Drug Delivery Technology®

September 2009 Vol 9 No 8 www.drugdeliverytech.com

The Potential of hMTS

The science & business of drug development in specialty pharma, biotechnology, and drug delivery

Bradley Thompson, MBA
FDA's New Draft Guidance on Technical Considerations for Pen, Jet & Related Injectors Intended for Use With Drugs & Biological Products

Kris Hansen, PhD
A Hollow Microstructured Transdermal System for Needle-Free Delivery of Biopharmaceuticals

Cindy H. Dubin
Healthcare Reform & Needlestick Prevention Laws Inject Life Into Hand-Held Devices

IN THIS ISSUE

INTERVIEW WITH COLORCON'S VICE PRESIDENT, CORPORATE DEVELOPMENT

JAMES COWARD

FEATURING

SPECIALTY PHARMA Strategies For Business Development

μco™ System

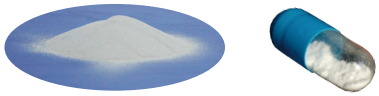
Innovation in Intranasal Delivery

"PK comparable to injections!"

"Safe, no irritation."

"Easy to use."

Novel Nasal Carrier

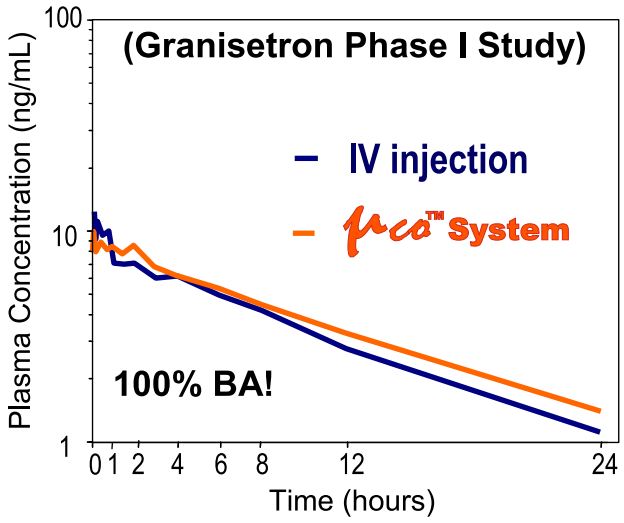


Novel Nasal Devices

Capsule loading
Multiple-use Device

Pre-loaded
Single-use Device

Sample PK Profile



Licensing Opportunities

Nasal products using μco™ System are available for licensing.

Nasal Granisetron (Phase II data available)
Nasal Zolmitriptan, Nasal Morphine, Nasal Insulin, etc.

μco™ System is also available for licensing in various treatments.

Systemic Treatment | Vaccine | Nose-to-Brain | Local Treatment

Contact: info@trltd.co.jp

Translational Research Division
SNBL, Ltd.
http://www.trltd.co.jp/

With DPT,
development and manufacturing piece together seamlessly.

DPT is the contract development and manufacturing organization (CDMO) that specializes in semi-solid and liquid dosage forms. With unmatched technical expertise and fully integrated drug development and manufacturing services, we can help you successfully develop and commercialize your next product. Partnering with DPT gives you a seamless transition from pre-formulation to clinical supplies to commercial supply. After all, keeping it all together is what sets us apart. To get started, visit us at www.dptlabs.com or call 1.866.CALL.DPT.

DPT®

SOURCE WITH CONFIDENCE®

SEMI-SOLIDS • LIQUIDS • NASAL SPRAYS • METERED-DOSE INHALATION • AEROSOL FORMULATIONS • COMPLEX DELIVERY SYSTEMS

1.866.CALL.DPT • WWW.DPTLABS.COM • SAN ANTONIO, TX • LAKEWOOD, NJ

LCP
LIFECYCLE PHARMA

Improving Treatments
Improving Lives

MELTDOSE® – A BETTER WAY TO BETTER DRUG ABSORPTION

MELTDOSE® – BREAKTHROUGH TECHNOLOGY THAT'S MORE EFFECTIVE

Now there is a faster and more cost-effective way to enhance absorption in order to improve drug availability and clinical profile.

Improving drug absorption can:

- increase a drug's efficacy
- enable lower dosing
- reduce food effect
- and in some cases, even reduce side effects

MeltDose® technology is a one step industrial process designed to enhance the oral bioavailability of poorly water soluble drugs.

MeltDose® has been validated:

- in numerous clinical studies
- in partnerships with several leading pharmaceutical companies
- by the FDA approval and launch of Fenoglide™ on the US market

5 REASONS TO CHOOSE MELTDOSE®

1. **Clinically proven**
   to improve bioavailability and/or reduce food effect
2. **Commerically viable**
   with the first MeltDose® based product, Fenoglide™ on the market in the US
3. **Patent protected**
4. **Easily scalable**
   and requiring only conventional manufacturing equipment
5. **Cost effective**
   as the cost of goods is comparable to conventional tablets

Learn more about LCP and MeltDose®. Visit our web site: www.meltdose.com or contact us at: meltdose@lcpharma.com

HEADQUARTERS: LifeCycle Pharma A/S - Kogle Allé 4 - DK-2970 Hørsholm - Denmark - Tel +45 70 33 33 00 - Fax +45 36 13 03 19 - www.lcpharma.com
US ADD RESS: LifeCycle Pharma Inc. - 100 Park Avenue - 13th floor - New York - NY 10017 - Tel +1 866 791 5715 - Fax +1 212 867 9403

Drug Delivery Technology

September 2009 Vol 9 No 8

PUBLISHER/PRESIDENT
Ralph Vitaro

EXECUTIVE EDITORIAL DIRECTOR
Dan Marino, MSc
dmarino@drugdeliverytech.com

CREATIVE DIRECTOR
Shalamar Q. Eagel

CONTROLLER
Debbie Carrillo

CONTRIBUTING EDITORS
Cindy H. Dubin
Debra Bingham
Jason McKinnie

TECHNICAL OPERATIONS
Mark Newland

EDITORIAL SUPPORT
Nicholas D. Vitaro

ADMINISTRATIVE SUPPORT
Kathleen Kenny

Corporate/Editorial Office
219 Changebridge Road, Montville, NJ 07045
Tel: (973)299-1200
Fax: (973) 299-7937
www.drugdeliverytech.com

Advertising Sales Offices

East & Midwest
Victoria Geis - Account Executive
103 Oronoco Street, Suite 200
Alexandria, VA 22314
Tel: (703) 212-7735
Fax: (703) 548-3733
E-mail: vgeis@drugdeliverytech.com

West Coast
Warren De Graff
Western Regional Manager
818 5th Avenue, Suite 301
San Rafael, CA 94901
Tel: (415) 721-0644
Fax: (415) 721-0665
E-mail: wjdegraff@drugdeliverytech.com

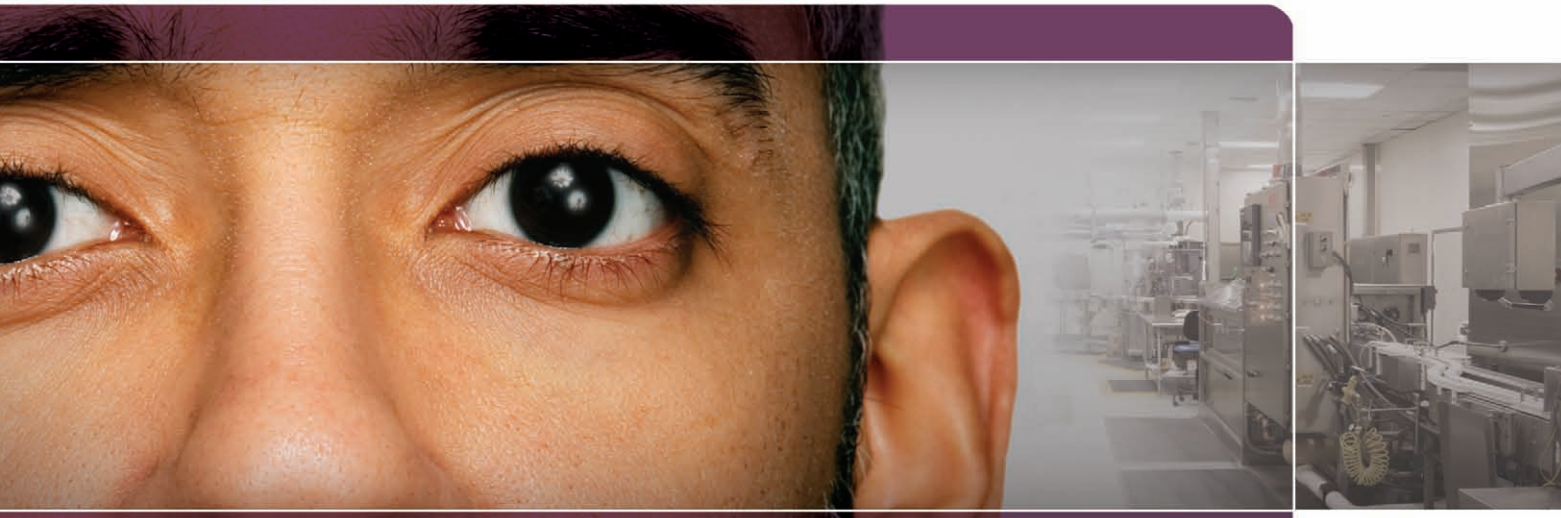
International
Ralph Vitaro
219 Changebridge Road
Montville, NJ 07045
Tel: (973) 299-1200
Fax: (973) 299-7937
E-mail: rvitaro@drugdeliverytech.com

Mailing List Rental
Candy Brecht
Tel: (703) 706-0383
Fax: (703) 549-6057
E-mail: cbrecht@mgilists.com

New Media Sales
Michael J. Masters - Director
Tel: (973) 299-1200
Fax: (973) 299-7937
E-mail: mmasters@drugdeliverytech.com

3M Drug Delivery Systems

MANUFACTURING SERVICES



We're in the "problem solving" business.

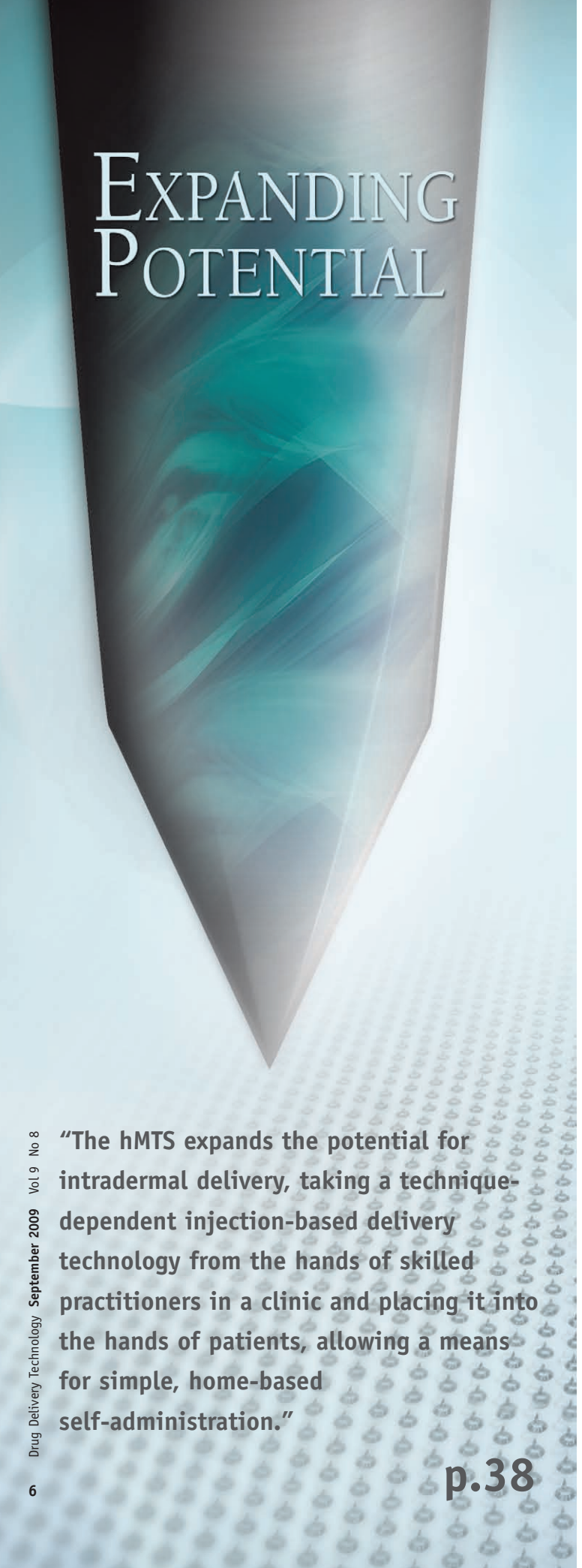
The reliable choice for inhalation and transdermal manufacturing services.

3M provides a full range of manufacturing services with the knowledge and capacity to meet your needs. When you work with 3M, you get more than a vendor. Our commitment to innovation combined with our 50 years of development, regulatory and manufacturing experience makes 3M a complete manufacturing partner. With cGMP compliant facilities capable of producing the necessary volumes from clinical to commercial production and expert supply chain management, you can be assured of reliable product delivery.

For further information contact: www.3M.com/ddsadv
US: 1 800 643 8086 ext 710
UK: 44 (0) 1509 613626

ENABLING YOUR SUCCESS.

3M

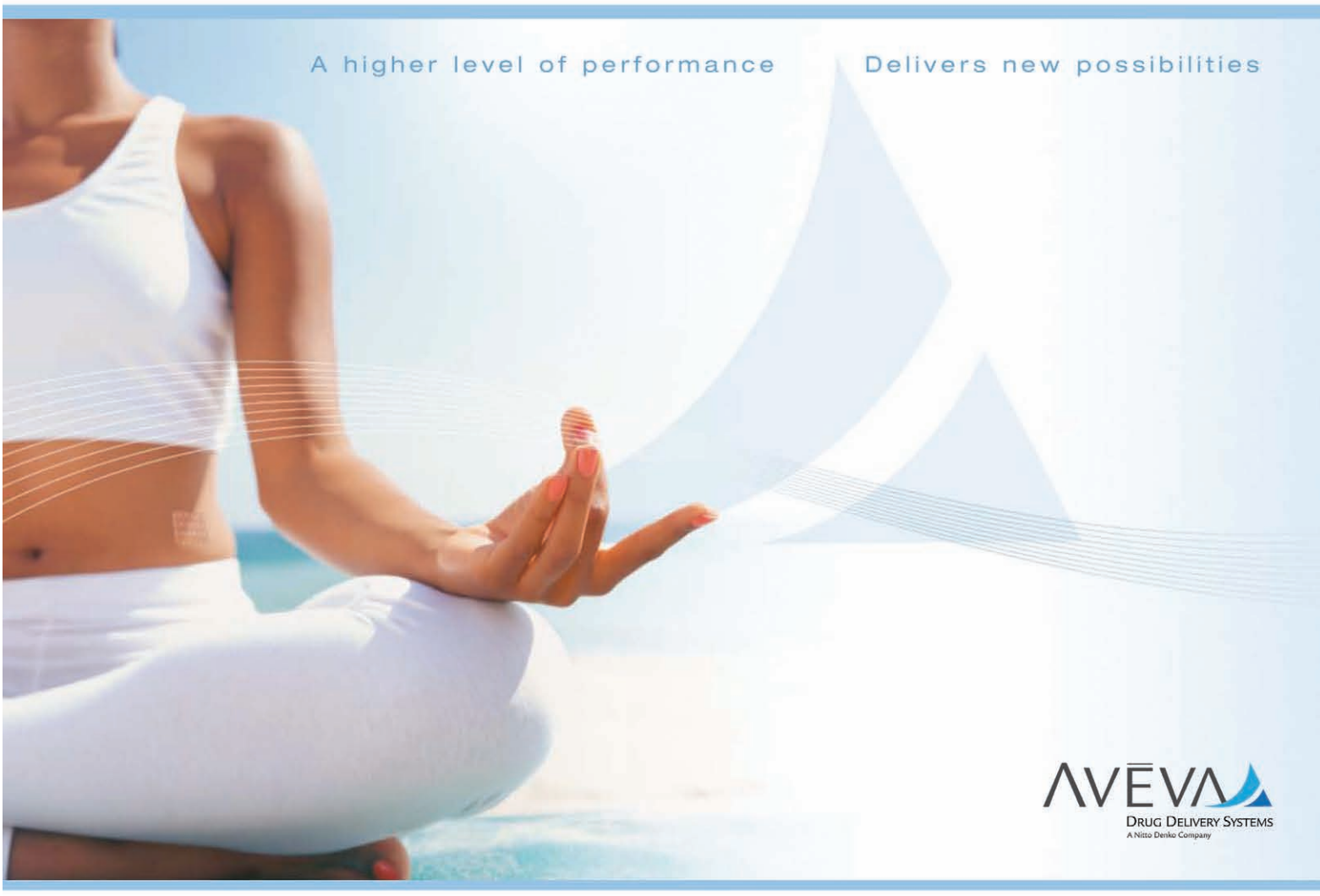


"The hMTS expands the potential for intradermal delivery, taking a technique-dependent injection-based delivery technology from the hands of skilled practitioners in a clinic and placing it into the hands of patients, allowing a means for simple, home-based self-administration."

p.38

Table Of Contents

TRANSDERMAL TRANSCENDENCE



That's the promise of Aveva Drug Delivery Systems, combining innovation and unparalleled industry experience to advance drug delivery and pioneer new frontiers in transdermal drug delivery for new chemical entities and life cycle management opportunities to enhance existing products.

As one of the world's largest manufacturers of transdermal patches offering a full range of research, development and manufacturing capabilities, Aveva transcends traditional limitations of patch technology and business partnerships to achieve new levels of product and corporate performance.

- Customizing solutions to the unique characteristics of each drug
- Masterfully balancing the patch properties of adhesion reliability and gentleness that lead to an enhanced patient experience.
- Managing a higher drug concentration in a smaller patch

A flexible, customer-oriented business philosophy that adds value to projects and exceeds customer expectations.

To license a product or to see how we can add value to your project, call Robert J. Bloder, Vice President Business Development, at **954.624.1374** or visit **www.AvevaDDS.com**

NITTO DENKO GROUP

Generating Momentum

"According to a September 2008 Deutsche Bank Global Market Research Report, US sales of biological drugs in 2007 were approximately $42 billion. The same report states that $25 billion worth of these drugs are losing patent exclusivity between now and 2016, making them prime targets for follow-on biologics. Self-administered injectable biologics account for the main portion, over $22 billion, of those facing future competition from follow-on biologics."

Table Of Contents

Departments

NEW from Elcam Medical

Flexi-Q PFS and DV

i3D
Injectable Drug Delivery Devices

The only fully disposable auto-injectors for complete life-cycle management for self injectable drugs.

- Product line is designed for administration of biologic drugs - both in liquid and lyophilized forms
- Each product is a single-use and disposable, passive needle shielding, automatic injection device
- Highly ***Flexible*** platforms are able to accommodate a wide variety of customization options such as, injection time and force, viscosity, with dosage range of 0.3 mL to 1.0 mL.

Flexi-Q PFS
Disposable
Auto-Injector for
Pre-Filled
Syringes

Flexi-Q DV
Disposable
Auto-Injector for
Drugs in Vials

Contact us for availability and potential collaboration or customization options.

Improving Quality of Life

Head Office / Manufacturer
Elcam Medical
BarAm 13860, Israel
Tel: 972-4-698-8120/1/2
Cell: 972-52-831-3890
Fax: 972-4-698-0777
menachem@elcam.co.il

USA
Elcam Medical Inc.
2 University Plaza, Suite 620
07601 Hackensack, NJ
Tel: +1 201 4571120
Fax: +1 201 4571125
info@elcam-medical.com
www.elcam-medical.com

Europe
MedNet GmbH
Borkstrasse 10
48163 Muenster Germany
Tel +49 (0) 251 32266 0
Fax: +49 (0) 251 32266 22
info@medneteurope.com
www.medneteurope.com

China
Elcam China Office
Room 25B, Building B, No. 1118 of Changshou Rd.,
Shanghai 200042, China
上海市长寿路1118号悦达国际大厦B幢25B室，200042
Tel: +86 2152375561
Fax: +86 2152375562
johnliu02@126.com

Elcam Medical

www.elcam-medical.com

The Editorial Advisory Board

Dan Marino, MSc
Executive Editorial Director
Drug Delivery Technology

Shaukat Ali, PhD, MSc
Technical Service Manager
BASF Pharma Solutions

John A. Bermingham
President & CEO
The Lang Companies

Der-Yang Lee, PhD
Research Fellow, R&D Technology, R&D Labs
McNeil Consumer Healthcare, Johnson & Johnson

Sarath Chandar, MBA
Vice President, Global Marketing & Commercial Development
SPI Pharma

Derek G. Hennecke, MBA
President & CEO
Xcelience

Gary W. Cleary, PhD, PharmD, MBA
President & CTO
Corium International

Ms. Debra Bingham
Partner
Valeo Partners

Clifford M. Davidson, Esq.
Founding Partner
Davidson, Davidson & Kappel, LLC

John Fraher
President, North America
Eurand

Philip Green, PhD
Senior Director, Drug Delivery Devices
Merck Bioventures, Merck Research Laboratories

Keith Horspool, PhD
Director, Research Formulations
Pfizer Global Research & Development

Ali Rajabi-Siahboomi, PhD
Global Technical Director, Modified Release Technologies
Colorcon

David Monteith, PhD, MBA
Senior Director, Drug Delivery & Life Cycle Development
Schering-Plough

Uday B. Kompella, PhD
Professor, Department of Pharmaceutical Sciences
University of Colorado Denver

James W. McGinity, PhD
Professor of Pharmaceutics
University of Texas at Austin

Josef Bossart, PhD
Managing Director
Bionumbers LLC

Marc Iacobucci, MBA
VP, Marketing & Project Management
DPT Laboratories

Michael A. Repka, PhD, DDS
Chair & Associate Professor
Department of Pharmaceutics
University of Mississippi

Peter Hoffmann, PhD
Vice President, New Technology Development
Genzyme Corporation

Cornell Stamoran
VP, Strategy & Business Process
Catalent Pharma Solutions

Tom Tice, PhD
Vice President, Research
SurModics Pharmaceuticals, Inc.

