CRS Leading Delivery Science and Technology

Newsletter

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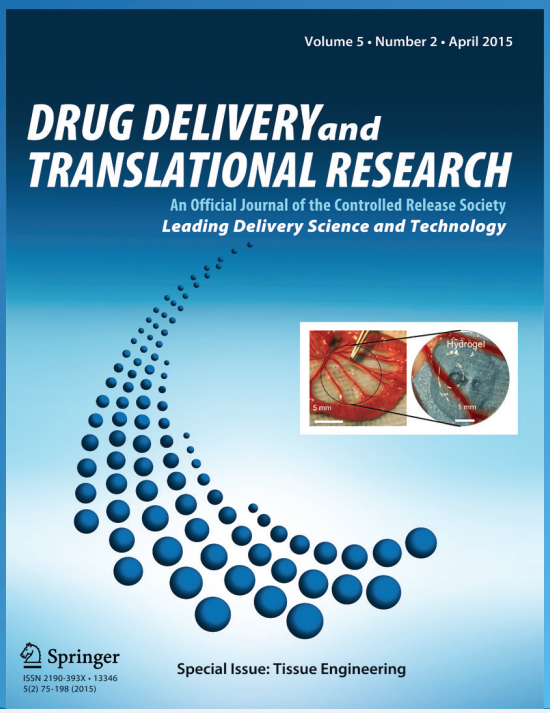
What's Inside



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An Official Journal of the Controlled Release Society

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CRS
Leading Delivery Science and Technology

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CRS Newsletter

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The *CRS Newsletter*—A 21st Century Transition

Effective January 2016, the *CRS Newsletter* will be digital only. The electronic *CRS Newsletter* is one of the most popular member benefits. The cost and environmental footprint associated with printing the newsletter and mailing it across the globe six times a year are substantial. With the transition to digital, the society realizes a significant savings, reduces its environmental impact, and meets members' interests. With this transition, CRS will provide members with more value, more connections, and more opportunities.

Cover image: Molecule body concept of the human DNA. ©watchara / Shutterstock.com

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

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

What Do We Have Now?

Several years ago, while vacationing in Door County, Wisconsin, I stepped into an art studio. Upon viewing several inspirational works, I struck up a conversation with the proprietor and asked for recommendations on inspirational artistic reading. Beyond my scientific discipline, I dabble in drawing and painting and had come into a dry spell. One recommendation was the book *Art and Fear: Observations on the Perils (and Rewards) of Artmaking*, by David Bayles and Ted Orland.

I eventually read the work and am currently reading it again. It is filled with philosophical thoughts on artmaking and what makes an artist. It expands on concerns such as whether it is possible to pretend to be an artist, what talent is, and the dangers of seeking perfection (which is both undesirable and unattainable). Two thoughts from the treatise are currently circulating in my mind: 1) the statement "whatever you have is exactly what you need to produce your best work" and 2) a focus on *quantity* yields *quality*.

Whether an interest is art, science, business, or any combination, we are all entrusted with an aptitude and circumstance to develop and nurture. Our best work at this point is related to what we have at this point. Hopefully, it is an improvement over what we had in the past and the future will be an improvement over what we have now. Our collective and shared interactions in CRS and other spheres of influence are a part of what we have and help set the bar for what is our best.

This thought is echoed in the balance of quantity and quality. Artists focused on quantity yield better quality work than those focused on quality. Quantity expands the scope of experimentation, knowledge, and skill needed to optimize quality. The expanding and accelerating pace of today's scientific work is adding to our knowledge base at an ever-increasing rate, which accelerates our understanding of the physical world and the means to address our challenges.

I encourage you to take time to peruse this sixth and final issue of the 2015 *CRS Newsletter*. It is one element of this vibrant society and a means to see what we have, what our best is, and how you can contribute to the quantity and quality of controlled release science.

I wish you all the best as 2015 comes to a close and the 2016 chapter begins!

Chuck Frey ■

Kinam Park
Purdue University
U.S.A.

2016 CRS Annual Meeting & Exposition—A Can't-Miss Event in the Making

As the Annual Meeting Program Committee Chair, I'm excited to announce several changes for the 2016 Annual Meeting & Exposition in Seattle, Washington, U.S.A., July 17–20. We believe that our refinement of past program components and the addition of a few new elements will greatly benefit attendees. The meeting will commence on Sunday with the Opening Session/Award Ceremony, along with a plenary lecture and the Exhibition Grand Opening and Happy Hour. This will then be followed by three full days of solid scientific programming, ending late afternoon on Wednesday.

Given the overwhelmingly positive feedback received from 2015 attendees, the scientific sessions will maintain the format used last year. Each session will consist of one or two invited speakers followed by several Research Highlight Talks (a five-minute podium presentation with a corresponding poster) and a moderated discussion. However, the topics of the scientific sessions have been changed to more accurately reflect the diverse research and industry topics of current member interest and importance. There will be four concurrent sessions each day. In addition, the program continues to include sessions dedicated to topics of the Consumer and Diversified Products (C&DP) and Preclinical Sciences and Animal Health (PSAH) Divisions. The 2016 Annual Meeting & Exposition will combine the best features from past meetings with these unique elements:

- A total of 21 sessions divided by delivery routes, such as oral, parenteral, transdermal, and ocular.
- Hot Topic Sessions and Roundtables focused on industry needs.
- A session highlighting the future of drug delivery systems: "Thinking Outside the Box" Delivery Technologies: Nanocarriers from Nature.
- A focus on critical areas of current interest to the delivery science and technology community.
- Sessions providing reflection on the current status of drug delivery: "Where are we, and are we telling it straight?"

Another unique feature of the 2016 program is the introduction of a Poster Pub session offered on Monday. This session is designed to further highlight the poster presentations with an exchange of ideas over light refreshments. This year, we have also increased the number of Research Highlight Talks to provide more presentation opportunities. These five-minute talks give attendees a snapshot of science and technology research to spark innovative partnerships and scientific brainstorming. Overall, attendees will have the chance to immerse themselves in more than 150 podium presentations!

We look forward to welcoming you to the 2016 CRS Annual Meeting & Exposition. Please join us in making this the best CRS meeting yet!

Please note: abstracts close January 15, 2016. There is a new one-page abstract format. Keep apprised of the latest news via CRS e-communiques or join the Controlled Release Society LinkedIn Group. ■

2016 Annual Meeting Program Committee

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2016 CRS Annual Meeting Session Topics

The 43rd CRS Annual Meeting & Exposition will be where delivery science and innovative technology connect! Join industry and academic leaders from across the globe exploring, presenting, and discussing the best in delivery science and technology innovations. The 2016 meeting features three full days of scientific programming, in-depth sessions to immerse you in science that reflects your interests, more opportunities to network with colleagues, and an exhibit hall with the latest products and services to help you find solutions. Submit your abstract today!

Comparative Pharmacokinetics in Preclinical Sciences. Preclinical science and animal models are key components in determining pharmacokinetics and pharmacodynamics of new drugs and delivery systems. Preclinical data obtained across species drives initial candidate drug design/selection and resultant optimization of development procedures needed for regulatory approval. This session will address how to design preclinical studies in select animal species. First, *in silico* modeling of data from administration routes will be examined relative to the target species, and second, the increasing complexity of designing dissolution studies in media relevant to true intestinal conditions will be discussed.

Delivery Technologies in Cosmetics, Personal Care, and Household Products. This session will cover all aspects of controlled release in personal and home care areas. Examples are cosmetics, cosmeceuticals, skincare, fragrances, deodorants and antiperspirants, hair care, mouth care, air fresheners, cleaning and sanitizing agents, and insect/pest/mold control agents and devices. This core area seeks to promote progress and applications across this diverse range of products, with particular emphasis on the research and manufacturing activities ongoing in the relevant industries.

Delivery Technologies in Nutraceuticals, Food, and Oral Products. This session will include all aspects of oral delivery science and product development, including immediate, sustained, delayed, and pulsed release. It includes oral delivery of drugs (from small molecules to biologics), food, feed, beverages, nutrients, nutraceuticals, flavors, probiotics, prebiotics, and supplements. Topics of interest are broad and include, but are not limited to, all aspects of systems that enhance oral absorption, introduce prolonged effect and stability of additives, product acceptability (including taste masking, rheology, etc.), targeted and/or more uniform delivery in the gastrointestinal tract, *in vitro* and *in vivo* models, analytical chemistry, formulation technology for poorly soluble agents, biopharmaceutics, equipment design, and computational modeling.

Encapsulation and Controlled Release for Industrial Applications. This session focuses on advances in encapsulation and controlled release products in agrochemicals, agriculture, aquaculture, textiles, and other industrial applications. Topics include, but are not limited to, more efficient biomass production for biofuels, genetic engineering (release of genetically engineered materials, enhancing organisms), anticorrosive and/or antifouling coatings (e.g., fish farms or offshore installations), self-healing coatings and materials (e.g., textiles), water storage systems, technologies for high-rise systems (fertilizing, light control), and more traditional areas involving controlled release of nutrients, vaccines, fertilizers, and pesticides.

Local Drug Delivery. With increasing awareness of challenges in systemic drug delivery and recent advances in imaging technologies, local drug delivery is revisited as a promising means to achieve target-specific drug delivery. This session covers new formulation technologies exploiting accessible local routes for target-specific drug delivery—such as lungs, eyes, nose, oral cavity, gastrointestinal tract, vagina, and peritoneal cavity—featuring clinical and industrial perspectives.

Manufacture, Characterization, Stability, and Regulatory Aspects. This session will cover technology development through scale-up of commercially viable processes and methods to prepare and characterize products designed for controlled release of active materials. Some examples of process technologies include spray-drying, hot-melt extrusion, co-precipitation, supercritical fluid technology, fluid bed coating, complex coacervation, 3D printing, inkjet printing, electrospinning, microfluidics, powder layering techniques, high-shear granulation techniques, membrane processes, and emulsion-based processes. The use of quality-by-design (QbD) concepts, analytical technologies for process end-point and real-time monitoring of preparation processes, imaging methods, and other approaches to ensure commercial viability are also critical to this area.

New Processes, New Materials, New Products. New manufacturing processes can lead to both new materials and new systems and hence new products. Sometimes new processes are, like electrospinning, old but have been more recently adopted because of the availability of appropriate materials and adapted technologies to produce new forms (such as fibers) with potential for drug delivery in more versatile ways. Two- and three-dimensional printing techniques are a case in point. This session will consider production techniques such as these but also new materials such as graphene and graphane analogues, magnetic surfactants, or other materials that allow more precise design and novel uses.

Ocular Drug Delivery. Ocular drug delivery has been a major challenge to drug delivery scientists owing to the complex anatomy and physiology of the eye. In addition, the demonstration of bioequivalence for generic ophthalmic products to their reference products can be challenging. This session will focus on the recent advances in ocular drug delivery with an emphasis on new materials for long-acting products that can be used to deliver both small and large molecules. This session will also highlight general recommendations for establishing bioequivalence of generic ocular drug products including *in vitro* approaches.

Oligonucleotide Delivery: New Applications and Opportunities. This session focuses on therapeutic approaches utilizing oligonucleotides including antisense oligonucleotides, siRNAs, and miRNAs. The session will highlight innovative chemistry (e.g., conjugate) and formulation-based delivery systems and therapeutic approaches requiring access to tissues and cell types outside of the liver. Novel approaches for targeting both actively (e.g., with targeting ligands) or passively (e.g., endogenous targeting approaches) will be discussed as well as approaches for efficient intracellular delivery. Immunomodulatory applications will also be highlighted.

Oral Delivery. This session focuses on advances in delivery science and technology for both systemically and locally acting oral formulations. This session will highlight the impact of key excipients on manufacturing, quality, and clinical performance of oral drug delivery systems. This session will also highlight the recent developments in locally acting gastrointestinal drugs with an emphasis on how to determine local drug dissolution. In addition, this session will highlight the efforts that have been made by industry, academia, and regulatory agencies to ensure the therapeutic performance of advanced oral drug delivery systems including amorphous solid dispersions and modified release drug products.

Overcoming Biological Barriers in Drug Delivery. Biological barriers were created during evolution to enable organisms to precisely control the interaction between inside and outside environments. The differentiation at interfaces to regulate water homeostasis, uptake of nutrition, gas exchange, or exchange of waste is manifold and constitutes a key hurdle in the field of drug delivery. This session will highlight advances in drug delivery through biological barriers that include, but are not limited to, the blood-brain barrier, blood-ocular barrier, mononuclear phagocyte system, tissue penetration barriers, cell uptake barriers, and intracellular barriers.

Parenteral Systemic Delivery of Biopharmaceuticals: Overcoming Product Development and Regulatory Challenges. This session will focus on current hot topics in the development of injectable biopharmaceutical products including formulation, delivery, stability, and regulatory considerations critical in advancing novel delivery based biopharmaceutical products to the clinic and commercialization. In addition, the session will highlight current approaches for the characterization of parenteral delivery systems and the bioactives contained within them, especially those of importance to regulatory agency approval.

Peptides, Proteins, and Vaccines. The global medicines market is undergoing a period of dramatic change, and it is forecast that by 2016 biopharmaceuticals will overtake small molecules' domination of the market. While biopharmaceuticals (including peptides, proteins, and vaccines) offer unique modes of action, which are highly specific with far fewer side effects, their commercialization requires significant innovation. This session will focus on strategies to maximize therapeutic effectiveness of peptide, protein, and vaccine formulations, including topics on formulations/devices/technologies that (1) improve targeted delivery, (2) enhance immunization efficacy, (3) minimize delivery invasiveness or increase patient adherence, (4) extend and control release, (5) enhance stability, and (6) lower development and manufacturing costs.

Physical Oncology: Modulating Tumor Microenvironment for Drug Delivery. The discrepancy between preclinical and clinical outcomes arises, in part, owing to the failure of conventional model systems to recapitulate the complexity of solid tumor tissues. One major factor in the complexity of tumors is their fibroinflammatory component (stroma), which increases tumor interstitial fluid pressure, blocking the delivery of anticancer therapies to tumor cells, and contributes generally to chemoresistance. This session focuses on advances in the delivery of drugs deep into tumor tissues achieved through modulation of components of the tumor microenvironment. Efforts that target the biophysical barriers to perfusion, diffusion, and convection imposed by the desmoplastic reaction will be highlighted.

Preclinical Science Challenges to Drug Delivery. How drug distribution occurs in different species is related in part to structure and function of drug transporters, and these can have a bearing on behavior of drug delivery systems in preclinical animal models. An alternative approach in preclinical research is the advances made in 3D cell culture models as well as organ-on-a-chip models of human and animal tissue. Apart from contributing positively to the three Rs (replacement, reduction, and refinement), these models have improved metabolism predictive capacity and also can be used to interrogate drug target interactions, as well as to screen drug candidates efficiently.

Predictive Modeling in Delivery and Targeting (Scaling: Mouse to Man; Probability of Reaching Targets; Stochastic Process in System Distribution). Mathematical modeling of drug delivery and targeting provides opportunities to reduce empiricism in our science. To achieve this we must have predictive models of the behavior of systems such as nanoparticles *in vivo*. There is a need for understanding the scaling factors in extrapolation from animal models to humans, and for evaluation of the mathematical probability of issues such as extravasation and binding to receptors, including a realization of the stochastic nature of many of the processes in targeting. This session will survey some approaches to allow the next generation of delivery systems to be designed more rationally.

Taking Stock of Progress and Challenges in Drug Delivery and Targeting. It is crucial after decades of research into new drug delivery and targeting systems that we reflect on true progress and define honestly the challenges that lie ahead. This session asks two questions: "where are we now?" and "are we telling it straight?" These questions apply not only to nanotechnology but also to instances wherein our science has translated into false promises. There is often a lack of quantitative data on the delivery of the active let alone the carrier to putative targets, and few papers discuss target pharmacokinetics let alone particokinetics. Contributions that address these issues are welcome.

