CONTROLLED RELEASE SOCIETY
Volume 20 • Number 1 • 2003

NEWSLETTER

www.controlledrelease.org

From the President

Call For Papers

Member Release

Thanks to members of the Publications Newsletter Subcommittee for helping with this issue: Martyn Davies, Agis Kydonieus, Harlan Hall, and Mike Rathbone.

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

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CONTROLLED RELEASE SOCIETY
NEWSLETTER

Volume 19 • Number 3 • 2002

inthisissue

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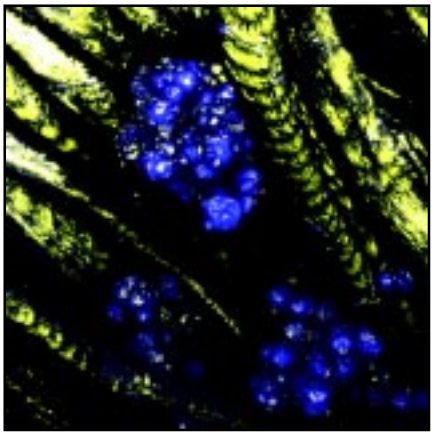

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Dedicated to the science and technology of controlled release and delivery and promoting education by releasing science to deliver a better future.

From the *Editors*

By Ijeoma Uchegbu & Bozena Michniak

Welcome to 2003. The start of the year is traditionally a time for broken New Year's resolutions and of course CRS Annual Meeting abstract deadlines. Have you done yours yet? 2003 is an especially important year for the Controlled Release Society as this year sees us celebrating our 30th birthday. Thirty years of sustained growth and interesting science and 30 successful Annual Meetings! Has it really been that long? With your support the next 30 years promise to be even better.

Over the past months we have been working hard to bring you a Newsletter packed with interesting articles. The aim of the CRS is to promote the science of controlled release and as such, your Newsletter will regularly present scientific issues, dissected and in an accessible format, such as the article on Inhalation Gene Therapy on page 11. The issues surrounding these therapeutics are highlighted by Cardiff University's James Birchall in this piece. Undoubtedly the best thing that can happen to your science is the exploitation for the benefit of end users, be they animal, vegetable or human. Nanomed Pharmaceuticals tells us how they have exploited recent technological advances in the Spotlight article on page 8. Have you ever wondered what happens to your prize winners after the glittering award ceremonies? Where do they go once the applause is over? A past CRS Young Investigator Award winner tells of his next move on page 21. Our veterinary section is pressing the case for animal health and the article on page 19 discusses the importance of dissolution testing to veterinary dosage forms. Our Consumer and Diversified Products arm regularly contributes to the Newsletter. Turn to page 15 for their latest offering. Your esteemed President gives a personal message for the first time and so those of you who do not know him have an opportunity to get to know Sandy Florence on page 5.

As this is your Newsletter, your editorial team value not just your readership but also your feedback. Have we got the balance right between hard science and the softer things that make our lives as scientists interesting? Are you happy with the format and layout? In summary are you pleased with your Newsletter and if not, do you have ideas which could improve your read? Drop us a line at newsletter@controlledrelease.org, but more importantly have a really wonderful New Year. We hope that the holiday gave you a chance to recharge your batteries and refresh your mind.•

JCR Highlights

By David Friend

There is a wide range of papers scheduled for publication in the upcoming issues of the *Journal of Controlled Release*. For example, the use of nanoencapsulation of furosemide microcrystals for controlled release will be published. Lvov and coworkers describe a nanoencapsulation process using charged linear polyions and gelatin to sequentially build up layers (and thus control thickness) on the drug microcrystals. Thus, wall thickness ranging from 45 to 115 nm were created. The coatings reduced release rates of furosemide 50 to 300 times compared with unencapsulated drugs.

A common goal during development of many drug delivery systems is the ability to establish a correlation between *in vitro* drug release and *in vivo* performance. Shabbits, Chiu, and Mayer have developed such a correlation for predicting the *in vivo* drug retention characteristics of liposome-based delivery systems. The *in vitro* assay relies on use of an excess of donor multilamellar vesicles containing sucrose. These vesicles act as acceptors for drugs encapsulated in unilamellar vesicles.

A series of papers focusing on veterinary applications of controlled release is scheduled for publication shortly. Most readers will find the topics unfamiliar and hopefully interesting and informative. With some certainty, the typical reader of the journal will find the article on a boar semen controlled delivery system by Torre and coworkers unusual and unique. •

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(continued on next page)

Value at your Fingertips

By Jaymie Griffin
Assistant Executive Director & Managing Editor

In this world of easy accessibility, scientists and educators know how important it is to have educational information available at their fingertips. With one click of a mouse, you can access personal web pages, news, educational information, shopping and much more. With the new Membership Directory and Peer-to-Peer Network™, the Controlled Release Society has made it easy to ask the hard questions, find the people that have the answers and access the latest news on controlled release and delivery.

The Membership Directory allows the member to update their information with a few clicks. The directory provides detailed profile information and a description of the individual's scientific discipline or focus. One of the many benefits of the Membership Directory is its ability to serve as a tool for Session Chairs who are choosing reviewers for sessions. The Membership Directory is synchronized weekly with the Controlled Release Society membership database, giving visitors the most current information available.

Another popular online tool for CRS members and non-members is the Peer-to-Peer Network™. This network connects the world to the Controlled Release Society members. If you need a format to expand your knowledge by sharing ideas and information with others in your area of expertise or seek the counsel of colleagues and mentors in matters of education or career choices, then you need to visit the Peer-to-Peer Network™. Perhaps you are looking for that one piece of valuable information that will further research or advance science. Come see what advances the Controlled Release Society has made in furthering education and the value of membership. Visit www.controlledrelease.org and experience the benefits the Controlled Release Society has to offer! •

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From the President

By Alexander Florence

As I write this I am more than ever conscious of the short time any President has with his or her hand on the gavel, and therefore how reliant we are on the efforts of past Presidents, in my case Richard Guy and Kinam Park. Working with them and the Board as Vice President and President Elect one absorbs the spirit of the team, and the strong commitment to the development of the Society. One issue to consider is what makes the CRS distinctive? How are we distinguished from, say, AAPS? We continually ask what will make the Society more attractive? Why should scientists and technologists join and, more importantly, renew their subscriptions?

We have been looking hard at how to improve the usefulness of the CRS. The *Journal of Controlled Release* is an extremely good journal. Members get a great bargain in receiving this on their desks at such an advantageous cost. The *Newsletter* is becoming a more effective communication tool and I know the editors are working hard at this, all of course in their spare time. We know that we need to make the Web Site a better resource. Ideas such as the Peer-to-Peer Network™ have worked and more developments are in the pipeline. What would you like to see or have access to?

I am conscious that we are a mixed scientific community. This is a strength that should be built on. We can break down disciplinary barriers that can and do exist. The science of controlled release that we share, whether we work in the field of pharmaceuticals, cosmetics, cosmeceuticals, foodstuffs, or other "consumer" products is the same. The emphasis may be different, but the Society has a role to play in bringing us together. We need to interact more, rather than inventing and reinventing our own disciplinary wheels. Many technologies which may not be viable in one field may well have applications in another. Professor Helmut Ringsdorf used lectures to show a cartoon with individual figures looking up at the sky from their separate cubicles and he would challenge his audience with "when do we look outside *our* boxes?". In my own field, working as I do with surfactants, dendrimers and vesicles I am impressed by the interest of physicists in these topics. The *European Journal of Physics Science E* is, for example, devoted entirely to research on "soft matter", the stuff of many delivery systems. This is at one end of the spectrum. How many physicists know about us? At the other end how many clinicians or veterinarians are members of the Society?

A membership drive is essential if we are to grow, not just in size but to increase the diversity of our membership. Gargantuan meetings have never excited me, only confused me as I battle my way to find even my own posters. I get distracted trying to navigate my way through multiple parallel sessions and the crowds.

Successful Annual Meetings, however, are essential not only as the showcase of our scientific effort each year, but to allow the Society to survive, for it cannot do so on subscriptions alone. Last year the CRS with an income of over US$2 million, did not break even, following our scientifically successful but less well attended meeting in Seoul. It was part of the commitment of the CRS to take its science and meetings throughout the world. This is one of our distinguishing features. But the Board with one eye on science and technology has to have the other on finances.

CRS President Alexander Florence visits CRS' booth at the AAPS Meeting

I make a personal plea for you all to attend the Glasgow 2003 meeting; I went to school there and then to University, did my PhD there, leaving only in 1989 to "emigrate" to England. My former college was renowned as a place of "useful learning" - what better motto for the CRS? Glasgow is within easy access of beautiful countryside, the Trossachs, many lochs and castles, golf courses, distilleries. Scotland has its own educational system, and even in the 18th Century had four Universities, Glasgow (founded 1451, Edinburgh, Aberdeen and St Andrew's) to England's two (Oxford and Cambridge). Glasgow alone now has three universities. The 'Scottish Enlightenment' of the 18th century produced writers, scientists, engineers and scholars who had a great influence the world over. Go to Glasgow and visit Edinburgh, only 45 miles away, to absorb some of that history and maybe a little "water of life" (whiskey).

The programme for the Glasgow meeting is an excellent one, carefully constructed by Clive Wilson. It has several new features, debates on controversial issues such as gene therapeutics, and putting into practice our educational aims with interesting workshops and a session for senior schoolchildren. The science we do is not only exciting, but of benefit to society. In many countries of the developed world children are opting out of science; we have to convince them that it is all worthwhile. We know it is. In Glasgow we will reach only the local youth, so I hope that we will be able to encourage enough members in time to prepare material at different levels for school, colleges and university students. Already some members may have suitable material or are willing to contribute. Perhaps you can let us know if you are willing to assist in fulfilling this vital educational role.