James Vaughan
Division Vice President
3M Drug Delivery Systems

Beth A-S. Brown, PhD, MS
Director, Pharmaceutical Development
Upsher-Smith Laboratories

Henry Y. Wu, PhD, MS
Director of Biopharmaceutics & Parenteral Delivery
Merck Research Laboratories

WHEN THE MOST CHALLENGING PROBLEMS ARISE, WE GET THE CALL.

PharmaForm has an international reputation for developing novel solutions to challenging problems in pharmaceutical product development, manufacturing, and analytical testing. We specialize in working side-by-side with our clients, to deliver customized solutions to product development challenges. **Our Expertise. Your Advantage.**

GMP/GLP Compliant
FDA Registered/Inspected
DEA Licensed/Inspected

Our Services:

- Formulation and Product Development
- Analytical Services
- GMP/GLP Manufacturing
- Method Development
- Validation Services
- Quality Control Testing and Stability Storage
- Reverse Engineering
- Patent Litigation Support
- Product and Platform Licensing Opportunities

PharmaForm® L.L.C.
Excellence & Innovation in the Pharmaceutical Sciences

To learn more about PharmaForm and how we can assist you with your product development needs, call:
Elizabeth Hickman (512) 834-0449 ext. 264, info@pharmaform.com or visit www.PharmaForm.com.

Market News and Trends

Biovail to Acquire Rights to Develop, Commercialize JP-1730/Fipamezole in North America From Santhera

Biovail Corporation recently announced that its subsidiary, Biovail Laboratories International SRL (BLS), has entered into an agreement with Santhera Pharmaceuticals (Switzerland) Ltd., a subsidiary of Santhera Pharmaceuticals Holding AG to acquire the US and Canadian rights to develop and commercialize Santhera's JP-1730/fipamezole for the treatment of Dyskinesia in Parkinson's Disease (DPD). JP-1730/fipamezole is a first-in-class compound that, in a recent Phase IIb study, displayed the potential to reduce levodopa-induced dyskinesia.

"This agreement with Santhera is directly on strategy and another important step in our efforts to build a sustainable product-development pipeline in specialty central nervous system disorders," said Bill Wells, Biovail's Chief Executive Officer.

"Biovail is an emerging key player in the area of neurodegenerative disorders. With its commitment to this therapeutic area and the strong track-record it has developed in a short period of time, I am confident that JP-1730/fipamezole will become a key product for the improved management of Parkinson's disease," added Klaus Schollmeier, Chief Executive Officer of Santhera."

Under the terms of the agreement, which covers only the US and Canada, and subject to customary closing conditions, Biovail will make an up-front payment of $8 million, a further payment of $4 million upon the successful closing of Santhera's acquisition of Oy Juvantia Pharma Ltd., and will pay up to $35 million in potential development and regulatory milestones associated with the initiation of a Phase III study, regulatory submissions, and approvals of JP-1730/fipamezole in DPD. The agreement also stipulates that Biovail make additional milestone payments of up to $145 million as certain sales thresholds are met. Biovail will also make royalty payments of 8% to 15% on net commercial sales of JP-1730/fipamezole. Should Biovail pursue a second indication, up to $20 million in additional success milestones would be payable to Santhera upon approval.

Biovail will be responsible for the remaining clinical development programs and costs in the US and Canada. The companies have agreed to collaborate on the development program. Santhera will have the right to use and sublicense data generated for development and commercialization purposes outside of North America. Initiation of the first Phase III study in the US is scheduled for 2011. Santhera will retain co-promotion rights in the US.

Fipamezole is an antagonist of the adrenergic alpha-2 receptor with a novel mode of action in the treatment of Dyskinesia in Parkinson's Disease. The rationale behind the development of fipamezole is to increase noradrenergic release in certain areas of the brain, resulting in rebalancing of the distorted brain network and potentially alleviating symptoms of advanced Parkinson's disease, such as dyskinesia, motor fluctuations, orthostatic hypotension, and cognitive impairment without exacerbating the underlying Parkinsonian features of the disease.

In a recent Phase IIb study, Santhera demonstrated that JP-1730/fipamezole has the potential to reduce Dyskinesia in Parkinson's Disease with the study results also suggesting that the drug has the potential to reduce "off time" and improve cognitive function. Furthermore, the reduction in dyskinesia was found to be strongly correlated with the investigator's clinical global impression of improvement in overall condition.

Biovail Corporation is a specialty pharmaceutical company engaged in the formulation, clinical testing, registration, manufacture, and commercialization of pharmaceutical products. The company is focused on the development and commercialization of medicines that address unmet medical needs in niche specialty central nervous system (CNS) markets.

Santhera Pharmaceuticals Holding AG is a Swiss specialty pharmaceutical company focused on the development and commercialization of small-molecule pharmaceutical products for the treatment of severe neuromuscular diseases, an area of high unmet medical need that includes many orphan indications with no current therapy. Santhera's first product, Catena to treat Friedreich's Ataxia, is marketed in Canada and in a well-advanced Phase III development program. Recently published study results suggest that the company's second compound, JP-1730/fipamezole, is efficacious in reducing levodopa-induced Dyskinesia in Parkinson's Disease.

We answered the cry.

Hydrophobic or hydrophilic.

Better ways to take your medicine.

NuSil Technology.

New drug delivery materials. They're making life-saving medicines easier to take. And that's helping save patients' lives, while improving their quality of life.

NuSil is proud to be part of it. As a leading provider of custom silicone solutions, our scientists are dedicated to helping innovators innovate.

From ingestible Simethicone to transdermal delivery materials, large batches or small, you can count on NuSil for precise, custom formulations, backed by nearly 30 years of healthcare expertise and extensive regulatory knowledge.

What? When? Where? If it's NuSil, it's no problem.

NuSil SILICONE TECHNOLOGY

What's your challenge?
www.nusil.com
USA 805-684-8780
Europe +33 (0) 4 92 96 93 31

Market News and Trends

Aradigm Receives Orphan Drug Designation for Inhaled Liposomal Ciprofloxacin to Treat Cystic Fibrosis in Europe

Aradigm Corporation recently announced the European Medicines Agency (EMEA) granted Orphan Drug Designation to the company's inhaled liposomal ciprofloxacin drug product candidate for the treatment of lung infections associated with cystic fibrosis (CF).

Under European guidelines, Orphan Medicinal Product Designation provides 10 years of potential market exclusivity if the product candidate is the first product candidate for the indication approved for marketing in the European Union. Orphan drug designation also allows the candidate's sponsor to seek assistance from the EMEA in optimizing the candidate's clinical development through participation in designing the clinical protocol and preparing the marketing application. Additionally, a drug candidate designated by the Commission as an Orphan Medicinal Product may qualify for a reduction in regulatory fees as well as a European Union-funded research grant.

"We are very pleased that the EMEA granted our liposomal ciprofloxacin Orphan Drug Designation for the treatment of cystic fibrosis," said Dr. Igor Gonda, the company's CEO and President. "This designation is an important step in our development of a new chronic treatment for management of respiratory infections commonly experienced by CF patients. Our once-a-day dosing has the potential to significantly decrease the burden of therapy for these patients."

Ciprofloxacin is a widely prescribed antibiotic in the form of oral and intravenous formulations to treat acute exacerbations of infections of the lung frequently experienced by cystic fibrosis patients. It is often preferred because of its broad-spectrum antibacterial action. The company's once-a-day novel inhaled formulation of ciprofloxacin delivered in liposomes is to be used for chronic maintenance therapy as it is expected to achieve high antibiotic concentration for efficacy at the site of infection and relatively low systemic antibiotic concentrations to minimize side effects.

The company was granted previously orphan drug designations by the US FDA for inhaled liposomal ciprofloxacin for the management of CF and for non-cystic fibrosis bronchiectasis. The company is also developing inhaled liposomal ciprofloxacin as a potential treatment for prevention and treatment of bioterrorism infections, such as inhaled anthrax.

According to the Cystic Fibrosis Foundation, CF affects roughly 30,000 children and adults in the US and roughly 70,000 children and adults worldwide. According to the American Lung Association, the direct medical care costs for an individual with CF are currently estimated to be in excess of $40,000 per year.

Aradigm is an emerging specialty pharmaceutical company focused on the development and commercialization of a portfolio of drugs delivered by inhalation for the treatment of severe respiratory diseases by pulmonologists. Current activities include self-initiated development programs addressing the treatment of cystic fibrosis, bronchiectasis, inhalation anthrax infections, and smoking cessation.

Penwest Enters Third R&D Agreement With Otsuka Pharmaceutical

Penwest Pharmaceuticals Co. recently announced it has signed its third research and development agreement with Otsuka Pharmaceutical Co., Ltd. of Japan to develop a formulation of an undisclosed Otsuka compound utilizing Penwest's TIMERx drug delivery technology. Under the terms of the agreement, Penwest will receive undisclosed fees and payments. Penwest announced its first agreement with Otsuka on September 7, 2007, and the second on November 25, 2008.

"We are very pleased to have signed our third research and development agreement with Otsuka. This new collaboration is further tangible evidence that we are successfully implementing our focused business plan for 2009, including the important goal to monetize the value of our proven drug delivery technologies and drug formulation expertise. These drug delivery technology collaborations not only cover the costs of some of our scientists and fixed overhead, they also provide valuable scientific experience for our formulation team as we collaborate with our partners on their molecules," said Jennifer L. Good, Penwest's President and CEO.

Penwest is a drug development company focused on identifying and developing products that address unmet medical needs, primarily for rare disorders of the nervous system. The company is currently developing A0001, a coenzyme Q analog drug candidate for inherited mitochondrial respiratory chain diseases. It is also applying its drug delivery technologies and drug formulation expertise to the formulation of product candidates under licensing collaborations with partners.

Zogenix & Astellas Enter Exclusive US Agreement for Newly Approved Sumavel DosePro

Zogenix, Inc., a privately held pharmaceutical company, and Astellas Pharma US, Inc. recently announced their exclusive co-promotion agreement for Sumavel DosePro (sumatriptan injection) needle-free delivery system. Sumavel DosePro received FDA approval in July 2009 and is a first-of-its-kind needle-free delivery system for subcutaneous sumatriptan, a treatment that provides migraine relief within 10 minutes for some patients.

"Partnering with Astellas is a significant milestone for Zogenix that will allow us to bring this cutting-edge treatment to a broader number of people suffering from migraines," said Roger Hawley, CEO and Director of Zogenix, Inc. "It was essential that we found the right partner for the introduction of our first product, Sumavel DosePro. Astellas will bring significant sales and marketing experience to our promotional efforts and help ensure the successful launch of Sumavel DosePro."

According to the National Headache Foundation, acute migraines affect nearly 30 million Americans, primarily women between the ages of 25 and 40, who are treated by primary care physicians and neurologists. Tablets are a treatment option for some of these migraine sufferers, but not all patients are satisfied with tablet therapy. Fast-acting, non-oral options are needed particularly for those who experience migraine episodes associated with sudden onset, waking, nausea, or vomiting.

"Part of Astellas' corporate strategy is to continue establishing successful partnerships, so we are especially pleased to bring Sumavel DosePro to market with Zogenix," said Seigo Kashii, President and CEO of Astellas. "We believe this innovative product will have a broad appeal that complements our current primary care efforts and enriches our local portfolio. We look forward to our collaboration with Zogenix to further meet the needs of patients."

Sumavel DosePro is expected to be commercially available in January 2010. Under the terms of the agreement, the companies will collaborate on the promotion and marketing of Sumavel DosePro with Zogenix focusing its sales activities primarily on the neurology market while Astellas will focus mostly on primary care physicians. Zogenix will have responsibility for manufacturing and distribution of the product. Product sales will be booked by Zogenix, and Astellas will be compensated based on sales performance within their prescriber audience.

The DosePro technology is an easy-to-use, prefilled drug delivery system designed to enable self-administration of single doses of liquid drug formulations, subcutaneously, without a needle. The DosePro technology has undergone more than 10 years of design, process engineering, clinical evaluation, and development work. DosePro is protected by more than 80 patents, issued and applied for, worldwide. Approximately 9,000 injections have been delivered in clinical trials in healthy volunteers using the DosePro needle-free drug delivery system.

Zogenix, Inc., with offices in Emeryville and San Diego, CA, is a privately held pharmaceutical company focused on the development and commercialization of medicines to treat neuroscience disorders and pain. The company's initial focus is the commercialization of Sumavel DosePro. Zogenix submitted an NDA with the US FDA for Sumavel DosePro in December 2007, and received FDA approval in July 2009. The company's pipeline also includes ZX002, a novel oral controlled-release formulation of hydrocodone without acetaminophen for the treatment of chronic pain, expected to enter Phase III clinical trials in 2009. Zogenix also plans to license the patented DosePro needle-free drug delivery system to other companies.

First Report on Results of US Phase II Clinical Study of Intranasal Granisetron

Shin Nippon Biomedical Laboratories, Ltd. (SNBL) is developing an intranasal form of the antiemetic drug granisetron (development code: TRG) in the US and recently announced the first report on the results of the Phase II clinical study of TRG.

The study, which was conducted at 14 specialist cancer treatment centers in the US, was a double-blind study to compare the preventive efficacy and safety of three doses of TRG (0.5 mg, 1.0 mg, 2.0 mg) in cancer patients (total 68 patients) at risk of chemotherapy-induced nausea and vomiting (CINV) associated with the administration of highly emetogenic chemotherapy.

According to the results of the study, 71.4%, 76.0%, and 90.9% of patients achieved complete control of CINV in the 24 hours post-chemotherapy in the TRG 0.5 mg, 1.0 mg, and 2.0 mg groups, respectively. The TRG 2.0 mg dose in particular demonstrated outstanding efficacy. Furthermore, in the global satisfaction assessment conducted in patients who were treated, patients rated their satisfaction with the TRG 0.5 mg, 1.0 mg, and 2.0 mg doses at 87.7%, 79.8%, and 96.6%, respectively, reflecting high levels of global satisfaction. In particular, those patients dosed with TRG 2.0 mg expressed extremely high levels of global satisfaction.

Concerning safety, of the adverse events observed, the majority were caused by chemotherapy; no adverse events of particular note to TRG itself were observed. Furthermore, from the perspective of potential local irritation of the nose from use of an intranasal formulation, patients in the study performed self-assessments of nasal irritation, including the subjective symptoms of nasal discomfort, nasal burning, nasal itching, and bad taste. At 30 minutes, 4 hours, and 24 hours after dosing, almost no nasal irritation was observed. The favorable safety profile of TRG was thus confirmed.

Patients undergoing chemotherapy for cancer suffer significantly from nausea and vomiting caused by chemotherapy. Currently, patients often refuse to continue treatment due to the heavy burden of nausea and vomiting, posing a problem in the treatment of cancer. TRG, with its excellent efficacy in swiftly controlling nausea and vomiting, high patient global satisfaction, and favorable safety profile, is in the future certain to make a significant contribution to reducing the suffering caused by chemotherapy, and to improving patients' quality of life.

This Phase II study serves as a successful proof-of-concept for TRG's utility in cancer patients receiving highly emetogenic chemotherapy, and justifies further investigation of TRG in Phase III. The results of this Phase II study raise the added value of TRG and are expected to make a significant contribution to the smooth progress of out-licensing activities in future.

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

Par Pharmaceutical Companies, Inc. recently announced that its licensing partner, Aveva Drug Delivery Systems, has received final approval from the US FDA for its Abbreviated New Drug Application for a clonidine transdermal system. Clonidine TDS is a generic version of Boehringer Ingelheim's Catapres TTS and is the first generic 7-day patch indicated in the treatment of hypertension. Clonidine TDS is available in 0.1 mg/day, 0.2 mg/day, and 0.3 mg/day strengths. Annual US sales of Catapres TTS were approximately $297 million, according to IMS Health data. Par will begin shipping clonidine TDS to the trade in the near future.

"We are very pleased to have received this critical approval," said Paul V. Campanelli, President of Par's Generic Division. "Par and Aveva have been working together tirelessly to bring this important product to market."

"We appreciate Par's support and commitment throughout the development effort and the extended approval process of this important first generic product," added Wallace Reams, President and Chief Operating Officer of Aveva Drug Delivery Systems.

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

Clonidine Transdermal System is indicated in the treatment of hypertension. It may be employed alone or concomitantly with other antihypertensive agents. Clonidine Transdermal System should not be used in patients with known hypersensitivity to Clonidine or to any other component of the transdermal system.

Aveva Drug Delivery Systems is a Nitto Denko company, which is one of the world's largest manufacturers of and a pioneer in transdermal drug delivery systems. Nitto Denko has a 40-year history of providing pharmaceutical partners with fully integrated, controlled-release transdermal products that fulfill unmet market needs or are high-quality, low-cost brand equivalents. Leveraging this experience, Aveva offers a full range of research, development, and manufacturing capabilities using a number of sophisticated technologies to produce proprietary and generic transdermal drug delivery systems that fortify R&D pipelines and maximize the life cycles of products.

Par Pharmaceutical, Inc. develops, manufactures, and markets generic drugs and innovative branded pharmaceuticals for specialty markets.

Elan Drug Technologies Announces First Approval of Long-Acting Injectable Formulation Using NanoCrystal Technology

Elan Drug Technologies, a business unit of Elan Corporation, plc recently announced the first approval of a long-acting injectable formulation using Elan Drug Technologies' proprietary NanoCrystal technology. Janssen, a division of Ortho-McNeil-Janssen Pharmaceuticals, received the approval of INVEGA SUSTENNA, the first once-monthly atypical antipsychotic injection, by the US FDA.

"The approval of INVEGA SUSTENNA, is an important milestone for our NanoCrystal technology as it marks the first long-acting injectable product approved by regulatory authorities using the technology," said Shane Cooke, Executive Vice President and Head of Elan Drug Technologies. "Our versatile NanoCrystal technology in this instance, allowed for a stable, low viscosity, high drug-loaded formulation in a small injection volume, to be developed."

The NanoCrystal technology, a technology enabling the formulation of poorly water soluble compounds for all routes of administration, allows for a ready-to-use 1-month duration intramuscular depot formulation of paliperidone palmitate, which can be administered by healthcare professionals. The intramuscular injection is administered using a small bore needle and small volume syringe, negating the need for a power injector. By applying the NanoCrystal technology to paliperidone palmitate, for the first time, healthcare professionals will be able to provide patients with consistent medication coverage for 1 month, potentially allowing them to improve compliance for schizophrenic patients.

NanoCrystal technology, is a proprietary technology developed by Elan Drug Technologies through Elan Pharma International Limited and other Elan affiliates. INVEGA SUSTENNA is the fifth licensed product approved by the US FDA using Elan's NanoCrystal technology for various formulations.

Elan Drug Technologies, one of the world's leading drug delivery businesses, is a business unit of Elan Corporation, plc. As a fully integrated drug delivery business, Elan Drug Technologies delivers clinically meaningful benefits to patients, by using its extensive experience and proprietary delivery technologies in collaboration with pharmaceutical companies. For almost 40 years, Elan Drug Technologies has been, and continues to be, a drug delivery provider of choice for a broad range of pharmaceutical companies, including many of the world's leading pharmaceutical companies. Elan Drug Technologies offer clients drug delivery expertise with a suite of commercially launched, proprietary, technology-driven solutions, from NanoCrystal technology for poorly water soluble compounds, to customized oral controlled-release drug technologies.

Covance Becomes First CRO to Globally Deliver Innovative Technique for TK/PK Sampling

Covance Inc. recently announced the addition of a new global integrated service supporting the Dried Blood Spot (DBS) sampling technique with Good Laboratory Practice (GLP) toxicology and bioanalytical analysis. Conforming to the three Rs guiding principles of research (reduction, replacement, and refinement), DBS sampling provides higher quality toxicokinetic data while reducing test article, shipping, and storage requirements.

"As the first CRO to globally support the DBS sample technique, this integrated service provides more efficient toxicology and bioanalytical testing to potentially improve data quality," said Steven Michael, Vice President and Chief Scientific Officer, Global Bioanalytical Services, Covance. "This service reduces sample volumes, provides a more refined sample collection process, and improved data quality to increase study speed and quality. Covance spent more than a year analyzing thousands of DBS samples from multiple studies to refine the bioanalytical technique."

The DBS sampling technique increases sample handling safety with chemically treated cards that inactivate HIV and hepatitis B. The technique also enhances compound stability and increases flexibility in study design while providing convenient collection, shipping, and storage of blood samples for toxicokinetic and pharmacokinetic data. DBS also offers clinical advantages as a preferred method of blood collection over venous cannula sampling.

"This new service provides our clients with sound ethical and cost benefits by significantly reducing sample volumes and improving data quality," added Steve Barkyoumb, Vice President, North America Toxicology, Covance.

Covance offers a dedicated, integrated team of toxicology Study Directors with an average of 15 years of industry experience and bioanalytical scientists with an average of 10 years of industry experience. Covance offers flexible global capacity with facilities located in Chandler, AZ; Greenfield, IN; Indianapolis, IN; Madison, WI; Vienna, VA; Harrogate, UK; Münster, Germany; and Shanghai, China. Covance, with headquarters in Princeton, NJ, is one of the world's largest and most comprehensive drug development services companies with annual revenues greater than $1.7 billion, global operations in more than 25 countries, and more than 10,000 employees worldwide.

AlphaRx Receives China Patent on its Drug Delivery Platform

AlphaRx Inc., an emerging biopharmaceutical company utilizing proprietary drug delivery technology to develop novel formulations of drugs, recently announced it has been granted a comprehensive patent in China for its topical platform technology titled *Vehicle for Topical Delivery of Anti-Inflammatory Compounds*. The platform is an integral part of the company's clinical stage product candidate Indaflex.

"China represents a major opportunity for AlphaRx because of its huge and growing market for innovative therapeutics products," said AlphaRx President and CEO Michael Lee. "The granting of this patent from the Chinese government intellectual property authority helps protect our innovative drug delivery technology and further endorses our competitive position in China."