Annual Meeting Session Topics continued on page 6

Annual Meeting Session Topics continued from page 5

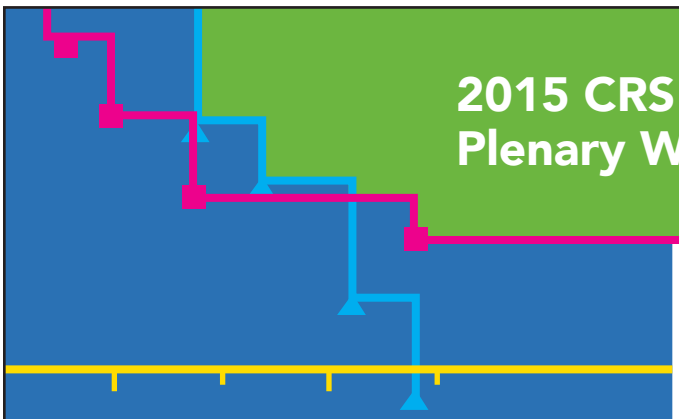
Integration of Imaging and Drug Delivery. In recent years, there has been tremendous effort to integrate imaging and drug delivery in order to improve therapeutic response and clinical outcomes. In particular, emphasis has been placed on exploiting imaging to deepen our understanding of drug and delivery vehicle transport, to guide interventions that enhance drug delivery, and to identify subpopulations of patients that are likely to respond to a specific therapy. This session will highlight exciting advances in this area of research with an emphasis on approaches that have advanced to late-stage preclinical or clinical development. Challenges in the clinical translation and development of image-guided interventions will be discussed.

"Thinking Outside the Box" Delivery Technologies: Nanocarriers from Nature. Living creatures have developed diverse bioactive materials with unique structures to survive and adapt to changing environments. This session will highlight two groups of natural nanocarriers, namely, exosomes and protein nanocages. Exosomes are nanometer-sized membranous vesicles that play a major role in intercellular communication owing to the ability to transfer proteins and nucleic acids from one cell to another. As a result, there has been significant interest in exploiting exosomes for applications in drug delivery. Nature in its wonders presents the most intricate and delicate protein structures, including those of cage-like architecture. Perfect and complex symmetry is ubiquitous in protein nanocages, and they can be engineered for applications in drug delivery. This session will largely highlight exosome and protein nanocage-based delivery strategies, with additional emphasis on drug delivery technologies formed from other natural materials.

Tissue Engineering. Tissue engineering that aims to recreate functional tissues and organs has emerged as a promising strategy to treat a series of tissue defects, to create *in vitro* cell culture platforms, and to engineer biological machinery. Despite the impressive results reported over the past decades, there is still a real need to improve the quality of engineered tissue by regulating transport and bioactivity of regenerative medicine, including incorporation of synthetic drug molecules, growth factors, DNA, and so on. To this end, this session will discuss current efforts and future directions to utilize and further modify advanced drug delivery technologies for enhanced tissue engineering in both academia and industry.

Transdermal Delivery. Transdermal delivery constitutes a popular alternative route of administering drugs. This session will cover new developments in all aspects of transdermal drug delivery, including understanding of transdermal permeation pathways, especially for macromolecules. Contributions on the development of devices and formulations to enhance transdermal drug delivery are welcome. Contributions reporting clinical translation of technologies are of particular interest. Novel analytical tools to study transdermal drug delivery and mathematical models for describing transport are also welcome. This session will also include new developments in topical drug delivery methods that focus on localized delivery of small and large molecules such as peptides and nucleic acids. ■

Present your research at the 2016 CRS Annual Meeting—submit an abstract by January 15, 2016.



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Nicholas A. Peppas
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Global Efforts and Successes in Needle-Free Peptide Delivery
Maria José Alonso
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CRS ANNUAL MEETING & EXPO
MEANS BUSINESS

July 17–20, 2016 • Seattle, Washington, U.S.A.

2015 STATS

ATTENDEES
1,435
54% FROM INDUSTRY
46% FROM ACADEMIA

LEADERS FROM AROUND THE GLOBE
52 countries

DEDICATED EXHIBITOR TIME
over 9.5 hours

HIGH EXPO INTEREST
75% attend Expo

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– Richard Korsmeyer, Pfizer

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Ocular Drug Delivery: Challenges of Matching New Technologies with Drug Pharmacokinetics

M. Naveed Yasin,[1] Ying-Shan Chen,[1] Di Huang,[1] Priyanka Agarwal,[1] Michael O'Rourke,[2] and Ilva Rupenthal[1]

The 42nd CRS Annual Meeting & Exposition was held at the International Conference Centre, Edinburgh, Scotland, July 26–29, 2015. Prior to the meeting, the premeeting Ocular Drug Delivery workshop, held on July 25, aimed at bringing together leading researchers from both academia and industry to share challenges and present recent approaches to deliver actives to the front as well as the back of the eye. Seventy-one attendees from academia and industry registered to listen to four speakers from academia and five from industry, as well as another four company presentations. The workshop was sponsored by Envisia Therapeutics, Novaliq GmbH, Genentech, Phoenix Research Labs, pSivida, GrayBug, and Ora.

The day started with a warm welcome by the chairs and organizers of the workshop, Ilva Rupenthal from the University of Auckland, New Zealand, and Michael O'Rourke from Scotia Vision Consultants, U.S.A. Ilva then kicked off the academic talks by providing a general overview of drug delivery approaches to the front and back of the eye, highlighting the limitations of current delivery technologies as well as the need to understand drug pharmacokinetics in order to accelerate the development process for emerging technologies. Arto Urtti from the University of Helsinki, Finland, then focussed on pharmacokinetic modelling and the limiting factors in developing predictive pharmacokinetic and pharmacodynamic models to evaluate ocular drug delivery approaches and follow the fate of the administered active.

Workshop chairs and organizers Michael O'Rourke and Ilva Rupenthal.

A full house at the Ocular Drug Delivery workshop with 71 attendees.

Carrying on with the talks after a short morning tea break, Rocío Herrero-Vanrell from the Universidad de Complutense, Spain, presented on intraocular delivery of biodegradable microspheres to achieve sustained delivery of actives and thus reduce the frequency of administration, increasing patient compliance. Rocío covered recent publications from her group including the benefits of encapsulation into microspheres with a focus on additives used to further sustain delivery and enhance the stability of the actives. "Engineering Biomaterials for Ocular Applications" was the topic presented by Heather Sheardown from McMaster University, Canada, highlighting the progress of her group to use contact lenses as effective delivery devices for proteins and various other actives. She also presented on a smart implantable drug delivery system that can be activated by light, thus controlling the drug release non-invasively. Ann L. Daugherty, Senior Manager of Drug Delivery at Genentech Inc., U.S.A., was the first industry speaker and presented the challenges and successes of delivering protein therapeutics to the back of the eye. Focusing on various approaches to enhance efficient delivery of actives to the back of the eye by formulation, chemical modification, and device-based approaches, she urged scientists working in the field to consider aseptic compounding requirements and ocular tolerability of novel materials and devices at an early development stage.

After a delicious and well-earned lunch, the afternoon session kicked off with four company presentations. Stuart Williams from Envisia Therapeutics, U.S.A., talked about ENV515 and ENV905, two biodegradable devices based on the proprietary PRINT® technology that can provide sustained drug delivery over extended periods. This was followed by a talk from Dieter

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[2] Scotia Vision Consultants, Tampa, Florida, U.S.A.

Ann L. Daugherty discussing the importance of ocular tolerability of novel materials. On stage from left to right: Ilva Rupenthal, Michael O'Rourke, Andy Whitlock, Dieter Scherer, Paul Ashton, and Eugene de Juan.

Scherer, Novaliq GmbH, Germany, who discussed their novel semifluorinated alkane technology, a non-aqueous vehicle that can improve formulation aspects and delivery of various actives. Dieter briefly touched on current products in the pipeline while highlighting the advantages of these novel vehicles to increase stability, solubility, and sterility of ocular formulations. Carrying on the company presentations, Scott Johnston from Phoenix Research Labs, U.S.A., presented on their Micron IV system designed to support eye research in laboratory animals. This retinal microscope produces high-quality digital fundus images of rodents and small animals for *in vivo* observations with capabilities in bright field, angiography, and fluorescent imaging. It can be acquired as a retinal imager alone or combined with optical coherence tomography, an image-guided laser for creating choroidal neovascularization (CNV), and/or with an image-guided focal electroretinogram (ERG) to measure retinal functionality. The final company presenter was Jeff Cleland, who presented on GrayBug's proprietary poly(lactic-*co*-glycolic acid) (PLGA) technology that causes minimal inflammation when degraded in the eye compared with conventional PLGA. Jeff talked about the injectable formulations in the pipeline fabricated from this proprietary PLGA to achieve sustained drug delivery in the treatment of ocular conditions such as wet age-related macular degeneration (AMD), glaucoma, and corneal graft rejection.

"Market Dynamics and Overview of Recent Developments in Industry" was the topic presented by Michael O'Rourke. Michael briefly covered the history of intravitreal devices for sustained delivery of actives to the posterior segment of the eye. He also highlighted recent financial figures revealing the shift from the anterior to the posterior segment of the eye and touched on the cost of developing a novel active compared with that of improving the delivery of existing actives by novel delivery technologies, emphasizing the market shift toward such delivery technologies. Andy Whitlock from Ora Inc., U.S.A., an independent ophthalmic contract research organization (CRO), then talked about the preclinical development of ocular drug delivery technologies emphasizing the important factors to be considered for successful commercial development. Following that, Eugene de Juan from ForSight Labs, U.S.A., shared his experiences in the translation of an ocular drug delivery device from the laboratory to clinical trials, highlighting important considerations and discussing "what it actually takes." The last presentation of the workshop entitled "The Complete Story—Going Through Regulatory Approval" was presented by Paul Ashton from pSivida Inc., U.S.A. Paul talked about his personal experience and involvement in the development of Vitrasert®, the first FDA-approved intravitreal device for sustained delivery of ganciclovir in the treatment of cytomegalovirus (CMV) infection. He also briefly described the most recently FDA-approved intravitreal device, Iluvien™, which is based on the Durasert™ technology and delivers sufficient amounts of drug over three years in the treatment of diabetic macular edema.

The meeting concluded with a panel discussion with all presenters gathering on stage and answering any questions related to their presentations. This triggered a constructive discussion, which was continued by speakers and workshop attendees over a glass of wine. Overall, the workshop was considered a great success, and we hope to offer similar events focussed on ocular drug delivery again in the near future. ■

Welcome New CRS Members

Mohamed Albed Alhnan
Bruce E. Artman
Sandra Boiteux
Daquan Chen
Carolina Diaz Quijano
Maribel Espinoza
Xinli Liu
Tamim Mosaiab
Ankitkumar Parikh
Emil Sohn

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Novel *In Vitro* Drug Release Automatic Monitoring System (DREAMS) for Nanoparticles

L. Xie,[a] S. Beyer,[b] V. Vogel,[a] M. G. Wacker,[b] and W. Mäntele [a,c]

Introduction

The past two decades have seen rapid advances in applying nanoparticles (NPs) as drug delivery systems. A variety of experimental methods have been reported to study drug release from NPs. However, owing to the miniscule dimension of NPs, an optimal dissolution method appears to be challenging. Although one of the most common methods, the sample-and-separate method suffers from disadvantages, such as premature release caused by the centrifugation and laborious sampling procedures. Alternatively, the application of dialysis membranes for sample separation has been introduced to release testing of pharmaceutical products. Typically, the release profiles measured from the acceptor phase have been reported as the cumulative drug release from the nanoparticulate system. Yet permeability through the dialysis membrane was discussed to be a rate-limiting step and could be responsible for a number of misleading results.[1]

In our recent study on drug release from NPs, a drug release automatic monitoring system (DREAMS) developed in-house was used to monitor the release process continuously by a fluorescence spectrometer. A four-step mathematical model adding up the released drug in both donor and acceptor phases was introduced to overcome the typical shortcomings of dialysis-based approaches. To assess the method, an experiment was designed introducing the free drug in the donor phase at different time points with known amounts. Also, Eudragit® RS 100 NPs that were loaded with a photosensitizer served as the model formulation for the establishment of dissolution testing and the quantification model.[2]

Experimental Methods

The DREAMS setup was built in-house, consisting of two compartments: a dialysis cell and a measuring cell (Figure 1). For the dialysis compartment, a cellulose ester membrane (molecular weight cut-off: 50 kDa) was used to separate the NPs from the released drug. A magnetic stir bar was placed in the base of the acceptor compartment to agitate the fluid inside and outside the chamber. A continuous flow (2 mL/min) of the acceptor medium was ensured by pumping the fluid into the measuring cell, where the concentration of active pharmaceutical ingredient (API) was determined spectrometrically by a charge-coupled device (CCD) microspectrometer. A blue LED (peak wavelength 405 nm) was adapted as the fluorescence excitation for the API. The suspension of photosensitizer-loaded Eudragit® RS 100 NPs was injected into the donor phase. Phosphate buffer (pH 6.8, 20 mM, containing 150 mM NaCl) was used as the release medium in both the donor and the acceptor phases. The volumes in the donor and acceptor compartments were 3 and 52 mL, respectively.

To evaluate the mathematical model, 1.5 mL of the free API (13.78 µg/mL) was dispersed in the donor phase. After 1.5, 3, and 4.5 h, 1.5 mL of the donor phase was replaced with 1.5 mL of the API solution (13.78 µg/mL). Data were processed by the four-step model that is described below and compared with the theoretical values.

For dissolution testing, NPs before and after a purification procedure were contrasted to free drug as a reference (Figure 2). Data obtained from the DREAMS were further processed by the model to exclude the impact of membrane kinetics on final results for the drug release.

Mathematical Theories

To apply the model to the experimental results, four steps are involved to process data obtained from the measuring system.

Step One: Determination of the drug permeability constant (k_m). For a system agitated in the donor and acceptor compartment, the diffusion process can be described by Fick's law,[3]

$$\frac{dC_a}{dt} = \frac{k_m \cdot A}{\delta \cdot V_a}\left[C_d(t) - C_a(t)\right] \quad (1)$$

where k_m denotes the drug permeability constant of the dialysis membrane. C_a and C_d are the concentrations in the acceptor and donor phases, respectively. V_a denotes the dissolution volume of the acceptor phase. δ and A denote the thickness and the surface area of the membrane.

When a certain amount (Q_0) of free API is dispersed into the donor phase in a closed system,

$$C_d(t) = \frac{Q_0 - C_a(t) \cdot V_a}{V_d} \quad (2)$$

V_d denotes the dissolution volume of the donor phase. Replacing $C_d(t)$ in equation 1 and solving the equation analytically yields the following:

$$C_a(t) = \frac{Q_0}{V_a + V_d}\left[1 - e^{\frac{-Ak_m(V_a+V_d)}{\delta V_a V_d} \cdot t}\right] \quad (3)$$

Equation 3 can be applied to fit the experimental data on free API passing through membrane to obtain k_m.