We would make no progress at all without the dedication of individuals on the Board such as our Treasurer Susan Cady, Scientific Secretary Martyn Davies, the President-Elect Jim Anderson and our new Vice President Jenny Dressman, along with members at large, and those who have volunteered to work with Executive Director Mark Ricker and his colleagues at ARDEL. The Board of Scientific Advisors is being convened to assist in the development of our Strategic Plan, but ultimately you must tell us what you want, and we will do our best to ensure that the CRS develops as science grows and changes. •

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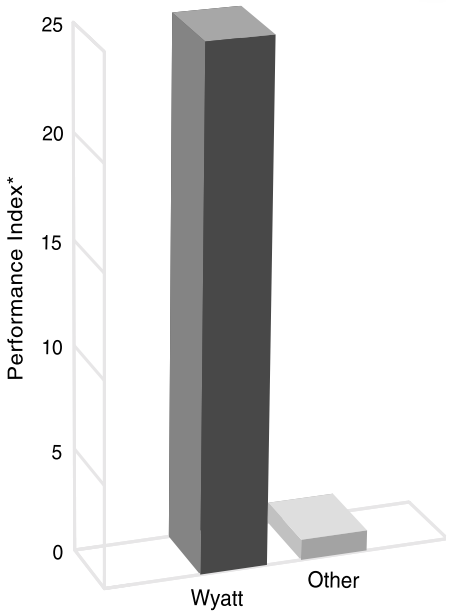

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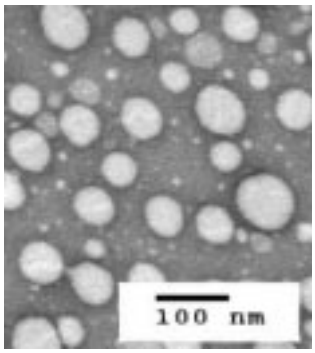
SPOTLIGHT:
NanoMed Pharmaceuticals

By Stephen Benoit

With the rush to add "nano" as a prefix to company names and technology descriptions, and venture capitalists and private equity investors using their Blackberries® to check email at "Investing in Nano" conferences from New York City to San Diego, one cannot be faulted for suggesting that the current hype surrounding nanotechnology is reminiscent of a time not so long ago when "dot com" was every company's corporate suffix. To be sure, much of the nano-hype is just that; hype. However, the application of nanotechnology in drug delivery is also very real and this reality is taking shape today.



Nanoparticles containing gadolinium that are <100 nm, stable in blood, and are comprised of as high as 50% pure gadolinium.

In this issue, we spotlight NanoMed Pharmaceuticals; an early-stage start-up company, developing novel nanoparticle-based advanced drug delivery systems.

Size matters, in drug delivery. Smaller is better, in targeting biotech therapeutics to specific cells and tissues. Size matters. Smaller is better. This was the thinking of NanoMed's scientific co-founders, Russell J. Mumper, Ph.D., and Michael Jay, Ph.D., faculty members at the University of Kentucky, College of Pharmacy, and the Assistant Director and Director, respectively, of the University's Center for Pharmaceutical Science and Technology. In 1999, Drs. Mumper and Jay set out to develop a novel nanoparticle manufacturing technology that would avoid the problems associated with polymeric nanoparticles and liposomes, and instead, combine the unique advantages of these systems with the advantages of microemulsions to engineer nanoparticles that could be targeted to specific tissues and cells. The overriding development criteria were that any new manufacturing technology had to be inexpensive, reproducible, and scalable.


Scientific Founders of NanoMed Pharmaceuticals, Inc. Dr. Russell Mumper (left) and Dr. Michael Jay (right) are currently faculty members in the College of Pharmacy at the University of Kentucky in Lexington, Kentucky. Dr. Mumper and Dr. Jay are inventors of Nanotemplate Engineering.

Dr. Mumper's and Dr. Jay's work resulted in the development of *Nanotemplate Engineering*, a platform manufacturing technology which enables the production – in minutes – of well-defined, uniform, solid nanoparticles less than 100 nanometers in diameter. These nanoparticles are made using all pharmaceutically-acceptable excipients and can be engineered to contain or carry small molecules, peptides, proteins, plasmid DNA, diagnostic agents, and radio- and bio-sensors.

The ability to rapidly and consistently produce sub-100 nanometer particles is a significant process development milestone since below 100 nanometers, materials exhibit different, more desirable physical, chemically, and biological properties. These enhanced properties are important, if not essential, when trying to create so-called next generation vaccines that stimulate both humoral and cellular immune responses, or formulating drugs that can be delivered systemically and subsequently targeted to the brain.

In 2000, NanoMed Pharmaceuticals, Inc., was formed. In 2001, the Company obtained from the University of Kentucky Research Foundation the exclusive, worldwide rights to the *Nanotemplate Engineering* technology invented by Drs. Mumper and Jay. Today, NanoMed is using this novel platform technology to develop nanoparticle-based drug delivery solutions for pharmaceutical and biotechnology partners to deliver drugs to the brain, and create the next generation of vaccines. NanoMed's development programs focus on therapeutics that will stop the progressively debilitating effects and ultimate outcome of neurodegenerative conditions like Alzheimer's and Parkinson's disease, stroke, and brain tumors; and prophylactic vaccines that will provide immunity against infectious diseases like HIV and hepatitis C.

More than 50 million people worldwide are infected with HIV and hepatitis. More than 10 million people worldwide are suffering from the progressively debilitating effects of Alzheimer's and Parkinson's disease, stroke, and brain cancer (collectively, neurodegenerative diseases). Unfortunately, the prognosis for these individuals is poor.

To delay the progression or stop the ultimate outcome of Alzheimer's, Parkinson's, stroke or brain cancer, a drug needs to be able to cross the blood-brain barrier (BBB) and get to the right part of the brain or brain tumor. 95% of today's therapeutics

(continued on next page)

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cannot cross the BBB and must be delivered via direct injection into the brain or cerebrospinal fluid, or utilize approaches that involve temporarily 'opening' the BBB, or be released from a device that has been implanted into the brain.

To provide immunity to HIV, a therapeutic (protein antigen) needs to get into the immune cells that stimulate – both – the production of protective antibodies and so-called killer T cells that seek out and destroy the virus. Today, no such vaccine exists.

NanoMed's founders are committed to improving the outlook for people with Alzheimer's disease or HIV by solving the needs of pharmaceutical and biotechnology companies seeking to deliver drugs to the brain or create the next generation of vaccines. In working with such companies, NanoMed has learned that alternative nanoparticle carriers do not appear to be able to be routinely or easily manufactured in a size range that is well-suited for cell- and tissue-specific targeting. Moreover, these alternative systems appear to employ processes that are intrinsically more complex, slower, less flexible, and potentially damaging to the therapeutics they intend to deliver.

In contrast, *Nanotemplate Engineering* has been shown to consistently produce nanoparticles that can: be coated with plasmid DNA or protein antigens; entrap plasmid DNA or model proteins; contain up to 33%-80% w/w low Mw drug with entrapment efficiencies of 80% to 100%; increase drug solubility up to 10,000-fold; are stable in biological fluids at 37°C; can be sterile-filtered and lyophilized; and can be formulated with various types of adjuvants, endosomolytic agents, and ligands (which are critical for cell- and tissue-specific targeting).

More significantly, NanoMed has generated extensive peer-reviewed data demonstrating: *in-vitro* receptor-mediated tumor cell uptake of folate-targeted gadolinium-entrapped nanoparticles in human KB cells (nasopharyngeal epidermal carcinoma); *in-vitro* receptor-mediated cell uptake and transfection of human dendritic cells with plasmid DNA nanoparticles; *in-vivo* (genetic) vaccine studies in mice showing significant enhancements of humoral, Th1-type, and proliferative immune responses with dendritic cell-targeted nanoparticles; and *in-situ* BBB transport of nanoparticles and absence of nanoparticle toxicity at BBB with uptake comparable to existing CNS therapeutics.

NanoMed's founders' labs are located at the University of Kentucky's Center for Pharmaceutical Science & Technology ("CPST") and Advanced Science & Technology Commercialization Center ("ASTeCC"). The CPST is a fully integrated analytical and formulation development and FDA-registered pharmaceutical clinical manufacturing facility utilizing current Good Manufacturing Practices (cGMP). The facility employs 24 trained professionals and occupies approximately 3,700 square feet. ASTeCC is the University of Kentucky's incubator for multidisciplinary collaborations and start-up ventures. This $17 million, 80,000-square-foot facility is located in the heart of the University of Kentucky campus.