In April 2006, AlphaRx licensed the global rights (with the exception of Asia and Mexico) for Indaflex to Proprius Pharmaceuticals, Inc. Under the terms of the agreement, AlphaRx is eligible to receive milestone payments of up to $116 million for the successful development and commercialization of Indaflex, as well as double-digit royalties on sales. Proprius was acquired by Cypress Biosceince Inc., in March 2008.

Indaflex is AlphaRx's topical NSAID formulation under clinical development for the symptomatic treatment of osteoarthritis. Arthritis is the most common chronic disease in North America and afflicts an estimated 10% of the world's population. Indaflex's active ingredient, Indomethacin, has a long-standing and proven clinical treatment record. With AlphaRx's enhanced proprietary delivery system, the company believes its clinical effectiveness will be significantly enhanced compared to other topical preparations. Topical Indaflex delivery, the company hopes, may circumvent the significant GI side-effects commonly found with orally ingested NSAIDs.

AlphaRx is a specialty pharmaceutical company dedicated to developing proven therapies by reformulating FDA-approved and marketed drugs, which through the application of its proprietary site-specific nano drug delivery technology, offers improved medical benefits and a potential for significant commercial product development.

BD Hypak™
Glass Prefillable Syringes

BD

Helping all people live healthy lives

Customizable Solutions & Unparalleled Support

Strategic Marketing
- An understanding of market trends for parenteral delivery systems
- Recognized leader in safety solutions
- Capable of adapting your product to meet regional needs in a global world

Quality and Regulatory Specialists
- BD Hypak Syringe materials conform to US, European, and Japanese pharmacopoeias
- Drug Master File and a Technical Dossier for product registration worldwide
- Our regulatory experts are ready to assist you

Technical Expertise
- Partnering with machine manufacturers to meet all your processing requirements
- Our Technical Support Team is ready to assist you during any phase of processing
- Expert project teams are ready to propose innovative solutions to meet your specific drug-delivery needs

For more information, please call 800.225.3310 or visit www.bd.com/pharmaceuticals

BD Medical
Pharmaceutical Systems
1 Becton Drive
Franklin Lakes, NJ 07417

BDPS_marketing@bd.com

EXCIPIENT UPDATE

Pharmaburst® 500: Meeting the Challenge of ODT Formulations

By: John K. Tillotson, RPh, PhD

INTRODUCTION

The suitable formulation of an orally disintegrating tablet (ODT) is typically more difficult than the formulation of a similar per-oral therapeutic modality. As with any tablet dosage form, the tablet must be substantially robust, exhibiting a suitable hardness and friability. However, in addition, the ODT must provide for a significantly increased rate of disintegration and superior organoleptic properties. In many cases, the pursuit of tablet durability is in direct opposition to the requirement for a rapid disintegration. Likewise, the need for suitable palatability (taste and mouthfeel) introduces another challenging dimension to the formulator.

ODT formulations offer patients significant advantages over similar per-oral formulations, including more rapid onset of action, increased convenience, greater bioavailability, and improved compliance with therapy.[1] Additionally, ODT formulations are particularly suitable for patients who exhibit difficulty swallowing conventional per-oral dosage forms. For example, the elderly and pediatric populations stand to benefit significantly from the further introduction of therapeutic moieties in the form of ODTs. Likewise, particular disease states are more amenable to treatment by ODT formulations, specifically Alzheimer's, epilepsy, Parkinson's, and schizophrenia. Furthermore, ODTs are particularly indicated in the treatment of conditions exhibiting nausea, such as migraine headaches, cancer, and pregnancy.

Finally, ODT formulations offer a significant economic opportunity to the pharmaceutical manufacturer. In fact, demand for ODT-adapted pharmaceuticals is expected to increase 8.9% annually to a total market value of $2.6 billion in 2012.[2] Additionally, it is noted that ODT technology offers considerable benefits for product lifecycle management, development timelines, patient convenience, and market share.[3]

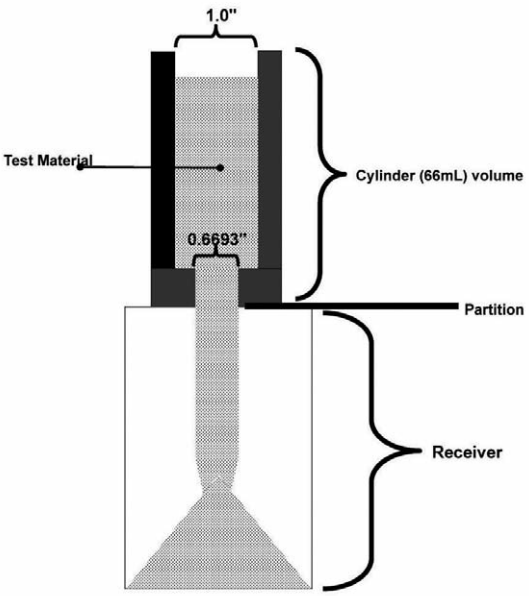
ODT MANUFACTURING

Numerous technologies have been employed for the purpose of manufacturing ODT products, including freeze-drying, molding, spray-drying, sublimation, direct compression, wet granulation, floss processing, and mass extrusion. Due to the use of typical in-house processing resources in lieu of employing more costly, specialized equipment, direct compression represents the most economical option for the manufacture of ODT dosage forms. However, simple dry blends of polyols, polysaccharides, and other excipients do not always optimally balance the requirements for tablet robustness, disintegration, and palatability required for suitable ODT manufacture. For this reason, preformulated excipient systems employing combinations of previously co-processed ingredients aimed at optimizing overall ODT performance are most preferred in the manufacture of ODT drugs.

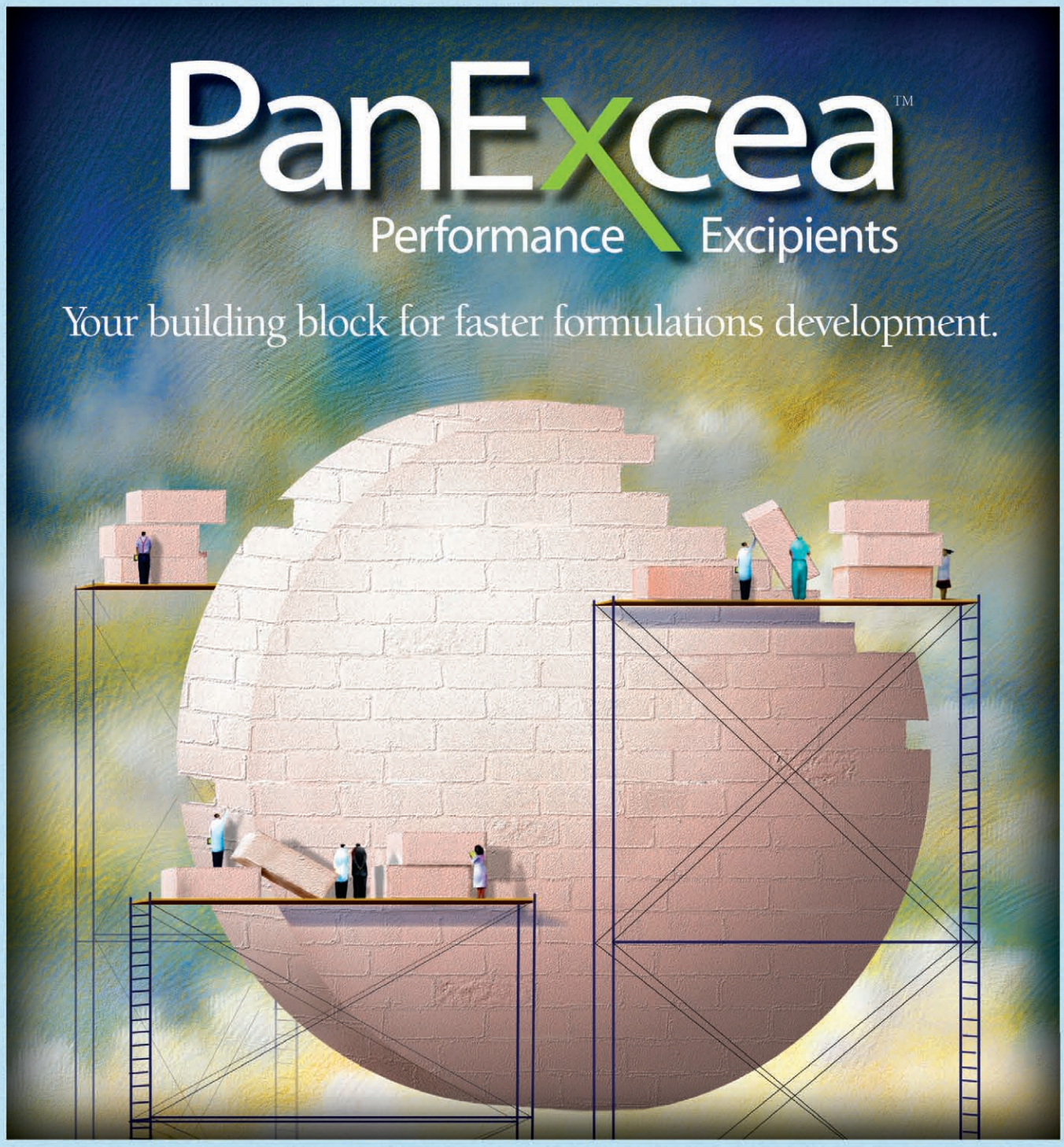
PHARMABURST® 500

Pharmaburst 500® is an IP-protected, co-processed, use-as-received, directly compressible (DC) excipient system expressly

FIGURE 1



Critical Flow Apparatus



Novel Technology. High-Quality. Optimized Performance.

The PanExcea MHC300G performance excipient serves as a filler, binder and disintegrant in one homogeneous particle — eliminating formulation steps and helping you get to market faster. Designed for immediate release applications, it delivers extensive API compatibility and variable load capability, dramatically increasing formulation flexibility.

FREE SAMPLE!

Find out how PanExcea performance excipients can help you build a better formulation. To collaborate with an application specialist and request a *FREE* sample, call 1-800-943-4747, 908-329-9910, or visit www.mallbaker.com/PanExcea1.

J.T.Baker®

Mallinckrodt Baker

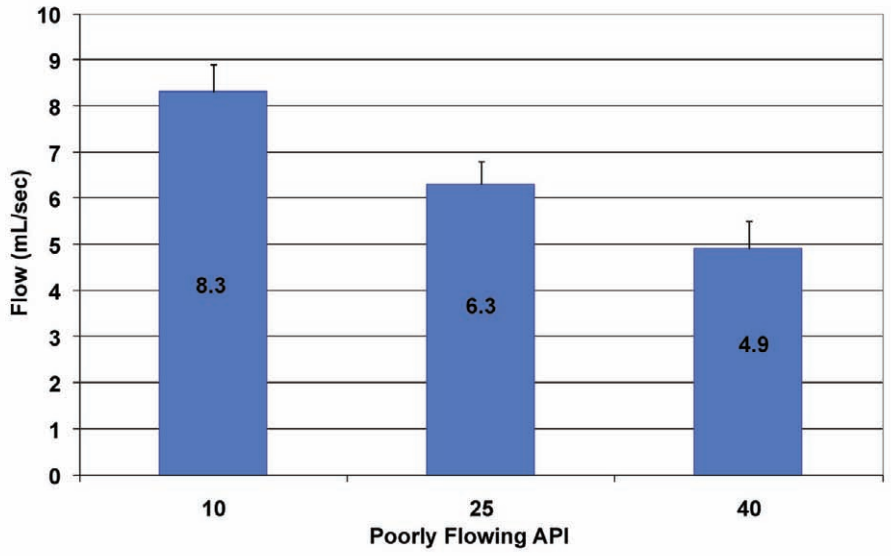
designed to provide for the optimum performance of ODT formulations. The system is designed to be employed with standard pharmaceutical blending and direct compression equipment and does not require special handling or environmental controls for processing. As such, it offers the pharmaceutical industry a highly cost-effective and speedy conduit for entry into the ODT marketplace. The system also significantly benefits from the IP-protected technology.

DESIGNING THE SYSTEM

The optimal ODT excipient system should be formulated to provide for the maximization of each characteristic simultaneously, and should therefore be formulated at the union of the three sets. This is not a trivial undertaking as typically what augments the magnitude of one characteristic simultaneously diminishes the magnitude of another.

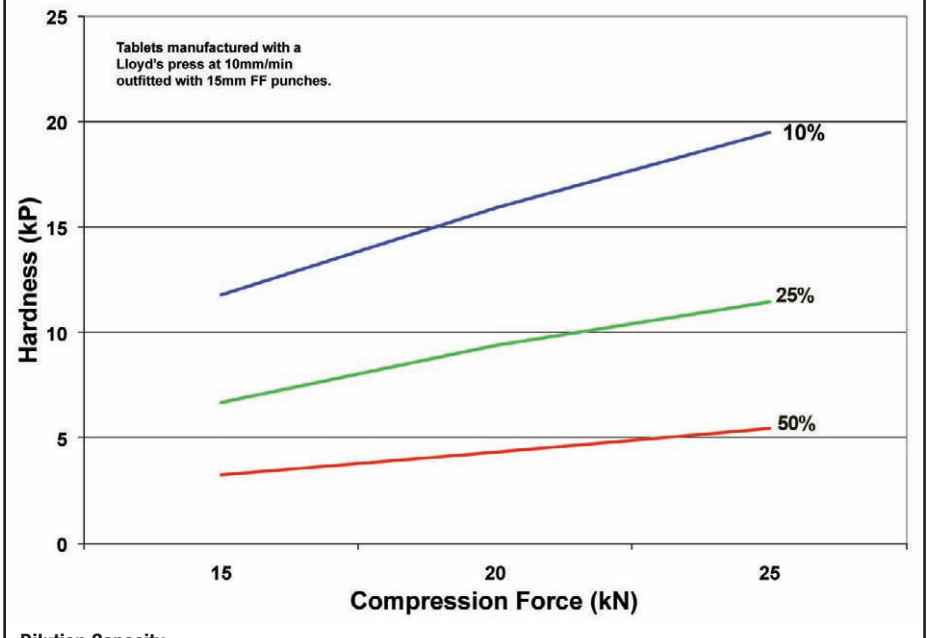
Therefore, in order to successfully develop a material that possessed these optimum characteristics, a 120-run, D-optimal, combined mixture, process factor, and categorical design of experiments was employed. Treatments in the design consisted of varying series of mixtures composed of a multitude of co-processed ingredients along with compression force and tablet size. The considered responses were organoleptic perception, compaction, friability, and disintegration time. Multiple-regression analysis of the responses resulted in the determination of the optimum co-processed mixture of excipients required to produce a maximally effective ODT system: Pharmaburst 500.

FIGURE 2



Critical Flow Results

FIGURE 3



Dilution Capacity

CAPTISOL® - Creating Pure Solutions

FREE SAMPLES
www.cydexpharma.com

The advanced drug formulation technology of CyDex, Captisol®, is based on a modified cyclodextrin molecule that enables creation of new products by significantly improving the solubility, stability, bioavailablity, safety and dosing of active pharmaceutical ingredients (APIs).

Captisol® is one of a series of anionically charged sulfobutyl ether β-cyclodextrins (SBE-CDs) that were synthesized and patented. The safety and other characteristics of Captisol® have been well profiled and are described in a Drug Master File (DMF) with the U.S. Food and Drug Administration.

CyDex works worldwide with companies interested in licensing Captisol® and other SBE-CD technologies. A Starter Kit of Captisol® is available upon the execution of a confidentiality agreement. Additional supplies can be purchased directly from CyDex.

CAPTISOL ® is process patent protected until 2018

- **Superior**
- **Safe**
- **Stable**
- **Soluble**

CYDEX
PHARMACEUTICALS, INC.

www.cydexpharma.com 913.685.8850

Living Beyond Our Legacy

PHYSICAL & FLOW PROPERTIES

Of paramount importance to a DC excipient system is its ability to flow, and furthermore, its resistance to dilution of its flow characteristics by active incorporation. Pharmaburst 500 exhibits a spherical morphology and, as indicated by its physical properties (Table 1), is expected to exhibit excellent flow.

In order to challenge its flow, the system was diluted with the poorly flowing excipient Crospovidone XL to replicate a poorly flowing API (angle of repose = 46º, Carr's index = 31.3) and subjected to critical orifice (0.6693" diameter) testing. 63 mL each of 10%, 25%, and 40% dilutions with Crospovidone XL were tested by placing the powder in the critical orifice apparatus (Figure 1). The partition was removed, and the time for the powder to flow to completion from the cylinder was recorded. The only force acting on the powder was gravity, and the walls of the cylinder were not beveled or funneled toward the orifice. Results of the critical flow testing are displayed in Figure 2. Also indicated in Figure 2, Pharmaburst 500 was capable of carrying large amounts of poorly flowing API through the critical orifice, while still maintaining suitable flow without the application of agitation or vacuum: approximately 2 g of the highest dilution blend passed through the orifice per second.

TABLE 1

Physical Properties of Pharmaburst 500®	Angle of Repose (º)	BD (g/mL)	TD (g/mL)	Carr's Index
Pharmaburst 500	33.1	0.411	0.485	15.3

DILUTION CAPACITY

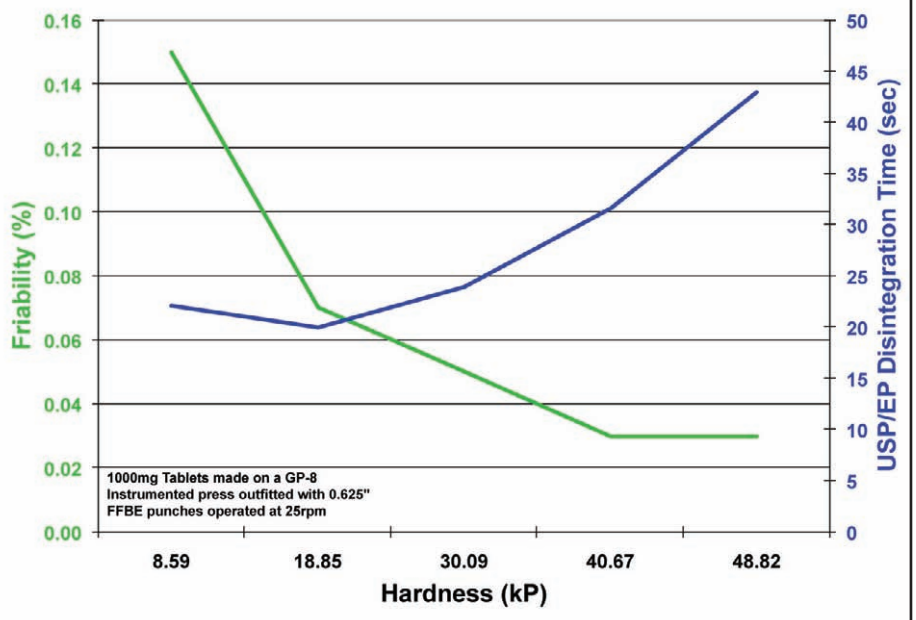
To demonstrate the dilution capacity of Pharmaburst 500, compactions were conducted with varying concentrations of Acetaminophen (APAP) non-DC powder at compression forces of 15, 20, and 25 kN. The compactions were realized on a Lloyd's press outfitted with a 15-mm FF punch. The press was operated at 10 mm/min. Results are displayed in Figure 3.

As indicated in Figure 3, Pharmaburst 500 is capable of diluting non-DC-grade APAP powder even at levels of 50%, without exhibiting compaction failure as determined by loss of hardness at higher compression forces. At all dilutions, increasing compression force resulted in increased hardness of the compact.

PLACEBO PERFORMANCE

To demonstrate the capabilities of Pharmaburst 500, 1000 mg of placebo (Pharmaburst 500 blended with 2.5% sodium stearyl fumarate) tablets were manufactured on a GP-8 instrumented tablet press outfitted with 0.625" FFBE punches and operated at 25 rpm at the following compression forces: 10, 15, 20, 25, and 30 kN. Resultant tablets were tested for hardness, friability, and disintegration time. The results are displayed in Figure 4.

FIGURE 4



Composite Performance of Pharmaburst 500® Placebo Tablets

NEW THIS YEAR!
AAPS has changed the registration process to **one deadline.**
Register by September 11, 2009 to receive the discounted rate to attend the Annual Meeting!

The 2009 AAPS Annual Meeting and Exposition Online Preliminary Program IS NOW AVAILABLE!

2009 AAPS Annual Meeting and Exposition

November 8–12, 2009

Los Angeles Convention Center, Los Angeles, CA, USA

Register as a group for the AAPS Annual Meeting and save hundreds of dollars!
Four fully paid registrations qualify for a $100.00 discount for everyone in the group.

For Up-to-Date Information, Log on to: www.aapspharmaceutica.com/annualmeeting

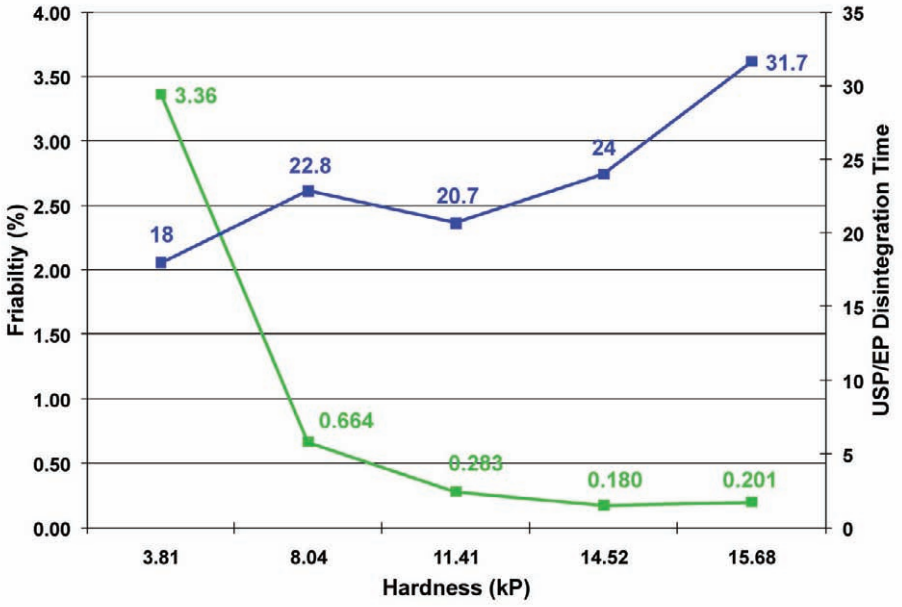
aaps®
American Association of Pharmaceutical Scientists

The Pharmaburst 500 system is highly compactable, producing tablets as hard as 48.8 kP at a compression force of 30 kN. At only 10 kN of compression force, tablets of 8.6 kP were produced. This superior compaction is of paramount importance, when operating on high-speed presses with reduced dwell times, in order to produce robust tablets. The Pharmaburst 500 system exhibits very low friability (less than 0.2% at compression forces from 10 to 30 kN). While manufacturing extremely robust tablets, Pharmaburst 500 also provides for rapid disintegration (at 40.6 kP, tablet hardness the USP/EP disintegration time is around 30 seconds).