Step Two: Computation of the concentration rate in the acceptor phase ($\Delta C_a/\Delta t$). A continuous profile of $C_a(t)$ can be obtained by

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the setup. Therefore, equation 1 can be expressed numerically,

$$\frac{dC_a}{dt} \approx \frac{\Delta C_a}{\Delta t} = \frac{k_m \cdot A}{\delta \cdot V_a}\left[C_d(t) - C_a(t)\right] \quad (4)$$

Step Three: Computation of the concentration profile in the donor compartment, $C_d(t)$. $C_d(t)$ can be computed from equation 4 with all parameters (k_m, V_a = 3 mL, A = 8.0 cm², and δ = 80 µm) known:

$$C_d(t) = \frac{\Delta C_a}{\Delta t} \cdot \frac{\delta V_a}{k_m A} + C_a(t) \quad (5)$$

Step Four: Adding up the total accumulated amount of released drug in both compartments. Adding together $C_d(t) \times V_d$ and $C_a(t) \times V_a$ results in the total released amount of the API. $Q_r(t)$ represents the total amount of free drug in the system:

$$Q_r(t) = \left[\frac{\Delta C_a}{\Delta t} \cdot \frac{\delta V_a}{k_m A} + C_a(t)\right] \cdot V_d + C_a(t) \cdot V_a \quad (6)$$

Results and Discussion

The concentration in the acceptor phase was monitored (Figure 3), and the sampling procedure of replacing the liquid in the donor phase was undertaken at the defined time points. A concentration profile of the donor phase was computed using equation 5, indicating that the changes of concentrations in the donor phase reflected the impact of the replacement procedure. By multiplying the related volumes, the drug amounts in both compartments were summed up and found to be in accordance with the theoretical values. This feature shows that DREAMS is able to monitor the initial burst of drug release kinetics.

Dissolution testing was carried out to investigate NP suspensions with or without a purification procedure. Free drug experiments were carried out to determine the permeability constant k_m by fitting to equation 3, and (1.8 ± 0.093)×10⁻³ cm²/h as k_m ± SD was determined.

As seen in the Figure 4A, it is apparent that the system was able to discriminate the three types of samples. The experimental

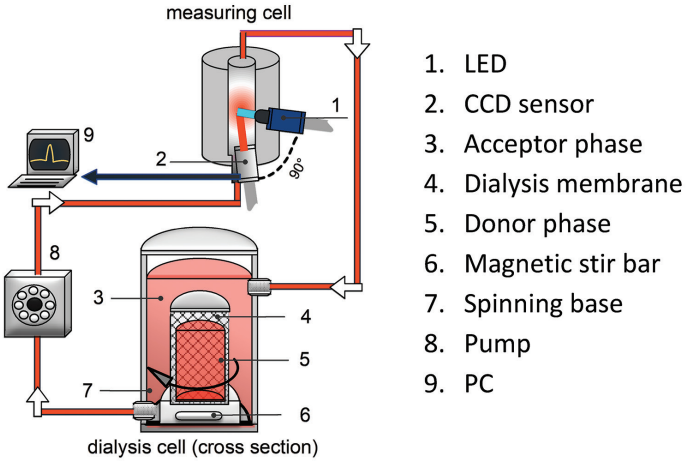

Figure 1. *The schema of the specially designed apparatus for dissolution testing of NPs. A dialysis membrane was used to separate the NPs and released API. The concentration in the acceptor phase was monitored continuously by a home-built fluorescence spectrometer. ©Elsevier, reproduced with permission.[4]*

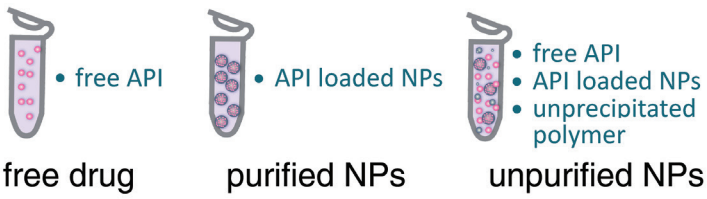

Figure 2. *The composition of different samples. Free drug was used as the control. Purified NPs, which only contain encapsulated drug in the NPs, were tested relative to the unpurified NPs.*

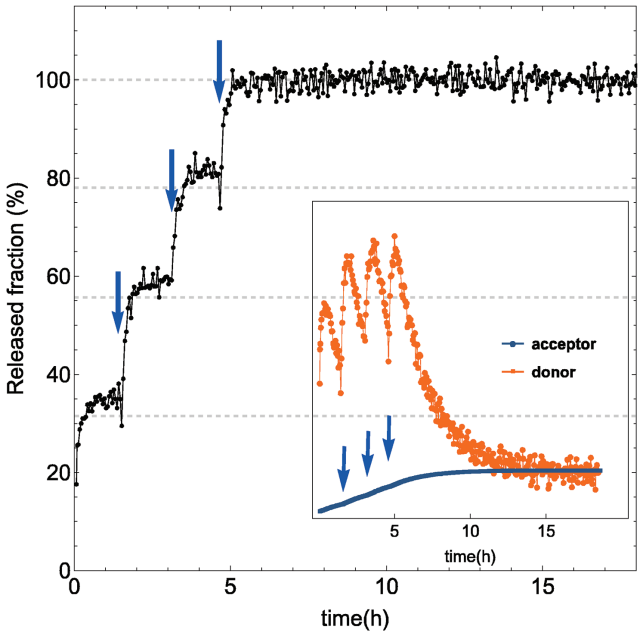

Figure 3. *Free API was replaced in the donor phase at 1.5, 3, and 4.5 h (shown as arrows). Data monitored in the acceptor phase were normalized by the total amount of the photosensitizer in the system (blue line). Computed API fraction in the donor phase (orange line) using the four-step model. The main figure shows the total amount of free API in the system processed by the model (black line), which is in comparison with theoretical values (grey dashed line).*

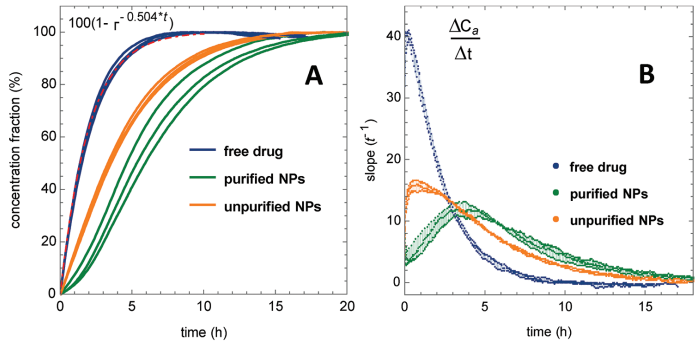

Figure 4. *The results of free drug (blue line), unpurified NPs (orange line), and purified NPs (green line). (A) Normalized by the peak value of the raw data measured by DREAM. (B) The numerical values of dC_a/dt (equation 4). ©Elsevier, reproduced with permission.[4]*

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results were also highly reproducible. For step two of the model, Figure 4B presents the computational results of numerical values of dC_a/dt. The slower rate in the decrease of unpurified and purified samples suggested a continuing release of the drug from NPs.

Using equation 5, the concentration profiles in the donor compartment can be obtained (see Figure 5). The results were then normalized by the cumulative drug release measured by HPLC. As Figure 5B presented, there was a steady increase in the concentration in the donor compartment of purified NPs. Unlike purified NPs, unpurified samples (Figure 5C) reached the peak concentration in the donor compartment almost immediately after the experiments began, which indicates a certain amount of free drug initially in the samples.

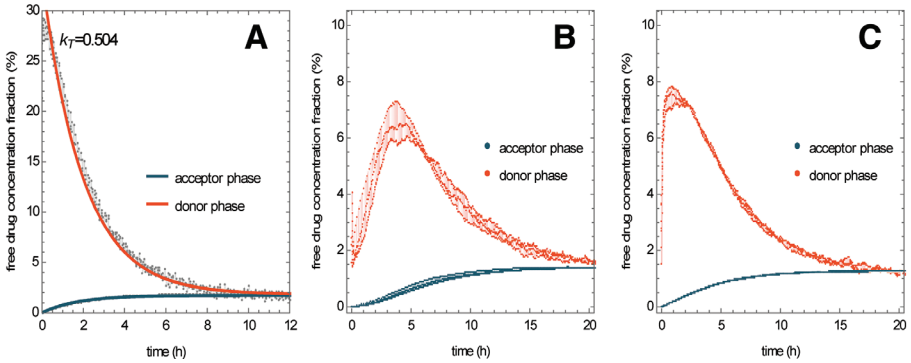

Figure 5. *The computed concentration profiles in the donor compartment (red line) of (A) free drug, $k_T = A\ k_m(V_a+V_d)/(\delta V_a V_d)$; (B) purified NPs; and (C) unpurified NPs, plotted together with the concentration profiles measured in the acceptor compartment (blue line). ©Elsevier, reproduced with permission.*[4]

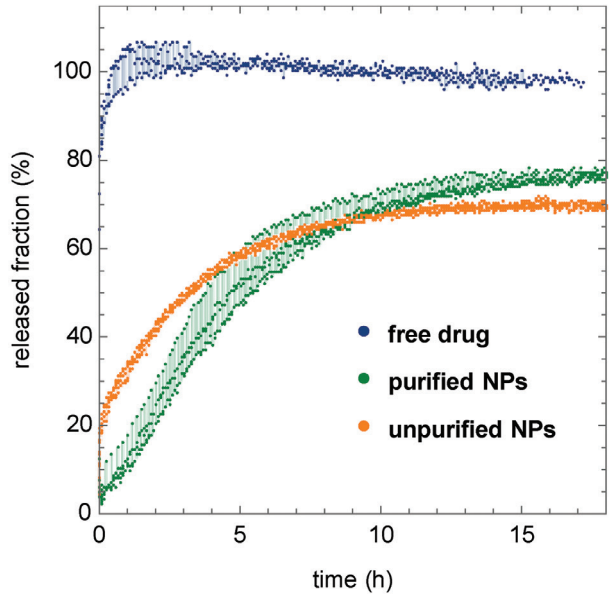

Figure 6. *Corrected release profiles treated by the mathematical model. The total free drug amount fraction in both donor and acceptor compartments, computed according to equation 6. ©Elsevier, reproduced with permission.*[4]

Figure 6 presents the corrected release profiles after applying step four of the mathematical model. For the control experiment, the amount of free API in the system remained unchanged throughout the experiment. It also shows that the purified samples underwent a more sustained release relative to unpurified ones, which can be explained by the higher amount of NPs contained in the samples. Interestingly, the *y*-axis interceptions of the three groups indicate the initial amount of free drug in the system (both donor and acceptor compartments). This can be beneficial for the quality control purpose for drug preparation.

Conclusion

The current study has demonstrated an innovative apparatus for dissolution testing of nanosized dosage forms. The feasibility of the approach was successfully tested on the free drug and drug release from NPs (with or without a purification procedure). The system together with the four-step model was able to study the drug release quantitatively regardless of the rate-limiting step caused by the membrane. Moreover, the novel method can be applied to quantify the initial amount of free drug in the sample, which is usually challenging for conventional methods sampling noncontinuously.

This work can be further adapted to other model particles for dissolution testing to facilitate the tedious and laborious sampling procedures as well as to obtain quantitative results.

Acknowledgements

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Mass Balance: An Old Concept for the New Challenges Proposed by Personalized Medicine

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Introduction

The concept of personalized medicine implies the treatment of each single patient as a unique subject,[1] thus overcoming the old idea of the average patient. This strategy, via an optimized dosing, is greatly beneficial for the patient, because it allows the reduction of side effects and the improvement of the effectiveness of the therapeutic treatment. On the other hand, it poses the not negligible problem of patient uniqueness. Indeed, uniqueness requires the definition of a rational approach that can be fitted to each patient. For this purpose, mathematical models, defined as a mathematical metaphor of some aspects of reality,[2] can be of great utility.[3] Of course, to represent a reliable and effective theoretical tool in the field of personalized medicine, the mathematical model must account for the most important aspects of drug release and the absorption, distribution, metabolism, and excretion (ADME) processes. Moreover, it is mandatory to account for the simultaneous time evolution of drug release and ADME, processes that are not independent but mutually affect each other. This requirement reflects the conviction that the new challenge in the drug delivery field, for what concerns mathematical modeling, resides in the possibility of developing mechanistic theories able to consider together drug release and ADME phenomena within the human body.[4]

Accordingly, this work focuses attention on the bridging role played by the drug mass balance between drug release and ADME processes. Indeed drug mass balance represents the theoretical tool that enables accounting for the simultaneous development of drug release and ADME processes. Notably, the mathematical expression of the overall model (drug release plus ADME) will depend on the different administration routes and drug delivery systems considered. Indeed, depending on these two aspects, different phenomena will play the role of key factors in determining drug pharmacokinetics (PK). However, the validity of the mass balance approach holds regardless of the administration route and the drug delivery system considered.

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The only requirement for this approach is that all the equations used to build up the model are expressions of local mass balances.[5]

Mathematical Modeling

During release, the drug is absorbed by the surrounding tissues and blood and then, eventually, it spreads into less perfused tissues and organs. Thus, the first part of the model has to deal with the release step, that is, with the factors affecting drug release such as swelling, erosion, drug dissolution (possibly recrystallization), drug transport (by diffusion and convection), drug interaction with the delivery system structure, osmotic pressure, and system geometry.[3] The usual way to deal with this part of the model consists in adopting the local mass balance referred to the moving species (typically, drug and the physiological fluid):

$$\frac{\partial C_i}{\partial t} = -\nabla F_i + G_i \qquad (1)$$

t = time
C_i = ith component (drug/solvent) concentration
F_i = matter flux
G_i = generative term (drug dissolution and/or chemical reactions involving the drug).

where the expression of F_i, the matter flux, is dictated by the most relevant factors ruling the release kinetics. The mathematical modeling of the ADME steps is usually performed by means of ordinary differential equations expressing the time variation of the drug concentration in the different sections, or compartments, into which the human body can be subdivided:[6]

$$\frac{dC_d^j}{dt} = Q_I^j - Q_O^j - E^j \qquad (2)$$

C_d^j = drug concentration in the jth body compartment
Q_I^j = drug mass flow entering the jth body compartment
Q_O^j = drug mass flow leaving the jth body compartment
E^j = drug elimination/metabolism in the jth body compartment

Regardless of the specific choice adopted for the body subdivision into compartments, it is mandatory that each differential equation is an expression of the time-dependent drug mass balance referred to the pertinent compartment. Indeed, if this were not the case, it would be impossible to link the two model parts (drug release and ADME) by means of the bridge (i.e., the drug mass balance carried out on the whole body):[5]

$$M_0 = V_r C_r + V_{RS} C_{RS} + \sum_{j=1}^{N_C} V_j C_j + M_c + M_{el} \qquad (3)$$

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Equation 3 simply states that, at any time, the sum of the drug mass present in the release environment ($V_r C_r$), in the delivery system ($V_{RS} C_{RS}$), and in the N_C compartments ($V_j C_j$), plus the drug amount recrystallized (M_c) and eliminated or metabolized (M_{el}) must be equal to the administered dose (M_0).

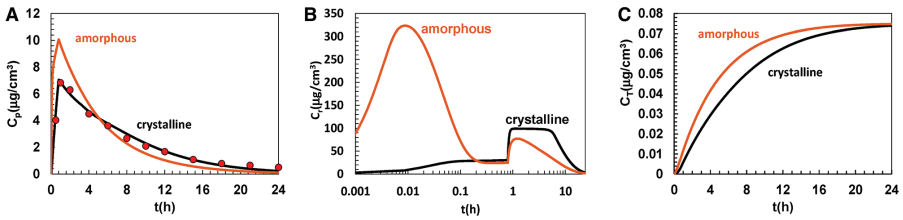

Figure 1. *Modeling of nimesulide concentration: (A) plasma concentration; (B) concentration profile in the gastrointestinal lumen; and (C) concentration in the scarcely perfused tissues and organs.*

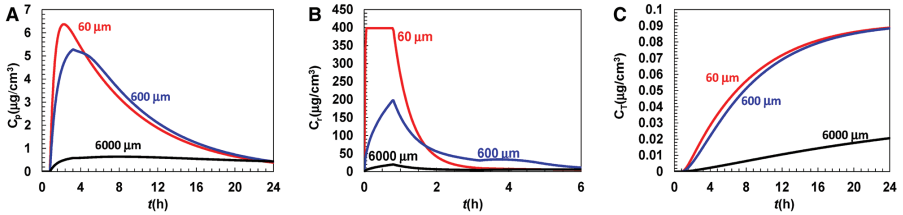

Figure 2. *Modeling of theophylline concentration: (A) plasma concentration; (B) concentration in the gastrointestinal tract; and (C) concentration in the scarcely perfused tissues and organs.*

Results and Discussion

Different delivery systems and administration routes were considered. In particular, attention was focused on oral administration of drug-loaded spheres.

