals

- Background into suitability of MP systems for oral
- MP options available: core design and formulation, polymers, technologies
- What is new on the formulation and design of MP
- Practical aspects of manufacturing and scale up for MP systems
- Up-to-date information on QbD and PAT aspects for MP systems
- Potential mathematical prediction of formulation and description of drug release
- Regulatory preferences and guidelines on MP systems as compared to monoliths

Topics

Delivery of small multi-unit systems into GIT for local and systemic drug delivery
Multi-particulate systems: Formulation design and manufacturing considerations
The principal criteria for polymer selection in extended release MP systems
Use of functional polymers on multi-particulate systems for design of drug delivery to site specific regions of the GIT
System suitability, critical coating process parameters and scale up of MP systems, PAT
Encapsulation of multi-particulates; Critical process parameters and performance variables
Matrix particles (wet/melt extrusion)
Compression of multi-unit particulate systems into tablets (MUPS)
In-vitro dissolution testing of multi-particulate systems for *in-vivo* performance prediction

Mathematical description of drug release from MP systems
Multi-particulates systems versus single units, a regulatory prospective and preferences
Quality by design aspects of multi-particulate systems:
Formulation and related processing
Suitability of multi-particulate systems for pediatric applications
Multi-particulate systems versus single units, a regulatory prospective and preferences

Case Studies

Characterization of critical physico-mechanical properties of the barrier membrane files
Multi-particulate systems as platform drug delivery technologies
Compression of multi-particulates into tablets
IVIVC aspects of MP drug delivery systems

Invited Speakers

Goran Aldeborn, Uppsala University, Sweden
Abdul Basit, London School of Pharmacy, U.K.
Linda Felton, University of New Mexico, U.S.A.
Thomas Fuerst, Evonik Industries, Pharma Polymers, Germany
Rob Havenaar, TNO, The Netherlands
Catherine Herry, Ethypharm, France
Peter Kleinebudde, University of Dusseldorf, Germany
Marina Levina, Colorcon, Inc., U.S.A.
Jobst Limberg, German Registration Authorities, Germany
Michael Melichar, GEA, Switzerland
Ali Rajabi-Siahboomi, Colorcon, Inc., U.S.A.
Harald Rettig, BioVista, Switzerland
Karlheinz Seyfand, Harro Hoeflinger, Germany
Juergen Siepmann, Lille University, France
Brigitte Skalsky, Evonik Industries, Pharma Polymers, Germany
Catherine Tuleu, University of London, U.K.
Iris Ziegler, Nycomed, Germany

Watch for more details to come and registration to open soon!

The Many Strong Voices of CRS—We Want to Hear What You Think!

It has been a number of years since we asked our members to spend a few minutes to help us keep the Society focused on your future needs. Well, we think the time is right to ask for your feedback, and we want you to have your say now to help shape the future of CRS.

We all know the industry is evolving and that the ways in which we work on optimising and targeting the delivery of bioactives and other functional materials will have a key role to play in new, successful products for the future. So, our questions to you revolve around what the CRS can deliver for you to help keep you up-to-date with the latest advances in bioactive delivery.

We are currently working with a professional group to put together a short, web-based survey that will ask for your feedback on a number of different topics. Our questions will be designed such that we can better understand you and your needs.

We need to ensure the Society meets the needs of all its members, so first of all, it's important to understand the demographics, job roles, and key areas of current focus to you specifically. We then need to find out what makes the Society work for you, how you want to get involved, and why you choose to be a member. After that, we want to explore with you existing and new offerings that would provide additional value to you in your job. With your feedback and a lot of data crunching, we can then work on implementing ideas over the forthcoming months and years.

When can you expect to hear from us about participating in the survey? The date of the survey is scheduled for early next year, sometime between February 16 and 27, 2009. Whether you are a long-standing CRS member or a new member, we want every voice to be heard so we can deliver an even better Society for you. ■

Call for Papers

36th CRS Annual Meeting & Exposition Copenhagen, Denmark • July 18–22, 2009

The abstract and award submissions for the 36th CRS Annual Meeting & Exposition are now open. With more than 30 session topics to choose from, you'll find the right one for your abstract. Visit www.controlledreleasesociety.org/meeting/program for all of your submission needs.

This is your opportunity to highlight your research results and findings and join these outstanding CRS plenary speakers:

Gary Cleary, Corium International, Inc., U.S.A.
The Emergence of Innovative Transdermal-based Delivery Systems

Heico Frima, European Commission, Belgium
Nanomedicine Research in the EU 7th Framework Program for RTD

Silvio Garattini, Mario Negri Institute for Pharmacological Research, Italy
What Is Needed to Further Improve the Health in the World?

Allan Hoffman, University of Washington, U.S.A.
The Early History and Evolution of the Controlled Drug Delivery Field

Robert Kiss, Belgian National Fund of Scientific Research, Belgium
Targeting the Na⁺-ATPase to Combat Metastatic and/or Multidrug-Resistant Cancers

R. K. Pachauri, Chair of the Intergovernmental Panel on Climate Change and 2007 Nobel Peace Prize Winner, India

Abstract and award submissions close on January 29, 2009, so beat the rush and get your abstracts and nominations in before the end of 2008. You'll be glad you did.

At the 36th CRS Annual Meeting & Exposition in Copenhagen, you'll experience the diverse programming, high-quality science, and in-depth discussions that you've come to expect from CRS and more. Mark your calendar now for the summer event in Denmark's capital. Visit the CRS website often for annual meeting news and updates and check the exhibitor list for the companies you want to see.

Complete your research, get the appropriate clearance to submit your work, and we'll see you there!

CRS Foundation

The CRS Foundation was established in 2007 to provide a durable source of financial support for the advancement of education and activities related to CRS-associated technology platforms. The following interview includes Foundation Board members and CRS Past Presidents Susan Cady, Randall Mrsny, and Kinam Park.

Why a CRS Foundation and why now?

Mrsny: There has been discussion regarding a foundation for years, and during my CRS presidency, the Board of Directors further envisioned what a successful foundation would provide, supporting the scientific training of its future leadership and honoring individuals who have made notable contributions to the Society and its technology.

What kind of programs are you creating?

Cady: The first step is to build a durable endowment and, as assets grow, to establish a portfolio of international postdoctoral programs, travel for scholarly study, visionary educational platforms, and academic-industrial partnerships. The first Joseph R. Robinson Postdoctoral Fellowship will be presented at the 36th CRS Annual Meeting & Exposition in Copenhagen next July 2009.



*Joseph R. Robinson
1939-2006*

Can you tell us more about the Joseph R. Robinson Postdoctoral Fellowship?

Park: I'd like to start by telling you about the person for whom it is named—my professor, mentor, and friend Joe Robinson whom we lost to cancer in 2006. He was one-of-a-kind, and we miss him dearly. He set a high bar of excellence not only for teaching and research at the University of Wisconsin, Madison, but also for human relationships. Wherever he went, he lit up the entire place. He

would talk about any topic any place any time, and we loved him because he was one of us. We wanted to honor him by cultivating future leaders, and one of the best ways to do so is to support a post-doc each year.

Mrsny: As we were setting up the Fellowship, I learned a lot more about the fingerprint Joe Robinson left on CRS, a major focus and passion of his professional life. He was a longtime member and its president from 1991 to 1992. He enthusiastically advanced the work of the Society and was instrumental in helping it develop into a highly renowned scientific organization that bridges academia and industry.

Park: He was also a founding member of the *Journal of Controlled Release* (JCR), and his participation was critical in making CRS and JCR the premier Society and journal.

What will the Joseph R. Robinson Postdoctoral Fellowship be given for?

Cady: To honor Joe's lifelong commitment to teaching and CRS, we wanted the first initiative of the CRS Foundation to be a prestigious \$30,000 fellowship award that parallels Joe's paradigm for preparing his students for a meaningful career in drug delivery science. The postdoctoral program for advanced study and travel will expand networks and collaborative opportunities with legendary figures in controlled release and delivery science. Kinam Park will chair the selection committee.

Park: We are defining the criteria for selection, and the committee members include Bob Langer and Jorge Heller who worked closely with Joe through the years. When applications are available in early January 2009, we will invite the best and brightest post-docs in controlled release and delivery to apply.

What are your Foundation goals for 2009?

Cady: Our short-term goal is to present \$30,000 for the initial fellowship, with \$30,000 in reserve for the 2010 fellowship. We invite everyone who values CRS to contribute to the fellowship and the endowment. All kinds of donations are welcome as we grow the endowment, but the most important contribution for 2009 support of the Joseph R. Robinson Fellowship is a cash donation. Individual donations to date range from \$10 to \$5,000. As you consider a donation, or if you have already given one, we encourage you to ask if your employer has a matching contribution program that could potentially double your gift.

Are there tax considerations?

Cady: Absolutely. We're nearing year end and, for many in the United States who itemize deductions, your donations may be tax deductible. The CRS Foundation is a 501(c)(3) charitable organization, so we recommend consulting your tax advisor to determine how the current law applies to you.