LOW-DOSE PERFORMANCE

The majority of ODT formulations available in the market today are low dose (active weight < 50 mg). For this reason, experimentation was conducted to demonstrate the utility of Pharmaburst 500 in manufacturing a low dose ODT. A blend of the antihistamine, Loratidine, 10 mg (10%) and Pharmaburst 500 (87.5%) was mixed for 10 minutes using a PK blender. Subsequently, Lubripharm™ SSF (2.5%) was added to blend 1 and mixed for 5 minutes using a PK blender. The resultant blend was compressed into tablets weighing 100 mg using a GP-8 instrumented tablet press outfitted with 0.25" FFBE punches. Tablets were compressed with 1.2 kN of force. Tablet weight, thickness, hardness, friability, USP/EP disintegration time, and oral disintegration time were recorded. The physical test results for the manufactured tablets are displayed in Table 2.

FIGURE 5



Composite (500 mg APAP ODT)

HIGH DOSE PERFORMANCE

Low dose ODT formulations are less challenging to formulators than high dose ODTs. A trend toward higher dose ODTs is emerging, especially in the OTC market. One of the major performance benefits of Pharmaburst 500 is its robust compaction that allows for the incorporation of high dosing of actives, while still maintaining robustness, rapid disintegration, and superior organoleptics.

To demonstrate this property, a blend of the analgesic, Acetaminophen, 537 mg of taste-masked (TM) material (44.8%) equivalent to an active dose of 500 mg of Acetaminophen and Pharmaburst 500 (52.8%) were mixed for 10 minutes using a PK blender. Subsequently, blend 1 was mixed with Lubripharm SSF (2.5%) for 5 minutes. The resultant blend was compressed into tablets weighing 1200 mg on a GP-8 tablet press outfitted with 0.625" FFBE punches. To demonstrate formulation robustness, tablets were compressed at forces of 10, 15, 20, 25, and 30 kN. A pre-compression of 3 kN was also applied. Tablet weight, thickness, hardness, friability, and USP/EP disintegration time were recorded.

The manufactured tablets physical characteristics are displayed in Figure 5. Here, it is apparent that high dose APAP tablets of suitable hardness, friability, and disintegration times were manufactured over a compression force range of 15 to 25 kN.

TABLE 2

Tablet Weight	100 mg
Thickness	3.445 mm
Hardness	2 kP
Friability	0.0975%
USP/EP Disintegration Time	4.8 seconds
Oral Disintegration Time	7 seconds

Loratidine ODT Characteristics

COMPACTION OF MULTIPARTICULATE SYSTEMS

The majority of pharmaceutical actives require some form of taste-masking prior to their incorporation into an ODT formulation. Strategies for taste-masking include ion-exchange complexation, coacervation, and spray-coating amongst others. Generally, the taste-masking process produces a multiparticulate system that includes the drug and the taste-masking materials. It is apparent that for the taste-masked systems to be effective, they must withstand the process of compaction without compromising their taste-masking effects. This is especially important in high dose ODTs in which taste-masked particles can be pressed together forming coalesced units, which significantly reduces palatability. The highly compactable nature of Pharmaburst 500 allows for the manufacture of hard, robust tablets at relatively low compression pressures, which preserves the integrity of taste-masking.

SUMMARY

Pharmaburst 500 is an ODT system specifically designed to provide for optimum performance with regard to organoleptics, compaction, and disintegration. Pharmaburst 500 is easily blended and compressed with actives of choice using standard pharmaceutical manufacturing equipment and under standard processing conditions. The system is readily employed in both low and high dose formulations to quickly and easily manufacture robust ODTs. Due to its high compactability, Pharmaburst 500 is an excellent option for the incorporation of high dose actives and taste-masked multiparticulates. In summary, it offers superior ODT performance in a cost-effective, IP-protected platform.

REFERENCES

1. Dollo G, Chevanne F, Le Corre P, Chemtob C, Le Verge R. Bioavailability of phloroglucinol in man. J Pharm Belg. 1999;54(3):75-82.
2. Maritneau B. A look at fast-dissolving drug delivery systems. Drug Delivery Technology. 2009;9(4):36-38.
3. Harmon T. Orally disintegrating tablets: a valuable life cycle management strategy. Pharmaceutical Commerce. March 2007.

BIOGRAPHY

Dr. John K. Tillotson is a Senior Scientist and ARTS (Applications, Research and Technical Services) Department Lead at SPI Pharma, Inc., a mannitol and co-processed drug delivery platform processing and manufacturing company. Dr. Tillotson earned his BS in Pharmacy from Ferris State University, Big Rapids, MI, and his PhD in Industrial Pharmacy from the University of Cincinnati, Cincinnati, OH, where he trained under Dr. Adel Sakr. He has held industrial positions in Guatemala and the US. Dr. Tillotson's primary areas of interest are quick-dissolve tablet technologies, particularly directly compressible modalities. Additionally, he specializes in multiple-regression analysis and optimizations of quick-dissolve technologies, solutions, and systems. Previously, Dr. Tillotson was involved with the development and optimization of bumetanide sustained-release technologies through multiple-response optimization. He has developed several quick-dissolve systems for nutraceuticals, OTC, and prescription products. Additionally, he has participated in idiosyncratic ODT formulation development for various APIs. Dr. Tillotson has presented various original, workshop, invited symposium, and/or poster presentations at national and international meetings. He has published papers discussing the use of multiple-response optimization for the development of extended-release formulations, as well as papers discussing the benefits of various ODT excipient systems. He is a member of the Rho Chi Pharmaceutical Honor Society and of the American Association of Pharmaceutical Scientists.

FDA's New Draft Guidance on Technical Considerations for Pen, Jet & Related Injectors Intended for Use With Drugs & Biological Products: Comments & Concerns

By: Bradley Merrill Thompson, MBA, and Leah R. Kendall

On April 27, 2009, the US FDA issued a new draft guidance document that was much-anticipated by many in the drug delivery world.[1] The draft guidance, *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products*, covers a wide array of injector products and topics.[2] It is of particular significance to companies that develop and manufacture therapeutic products administered by pen, jet and other types of injectors, as well as to medical device manufacturers that develop and make injectors. The FDA required comments to be submitted by July 27, 2009, to ensure they are reviewed before the agency started finalizing the guidance.[3]

The following provides an overview of the draft guidance and highlights some of the key comments submitted in response. Overall, stakeholders expressed several fundamental concerns regarding the guidance that, if adopted by the agency, will require major revisions. It remains to be seen how the agency will respond.

OVERVIEW OF THE DRAFT GUIDANCE

Scope

The draft guidance casts a wide net to a broad range of products in two important respects. First is the way in which injector is defined. It includes - but is not limited to - jet injectors, pen injectors, piston syringes, needle-free injectors, mechanically operated injectors, and injectors with computerized or electronic elements. Thus, the draft guidance encompasses several types of technologically diverse injectors and could include even more now or in the future. On the other hand, the guidance excludes some injectors, such as dental surgery jet injectors, without explaining why. Stakeholders commenting on the draft guidance expressed concern over how they could assess what other injectors may be included or excluded from the guidance's scope, given the lack of explanation on the definition.

Second, the draft guidance addresses nearly all configurations of injectors: stand-alone, general use injectors, injectors intended for a product class or product line, and injectors intended for use with a specifically named drug or biological product. In other words, the draft guidance extends to combination products of which a device injector is a constituent part, and to general use device injectors that are not combination products.[4] Here, commentors expressed confusion on what injectors are intended for a product class or product line and asked for examples of what the agency means.

Technical & Scientific Issues for Injectors

The draft guidance primarily focuses on the technical and scientific issues to be considered when developing injectors intended for use with drugs or biological products, as well as content and format information for injectors that are reviewed under a 510(k) submission or as part of an NDA or Biologics License Application (BLA). However, a significant concern expressed in comments is that, despite its wide breadth of scope, the draft guidance does little to differentiate among the requirements that may apply to different types of injectors. Instead, the document provides wide-ranging lists of scientific and technical considerations that may or may not be relevant depending upon the type of injector at issue. Though the information provided is quite comprehensive, the draft guidance fails to connect the information to specific types of injectors. This issue fundamentally impacts the structure and content of the guidance.

In addition to this key issue, commentors questioned the document's apparent inconsistency with other guidance documents, such as the FDA's *Guidance on the Content of Premarket Notification (510(k)) Submissions for Piston Syringes*, FDA device design control guidance, and the draft ISO document *Needle-Based Injection Systems for Medical Use - Automated Functions - Requirements and Test Methods*.

As a result, if the final version remains substantially as written, it could significantly increase regulatory burdens for injector marketing submissions, particularly the relatively simpler, general use device injectors. Applicants submitting injector-related marketing submissions would need to study the draft guidance carefully to glean the most pertinent information for their products.

Policy Considerations

Commentors also expressed a variety of concerns with the guidance's lack of discussion on policy issues impacting the development and approval of injectors. One example is with

I THREE GOOD REASONS TO PUT YOUR TRUST IN PFEIFFER I

ENGINEERED IN GERMANY
First of all we develop our systems and products in a place where precision and quality are top priorities.

INNOVATION BASED ON EXPERIENCE
Then we produce them ourselves to be totally sure that every design detail is translated into operational excellence.

SERVICE TO SATISFY
Finally we tailor the benefits of our systems and products to meet all your requirements, exactly and quickly.

| Pfeiffer |

Pfeiffer of America

742 Alexander Road | Suite 201 | Princeton | NJ 08540 | United States | phone +1 609 987 0223 | fax +1 609 987 1511 | www.pfeiffer-group.com

respect to clinical studies on injector-related products, which the guidance addresses in a way that raises more questions than it answers. For example, while the draft guidance notes that specific considerations for clinical trial design are beyond its scope, it makes the broad statement that clinical trials for some injectors may focus on the injector itself without providing examples of this seemingly atypical situation. The current draft also does not acknowledge situations in which clinical trials may not be required or where simulated use studies may be preferred.

Further, although the draft guidance is directly focused on injector development and submissions, it fails to address a number of fundamental, intertwined policy issues. By way of example, the draft guidance does not provide much detail on the appropriate type(s) of marketing application for injector combination products. Thus, while the draft guidance provides detailed information on the content requirements of an application for an injector or incorporating an injector, it does not address fundamental questions about the type or number of application(s) required. Another example is the rules pertaining to device modifications, including any needed FDA submissions. As commentors observed, because general guidance on this issue for combination products is limited, manufacturers of combination products incorporating injectors have struggled with these ambiguities.

In addition to the aforementioned issues, commentors identified numerous concerns and questions with specific language and provisions in the draft guidance. Those interested in reviewing the submitted comments can obtain them on www.regulations.gov.[5]

SUMMARY

In all, the draft guidance could have important implications for both stand-alone injector products and injectors that are part of a drug-device or biological-device combination products, including potential significant increases in submission requirements. Manufacturers of injectors or products incorporating an injector component will want to review the draft guidance and track future FDA communications regarding plans to revise and finalize the guidance. ◆

REFERENCES

1. 74 Fed Reg. 19094, Draft Guidance for Industry and Food and Drug Administration Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use With Drugs and Biological Products. Availability April 27, 2009.
2. The draft guidance is available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf.
3. FDA regulations allow for public comment on guidance documents at any time.
4. This could be a drug-device or a biological-device combination that is combined or produced as a single entity or that is packaged or labeled for use in combination. See 21 CFR § 3.2(e).
5. Comments submitted on the draft guidance are available at: http://www.regulations.gov/search/Regs/home.html#docketDetail?R=FDA-2009-D-0179 (FDA Docket No. 2009-D-0179).

BIOGRAPHIES

Bradley Merrill Thompson is a shareholder in the Health Practice in Epstein Becker & Green's Washington, DC, office. Mr. Thompson counsels medical device, drug, and combination product companies on a wide range of issues involving compliance with the laws administered by the FDA, as well as reimbursement issues. He serves as General Counsel to the Combination Product Coalition and Counsel to AdvaMed for payment issues. In addition to a law degree, Mr. Thompson earned an MBA and often works with clients on strategic planning.

Leah R. Kendall is a Senior Associate in the Health Practice in Epstein Becker & Green's Washington, DC, office. She advises clients on the regulatory requirements of the FDA and on reimbursement issues. Ms. Kendall also serves as Counsel to the Combination Products Coalition and develops and advocates for FDA policy and rule-making on issues impacting combination products. She earned her BS in Chemistry and graduated first in her class from law school.

Consultant level information and analysis on companies, pipeline/products, technologies, deals, acquisitions and venture capital investments in pharma/biotechnology, specialty pharma and drug delivery.

PHARMACIRCLE™

Innovation in Pharmaceutical Knowledge Management

www.pharmacircle.com go

Comprehensive, Innovative, Updated daily, Easy access and use

- Global pipeline and product information searchable by indication, phase, mechanism of action, route of administration and formulation type (180+ categories). Product information integrates sales, partnerships, deals, news, approval/market launch dates, clinical trials, labels, patents and exclusivity information.
- Powerful search engine that filters product and pipeline data by molecule properties (solubility, MW, food effect, first pass, bioavailability by route, BCS class…) as well as product attributes (dose, route of delivery, formulation type, frequency of administration, excipients, exclusivity…). Results are transferrable to Excel tables and interactive charts.
- Searchable FDA product module integrates most sought out content from Drugs@FDA (approval package/history, route, dosage forms, therapeutic equivalents), Electronic Orange Book (market and patent exclusivity), NDC (packaging info), Excipient data base (amount of excipients used in each dosage form) and Product Labels (non-PDF labels).
- Detailed and up-to-date analysis of drug delivery technologies with specific applications to products and pipeline.

Check out the free and comprehensive Contract Pharma data base which provides a multitude of search criteria and a module for side by side comparison of company services.

PHARMACIRCLE™

(760) 436 1199

or contact@pharmacircle.com

SOLID LIPID NANOPARTICLES

Solid Lipid Nanoparticles for the Delivery of Pharmaceutical Actives

By: Andrew Loxley, PhD

INTRODUCTION

An increasing number of active pharmaceutical ingredients (APIs) under development are poorly water soluble and therefore have poor bioavailability. These are designated Biopharmaceutical Classification System (BCS) class II and class IV APIs.[1-3] Creative formulation efforts are required to produce a finished drug product from these APIs that has acceptable pharmacokinetics. A common formulation approach with such compounds is to focus on creating and stabilizing very small particles of the API in an attempt to increase the surface area available for dissolution in vivo, and hence the rate of dissolution, and consequently plasma or tissue levels of API. Another approach is to create so-called solid solutions of the API.[4]

Biologics (proteins, peptides, oligonucleotides, and SiRNAs) are water soluble but bring their own formulation and delivery challenges. Shelf-life stability and enzymatic degradation are two main areas of concern, and formulation design focuses on stabilizing the API in storage and protecting it from endogenous enzymes until it reaches its therapeutic target. In more advanced formulations, the API is formulated into a delivery vehicle that specifically targets tissue or cells to maximize the therapeutic index.

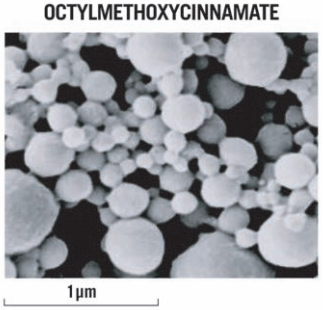
NANOPARTICLE FORMULATIONS

Many of the aforementioned formulation approaches utilize nanotechnology, that is, the preparation of sub-micron structures containing the API. For BCS class II and IV APIs, the simplest nanoparticle is made of pure API, formed by top-down processes starting with bulk API, such as milling, grinding, homogenization, ultrasonication, and are stabilized in dispersion by the presence of a surfactant.[5] Alternatively, bottom-up "self-assembly" processes can be used, such as anti-solvent precipitation and micellar incorporation by dilution. For example, insoluble APIs may be incorporated into nano-sized vesicles or liposomes, in the form of particles dispersed in the aqueous core of the vesicles, or as molecularly dissolved material in the lipid bilayer.[6] Biodegradable polymers have also been used to form API-loaded nanoparticles or block copolymer micelles or polymersomes, usually by emulsification/solvent-evaporation techniques.[7,8] Biocompatible and biodegradable inorganic nanoparticles can be loaded with API via a microemulsion technique.[9] Biologics and other water-soluble drugs have been incorporated into the aqueous core of liposomes, into the aqueous domains of biodegradable polymer nanoparticles prepared by water-in-oil-in-water emulsion/solvent evaporation, and charge-neutralization nano-complexes made by interaction with oppositely charged polyelectrolyes, or by attachment to gold nanoparticles.[10-13]

Issues with shelf-life stability of the finished product or the need for organic solvents in processing for many of these approaches render them less than ideal.

FIGURE 1

SEM OF SLNs CONTAINING OCTYLMETHOXYCINNAMATE



Particle Sciences

PPD's Global Central Labs

Transforming Sample Management

Success should never be taken for granted...

so at PPD's global central labs, we work hard to make sure you are in control of your study goals and in touch with your samples to ensure their life cycle is successful.

As the testing industry evolves and your needs change, PPD is taking a fresh look at sample management and redefining it. We're not waiting for the future, we're shaping it.

Technology you can count on

- Unique labeling system for accurate sample tracking
- Temperature-controlled specimen storage
- 24/7 data access, monitoring and flexible reporting

Results you can bank on

- Fast start-up & on-time data delivery help you be first to market
- Vendor contracts save on transportation costs
- Tight quality controls minimize errors

The people who make it happen

- Expert consulting
- Dedicated project management
- Highly trained site personnel

Call Rob Danziger at +859 442 1300, e-mail us at **labs@rtp.ppdi.com** or visit us at **www.ppdi.com**

Millions of Samples Successfully Managed

PPD'S GLOBAL CENTRAL LABS
A 20 Year History of Success
A FUTURE OF ENDLESS INNOVATION

PPD®

PRECLINICAL/PHASE I > PHASE II-IIIb > POST-APPROVAL > **LABS**

No one gets medicine into the system faster®

SOLID LIPID NANOPARTICLES

SOLID LIPID NANOPARTICLES – MATERIALS & SYNTHESIS

Many biocompatible/biodegradable lipids are solid at room temperature, can be obtained in high purity, are generally recognized as safe (GRAS), and are inexpensive. Some common solid lipids used to make solid lipid nanoparticles (SLNs) include triglycerides (eg, Compritol 888 ATO and Dynasan 112), carnauba wax, beeswax, cetyl alcohol, emulsifying wax, cholesterol, and cholesterol butyrate.

Nano- and microparticles made of these lipids and suspended in water offer an option for formulating both BCS class II and IV APIs as well as biologics that may overcome the issues of shelf-life stability and the cost and toxicity associated with the use of organic solvents. In effect, the concepts of nanoparticles and solid solutions are being combined.

Nanoparticles of these lipids may be made using a templated synthesis from a microemulsion of the molten lipid in aqueous surfactants, by precipitation of the wax from a solution in a non-ionic surfactant on addition of water, or by emulsifying the molten lipid into a hot aqueous surfactant solution with high-shear mixing to obtain the desired submicron particle size.[14-16]

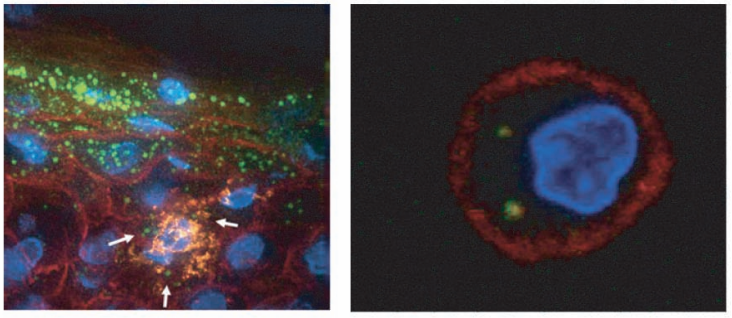
API ENCAPSULATION IN SLNs

Small molecules can be entrapped within the lipid matrix of the nanoparticles by dissolving or dispersing the material in the molten lipid prior to particle formation. Souto's PhD thesis on the delivery of APIs using SLNs lists more than 100 APIs that have been encapsulated in SLNs.[17]

An SEM of the particles of a typical SLN dispersion (in this case of particles containing the sunscreen octylmethoxycinnamate) is shown in Figure 1. Particles of this type are made at commercial scale for formulation into

FIGURE 2

LOCATION OF FLUORESCENT SLNs AFTER EXPOSURE



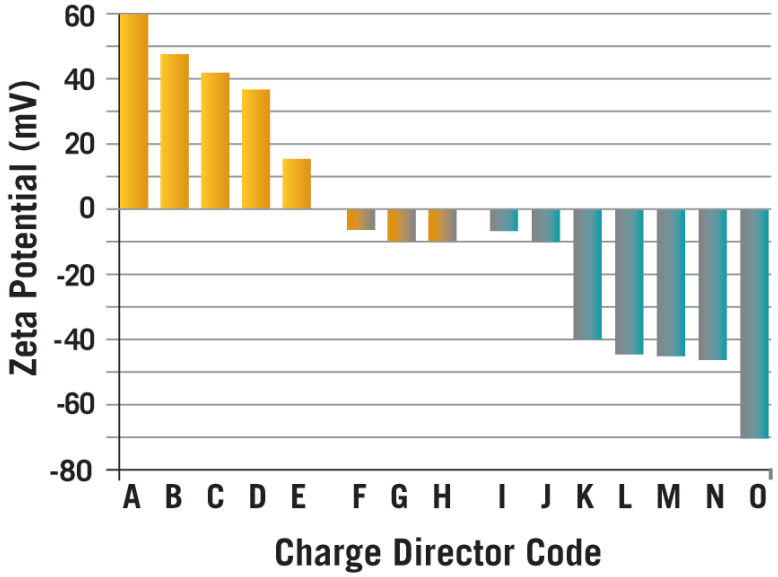
(a) Mucosal tissue

(b) After internalization by dendritic cells.