Figure 1A shows the best fitting (solid line) of a mathematical model based on equations 1–3. Red dots represent the experimental plasma concentration (C_p) of nimesulide, a typical nonsteroidal anti-inflammatory drug. These data refer to the oral administration (three humans) of a commercial prompt-action formulation containing nimesulide (100 mg) in crystalline form. Relying on this fitting and on literature PK data about nimesulide, it is possible to simulate the C_p trend (orange line), assuming that nimesulide is completely amorphous inside the delivery system. Indeed, the solubility of amorphous nimesulide is considerably higher than crystalline nimesulide. Figure 1B shows the theoretical concentration profile of nimesulide in the gastrointestinal lumen (C_r), assuming crystalline (black line) or amorphous (orange line) nimesulide. Interestingly, it can be noticed that the best performance of amorphous nimesulide implies a high concentration (orange line) in the stomach and in the small intestine within the first 12 min after administration. The rapid increase of C_r occurring after 1 h, in both the crystalline and amorphous case, is simply owing to the reduced value of drug permeability in the large intestine. Finally, Figure 1C shows nimesulide concentration (C_T) in the scarcely perfused tissues and organs. Drug concentration monotonically increases, reaching (for both the crystalline and amorphous case) values that are about two orders of magnitude smaller than C_p. Again, amorphous nimesulide implies a higher concentration with respect to that of crystalline nimesulide.

Figure 2A reports the simulated theophylline plasma concentration (C_p) according to a mathematical model based on equations 1–3. Simulations refer to the oral administration of 100 mg of theophylline dispersed in an ensemble of all equal polymeric particles whose total volume is 1 cm^3. In particular, the red, blue, and black lines refer, respectively, to particles characterised by a radius equal to 60, 600, and 6,000 µm. Obviously, the smaller the radius, the faster is the theophylline appearance inside plasma. Figure 2B reports the theophylline concentration in the gastrointestinal tract. The flat profile of the 60 µm particles (red line) is simply due to the negligible permeability of theophylline in the gastric lumen. Accordingly, the drug initially keeps its maximum value, and it decreases only after getting into the small intestine, where theophylline permeability is of the order of 10^{-4} cm/s. Figure 2C makes clear that theophylline concentration in scarcely perfused tissues and organs (C_T) is low in comparison to C_p and C_r. In addition, the 60 and 600 µm particles are characterised by a similar C_T trend.

Conclusions

The mass balance approach was demonstrated to be robust and versatile concerning the simulation of *in vivo* drug release and ADME processes. While the robustness refers to the model numerical solution, the versatility relies on the possibility of an easy improvement of the model by simply updating the mathematical interpretation of the release and the ADME parts.

Acknowledgements

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Young Scientist Committee Update

Jennifer Wong[1] and Patrick Baumhof[2]

This year, the Young Scientist Committee (YSC) breathed fresh air into their variety of workshops, Get Up! Get Educated! sessions, roundtable discussion, the popular Mentor-Protégé Program, and a sell-out networking event. As expected, all the events were a great success, but two deserve special mention.

The Saturday workshop is now interactive! The Young Scientist programme kicked off on Saturday with a workshop titled "The Rise, and Rise, of Precision Medicine." Our three guest speakers were Devendra Pade (Simcyp Limited), Carlos Garcia-Echeverria (Sanofi), and Heinrich Haas (BioNTech RNA Pharmaceuticals GmbH). All three had a range of industry experience and provided interesting insights into their view of how drug delivery platforms could be leveraged to take advantage of precision medicine strategies. The biggest hits seemed to be the interactive sessions between talks. The ice breaker at the beginning involved pairing people up and allowing one minute for both of them to introduce themselves, their research topic, and how their research could help the other person. This gave people the chance to start a conversation and engage with everyone in the room. It was great fun, and many attendees said they were able to recognise faces and say hi to people throughout the rest of the conference. Later, attendees were divided into groups, and they were asked to brainstorm and present a pitch on their vision of a precision medicine product that could make a difference. Our guest speakers had a wonderful time judging these refreshing concepts from the next generation of scientists, and members of the winning team took home tickets to the Lunch with the Luminaries. Afterward, the attendees also had the opportunity to discuss the prospects of precision medicine directly with the speakers in small groups.

Devendra Pade in close discussion with a group of young scientists.

The energetic Speed Mentoring Event at the CRS Annual Meeting.

The tables for your career development are turning (pun intended)! This year, the ever-popular Mentor-Protégé Program was reborn as the fast-paced and energetic Speed Mentoring Event. Up to 70 protégés were divided among ten tables, and mentors rotated through each table to provide protégés with guidance and career advice. The ticking clock meant that it didn't take long for the room to be filled with the roar of voices as protégés enthusiastically asked questions to capitalise on the experience of mentors. Everyone thoroughly enjoyed the dynamic interaction, and the hour passed by in an instant.

This year has been an amazing experience, and the YSC team are excited to bring even bigger and better things in the year ahead. Stay tuned for more! ■

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Drug Delivery and Translational Research Update

Vinod Labhasetwar, Editor-in-Chief, Cleveland Clinic, Cleveland, Ohio, U.S.A.

Thanks to Authors, Reviewers, and Guest Editors
The editorial team of *Drug Delivery and Translational Research* (*DDTR*) and the Controlled Release Society are thankful to authors, reviewers, and special issue guest editors. Because of their efforts and contributions, we not only successfully completed five years of publication but maintained a high quality of published papers. Exclusively focused on translational aspects of drug delivery, *DDTR* provides a unique forum for publication of high-quality research with significance in drug delivery science and technology. Join the leading scientists who are publishing their work in *DDTR*. It is available online to CRS members as a membership benefit. The members must login to the CRS website first and then click the Publications tab to get to the member access link.

In this issue of *CRS Newsletter*, I would like to acknowledge the guest editors who have developed 12 special issues.

"Advances in Vaginal Drug Delivery," with guest editor David R. Friend (CONRAD, U.S.A.), volume 1, issue 3, June 2011.

Vaginal drug delivery systems are gaining widespread interest because they allow the local administration of drugs to prevent transmission of sexually transmitted diseases such as HIV-1 and HSV-2. These systems may also apply for contraception. This special issue describes various "multipurpose" drug delivery technologies for drugs of different physicochemical properties including peptides and vaccines, either alone or in combination, for a number of indications. Since sexually transmitted diseases are on the rise worldwide, an effective vaginal drug delivery technology could have global implications.

"Advances in Image-Guided Drug Delivery," with guest editors Arash Hatefi and Tamara Minko (Rutgers, The State University of New Jersey, U.S.A.), volume 2, issue 1, February 2012.

Image-guided drug delivery (IGDD) is an emerging therapeutic approach in which imaging modalities are used to guide and monitor localization of therapeutics to the site of action. Therefore, a methodical approach to IGDD entails systems for delivery, targeting, and monitoring (imaging) of the course of action. This special issue covers various technologies that are being developed for simultaneous drug delivery validation and therapeutic response evaluation in disease conditions.

"Drug Delivery to the CNS," with guest editor Pericles Calias (Shire HGT, U.S.A.), volume 2, issue 3, June 2012.

Strategies for treating the central nervous system (CNS) manifestations of diseases have evolved well beyond the traditional size/lipophilicity paradigm. This special issue describes the challenges of developing therapies targeted to the CNS, from bench to clinical development. A review of the biological hurdles and current strategies for overcoming them

sets the stage for discussions on the assessment of the product's pharmacologic effect within the CNS and regulatory considerations for the incorporation of biomarkers into product development programs.

"Regenerative Medicine," with guest editor V. Prasad Shastri (University of Freiburg, Germany), volume 2, issue 5, October 2012.

The main objective of this themed issue on biomimetic and biofunctional materials in regenerative medicine is to highlight the evolution of concepts in materials engineering for inducing autologous regeneration and the challenges associated with clinical translation. In this context, material design that incorporates principles of directed self-assembly, surface engineering, metabolic engineering, extracellular matrix mimicry, and synthetic biology for driving functional cellular organization and for recapitulation of signaling environments in embryonic and fetal development are highlighted.

"Nasal Drug Delivery," with guest editors Elka Touitou (Hebrew University of Jerusalem, Israel) and Lisbeth Illum (Critical Pharmaceuticals, United Kingdom), volume 3, issue 1, February 2013.

The nasal route of administration for systemic action of drugs is an exciting growing field of research that opens avenues for investigation and design of new and more efficient products. This issue focuses on translational nasal drug delivery research. Reviews on the nasal administration route for systemic and nose-to-brain delivery cover absorption pathways, delivery systems, and devices. They are followed by papers on specific case studies on new carriers, drugs, and vaccines investigated in animals or administrated to humans.

"Cancer Stem Cells," with guest editor Jayanth Panyam (University of Minnesota, U.S.A.), volume 3, issue 2, April 2013.

There is growing evidence that cancers contain a small subset of stem-like cells called cancer stem cells (CSCs) that can self-renew. CSCs may play a critical role in cancer treatment outcomes because they are resistant to conventional chemotherapy and can initiate tumor recurrence following treatment. This theme issue reviews the role that CSCs may play in tumor response to therapy and strategies to inhibit CSCs.

"Nano/Bio Interface: Impact on Drug Delivery Applications," with guest editors Subhra Mohapatra, Srinivas Nagaraj, and Shyam S. Mohapatra (University of South Florida, U.S.A.), volume 3, issue 4, August 2013.

This special issue is partly based on the Collaborative International Conference 2012 (NBCIC 2012) that was organized by the University of South Florida Nanomedicine Research Center and was held March 22–24, 2012. NBCIC 2012 brought together engineers, chemists, physicists, biologists, and clinicians from across the globe to discuss recent advances, opportunities, and barriers in nanoscience and nanotechnology and its applications to diagnosing and treating diseases.

"Nanomedicine: Prospects and Challenges," with guest editors Padma V. Devarajan and Vandana B. Patravale (Institute of Chemical Technology, India), volume 3, issue 5, October 2013.

This special issue is a fallout of the Indo–U.S. joint symposium "Nanomedicine—Prospects and Challenges" organized at the Institute of Chemical Technology (Mumbai, India), jointly with Vinod Labhasetwar (Cleveland Clinic, U.S.A.) and supported by the Indo-US Science and Technology Forum. The issue is a blend of reviews and research manuscripts, covering diverse aspects of nanomedicine.

"RNA Interference-Based Therapeutics and Diagnostics," with guest editor Ken Howard (Aarhus University, Denmark) and Dan Peer (Tel-Aviv University, Israel), volume 4, issue 1, February 2014.

The capability to control and study cellular gene expression by the process of RNA interference (RNAi) has provided researchers with an unprecedented tool for investigating functional genomics and the potential to harness the RNAi mechanism as a potent therapeutic. The special issue covers the processes, molecules, and delivery solutions relevant for the clinical translation of RNAi.

"Proceedings of the Drug Delivery Australia 2012 Symposium," with guest editors Ben J. Boyd (Monash University, Australia) and Paul Young (University of Sydney, Australia), volume 4, issue 3, June 2014.

This issue is based on the 2012 Drug Delivery Australia conference, hosted by the Australian Local Chapter of the Controlled Release Society. In addition to research and review articles, the issue includes articles on clinical trials and clinical research.

"Tissue Engineering," with guest editors Sing Yian Chew (Nanyang Technological University, Singapore) and Kam Leong (Columbia University, U.S.A.), volume 5, issue 2, April 2015.

The issue contains articles on nanofibers and their use for growth factor delivery, scaffolds and their interactions with cells, and hydrogels and other drug delivery systems for regenerative medicine.

"Microneedles for Drug and Vaccine Delivery and Patient Monitoring," with guest editors Ryan Donnelly (Queen's University Belfast, Ireland) and Dennis Douroumis (University of Greenwich, United Kingdom), volume 5, issue 4, August 2015.

In this issue, there is a focus on novel applications of microneedles in drug, vaccine, and gene delivery, as well as in minimally invasive monitoring and diagnosis. Topics include gene and drug delivery systems, vaccine delivery systems, and material design and production, with a strong focus on clinical translation and commercialization.

Most Downloaded *DDTR* Articles in 2015

Nasal Drug Delivery Devices: Characteristics and Performance in a Clinical Perspective—A Review
Per Gisle Djupesland
Drug Delivery Transl. Res. 3(1): 42-62 (2013)

Microneedle-Based Drug and Vaccine Delivery via Nanoporous Microneedle Arrays
Koen van der Maaden, Regina Luttge, Pieter Jan Vos, Joke Bouwstra, Gideon Kersten, and Ivo Ploemen
Drug Delivery Transl. Res. 5(4): 397-406 (2015)

A Paradigm Shift for Extracellular Vesicles as Small RNA Carriers: From Cellular Waste Elimination to Therapeutic Applications
Keitaro Hagiwara, Takahiro Ochiya, and Nobuyoshi Kosaka
Drug Delivery Transl. Res. 4(1): 31-37 (2014)

Vaginal Deployment and Tenofovir Delivery by Microbicide Gels
Y. Gao, A. Yuan, O. Chuchuen, A. Ham, K. H. Yang, and D. F. Katz
Drug Delivery Transl. Res. 5(3): 279-294 (2015)

Strategies for Intranasal Delivery of Vaccines
Mehfuz Zaman, Saranya Chandrudu, and Istvan Toth
Drug Delivery Transl. Res. 3(1): 100-109 (2013)

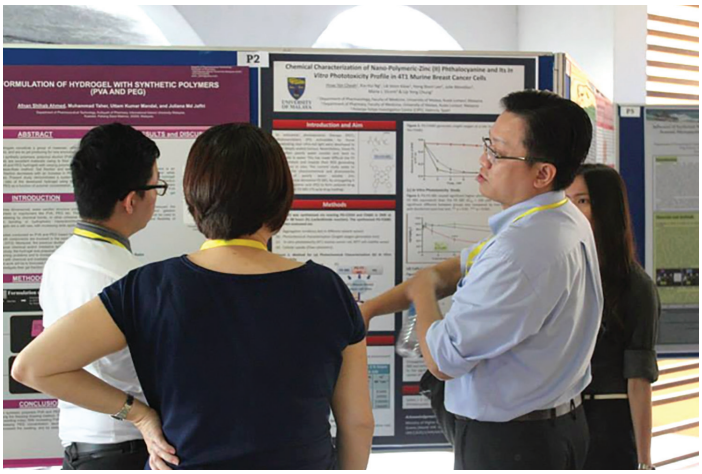
DDTR Outstanding Research Paper Award

It is time to consider submitting your best research for the 2016 *DDTR* Outstanding Research Paper Award. The paper will be selected from the research articles, clinical research, and clinical trials published in *DDTR* during 2016. The award will be presented during the 44th CRS Annual Meeting, to be held July 16–19, 2017, at Hynes Conventional Center, Boston, MA, U.S.A. Visit the CRS website for award criteria (www.controlledreleasesociety.org/about/Awards/Pages/DDTROustandingPaper.aspx). ■

Controlled Release & Drug Delivery Symposium 2015

The Malaysia Local Chapter of the Controlled Release Society (MyCRS) has successfully organised the first MyCRS Scientific Conference 2015 in conjunction with CRDDS2015. The event was held August 15–16 in Kuala Lumpur and coorganized with the Centre for Drug Delivery Research, Universiti Kebangsaan Malaysia. The conference attracted more than 50 participants from various countries including Taiwan, Thailand, India, and Iran. ■

A group photo with all participants.