Is there any other information you'd like to share?

Mrsny: This is an important initiative that will advance controlled release technologies and partnerships in ways we have not yet imagined. On behalf of the CRS Foundation Board, thank you for making a contribution that will honor past achievements, support the present, and positively impact the future.

To donate to the CRS Foundation, please use the form on the opposite page. For more information, contact:

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+1.651.994.3817, dwoodard@scisoc.org
Susan Cady: +1.732.729.5755, Susan.Cady@Merial.com
Randall Mrsny: +1.650.575.5171, rjm37@bath.ac.uk
Kinam Park: +1.765.494.7759, kpark@purdue.edu

CRS Foundation Donation

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Your donation will be a part of the first prestigious scholarship offering of the CRS Foundation, a postdoctoral fellowship that honors the life of inspiring teacher and CRS leader Joseph R. Robinson, while furthering advanced research in controlled release platforms.

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Your donation will build the endowment, supporting the creation of a portfolio of future fellowships and programs.

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Total should equal the amount selected in level of donation above.

If in memory of, or as a tribute, please include the name of the person to be honored:

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Online: Select "Foundation" on the CRS website, www.controlledreleasesociety.org

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The CRS Foundation is a 501(c)(3) charitable organization, qualified to accept tax-deductible contributions during donor lifetime or bequests by will. Donations may be tax deductible. Consult your tax advisor on how the current law applies to you.

Please forward this form and donation to:

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Upon receipt of payment, a confirming receipt will be sent to you.

Questions? Please contact:

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Tel (general): +1.651.454.7250
E-mail: dwoodard@scisoc.org

www.controlledreleasesociety.org



*On behalf of the CRS Foundation,
thank you for your support.*



People in the News

Compiled by Steven Giannos
Industrial Editor

MicroCHIPS CEO Named in Popular Science's 'Seventh Annual Brilliant 10'

NewsRx.com: October 24, 2008 – BOSTON, Mass. – John Santini, Jr., Ph.D., CEO of MicroCHIPS, Inc., and CRS member, has been named by *Popular Science* magazine as a member of the 2008 class of “young geniuses shaping the future of science.” In the history of this annual list, Dr. Santini is the only honoree who is also a successful life sciences entrepreneur who runs his own commercial venture. His company, MicroCHIPS, is pioneering intelligent medical devices for drug delivery and biochemical sensing.

Dr. Santini began developing the microreservoir technologies that are at the core of his company's products as a doctoral student in the labs of Dr. Robert Langer and Dr. Michael Cima at the Massachusetts Institute of Technology. He founded MicroCHIPS with Drs. Langer and Cima, as well as Terry McGuire of Polaris Venture Partners, in 1999. MicroCHIPS is developing next-generation biosensing and drug delivery devices to increase therapeutic control and effectiveness for people with diabetes, osteoporosis, and other debilitating diseases.

“I am honored to be a part of a list of such accomplished individuals,” said Dr. Santini, president and CEO, MicroCHIPS. “It is exciting to see our unique technologies take shape as products that can transform how clinicians and patients manage serious, chronic conditions.”

“It is gratifying to see how John is helping to move microreservoir technology from ‘bench to the bedside,’” said Robert Langer, Sc.D., Institute Professor at MIT. “He is working to realize our vision of innovative long-term devices that can deliver drugs and sense chemicals with exquisite control.”

Under Dr. Santini's leadership, MicroCHIPS plans to begin clinical work in 2009 on its lead products, a long-term continuous glucose monitor for diabetes, and a drug delivery device for osteoporosis.

Altea Therapeutics Forms Premier Scientific Advisory Board

Business Wire: August 8, 2008 – ATLANTA, Ga. – Altea Therapeutics has announced that several preeminent medical practitioners and scientists in the fields of drug delivery, skin physiology, engineering, and clinical medicine have joined its new Scientific Advisory Board. Prof. Richard H. Guy, Ph.D., of the University of Bath, U.K., has been appointed chair of the Scientific Advisory Board. Members of the Scientific Advisory Board:

Richard H. Guy, Ph.D., is a leading scientist in the physicochemical characterization of transport phenomena in biological membranes and in theoretically defining transdermal drug delivery processes. He is professor and head of the Department of Pharmacy & Pharmacology, University of Bath, U.K., and CRS member.

Mark R. Prausnitz, Ph.D., is a renowned scholar in the fields of drug and vaccine delivery to the skin. He is a professor at the School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, where he and his team research, develop, and characterize novel biophysical methods for administering drugs. Prausnitz is a member of CRS.

David J. Ensore, Ph.D., managed the commercial development of four controlled release pharmaceuticals while at ALZA, a leading drug delivery company subsequently acquired by Johnson & Johnson. He was formerly SVP product research and development at Altea Therapeutics and is an inventor on 25 U.S. patents in drug delivery and medical devices.

Walter M. Holleran, Pharm.D., is a world expert in epidermal structure, lipid metabolism, and barrier function. He is adjunct professor of dermatology and pharmaceutical chemistry in the Schools of Medicine and Pharmacy at the University of California, San Francisco, as well as research chemist in the Department of Veterans Affairs Medical Center in San Francisco.

Jay S. Skyler, M.D., is a pioneering clinical researcher and international leader in the diabetes field. He has played a pivotal role in developing the concepts of intensive insulin therapy. He has served both as president and director of the American Diabetes Association and is currently chair of multiple NIH-sponsored, nationwide clinical studies focused on the treatment and prevention of type 1 diabetes. Dr. Skyler is professor of medicine at the University of Miami.

Richard L. Gallo, M.D., Ph.D., is a leading investigator in the field of skin research, with a focus on the role of the innate immune system in skin health and disease, the role of antimicrobial peptides, and aspects of the interaction of the skin with the immune system. Dr. Gallo is professor and chief of dermatology at the University of California, San Diego.

Brian B. Hoffman, M.D., is a professor of medicine at Harvard Medical School, Boston, MA. He is an emeritus professor of medicine at Stanford University, where he was on the faculty for more than 20 years. He is also the former chief of medicine in



the VA Boston Health Care System. Dr. Hoffman is a clinical pharmacologist, with long-standing research interests in signaling mechanisms of G-protein-coupled receptors in vascular smooth muscle cells and in the effects of drugs on the cardiovascular system in humans.

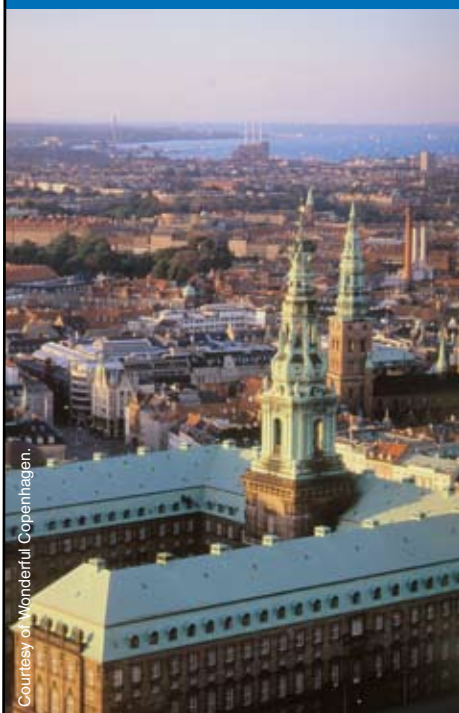
“Now that our novel transdermal delivery technology is demonstrating clinical effectiveness for drugs that were previously administered as injections, it is timely to establish the SAB to review and guide the Company’s approaches to applying its technology in numerous clinical areas,” said Eric Tomlinson, Ph.D., D.Sc., president and CEO of Altea Therapeutics. “We anticipate that the SAB will be most valuable in helping to reinforce the Company’s scientific capabilities and in selecting and guiding its product development programs.” ■

Welcome New Members

Mir M. Ali
Isabelle Bonnet
Fei Cai
Mark Gandara
Christopher Gilmore
Stefan Henke
Randolph M. Johnson
Patrick Moya
ZB J. Pietrzkowski
Shobhan S. Sabnis
Felix Theeuwes
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The Emergence of Innovative Transdermal-based Delivery Systems

Heico Frima, European Commission, Belgium
Nanomedicine Research in the EU 7th Framework Program for RTD

Silvio Garattini, Mario Negri Institute for Pharmacological Research, Italy
What is Needed to Further Improve the Health in the World?