Particle Sciences

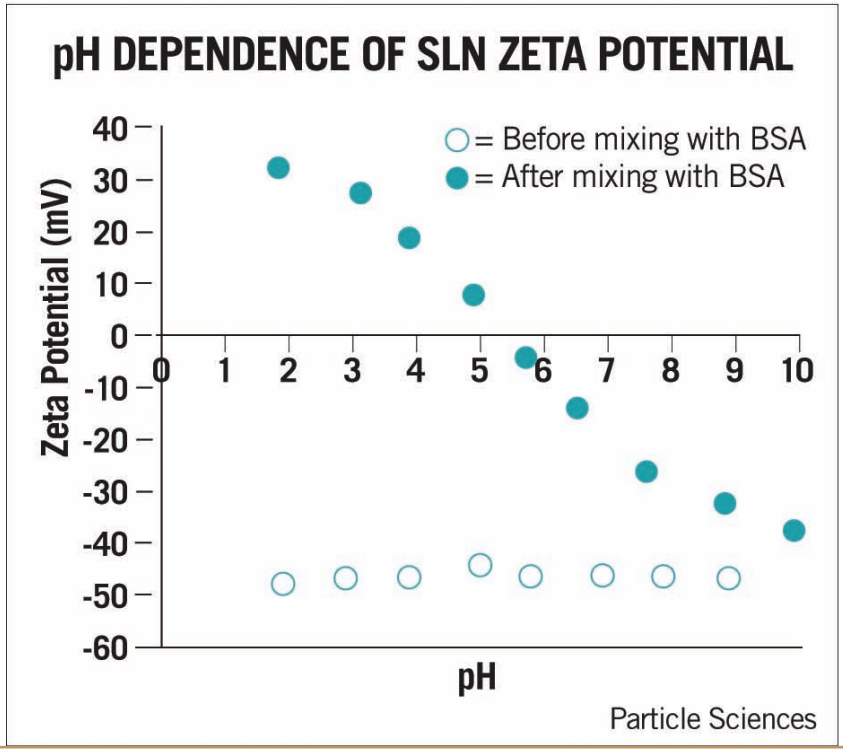
FIGURE 3

DEPENDENCE OF ZETA POTENTIAL OF SLNs ON EMULSIFIER TYPE



Particle Sciences

FIGURE 4



topical products to provide UV-protection.

In some cases, the API is not compatible with the lipid and is expelled from the nanoparticle, usually during cooling and solidification. This can lead to undesirable macroscopic crystals of API in the final formulation or phase separation of the particles to structures as complex as "nano-spoons."[18] By mixing liquid lipids with the solid lipid prior to particle formulation, lipid crystallization is hindered or prevented, and a more amorphous nanoparticle internal structure is achieved. In this way, APIs are less likely to be expelled from SLNs during the cooling step of their preparation, and stable SLNs may be formulated with a wider range of APIs.[19]

As one example created at Particle Sciences, fluorescent SLNs have been prepared by adding a fluorescent dye to the molten lipid prior to particle preparation. Green fluorescent SLNs were prepared with pyrromethene 567A dye, and red fluorescent SLNs with 1,1'-dioctadecyl-3,3,3',3'-tetramethylindocarbocyanine perchlorate (DiI) by a modified preparation technique to accommodate the low solubility of DiI in the molten lipid. Fluorescent SLNs are useful to follow the fate of particles applied mucosally in vivo and determining efficiency of uptake by antigen presenting cells in vitro in the development of a novel HIV vaccine.[20] Tissue samples taken from penile epithelial explants after application of fluorescent SLNs show particles penetrated well into the tissue (Figure 2A), and dendritic cells are shown to internalize green fluorescent SLNs following incubation in vitro (Figure 2B).

The green fluorescent particles were also used in a proof-of-concept study for the development of an inhalable API-loaded SLN dispersion. A fluorescent dye-loaded SLN dispersion was aerosolized using an OTC nebulizer, and the aerosol plume from the mouthpiece was illuminated by UV light. The green fluorescent glow of the plume showed that the SLNs were indeed in the aerosol droplets, and analysis of the condensed aerosol showed that the particle size distribution of the SLNs in the original dispersion was maintained in the droplets. The droplet size of the aerosol was also found to be ideal for delivery to the deep lung (around 5 microns). This work could lead to improved pulmonary delivery of water-insoluble APIs for acute treatment in hospitals where doses may need to be high.

SURFACE ENTRAPMENT OF APIs WITH SLNs

Instead of incorporating the drug into the particle, an additional way to exploit SLNs is to attach the API to the surface of the particle. The surface properties of SLNs can be varied widely and tailored to the final application. For example, the choice of emulsifier (cationic, non-ionic, anionic, and polymeric) has a strong influence on the surface electrical charge on the nanoparticles, measured by the zeta potential of the particles, as shown in Figure 3.

For SLNs that contain long-chain fatty acids or use them as the emulsifier, the carboxyl groups present at the particle surface can be used to covalently attach proteins and amine-terminated peptides using standard coupling chemistries (such as carbodiimide coupling).

Biologics are generally charged in aqueous solution, and as such are attracted electrostatically to surfaces of opposite charge, and may become strongly attached there as a result. We have found that electrically charged SLNs (cationic or anionic) strongly and irreversibly bind proteins with attachment efficiencies of around 90% (around 650 micrograms protein per mg of SLN solids). Evidence that the protein is attached at the particle surface is provided by the observation that after mixing the SLN and protein and allowing enough time for the protein to adsorb at the particle surface, the pH-dependence of the SLN's zeta-potential goes from that of the naked SLN to that of the pure protein.

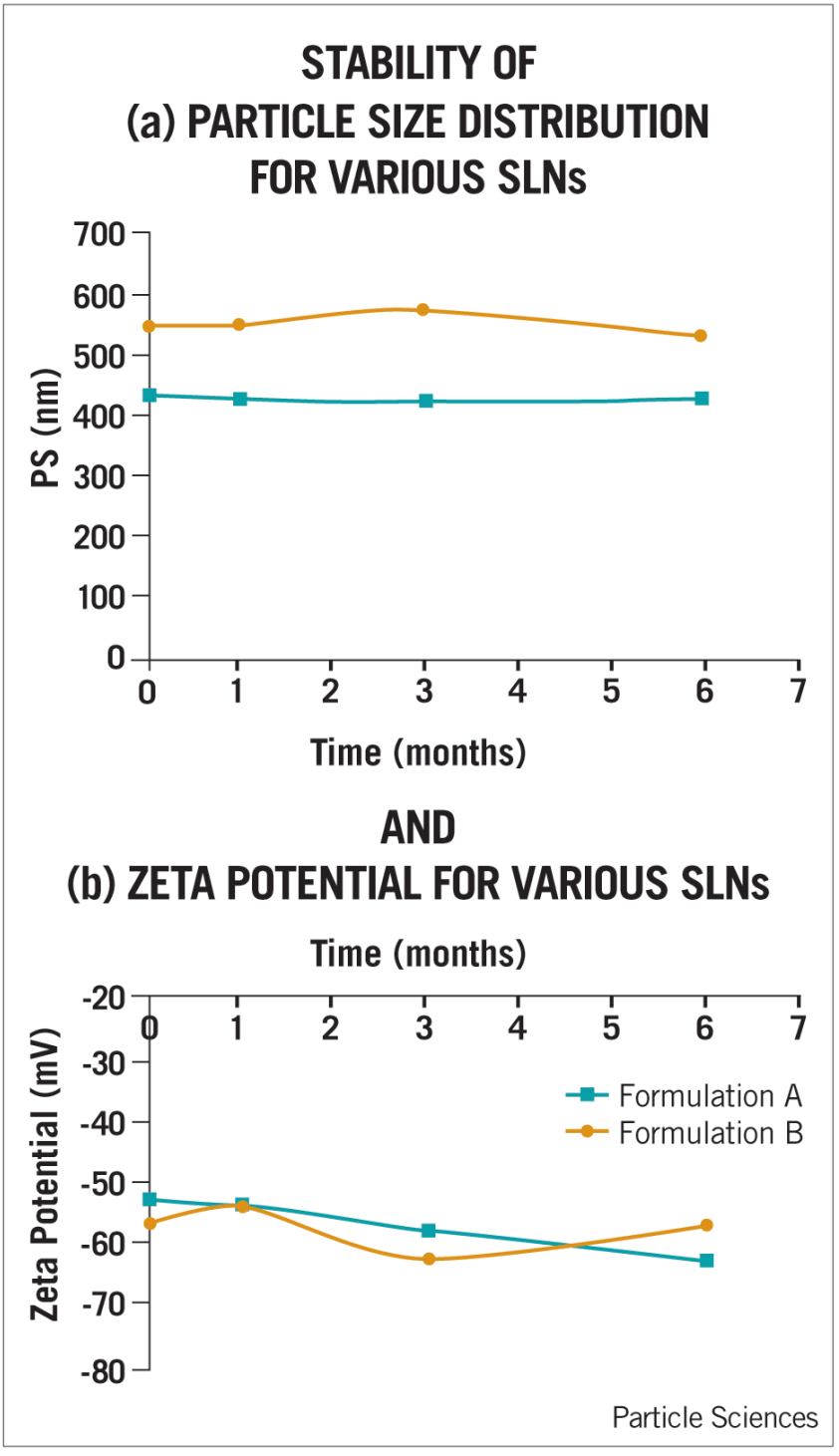
Essentially the SLNs surface properties become dominated by the protein attached there (Figure 4).

Based on the encouraging tissue and cellular uptake results and the ability to efficiently and simply attach proteins to the SLN surface, nanoparticles made of carnauba wax and formulated to carry gp140 (a model HIV antigen) were applied to the vaginal mucosa of mice to evaluate this route of administration as a novel approach to vaccination against HIV. As controls in this experiment, mice were also vaccinated by subcutaneous injection of the SLN-gp140 formulation as well as a formulation using alum, the only particles used in generally approved particle-containing vaccines in the US. The systemic challenge results with the SLNs were equivalent to the alum control (data not shown), indicating that these particular SLNs are potentially promising adjuvants for systemic vaccination.

STERILIZATION

For parenteral administration, SLN dispersions must be sterile. The mean particle diameter of SLNs is often more than 200 nm, so sterile filtration is not possible in these cases. Autoclaving the finished dispersion is not practical as the lipids melt at temperatures used to terminally heat-sterilize pharmaceutical products, and the molten lipid droplets coalesce as there is no applied shear to prevent this. Options are therefore limited to aseptic manufacturing processes following sterilization of the starting materials (gamma or e-beam irradiation of the final dispersion) or exposure to ethylene oxide gas (EO). Bacterial endotoxins in raw materials need to be monitored, especially when raw materials are of natural origin. It may be possible to lyophilize the SLN dispersion, and this lyophile can be irradiated or exposed to EO. We have demonstrated that lyophilized SLNs

FIGURE 5



made of carnauba wax are readily redispersed, and the original particle size distribution is recovered. Of course, SLN with appropriately small particle size can be sterilized using filtration.

STABILITY

The shelf-life stability of SLNs can be very good. Lipids can be chosen that do not hydrolyze in aqueous suspension (another advantage over nanoparticles made from polymers, such as PLGA, which hydrolyzes with a rate that is dependent on polymer structure, and therefore must be lyophilized for practical use). The very small particle size and density close to unity of SLNs means gravity has little effect on the particles in dispersion, and Brownian motion is sufficient to maintain colloidal dispersion without creaming or sedimentation. Any such separation can usually be completely reversed by gentle agitation, even if it is observed. The particle size distribution and zeta potential remains stable over time (Figure 5) as neither Ostwald ripening nor particle dissolution occur in these systems, and the surface charge determining moieties are immobile. For SLNs made with natural lipids, and not made by an aseptic process, they can be prepared with long-term stability against biological growth using standard preservatives when tolerable.

SUMMARY

SLNs are easily prepared nanoparticles made from inexpensive, safe, stable, and biodegradable materials and can be loaded internally or externally with APIs for controlled delivery. As such, they offer a highly versatile platform and one that should be considered when working with APIs that present solubility and/or bioavailability challenges.

REFERENCES

1. Takagi T, et al. A provisional biopharmaceutical classification of the top 200 oral drug products in the united states, Great Britain, Spain, and Japan. Mol Pharm. 2006;3(6):631-643.
2. Kasim NA, et al. Molecular properties of WHO essential drugs and provisional biopharmaceutical classification. Mol Pharm. 2004;1(1):85-96.
3. Lobenberg R, Amidon GL. Modern bioavailability, bioequivalence, and biopharmaceutics classification system. new scientific approaches to international regulatory standards. Eur J Pharm Biopharm. 2000;50(1):3-12.
4. AAPS PharmSciTech. 2007;8(2) :Article No. 50. Website visited: http://www.aapspharmscitech.org/articles/pt0802/pt080250/pt0802050.pdf.
5. Liversgidge GG, et al. Surface modified drug nanoparticles. US Patent No. 5145684. September 8, 1992.
6. Website visited: http://www.orthobiotech.com/orthobiotech/doxil.html.
7. Bala I, Hariharan S, Kumar MNVR. PLGA nanoparticles in drug delivery: the state of the art. Critical Rev in Therapeut Drug Car Sys. 2004;21(5):387-422.
8. Ahmed F, Polymersomes: from controlled release to anti-cancer. (January 1, 2005). Univ. of Pennsylvania - Electronic Dissertations. Paper AAI3179695. Website visited: http://repository.upenn.edu/dissertations/AAI3179695.
9. Kester M, et al. Calcium phosphate nanocomposite particles for in vitro imaging and encapsulated chemotherapeutic drug delivery to cancer cells. Nano Lett. 2008;8(12):4116-4121.
10. Van Slooten ML. Liposomes as sustained release system for human interferon-gamma: biopharmaceutical aspects. Biochim Biophys Acta. 2001;1530:134-145.
11. Ho ML, et al. Controlled release carrier of BSA made by W/O/W emulsion method containing PLGA and hydroxyapatite. J Control Release. 2008;128(2):142-148.
12. Lai E, van Zanten JH. Monitoring DNA/poly-l-lysine polyplex formation with time-resolved multiangle laser light scattering. Biophysical J. 2001;80(2):864-873.
13. Pacioti GF, et al. Colloidal gold: a novel nanoparticle vector for tumor directed drug delivery. Drug Delivery. 2004;11:169-183.
14. Mumper RJ. Microemulsions as precursors to solid nanoparticles. US Patent No. 7153525. December 26, 2006.
15. Particle Sciences (unpublished)
16. Mitchnick M, et al. Composite UV sunblock compositions. US Patent No. 5733531. March 31, 1998.
17. Souto EB. SLN and NLC for topical delivery of antifungals. PhD Thesis, Free Univeristy of Berlin, 2005.
18. Jores K, et al. From solid lipid nanoparticles (SLN) to nanospoons. visions and reality of colloidal lipid dispersions. Proceedings of the 30th Annual Meeting & Exposition of the Controlled Release Society. Abstract No. 181. July 19-23, 2003. Glasgow, Scotland, UK.
19. Khurana S. Nanostructured lipid carriers and their application in drug delivery. Int J Biomed Eng Tech. 2009;2(2):152-171.
20. Arias M, et al. HIV-gp140 antigen-adsorbed wax nanoparticles induce strong in vivo systemic and mucosal humoral immune responses. Poster presented at AIDS Vaccine Meeting, Cape Town; 2008.

BIOGRAPHY

Dr. Andrew Loxley is Director of New Technologies at Particles Sciences Inc., a contract research organization in Bethlehem, PA, specializing in pharmaceutical formulation development. He leads a variety of projects, many based on novel and proprietary nanotechnologies, in fields from HIV vaccine and microbicide development to gene-silencing SiRNA delivery. Prior to joining Particles Sciences, he led the development efforts in next-generation lithium ion batteries at A123 Systems Inc, electrophoretic displays at EINK Corp., and latex-based adhesives at Synthomer Ltd. He earned his BSc in Chemistry from the Univeristy of Sussex and his PhD in Physical Chemistry focusing on microencapsulation from the University of Bristol.

TRANSDERMAL DELIVERY

A Hollow Microstructured Transdermal System (hMTS) for Needle-Free Delivery of Biopharmaceuticals

By: Kris Hansen, PhD; Scott Burton, PhD; and Mark Tomai, PhD

INTRODUCTION

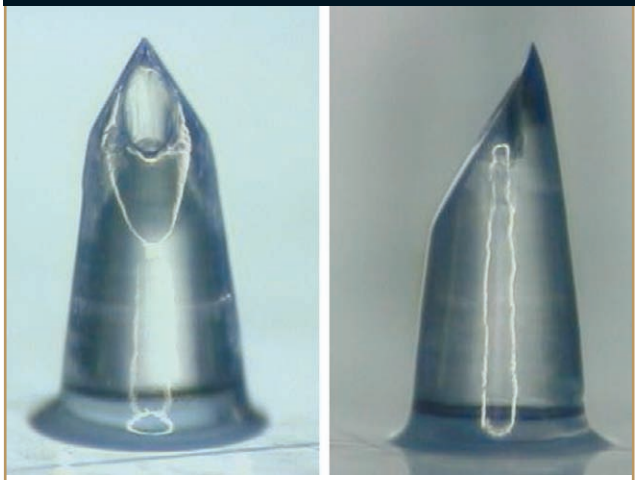
As the $80-billion drug delivery market expands to accommodate growing requirements from physicians, patients, and regulatory bodies, there is a desire to develop convenient and efficient options for self-administration of a wide variety of drugs.[1,2] The fast-growing biopharmaceutical industry has created an abundance of highly effective therapeutic peptides and proteins, drugs not compatible with oral delivery and most commonly administered by IV or syringe injection. 3M's hollow microstructured transdermal system (hMTS) uses hollow microstructures to penetrate the stratum corneum and provide fast, high-volume intradermal delivery of molecules traditionally restricted to syringe injection. The device is designed for self-administration and integrates application of the small polymeric microstructures with a traditional glass API reservoir, along with a means of powering the intradermal delivery. The hMTS provides a comfortable and repeatable means of administering intradermal delivery of small molecule salts, peptides, and proteins, including antibodies, molecules not readily compatible with oral, pulmonary, or traditional transdermal delivery technologies. The hMTS accesses the intradermal space providing fast and efficient delivery into the systemic circulation, bridging the patient-friendly characteristics of a transdermal patch with the versatility and delivery efficiency of a syringe.

BIOPHARMACEUTICALS & TRANSDERMAL DELIVERY: A GROWING CHALLENGE

According to the pharmaceutical research firm, IMS Health, global sales of biologics rose over 12% in 2007, a growth rate roughly double that of classic small molecule-based pharmaceutical products. This same group estimates that biotech products account for 25% of the total pharmaceutical pipeline.[3] The relative instability of protein-based APIs and their near universal incompatibility with oral administration have resulted in the vast majority of these drugs being administered by intravenous infusion or subcutaneous/intramuscular injection. While extremely effective therapeutically, biopharmaceuticals typically provide more potent and specialized therapy than traditional pharmaceuticals do; however, the pain, deep tissue trauma, complexity, and anxiety associated with frequent injections can adversely affect patient compliance.

Biopharmaceuticals are significantly more costly than traditional chemically synthesized pharmaceutical products, often costing hundreds, thousands, or even tens of thousands of dollars per dose. Biopharmaceuticals are produced from microbial or mammalian cell lines, and the

FIGURE 1



hMTS structure, approximately 900 micrometers tall, a polymeric mini-hypodermic needle.

Register Now and Receive $300 Off with Booking Code 10386004XA134PA.

BioNetwork '09

October 5-7, 2009
The Ritz-Carlton Laguna Niguel, CA

* Evaluate Potential Partners * Fill Your Pipeline
Learn Innovative Deal Structures * Protect Your IP

"Excellent forum for private meetings with decision makers – very productive for growth and tangible outcomes."
- James Hattersley, Vice President of Business Development, Sun Pharmaceuticals

Attend BioNetwork To:

- ✔ Gain the most **current updates on innovative deal structures and options maximizing non-capital assets**
- ✔ **Interact with biotech and pharma companies** who have found creative financing strategies to survive the economic downturn
- ✔ **Avoid common IP pitfalls** while expediting the due diligence process
- ✔ Maximize the private, **face-to-face meetings to evaluate potential investments and partnerships**
- ✔ Work more closely with your **IP and Patent Counsel to protect and extend your assets**

2009 Speakers Include:

Bayer HealthCare Pharmaceuticals · BIOMARIN · Bristol-Myers Squibb · Cerimon Pharmaceuticals · EyeGate pharma · genzyme Biosurgery · Johnson & Johnson · madeira THERAPEUTICS · MERCK Research Laboratories · NOVARTIS Institutes for Biomedical Research · novo nordisk · Pfizer · PORTOLA Pharmaceuticals, Inc. · SANDOZ · Shire · TARGACEPT · Takeda MILLENNIUM The Takeda Oncology Company

What's New For 2009?