Judges in serious discussion during the poster presentation.

A postgraduate student in action during the student 3-minute pitching competition.

Networking during the conference dinner.

People in the News

Compiled by Steven Giannos, Independent Consultant

Unorthodox Approach to Drug Delivery Research Lands Carnegie Mellon Professor on *Popular Science*'s 2015 Brilliant 10 List

Business Wire: September 23, 2015 – PITTSBURGH, PA, U.S.A. – Kathryn Whitehead, an assistant professor of chemical engineering at Carnegie Mellon University, has been named by *Popular Science* as a 2015 Brilliant Ten winner for her innovative work on drug delivery systems.

Annually, *Popular Science* combs through hundreds of nominations from around the country to select the brightest minds in engineering and science. Whitehead earned the honor this year for designing nanoparticles that treat disease by delivering therapeutic drugs to specific areas in the body. Her research will revolutionize how we treat formidable diseases, such as cancer, diabetes, and hereditary disorders.

During her career, Whitehead has synthesized and tested nearly 5,000 nanoparticle delivery vehicles en route to identifying a select few that potently shuttle drugs into exactly the right cells. This feat was challenging, in part, because the body's immune system considers therapeutic nanoparticles to be foreign substances that need to be destroyed. However, Whitehead's nanoparticles circumvent the immune system and are free to deliver medicine to cells in many parts of the body, including the liver, the skin, and the intestine. Whitehead's research group is now using her nanoparticles to engineer therapies for maladies that include inflammatory bowel disease, chronic wounds, and non-Hodgkin's lymphoma, a type of blood cancer.

"Cancer therapy is so difficult for patients, in large part, because of the toxic side effects of chemotherapy," said Whitehead. "In contrast, our targeted nanoparticles deliver drugs only to cancerous tissue, sparing healthy cells. We expect these targeted treatments to extend the lives of cancer patients while increasing their quality of life through a reduction in side effects."

Whitehead's approach to finding the right nanoparticles for drug delivery was unorthodox in that it required her to examine a very large number of nanoparticles using high-throughput screening.

"Although high-throughput screening has not been a well-accepted approach to scientific discovery, I felt strongly that we needed to test many compounds to maximize our chances of success," said Whitehead. Her hard work has paid off in the discovery of these versatile nanoparticles, and she has broadened the scientific community's understanding of how drug delivery chemistry affects efficacy. She is now able to predict which nanoparticles will work in living animals.

"The *Popular Science* Brilliant 10 award acknowledges the power of Katie's ideas and the important contributions that faculty members can make early in their careers," says James H. Garrett, dean of the College of Engineering at Carnegie Mellon University.

"I'm here at Carnegie Mellon because I want to use my creativity and scientific skills for the betterment of society," said Whitehead. "Knowing that our work could improve the lives of millions of patients is deeply satisfying."

Past CRS President Tsuneji Nagai Received Honorary Doctorate

In early October, legendary professor and past CRS president Tsuneji Nagai received an honorary doctorate from Chulalongkorn University in Bangkok, Thailand. It was presented by Her Royal Highness Princess Maha Chakri Sirinthorn on behalf of the king and was the university's first honorary degree presented in the pharmaceutical field.

Prof. Nagai's work in bioavailability studies and controlled drug delivery formulations has contributed greatly to the pharmaceutical science of Japan, Asia, and the world. His distinguished career includes leadership positions at Hoshi University, service on multiple boards, direction for the Nagai Foundation Tokyo, and a body of work that includes drug products, more than 60 patents, and more than 500 peer-reviewed research papers. Prof. Nagai has immensely influenced students and colleagues, whose work continues to significantly impact delivery science. Through the Nagai Foundation Tokyo, he co-sponsors the annual CRS T. Nagai Postdoctoral Research Achievement Award.

Past CRS President Robert Langer Presented with the Queen Elizabeth Prize for Engineering

On October 26, Robert Langer of the Massachusetts Institute of Technology was presented with the Queen Elizabeth Prize for Engineering, which includes a £1 million award.

One of the highlights of the day was the Engineering Ambassadors' reception at the Royal Academy of Engineering, featuring Langer's address, "The Struggles and Dreams of a Young Engineer." He recounted early

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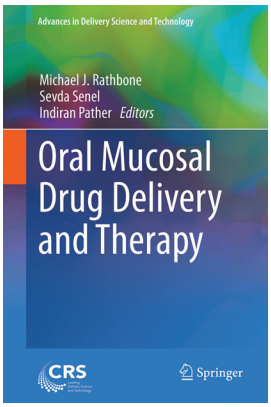
career challenges in which he was refused research funding and continuously discouraged. His speech is available at http://qeprize.org/createthefuture/trophy-presentation-2015.

Later in the day, guests gathered at Buckingham Palace to watch as Queen Elizabeth II presented the trophy, saying, "I am delighted to honour the achievements of Dr. Langer, whose pioneering research has brought enormous benefit to millions of people."

Langer runs one of the largest academic laboratories in the world and is the most cited engineer in history (170,000 times). He has more than 800 patents granted or pending and has co-founded over 20 companies. His connections with CRS include belonging to the CRS College of Fellows, being a past president of CRS (1991–1992), and receiving the Founders Award (1989). Many prominent CRS members are connected in some way to the Langer Lab at MIT. Langer is known for bringing together researchers from many different disciplines, and this interdisciplinary approach is central to CRS and to our members' work. ■

A Valuable Resource—*Oral Mucosal Drug Delivery and Therapy*



The book *Oral Mucosal Drug Delivery and Therapy,* edited by Michael Rathbone, Sevda Senel, and Indiran Pather, examines the formulation challenges and clinical opportunities for delivering drugs locally and systemically to the oral cavity. The book contains 11 authoritative chapters that evaluate the major issues associated with the oral mucosa as a route for drug administration and provides solutions to overcome these challenges. There is a comprehensive description of how the anatomy and physiology of the oral cavity affects the design of oral mucosal drug delivery systems and provides a detailed description of current oral mucosal drug delivery technologies, including research, development, and assessment methods. Furthermore, solutions on how to improve drug permeability across, and increase retention time on, oral mucosa are also provided. The book also provides an insightful look into the future directions in research and product development of oral mucosal drug delivery systems. *Oral Mucosal Drug Delivery and Therapy* is a valuable resource for undergraduate and postgraduate students, academic staff, and researchers wanting to extend their knowledge in this field.

To order visit **controlledreleasesociety.org/publications/Pages/CRSBooks.aspx.** ■

In the News

Compiled by Steven Giannos, Independent Consultant

October

Braeburn Pharmaceuticals Commends President Obama's Commitment to Improving Treatment for Opioid Addiction

PRNewswire: October 22, 2015 – PRINCETON, NJ, U.S.A. – Braeburn Pharmaceuticals commends President Barack Obama for highlighting the importance of removing barriers to medication-assisted treatment (MAT) for people with opioid addiction. The president announced a series of initiatives among the public and private sectors and at all levels of government to address the opioid abuse epidemic. The president's engagement amplifies the recent announcement by Department of Health and Human Services (HHS) Secretary Sylvia Burwell that HHS will revise federal regulations to expand access to MAT.

President Obama's announcement focused on nationwide efforts to generate greater public awareness, educate opioid prescribers, and improve access to MAT for opioid use disorders. The Obama Administration has expanded insurance coverage of treatment for substance use disorders under the Affordable Care Act and has committed to improving access to FDA-approved medications containing buprenorphine for the treatment of opioid use disorders.

"President Obama's personal engagement is critical to raising awareness of the fact that opioid addiction is a problem for all of us and requires action from both the private and public sectors," said Behshad Sheldon, president and CEO of Braeburn.

The Obama Administration has supported public-private cooperation to improve care for people with opioid use disorders since the president's first year in office. In 2009, the National Institute on Drug Abuse (NIDA) provided a research grant to expedite the development of Probuphine®, an investigational, long-acting, implantable formulation of buprenorphine under development by Braeburn with Titan Pharmaceuticals, Inc. The Probuphine implant is intended to provide a consistent level of the medication for six months following a single treatment.

In addition to HHS and NIDA, the Food and Drug Administration (FDA) is also actively implementing the president's plan to reduce opioid abuse and addiction, including issuance of guidance on abuse-deterrent formulations of opioids. FDA has provided Braeburn with guidance on the design of clinical trials of Probuphine and granted priority review for the Probuphine New Drug Application. FDA has designated February 27, 2016, as the target date for agency action.

"Our vision is for patients to have safe and effective long-acting, pill-free options that deliver precision medicine in neuroscience. This means ensuring that patients get the right dose for an optimal duration. Probuphine is our foundational product, and we are dedicated to continuing research, development, and education in collaboration with both public and private partners active in treatment of opioid addiction and pain," Sheldon said.

Currently available buprenorphine medications for opioid addiction are oral forms that require daily self-administration by patients. These traditional formulations are highly susceptible to risks of diversion, misuse, abuse, and accidental exposure given that patients must take responsibility for their postdispensing storage, proper use, and disposal.

If approved by FDA, Probuphine and other long-acting implants and injectables for addiction, pain, and other conditions could help reduce the problems that President Obama, Secretary Burwell, NIDA, FDA, and other stakeholders nationwide are working to address.

Probuphine is an investigational subdermal implant designed to deliver buprenorphine around the clock for six months following a single treatment and to promote patient compliance and retention. Buprenorphine, which is the active ingredient in multiple FDA-approved drug products for the treatment of opioid dependence, is currently available in tablet and film formulations that require self-administration by patients on a daily basis.

Probuphine was developed using ProNeura™, Titan Pharmaceuticals' continuous drug delivery system that consists of a small, solid implant made from a mixture of ethylene-vinyl acetate (EVA) and a drug substance. The resulting construct is a solid matrix that is placed subdermally, normally in the upper arm, in an outpatient office procedure, and removed in a similar manner at the end of the treatment period.

The efficacy and safety of Probuphine has previously been studied in several clinical trials, including a 163-patient, placebo-controlled study over a 24-week period (published in the *Journal of the American Medical Association*), and a follow-on study of 287 patients (published in the journal *Addiction*).

Braeburn Pharmaceuticals, an Apple Tree Partners company, is a pill-free pharmaceutical company delivering precision medicine in neuroscience. In September 2015 the Food and Drug Administration (FDA) accepted for review Braeburn's New Drug Application for its lead candidate, Probuphine, a six-month buprenorphine implant for treatment of opioid addiction. The agency set February 27, 2016, as the target date for action.

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Long-acting therapeutic treatment options can be essential to improving patient outcomes and facilitating recovery in these conditions, which are often complicated by stigma and present significant public health challenges. Braeburn's investigational product pipeline consists of long-acting therapies for serious neurological and psychiatric disorders, including addiction, pain, and schizophrenia. Candidates include: Probuphine, a six-month buprenorphine implant for treatment of opioid addiction; CAM2038, weekly and monthly subcutaneous injection depot formulations of buprenorphine for treatment of opioid addiction and pain; a risperidone six-month implant for treatment of schizophrenia; and a novel molecule, ATI-9242, for treatment of schizophrenia. More information on Braeburn, an Apple Tree Partners company, can be found at www.braeburnpharmaceuticals.com.

Ocular Therapeutix™ Announces Topline Results of Phase 3 Clinical Trial for Dextenza™ for the Treatment of Allergic Conjunctivitis

Business Wire: October 22, 2015 – BEDFORD, MA, U.S.A. – Ocular Therapeutix™, Inc. (NASDAQ: OCUL), a biopharmaceutical company focused on the development and commercialization of innovative therapies for diseases and conditions of the eye, announced today topline efficacy results from a phase 3 clinical trial to evaluate the safety and efficacy of Dextenza™ (sustained release dexamethasone) 0.4 mg, intracanalicular depot for the treatment of allergic conjunctivitis. Dextenza is a product candidate administered by a physician as a bioresorbable intracanalicular depot and designed for extended drug release to the ocular surface for 30 days.

Treatment success was evaluated separately in this trial for ocular itching and conjunctival redness, and attainment of endpoints for both ocular itching and conjunctival redness has not been historically required by the U.S. Food and Drug Administration (FDA) for approval of drugs for allergic conjunctivitis.

The primary endpoint of treatment of ocular itching associated with allergic conjunctivitis was successfully achieved in this trial. There was a statistically significant difference ($p < 0.0001$) in the mean scores between the Dextenza treatment group and the placebo group for ocular itching at all three time points measured on day 7 postinsertion of the drug product. The difference in the scores for ocular itching between the Dextenza group and the placebo group was greater than 0.5 units at all time points on day 7 postinsertion and was greater than 1 unit at a majority of the time points on day 7 postinsertion.

The primary endpoint of conjunctival redness is typically an endpoint included in phase 3 trials for allergic conjunctivitis but has not been required for approval. The Dextenza treatment group did not achieve the primary endpoints for conjunctival redness in this trial. Many commercially available prescription medications for the treatment of allergic conjunctivitis have an ocular itching indication only. In this clinical trial, as well as other clinical trials completed to date, Dextenza has exhibited a strong safety profile and has been well tolerated.

"We are very pleased with the results of this phase 3 clinical trial in terms of the treatment of ocular itching associated with allergic conjunctivitis," stated Amar Sawhney, Ph.D., chairman, chief executive officer, and president. "We believe that the design modifications made from our phase 2 program contributed to the successful achievement of the primary endpoint for ocular itching. Based on the results from this trial, we expect to advance this program into a second phase 3 clinical trial in allergic conjunctivitis before the end of 2015. We believe the results from this trial, as well as data from the previous phase 2 study, provide evidence supporting the safety and efficacy of our sustained release drug delivery platform that we continue to leverage across multiple ocular diseases and conditions."

Michael B. Raizman, M.D., Ophthalmic Consultants of Boston, New England Eye Center, Tufts University School of Medicine, stated, "The clinical data for Dextenza indicate that this promising product candidate has potential to serve as an effective alternative to self-administered drops for patients experiencing itching associated with allergic conjunctivitis. Dextenza offers one-time seasonal administration in a preservative-free product, is designed to avoid the peaks and valleys associated with topical dosing, and has the potential to minimize or eliminate the side effects associated with eye drops. The results for ocular itching are encouraging given that I consider itching to be the most relevant endpoint for my patients."

Ocular Therapeutix, Inc. (NASDAQ: OCUL) is a biopharmaceutical company focused on the development and commercialization of innovative therapies for diseases and conditions of the eye using its proprietary hydrogel platform technology. Ocular Therapeutix's lead product candidates are in phase 3 clinical development for postsurgical ocular inflammation and pain and allergic conjunctivitis, and phase 2 clinical development for glaucoma and inflammatory dry eye disease. The company is also evaluating sustained-release injectable anti-VEGF drug depots for back-of-the-eye diseases. Ocular Therapeutix's first product, ReSure® sealant, is FDA-approved to seal corneal incisions following cataract surgery.

Impax Receives FDA Approval for Generic Version of Intuniv® (Guanfacine) Extended-Release Tablets, 1, 2, 3, and 4 mg

PRNewswire: October 21, 2015 – HAYWARD, CA, U.S.A. – Impax Laboratories, Inc. (NASDAQ: IPXL) today announced that the U.S. Food and Drug Administration (FDA) has approved its generic version of guanfacine extended-release tablets 1, 2, 3, and 4 mg.