Allan Hoffman, University of Washington, U.S.A.
The Early History and Evolution of the Controlled Drug Delivery Field

Robert Kiss, Belgian National Fund of Scientific Research, Belgium
Targeting the Na⁺-ATPase to Combat Metastatic and/or Multidrug-Resistant Cancers

R.K. Pachauri, Chairman of the Intergovernmental Panel on Climate Change, **2007 Nobel Peace Prize Winner**, India



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In the News

Compiled by Steven Giannos
Industrial Editor

OCTOBER 2008

AlphaRx and Gaia BioPharma Enter into Feasibility and Option Agreement

PRNewswire-FirstCall: October 22, 2008 – MARKHAM, Ontario, Canada – AlphaRx Inc. (OTCBB: ALRX) and Gaia BioPharma Limited, a privately held, early-stage biopharmaceutical company focused on hospital-based injectable therapeutics, have announced the signing of a feasibility and option agreement. Under the terms of the agreement, AlphaRx will use its proprietary nano drug delivery platforms to formulate two injectable products targeting underserved medical conditions. These represent market opportunities potentially exceeding US\$200 million in annual revenue for Gaia. Gaia will have 12 months to evaluate the formulated products and exercise its option right for a pre-negotiated license agreement.

AlphaRx is responsible for completing the product development work and will be eligible to receive an upfront non-refundable option fee and reimbursements in exchange for completing certain pre-defined development milestones. AlphaRx will also receive royalty and milestone payments from future product sales that utilize AlphaRx's delivery technology. Gaia BioPharma will be responsible for performing all aspects of clinical development, regulatory submission, manufacture, and commercial operations. The first product is expected to reach commercial stage by 2011.

Novartis to Buy Nektar's Pulmonary Unit for \$115 Million

AP Online via NewsEdge: October 21, 2008 – BASEL, Switzerland – Novartis AG has said that it will buy the pulmonary drug unit of California-based Nektar Therapeutics for \$115 million. The transaction is expected to be completed by the end of 2008, pending regulatory approval, Novartis said.

San Carlos-based Nektar develops drug products and candidates using its own drug delivery technologies, including PEGylation technology—a chemical process aimed at improving the performance of drugs, such as by making them more soluble or reducing immune responses to them. The company's pulmonary technology makes drugs inhalable to deliver them through the lungs.

Nektar's drugs in the pipeline include an aminoglycoside antibiotic against pneumonia, a PEGylated form of irinotecan against tumors, and an oral drug to treat bowel dysfunction. Novartis said it will use Nektar's expertise to accelerate its pipeline for drugs against chronic obstructive pulmonary disease, asthma, cystic fibrosis, and other illnesses. The acquisition excludes Nektar's inhalation programs for insulin and the antibiotics vancomycin, ciprofloxacin, and amikacin. Around 140 Nektar employees will join Novartis but stay in San Carlos.

Nektar President and Chief Executive Howard W. Robin said, "This agreement will allow us to focus our efforts on the development of novel therapeutics using our PEGylation and conjugate chemistry-based drug development platforms." Nektar said it will also transfer manufacturing and royalty rights to the tobramycin inhalation powder program, already partnered with Novartis.

3M and VaxInnate Collaborate to Develop Flu Vaccine Patch

Business Wire: October 20, 2008 – ST. PAUL, Minn. – 3M Drug Delivery Systems has entered into an agreement with VaxInnate Corporation to develop a flu vaccine patch for use against a pandemic flu outbreak. The non-exclusive license agreement provides VaxInnate with use of patented 3M Microstructured Transdermal System (MTS) microneedle technology to deliver its M2e universal flu vaccine using a convenient skin patch instead of a traditional injection.

3M's innovative microneedle technology penetrates the skin with minimal discomfort, providing intradermal delivery for drugs, vaccines, and protein therapeutics that are typically available only via injection. This application expands the range of active pharmaceutical ingredients that can be delivered via a skin patch, while eliminating the need for sharps disposal.

"Our technology combines the ease, convenience and self-administration potential of a transdermal patch with the speed and efficiency of a traditional injection," said Kris Hansen, MTS technical manager for 3M Drug Delivery Systems. "Studies using model vaccines have validated the potential effectiveness of delivering vaccines with the solid Microstructured Transdermal System." "The ability to deliver VaxInnate's M2e universal flu vaccine using 3M's transdermal patch could make it possible to vaccinate people rapidly for seasonal flu or in the event of a pandemic flu, when doing so is critical to stopping the spread of disease," added Alan Shaw, VaxInnate CEO. "Through this collaboration, we have an opportunity to make a major contribution to global public health."

"MTS technology has the potential to improve vaccine potency, which would provide optimal vaccine efficacy and could make intradermal delivery superior for certain antigens," said Mark Tomai, head of vaccine business development, 3M Drug Delivery Systems. "In addition, this technology has the potential for reducing cold-chain storage, an issue with many current vaccines."

VaxInnate has reported impressive results from early human testing of its M2e universal flu vaccine candidate, which could

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end the need for annual flu shots and provide protection against seasonal and pandemic flu strains. The vaccine candidate will advance into further human studies in 2009.

Bend Research Offers Broad Access to Drug-Delivery Solutions

PRNewswire: October 20, 2008 – BEND, Oreg. – Bend Research Inc. has announced that it will independently offer unique drug-delivery expertise and technologies to outside firms in the pharmaceutical and biotechnology industries. Bend Research will continue its 23-year collaboration with Pfizer but will also be free to work with outside firms using proprietary technologies developed jointly by the two firms. These technologies include their spray-dried dispersion (SDD) technology (which increases the oral bioavailability of low-solubility compounds), controlled-release, multiparticulate, and pulmonary delivery platforms.

Bend Research CEO Rod Ray commented, “Our work with Pfizer has helped us tremendously to grow and develop our capabilities over the past two decades. In return, we have helped Pfizer advance a significant number of their compounds. Today, we’re pleased to have the opportunity to collaborate with additional clients to enable the delivery of new medicines.” Kelvin Cooper, senior vice president of worldwide pharmaceutical sciences for Pfizer Global Research and Development, agreed, “Our collaboration with Bend Research has proved to be valuable and we look forward to continued work with Bend Research. Through this agreement, we hope the technologies we’ve developed together will help speed the introduction of new medicines to patients throughout the world.”

Under the terms of the agreement with Pfizer, Bend Research will have the ability to employ expertise and processes developed with Pfizer to benefit other drug developers. These include optimized drug discovery, dosage form development, engineering capabilities, and manufacture of supplies for clinical trials under Good Manufacturing Practice (GMP) conditions. Bend Research will continue to work exclusively with Pfizer on certain specific technology platforms.

Studies in Drug Delivery Reported by R. I. Moustafine and Co-researchers

NewsRx.com: October 17, 2008 – A new study, “Comparative Evaluation of Interpolyelectrolyte Complexes of Chitosan with Eudragit L100 and Eudragit L100-55 as Potential Carriers for Oral Controlled Drug Delivery,” is now available. According to recent research from Tatarstan, Russian Federation, “With a view to the application in oral controlled drug delivery systems, the formation of interpolyelectrolyte complexes (IPEC) between chitosan (CS) and Eudragit L100 (L100) or Eudragit L100-55 (L100-55) was investigated at pH 6.0, using elementary analysis. The interaction or binding ratio of a unit molecule of CS with Eudragit L copolymers depends on the molecular weight of CS, and changes from 1:0.85 to 1:1.22 (1.17 <0.82) for L100 and from 1:1.69 to 1:1.26 (0.60 <0.79) for L100-55, respectively.”

“Based on the results of FT-IR, the structure of the IPECs can change substantially as a function of pH (from 5.8 till 7.4). Swelling behavior of physical mixtures (PM) is definitely different, and potential interactions between the two polyelectrolytes were not observed,” wrote R. I. Moustafine and colleagues.

The researchers concluded, “The release of the model drug diclofenac sodium (DS) was significantly delayed from tablets made up of the IPEC and can be modified by two ways: choosing Eudragit L copolymer types and/or changing the molecular weight of CS in the IPECs composition.” Moustafine and colleagues published their study in the *European Journal of Pharmaceutics and Biopharmaceutics* (European Journal of Pharmaceutics and Biopharmaceutics, 2008;70(1):215-25). For additional information, contact R. I. Moustafine, State Medical University of Kazan, Department of Pharmaceutical, Toxicological and Analytical Chemistry, Tatarstan, Russian Federation.

Study Data from Peking University, Department of Pharmaceutics, Provide New Insights into Drug Delivery

Women’s Health Weekly via NewsEdge: October 16, 2008 – Research findings on “Self-microemulsifying Drug Delivery System (SMEDDS) Improves Anticancer Effect of Oral 9-Nitrocamptothecin on Human Cancer Xenografts in Nude Mice” are discussed in a new report. According to a study from Beijing, People’s Republic of China, “9-Nitrocamptothecin (9-NC) is an orally administered topoisomerase-I inhibitor for the treatment of pancreatic carcinoma, but its oral absorption and bioavailability are poor. The main objective of this study was to develop optimal 9-nitrocamptothecin (9-NC) microemulsion prepared by [a] self-microemulsifying drug delivery system (SMEDDS).”