Dedicated IP track and Increased IP Counsel participation

As the licensing and acquisition environment copes with the current economic environment, BioNetwork offers you a forum to leverage the strengths of both the BD and IP leaders to improve partnering strategies

A Streamlined Process In the Round Table Format

Choose the round table topic of your choice as you register for the event. Engage in dynamic discussion with your peers and learn from great insights about the changes in the industry impacting your business

Improved Networking Activities

No time is wasted at BioNetwork – build and strengthen relationships through the fun networking activities, relaxing cocktail receptions and exclusive 1:1 meetings

Follow The Conversation On Twitter @BioNetwork

Sponsored by:

Abbott A Promise for Life · Boehringer Ingelheim · Dean & Company Strategy Consultants · Evaluate Pharma® · Genentech In Business For Life · INTRALINKS · Lilly · Roche · sanofi aventis · UPSHER-SMITH · ZS Associates

Organized By:

WBR Worldwide Business Research

Register Now: Call 1.888.482.6012 or 1.646.200.7530 Fax 1.646.200.7535
Web www.bionetworkus.com Email bionetwork@wbresearch.com

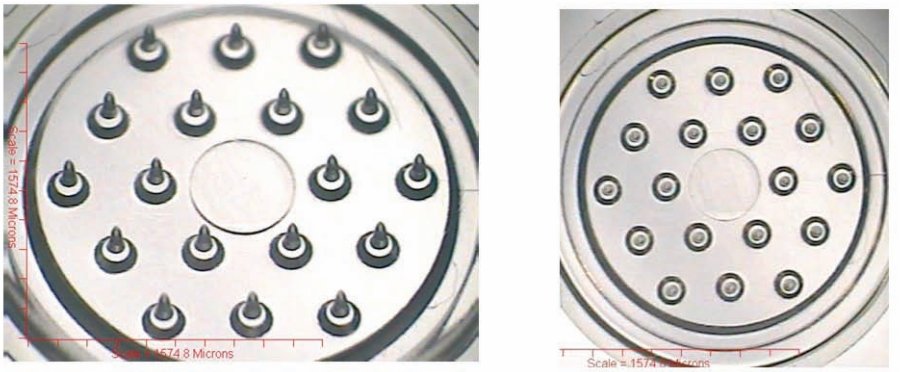
production, isolation, and purification of the target compounds can be space, time, and resource intensive, requiring extensive controls to maintain the sterility and stability of the final product. This complex and tightly controlled production process places added demands on the delivery technology to keep the cost of goods associated with the API acceptable to providers; the delivery efficiency of the biopharmaceutical product must be high.[4]

The industry's reliance on hypodermic needle-based delivery offers a significant opportunity to achieve product differentiation. For those drugs administered by painful or onerous injections, new delivery technologies may provide a more convenient and comfortable experience for the patient, reducing the burden on the practitioner, and improving patient compliance. Ideally, these new delivery systems should not diminish the efficiency and speed of delivery commonly associated with traditional needle-based delivery methods. The fast growing arena of biopharmaceutical drug products is ripe for alternative delivery technologies that can maintain or improve upon the delivery efficiency of a traditional syringe without compromising patient safety.

Traditional transdermal patch technology has been limited to the delivery of smaller, lipophilic molecules that can, in the presence of an adhesive patch, diffuse though the stratum corneum and pass into systemic circulation. Given the whole of the pharmaceutical market, and especially the biopharmaceutical market, there are few APIs compatible with this technology. Yet the transdermal patch offers convenient, controlled release of the therapeutic through a continuous, diffusion-controlled delivery system. It is an elegant system, and given a choice of non-oral delivery routes, transdermal drug delivery is preferred by both patients and doctors.[2] A patch is easy to use, and the comfort and convenience associated with a patch rank higher than either pulmonary, injection, or intranasal delivery.

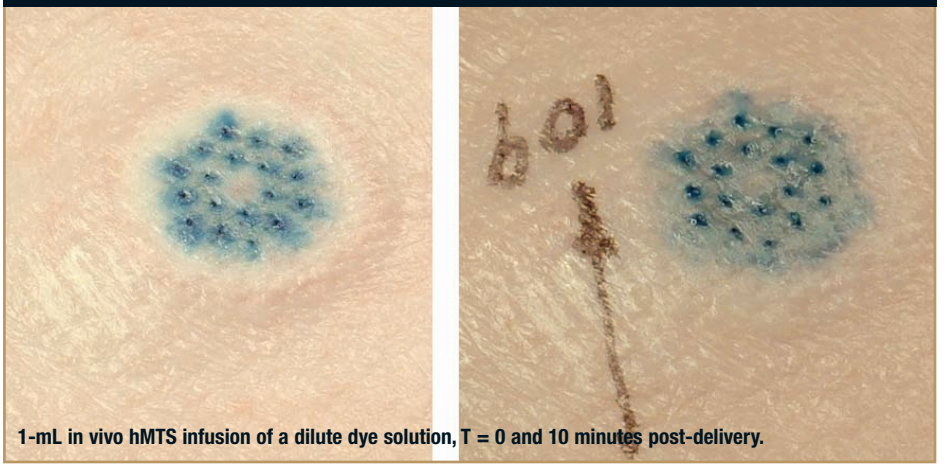
The higher efficiency of drug uptake and the rapid onset of action associated with the therapeutic are noted by both patients and physicians as significant benefits associated with injection systems.[2] A drug delivery platform that can provide the efficiency, versatility, and speed of delivery associated with a

FIGURE 2



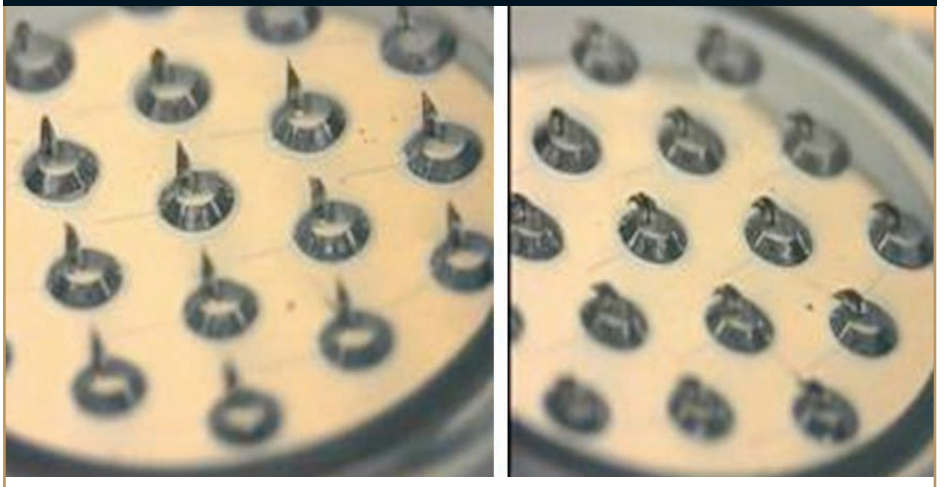
hMTS Array, 18 "mini-hypodermic" structures positioned across a 1-cm^2 array.

FIGURE 3



1-mL in vivo hMTS infusion of a dilute dye solution, T = 0 and 10 minutes post-delivery.

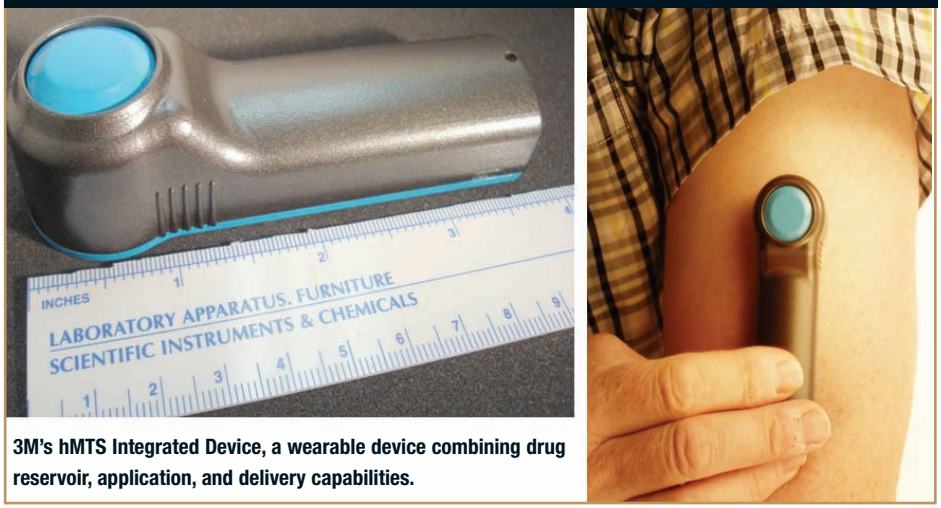
FIGURE 4



3M's hMTS array before and after the application of 245 N of force applied against a rigid surface.

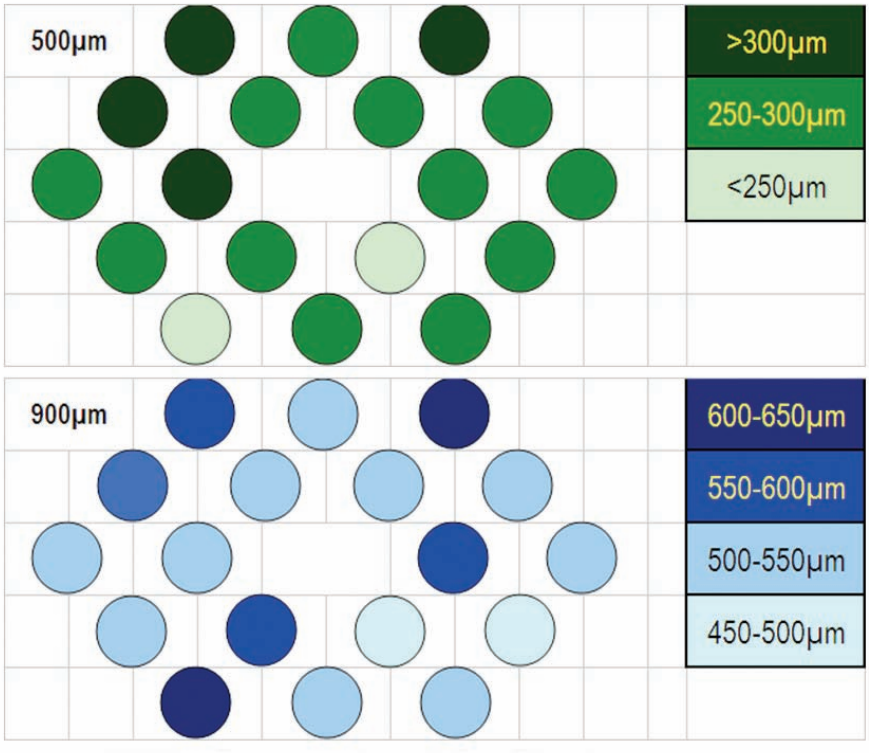
syringe injection with the comfort and convenience of a transdermal patch offers the opportunity to differentiate an existing product in a crowded market space or enhance the utility and acceptance of a new molecule in an emerging biopharmaceutical market.

FIGURE 5



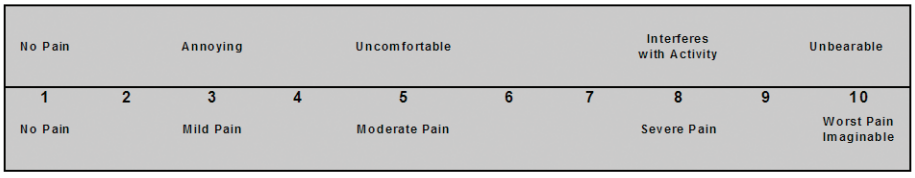
3M's hMTS Integrated Device, a wearable device combining drug reservoir, application, and delivery capabilities.

FIGURE 6



Depth of penetration associated with in vivo application of 900- and 500-micrometer long structures. Each circle represents one microstructure on the array.

FIGURE 7



Pain-scale used to rate discomfort during high volume, fast delivery with the hMTS.

THE HOLLOW MICROSTRUCTURED TRANSDERMAL SYSTEM (hMTS)

The hMTS utilizes biocompatible, medical-grade, polymeric microstructures to overcome the barrier properties of the stratum corneum and deliver the salt forms of small molecules, peptides, proteins, and even antibodies, regardless of molecular weight. The hMTS expands the potential for intradermal delivery, taking a technique-dependent injection-based delivery technology from the hands of skilled practitioners in a clinic and placing it into the hands of patients, allowing a means for simple, home-based self-administration. The hMTS is composed of polymeric hollow microstructures, modeled as mini-hypodermic needles, 500 to 900 micrometers tall (Figure 1). Eighteen structures are configured across a 1-cm^2 array, providing a diffuse area for intradermal infusion (Figure 2).

Upon application, these structures penetrate the stratum corneum and pass through the epidermis into the dermis, well above the nerve endings that could cause discomfort.[5] Depending on the length of the structures, the depth of penetration (DOP) associated with the hMTS integrated device ranges from 275 to 650 micrometers. Channels in each structure allow for fluid communication between the top and the bottom of the array, offering a means for effectively and painlessly delivering liquid formulations into the skin. The array is one element of a system that integrates applicator, drug reservoir, and infusion mechanism into a single device.

Following application, a relatively high volume of liquid formulation (0.5 to 1 mL) is delivered into the dermis after which the device is removed. Figure 3 shows a 1-mL hMTS infusion of a blue

dye solution immediately after infusion and then several minutes later; the surface of the skin is dry to the touch, and all of the blue dye is below the surface.

Because hMTS requires an external application force sufficient to enable penetration of the skin by the microstructures, there is virtually no risk of accidental needlestick injuries associated with the use or disposal of this device. A study published in 2006 documented the incidence of accidental needlesticks associated with the use of disposable syringes and injection pens. Due to the additional handling required to assemble, and then disassemble, the needle on the injector, the survey noted that pen injectors accounted for approximately 6 times as many accidental needlestick injuries as disposable syringes. The survey, conducted in 24 French public hospitals, showed that accidental needlestick injuries associated with the use of pen injectors represented over 8.5% of total accidental blood exposures reported in France between 2002 and 2003.[6]

The hMTS array has sufficient strength to penetrate the stratum corneum and sufficient flexibility to prevent fracture of the microstructures. The microstructures maintain integrity during insertion studies conducted in swine, hairless guinea pigs, and humans. Under extreme force, the microstructures will bend rather than fracture or break off (Figure 4), as might be expected from microstructures made of glass or metal.[7] The hMTS device is disposable and designed for self administration to the upper arm or upper thigh. A prototype hMTS device is shown in Figure 5.

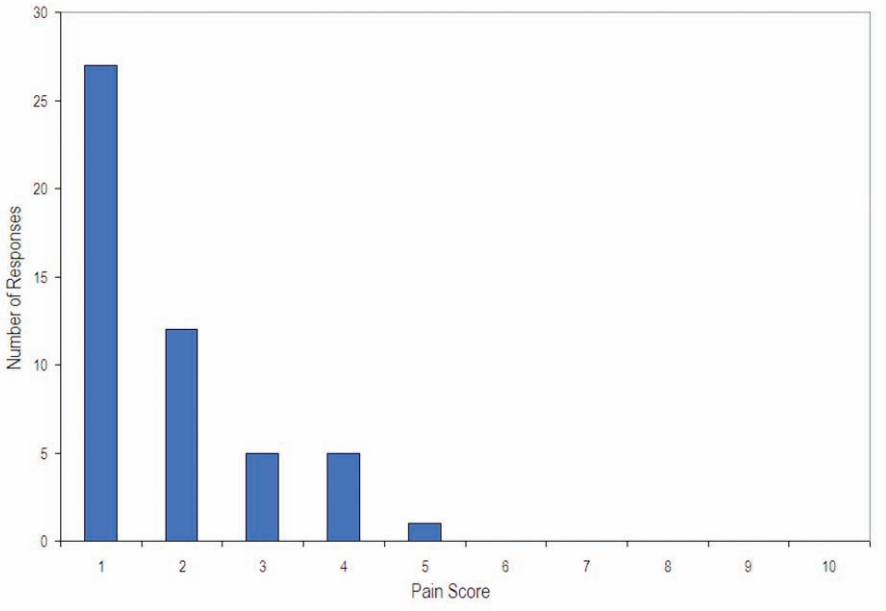
The device accommodates a traditional 1-mL glass cartridge as a reservoir for the formulation and is intended to be worn throughout the delivery period, which can range from 5 to 40 minutes depending on the formulation.

The depth of penetration of the structures was determined by applying a water-soluble dye to the microstructures. Following in-vivo application (swine), the "water mark" associated with the dye on each structure was measured microscopically and recorded. Typical results for a depth study conducted on 500- and 900-micrometer structures, respectively, are shown in Figure 6.

hMTS HUMAN TOLERABILITY

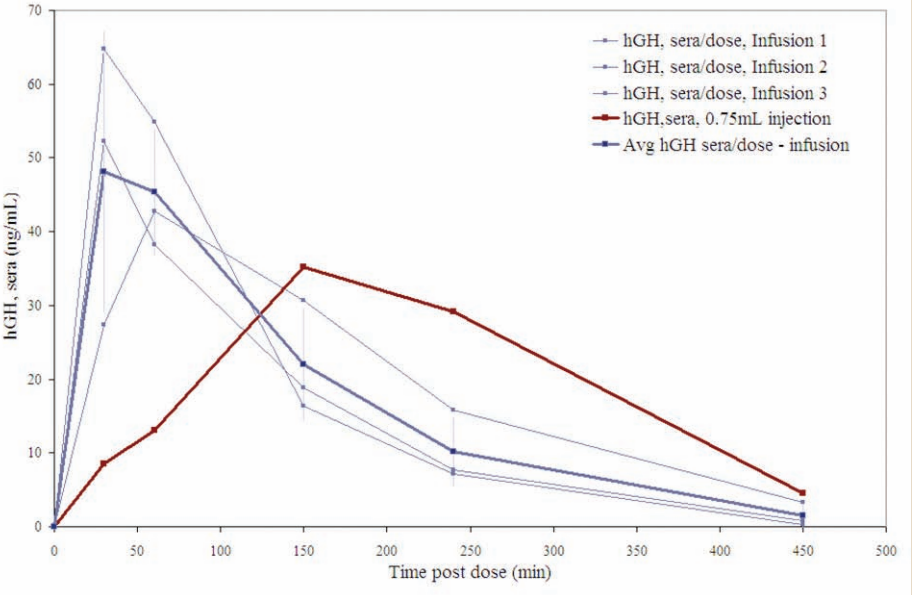
An hMTS tolerability study was conducted in humans, using a placebo formulation administered with the hMTS

FIGURE 8



Distribution of max pain scores associated with high volume (0.75 to 1 mL) placebo delivery via the hMTS.

FIGURE 9



PK profiles associated with hMTS integrated device delivery of a commercial hGH formulation (blue trace) and a syringe injection of the same formulation (red trace).

proof-of-concept (POC) device. The POC device utilized 500-micrometer hollow structures to deliver the liquid formulation; the rate and volume of the placebo delivery were controlled by a medical syringe pump to ensure tight control over the infusion. A total of 48 deliveries between 0.75 to 1 mL were administered to the upper arm or upper thigh of healthy subjects between the ages of 18 to 40 years. The rate of delivery was varied with some high-volume deliveries being completed in as little as 8 minutes; slower deliveries ran to 30 minutes. Results indicate that neither the application of the hMTS array nor subsequent deliveries (up to 1 mL) caused discomfort in the patient. Subjects were asked repeatedly during the test to rate their pain using a 10-point scale (Figure 7).

For those subjects receiving the highest volume (0.75 to 1 mL), the average pain associated with delivery was 1.8 ± 1.12. The discomfort associated with application of the hMTS array was also recorded; the average score was 1.4. Figure 8 shows the distribution of max pain scores associated with the high-volume placebo administrations.

During this study, both the hMTS array and the delivery were well tolerated. Two hours following patch removal, nearly 50% of all application sites showed no visual vestige of the treatment, and after 3 days, that number had increased to 88%, with the remaining infusion sites being rated by the attending physician as "minimal erythema, barely perceptible."

Although there are expected to be significant variations in patient experience, due partly to personal preferences and partly to the characteristics of the formulation, these clinical results demonstrate the potential for hMTS to provide a differentiating and patient-friendly technology for many biopharmaceutical products.

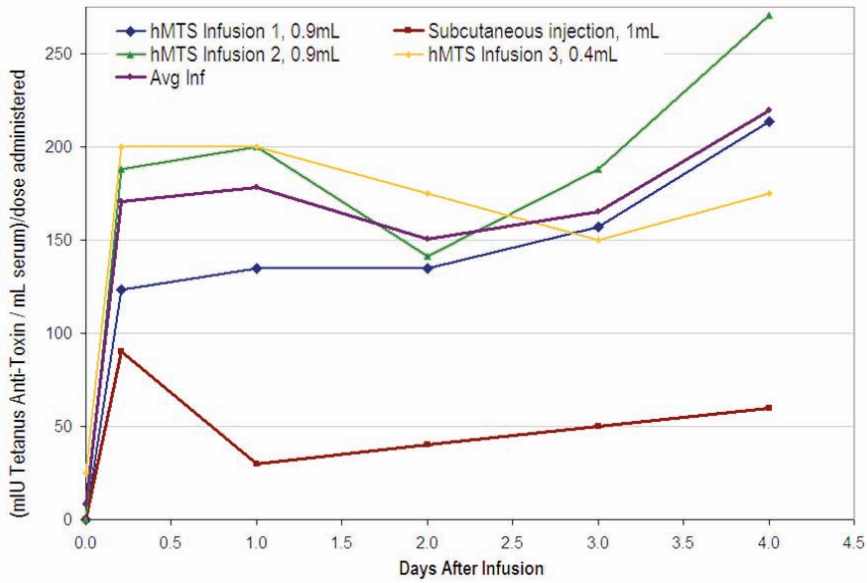
hMTS DELIVERY CAPABILITIES

To better understand the potential of the hMTS to deliver non-traditional therapeutics as efficiently as a syringe, a number of pharmacokinetic (PK) studies were conducted. Studies were conducted in swine using the hMTS integrated device. A human growth hormone (hGH) formulation (1 mg/mL) was administered to anesthetized swine using the hMTS device or by subcutaneous injection. Blood samples were collected at intervals over a 2-hour period. The serum was separated from the whole blood and analyzed for hGH using a commercial ELISA assay. The 0.9-mL infusions were complete in less than 15 minutes; the average bioavailability associated with the hMTS delivery is equivalent to that determined by syringe administration. The results of the comparative PK profiles are provided in Figure 9.