Fred Wilkinson, president and chief executive officer of Impax, stated, "Since the resolution of the warning letter at the Hayward facility in early September, the FDA has approved three generic products from this facility in the last five weeks. Generic guanfacine was one of the products waiting for the resolution of the warning letter, and we did not include it in the 14 potential

generic product launches for 2015. We are now evaluating the viability of this very competitive multi-player market and potential commercialization of this product. Additionally, we will continue to work with the FDA toward approval of our pending Abbreviated New Drug Applications at our Hayward facility."

According to IMS Health (NSP), U.S. brand and generic sales of guanfacine extended-release tablets 1, 2, 3, and 4 mg were approximately $689 million for the 12 months ending in August 2015.

Impax Laboratories, Inc. (Impax) is a specialty pharmaceutical company applying its formulation expertise and drug delivery technology to the development of controlled-release and specialty generics in addition to the development of central nervous system disorder branded products. Impax markets its generic products through its Impax Generics division and markets its branded products through its Impax Specialty Pharma division. Additionally, where strategically appropriate, Impax develops marketing partnerships to fully leverage its technology platforms and pursues partnership opportunities that offer alternative dosage form technologies, such as injectables, nasal sprays, inhalers, patches, creams, and ointments. For more information, please visit the company's website at www.impaxlabs.com.

Flowonix Medical Inc. and Cerebral Therapeutics, LLC, Announce Exclusive Agreement for Drug Delivery to Brain

PRNewswire: October 21, 2015 – MOUNT OLIVE, NJ, U.S.A. – Flowonix Medical Inc. of New Jersey and Colorado-based Cerebral Therapeutics, LLC, announced today that they have entered into an exclusive agreement to develop a unique implanted drug delivery system that provides direct infusion of a therapeutic drug into targeted areas of the brain for treatment of neurological diseases. By delivering microdoses of medication directly to the brain, this system will be able to bypass the blood-brain barrier and deliver the medication to a specific targeted region.

"Neurological disorders can be devastating to patients and their families, and patients are often left with few options," stated Steven Adler, president and CEO of Flowonix Medical Inc. "Flowonix has long been a world leader in implantable infusion systems, and we have specific expertise in the accurate and reliable delivery of microdoses of medication. We are pleased to partner with Cerebral Therapeutics to bring this safe, effective, and successful drug delivery technology to one of the most challenging frontiers in medicine—the brain."

"The combination of small-molecule therapy with established infusion pump delivery could be a treatment alternative with profoundly positive ramifications," stated Dr. Ashwini Sharan, neurosurgical and neurological professor at Jefferson University and president-elect for the North American Neuromodulation Society (NANS). "The use of implantable infusion pumps to deliver novel therapeutic agents holds great promise."

"Cerebral Therapeutics chose to work with Flowonix because the Prometra® and Prometra® II infusion pumps offer a patented valve-gated drug delivery system that allows for very precise dosing of medicine," stated Dr. Dan Abrams, CEO of Cerebral Therapeutics. "The state-of-the-art Prometra pump platform will be used to deliver medication directly to the brain. For certain agents, this may reduce the doses necessary for therapeutic effect, lessen the risk of systemic toxicity, and possibly ameliorate the side effects associated with certain types of neurological therapies."

The new agreement will allow Cerebral Therapeutics, LLC, and Flowonix Medical Inc. to develop drug-pump combination products aimed at addressing unmet needs in neurological therapies.

"Clinical trials will be needed to ascertain how targeted delivery of drugs directly to the brain may benefit neurological patients," continued Dr. Dan Abrams. "Experience with intraspinal drug therapy demonstrates the many advantages of controlled and targeted drug therapy. We look forward to working with Flowonix because of their state of the art technology, commitment to developing new therapies, and leadership in infusion pump devices."

Steve Adler continued, "This is an important partnership for Flowonix, which already has the privilege of being a leader in bringing infusion pump technology to address the largely unmet need of chronic pain. It demonstrates our commitment at Flowonix to bringing the most advanced technology to our physicians when treating their most challenging patients, particularly those with neurological conditions and with few other treatment options."

Flowonix Medical Inc. (www.flowonix.com) headquartered in Mt. Olive, New Jersey, is dedicated to working with healthcare professionals to help ease suffering associated with chronic pain and allow patients to reclaim their lives through innovation and therapy advancements. The strategic business goal of Flowonix Medical Inc. is to become the leading implantable drug delivery company in the world. Founded in 2005, Flowonix Medical Inc. received approval to conduct its first clinical trial in 2007 on the Prometra programmable implantable pump. The company received approval by the FDA to market the Prometra in 2012. Flowonix Medical Inc. has been granted multiple patents and is focused on working closely with physicians to rapidly improve the capabilities of implantable drug delivery and management systems. For more information, please visit www.flowonix.com.

Cerebral Therapeutics, LLC (www.cerebraltherapeutics.com) is a privately held company founded with the goal of addressing the well-recognized limitations of existing treatments for uncontrolled neurological diseases. Cerebral Therapeutics is combining advanced micro-dosing technology with proprietary medications to precisely deliver treatments to the other side of

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the blood-brain barrier to improve the lives of patients with uncontrolled neurological disease. With a promising route of administration, Cerebral Therapeutics offers a new approach to managing neurological diseases by means of delivering ideal dosing to targeted sites within the brain. Initially, Cerebral Therapeutics is focused on improving outcomes for patients with refractory epilepsy by targeting the site of the seizure generation and propagation in the brain. Future cerebral therapeutic areas include obesity, Alzheimer's disease, Parkinson's disease, anxiety spectrum disorder, and brain cancer.

Portal Instruments Closes a $25 Million Series B Financing to Commercialize Its Transformative Needle-Free Drug Delivery System

PRNewswire: October 20, 2015 – CAMBRIDGE, MA, U.S.A. – Portal Instruments, Inc., a clinical stage drug delivery device company, announced today that it has closed a financing for $25 million of its series B preferred stock led by 5AM Ventures and joined by Portal's existing private and strategic investors, including Sanofi Sunrise. The company has received an initial investment of $10 million, with an additional $15 million due upon the achievement of certain milestones.

Proceeds from the series B financing will be used to further develop Portal's groundbreaking computerized needle-free drug delivery system for injectable biologics for chronic diseases and to advance commercialization of its first product. The underlying technology is supported by a unique intellectual property portfolio of more than 50 patents conceived and prototyped at Massachusetts Institute of Technology (MIT) by world renowned inventor, scientist, and entrepreneur Ian Hunter, Ph.D., Hatsopoulos Professor of Mechanical Engineering and head of the Bio Instrumentation Laboratory at MIT, a founder of the company, and to which Portal Instruments has a worldwide exclusive license.

"Portal Instruments is transforming the patient experience for the delivery of injectable biologics for chronic diseases," said Patrick Anquetil, CEO. "Administering high viscosity, high concentration biologics is a challenge for the biopharma industry as the drugs have to be needle-injected subcutaneously, which is a slow and painful experience for patients. Drug adherence is a huge problem in chronic diseases, and needle-related safety concerns are real. The Portal device offers a transformed patient experience. The injection is needle-free, fast, with shorter injection duration and sensation for the patient. The device is easy to use, and digital health features empower the patient to holistically manage their chronic condition and improve their adherence. We are excited to have a respected life sciences venture capital firm such as 5AM Ventures join us on our mission."

Jim W. Young, Ph.D., venture partner at 5AM Venture Management, said, "Portal's breakthrough drug delivery system has the potential to address the administration of high concentration, viscous biologics in a safe, accurate manner that can significantly improve the patient experience." Young continued, "Portal has an extensive intellectual property portfolio, a first-class team of scientists and engineers, and a management team with a strong track record in the biotech industry. We are excited to be part of the company."

Portal Instruments is developing a unique platform technology to transform the delivery of modern medicines and improve the patient experience. Portal's patented technology enables the precise delivery of the exact amount of drug at the desired tissue depth irrespective of drug viscosity and composition, particularly important for today's new biological drugs. The company's injection mechanism delivers the injection with minimal sensation and is highly customizable across a large variety of medical, animal, agricultural, and cosmetic applications.

Portal Instruments seeks to partner with biopharmaceutical companies to enable greater differentiation and penetration of their individual billion dollar biologic franchises. Portal is backed by venture investors and strategic partners, including 5AM Ventures and Sanofi Sunrise, and seeks additional biopharmaceutical partners to collaborate on specific drug-device combination products that can drive new market growth, improve differentiation, and help with patient adherence. For more information, please visit www.portalinstruments.com or follow @portalcambridge on Twitter.

Enteris BioPharma's Formulation Technology Enables Oral Delivery of Tarsa Therapeutics' TBRIA™

PRNewswire: October 19, 2015 – BOONTON, NJ, U.S.A. – Enteris BioPharma, Inc., an industry leader in oral peptide delivery, congratulates Tarsa Therapeutics on the submission of a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for TBRIA™ (calcitonin-salmon [rDNA origin] delayed release tablets) in July 2015, which has now been accepted for review by the FDA with a user fee goal date of May 30, 2016. TBRIA is a once-daily oral recombinant salmon calcitonin tablet for the treatment of postmenopausal osteoporosis in women greater than 5 years postmenopause when alternative treatments are not suitable (e.g., patients for whom other therapies are contraindicated or for patients who are intolerant or unwilling to use other therapies).

Tarsa's formulation of TBRIA uses proprietary, patented oral delivery technology licensed from Enteris BioPharma. Tarsa has exclusive development and worldwide commercialization rights to the oral calcitonin product developed with Enteris' technology, with the current exception of China.

Enteris BioPharma, Inc., is a privately held, New Jersey–based biotechnology company offering innovative formulation solutions built around its proprietary drug delivery technologies. Enteris' proprietary oral delivery technology has been the subject of numerous feasibility studies and active development programs, several of which are in late stage clinical development. For more information on Enteris BioPharma and its proprietary oral delivery technology, please visit www.EnterisBioPharma.com.

Positive Four-Year Clinical Data from Micell Technologies' MiStent SES Presented at TCT 2015

PRNewswire: October 13, 2015 – DURHAM, NC, U.S.A. – Micell Technologies, Inc., today announced four-year clinical results from the DESSOLVE I and II trials of its MiStent sirolimus-eluting absorbable polymer coronary stent system (MiStent SES®) were presented at the 27th Annual Transcatheter Cardiovascular Therapeutics (TCT) Conference held in San Francisco, October 11–15. TCT is the world's largest educational meeting specializing in interventional cardiovascular medicine. MiStent SES was designed to optimize vessel healing in patients with coronary artery disease, and data presented at TCT demonstrated both sustained and desirable long-term clinical and safety outcomes.

An oral presentation titled "Device and Clinical Program Highlights: Micell" was delivered by Alexandra Lansky, M.D., director of interventional cardiovascular research, Yale University School of Medicine, New Haven, Connecticut. Highlights of the data included no target lesion events in the DESSOLVE I study and sustained clinical outcomes in both DESSOLVE I and II through four years' follow-up. There have been no probable or definite stent thromboses in either study. Importantly, the MiStent SES continues to show a low combined target lesion revascularization (TLR) rate for DESSOLVE I and II of 2.7% at 4 years' follow-up, which is consistent with previously demonstrated lack of late loss progression in the DESSOLVE I study.

Dr. Lansky commented, "A key advantage that appears to be conferred by MiStent SES is sustained local drug delivery beyond the presence of the polymer. That's exciting to me as a clinician because it means MiStent may provide therapeutic sirolimus levels in the tissue around the stent for up to nine months, while limiting the duration of that patient's exposure to polymer. Currently, there is no approved drug-eluting stent that provides full elimination of the polymer by three months without concomitant loss of anti-restenotic drug effects."

Dennis Donohoe, M.D., Micell's chief medical advisor, added, "DESSOLVE data, now reported out to four years' follow-up, has been remarkably consistent in demonstrating that the unique bioabsorbable drug-eluting stent design of MiStent SES provides clinically meaningful results without probable or definite stent thromboses related to its use."

MiStent SES® is designed to optimize healing in patients with coronary artery disease. The rapidly absorbable coating of MiStent SES, which contains crystalline drug (sirolimus) and an absorbable polymer, is intended to precisely and consistently provide for local drug delivery and limit the duration of polymer exposure. These characteristics potentially reduce the safety risks associated with currently commercially available drug-eluting stents.

Using an approved drug (sirolimus) and polymer (PLGA), Micell's patented supercritical fluid technology allows a rigorously controlled drug/polymer coating to be applied to a bare-metal stent. MiStent SES leverages the benefits of a cobalt chromium coronary stent system—a state-of-the-art, thin-strut, bare-metal stent that has demonstrated excellent deliverability, conformability, and flexibility.

The European Union's approval of MiStent SES was supported by clinical data from two studies, DESSOLVE I and II. DESSOLVE II demonstrated superior in-stent late lumen loss rates and an excellent safety profile. In 2015, clinical sites in Europe and China began enrolling patients in DESSOLVE III and DESSOLVE C, respectively. DESSOLVE III is a prospective, randomized, balanced, controlled, single-blind, multi-center study comparing clinical outcomes between MiStent SES and Xience in a "real world, all-comers" patient population. DESSOLVE C is a prospective, randomized, controlled, single-blind, multi-center clinical trial to demonstrate MiStent SES's efficacy and safety. DESSOLVE C, intended to support regulatory approval of MiStent SES in China, is being sponsored by Hefei Life Science Technology Park Investment and Development Co., Ltd., in conjunction with Micell. MiStent SES is not approved by the Food and Drug Administration for sale or use in the United States.

SynAgile Corporation Announces Positive Phase 2a Results for Continuous, Noninvasive, Intraoral Levodopa-Carbidopa Administration to Treat Parkinson's Disease

PRNewswire: October 8, 2015 – WILSON, WY, U.S.A. – SynAgile Corporation (www.SynAgile.com), a privately held pharmaceutical company that develops and commercializes drug delivery systems using its proprietary OraFuse™ intraoral technology platform, today announced positive results from a proof-of-concept, phase 2a, open-label clinical trial of continuous intraoral administration of levodopa-carbidopa (LD/CD).

"We are extremely pleased that the primary and secondary endpoints in our phase 2a trial were met, demonstrating that continuous intraoral delivery of LD/CD provides reduced variability in plasma levodopa concentrations and a significant reduction in motor complications. OFF time was reduced by 43% compared with standard oral LD/CD tablet therapy," said Ephraim Heller, CEO of SynAgile. "SynAgile is developing its DopaFuse™ product as a continuous, noninvasive LD/CD therapy to address the problem of levodopa-induced motor complications, a large, unmet need facing Parkinson's patients today. These results were achieved with a noninvasive therapy that requires no surgery, bulky pumps, or needles. Continuous intraoral LD/CD therapy will appeal to many patients whose motor complications are not adequately controlled with standard oral medications. Furthermore, DopaFuse™ will potentially avoid the side effects and human factor problems associated with deep brain stimulation and Duodopa™ therapy."

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Motor complications include OFF time and dyskinesia associated with chronic levodopa treatment. Motor complications affect most patients with advanced Parkinson's disease and are considered to be one of the most important issues facing Parkinson's disease patients today.

"Motor complications, and specifically OFF time, can have a profoundly negative impact on the lives of Parkinson's disease patients. A safe, convenient, noninvasive, nonsurgical, oral levodopa therapy would be a major advance in treatment," said Prof. Warren Olanow, co-principal investigator of the study, chairman emeritus, Department of Neurology, Mount Sinai School of Medicine, CEO of Clintrex LLC, and a member of the SynAgile Scientific Advisory Board. "The reduction in OFF time was clinically significant, and there were no treatment-related adverse events. The results suggest that continuous intraoral LD/CD administration may provide a safe, noninvasive approach for controlling OFF time," said Prof. Olanow.