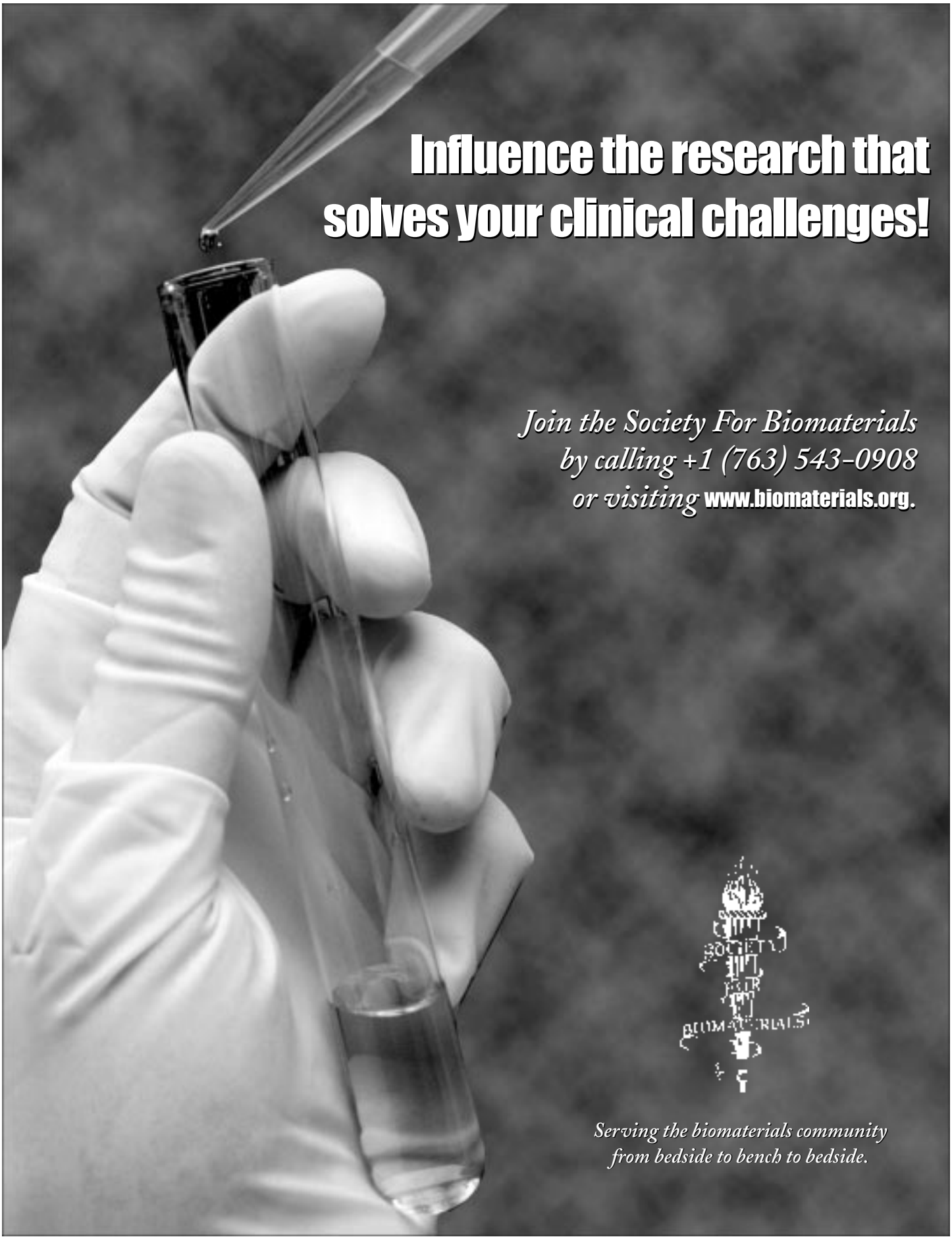
Collectively, NanoMed's management team represents a unique balance of commercial and academic experience; large and small company experience; start-up and operating general management experience; and broad expertise in developing advanced drug delivery systems. Most importantly, each member of the team has a strong background in product development.

In addition to a strong management nucleus, NanoMed has attracted a group of scientific advisors that augments the Company's strengths in developing advanced drug delivery systems with expertise in the physiology and function of the blood-brain barrier with primary focus on drug delivery to the central nervous system, polymers for supplementing or stimulating the immune system, cell interactions with polymers, and global experience in all phases of clinical development, including supervision of more than three hundred clinical trials across numerous therapeutic areas and drug classes.

Dr. Michael Jay (left) and Dr. Russell Mumper (right) are testing the viscosity of a nanotemplate suspension used to engineer nanoparticles that are being developed by NanoMed as a potential new vaccine for AIDS.

NanoMed is following a growth strategy proven successful by today's leaders in the drug delivery industry. The Company will enter into strategic alliances with pharmaceutical and biotechnology company partners and is now performing seven feasibility studies involving nanoparticle-based drug delivery solutions that capitalize on NanoMed's competitive strengths in brain delivery and vaccine development. As NanoMed grows, it will seek opportunities to use its proprietary drug delivery systems to develop and independently market its own drugs. Consistent with this longer-term phase of its growth strategy, NanoMed has initiated the development of proprietary products for neurodegenerative diseases and a next generation HIV-1 vaccine.

Size matters. Smaller is better. The application of nanotechnology in drug delivery is happening today, and is manifested in NanoMed Pharmaceuticals nanoparticle-based advanced drug delivery system. The successful utilization of this system by NanoMed and its pharmaceutical and biotechnology partners will mean a brighter outlook for persons suffering from many neurodegenerative and infectious diseases. •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SCIENTIFICALLY SPEAKING
Inhalation Gene Therapy

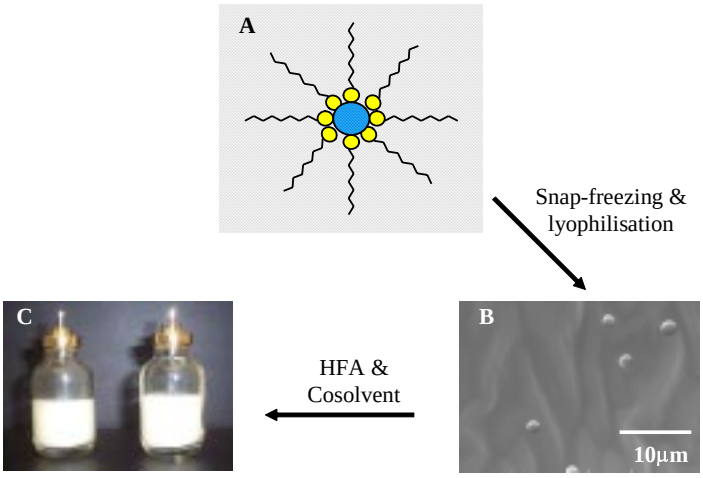
By Dr James Birchall
Lecturer in Drug Delivery, Welsh School of Pharmacy, Cardiff University

The ability to deliver appreciable quantities of functional plasmid DNA (pDNA) to the lower respiratory tract may provide for the treatment of a number of acquired and inherited genetic defects with respiratory manifestations. At present, the most notable disease targets for pulmonary gene therapy include genetic disorders arising from a single genetic defect, *e.g.* cystic fibrosis, and neoplastic disease. Further, as the understanding of the genetics, immunology and pathophysiology of diseases becomes more advanced, the gene-based treatment of additional pulmonary disorders, *e.g.* asthma, may become a distinct possibility.

Aerosolisation of gene vectors is required to present the genetic therapy locally to the appropriate region of the lower respiratory tract. To date, nebulisation has provided the most practical system for the aerosolisation of synthetic non-viral gene vectors. Although non-viral gene vectors are capable of mediating gene transfer both *in vitro* and *in vivo* following jet nebulisation, the delivery efficiency of conventional nebuliser systems is greatly reduced due to the restrictions of the device and the physico-chemical characteristics of the particles at elevated concentrations in the nebuliser reservoir[1]. In addition, due to the limited aqueous stability of many non-viral vectors, administration of gene vectors via nebulisation is required immediately following preparation making it impossible to ensure the preparation of non-viral vectors with reproducible physical and biological characteristics. Pressurised metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs) may provide more viable alternatives for delivering therapeutically active macromolecules, particularly genes, to the lung.

The pMDI has substantial advantages in portability and robustness over other devices. Currently most pMDIs are formulated as suspensions in the propellant. This invariably leads to central lung and oro-pharyngeal deposition as the drug particle size cannot be reduced sufficiently. A novel, patented technology for producing drug nanoparticles for dispersion in hydrofluoroalkane (HFA) propellant[2] is currently being developed for pulmonary gene therapy. Initially, pDNA is loaded into the aqueous pool of the reverse micelles that form when a water-in-oil microemulsion is formed between water, organic solvent and surfactant (Figure 1A). Following removal of the water and organic solvent, the dimensions of the surfactant-coated particles (Figure 1B) and their ability to disperse in HFA propellants allows for the production of stable medicinal aerosols (Figure 1C) capable of deep pulmonary delivery by pMDI. Further studies are required to develop the surfactant system employed to provide for HFA dispersibility in the absence of co-solvent and to enhance cellular delivery of the pDNA.

Figure 1. *Production of surfactant-coated pDNA particles for dispersion in HFA. A – Water-in-oil reverse micelle; B – Scanning electron micrograph (SEM) of dried surfactant-coated pDNA particles; C – Homogenous dispersions of pDNA particles in HFA propellant.*



Dry powder dispersion devices, which do not rely on propellant aerosol technology, are also promising for delivering medicaments that may be readily formulated as dried particles. Freeze-drying is currently the method of choice for preparing dry powder dispersions of macromolecules for delivery to the lung. The structure of freeze-dried powders (Figure 2A) is such that their pulmonary deposition is insufficient without potentially deleterious further processing. Spray-drying, a one-step process that produces small (<5m), spherical and potentially respirable dried particles (Figure 1B), has not been extensively investigated for formulating non-viral pulmonary gene delivery vectors due to concerns of causing physical damage to the enclosed DNA. Recent studies, however, demonstrate that lipid:polycation:DNA (LPD) non-viral gene vectors, retain their structural integrity following freeze-drying *and* spray-drying in the presence of a suitable protecting excipient[3]. The functionality, i.e. *in vitro* gene expression efficiency, of spray-dried powders following prolonged storage at room temperature has been shown to be at least comparable to that of freshly prepared aqueous systems (Figure 2C). Current research is focussed on decreasing the aggregation and increasing the respirable fraction of the spray-dried particles whilst retaining the stability and functionality of the delivered gene.

*(**Scientifically** continued on page 17)*

Call For Papers!