Upon removal of the device, a small bleb (< 1 mm) was visible on the skin of the swine. The Tmax associated with the hGH infusion occurs earlier than when the API is administered via injection; the C_{max} is higher in the intradermal administrations. The mechanism responsible for the faster uptake of the drug administered via the hMTS device has not been verified but may result from the larger surface area associated with the infusion, facilitating uptake by the capillaries. Alternatively, the transport of a large molecule (hGH is 22 kD) through a tissue like the dermis with a rich interstitial fluid supply may be easier, providing faster uptake than when the protein is introduced into fat tissue, for example.

To determine if there are any meaningful molecular weight limits associated with hMTS delivery, a sample of equine tetanus anti-toxin (ETAT) was prepared and administered via the hMTS device. Although technically a polyclonal antibody, the ETAT is a reasonable model for a monoclonal antibody (mAb) therapeutic. The formulation was prepared at 52 mg of IgG/mL, which compares well to some commercially available mAb formulations, such as

FIGURE 10



PK profiles associated with the hMTS delivery of a model monoclonal antibody; the PK profile associated with a subcutaneous injection of the same formulation is presented for comparison.

Humira (50 mg/mL). The mAbs are large molecules administered as intact IgG (~ 150 kD) or as Fab2 fragments (~100 kD).

Currently, there are 21 FDA-approved mAb therapies on the market, and many more in development. In 2007, mAbs represented $32 billion of the $80-billion biopharmaceutical market and are the fastest growing segment of the biopharmaceutical market.[4,8] The approved mAbs are typically administered as high-volume IM injectables (0.5 to 3 mL) or via IV infusion administered in a clinical setting.

The PK profiles associated with the ETAT infusions were assessed over a 96-hour period. Blood samples were collected at specified time points, and the sera fraction separated from the whole blood. The ETAT levels in the blood were determined using an in-house ELISA-based assay that referenced an FDA-approved veterinary ETAT product as a standard. Three hMTS administrations (two 0.9 mL and one 0.4 mL) were administered using the hMTS integrated device. A single, 1-mL aliquot of the same formulation was administered via subcutaneous injection for comparative purposes. The dose-adjusted PK profiles for these infusions, along with a single 0.9-mL subcutaneous injection of the same formulation, are shown in Figure 10.

As with the hGH data, the ETAT infusion data indicate fast uptake of the API into the systemic circulation. Although only a single subcutaneous injection was performed over this 4-day experiment (an incomplete PK profile), it appears that the hMTS delivery of the model mAb compares favorably with respect to bioavailability to the subcutaneous injection of the same compound.

CONCLUSIONS

A preferred delivery system for biopharmaceuticals offers the speed, efficiency, and versatility of a conventional syringe with the comfort and convenience of a transdermal patch. 3M's hMTS has demonstrated good tolerability in humans, with minimal discomfort associated with application and infusion of a high volume of liquid formulation over a short infusion period, and minimal and rapidly resolving site reactions. The hMTS integrated device is designed for easy use by the patient. The wearable system integrates a polymeric microstructured array with a conventional glass injection cartridge and a non-electric, disposable infusion system. The device has been used to provide efficient and fast in-vivo delivery of small molecule salts and proteins, including high molecular weight antibodies. This unique device makes efficient use of biopharmaceuticals and provides a means of differentiating commercial products in crowded market places. The hMTS offers the potential for increased utility and acceptance of a new high-volume liquid therapeutic.

REFERENCES

1. Martineau W, Bayrer R. Drug Delivery Systems. Freedonia Industry Study 2294; March 2008.
2. US Drug Delivery, Usage Patterns, Preferences, and Opportunities in the US. Frost & Sullivan Report. 2008; Volume 1-2.
3. Silver S. Standard & Poor's Industry Surveys Biotechnology; February 2009.
4. Fraser-Moodie I. Delivery Mechanisms for Large Molecule Drugs, Successes and Failures of Leading Technologies and Key Drivers for Market Success. Business Insights Ltd; 2008.
5. Prausnitz MR. Miconeedles for transdermal delivery. Advanced Drug Delivery Reviews. 2004;56:581-587.
6. Pellissier G, Migueres B, Tarantola A, Abiteboul D, Lolom I, Bouvet E. Risk of needlestick injuries by injection pens. J Hosp Infect. 2006;63:60-64.
7. David SP, Landis BJ, Adams ZH, Allen MG, Prausnitz MR. Insertion of microneedles into skin: measurement and prediction of insertion force and needle fracture force. J Biomech. 2004;37:115-1163.
8. La Merie Business Intelligence. R&D Pipeline News; March 2009.

BIOGRAPHIES

Dr. Kris Hansen is the MTS New Technology and Product Development Manager for 3M Drug Delivery Systems in St. Paul, Minnesota. She earned her PhD in Chemistry from the University of Colorado at Boulder and received an NRC Fellowship for Post-Doctoral research focusing on aerosol analysis. Her research interests include development of inhalation, oral, and transdermal drug delivery systems. She leads the technical development of 3M's full platform of MTS drug delivery technologies.

Dr. Scott A. Burton is the hollow MTS Project Leader for 3M Drug Delivery Systems in St. Paul, MN. He earned his PhD in Pharmacology from the University of Utah and received a post-doctoral fellowship from the University of Utah College of Pharmacy. His R&D activities have included transdermal drug delivery and medical skin and wound products.

Dr. Mark Tomai is the Business Development Director for 3M Drug Delivery Systems in St. Paul, MN. He earned his PhD in Microbiology/ Immunology from the University of Minnesota. Dr. Tomai is considered an expert in immunology, holds many patents, and has published over 75 publications. He leads the Microstructured Transdermal business development team.

DISINTEGRATION PROFILE

Enteric-Coated Aspirin Tablets: Disintegration Time

By: Antoine Al-Achi, PhD, and Divyesh D. Patel

ABSTRACT

Aspirin (acetyl salicylic acid) is available in the US as a non-prescription medication. The purpose of this study is to establish a disintegration profile for enteric-coated aspirin tablets as the US Pharmacopeia (USP) does not provide this information in its monograph pertaining to this dosage form. Six different bottles of Bayer Low Dose tablets [Bayer Low Dose (81 mg), 32 Enteric-Coated Tablets; Bayer HealthCare LLC] were purchased from local stores in Raleigh, NC. Six tablets from each bottle were tested using the disintegration test outlined by the USP for delayed-action units. Overall, tablets disintegrated within a period of 7.87 to 10.23 minutes. Despite a statistical difference in the average disintegration times among the six bottles, this difference would not be considered to be of practical importance.

INTRODUCTION

It is well known that aspirin can reduce the risk of heart attack and stroke if taken on a prophylactic basis. Commercially available low-dose aspirin tablets containing 81 mg/tablet should provide good control for these conditions.[1] The beneficial effect of aspirin on cardiovascular health is due to the drug's ability to irreversibly inhibit platelet cyclooxygenase 1 (COX-1) and thus inhibit the conversion of arachidonic acid to thomboxane A2.[2] Differences in response to aspirin's anti-platelet activity exist among individuals (due to genetic makeup) and to gender (female appears to have a lower response to aspirin's anti-platelet effect than men).[2-4] Because aspirin is an acid, repeated daily intake for a prolong period could result in a damage to the stomach mucosal lining. Thus, the commercial formulations contain enteric coating materials to prevent the disintegration of the unit in the stomach. The enteric film on the tablets investigated in this study is primarily made of methacrylic acid copolymer type C and shellac. Methacrylic acid copolymer type C is also known as EUDRAGIT® L 100-55, and it is soluble in intestinal fluid from pH 5.5.[5] Shellac is a natural resinous complex produced by an insect, Laccifer (Tachardia) lacca Kerr. The resinous material is insoluble in water; however, it is soluble in aqueous solutions of alkalies.[6] The film on the tablets also contains carnauba wax, a material often used with EUDRAGIT® in controlled-release formulations.[5]

The USP (USP 30-NF 25) lists a monograph titled *Aspirin Delayed-Release Tablets* requiring a dissolution test <711>, but not a disintegration test.[7] The purpose of this study was to describe and report findings of a disintegration test applied on delayed-release (enteric-coated) tablets containing 81 mg of aspirin per tablet.

MATERIALS

Bayer Low Dose aspirin (Lot No. 242387B, all bottles) was purchased from a local pharmacy during the week of June 4, 2007. The preparation contains aspirin 81 mg, black iron oxide, brown iron oxide, carnauba wax, corn starch, D&C yellow No. 10

aluminum lake, hypromellose, methacrylic acid copolymer type C, polysorbate 80, powdered cellulose, propylene glycol, shellac, sodium lauryl sulfate, triacetin, and triethyl citrate. Pepsin from porcine stomach mucosa (Lot No. 074K7717) and pancreatin (Lot No. 102K1064) were from Sigma (St. Louis, MO). All other chemicals were from Fisher Scientific (Pittsburgh, PA) and were of reagent grade.

METHODS

Preparation of Simulated Gastric Fluid (SGF)

This solution was prepared according to USP. Sodium chloride (2 g) was dissolved along with pepsin (3.2 g) in 7 mL of hydrochloric acid. The solution was made to the desired volume (1000 mL) by the addition of purified water. The resulting solution had a pH of 1.2. This solution was freshly prepared on the day of the experiment.

Preparation of Simulated Intestinal Fluid (SIF)

One liter of this solution was prepared by dissolving 6.8 g of monobasic potassium phosphate in 250 mL of purified water. Sodium hydroxide solution (0.2 N, 77 mL) was then added, along with 500 mL of purified water. After mixing, pancreatin (10 g) was added with continuous mixing to affect dissolution. The final volume was made by the addition of purified water. The solution had a pH of 6.8. SIF was freshly prepared on the same day of the experiment.

TABLE 1

	Bottle No.						
	1	2	3	4	5	6	Overall
Mean[a]	8.64	9.43	8.71	8.27	8.28	8.17	8.58
S.D.	0.02	0.60	0.07	0.34	0.19	0.12	0.52
P_{90}	8.67	10.23	8.85	8.87	8.57	8.32	9.43
P_{75}	8.67	9.95	8.85	8.48	8.44	8.27	8.70
P_{50}	8.63	9.50	8.69	8.23	8.25	8.17	8.63
P_{25}	8.63	8.79	8.67	8.04	8.14	8.07	8.19
Maximum	8.67	10.23	8.85	8.87	8.57	8.32	10.23
Minimum	8.63	8.68	8.67	7.87	8.03	8.02	7.87

[a] Data are for 6 tablets per bottle.

Disintegration Time (Minutes) Profile for Aspirin Tablets (81 mg) in SIF

Disintegration Test, USP

Six tablets per bottle were used per test. The tablets were placed in the six columns of the basket-rack, and the entire basket-rack was immersed in purified water (room temperature) for 5 minutes. The basket-rack was transferred to the disintegration device with SGF being the immersion medium (maintained at 37°C by immersing the beaker containing SGF in a constant temperature water bath). The tablets remained in contact with SGF for the first hour of operation. Following the first hour, the immersion fluid was replaced with SIF (maintained at 37°C), and the operation continued until all the tablets disintegrated. The disintegration time for the six individual tablets was recorded in minutes.

RESULTS & DISCUSSION

Tablet disintegration test is a quality control test routinely done on final products during manufacturing. Most tablets should disintegrate within 15 to 30 minutes when immersed in their appropriate medium (in the case of enteric-coated tablets, the medium is SIF).[8] Several disintegrating agents can be used in the formulation, with most of the agents made of cellulose or starch derivatives.[2] Bayer Low Dose tablets contain corn starch, which serves as a

disintegrant, as well as a bulking agent. None of the tablets showed any sign of disintegration, softening, or cracking in plain water or in SGF. Tablets remained intact within the first hour of operation when immersed in SGF. Upon a change in the immersion medium to SIF, tablets disintegrated within a period of less than 11 minutes. On average, tablets took 8.58 minutes (range: 7.87 to 10.23 minutes) to disintegrate, with 90% of the tablets having a disintegration time of less than 9.43 minutes (Table 1). Interestingly, there was a statistically significant difference in the disintegration time among the six bottles. Bottle 2 produced a significantly longer disintegration time than all other bottles. Bottle 6 showed lower values for disintegration time than bottles 2 and 3, but not significantly different from bottles 1, 4, and 5 ($p < 0.0001$). Bottles 1, 3, 4, and 5 had statistically similar average disintegration time. Despite this statistical difference, however, from the practical point view, this difference is clinically insignificant.

CONCLUSION

Commercially available delayed-release aspirin tablets showed an acceptable disintegration time of less than 11 minutes when placed in simulated intestinal fluid. No change in the appearance of tablets resulted from immersing the tablets in purified water or in simulated gastric fluid. There was a statistical difference in the disintegration time among the bottles, however, this difference should not be clinically important.

REFERENCES

1. Hennekens CH. Update on aspirin in the treatment and prevention of cardiovascular disease. Am J Manag Care. 2002;8(22 Suppl):S691-S700.
2. Maree AO, Curtin RJ, Chubb A, Dolan C, Cox D, O'Brien J, Crean P, Shields DC, Fitzgerald DJ. Cyclooxygenase-1 haplotype modulates platelet response to aspirin. J Thromb Haemost. 2005;3(10):2340-2345.
3. Faraday N, Becker DM, Becker LC. Pharmacogenomics of platelet responsiveness to aspirin. Pharmacogenomics. 2007;8(10):1413-1425.
4. Becker DM, Segal J, Vaidya D, Yanek LR, Herrera-Galeano JE, Bray PF, Moy TF, Becker LC, Faraday N. Sex differences in platelet reactivity and response to low-dose aspirin therapy. JAMA. 2006;295(12):1420-1427.
5. Kibbe AH, ed. Poly methacrylates. In: Handbook of Pharmaceutical Excipients. 3rd ed. Washington, DC: American Pharmaceutical Association;2000:401-406.
6. The Merck Index. 13th ed. Merck Research Laboratories, Whitehouse Station, NJ; 2001:1521.
7. Aspirin Delayed-Release Tablets. USP30-NF25. Website: www.uspnf.com.
8. Allen LV, Jr. Tablets. In: The Art, Science, and Technology of Pharmaceutical Compounding. 2nd ed. Washington, DC: American Pharmaceutical Association; 2002:161-169.

BIOGRAPHIES

Dr. Antoine Al-Achi is Associate Professor of Pharmaceutical Sciences at Campbell University School of Pharmacy. In this role, he teaches pharmaceutics and biostatistics in both the PharmD program and the MS (Pharmaceutical Sciences) major. Dr. Al-Achi earned his PhD in Biomedical Sciences/Pharmaceutics/ Pharmacokinetics from Northeastern University, Boston, MA. He completed his Post-Doctoral studies in Cancer Pharmacology at Dana-Farber Cancer Institute/Harvard Medical School. He has published more than 100 scientific papers, reviews, book chapters, and abstracts. His research area of interest is in drug delivery systems for peptides and proteins.

Mr. Divyesh (Savan) Patel is currently working at Liquidia Technologies in Research Triangle Park, NC, as an Analytical Chemistry intern. He graduated from Campbell University with a BS in Pharmaceutical Sciences in 2008. While an undergraduate at Campbell, he was responsible for the foundation of the AAPS (American Association of Pharmaceutical Scientists) student chapter, and served as President for the first year. Mr. Patel also served as secretary for the ISPE (International Society for Pharmaceutical Engineering) student chapter, and is currently serving as its President.

SPECIAL FEATURE

HEALTHCARE REFORM & NEEDLESTICK PREVENTION LAWS INJECT LIFE INTO HAND-HELD DEVICES

By: Cindy H. Dubin, Contributor

Government intervention with regard to OSHA's needlestick legislation and President Obama's interest in reforming healthcare might ultimately prove beneficial to the hand-held injection market. "With healthcare reform on the horizon, there will be continued efforts to get more patients into the system at a lower cost," says Menachem Zucker, PhD, Vice President, Injectable Drug Delivery Devices at Elcam Medical. "Self-injection, instead of going to a clinic or doctor's office, is very much in line with this direction. Therefore, we will see more drugs launched in forms that are compatible with self-injection."

With the increasing demand for self treatment, there is no doubt hand-held injection devices will be used for more therapeutic areas. "There is a constant need to increase the quality of life for patients living with chronic diseases and who are dependent on medicine," says Tanya Arp-Nielsen, Business Development Manager, Injection Solutions, B&O Medicom A/S. "This need can be addressed by hand-held injection devices."

"The growth in home-based drug administration is forcing pharmaceutical companies to require that devices promote safe self-medication and compliance with a dosing regimen," says Graham Reynolds, Vice President, Innovation Strategic Marketing, at West. "What's more, there is an increasing need for devices and systems that can prevent accidental needlestick injuries."

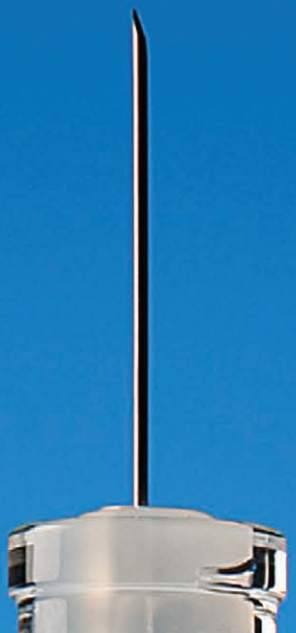
The need to comply with needlestick prevention laws in the US, Canada, and Europe is driving pharmaceutical companies toward prefilled syringes with passive safety features. In addition to improved safety, the design feature of an injection device could be just what is needed to counter the possible threat of follow-on biologics. According to a September 2008 Deutsche Bank Global Market Research Report, US sales of biological drugs in 2007 were approximately

UNILIFE
medical solutions

What you've been waiting for

Universe of Prefilled Syringes
October 27 - 28
Venice, Italy

www.unilife.com



$42 billion. The same report states that $25 billion worth of these drugs are losing patent exclusivity between now and 2016, making them prime targets for follow-on biologics. Self-administered injectable biologics account for the main portion, over $22 billion, of those facing future competition from follow-on biologics.

Legislative proposals to permit FDA approval of follow-on biological drugs that are similar to, but not exact replicas of, the innovators' products pose a potentially significant change in the competitive landscape for biological products. Because follow-on biologic molecules will be nearly identical to the innovator biologic, both the innovator and follow-on manufacturers will seek other ways to differentiate their products in the market.

"We believe manufacturers will look to proprietary advantages in the designs of the self-administration devices as a key way to differentiate and compete in the market," says John Hayes, Vice President, Corporate Marketing, Antares Pharma, Inc.

While hand-held injection technology continues to garner interest from drug developers and healthcare decision-makers, companies making and marketing needle-free injectors (NFIs) are evolving as they search for a strategy that will achieve commercial success, according to information from Greystone Associates. To increase the commercial prospects for NFIs, companies have invested in new device models that incorporate design enhancements and improved human engineering. The new generation of devices is lighter, have a sleek profile, and employ warm colors, increasing their acceptance with end-users. The business approach of NFI companies is also evolving. The historical model of the NFI developer as a device company licensing its technology to pharmaceutical firms is being challenged by newer companies that own NFI technology and use it to develop combination drug-device products in-house.

"More and more, we see pharmaceutical and biopharmaceutical companies emphasizing combination products as drug developers recognize the value of adding a device to their drug," says Mr. Reynolds. "As this trend develops, pharmaceutical companies are turning to resources that can help them understand combination products, especially the interdependence between prefillable syringes and auto-injectors. With a thorough understanding of this relationship, companies can overcome incompatibility problems, and ensure consistent, accurate dosing."

FIGURE 1

Antares' needle-free device is being marketed by Teva Pharmaceuticals as the Tev-Tropin® Tjet Injector System.

ANTARES PHARMA–FOCUS ON DRUG/DEVICE COMBINATIONS

Staying focused on its core business is what is behind Antares success during these adverse economic conditions, says Mr. Hayes. Within the parenteral products group, that core business is developing and gaining market approval of drug/device combination products. Antares' most recent accomplishment, in collaboration with Teva Pharmaceuticals, is the FDA approval of a Supplemental New Drug Application (sNDA), which added needle-free injection to Teva's Tev-Tropin® [somatropin (rDNA) for injection] brand human growth hormone (hGH) drug label. Teva is marketing the Antares needle-free device as the Tev-Tropin Tjet Injector System. Tev-Tropin (Figure 1) competes in the $1-billion US market for hGH.

"We believe the Tjet Injector System helps Teva compete in this market by offering pediatric patients the benefits of avoiding the use of needles as well as the rapid injection speed associated with giving needle-free injections," explains Mr. Hayes.

In addition to the Tev-Tropin Tjet Injector System, Antares' partnership with Teva includes development programs for four additional products that are alternatives to currently marketed self-injected drugs that, combined, generated nearly $2 billion in US sales in 2008.

FIGURE 2

The BD Hypak™ PRTC (left) provides a syringe tip closure design that ensures secure tip cap attachment, and the Hypak Physiolis (right) is a staked prefillable syringe that is designed to improve patient comfort.

FIGURE 3

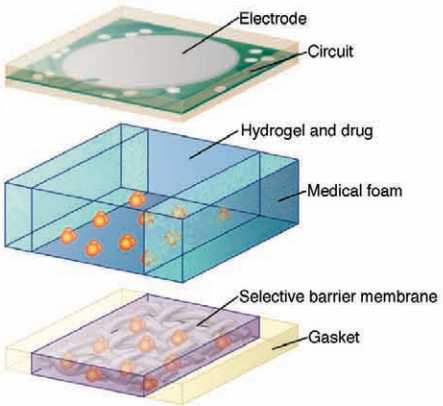
B&O Medicom's LEVA® auto-injector was designed with user friendliness in mind.

Isis Biopolymer, Inc.

Innovative. Intelligent.

IsisIQ™

Transdermal Drug Delivery & Biosensors with Wireless Integration



Isis Biopolymer's IsisIQ™ is an innovative and intelligent transdermal drug delivery (TDD) patch that provides biosensors and drug delivery ensuring safe and accurate administration through the skin using proprietary selective barrier membrane and single electrode design technology in combination with iontophoresis. Transport can be modulated for up to three drugs per patch and is fully programmable for customized delivery and monitoring via an integrated wireless communication platform.

(actual size)

Antares has three distinct self-injection devices. Medi-Jector VISION® is a reusable, variable-dose device engineered to last for a minimum of 2 years. The disposable plastic needle-free syringe delivers liquid through an opening that is approximately half the diameter of a 30-gauge needle, and it is designed to last for approximately 1 week.