The study compared continuous intraoral administration of LD/CD versus standard intermittent LD/CD tablets taken 4–8 times daily in patients with advanced Parkinson's disease. Continuous administration was defined as administration of a dose of LD/CD suspension every 5–10 minutes. Each patient served as his/her own control (described below). For the primary endpoint, statistically significant improvements were observed for variability in plasma levodopa concentration (as determined by linearity) and for reduction in 1-hour and 2-hour fluctuation indexes ($p < 0.001$ for each). OFF time was reduced by 43% ($p < 0.001$), and the UPDRS Part III motor score improved ($p = 0.010$).

The phase 2a trial was an open-label, single-center study of 18 Parkinson's disease patients who experienced ≥2 hours of OFF time per day. Profs. Warren Olanow and Fabrizzio Stocchi served as co-principal investigators. Standard intermittent oral LC/CD tablets were compared with the same total doses of LD/CD suspension delivered into the mouth every 5–10 minutes. The study was conducted at Hospital San Raffaele in Rome, Italy. Patients were admitted to the clinic on day 1 for baseline evaluations. On day 2 (the "control day"), LD/CD was administered as commercially available LD/CD tablets at each patient's pre-baseline dosing regimen. Plasma levels of levodopa as well as ON and OFF time were measured repeatedly over the course of 8 hours. On day 3 (the "PK day"), a suspension of LD/CD was administered intraorally every 5–10 minutes over a period of 8 hours at a dose equal to the total dose of standard oral LD/CD that the patient consumed over the same 8-hour period on the control day, and plasma levels of levodopa were obtained. On day 4 (the "efficacy day"), each patient received his or her first LD/CD morning dose as an oral tablet at the same dosage as the first morning dose on the control day. They then received the balance of the total 8-hour dose that they took on the control day by way of intraoral administration of a suspension of LD/CD every 5–10 minutes over a period of 8 hours. ON and OFF time were assessed as on day 2. Patients were then discharged from the clinic on their standard medication and returned on day 18 for a safety evaluation.

The primary endpoint was defined as the variability of the levodopa concentrations; we compared standard intermittent oral and continuous intraoral administration. Pharmacokinetic endpoints included deviation from linearity and the mean levodopa fluctuation index (Cmax–Cmin)/Caverage). Efficacy was measured by neurologist-based assessment of motor state and dyskinesia at 30-minute intervals over the 8 hours and by UPDRS Part III, assessed at 0, 2, 4, and 8 hours on the control day (day 2) and the efficacy day (day 4).

Safety parameters measured included physical examinations, neurological examinations, ECGs, vital signs, blood and urine laboratory assessments, and oral site assessments by both the neurologist and the patient. Full results of the study will be presented at an upcoming scientific meeting.

SynAgile is developing the OraFuse™ drug delivery platform for the continuous oral delivery of drugs with poor pharmacokinetics. OraFuse™ consists of a miniature, disposable, drug-delivery device carried on a small, tooth-attached retainer that continuously infuses medication into the mouth. SynAgile's first product is DopaFuse™, which uses the OraFuse™ device to infuse a proprietary formulation of LD/CD into the mouth for the treatment of Parkinson's disease. DopaFuse™ is being developed for daily use by Parkinson's disease patients. The LD/CD is swallowed with the patient's saliva and absorbed via the conventional gastrointestinal route. The DopaFuse™ drug formulation has no taste, and the infusion is imperceptible to the patient. The DopaFuse™ system is not visible to others, is comfortable to wear, and does not interfere with speech, swallowing, or drinking. DopaFuse™ is intended to enable patients with Parkinson's disease to achieve more-constant plasma levodopa levels and reduce their motor complications. DopaFuse™ will provide patients with a safe, convenient, noninvasive therapy to reduce motor complications. In contrast to other continuous levodopa delivery systems, DopaFuse™ requires no surgical procedures or needles.

Levodopa is widely recognized as the most efficacious treatment for Parkinson's disease symptoms. However, levodopa is quickly broken down in the body, and its absorption is unpredictable. Even when taken 4–8 times per day, standard oral levodopa tablets often produce widely varying plasma levodopa concentrations over the course of the day. Low plasma levodopa concentrations typically result in OFF time, characterized by tremor, rigidity, slowness of movement, and postural instability. High plasma levodopa concentrations often result in dyskinesia, characterized by involuntary muscle movements. Patients with advanced Parkinson's disease can spend many hours each day in the OFF state or with dyskinesia.

Over one million people in the United States and over seven million people worldwide suffer from Parkinson's disease, a neurodegenerative disorder caused by the diminished production of dopamine, which results in progressive impairment of motor function, including tremors at rest, rigidity, and impaired movement. Even when treated with the current standard of care,

the majority of patients with advanced Parkinson's disease continue to experience motor complications (OFF periods and dyskinesia). These motor complications reduce patients' ability to lead productive, independent lives and are recognized by patients, caregivers, and healthcare professionals as one of the most troubling and debilitating issues associated with the disease.

SynAgile is a biopharmaceutical company focused on developing and commercializing transformative therapeutics using its proprietary OraFuse™ intraoral continuous dosing technology, with an initial focus on treating debilitating motor complications in patients with Parkinson's disease using its DopaFuse™ levodopa-carbidopa therapy. OraFuse and DopaFuse are trademarks of SynAgile Corporation. Duodopa is a trademark of AbbVie Inc.

Perrigo and Flamel Enter Into Exclusive Licensing Agreement for LiquiTime® Extended Release Suspension Technology in the U.S. OTC Market

PRNewswire: October 5, 2015 – DUBLIN, Ireland – Perrigo Company plc (NYSE: PRGO; TASE) and Flamel Technologies (NASDAQ: FLML) announced today that they have entered into an exclusive licensing agreement for LiquiTime® extended release suspension. The technology will be utilized in the development of a portfolio of extended release suspension products intended for the U.S. OTC marketplace.

Michael Anderson, CEO of Flamel, said, "We are very pleased to partner with Perrigo on our LiquiTime® technology and look forward to continued successful development programs and commercial launches with Perrigo."

Perrigo's chairman and CEO Joseph C. Papa stated, "This partnership with Flamel on their innovative LiquiTime® technology demonstrates our continued focus on the 'Base Plus Plus Plus' strategy. This is yet another excellent example of Perrigo's commitment to providing Quality Affordable Healthcare Products® for our customers across the globe."

Impax Receives FDA Approval for Generic Version of Diabeta® (Glyburide) Tablets, USP, 1.25, 2.5, and 5 mg

PRNewswire: October 5, 2015 – HAYWARD, CA, U.S.A. – Impax Laboratories, Inc. (NASDAQ: IPXL) today announced that the U.S. Food and Drug Administration (FDA) has approved its generic version of glyburide tablets 1.25, 2.5, and 5 mg. The company is preparing for commercialization of this product through Impax's generic division.

"We are pleased to receive approval of generic glyburide tablets, a product that was developed at our Middlesex, New Jersey, facility," said Fred Wilkinson, president and chief executive officer of Impax. "Our diversified internal and external R&D network has delivered seven generic product approvals this year. With a pending Abbreviated New Drug Application pipeline of 30 products, we have multiple opportunities to further expand our commercialized portfolio."

According to IMS Health (NSP), U.S. brand and generic sales of glyburide tablets 1.25, 2.5, and 5 mg products were approximately $14 million for the 12 months ending in August 2015.

Genisphere Closes $4 Million for Expansion of 3DNA® Targeted Drug Delivery Platform

PRNewswire: October 1, 2015 – HATFIELD, PA, U.S.A. – Genisphere LLC, provider of the 3DNA® nanotechnology platform, announced it has closed a $4 million equity round. This round of fundraising will extend and expand development of Genisphere's targeted drug delivery platform, with the goal to license the 3DNA® platform to pharmaceutical partners and complete the preclinical work necessary to advance the company's lead drug candidates.

One of the significant investors is Main Line Health's Lankenau Institute for Medical Research (LIMR), a nonprofit biomedical research center committed to investing in promising and innovative research that will advance medical breakthroughs, improve patient care, and contribute to positive outcomes. George Prendergast, LIMR president and CEO, said, "We are looking forward to collaborating with Genisphere to fulfill our mission of translating our promising research into practical application at the bedside."

Previously, Genisphere established several programs and key collaborations to generate preclinical data showing the versatility and efficacy of the 3DNA® platform in targeted delivery of small molecules, biologics, and nucleic acids. Bob Getts, chief science officer at Genisphere, said, "The results from each of our studies support the value of targeting and the versatility of the platform to cross biological barriers, like the blood brain barrier, to deliver therapeutic candidates. Our efficacy data continues to demonstrate that we can impact tumor growth and increase the life span in our treatment groups using a variety of therapeutic candidates, including small drugs and siRNAs." According to Getts, the recent funds will be used to support focused preclinical projects designed to mature one of the company's therapeutic leads with an eye on the clinic and getting first in human data.

Genisphere's newly appointed CEO, Tom Bliss, pointed out while research has shown DNA to be a nontoxic, biocompatible drug delivery material, Genisphere is the only commercial source of DNA-based nanocarriers. He summarized, "The company has built a strong portfolio in the area of drug delivery. We are uniquely positioned to continue to support our pharmaceutical partners and complete the GLP work necessary for an IND filing."

Genisphere LLC is the provider of the 3DNA® platform for targeted drug delivery. 3DNA® is a nanoscale, multivalent scaffold made from proprietary, synthetic DNA formed in a flexible, branched structure. 3DNA® nanocarriers are engineered and

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cross-linked to form a stable architecture while maintaining the biocompatibility of the nucleic-acid building blocks, and demonstrate efficacy and safety with a variety of drug cargos across multiple indications. Genisphere's technology is IP-protected and fully customizable to deliver small molecules, biologics, and nucleic acids with precise specificity enabled by multivalent targeting via antibodies, peptides, and other molecular entities. Genisphere leverages a collaborative model to advance its 3DNA® drug delivery platform, and seeks additional partnerships with biotechnology and pharmaceutical companies to improve efficacy and reduce toxicity. Genisphere is also advancing its own lead compounds based on 3DNA® nanotechnology. For more information, please visit http://genisphere.com.

Tris Pharma Launches Generic Tussionex® as Par's Rights Expire

PRNewswire: October 1, 2015 – MONMOUTH JUNCTION, NJ, U.S.A. – Tris Pharma, a specialty pharmaceutical company that develops innovative drug delivery technologies, announced the launch of Tris-labeled generic Tussionex®, an extended-release suspension containing hydrocodone polistirex and chlorpheniramine polistirex.

Tussionex®, originally approved in the early 1980s, had no generic competition until 2010 when Tris Pharma's generic product entered the market under an exclusive distribution agreement with Par Pharmaceuticals. Under the terms of the distribution agreement, Par had the exclusive right to market Tris Pharma's hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension for a five year period ending September 30, 2015. With the conclusion of the five year term, the rights have reverted back to Tris and as of October 1, 2015, hydrocodone polistirex and chlorpheniramine polistirex ER suspension in 115 and 473 mL bottles (compare to Tussionex®) will be marketed and distributed by Tris Pharma's generic business.

Unlike the original product based on 1970s technology involving organic solvent based coating, Tris's product is based on its patented and highly versatile technology, LiquiXR®, which avoids the use of toxic organic solvents by employing an aqueous based coating system. Tris has pioneered the delivery of taste-neutral, extended release dosage forms such as liquids, ODT/chewable tablets, and film strips that are otherwise traditionally associated with immediate release.

Manufactured at Tris's U.S. Food and Drug Administration (FDA)-inspected, state-of-the-art facility in Monmouth Junction, New Jersey, hydrocodone polistirex and chlorpheniramine polistirex 10 mg/8 mg ER suspension in 115 and 473 mL bottles (compare to Tussionex®) are now available in the United States through wholesalers and distributors, as well as directly to the trade. Hydrocodone polistirex and chlorpheniramine polistirex 10 mg/8 mg ER suspension was approved by the FDA on October 1, 2010. It is distributed in accordance with FDA and U.S. Drug Enforcement Administration (DEA) regulations governing the handling of CII controlled substances.

September

ViaCyte Announces the Publication of a Report on Macroencapsulated Stem Cell-Derived Insulin-Producing Cells and the Issuance of Three Patents

PRNewswire: September 10, 2015 – SAN DIEGO, CA, U.S.A. – ViaCyte, Inc., a privately held regenerative medicine company with the first stem cell-derived islet replacement therapy for the treatment of diabetes in clinical trials, today announced publication of a study demonstrating that insulin-producing cells created *in vitro* from human embryonic stem cells can mature and function after being encapsulated and implanted into an animal model. In addition, the company announced the addition of three patents to its extensive portfolio covering its cell therapy platform.

The article, entitled "Insulin-Producing Endocrine Cells Differentiated *In Vitro* from Human Embryonic Stem Cells Function in Macroencapsulation Devices *In Vivo*," is published in *Stem Cells Translational Medicine* (October 2015 issue; e-published online August 24, 2015). In the June 2015 issue of the same journal, ViaCyte scientists published a review article summarizing the advances in bioprocessing and scale-up that have enabled ViaCyte's VC-01™ product candidate to be the first stem cell–based treatment for type 1 diabetes to enter clinical testing.

The current article describes beta-like cells that have similar properties to the pluripotent stem cell-derived insulin-producing cells reported by other groups, except that ViaCyte produced populations with substantially higher endocrine cell content. The results demonstrated for the first time that nearly pure *in vitro*-produced endocrine cells can function *in vivo*. Populations comprised of up to 98% endocrine cells (and less than 2% pancreatic progenitor cells) exhibited robust glucose-responsive insulin production in a mouse model.

The cells in the study were differentiated further down the beta cell lineage than the PEC-01™ pancreatic progenitor cells being tested in ViaCyte's VC-01 product candidate, which is currently in a phase 1/2 clinical trial for treatment of type 1 diabetes. The animal study also demonstrated for the first time that when encapsulated in a device and implanted into mice, these more mature cells are capable of producing functional pancreatic beta cells. ViaCyte is also the first to show that these further differentiated cells can function *in vivo* following cryopreservation, a valuable process step when contemplating clinical and commercial application.

"The tremendous progress in understanding pancreatic cell differentiation has enabled development of the first clinical-stage therapy with potential to effectively cure type 1 diabetes," said Paul Laikind, Ph.D., president and CEO of ViaCyte. "For a number of reasons we believe that the pancreatic progenitor cells that are the active component of the VC-01 product candidate are better suited for cell replacement therapy. However, the current work has expanded our fundamental knowledge of beta cell maturation and could lead to further advances for the field."

In addition to demonstrating *in vivo* functionality, the time to functional maturation (i.e., glucose-responsive insulin production) following implantation of the more highly differentiated cells was compared with that of pancreatic progenitors. The results showed no appreciable differences between the two cell populations, suggesting that engraftment and acquisition of a robust glucose response, not differentiation from progenitor cell to endocrine cell, are the rate-limiting steps following implantation.

In addition to the research progress, ViaCyte continues to build its large patent portfolio with three more U.S. patents having issued since November 2014. These patents are directed to the following: methods for making and enriching pancreatic endocrine type cells (U.S. patent no. 9,045,736); scale-up technology directed to pluripotent stem cell aggregates in suspension in a roller bottle (U.S. patent no. 8,895,300); and pancreatic endoderm cell cultures with an ERBB receptor tyrosine kinase activating agent (U.S. patent no. 9,109,245). These patents bolster and further protect the company's VC-01 product candidate and its cell therapy platform technology.