30th Annual Meeting & Exposition
of the
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July 19-23, 2003
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Abstract Submission Deadline
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www.controlledrelease.org/meeting/glasgow/index.htm

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EURAND Award 2003

For Outstanding Research in Oral Drug Delivery

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May 16, 2003

Winning Submissions To Be Honored And Presented At:
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Selection Criteria for Grand Prize, Second Prize and Honorable Mention
All submissions should be original, non-published work detailing innovative research and must be in the field of oral drug delivery. Research cannot be previously published or presented but may contain references to previously published or presented work. Submissions will be judged on the following:

- *Innovation*
- *Potential commercial application*
- *Quality of research and technical content*
- *Potential impact on the drug delivery industry*
- *Potential to solve an industry-wide drug delivery challenge(s)*

Selection Criteria for Career Achievements in Oral Drug Delivery
An award will also be presented to an industry thought leader that has demonstrated innovation in the field of oral drug delivery throughout their career. Nominations are encouraged and will be broadly accepted. The Eurand Award Evaluation Board will judge nominees on the following:

- *Quality and quantity of research over the duration of their career*
- *Research resulting in innovative and applicable drug delivery technologies*
- *Applicable patents*
- *Entrepreneurial activities related to drug delivery*
- *Broadly recognized by their peers*
- *Editorial contributions to industry publications*
- *Participation on applicable boards and in industry associations*

Selection Process
The Eurand Award Committee will review all submissions and select all of the award winners. The decision of the board will be final. The selection committee will also be responsible for selecting the recipient of the career achievement award. All award recipients must be available to attend the Controlled Release Society's 30th Annual Meeting & Exposition in Glasgow, Scotland to present their winning submissions during the Eurand Award Special Session. If the selected winners are unable to attend, prizes may be forfeited and another winning submission may be selected.

Awards and Presentations
Winning researchers will receive the following:

- *Career Achievement Award: $5,000*
- *Grand Prize: $5,000*
- *Second Place Prize: $3,000*
- *Honorable Mention: $1,700*

All winners will also receive:

- *Waived registration to the 2003 CRS conference*
- *Roundtrip transportation to the conference (coach class)*
- *Two nights lodging in Glasgow*
- *A ticket to attend the CRS banquet*
- *Winners names will be published in 1-2 industry publications*
- *Winners will have an opportunity to present research opportunities to Eurand and potentially gain additional research grants*

For more information, please contact Courtney Walker at cwalker@eurand.com or call +1 212-389-5775 (United States) or visit the Eurand Award Web Site at www.eurandaward.com

CONSUMER & DIVERSIFIED PRODUCTS

PERFORMING SCALE-UP AND SCALE-DOWN OF CONTROLLED RELEASE PROCESSES IN AN ENVIRONMENT OF TIME AND COST CONSTRAINTS

By Irwin C. Jacobs

Introduction. The scale-up of controlled release processes involves a fundamental understanding of a number of physical phenomena as well as the practical and theoretical limits of the process equipment. Also, scale-up of controlled release processes should necessitate a wide-ranging analysis of many variables as well as a strong sense of the process chemistry and the performance goals for a product. Traditionally, considerable attention has been given to process scale-up. Recently, there has been a trend to attempt to scale-down traditional laboratory-sized controlled release processes for the formulation development of very high value ingredients. This might be termed micro-scale requirements where only 0.2 gram to 10 gram quantities might be available when 50 to 500 grams of materials would be traditionally handled in the same processes. One further complication in strategies for scaling of controlled release processing is the need to reduce costs or research time while maintaining scientific integrity. In this era of cost cutting strategies, the normal experimental design may not be possible, so further consideration should be given to reduce the number of experiments or intermediate scaling steps.

Definitions and Controlled Release Processes. Scale-up can be defined as the attempt to accomplish a production rate larger than previously attempted for a given formulation and process. In some controlled release methods, this might be moving from a laboratory scale of approximately 10 grams up to 1 kg to an intermediate scale of tens to hundreds of kilograms per batch. A production scale would then be moving from this intermediate or pilot scale to perhaps several metric tons per batch. Scaling multiples of approximately five to ten-fold should be used although appropriate equipment availability may have an impact on this value. A look at moving down in process scale might be taking a traditional laboratory scale of 25 grams to a few hundred grams down to fractions of a gram.

Controlled release processes as practiced in our laboratory has generally consisted of spray drying, fluid bed coating, spinning disk coating (a modification of rotary atomization), interfacial polymerization, solvent evaporation processes, some unusual atomization methods, and a unique granulation/coating process. Each of these processes has its own normal range of throughput for laboratory, pilot, and commercial scales. Each controlled release process has its unique requirements in considering scaling to pilot or production quantities. Understanding how process fundamentals change with each change of commercial equipment size cannot be overemphasized for smooth ramping up of production throughput. Scale-up trials can involve production quantities of several grams per batch to hundreds of kilograms per hour.

Physical Phenomena and Troublesome Assumptions
A strong understanding of the various phenomena in controlled release processes should be in place before attempting scaling. These include emulsification, dissolution, agitation or suspension, atomization, crystallization, chemical reaction, drying, heating, cooling, and fluidization. Each of these phenomena has its own set of variables that can enter the scale-up design and this is often where incomplete understanding of these important variables and the physics of the process steps can cause one to make incorrect assumptions. The assumptions for scaling these phenomena might include geometric similarities of the two scales, dynamic similarity of the two scales, and knowledge of the practical and theoretical limits of the types of equipment used for each scale. There may be several process phenomena occurring simultaneously which can produce complex process interactions. An understanding of fluid motion and entrained particle motion has led to the solving of numerous problems in the scale-up and scale-down of a number of products. Lack of good mathematical models for many of these steps used in controlled release processes can lead one to rely on hard-won but sometimes unreliable experience and intuition rather than firm theoretical grounding for decisions in scale-up. It has often become painfully clear that operating personnel in the pilot lab or production facility may use a different knowledge, experience, and nomenclature base than the person supervising the scale-up trial moving from the research experience.

Time and Cost Constraint Environment. In the current environment of cost constraints and the pressures placed on research and engineering groups by marketing and sales, one may be forced into reasoned reductions in throughput optimization experiments or even gambles of time and material in order to get a product to the marketplace in a timely manner. This is all the more reason to fully understand process dynamics, formulation integrity, and the practical limitation of equipment and personnel.

New Micro-Scale Equipment. In the last several years, it has become apparent that there was a need for scaling down the normal laboratory spray drying process to facilitate formulation development of high value, heat sensitive ingredients.

(C&DP continued on page 23)

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Editor: **Dr. Ronald T. Borchardt**,
The University of Kansas,
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Member Release

Your Controlled Release Society; www.controlledrelease.org

By Ijeoma F. Uchegbu

I decided to take the membership benefits exhortation on the Controlled Release website literally and see what I, as a member, am entitled to. Some of the links were very informative, such as the Peer-to-Peer Network™. I typed in a few key words, such as brain targeting and bioavailability and came up with a list of scientists who might be able to help me with my brain targeting difficulties. I resisted the urge to email them however. There is more on this and other useful links in the article "At your fingertips" on page 3. I typed in the names of a few small companies and got back a "No results" response to my query. Fair enough, as the "Information Gateway" is in a constant state of improvement. Other links were much more informative. The "Meetings" link, for example, was excellent with the edited highlights of the Controlled Release Winter Symposium link giving me a foretaste of what to expect from the meeting. The link to the Society's 30th Annual Meeting and Exposition also produced a wealth of information on this forthcoming meeting. There was information from the profound – "Call for Papers" to the merely interesting "Glasgow is a … pulsating, dynamic community …". If pulsating dynamism is not for you, you could settle for a visit to one of Glasgow's historic buildings, e.g. Ross Priory, instead (pictured opposite). While most buildings are open to the public, you will need to be accompanied by a staff member of the University of Strathclyde to visit Ross Priory, which has spectacular grounds and a nine hole golf course, for those of you interested in a putt or two. I then decided to go job hunting and clicked on the "job search" link. Alas, there was only one recruiter listed: Brassring an "e-recruiting provider". Evidence of the economic down turn, I suppose. I could have posted my resume if I had wanted to, as this lets "employers come to you". If you have successfully used this service, please let us know.

Ross Priory – Historic Building owned and managed by the University of Strathclyde, Glasgow

The website is only a fraction of the story as nothing beats a face-to-face meeting. The Controlled Release Society, as a learned society, offers you the chance to meet like-minded scientists at its various scientific meetings. These meetings are the most valuable membership benefit. Use the website, as this is an important resource from a distance. While using the website, click on the meetings link and register for one of the meetings being held next year in either Salt Lake City or Glasgow. A question to an eminent scientist during a meeting will be guaranteed an answer and may even lead to a fruitful collaboration. An advertisement for a UK telephone company used to use the line "It's good to talk". It really is good to talk, however, I shall stop for now. Until the next time that is. •

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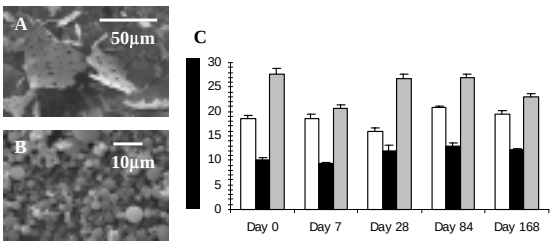
*(**Scientifically** continued from page 11)*

Figure 2. *A - SEM of freeze-dried excipient-LPD complexes; B - SEM of spray-dried excipient-LPD complexes; C - Reporter gene (Green Fluorescent Protein) expression efficiency of LPD complexes in human bronchial carcinoma (A549) cells: Freshly prepared LPD complexes (white bars), stored and reconstituted freeze-dried LPD complexes (black bars), stored and reconstituted spray-dried LPD complexes (grey bars).*



To conclude, these studies demonstrate the potential for developing pMDI and DPI formulations of non-viral vectors for pulmonary gene therapy.