“Two SMEDDS formulations of 9-NC prepared from a mixture of ethyl oleate, Tween-80 (T-form) or Cremophor EL (C-form), and PEG-400/ethanol were formed as microemulsions under dilution with aqueous phase. The resulting microemulsions were evaluated in vitro and in vivo, including the kinetics and antitumor effects in SKOV-3 human ovarian cancer xenograft in nude mice. Following 1:10 aqueous dilution of optimal 9-NC SMEDDS, the droplet sizes of resulting microemulsions were (30.8±4.6)nm and (39.8±8.2)nm for SMEDDS T-form and C-form, respectively, and the zeta potential values were -(4.3±0.5)mV and -(5.7±0.5)mV, respectively. In SKOV-3 cells, the growth inhibition (IC₅₀) of various 9-NC formulations was greatest with SMEDDS T-form (3.5±0.7 nM) followed by SMEDDS C-form (4.6±0.4 nM), 9-NC solution (6.6±1.4 nM) and 9-NC suspension (26.0±2.9 nM) (p <0.01). It was indicated that the area under the plasma concentration-time curve (AUC_{0→8h}) values of various formulations of 9-NC after oral administration ranked as the following sequence: SMEDDS T-form (360.12±19.44 ngh/ml) approximately SMEDDS C-form (351.71±33.66 ngh/ml) >9-NC solution (241.21±24.67 ngh/ml) >9-NC suspension (161.24±24.31 ngh/ml). The 9-NC SMEDDS formulations also produced significantly more tumor shrinkage (p <0.01) when

compared to 9-NC suspension in nude mice bearing human ovarian cancer xenografts,” wrote J. L. Lu and colleagues, Peking University, Department of Pharmaceutics.

The researchers concluded: “The results suggest that SMEDDS is a promising drug delivery system to increase the oral bioavailability and antitumor effects of 9-NC and may be applied to other lipophilic drugs. 9-NC SMEDDS represents a novel 9-NC therapy for cancer patients.” Lu and colleagues published their study in the *European Journal of Pharmaceutics and Biopharmaceutics* (European Journal of Pharmaceutics and Biopharmaceutics, 2008;69(3):899-907). For more information, contact J. L. Lu, School of Pharmaceutical Sciences, Department of Pharmaceutics, Peking University, Beijing, People’s Republic of China.

Philips and Celsion Announce Research Agreement to Develop New Cancer Treatment that Combines Ultrasound, Drug Delivery Technology

Business Wire: October 16, 2008 – ANDOVER, Mass., and COLUMBIA, Md. – Royal Philips Electronics (NYSE: PHG; AEX: PHI) and Celsion Corporation (NASDAQ: CLSN) have announced the signing of a joint research agreement focusing on a new cancer treatment that combines Philips’ ultrasound technology with Celsion’s drug delivery solution to target tumors with high concentrations of a cancer-fighting drug.

Under the terms of the agreement, Philips and Celsion will collaborate to explore the potential for using Philips’ investigational magnetic resonance imaging (MRI)-guided high-intensity focused ultrasound (HIFU) system in combination with Celsion’s leading drug candidate, ThermoDox®, to treat a broad range of cancers. The research uses the HIFU system to position doxorubicin, an approved and frequently used anti-cancer drug, and create a mild hyperthermia that releases the drug directly into the tumor. The result would be the ability to treat tumors that would otherwise be inaccessible.

The Philips HIFU system is designed to precisely control and deliver energy non-invasively to targeted tissues. HIFU is being researched to evaluate its use in activating Celsion’s temperature-sensitive liposome technology to release encapsulated chemotherapy drugs such as doxorubicin. Doxorubicin is the potent anti-cancer agent in ThermoDox®. Using Philips’ HIFU technology to deliver targeted, localized activation temperatures, Philips’ and Celsion’s research will explore the potential for ThermoDox® to non-invasively treat a number of solid-tumor cancers that may be susceptible to the combination of a high concentration of doxorubicin and concurrent hyperthermia.

“Localized drug delivery is being evaluated to determine the potential for increasing the potency of drugs in their target regions with equal or less toxicity to critical organs,” said Falko Busse, vice president and chief technology officer, MR, for Philips Healthcare. “The Philips MR-HIFU system could be a powerful tool to deliver these thermally activated drugs. Our volumetric heating with feedback technology is being designed to allow control of both the tissue temperature and the heating

area. We are very excited about this research collaboration with Celsion in the promising field of localized drug delivery.”

“We are very pleased to be working with Philips, a recognized world leader in healthcare technology. Philips’ vision and commitment to the advancement of effective cancer treatment is inspirational and consistent with that of Celsion’s overarching mission to bring the promise of temperature-sensitive liposomal technology to effectively treat difficult cancers,” stated Michael H. Tardugno, Celsion’s president and chief executive officer. “Moreover, Philips’ MRI-guided HIFU technology has the potential to heat a defined area while providing a real-time visualization of the heated area through the use of MRI.”

Philips and Celsion are conducting research to test two premises. First, ThermoDox® has the potential to eliminate cancer cells that may otherwise remain viable and be responsible for secondary tumors, using HIFU to aid in releasing the concentrated drug within and around the margins of the heated area. Second, using HIFU in low temperature activation mode in combination with ThermoDox® has the potential to provide a means to deliver high concentrations of chemotherapeutics to multiple sites at virtually any location in the body. Tardugno concluded, “If our thesis proves to be correct, the Celsion-Philips tumor targeting combination has the potential to shift the paradigm for the treatment of primary and metastatic disease.”

Research from University of Montreal Provides New Data About Drug Delivery Science and Technology

NewsRx.com: October 10, 2008 – According to a study from Montreal, Canada, “Tributyryn, an oil with anticancer properties, is a good solubilizer for docetaxel, an agent used in the treatment of several cancers. In this paper, the interaction between tributyrin and docetaxel was investigated in vitro in search of a potential synergistic effect.”

“Then, nanosized emulsions (ca. 100 nm) combining both tributyrin and docetaxel were developed and tested for their cell growth inhibition properties and their systemic toxicity in healthy mice. Tributyrin alone or in combination with docetaxel, and formulated or not in a nanoemulsion, was found to exhibit a modest in vitro antimetabolic activity. No synergism could be detected under the conditions tested. Furthermore, no induction of apoptosis was revealed by flow cytometry experiments when treating HL-60 and PC-3 cells with tributyrin. When injected intravenously into mice as a nanoemulsion, the docetaxel/ tributyrin combination displayed extreme toxicity,” wrote M. E. Perron and colleagues, University of Montreal.

The researchers concluded: “The current data preclude its combination with docetaxel in nanoemulsions for intravenous administration.” Perron and colleagues published their study in the *Journal of Drug Delivery Science and Technology* (An Investigation on the Use of Tributyrin Nanoemulsions for Docetaxel Delivery. *Journal of Drug Delivery Science and Technology*, 2008;18(3):189-195). For more information, contact

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J. C. Leroux, University of Montreal, Canada Research Chair Drug Delivery, Faculty Pharmacy, Downtown Station, POB 6128, Montreal, PQ H3C 3J7, Canada.

Research from the University of Milan Broadens the Understanding of Drug Delivery Science and Technology

NewsRx.com: October 10, 2008 – “Drug/cyclodextrin (CD) interaction compounds are widely used in the design of solid dosage forms for their ability to improve drug bioavailability, especially where poorly soluble active ingredients are concerned. Because of high CD molecular weights and fixed drug/CD interaction ratios (generally ≤ 1 mol/mol), major issues may have to be faced when formulating high-dose drug products,” scientists in Milan, Italy, report.

“In the present work, high-density pellets prepared by rotary processing in fluid bed equipment are proposed for the oral administration of drug/CD interaction compounds. The manufacturing process of pellets containing approximately 75% of an acetaminophen/beta-CD kneaded product was developed based on a sequential statistical optimization study. In particular the effect of the quantity of water, air-flow rate and plate rotational speed on the process yield and physical-technological characteristics of pellets was studied,” wrote L. Zema and colleagues, University of Milan.

The researchers concluded: “The optimization study performed was helpful in providing an overall understanding of the process and a predictive model for its further development.” Zema and colleagues published their study in the *Journal of Drug Delivery Science and Technology* (Pelletization of a Beta-cyclodextrin-Acetaminophen Interaction Compound in a Rotary Fluid Bed Granulator: An Optimization Study. *Journal of Drug Delivery Science and Technology*, 2008;18 (3):197-202).

Abbott Opens New Research Facility and Pilot Plant in Ludwigshafen

PRNewswire-FirstCall: October 9, 2008 – LUDWIGSHAFEN, Germany – Abbott (NYSE: ABT) has announced the opening of new development laboratories and a pilot-plant facility that will research groundbreaking technologies and test large-scale production of newly developed drug formulations. The expansion is part of Abbott’s global drug delivery business, SOLIQS, which is based in Ludwigshafen.