ViaCyte's VC-01 product candidate, comprised of human PEC-01 pancreatic progenitor cells macroencapsulated in the Encaptra® drug delivery system, has previously been demonstrated to regulate glucose levels in animal models and is in an ongoing clinical trial designed to evaluate safety and efficacy in type 1 diabetes patients. More information on the phase 1/2 clinical trial, called STEP ONE, for Safety, Tolerability, and Efficacy of VC-01 Combination Product in Type One Diabetes, can be found at www.clinicaltrials.gov.

ViaCyte is a privately held regenerative medicine company focused on developing a novel cell replacement therapy for the treatment of diabetes. ViaCyte is conducting a phase 1/2 clinical trial of the company's lead VC-01 product candidate in patients with type 1 diabetes who have minimal to no insulin-producing beta cell function. ViaCyte's VC-01 combination product candidate is based on the production of pancreatic progenitor cells derived from human pluripotent stem cells. These progenitor cells are implanted in a durable and retrievable encapsulation device. Once implanted and matured, these cells are designed to secrete insulin and other hormones in response to blood glucose levels. The VC-01 product candidate is being developed as a potential long-term diabetes treatment without immune suppression, and without risk of hypoglycemia or other diabetes-related complications.

ViaCyte is headquartered in San Diego, California, with additional operations in Athens, Georgia. The company is funded in part by the California Institute for Regenerative Medicine (CIRM) and JDRF. For more information please visit www.viacyte.com. Connect with ViaCyte here: www.twitter.com/viacyte and www.facebook.com/viacyte.

OncoSec Presents Advancements in Intratumoral Gene Electro-Transfer Devices for Immuno-Oncology

PRNewswire: September 9, 2015 – SAN DIEGO, CA, U.S.A. – OncoSec Medical Incorporated ("OncoSec") (NASDAQ: ONCS), a company developing DNA-based intratumoral cancer immunotherapies, today presented recent advancements in the field of electroporation (EP) and the future of catheter-based devices to perform minimally invasive intratumoral immunotherapy treatment at the First World Congress on Electroporation and Pulsed Electric Fields in Biology, Medicine and Food & Environmental Technologies in Portoroz, Slovenia.

In a keynote presentation entitled "Advances in Clinical Electroporation: Tissue Sensing, Feedback Control, and Catheter Technology," Robert H. Pierce, M.D., chief scientific officer, discussed OncoSec's advances in intratumoral gene electro-transfer, using "smart" tissue-sensing technology and the development of catheter-based electrodes, enabling treatment of deep and visceral tumors.

"We are excited to be presenting our engineering advances at the First World Congress," said Dr. Pierce. "The development of minimally invasive electroporation devices capable of high-efficiency delivery of immunotherapeutic genes into tumors located anywhere in the body is critical to establishing intratumoral EP-mediated gene therapy as a standard therapeutic modality in immuno-oncology."

OncoSec's new catheter-based electrodes are designed to be compatible with standard medical instrumentation, allowing access to deep and visceral tumors, where they are capable of anchoring to and treating the tumor using OncoSec's proprietary technology. These all-in-one devices have the ability to inject a DNA-based agent, while deploying electrodes to perform electroporation in a single procedure. Moreover, these devices have an adjustable needle and electrode penetration depth allowing clinicians to treat tumors of varying dimensions to perform minimally invasive intratumoral immunotherapy.

OncoSec is developing "smart" electroporation technology capable of tissue sensing and real-time feedback control of electroporation pulse trains in order to attain optimal gene transfer and minimal electroporation-mediated tissue damage. Dr. Pierce added: "Taken together, these engineering advances can enable access and high-efficiency gene delivery to tumors throughout the body. This is key as we move forward in developing OncoSec's pipeline of novel intratumoral therapies."

"Our partnership with Rev.1 Engineering and internal bioengineering expertise have allowed OncoSec to enhance our ImmunoPulse™ platform and position the company as a leader in gene electro-transfer technologies in cancer immunotherapy," said Punit Dhillon, president and CEO of OncoSec. "We are also strengthening our intellectual property portfolio in the area

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of gene and drug delivery via electroporation to reach visceral tumors and enhance the uptake of therapeutic agents."

OncoSec secured an exclusive license for a specific patented technology from the University of South Florida Research Foundation (USFRF). The patent provides a device and related methods to deliver molecules to cells that comprise any tissue. The patent includes a catheter-based electrode and methods to deliver molecules to cardiac tissue, blood vessels, other tissues/organs that can be accessed through a luminal tissue, and luminal tissues. The device also functions as a non-catheter based electrode for performing the same functions. Financial terms of this agreement were not disclosed. For more information about OncoSec and its technologies, please visit www.oncosec.com.

OncoSec is a biopharmaceutical company developing DNA-based intratumoral immunotherapies with an investigational technology, ImmunoPulse™, for the treatment of cancer. ImmunoPulse™ is designed to enhance the local delivery and uptake of DNA-based immune-targeting agents, such as IL-12. In phase I and II clinical trials, ImmunoPulse™ IL-12 has demonstrated a favorable safety profile and evidence of anti-tumor activity in the treatment of various skin cancers as well as the potential to initiate a systemic immune response. OncoSec's lead program, ImmunoPulse™ IL-12, is currently in phase II development for several indications, including metastatic melanoma, squamous cell carcinoma of the head and neck (HNSCC), and triple-negative breast cancer (TNBC). In addition to ImmunoPulse™ IL-12, the company is also identifying and developing new immune-targeting agents for use with the ImmunoPulse™ platform. For more information, please visit www.oncosec.com.

Specialty Drug Delivery Firm Integral BioSystems LLC Receives Phase I SBIR Grant to Develop its Novel Ophthalmic Sustained Release Glaucoma Formulation

PRNewswire: September 9, 2015 – BEDFORD, MA, U.S.A. – Integral BioSystems LLC has just received a phase I SBIR research grant for the development of a bio-engineered, preservative free, and biocompatible sustained-release treatment for glaucoma, EySite-NanoM™ (patent pending).

Currently, most ophthalmic drugs are administered in the form of eye-drops. With a single eye-drop, only about 5% of the drug administered is absorbed by ocular tissue, and the rest is lost through naso-lacrimal drainage. Additionally, fast drainage of eye-drop formulations from the ocular space makes frequent administration regimens necessary. This leads to patient incompliance due to inconvenience, leading to a lower therapeutic value of the treatment.

Most commercial formulations for glaucoma treatment contain a commonly used preservative, benzalkonium chloride, which has been correlated with ocular toxicity in both *in vivo* and *in vitro* studies, including corneal neurotoxicity. Chronic use of a preservative has been correlated with inflammation of ocular tissues. Thus, EySite-NanoM™ leads the way to preservative-free strategies for glaucoma treatment in future therapeutic regimens.

EySite-NanoM™ is a sustained-release delivery system designed to provide continuous release of its therapeutic anti-glaucoma agent to avoid the peak and trough drug levels that occur with topical dosing. It can be fairly said that EySite-NanoM™ utilizes a sustained release delivery system for front-of-the-eye ocular delivery with the dosing advantages of punctal plugs and drug-coated contact lenses, without the disadvantages. For example, in addition to manufacturing challenges, drug-eluting contact lenses impact the vision field with inherent alterations in the visual acuity of the lens as the drug depletes, and punctal plugs require installation by a clinician. EySite-NanoM™ does not interfere with a patient's field of vision, nor does it have to be installed by a clinician.

"This delivery system is transformational and has the potential to replace frequent and inefficient eye-drop administration for chronic ocular disorders," says Shikha Barman, Ph.D., chief executive officer of Integral BioSystems.

Integral BioSystems is a specialty drug delivery research organization that offers an integrated, practical approach to formulation development projects for both small molecule and large molecule drug candidates. The company offers contract services to pharmaceutical companies to develop its drug products, through its CMC offerings in analytical method development, formulation development, process development, scale-up, and technology transfer. The company also partners with pharmaceutical companies to co-develop products based on its proprietary ophthalmic delivery systems, OcuSurf™ and EySite™, both of which are patent pending.

Starpharma Signs Drug Delivery License with AstraZeneca

Business Wire: September 7, 2015 – MELBOURNE, Australia – Starpharma (ASX: SPL) (OTCQX: SPHRY) today announced the signing of a licensing agreement with global pharmaceutical company AstraZeneca. The agreement enables the development and commercialisation by AstraZeneca of compounds directed at a defined family of targets using Starpharma's DEP® drug delivery technology. The DEP® platform centres on use of Starpharma's proprietary dendrimers, with the aim of enhancing the dosing and efficacy characteristics of pharmaceuticals.

Under the agreement Starpharma is eligible to receive signature and milestone payments on one or more AstraZeneca DEP® products if they progress through the development pipeline, and milestone and royalty payments on any net sales of the resultant products. AstraZeneca will fund all development and commercialisation costs under the agreement, including ongoing and future collaborative work conducted with Starpharma.

Starpharma's other programs, including the company's wholly owned DEP® docetaxel product, are not negatively impacted by this arrangement.

A signature payment of US$2 million (A$2.9 million) became payable on execution of the agreement. For the initial product,

development and launch milestones could total up to US$64 million (A$91 million), and sales milestones based on specified annual sales levels could total up to US$60 million (A$86 million). The license agreement allows for additional products to be incorporated, with development and regulatory milestone payments of up to US$53.3 million (A$76 million), and potential sales milestones based on specified annual sales levels for qualifying additional products could total up to US$40 million (A$57 million). Any AstraZeneca DEP® products would also attract tiered royalties on net sales.

"Today's agreement with AstraZeneca is an exciting development for Starpharma and its DEP® platform. It follows a successful collaboration in which Starpharma's DEP® drug delivery technology has been applied to an important AstraZeneca oncology candidate," said Dr Jackie Fairley, Starpharma chief executive officer.

"The agreement clearly illustrates both the commercial potential and platform nature of Starpharma's DEP® drug delivery technology. We estimate that each qualifying product successfully commercialised under this agreement could be worth over its life around US$450 million (A$643 million) to Starpharma and, depending on the range of indications and degree of commercial success in the market, potentially significantly more," Dr Fairley added.

"The fact that this deal is structured for multiple products underlines the real potential for additional upside for both companies. It is worth noting that Starpharma retains all rights outside of a well-defined and narrow area of application, meaning that its platform remains unencumbered and available for licensing in the vast majority of oncology and other applications for future deals with other partners."

Susan Galbraith, head of the Oncology Innovative Medicines Unit at AstraZeneca, said: "We already have a long-standing and successful working relationship with Starpharma. This license agreement will enable us to further harness the DEP® technology and evaluate its potential across novel molecules within our oncology portfolio."

Cancer is a leading cause of death worldwide, accounting for 8.2 million deaths in 2012. The number of new cases is expected to rise by about 70% over the next two decades. The global market for cancer drugs has reached US$100 billion in annual sales, and could reach US$147 billion by 2018, according to a new report by the IMS Institute for Healthcare Informatics, a unit of drug data provider, IMS Health.

Starpharma's DEP® technology is used to improve the performance of pharmaceuticals. Both preclinical and early clinical data have shown DEP® versions of drugs to be superior in a variety of ways to the unmodified drugs in currently marketed formulations. Preclinical studies of DEP® conjugates with a number of different cancer drugs have already established improved efficacy and reduced toxicities compared with marketed versions.

Starpharma's lead internal development candidate, DEP® docetaxel, continues to demonstrate excellent tolerability and improved pharmacokinetics in the clinic compared with the available data for its reference drug, Taxotere®. Starpharma's licensing agreement with AstraZeneca focuses on novel compounds, and not on unmodified drugs in currently marketed formulations.

Cipla to Acquire 100% of Generic Businesses in the United States for $550M

PRNewswire: September 3, 2015 – MUMBAI, India – Cipla, a global pharmaceutical company that uses technology and innovation to meet the everyday needs of all patients, today announced that its U.K. arm, Cipla EU, has entered into definitive agreements to acquire two U.S.-based companies, InvaGen Pharmaceuticals Inc., and Exelan Pharmaceuticals Inc. The transaction being subject to certain closing conditions, is valued at $550 million and will be an all cash transaction. The combined revenue from these transactions is over $200 million for the year ended December 2014 and over $225 million in LTM June 2015. This acquisition, which is the second landmark acquisition in Cipla's 80 years of history, will give the company scale in the U.S. generics market through a wide ranging product portfolio in CNS, CVS, anti-infectives, diabetes, as well as other value-added generics. InvaGen offers a large capacity manufacturing base in Hauppauge, New York, and a skilled U.S.-based R&D organization, Cipla's first such presence in the United States.

The acquisition of InvaGen pharmaceuticals also provides Cipla with about 40 approved ANDAs, 32 marketed products, and 30 pipeline products that are expected to be approved over the next four years. They represent a balanced, diversified, and growing portfolio targeting highly attractive, large, and niche markets. In addition, InvaGen has filed five first-to-file products that represent a market size of ~$8 billion in revenue by 2018. Dosage forms include immediate release, modified release, and extended release tablets and capsules. With a manufacturing footprint of ~350,000 square feet of GMP area, InvaGen has three units located in Long Island, New York, with a total production capacity of 12 billion tablets and capsules per annum and about 500 employees. This acquisition further provides Cipla with an access to large wholesalers and retailers in the United States.

The acquisition of Exelan Pharmaceuticals provides Cipla access to the government and institutional market in the United States through Exelan's deep expertise, engagement, and experienced management team in the business.

Commenting on the acquisition, Mr. Subhanu Saxena, M.D., global CEO of Cipla Limited, said: "This investment is in line with Cipla's strategy to grow Cipla's share in the U.S. pharmaceutical market. We see InvaGen as a strong strategic fit with a relevant diverse portfolio as well as a strong market and customer presence. With a local manufacturing facility, Cipla can further strengthen its presence and commitment to serve patients in the country."

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Tim Crew, CEO North America and director of Cipla USA Inc., added: "We are delighted with the immediate and substantial relevance this combination brings to Cipla in the United States. We are committed to an orderly transition process with customers and InvaGen to ensure the ongoing continuity of a high quality and reliable supply to our customers and their patients."

Dr. Sudhakar Vidiyala, president and CEO, InvaGen Pharmaceuticals Inc., commented: "This is an exciting o pportunity for InvaGen to join with Cipla. InvaGen brings an experienced team and good manufacturing capabilities to the partnership. We are confident that the combination of InvaGen and Cipla will significantly enhance the product portfolio offering, including specialty products, to the U.S. patients and will give InvaGen access to Cipla's global expertise and presence."

Cipla is a global pharmaceutical company that uses cutting-edge technology and innovation to meet the everyday needs of all patients. For around 80 years, Cipla has emerged as one of the most respected pharmaceutical names in India as well as across more than 150 countries. Our portfolio includes over 1,500 products across wide range of therapeutic categories with one quality standard globally.

While delivering a long-term sustainable business, Cipla recognises its duty to provide affordable medicines. Cipla's emphasis on access for patients was recognised globally for the pioneering role played in HIV/AIDS treatment as the first pharmaceutical company to provide a triple combination antiretroviral (ARV) in Africa at less than a dollar a day and thereby treating many millions of patients since 2001. Cipla's research and development focuses on developing innovative products and drug delivery systems.

Through a comprehensive partnership model, Cipla has been dedicated to providing access to medicines at an affordable price for over 30 years in the United States.

Cipla USA own label was launched in January 2015. Cipla has executed over 20 U.S. partnerships and currently has over 40 commercialized products in the United States. The company has supported the development of more than 150 ANDAs and has received 75+ final approvals in addition to two NDAs approved and marketed in the United States.

Cipla USA brings a variety of technologies to the U.S. markets in order to keep its ongoing commitment to provide access to high quality complex products at affordable prices. For more information on Cipla, please visit www.cipla.com and www.ciplausa.com. ■

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