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The author acknowledges the support of The Wellcome Trust and the contributions of Professor Ian Kellaway (School of Pharmacy, London), Dr Peter Seville (Aston University), Dr Mark Gumbleton, Dr Paul Dickinson, Dr Steven Wyn Howells, James Young, Natalie Harris and Emma Juggins.

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Our Technology

Use of *In vitro* Dissolution Testing Procedures for Veterinary Drug Products. Part II. The potential role of *in vitro* dissolution testing for products intended for multiple animal species

By Marilyn Martinez and Charles Collins

This is the second of two articles exploring the use of in vitro *dissolution testing procedures for veterinary drug products. These articles are solely intended to be exploratory, seeking perspectives on questions facing both regulators and manufacturers of veterinary pharmaceuticals. In this second article, a didactic interaction is presented to address some of these questions and to provide one set of perspectives on the issue of* in vitro *dissolution testing of veterinary drug products.*

Introduction

The following didactic interaction is intended to address some questions and to provide one set of perspectives on the issue of in vitro dissolution testing of veterinary drug products. The authors recognize that there may be different thoughts on some of these questions, and there may be additional questions regarding *in vitro* dissolution of veterinary drug products that may need to be addressed. Therefore, it is our hope that this article will be a stimulus for further dialogue on this topic.

Points for discussion

Q1 - The use of sink conditions:

Dissolution testing is generally conducted in 900 mL of an aqueous medium to ensure the presence of sink conditions. However, when establishing an IVIVC, we know that drug solubility is an important issue and that at some critical volume, the product will no longer dissolve (saturation conditions). In terms of formulation, that which defines a critical volume may vary depending upon whether or not surfactants are included in the product formulation. Alternatively, for low solubility, high permeability compounds, the drug absorption process may ensure that constant sink conditions exist, even in the presence of relatively low fluid volumes. With these points in mind, is it appropriate to attempt to maintain sink conditions when using *in vitro* data as a surrogate for *in vivo* bioavailability data? Alternatively, can we predict those drugs that may require testing under non-sink conditions?

Answer:

The use of sink conditions for QC tests is based on the principle of a reproducible condition and an attempt to minimize the possible variables. As drug concentration in solution approaches the saturation point, the process (rate) of dissolution is adversely affected (reduced). Once drug enters solution, in an *in vitro* test, it remains in solution in the dissolution vessel. This is a closed system. It can be argued that in the patient, sink conditions (in terms of volume of fluid), may not exist. If this were true for human patients, this would be even truer in animals that are smaller than humans. However, once drug enters solution, this is not a closed system, and drug is then available, *in vivo*, for absorption.

For a drug delivery system designed as an immediate release product, the rate of absorption is often slower than the rate of dissolution. Factors that would dictate the total amount of drug in solution would be those related to the 'media' into which drug dissolves, including its volume, pH, other components (food, surfactants, etc.) and ionic properties. Evaluated in this fashion *in vivo*, this may be best simulated using sink conditions *in vitro*.

If the rate of absorption is faster than the rate of dissolution, such as the case for sustained release formulations, then the rate of appearance of drug in the body is mainly a function of the slowest or rate-controlling step, specifically the rate of dissolution. Drug concentration is reduced as drug is absorbed, thus removing drug from the area around the remaining undissolved particles. Since the removal of drug from the solution by absorption would be faster than that of its appearance in solution, this situation again mimics sink conditions. Thus, both for sustained release and immediate release oral formulations, *in vitro* test conditions should be conducted under sink conditions whenever possible.

Q2 - Apparatus speed:

We know that GI motility differs across target animal species. Should these differences be considered when establishing the rotational speed associated with a particular *in vitro* dissolution test, or can rotational speed be a variable that can be set once for a particular product, irrespective of the ultimate target animal species recipient?

Answer:

If using Apparatus 1 or 2, rotational mixing speed would be largely independent of species. For many drug delivery systems, the faster the speed of rotation, the faster the rate of solution. Slower speeds would be less 'interfering'. If using Apparatus 3, the nature of this mixing may need to be varied for the species, as the nature of this mixing tends to be more complete than in Apparatus 1 or 2. A reasonable starting point would be to use higher dip rates (in dpm or dips per minute) for smaller species (about 30 dpm) and slower rates for larger species (about 5 to 10 dpm). This would help to account for potential interspecies differences in the strength, frequency, and shear force associated with GI contractions.

*(**Technology** continued on page 24)*

InTheNews

New Developments for LCMCD
The LCMCD Technology Development Center, Fort Myers, Florida, has been developing a coating-carrier formulation system for controlled delivery of a variety of bioactive agents (Matricap technology). Regulation of controlled delivery is based on admixture sequences of a series of fatty acids, fatty alcohols, fatty acid esters, fatty alcohol esters, phthalyl esters, waxes, or specific plasticizers with bioactive agents and carriers.

This technology is currently being evaluated for applications in pest, agricultural, veterinary, and health management under a series of agreements with industry. The following LCMCD patents are related to this technology: U.S. Patents Nos. 5,698,210 (RE 37,890); 5,846,553; 5,858,384; 5,858,386; 5,885,605; 5,902,596; 6,001,382; 6,335,027; 6,337,078; 6,346,262; 6,350,461; 6,387,386; 6,391,328; Australian Patent No. 689716 (WO 96/28973). Additional foreign patents are pending.

WellPoint Teams Up With American Dietetic Association to Fight Childhood Obesity
WellPoint is teaming up with the American Dietetic Association to develop a user-friendly print and Web-based guide that will support America's youth in achieving and maintaining a healthy weight. The guide will provide parents with concrete recommendations based on the clinical observations of registered dietitians (RDs) and will give health care professionals a vehicle by which they can begin to discuss the issue of childhood obesity with families.

"The increasing incidence of obesity, especially in children, is a serious national health issue," said ADA President and registered dietitian Julie O'Sullivan Maillet. "ADA believes that education of health care providers, parents and children is key to helping America's young people achieve and maintain a healthy weight. This guide will serve as an important new tool to help parents and children set and meet weight management goals."

The guide, which represents the first collaboration between ADA and a leading health insurer, is a key component of WellPoint's broader national "Healthy Parenting Initiative," which focuses on empowering families with information and resources to lead healthier lives.

"WellPoint is committed to providing education and support to help people take charge of their health," said Joan Herman, president of WellPoint's Senior, Specialty and State Sponsored Programs Division. "The objective of this consumer guide is to help facilitate a dialog on obesity between families and their health care professionals."

The guide will be made available in the next several months to the general public, health care professionals, WellPoint's members and to nearly 70,000 registered dietitians. It will be distributed in print format and electronically through WellPoint's Web site, http://www.wellpoint.com/ and via the ADA Web site, http://www.eatright.org/ .

"Overweight adolescents have a 70 percent chance of becoming overweight or obese adults, and are at greater risk of developing type 2 diabetes, gallbladder disease, and asthma," stated Peter Juhn, M.D., M.P.H., WellPoint's vice president of health improvement resources. "By empowering health care professionals with tools to stimulate conversation with parents and children on obesity, WellPoint is taking a critical step toward helping America's youth grow up to be strong, healthy adults."

Pacific Nanotechnology Offers Guide to Recognizing Atomic Force Microscope Image Artifacts
Pacific Nanotechnology, Inc. (PNI) has published a guide to recognizing image artifacts produced by an atomic force microscope (AFM). The PNI "Guide to AFM Image Artifacts" can be viewed and downloaded as a PDF file at www.pacificnanotech.com/tech/artifacts.htm. The addition of this guide to PNI's web site underscores the company's mission to facilitate the growth and expansion of nanotechnology efforts by providing the tools and instructions that any researcher can use.

Images produced by an AFM can have "artifacts," distortions and spurious features caused by the manner in which the image is produced. The 12-page full-color document, illustrated by 27 figures, describes and illustrates artifact examples caused by the probe tip, scanner, image processing software, vibration, contamination, electronics, and the vacuum chuck. Users can then recognize and take steps to avoid or minimize common image distortions and artifacts. Contact lara@technicalmarketing.com for an example AFM image artifact.

Aventis Behring Foundation Awards Second Round of Grants To Benefit Bleeding Disorders Community
The Aventis Behring Foundation for Research and Advancement of Patient Health has selected a second round of 2002 grant recipients. In total for 2002, the Foundation awarded $1 million to fund a variety of educational and outreach initiatives designed to benefit the bleeding disorders community.

Governed by an independent Advisory Council that has the sole authority to award grants, the Aventis Behring Foundation is a non-profit organization dedicated exclusively to charitable, scientific and educational purposes that advance the standard of care for persons affected by bleeding disorders. In response to two grant cycles initiated in 2002, the Foundation received over 100 grant applications from hemophilia treatment centers (HTCs), non-profit organizations such as hemophilia chapters, foundations, associations and healthcare professionals dedicated to the treatment of people with bleeding disorders.

"Given the high quality of the applications and the merit of the proposed projects, the Advisory Council found the selection process for this recent grant cycle to be particularly challenging," explained Val Bias, Advisory Council Chair. "After much consideration, we selected the applicants who most clearly demonstrated the positive impact of their proposed work in the bleeding disorder community, with special consideration given to projects that would help to fill currently unmet needs."