“Abbott is committed to advancing scientific innovation and bringing new medicines to patients,” said John M. Leonard, senior vice president, pharmaceuticals, research and development, Abbott. “Innovative drug formulation is critical to the development of effective new treatments that make a difference for patients.” “Nearly 40 percent of pharmaceutical compounds never reach the clinical study phase because they cannot be absorbed in the human body,” said Jorg Breitenbach, senior director of drug product development and head of SOLIQS. “The SOLIQS expansion builds on Abbott’s expertise in drug delivery technology and addresses the rising demand for innovative, patient-focused formulations.”

The facility will evaluate new processes to complement its current proprietary technologies—Meltrex™, Xellex®, NanoMorph®, and smartCrystals®—that target the formulation of soluble complex pharmaceutical substances. Using the Meltrex™ technology, Abbott has developed a new tablet formulation of its leading protease inhibitor lopinavir/ritonavir (known as Kaletra®), which is the first and only co-formulated protease inhibitor tablet that does not require refrigeration and can be taken with or without food—two important advances in delivering HIV medicine, especially in developing countries where disease prevalence is highest. The tablet formulation also offers the increased dosing convenience of fewer pills (a total daily dose of four tablets, instead of six soft-gel capsules).

Novo Nordisk Assigns Inhaled Insulin Patent Portfolio to Aradigm

Business Wire: October 8, 2008 – HAYWARD, Calif. – Aradigm Corporation (OTCBB: ARDM), a specialty pharmaceutical company, has announced that Novo Nordisk transferred to Aradigm, at no charge, a portfolio of inhaled insulin-related patents pursuant to a license agreement between Aradigm and Novo Nordisk that was terminated in May 2008. Novo Nordisk purchased a significant portion of the portfolio from Aradigm in July 2006 and supplemented the portfolio with certain of its own related patents. The portfolio includes both U.S. and foreign patents. Aradigm assumes responsibility for the maintenance of this portfolio.

In addition to the patent portfolio, Novo Nordisk will transfer to Aradigm a significant preclinical safety database that was developed during the Aradigm/Novo Nordisk collaboration, the rights to a miniaturized second-generation electronic insulin inhaler, and data from Novo Nordisk’s inhaled insulin clinical program, which included nine phase 3 trials in type 1 and type 2 diabetes patients.

“We believe Aradigm’s pioneering team developed a strong intellectual property position in the area of inhaled drugs, and inhaled insulins in particular, which was expanded during the collaboration with Novo [Nordisk]. Aradigm’s inhaler has unique features, including features to facilitate proper usage of the inhaler and convenient dosage flexibility. We wish to find a new partner interested in completion of the development and commercialization of our insulin inhaler for diabetes patients who are unable or unwilling to inject insulin,” said Igor Gonda, the CEO and president of Aradigm Corporation.

Phosphagenics Announces Initiation of Phase 1 Clinical Trial in Humans for Its Transdermal Lidocaine

NewsRx.com: October 6, 2008 – Phosphagenics Limited (ASX: POH; AIM: PSG; OTCQX: PPGNY) has announced that it has initiated a phase 1 human clinical trial using its patented drug delivery system TPM for the targeted delivery of a leading pain-relief drug, lidocaine. The trial will compare the dermal bioavailability and measure the systemic exposure of lidocaine in one of the leading marketed products, Xylocaine® (5% lidocaine), and Phosphagenics’ lidocaine (5% lidocaine).

Earlier this year, the Phosphagenics' pre-clinical results demonstrated that through the utilization of Phosphagenics' patented lidocaine formulation, the skin concentration of lidocaine was approximately 900% higher 5 hr after topical application as compared to Xylocaine®. In addition, Phosphagenics' lidocaine was able to significantly increase the depth of lidocaine penetration by approximately 500% in the thigh muscle of animals treated compared to Xylocaine®.

Dr. Esra Ogru, executive vice president of research and development at Phosphagenics, said, "Lidocaine is a well known topical anaesthetic used for a wide variety of ailments, including temporary relief of rashes, stings, sprains, strains, bites, and burns. However, it has poor penetration into the dermis, frequently rendering it largely ineffective. Our pre-clinical study showed that Phosphagenics' lidocaine formulation has the potential to provide patients with rapid pain relief, while not increasing systemic exposure, and we are excited to continue moving this program forward efficiently."

This most recent trial is being conducted at the Centre for Pharmaceutical Research, University of South Australia, under the guidance of Dr. David Foster, as the principal investigator. It is an open-label, single-centre bioavailability trial of dermal and systemic pharmacokinetics in 12 healthy adult volunteers, incorporating secondary endpoints of safety and tolerability. The Phosphagenics expects to report results of the phase 1 trial in the first quarter of 2009. Harry Rosen, president and CEO at Phosphagenics, said, "We believe we have a very attractive commercial product that has shown the potential to substantially enhance the current standard of care."

Critical Pharmaceuticals Enter Sustained Release hGH Arena

PRNewswire: October 1, 2008 – NOTTINGHAM, England – Critical Pharmaceuticals, the Nottingham, U.K.-based specialty pharmaceuticals company, has announced the successful completion of preclinical trials of a sustained release formulation of the synthetic human growth hormone (hGH) somatotropin. Trials demonstrated therapeutic plasma concentrations were achieved over an extended period of time, supporting the development of the product as a once every two weeks injection. In addition, the efficacy profile using biomarkers was comparable to current daily formulations.

The new formulation was produced using Critical's patented CriticalMix delivery technology, which is based on world-leading supercritical fluid expertise. This enables the optimal encapsulation of drugs into injectable microparticles with superior drug release properties. hGH delivery is a natural application for this technology, and the company now intends to take this product forward into phase 1 clinical trials. This decision coincides with a recent report by Frost & Sullivan valuing the European market at \$846.4 million in 2007, with a compound annual growth rate (CAGR) of 2.4% from 2007 to 2014. The report also highlighted new delivery methods together with approval for new indications as keys to success.

According to Chief Business Officer Gareth King, these preclinical results mark an important milestone for the company, "Over the past few years, we have concentrated on optimizing our delivery technologies and ensuring they are transferable from the lab into an industrial setting. Sustained release hGH is one of three projects we are now developing in areas of unmet need. There is no doubt that a sustained release version of hGH would be preferred by patients, particularly paediatric, but there are naturally concerns over safety and efficacy. We are confident the highly controlled release rates achieved with our technology will overcome these concerns. The plan is now to take this product into clinic either by ourselves or in partnership. We are also in preclinical development with sustained release Risperidone and, demonstrating the versatility of our technology platform, a once-daily nasal formulation of hGH."

SEPTEMBER 2008

BioChemics, Inc. Announces Collaboration Agreement with Leading Light-based Technology Company

Business Wire: September 30, 2008 – DANVERS, Mass. – BioChemics, Inc. (BCI), a specialty pharmaceutical company that enhances drug delivery through biophysical modulation, has announced the signing of a research collaboration agreement with Cynosure, Inc. (NASDAQ: CYNO), a leading developer and manufacturer of light-based aesthetic treatment systems, to evaluate the use of BCI's VALE®-based compositions in conjunction with light-based aesthetic treatments. VALE® (Vaso-active Lipid Encapsulated) is a novel, transdermal drug delivery system that allows a wide variety of actives to be delivered into the skin. "We are delighted to be working with Cynosure to evaluate broader applications of our VALE® based technology for light based procedures" said BCI President John J. Masiz.

According to Medical Insight, Inc., an independent aesthetic treatment market research firm, the number of non-invasive aesthetic treatment procedures worldwide using laser and other light-based technologies will increase from nearly 58 million in 2006 to over 170 million in 2011, representing a compound annual growth rate of over 24%.

VALE® may allow a substantial portion of the pharmacopoeia to be re-engineered, turning oral drugs into transdermals that are safer (no gastro-intestinal problems), cheaper, and potentially faster acting (applied directly to the treated area) than oral equivalents. BCI's focus is on the multi-billion dollar market opportunities currently underserved by existing therapies. Its two lead clinical products focus on treating diabetic peripheral neuropathy and osteoarthritis.

NicOx Signs Agreement with Capsugel for the Commercial Manufacture of Naproxinod Oral Capsules

PRNewswire-FirstCall: September 23, 2008 – SOPHIA ANTIPOLIS, France – NicOx S.A. (Euronext Paris: COX) has

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announced that it has signed an exclusive agreement with Capsugel, the leading producer of two-piece capsules, for the commercial manufacturing and global supply of naproxcinod capsules. Naproxcinod is NicOx' lead investigational product and the first compound in the cyclooxygenase-inhibiting nitric oxide-donating (CINOD) class of anti-inflammatory agents. The aim of this agreement is to ensure sufficient supplies of naproxcinod capsules to underpin its successful commercial launch. The filing of a new drug application (NDA) for naproxcinod with the U.S. Food and Drug Administration (FDA) is projected for mid-2009.

The agreement with Capsugel follows the signing of an agreement for the commercial manufacture and supply of naproxcinod active pharmaceutical ingredient (API) with Archimica in March 2008. NicOx recently announced the results of the second pivotal phase 3 study for naproxcinod in patients with osteoarthritis of the knee. This study met all three of its co-primary efficacy endpoints and supported naproxcinod's non-detrimental effect on blood pressure.