The Advisory Council selected 9 applicants from the second grant cycle to receive funding. This is the second disbursement of the initial $1 million in incremental funding provided to the Foundation upon its inception by Aventis Behring. Continuing its commitment to the Foundation, Aventis Behring has allocated an additional $1 million in

(News continued on page 26)

PEOPLEONTHE MOVE

After the Applause – Young Investigator Award Winner Professor Saghir Akhtar

By Ijeoma F. Uchegbu

Where do CRS Young Investigator award prize winners go when the applause is over? Saghir Akhtar, winner of this award in 2001, went to the Welsh School of Pharmacy and set up the Centre for Genome-based Therapeutics. Saghir Akhtar is used to building things from scratch as just prior to his appointment to a Chair in Cardiff he spent a few years setting up a pharmaceutics programme within the Department of Pharmaceutics at Kuwait University's Faculty of Pharmacy. His new Genomics centre will endeavour to tease out new anti-cancer and anti-diabetic therapies from the wealth of genomics data that is now available. Judging from his past performance, it will not be long before we begin to see significant advances originating from his laboratory. Saghir Akhtar already has the financial backing of the United Kingdom's largest cancer charity – Cancer Research UK, as well as the financial backing of the Association of International Cancer Research. Not bad considering that he only started working in Cardiff last August!

Saghir Akhtar began his career at the Leicester School of Pharmacy where he graduated with a first class honours degree. He completed a Ph.D. in Drug Delivery at the University of Bath and then spent a few years as a postdoctoral scientist under the expert tutelage of Rudy Juliano of the University of North Carolina Medical School. It was there that he first began studying the mechanisms of cellular uptake of antisense oligonucleotides. Saghir Akhtar then continued his work on antisense therapeutics as a lecturer at Aston University in Birmingham. A sabbatical in Ed Southern's laboratory in the Department of Biochemistry, Oxford University, exposed Saghir Akhtar to the new world of microarray technology and the rest, as they say, will be history. Expect to see interesting things coming out of this prize winner's laboratory. Saghir Akhtar has a number of prizes under his belt including the Lilly Prize, which he received in 1996, the Pfizer Academic Award received in 1997 and the British Pharmaceutical Conference Science Medal in 1998. Saghir Akhtar is married with five children and he puts his success down to "much hard work, working with good scientists, enjoying what you do and of course…lots of luck!" •

Prof. Saghir Akhtar

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*(**C&DP** continued from page 15)*

Control of particle size and temperature exposure became paramount rather than feed rates and process efficiencies. A new apparatus has been designed and tested which often provides over 90% collection efficiency with less than two grams atomized. Mean particle sizes have ranged from 3 to 60 microns. Even heat-sensitive proteins are not degraded during processing. Figure 1 shows a sample of polylactide/co-glycolide polymer particles prepared in high yield with this apparatus. Figures 2 and 3 show other products that have been successfully scaled recently.

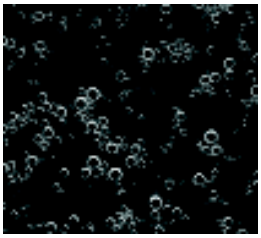

Figure 1. PLGA copolymer microspheres spray-dried from glacial acetic acid.

Figure 2. Encapsulated pigments scaled to commercial quantities for the cosmetic industry.

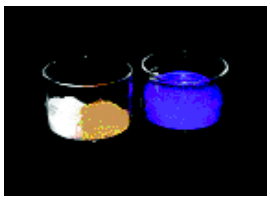

Figure 3. Microencapsulated ingredient for enhanced bioavailability scaled-up for the nutritional supplement industry.

Conclusions. Before a process can be considered as successfully scaled, the product has to pass performance testing as defined by marketplace requirements. Relating these performance requirements to a series of quality control specifications can be a daunting task. A process should not only be capable of producing a quality product but it must do that consistently. Each manipulation step in a process should be examined in detail (mixing, pumping, atomization, etc.) with the goal that the component process phenomena are well characterized and how these might interact is well understood. •

*(**Technology** continued from page 19)*

Q3 - Dissolution medium:
As described in the CDER's 1997 Guidance titled "Dissolution Testing of Immediate Release Solid Oral Dosage Forms" *In vitro* Dissolution Guidance (1997), the dissolution test conditions for products approved for use in human patients have been defined as follows:

Apparatus
The most commonly employed dissolution test methods are (1) the basket method (Apparatus 1) and (2) the paddle method (Apparatus 2). The basket and the paddle methods are simple, robust, well standardized, and used worldwide. These methods are flexible enough to allow dissolution testing for a variety of drug products. For this reason, the official in vitro *dissolution methods described in U.S. Pharmacopoeia (USP), Apparatus 1 and Apparatus 2 should be used unless shown to be unsatisfactory. The* in vitro *dissolution procedures, such as the reciprocating cylinder (Apparatus 3) and a flow-through cell system (Apparatus 4) described in the USP, may be considered if needed. These methodologies or other alternatives/modifications should be considered on the basis of their proven superiority for a particular product. Because of the diversity of biological and formulation variables and the evolving nature of understanding in this area, different experimental modifications may need to be carried out to obtain a suitable* in vivo *correlation with* in vitro *release data. Dissolution methodologies and apparatus described in the USP can generally be used either with manual sampling or with automated procedures.*

Dissolution Medium
Dissolution testing should be carried out under physiological conditions, if possible. This allows interpretation of dissolution data with regard to in vivo *performance of the product. However, strict adherence to the gastrointestinal environment need not be used in routine dissolution testing. The testing conditions should be based on physicochemical characteristics of the drug substance and the environmental conditions the dosage form might be exposed to after oral administration.*

The volume of the dissolution medium is generally 500, 900, or 1000 mL. Sink conditions are desirable but not mandatory. An aqueous medium with pH range 1.2 to 6.8 (ionic strength of buffers the same as in USP) should be used. To simulate intestinal fluid (SIF), a dissolution medium of pH 6.8 should be employed. A higher pH should be justified on a case-by-case basis and, in general, should not exceed pH 8.0. To simulate gastric fluid (SGF), a dissolution medium of pH 1.2 should be employed without enzymes. The need for enzymes in SGF and SIF should be evaluated on a case-by-case basis and should be justified. Recent experience with gelatin capsule products indicates the possible need for enzymes (pepsin with SGF and pancreatin with SIF) to dissolve pellicles, if formed, to permit the dissolution of the drug. Use of water as a dissolution medium also is discouraged because test conditions such as pH and surface tension can vary depending on the source of water and may change during the dissolution test itself, due to the influence of the active and inactive ingredients. For water insoluble or sparingly water soluble drug products, use of a surfactant such as sodium lauryl sulfate is recommended (Crison, et al., 1996;Dressman, et al., 1998). The need for and the amount of the surfactant should be justified. Use of a hydroalcoholic medium is discouraged.

We know that gastric and intestinal pH and the GI surfactants are not constant across target animal species (Martinez, *et al.*, 2002). With this in mind, are we still justified in using drug characteristics (e.g., pKa and solubility) rather than species-specific physiological characteristics as the basis for developing *in vitro* dissolution test conditions for assessing *in vivo* product comparability?

Answer:
Various attempts have been reported to create more 'physiological' media for human studies. These complex media are difficult to create, sample, and analyze for drug content. No clear advantage has been demonstrated for these media compared to the traditional aqueous buffer systems commonly in use. Examination of the literature for good IVIVC in humans shows selection of media to be based on the physicochemical properties of the drug and the drug delivery system and not the possible physiological environment. We should anticipate the same selection criteria for veterinary drug delivery systems without extensive consideration of the target species (except for the previously mentioned temperature adjustment for species).

*(**Technology** continued on next page)*

*(**Technology** continued from previous page)*

Q4 - Accommodating differences between monogastrics and ruminants:

Ruminants have a complex GI tract whereby ingested material passes through several chambers and is often regurgitated prior to entering the true stomach. Considering this complexity, would the USP Apparatus 3 be a more appropriate *in vitro* test apparatus for oral drug products used in ruminants as compared to Apparatus 1 or 2? Expanding upon this concept further, do we need to consider ruminants separately from monogastric species when using *in vitro* dissolution data to support *in vivo* comparability?

Answer:

Ruminants may be an exception to the answer given for question 3 above. Testing dissolution in a varied environment may be essential for these veterinary patients. The use of Apparatus 3, with the ability to easily move through several different media environments, would make for a better *in vitro* test in ruminants. In addition, as some of these drug delivery systems can be quite large (bolus tablets can be 10 to 15 grams in size), the mixing would be more effective and reproducible.[1] Also, 1-L vessels can be used in Apparatus 3, providing a sufficiently large sample size and number of samples since a dissolution profile is needed for a potential IVIVC.

Q5 - Gummy formulations:

Certain companion animal products are formulated as gummy tablet formulations. Since dogs characteristically swallow large chunks of food with minimal mastication, they are likely to swallow these gummy tablets whole. With this in mind, what dissolution method may be appropriate for testing chewable tablets that are developed as beefy-gummy chewable formulations?

Answer:

Dissolution testing of chewable products is always a challenge. In veterinary products, a semisolid mass will not easily dissolve. Apparatus 3 has the most vigorous mixing environment, and has been used for some human chewable products. Another suggestion would be to evaluate the dissolution of the chewable product in the form found in the manufacturing process immediately prior to it being compacted or formed into the final shape. This would resemble the final product after patient mastication. Even if it does not, it is a reproducible stage of the drug product.

Q6 - Medicated feeds:

Medicated feeds present problems that are unique to veterinary medicine. While many medicated feeds provide systemically available drug, in some cases, the administered drug does not get systemically absorbed to any measurable extent. In these cases, the drug is released from the feed within the GI tract where it effects a local therapeutic effect. When formulation changes/product improvements/generics are proposed for these products, we currently have no alternative but to recommend clinical trials. Equally complex are pelleted medicated feeds that are regulated as finished dosage forms. Regardless of whether the drug is simply mixed in feed or pelleted, the *in vitro* testing of these products present very significant challenges. Therefore, the question is what alternative to *in vitro* dissolution/drug release testing may be used when the drug chemical entity is integrated into a nondissolving matrix?

Answer:

No matter the form of the drug delivery system, if the site of action is in the GI tract, the role of the dissolution test becomes more directly important. Without having to account for the absorption process, we can test, *in vitro*, the same process controlling the movement of drug from the drug delivery system to the site of action *in vivo*. The media should be created to match the GI tract for its pH for the species in question. If, however, the matrix is a feed, then interfering substances are present in large concentrations relative to that of the drug. Treatment of the sample before analysis becomes very important, as does completeness of mixing. Here again, Apparatus 3 may be the best choice, where more vigorous mixing is present and a smaller receptor volume would allow more concentrated samples. Filtering of undissolved components would be an essential step in the sample preparation, and techniques such as HPLC may be needed for the quantitation of low drug concentrations.

Concluding comments

It is our hope that this article will provide a springboard for future discussions on the topic of *in vitro* dissolution testing for veterinary pharmaceuticals. Therefore, the authors request your comments and input. To provide other perspectives on issues that have been raised or to raise additional questions for discussion, please contact Dr. Marilyn Martinez at MMartin1@cvm.fda.gov.

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[1] Recently, scientists from CVM and the University of Maryland have developed *in vitro* dissolution methods for testing oral boluses. These methods can be conducted in 900 mL of dissolution media using USP Apparatus 2 (Fahmy, *et al.*, 2001a, b, c). Additional work with these methods is currently underway to characterize their ability to discriminate between inequivalent bolus formulations. •

(News continued from page 21)

incremental funding for 2003, with the initiation of the next grant cycle in January.

"We have already begun to see the positive impact that the Aventis Behring Foundation is making in the community. We are pleased to continue to support the Foundation's mission in 2003," said Michael Sumner, MD, Executive Director of the Foundation.

HPV Vaccine Offers Hope, Also Points Out Seriousness of Epidemic, Says The Medical Institute for Sexual Health

"News of a vaccine that can combat the type of human papillomavirus (HPV) that causes most cervical cancer is very hopeful, but also points out how prevalent and dangerous this sexually transmitted disease is," said Joe S. McIlhaney, Jr., president of The Medical Institute for Sexual Health.

"HPV is the most common viral STD. A recent major study of sexually active women ages 18 through 22 found that 50 percent were infected with HPV. It is the cause of almost all cervical dysplasia, which is the precancerous change of the cervix, and of 93 percent of all cervical cancer. It is estimated that 4100 women died as a result of cervical cancer in the United States in 2001, more than the number of women who died of AIDS that same year.

"We are hopeful that this vaccine leads to eradicating the threat of HPV but that is still several years away at best. Longer term follow up is still necessary to establish that the vaccine is safe and to determine how long the protection may last. And, since HPV 16 (the type targeted by this vaccine) is associated with only about half of all cases of cervical cancer, future vaccines will need to protect against various types of HPV which also can lead to cervical cancer.

"When and if it is time for widespread utilization of this vaccine, protocols will need to be established for identifying 'at-risk' populations and vaccinate them. In the study just published, about a fifth of the 16 to 23-year-olds who were originally enrolled had to be dropped from the study because they had become infected with HPV before the study had begun.

"This is an extremely positive development. Obviously there is more work to be done. In the meantime, women must understand that there is no evidence that condoms provide any risk reduction for the sexual transmission of HPV, even with 100 percent condom use. Indeed, the only context in which one can be certain of safety from sexually transmitted diseases is a lifelong monogamous relationship."

ViroLogic Announces Florida Medicaid Program Initiates Coverage Policy for HIV Drug Resistance Testing

ViroLogic, Inc. announced that the Florida Medicaid Program has initiated a benefit coverage policy for phenotypic and genotypic HIV drug resistance testing effective November 15, 2002. This brings the number of state Medicaid programs that have coverage policies enabling reimbursement of the Company's HIV drug resistance assays to 47 out of 50. Florida has the second largest number of reported persons living with HIV/AIDS in the United States, and Medicaid is the single largest payer for this patient population.

In addition to statewide Medicaid coverage, Medicare and many private payers, including but not limited to BlueCross BlueShield, AEtna US Healthcare, United HealthCare and Humana, provide reimbursement and benefit coverage for ViroLogic's HIV drug resistance assays. Several key states and the District of Columbia also provide funding for Ryan White Title programs, including those in Florida, California, New York, Michigan, Texas, Alabama, Georgia, South Carolina, North Carolina, Missouri, Pennsylvania, Kansas and Virginia.

"We are pleased that now most of our key markets have established favorable Medicaid reimbursement policies, and the HIV provider network has access to ViroLogic's technologies. Our sales team in Florida is primed and ready to capitalize on this opportunity," said Tien Bui, ViroLogic's Vice President of Sales and Marketing. "I am confident we can continue to build on the strong leadership foundation we have created to drive increasing utilization of resistance testing as a management tool for HIV providers and their patients to facilitate optimal care."

Questions about HIV drug resistance testing and reimbursement can be directed to ViroLogic's reimbursement hotline at 1-87-PHENOAID (1-877-436-6243), or to the websites www.virologic.com and www.phenosense.com.

Antex Receives Five New International Patents

Antex Biologics Inc. has been issued five new patents, increasing the Company's total patent portfolio to 116 issued patents. The Company also has over 300 pending patent applications.

Antex's worldwide patent portfolio includes claims for composition of matter, methods of production and methods of use. The new patents expand the Company's worldwide protection of its proprietary technologies and products. Specific bacterial pathogens covered by the patents include: Haemophilus influenzae and Moraxella catarrhalis, leading causes of pediatric respiratory diseases and the subject of licensing arrangements with Aventis Pasteur and GlaxoSmithKline; and Helicobacter pylori, the leading cause of peptic ulcers and stomach cancers.

In addition to specific claims covering novel proteins and the genes encoding them, Antex's proprietary platform technologies ART (antigen receptor technology) and NST (nutriment signal transduction) are also covered by the new patents. These patents broaden the Company's intellectual property portfolio in North America, Europe and Asia.

Pharma-Biotech Alliances: Answering the Pipeline Question

The pharmaceutical industry came under fire earlier this month when biotech pioneer William Haseltine said that Big Pharma will continue to see productivity drops as it relies on conventional research and fails to produce innovative treatments. Haseltine's remarks ring true as the number of new drug applications dropped 20% this year, while new drugs approvals fell 30%.

Recent consolidation in the pharmaceutical industry takes much of the criticism for slowing research cycles and releasing innovative drugs. However a study by pharmaceutical Cutting Edge Information shows that alliances between pharmaceutical and biotechnology companies could be the answer to the industry's pipeline problem.

"Building Pharmaceutical-Biotechnology Partnerships," available at http://www.pharmabiotechalliances.com/ , features 11 case studies and more than 90 metrics, which confirm that well-run pharmaceutical-biotech alliances are key

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to developing and maintaining the next generation of pharmaceutical blockbusters. The study shows how top companies such as Pfizer, Aventis, Bayer, Chiron and Amgen partner and collaborate to bring innovative treatments to market.

"Pharmaceutical companies that focus on biotech alliances gain access to a virtually untapped source of blockbuster potential," says Cutting Edge Information president Jason Richardson. "Those companies that master pharma- biotech alliances will greatly benefit pharmaceutical pipelines. This report highlights how to spot the superstar deals that will reward both partner companies."

Galapagos Genomics Receives Grant for Bone Disease Research
Galapagos Genomics, the Belgian functional genomics company, has been awarded a 1.2 million Euro technology development grant in Belgium for bone disease research.

IWT (The Flemish Institute for the Promotion of Industrial Scientific-Technological Research) has awarded Galapagos this grant for a project aimed at the identification and validation of drug targets in related bone diseases, focusing on rheumatoid arthritis, osteo-arthritis and osteoporosis. The project will broaden Galapagos' current program in osteogenesis, in which several novel targets have already been identified and validated which stimulate bone formation. Bone diseases represent a very large therapeutic market that is in need for novel targets that address the cause of the disease. Present therapies are focused in minimizing bone loss, whereas new drugs are needed that stimulate bone formation.

Galapagos will use its adenoviral target discovery platform in combination with cellular assays to identify novel genes that are key player in the bone disease processes. Functionally identified and validated targets will ultimately be partnered with pharmaceutical companies to develop new therapeutics based on such targets.

"We are very pleased with this IWT grant, as it enables us to apply our technology in an important disease area and move the Company from a technology provider into a disease focused drug discovery entity," said Onno van de Stolpe, CEO of Galapagos. "This third grant that we receive from the IWT confirms the quality of the research at Galapagos and helps us to rapidly expand our discovery programs."

Biomarin and Genzyme Release Additional Primary Endpoint Data From Their Phase III Open-Label Extension Study of Aldurazyme for MPS I
BioMarin Pharmaceutical Inc. and Genzyme General have released additional data from their ongoing open-label Phase III extension study of Aldurazyme(R) (laronidase), an investigational drug for the treatment of mucopolysaccharidosis I (MPS I).

The companies released data regarding the study's two primary endpoints: pulmonary function as measured by percent predicted Forced Vital Capacity (FVC); and endurance as measured by distance covered in the six-minute walk test. Measurements of these endpoints were taken 36 weeks after the commencement of the open-label extension study, or a total of 62 weeks after commencement of the placebo-controlled trial. This new data has recently been submitted to the U.S. Food and Drug Administration (FDA) for review as part of the Biologics License Application (BLA) that was submitted on July 26, 2002. The data will also be submitted to the European Agency for the Evaluation of Medicinal Products (EMEA).

The 22 patients who received Aldurazyme for 62 weeks demonstrated a mean FVC change of +5.4 percentage points compared to pre-treatment baseline. In the six-minute walk test, these patients had a mean +40.0 meter change from pre-treatment baseline. For both the FVC and the six-minute walk tests, these results indicate that patients maintained the improvements observed after 50 weeks of Aldurazyme treatment.