Staffan Stromberg, vice president of technical development and operations at NicOx, said, "We are very happy to have concluded this agreement with Capsugel, which is recognized as the world leader in capsule manufacturing. We believe Capsugel's flexibility and production capacity is well adapted to NicOx' launch preparations for naproxcinod. This agreement is also the result of the excellent collaboration between the two companies, in which Capsugel's technology has been used in the production of naproxcinod clinical trial supplies."

Under the terms of this exclusive agreement, Capsugel will be responsible for the formulation and encapsulation of naproxcinod API, using its patented LEMS™ (Liquid Encapsulation Microspray Sealing) technology. The manufacturing will be performed at one of Capsugel's plants in France. A 2001 study showed that 66% of patients prefer to take drugs as capsules, compared to 22% who prefer tablets.

NicOx chose Capsugel as an exclusive supplier following a long-standing, fruitful collaboration, in which Capsugel has been responsible for the manufacturing of naproxcinod capsules for clinical studies. Capsugel produced 160 billion capsules in 2007, giving it a 50% share of the capsule market. Its experience, expertise and capabilities make Capsugel a good partner for high-quality and efficient manufacture of naproxcinod capsules. Capsugel can bring to NicOx its expertise both in formulation and encapsulation due to its leading-edge capsule manufacturing technology and formulation development capabilities.

"We are very pleased to continue our collaboration with NicOx through this agreement," commented Keith Hutchison, vice president of research and development at Capsugel. "Naproxcinod is a new therapeutic approach addressing a huge market need and we believe this agreement represents an exciting opportunity for Capsugel. We are looking forward to leveraging our expertise to ensure substantial supplies of naproxcinod capsules and to be thus part of the expected success for this novel compound."

NicOx is developing naproxcinod in phase 3 clinical studies, which are designed to demonstrate that it is safe, well tolerated, and effective for treating the signs and symptoms of osteoarthritis, in addition to having no detrimental effect on blood pressure, in contrast to traditional non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors. The results of the third phase 3 trial for naproxcinod are expected by the end of 2008.

HFA Transition Provides an Opportunity to Improve Aerobid® Inhaler

Business Wire: September 23, 2008 – LONDON, Ontario, Canada – Trudell Medical International is pleased to announce the selection of the AEROCOUNT® dose indicator for use with Forest's proprietary product containing the active ingredient Flunisolide in a HFA formulation.

As the CFC to HFA transition deadline for pressurized metered dose inhalers (MDIs) approaches, Flunisolide, an existing CFC-based inhaled corticosteroid (ICS) branded as Aerobid®, has been reformulated with a non-ozone-depleting propellant to transition through the CFC phase out. A notable change in Forest's Flunisolide HFA product will be the integration of the AEROCOUNT® dose indicator to remind patients how much medication remains in their inhaler.

"The CFC to HFA transition has presented an opportunity to provide patients with the added benefit of our dose counting technologies," explained Mark Pickard, VP and general manager of Trudell Medical International. "We are extremely pleased to have signed a multi-year supply agreement with Forest and to compliment their efforts to bring Flunisolide HFA through the transition."

Earlier this year Freedonia forecast the inhalation market to have a healthy growth rate of 9% through to 2012 and that MDIs will see significant gains from improvements to propellant safety and particle manufacturing technologies. Despite the range of respiratory delivery innovations, the MDI is likely to maintain its market dominance by being a low cost and easy-to-use platform. The AEROCOUNT® dose indicator is designed to maintain the same look and feel of the MDI, with the added benefit of tracking the number of doses remaining.

Vyteris Announces Growth Initiative Through Expanded Business Development Team

Business Wire: September 23, 2008 – FAIR LAWN, N.J. – Vyteris, Inc. (OTCBB: VYTR), developer and manufacturer of the first FDA-approved active patch transdermal drug delivery system (LidoSite®) and a leader in active transdermal drug delivery technology, has announced the establishment of its Business Development Team. Vyteris' Business Development Team will focus on attracting opportunities with biopharma companies and others to jointly develop products involving delivery of compatible drugs with Vyteris' patented Smart Patch transdermal drug delivery technology.

“The formation of this team is an integral step in our previously announced strategy to bring in top notch business development experts in the biopharmaceutical industry and pursue compatible molecular compounds for use in our transdermal technology,” said Haro Hartounian, president of Vyteris, Inc. “Following our current female infertility project with Ferring Pharmaceuticals, Inc., our goal now is to expand the availability of our proprietary technology to compounds that may benefit through the potential for optimized dose scheduling, improved patient compliance efficacy and extended patent protection when combined with our drug delivery system.”

Research on Drug Delivery Published by Scientists at Shenyang Pharmaceutical University

NewsRx.com: September 19, 2008 – New investigation results are detailed in a study, “Development of Solid Self-emulsifying Drug Delivery Systems: Preparation Techniques and Dosage Forms,” published in *Drug Discovery Today*. According to recent research from the People’s Republic of China, “Approximately 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system[s], because of their low bioavailability. Self-emulsifying drug delivery systems (SEDDS) are usually used to improve the bioavailability of hydrophobic drugs.”

“Conventional SEDDS, however, are mostly prepared in a liquid form, which can produce some disadvantages. Accordingly, solid SEDDS (S-SEDDS), prepared by solidification of liquid/semisolid self-emulsifying (SE) ingredients into powders, have gained popularity. This article gives an overview of the recent advances in the study of S-SEDDS, especially the related solidification techniques and the development of solid SE dosage forms,” wrote B. Tang and colleagues, Shenyang Pharmaceutical University.

The researchers concluded: “Finally, the existing problems and the possible future research directions in this field are pointed out.” Tang and colleagues published their study in *Drug Discovery Today* (Drug Discovery Today, 2008;13(13-14):606-612). For additional information, contact B. Tang, Shenyang Pharmaceutical University, Shenyang City 110016, Liaoning Province, People’s Taiwan.

Calando Pharmaceuticals Announces Next siRNA Therapeutic Candidate for Oncology

Business Wire: September 15, 2008 – PASADENA, Calif. – Calando Pharmaceuticals, a majority-owned subsidiary of Arrowhead Research Corporation (NASDAQ: ARWR), has announced that pre-clinical development of a second siRNA oncology therapeutic, CALAA-02, is underway. The intracellular target for CALAA-02 is HIF-2alpha, or hypoxia inducible factor-2 alpha. HIF-2alpha is overexpressed in a number of solid tumors and is critical for many aspects of tumorigenesis, such as metastasis, angiogenesis, tumor cell proliferation, and tumor response to radiation. HIF-2alpha has been difficult to target using traditional drugs but is effectively targeted by the proprietary siRNA in CALAA-02.

“We are encouraged by the results obtained thus far with our proprietary anti-HIF-2alpha siRNA and are excited to pursue pre-clinical development of CALAA-02,” said Calando CSO for siRNA delivery, Jeremy Heidel. “We expect our experience with CALAA-01 will simplify and accelerate CALAA-02 development.”

Calando’s first siRNA therapeutic, CALAA-01, which targets the M2 subunit of ribonucleotide reductase, is currently in a phase 1 clinical trial. Calando intends to move CALAA-02 into the clinic in 2009 to demonstrate the ability of the RONDEL™ delivery system to rapidly enable the pathway from target identification through pre-clinical development to clinical application of siRNA therapeutics.

Calando Pharmaceuticals Inc. (www.calandopharma.com), a majority-owned subsidiary of Arrowhead Research Corporation, is a biopharmaceuticals company using proprietary technologies developed at Caltech to create targeted siRNA-based therapeutics and small molecule nanoparticle drug conjugates. Calando uses its innovative CycloSert™ and RONDEL™ nanoparticle systems to solve the long-standing obstacle of effective delivery and targeting for oligonucleotide and small molecule therapeutics.

Zosano Pharma, Inc. Announces Positive Results of a Phase 2 Trial with PTH Transdermal Patch for Osteoporosis

Business Wire: September 11, 2008 – FREMONT, Calif. – Zosano Pharma, Inc., a privately held pharmaceutical company developing a novel transdermal delivery technology, has announced that an abstract detailing results of its phase 2 study of Zosano PTH patch, a proprietary transdermal patch formulation of parathyroid hormone (PTH) for the treatment of established osteoporosis, has been accepted as a poster presentation at the 2008 American College of Rheumatology Annual Scientific Meeting. In the study, treatment with the Zosano PTH patch was significantly better than a placebo in increasing BMD (bone mineral density) values measured for the lumbar spine, which was the primary endpoint. Overall, treatment with the Zosano PTH patch was very well tolerated.

The study results, titled “Transdermal Delivery of hPTH (1-34) (zp-pth) Is Effective in Increasing Bone Mineral Density of the Lumbar Spine and Hip in Postmenopausal Women with Osteoporosis,” were presented by Dr. Nancy E. Lane, director and endowed professor, aging center, medicine and rheumatology, at the University of California, Davis Medical Center, on behalf of the study’s participating investigators.

The phase 2 program evaluated the safety and BMD changes with three doses of the Zosano PTH patch formulation relative to a placebo and injectable Forteo® in postmenopausal women. The study enrolled 165 patients between 50 and 81 years of age with severe osteoporosis and was conducted at multiple sites across North and South America. “Zosano is pleased to present

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important data from our first long-term trial assessing bone mineral density improvements with the Zosano PTH Patch, and we look forward to further exploring the products' clinical advantage in our Phase 3 program," stated Gail Schulze, Zosano's chair and CEO.

Xel Pharmaceuticals Announces Successful Completion of a Prototype Once-a-Week Huperzine A Transdermal Patch for Alzheimer's Disease

Business Wire: September 10, 2008 – DRAPER, Utah – Xel Pharmaceuticals, Inc. has announced the completion of the development of its once-a-week Huperzine A transdermal patch for the treatment of Alzheimer's disease (AD). The prototype transdermal patch can deliver 400–800 mcg of Huperzine A per day for up to 7 days. Huperzine A is a naturally occurring alkaloid found in the club moss *Huperzia serrata* and has been used for decades in China as a prescription medication for the treatment of dementia. Huperzine A is a potent, highly selective, and reversible inhibitor of acetyl cholinesterase. Additionally, Huperzine A has anti-oxidative properties and possesses neuro-protective properties against glutamate that induce neuronal toxicity at the *N*-methyl-D-aspartate (NMDA) receptor.

Dr. Danyi Quan, chief scientific officer of Xel, said, "The failure of recent Phase III clinical trials for AD treatment may cast some new doubt on that theory, as well as on other experimental drugs. In addition, some new Alzheimer drugs show potential risks including serious side effects. However, the clinical studies performed in China to date showed Huperzine A to be more effective than other cholinesterase inhibitors currently on the market, and the U.S. clinical Phase II trials with Huperzine A oral tablets conducted by the nation's leader in AD therapy, Dr. Paul Aisen, clearly demonstrated the efficacy and safety of Huperzine A in the treatment of patients with AD."

"In the past 10 years, there have been limits and some real difficulties in finding a good candidate from existing Western medicines to develop transdermal drug delivery systems. However, many drug candidates derived from botanic sources with proven safety and efficacy data are available for further development, which now has become a fast and effective way for us to select candidates for designing our advanced drug delivery systems. Huperzine A is one of our most promising and successful transdermal products. Its low therapeutic dose and molecular weight makes Huperzine A ideal for transdermal drug delivery. Our once-a-week transdermal patch is a clearly preferable treatment method to AD patients and caregivers. The prototype Huperzine A transdermal patch is ready for IND filing and further development," Dr. Quan added.

According to Wade Xiong, president and CEO of Xel, "We are delighted to announce the completion of the development of our prototype Huperzine A transdermal patch. Xel has two world-renowned scientists, Dr. Dinesh C. Patel and Dr. Danyi Quan, both of whom pioneer in transdermal delivery technology.... Xel's business strategy is to identify compounds having proven safety and efficacy, and to further develop advanced drug delivery

systems in order to provide better delivery profiles, as well as patent protection. Currently, Xel has several co-development and licensing opportunities available for major pharmaceutical companies."

AUGUST 2008

BioDelivery Sciences Anticipates First Half 2009 Approval of BEMA™ Fentanyl (ONSOLIS™)

Business Wire: August 28, 2008 – RALEIGH, N.C. – BioDelivery Sciences International, Inc. (Nasdaq: BDSI) has announced the receipt of a complete response letter from the U.S. Food and Drug Administration (FDA) regarding the company's new drug application (NDA) for BEMA™ fentanyl, which will be marketed in the United States as ONSOLIS™ (fentanyl buccal soluble film). The FDA has requested that the company make modifications to the submitted risk-management program. All aspects of the review were complete, and no deficiencies were noted in chemistry, manufacturing and controls, nonclinical, or clinical efficacy/safety. The company will submit the requested information and anticipates approval in the first half of 2009.

The FDA requested conversion of the risk minimization action plan (RiskMAP) submitted as part of the NDA for ONSOLIS™ into a risk evaluation and mitigation strategy (REMS). REMS is a new term for a strategy and plan aimed at ensuring the benefits of a drug outweigh its risks. The REMS requested of BDSI is believed to be the result of the FDA's recent experience with other high-potency opioid products and the new authority granted under the Food and Drug Administration Amendment Act (FDAAA) enacted in March 2008. This followed BDSI's submission of its ONSOLIS™ NDA in October 2007.

"We are pleased with this significant and extremely positive development for our Company," stated Dr. Mark A. Sirgo, president and chief executive officer of BDSI. "We have been anticipating the REMS request and have been proactively evaluating a series of options that will enable us to mitigate any delay in approval. All other aspects of our ONSOLIS™ NDA were reviewed positively and with no deficiencies noted."

Dr. Sirgo continued, "We believe that FDA approval of ONSOLIS™ and its U.S. commercial launch should add considerable value to BDSI based on the aggregate \$30 million in approval and launch milestone payments, sales-based milestone payments, and double-digit royalty on sales, which provide the means to accelerate development of our pipeline. In addition, the outcome of the ONSOLIS™ NDA review validates the BEMA™ drug delivery platform and should immediately enhance the value of other BEMA™ products in development, particularly BEMA™ Buprenorphine, our second pain product. We believe that the future of BDSI continues to be very promising."

DURECT Announces the IND Submission for a Third Abuse-Resistant Opioid Pain Medication Based on Its ORADUR™ Technology

PRNewswire-FirstCall: August 27, 2008 – CUPERTINO, Calif. – DURECT Corporation (Nasdaq: DRRX) has reported

that Pain Therapeutics (Nasdaq: PTIE), its licensee, has submitted an investigational new drug (IND) application to the U.S. Food and Drug Administration (FDA) for an abuse-resistant opioid pain drug candidate based on DURECT's patented ORADUR™ technology. This is the third ORADUR™-based opioid drug candidate covered by DURECT's collaboration with Pain Therapeutics, for which King Pharmaceuticals (NYSE: KG) holds the commercialization rights. Pain Therapeutics and King Pharmaceuticals have stated that they expect to announce shortly the initiation of a clinical study with this new investigational drug candidate.

"We are very pleased with the progress and speed with which Pain Therapeutics and King Pharmaceuticals are developing this series of four opioids licensed from us," stated James Brown, chief executive officer of DURECT. "This marks another milestone for our ORADUR technology as a versatile platform that provides for the controlled delivery of pharmaceuticals that are commonly abused."

This new drug candidate is the third ORADUR™-based opioid drug to enter development. The first drug candidate, REMOXY® (ORADUR™-based oxycodone), was submitted in a new drug application to the FDA on June 10, 2008, and has been granted priority review designation by the FDA. Pain Therapeutics has previously announced positive results from a phase 1 clinical trial for the second of these drug candidates. The active pharmaceutical drug in the second and third ORADUR™-based opioid drug candidate has not been disclosed.

QLT Announces Agreement to Exclusively License Atrigel® Technology to Reckitt Benckiser Pharmaceuticals Inc.

CNW: August 26, 2008 – VANCOUVER, British Columbia, Canada – QLT Inc. (NASDAQ: QLTI; TSX: QLT) has announced that QLT USA, Inc., its wholly owned subsidiary, has entered into an exclusive license agreement with Reckitt Benckiser Pharmaceuticals Inc. for its Atrigel® sustained-release drug delivery technology, except for certain rights being retained by QLT USA and its prior licensees. Under the terms of the license agreement and related asset purchase agreement, QLT USA received an aggregate upfront payment of US\$25 million and may receive potential milestone payments of up to US\$5 million based on the successful development of two Atrigel®-formulated products. As part of the transaction, Reckitt acquired 18 employees from QLT USA and will take over its corporate facility located in Fort Collins, CO.

"We are extremely excited to announce this transaction for our third non-core asset, Atrigel. This licensing deal will bring our total proceeds from our announced non-core asset transactions to approximately US\$240 million," said Bob Butchofsky, president and chief executive officer of QLT. "We have worked diligently towards streamlining the Company and believe we are close to reaching this goal. Eligard, our leuprolide acetate for injectable suspension for the palliative treatment of advanced prostate cancer, is our remaining non-core asset which we hope to divest in the near future."

Vyteris Announces Launch of Initiative to Pursue Joint Development Agreements in Pain Management

NewsRx.com: August 24, 2008 – FAIR LAWN, N.J. – Vyteris, Inc. (OTC BB: VYTR), manufacturer of the first U.S. Food and Drug Administration (FDA)-approved active patch transdermal drug delivery system, has announced an initiative to identify and target candidate drugs in the pain management field that could potentially be delivered using Vyteris' active patch transdermal system.