After 36 weeks, the 23 patients who received placebo during the placebo-controlled portion of the trial demonstrated a mean +2.6 percentage point increase in FVC from their pre-Aldurazyme treatment baseline. Most of the improvement was observed between weeks 25 and 36 of the open-label extension study. In the six-minute walk test, these patients demonstrated a mean +32.4 meter change from pre-treatment baseline, an increase in the improvement observed following 24 weeks of Aldurazyme treatment.

The safety profile in the extension study has been comparable to the double-blind period. The most commonly reported adverse events were headache, rhinitis, and pharyngitis. As previously reported, one patient in the extension study died of causes considered by the principal investigator to be unrelated to Aldurazyme.

College of American Pathologists Group Recommends Smallpox Vaccinations For Health Workers and Others
The College of American Pathologists (CAP) today announced its new policy recommending a voluntary, pre-outbreak approach to smallpox vaccinations for "first responders" to a bioterrorism attack including health care providers, certain laboratory workers, emergency room personnel, police, firefighters, medical examiners and others. The CAP policy also recommends offering pre-outbreak vaccinations to the general public but only after the FDA licenses a smallpox vaccine.

"Physicians, laboratory workers, hospital employees and other emergency response personnel will be on the frontlines should a bioterrorist attack occur," said Jared N. Schwartz, MD, PhD, FCAP and chair of the CAP Committee on Emergency Preparedness. "It is in their best interest, and in the best interest of the public they serve, for these first responders to be protected through smallpox vaccination." The CAP policy also states that the general public should be offered the option of smallpox vaccination, but only after they have been fully informed of the risks and benefits of inoculation and have signed an informed consent document. The policy notes that widespread, pre-outbreak vaccinations should not occur in the general public until a sufficient stock of Vaccinia Immune Globulin (VIG), a blood product used to treat immuno-suppressed patients with vaccine associated infections, is developed.

"Without a stock of VIG, there is no compelling treatment option for those people with suppressed immune systems who develop vaccination associated infections related to this inoculation," said Dr. Schwartz. "That is why the College has recommended this phased approach, to maximize the protection of those most at risk from bioterrorist attack while minimizing any potential danger associated with this vaccine."

"The College is hopeful that a new and safer vaccine will be available soon," added Dr. Schwartz. •

The 30th Annual Meeting and Exposition of the Controlled Release Society

Come for the Science, Stay for the Scenery

Looking across the calm, glimmering water of the River Clyde you lose yourself in the aura of Scotland. You imagine yourself teeing up at the 18th hole, at any of the world famous golf courses Scotland provides, where generations of great golfers have walked the same ground you are walking right now. Before you know it, you are off of the links, cruising along the etched landscape of the Scottish shoreline, where centuries of wind and water have created some of the most beautiful scenery in Europe. Scotland is beautiful, alluring, and always entertaining. Whether it is tossing a 20 foot pole, wearing a kilt and listening to bagpipes or simply kicking back and having an ale at one of the local pubs, Scotland is a great place to visit!

Glasgow is THE choice for the 30th Annual Meeting and Exposition! Glasgow, the largest city in Scotland, is a pulsating and dynamic community with a vibrant economy, upbeat café society, international restaurants, and great nightlife. Glasgow is also the home of the Scottish Exhibition & Conference Centre which will host the Controlled Release Society's 30th Anniversary Annual Meeting and Exposition from July 19-23, 2003. This year's meeting will feature the top names in Bioactive Materials, Consumer and Diversified Products, and Veterinary Products Scientific Sessions. Do not miss the Pearls of Wisdom Sessions, a new feature in honor of the 30th Anniversary, and an opportunity to network with leading companies at the exposition!

While attending the 30th Anniversary Meeting, there are several opportunities for attendees to take in some of the Scottish heritage. The Grand Banquet at Stirling Castle is the entertainment highlight of the meeting. One of the most historically important landmarks in Scottish history, Stirling Castle was once destroyed by Robert the Bruce and home to Mary, Queen of Scots. Sign up now for this spectacular evening, seating is limited to 500 people!

Don't forget to allow time to take advantage of the pre and post tours that are available. From touring several world famous castles to golf at Gleneagles or a visit to St. Andrews Bay, there are tours for all tastes and budgets. Please visit www.controlledrelease.org/meetings/glasgow/tours.htm for detailed information or to sign up.

Make plans now to attend the 30th Annual Meeting of the Controlled Release Society. Details are available online at www.controlledrelease.org!

Registration Form

Register by any of these methods:

online: www.controlledrelease.org
phone: +1 (763) 512-0909
facsimile: +1 (763) 765-2329
mail: Controlled Release Society
13355 Tenth Ave. N., Suite 108
Minneapolis, MN, USA 55441-5554

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Special Requests (ADA, Dietary, Etc.) _____

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CRS Membership Number (if known)

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***Student status verification required.**

❑ I attest that the named individual is a full-time, degree-seeking student.

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Annual Meeting

	On or Before May 30	May 31-June 23	After June 23 and Onsite
Member	❑ $650	❑ $750	❑ $850
Non-Member	❑ $850	❑ $950	❑ $1,050
Student* Member	❑ $165	❑ $210	❑ $250
Student* Non-Member	❑ $195	❑ $250	❑ $290
One Day Only Member Day Attending _____	❑ $500	❑ $500	❑ $500
One Day Only Non-Member Day Attending _____	❑ $550	❑ $550	❑ $550
Extra Opening Night Tickets (each) *space is limited--register early* Quantity desired _____	❑ $45	❑ $45	❑ $50
Grand Banquet (each) *space is limited--register early* Quantity desired _____	❑ $110	❑ $115	❑ $120
Attendance to Soapbox Session Only	❑ $50	❑ $50	❑ $50
Exhibition Only	❑ FREE	❑ FREE	❑ FREE
Proceedings CD-ROM Additional Quantity desired _____ *(One CD-ROM of Proceedings included with registration)*	❑ $60	❑ $75	❑ $90
Proceedings Book (2-book set) Quantity desired _____	❑ $75	❑ $90	❑ $105
Travel Grant Contribution		❑ $_____	

Workshops

Modified Release Products			
Member or Non-Member	❑ $650	❑ $700	❑ $850
Student*	❑ $200	❑ $250	❑ $275
Shared Concepts - Veterinary Science			
Member or Non-Member	❑ $650	❑ $700	❑ $850
Student*	❑ $200	❑ $250	❑ $275
Micro Encapsulation			
Member or Non-Member	❑ $650	❑ $700	❑ $850
Student*	❑ $200	❑ $250	❑ $275
Releasing Technology Workshops *(included with registration)*	❑ FREE	❑ FREE	❑ FREE

❑ A ❑ B ❑ C ❑ D

TOTAL $_____

Payment Options

❑ Check # _____

Checks must be in U.S. dollars drawn on a U.S. bank and made payable to the Controlled Release Society.

❑ MasterCard ❑ VISA ❑ American Express

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NEWSLETTER
CONTROLLED RELEASE SOCIETY
13355 Tenth Avenue North, Suite 108
Minneapolis, MN 55441-5554 USA

Next issue deadline
March 14, 2003

who...what...where...when

eventcalendar

University of Miami & Sylvester Cancer Center
2003 Miami Nature Biotechnology Winter Symposium
February 1-5, 2003
Radisson Deauville Resort Hotel
Miami Beach, FL, USA
mnbws-biochem@miami.edu
www.med.miami.edu/mnbws
ph: +1 305-243-3597

Orthopaedic Research Society
49th Annual Meeting
February 2-5, 2003
New Orleans, Louisiana, USA
ors@aaos.org
www.ors.org

Controlled Release Society
Winter Symposium & 11th International Symposium on Recent Advances in Drug Delivery Systems
March 3-6, 2003
Grand America Hotel
Salt Lake City, Utah, USA
director@controlledrelease.org
www.controlledrelease.org
ph: +1-763-512-0909

GRIBOI
13th Interdisciplinary Research Conference on Biomaterials
March 14-15, 2003
Baltimore, MD, USA
www.jhbmc.jhu.edu/griboi03

Messe Muenchen International
BioAnalytica
April 1-4, 2003
New Munich Trade Fair Centre,
Munich, Germany
Rwest@mtfna.com
www.munichtradefairs.com
ph: +1 312-377-2650

American Society for Artificial Internal Organs
ASAIO - ISAO Joint Conference 2003
June 19-21, 2003
Hilton Washington
Washington DC, USA
info@asaio.com
www.asaio.org
ph: +1 561-391-8589

AO Foundation
ECM IV: Bone Tissue Engineering
June 30 - July 2, 2003
Congress Centre
Davos, Switzerland
sonia.wahl@ao-asif.ch
www.aofoundation.org/events/ao/ecm/ECMIV
ph: +41-81-4142-541

AO Research Institute
Bone Tissue Engineering
June 30 - July 2, 2003
Congress Centre
Davos, Switzerland
www.aofoundation.org/events/ao/ecm/ECMIV

Controlled Release Society
30th Annual Meeting and Exposition
July 19-23, 2003
Glasgow, Scotland
register@controlledrelease.org
www.controlledrelease.org
ph: +1 763-512-0909

OsteoArthritis Research Society International (OARSI)
2003 World Congress on Osteoarthritis
October 12-15, 2003
Berlin, Germany
oarsi@oarsi.org
www.oarsi.org
ph: +1 202-367-1177

Surfaces in *Biomaterials* Foundation presents BioInterface 2003
October 22-24, 2003
Savannah Marriott Riverfront
Savannah, GA, USA
member@surfaces.org
www.surfaces.org
ph: +1 763-512-9103

For complete calendar information, and to add your own events, log on to www.controlledrelease.org/global/index.htm