"Our first successful FDA approval for our active patch transdermal system was for topical delivery of lidocaine, and we are now examining other drugs in pain management for use in our system as the next step in our market development," said Haro Hartounian, president of Vyteris, Inc. "We believe the unique properties of several pain medications make them excellent candidates for testing and use with our system. We have proven the concept of transdermal delivery of pain medication using our system – now we are looking to demonstrate that our system is versatile and can work with a variety of different drugs in the pain management area."

Vyteris' pain management initiative will examine several candidate drugs to improve their safety and efficacy profiles using Vyteris' proprietary controlled drug delivery technology and to potentially extend their patent protection. The initiative will include efforts to secure joint development agreements with pharmaceutical manufacturers for *in vitro* and *in vivo* testing of pain medication compounds.

Compounds under investigation for possible use include NSAIDs, opioids, narcotic analgesics, and anaesthetic agents. In contrast to other transdermal drug delivery technologies being developed, iontophoresis is a well-established technology that is unique in its ability to control the flux of drug through the skin for either topical or systemic drug delivery applications.

Vyteris is currently in phase 1 testing of transdermal delivery of a peptide molecule for use in treating female fertility as part of a joint development agreement with Ferring Pharmaceuticals and has already demonstrated successful delivery of a peptide.

Noven Signs License and Supply Agreements with Procter & Gamble Pharmaceuticals for Patches to Treat HSDD

Business Wire: August 20, 2008 – MIAMI, Fla. – Noven Pharmaceuticals, Inc. (NASDAQ: NOVN) has announced that it has entered into global license and supply agreements with Procter & Gamble Pharmaceuticals, Inc. (P&GP), a subsidiary of The Procter & Gamble Company, relating to the development and commercialization of prescription transdermal patches for the treatment of hypoactive sexual desire disorder (HSDD) in women.

Under the agreements, Noven has granted P&GP an exclusive worldwide license to a testosterone patch for the treatment of

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HSDD in women, as well as potential next-generation patches in the same therapeutic category. The agreements provide for payment to Noven of royalties and manufacturing fees, as well as development and sales milestones, relating to the licensed products. P&GP will fund any clinical development costs and will be responsible for any regulatory filings and marketing applications associated with the licensed products, as applicable.

Noven successfully formulated the licensed testosterone patch utilizing its patented DOT Matrix® transdermal delivery technology pursuant to a development agreement between Noven and P&GP established in 2003. Peter Brandt, president and chief executive officer of Noven, said, “We are excited to be advancing our collaboration with one of the world’s best-regarded companies to bring advanced DOT Matrix® patches to women suffering from HSDD.”

Michael J. Fox Foundation Awards \$1 Million for Development of “Trojan Horse” Delivery Technology to Treat Parkinson’s Disease

PRNewswire-USNewswire: August 15, 2008 – NEW YORK, N.Y. – As part of its mission to drive transformative treatments and a cure for Parkinson’s disease, The Michael J. Fox Foundation has announced that it will award Santa Monica-based biotech ArmaGen Technologies, Inc. up to \$1 million if all milestones are met to take practical steps toward developing a “Trojan horse” delivery technology for the treatment of Parkinson’s disease (PD).

ArmaGen’s novel approach would use molecular bio-engineering techniques to “trick” the brain into allowing large-molecule (e.g., protein-based) therapeutics across the blood-brain barrier to access targeted regions of the brain and address the neuronal loss that characterizes Parkinson’s disease. If successful, the work could yield a first-in-class drug that would increase the feasibility of treating PD with therapeutics, including trophic factors—specialized, naturally occurring proteins that protect and nourish neurons—by allowing for delivery via non-invasive intravenous administration.

“At The Michael J. Fox Foundation, we believe that our capital has an obligation to fund high-risk, high-reward projects that, if successful, could significantly improve the lives of people with Parkinson’s,” said Katie Hood, CEO of MJFF. “A major element of our work is the identification and prioritization of approaches like ArmaGen’s – efforts that without our backing would likely stall for lack of resources.”

The blood-brain barrier surrounds the brain and functions to keep out pathogens and other harmful agents. While critical to human health, it presents one of the most daunting challenges for delivery of drugs used to treat PD and other central nervous system disorders. Some of the therapeutic approaches that currently show the most promise to yield transformative treatments for PD involve the use of so-called “large molecules” that are unable to penetrate the barrier. These approaches, which

include trophic factors, currently require brain surgery, an inherently risky and invasive intervention, to access the brain regions affected in Parkinson’s.

Building on earlier work funded by MJFF under its Community Fast Track initiative, the ArmaGen team, led by principal investigator Ruben J. Boado will work with the trophic factor GDNF. They will try to enable it to cross the blood-brain barrier by re-engineering it using Trojan horse technology. The end goal is to create a safe and effective treatment in which GDNF, fused to a genetically engineered antibody that is naturally capable of crossing the blood-brain barrier, can be injected intravenously into the blood. The antibody, “hiding” the GDNF inside itself—as the Trojan horse of Homer’s *Iliad* hid Greek soldiers, allowing them to enter Troy—would then ferry the attached GDNF across the blood-brain barrier, from the blood to the target site in the brain.

“Trojan horse technology has intrigued Parkinson’s researchers for years because of its theoretical potential to overcome the drug delivery hurdle, one of the single most significant challenges facing the entire field,” said Gene Johnson, chief scientific advisor to MJFF. “It is fitting that The Michael J. Fox Foundation, which is searching urgently for treatments that will significantly modify Parkinson’s disease, should provide funding to vet the potential of this technology to yield new therapies that could transform patients’ lives.”

The researchers have three major goals: first, to successfully engineer the fused GDNF; second, to inject it into non-human primates and test its safety, its potential toxicity, and its ability to penetrate the blood-brain barrier and permeate the targeted regions of the brain; and third, to determine whether the treatment alleviates symptoms and pathology of PD in the animal model. To receive full funding, the team must demonstrate that it has achieved all three of these goals. Assuming all milestones are met and the treatment proves safe and effective in animals, the researchers hope to initiate clinical testing in human patients within five to seven years.

KV Signs Expanded Worldwide Partnership with Acrux, Including the Development of Six New Branded Products

August 12, 2008 – ST. LOUIS, Mo. – KV Pharmaceutical Company (NYSE: KVa/KVb), a fully integrated specialty pharmaceutical company, has announced a significant expansion of its commercial collaboration with Australian drug delivery company Acrux (ASX: ACR), under which KV will incorporate Acrux’s unique spray technology for delivering drugs through the skin in up to six additional new branded products to be designated by KV for future development.

The agreement also calls for KV to license to Acrux the regulatory data and FDA filings pertaining to KV’s recently launched Evamist™, the first and only estradiol transdermal spray for moderate-to-severe vasomotor symptoms associated with menopause, to Acrux for filing a similar product to launch in key international markets.

Under the expanded agreement, KV has licensed Acrux's transdermal spray technology for new applications, including up to six additional branded products that, upon completion of development and necessary regulatory approvals, would be launched by KV's Ther-Rx branded products subsidiary for sale in the United States or, for certain products, on a worldwide basis. The agreement also provides a framework for the potential to add further products in the future, for sale in the United States and/or on a worldwide basis. Three of these products are in the pre-clinical development stage. The agreement is consistent with the company's goal of expanding its Ther-Rx subsidiary into new therapeutic areas.

"Acrux's promising transdermal spray technology creates exciting opportunities for us to further diversify Ther-Rx's therapeutic focus into new categories," stated Marc S. Hermelin, KV's chair of the board and chief executive officer. "Acrux is a great collaborator for KV, one that ably demonstrates our vision of combining great in-house development with top-notch external partners to maximize both our product pipeline and our participation in key pharmaceutical markets around the world."

Acrux CEO Richard Treagus commented, "The collaboration with KV not only allows us to proceed immediately with the commercialisation of our estradiol product in the major markets outside the U.S., but just as importantly it aligns us strongly with

a very capable and committed marketing partner. I am delighted that, following the launch of Evamist™, KV has seen the value and potential in our unique spray technology."

Acrux's spray technology was the foundation of Evamist™, which was recently launched in the United States by Ther-Rx Corporation. As the first and only estradiol transdermal spray of its kind, Evamist™ targets a menopause market that is one of the largest in women's health. Evamist™ has been showing increasing prescription trends in the United States since its launch in April 2008 and has already become the second largest transdermal hormone therapy, as measured by NBRx (new to brand prescriptions).

Under the new agreement, Acrux will gain the right to use the data contained in KV's filing with the U.S. Food and Drug Administration (FDA) to enable it to seek approval for Evamist™ outside the United States. KV will select the products to be developed and fund all clinical development costs for each KV product utilizing Acrux's transdermal spray technology, and Acrux will receive royalties on KV's sales plus milestone payments. Evamist™ was originally licensed by Acrux to VIVUS Inc., which subsequently sub-licensed rights to KV. With Acrux's consent, VIVUS has assigned the license to KV, so that KV is now Acrux's direct licensee. ■

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