Vibex™ injectors employ the same core technology developed for the VISION, using a coil-spring power source to deliver medication. This spring is combined with a tiny hidden needle in a disposable, single-use injection system.

Antares pen injectors address the need for a multi-dose injector that offers portability and convenience. Incorporating conventional prefilled glass cartridges, this injector uses standard primary drug containers and filling processes.

"We believe many injectable drugs currently under development will be administered by self-injection once they reach the market," says Mr. Hayes. "Our belief is supported by the continuing development of chronic care products that can only be given by injection and the new classes of drugs that require injection."

FIGURE 4

The Zetajet™ NFI system from Bioject recently received FDA clearance for delivering injectables into the subcutaneous or intramuscular tissue.

FIGURE 5

Duoject has partnered with Hyaluron to develop the Smart-Rod Plus systems, which lyophilize drugs directly in a standard sterile glass syringe.

BD MEDICAL–PHARMACEUTICAL SYSTEMS: PREFILLABLE SYRINGES FOR PROS & PATIENTS

BD Medical-Pharmaceutical Systems is a leading player in the hand-held injection market offering a variety of prefillable syringes and self-injection systems. BD provides a range of parenteral drug delivery systems designed to meet healthcare professionals' demands for safety and convenience while fulfilling patients' needs for comfort, says Janice Fajarito, Marketing Leader, BD Medical-Pharmaceutical Systems.

"Overall, we have seen that the market is more focused on safer delivery systems and administration practices to reduce errors," says Brian Lynch, Marketing Manager, BD Medical-Pharmaceutical Systems. "We have also seen a shift toward unit-dose packaging to better enable drug traceability in the marketplace. The use of prefillable syringes can help address these issues."

BD has developed two container glass prefillable syringe systems addressing healthcare market needs for security and patient injection comfort. BD Hypak™ PRTC (Figure 2) provides a syringe tip closure design that ensures secure tip cap attachment from handling and processing through administration. BD Hypak Physiolis™ combines a 29-gauge, half-inch, 5-bevel-thin wall needle and new needle shield material that preserves the needle-point integriety for patient injection comfort. This results in a 40% reduction in patient injection pain perception and a 70% reduction in skin penetration force, describes Ms. Fajarito. Both of these products are available today.

"On the vaccine side, we have seen the continued trend for preservative-free container closure systems," says Ms. Fajarito. "This has fueled the trend away from multi-dose vials for vaccines and toward unit-dose packaging, primarily prefillable syringes. This has also helped extend vaccine availability because of the significant reduction in overfill required with prefills (versus vials)."

With the continued growth in the vaccine and biotechnology sectors, there has been a need for the scientific understanding of the compatibility of complex molecules and container closure systems, says Marty Coyne, Senior Product Manager. "Through collaboration with customers, BD is focused on developing solutions to ensure long-term drug suitability for prefillable drug delivery systems."

B&O MEDICOM–FOCUSED ON USER FRIENDLINESS

B&O Medicom has been in the device industry for 20 years, working as a consultancy company (servicing all stages of development projects) and offering its own solutions, which include off-the-shelf products and fully customized solutions. The latest development of its own is the disposable LEVA® auto-injector (Figure 3).

"The technology behind LEVA is developed with simplicity in mind," says Ms. Arp-Nielsen. "This means that LEVA is a very flexible solution and can therefore be custom designed to different

requirements and functions. Further, LEVA has a unique shape that makes it easy to hold by patients with impaired dexterity, and the trigger button is designed for easy actuation."

The first off-the-shelf variant of LEVA is available with a 1-mL prefilled syringe and staked needle. A 510K application has been submitted to the FDA, and Medicom expects approval by the end of this year.

"The development of LEVA has been focused on ease of use. Therefore, B&O Medicom has executed several user trials," says Ms. Arp-Nielsen. The latest trial has included more than 60 patients ranging in age from 7 to 78. Four patient groups were included in the study: those with rheumatoid arthritis, multiple sclerosis, diabetes, and non-patients.

"With the focus on patient convenience today, there is no doubt treatments that enable patients to inject their own medicine off hospital grounds are much more convenient," says Ms. Arp-Nielsen.

BIOJECT–SETTING NFI THERAPY STANDARDS

Bioject Medical Technologies Inc. markets and develops technology for needle-free injection of liquid medications. Bioject's technology forces liquid medication at high speed through a tiny orifice. This creates an ultra-fine stream of fluid that penetrates the skin, delivering medication in a fraction of a second.

This past April, Bioject was granted 510(k) market clearance for general use from the FDA for the Zetajet™ Needle-Free Injection Therapy System (Figure 4). Zetajet is a compact, spring-powered device intended to deliver vaccines and injectable medications. The Zetajet uses jet force to propel a finely dispersed stream of injectable medication, between 0.05 and 0.5 mL, into the subcutaneous or intramuscular tissue.

The syringe assembly has a unique auto-disable feature that prevents re-use of the syringe. The plunger is pre-assembled into the syringe and can be used for reconstitution and other pre-injection tasks. Based upon partners' requests, the exterior molding of the device can be customized in shape, texture, and color for a variety of therapeutic and patient segments, including pediatric vaccines, fertility injections, hGH, and injectables used for chronic conditions.

"Zetajet sets a new standard in needle-free injection, and we look forward to working with partners interested in leveraging the benefits of the device," says Ralph Makar, President and CEO of Bioject. "The company's goal is to begin commercial manufacturing of Zetajet by the end of this year."

Additionally, Bioject offers the Iject®, a small, lightweight, gas-powered injection system for home or professional use. The device is available now for investigational use and is a prefilled, single-use disposable injector. The Iject needle-free injection system is intended to deliver subcutaneous, intramuscular, and intradermal injections and a variety of injection volumes.

Finally, Bioject is working on Jupiter Jet™, an intradermal, multi-dose, gas-powered cartridge to deliver low-volume and long-acting medications in multiple injections. Mr. Makar expects the product could be available in the next few years with the right partnership.

"New options like Zetajet, Iject, and Jupiter Jet cater to a range of strategic partners, therapeutic segments, and patients, which is positive for the company in attracting new opportunities during the current market conditions," he says.

DUOJECT–STREAMLINING RECONSTITUTION

Duoject is focused on advancing parenteral technology, developing medical devices for pharmaceutical clients that meet patient needs for safety, precision, and ease of use in drug reconstitution and delivery. "Innovation in reconstitution and delivery systems supports faster market entry and brand image for a new drug, as well as improves market penetration and market share of existing products," says Simon Williams of Duoject.

FIGURE 6

Elcam has designed both the Flexi-Q PFS (top) and Flexi-Q DV (bottom) as single-use, disposable auto-injectors for delivering drugs in liquid and lyophilized forms.

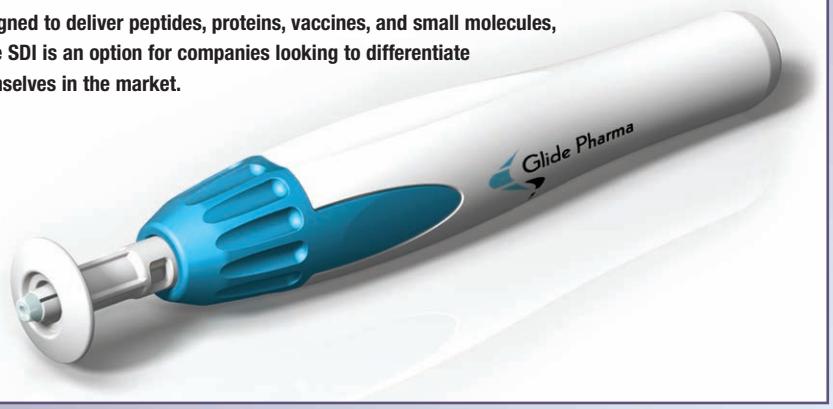
Duoject's technology platforms include a prefillable syringe system as well as effective drug reconstitution device technologies, complemented by engineering consulting services. "We have seen a significant increase in interest for reconstitution systems across a range of applications and therapeutic categories," says Mr. Williams.

Duoject's SMART-ROD™ XR, Xpress Reconstitution, is a prefilled diluent syringe, including the 1-mL staked-in needle syringe. The one-step activation SMART-ROD XR features a retractable self-purging transfer needle hidden in the plunger rod to provide safe reconstitution and minimize drug waste.

Duoject has partnered with

FIGURE 7

Designed to deliver peptides, proteins, vaccines, and small molecules, Glide SDI is an option for companies looking to differentiate themselves in the market.



Hyaluron to develop the syringe lyophilization process for its SMART-ROD PLUS systems (Figure 5). This means lyophilizing drugs directly in a standard sterile glass syringe. "Market interest is reinforcing our belief that this will be a process for the future," says Mr. Williams.

Duoject's PEN-PREP XR Xpress Reconstitution System is packaged sterile, pre-attached to a threaded pen cartridge holder containing a prefilled diluent cartridge. The system is ready for rehydration and recovery of dry-form drugs contained in standard vials.

Duoject's E-Z-LINK™ is a vial socket connector with a patented "captured needle" feature to reconstitute a solid form drug using any ISO standard prefilled diluent syringe and a traditional pharmaceutical vial.

The company is also expanding its product range to address needlestick legislation and ensure that injection systems are intuitive, says Mr. Williams. "This becomes even more important with the growing industry trends of home medication and self-administration. To meet this goal, we are working to finalize the designs and bring to market a cost-effective, single-use system, targeting the high-volume vaccination market."

Both a fully automatic, reconstitution and liquid fill version will be available, each having a safety system fully protecting the needle.

ELCAM MEDICAL–USER INTERFACE MUST BE SIMPLE

In the past year, Elcam introduced two hand-held injection products (Figure 6). First is the Flexi-Q DV, a fully disposable auto-injector for drugs in vials in both lyophilized and liquid forms. The single-use injector allows simplified reconstitution and aspiration from conventional vials, features safety needle shielding throughout the process, provides life cycle management capabilities for new and existing drugs, encourages patient compliance, and improves self-injection safety, says Dr. Zucker.

"Many pharma companies are commercializing sooner, meaning they will bring products to market in lyophilized form rather than wait for them to be stabilized in a liquid for prefilled syringes. We've learned a lot about user interface through extensive human factors testing. As a result, Elcam's devices are easy-to-use. Just remove the cap and inject," he adds.

Second is the Flexi-Q PFS, a fully disposable auto-injector for prefilled syringes. This single-use injector features passive needle shielding. According to Dr. Zucker, the potential target audience and therapeutic focus for both products include patients with rheumatoid arthritis, psoriasis, multiple sclerosis, anemia, or in need of human growth hormone.

Some products currently under development at Elcam include the Safe Auto-Needle (SAN), a single-use, disposable automatic needle for use with a syringe. Designed for automatic needle insertion with passive needle shielding, it can attach to any conventional plastic, prefilled, and dual-chamber syringe.

Elcam has also designed a disposable auto-injector, with passive needle shielding, using standard prefilled syringes with high-viscosity drugs. Moving forward, the company has its sights set on partnerships, acquisitions, and product development. Elcam recently acquired a majority interest in Injectech LLC, an OEM provider of customer injection molded components, giving the Elcam a US-based manufacturing option.

GLIDE PHARMA–TAKING THE RISK

Glide Pharma has developed the Glide Solid Dose Injector - Glide SDI™, an easy, safe, and convenient way for injecting drugs and vaccines in a solid dosage form, says CEO Dr. Charles Potter. The drug is formulated as a tiny rod, smaller than a grain of rice, with a point on one end. This dosage is prefilled into a drug cassette, which is a single-use, disposable component. In use, a drug cassette is placed in the end of a reusable, spring-powered actuator, which is pushed against the skin. Upon actuation, the dosage is automatically pushed into the skin where it subsequently dissolves.

The Glide SDI (Figure 7) is being tested by six pharmaceutical companies with their proprietary drugs or vaccines. Glide SDI has a range of applications with the majority of interest coming from companies wanting to make self-injection of peptides and proteins better for patients or looking for a better way of injecting vaccines.

"Pharma and biotech companies looking for a differentiated product that is easier, more convenient, and safer to use than needle-based delivery systems are our target audience," he says.

The Glide SDI addresses a number of needs in the market, including enhanced stability over liquid formulations, the potential to avoid cold-

chain storage, controlled or immediate release of the drug or vaccine, and no potential for cross-contamination due to the needle-free design.

The Glide business model is to develop Glide Pharma own-brand products with generic drugs in addition to developing products (incorporating generic drugs) for its partners, incorporating their proprietary drugs or vaccines. Glide recently completed a Phase I study with a fentanyl product for treating acute pain.

"The more progress made with our internal programs, the more interest we receive from industry, as we 'derisk' the technology in the eyes of pharma partners.

"Several drug delivery companies have failed in the past during scale-up and manufacturing," continues Dr. Potter. "Pharma companies are wary of manufacturing issues and the problems these have caused in the past, which is one reason why they are slow to adopt new technologies. By developing our own products, we are demonstrating that we have a robust manufacturing process and a commercially viable technology."

UNILIFE MEDICAL SOLUTIONS–FULLY PASSIVE SAFETY FEATURES

Unilife Medical Solutions Limited develops a proprietary range of clinical and prefilled retractable syringes with passive, fully integrated safety features with user-controlled needle retraction that can prevent needle-stick injury.

"With the US mandating sharps injury protection for healthcare workers, and European safety legislation continuing to gain momentum, the need for cost-effective, intuitive safety devices that meet the criteria established by OSHA (integrated passive safety features) is greater than ever," says Mark Hassett, Director of Sales and Marketing, Unilife Medical Solutions, Inc.

The Unilife Prefilled Syringe is to compete in the fast-growing market for prefilled safety devices, he adds. "We are not aware of any other product with fully passive safety features that are integrated inside the glass barrel, making it compatible with the filling and packaging systems of pharmaceutical customers."

As a result of a 5-year business relationship with sanofi-aventis, the Unilife Prefilled Syringe (Figure 8) has been engineered for high-volume production and is compatible with target injectable drugs and their associated dose filling systems. By eliminating the need for pharmaceutical companies to purchase bulky clip-on safety products that must be attached separately onto a standard prefilled syringe, the Unilife prefilled syringe has the potential to reduce filling, packaging, and shipping costs by up to 70%, says Mr. Hassett. Unilife Medical Solutions is focused on expanding corporate functions and operations in the US and Europe, which represent the largest and fastest-growing global markets for innovative safety medical devices, says Stephen Allan, Vice President of Marketing at Unilife.

In addition to its agreement with sanofi-aventis, Unilife has established relationships with key supply chain partners in the US and China. Unilife is in negotiations with several pharmaceutical companies and global distribution organizations that are interested in gaining access to the safety syringe products, says Mr. Hassett.

"Our receipt of a EU10m exclusivity fee from sanofi-aventis for the right to negotiate the purchase of our prefillable syringe technology and their payment of our EU17m industrialization program has helped put Unilife in a strong financial position," explains Mr. Hassett. "As we build toward the completion of this industrialization program next year and open up discussions with other potential customers, we believe the future is very bright for Unilife."

WEST–FLEXIBLE SYSTEM FOR RANGE OF PATIENTS & DRUGS

West is investing in device development programs that encourage patients to take medications and help in the overall management of healthcare delivery costs. "We believe devices will have long-term benefits for our pharmaceutical customers and the patients who rely on their drug products," says Mr. Reynolds.

FIGURE 8

The Unilife Prefilled Syringe has been engineered for high-volume production.

One such device is the West ConfiDose® auto-injector, a prefillable syringe-based, disposable system (Figure 9). Able to deliver a range of drug viscosities, the system is easy to operate, even for patients with impaired dexterity. The needle is hidden before and after injection, which can help prevent accidental needlestick injuries, notes Mr. Reynolds.

Pharmaceutical and biopharmaceutical companies can incorporate a prefillable glass or plastic syringe into the ConfiDose, which is designed for home dosing of chronic therapies. It is ideally suited to pharmaceutical and biopharmaceutical drug products used to treat rheumatoid arthritis and other autoimmune diseases, multiple sclerosis, cancer, HIV, and hepatitis.

West supports its pharmaceutical and biopharmaceutical customers' commercialization of combination products with a flexible technology platform that can provide a solution for multiple drug characteristics with the same device.

"West will continue to invest in

FIGURE 9

The West ConfiDose auto-injector is a prefillable syringe-based system that delivers a range of drug viscosities.

platform technologies that will help customers mitigate the risks inherent in drug development and help improve time to market," says Mr. Reynolds. "We believe the flexibility of our platform technologies will enable West to partner with a number of customers to help them solve their drug delivery challenges."

YPSOMED AG–TARGETING PENS & AUTO-INJECTORS

Ypsomed is focused on new pen and auto-injector opportunities for insulin, GLP-1s, hormones, and autoimmune diseases as this market continues to grow. "The market for insulin pens requires more than 800 million insulin cartridges per year to satisfy demand for reusable and disposable pens," says Ian Thompson, Head of Business Development at Ypsomed.

Ypsomed has a particular focus on its new disposable UnoPen and reusable ServoPen, which are insulin pens. The company has redesigned its Clickfine pen needles and is concentrating efforts on the new safety pen needle, Clickfine AutoProtect. This pen needle will be launched this year for clinical use for insulin pen injections and with cartridge-based injection systems where needle safety and needle phobia may be an issue.

In addition to pen needle and insulin pen developments, Ypsomed has had success with its dual-chamber pen platforms and Silberhorn disposable auto-injector. All products are designed specifically for Big Pharma's therapeutic injectables and for insulin-dependent diabetics.

Be it the intuitive dual-chamber pens or reusable and disposable insulin pens or auto-injectors, there is a clear trend toward disposable injection devices that are more convenient, and reduce the chance of needlestick injuries, says Mr. Thompson.

"Many of pharma's new proprietary drugs are aimed at therapies such as diabetes, autoimmune diseases, and cancer that require less-frequent injections and, therefore, lower quantities of devices for each therapy," says Mr. Thompson. "Pharma companies are therefore looking for pen and auto-injector platform technologies that can be leveraged for use with a number of drugs. The number of drug candidates in Phase II and III is growing rapidly, and it is becoming more important to provide qualified devices that can be used by patients in clinical studies."

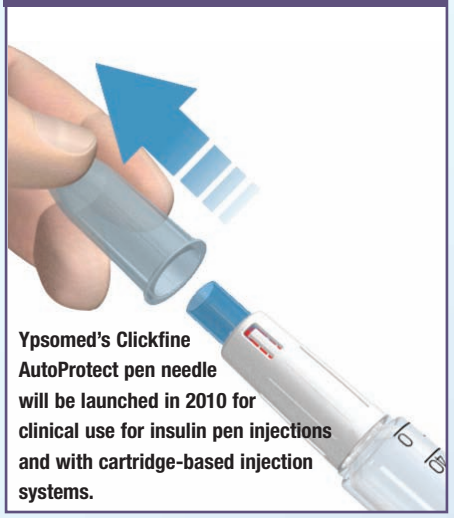
SUMMARY

Experts agree there is a lot of potential in the hand-held injection industry, with room for new trends and technologies to enter the market where the key focus is on more user-friendly products. And there is no doubt we will be seeing more devices on the market as the amount of biologics and biosimilars entering the market in the near future is increasing.

"As the pharma industry becomes more competitive with biogenerics/biosimilars gaining regulatory approval, pharma companies are going to have to differentiate their products through better delivery systems," says Dr. Potter of Glide Pharma.

Conventional injection methods for delivering the growing number of protein biopharmaceuticals may have limited commercial potential if patient compliance is lacking. One way to ensure patient compliance is by considering the human aspect early in the development process. Drug developers will investigate delivery devices earlier in the development cycle with the goal of producing more sophisticated devices that meet patients' needs for safety and convenience.

FIGURE 10



Ypsomed's Clickfine AutoProtect pen needle will be launched in 2010 for clinical use for insulin pen injections and with cartridge-based injection systems.

"The pressure is on for pharma to supply injectable drug products in a delivery device that can enhance injection safety outcomes whenever there is a risk of needlestick injury," says Mr. Hassett of Unilife. "The market has been waiting for the arrival of products that will herald a new generation of passive, integrated safety. Within 5 years, these technologies will generate a momentum that will be unstoppable." ◆

Drug Delivery Executive

Colorcon®

Colorcon: Continued Innovation in Formulation Partnership

James Coward
Vice President, Corporate Development

Colorcon

"Colorcon's success in bringing value to the pharmaceutical industry, via fully formulated, film-coating systems, is the basis of our overall business model. Key components of this model include continued product innovation, applications expertise, and a global infrastructure of technical service professionals and laboratories to support our customers' projects from proof-of-concept to scale-up."

Colorcon is a world leader in the development, supply, and technical support of formulated film-coating systems, modified-release technologies, and functional excipients for the pharmaceutical industry. Their best-in-class products and technologies are complemented by their value-added services, which support all phases of solid oral dose design and development. Colorcon understands the challenges facing the phamaceutical formulator; therefore, the company continues to invest in areas that facilitate involvement in all stages of product development to be the best and most valuable formulation partner. Drug Delivery Technology recently interviewed Vice President, Corporate Development, James Coward, to discuss Colorcon's current business model, what makes them unique, and their approach to the future.

Q: What is Colorcon's current business model?

A: Colorcon's success in bringing value to the pharmaceutical industry, via fully formulated, film-coating systems, is the basis of our overall business model. Key components of this model include continued product innovation, applications expertise, and a global infrastructure of technical service professionals and laboratories to support our customers' projects from proof-of-concept to scale-up. We have expanded this winning model in recent years with modified-release applications, which we define as delayed release, controlled release, and variants. The investments we have made in modified release include hiring a number of drug delivery professionals, additional laboratory capabilities, and extensive applications data. With our expanded functional excipient and modified-release product portfolio and formulation capability, we are now involved much earlier in our customers' projects.

Colorcon's target market has always been exclusively solid oral dosage forms. This has allowed us to build a unique solutions-focused partnership with the pharmaceutical formulator. Our portfolio of products and services has been steadily built and enhanced based on cumulative feedback from laboratory formulators over many years. Specialized formulated products have thus been developed for any coating application, inclusive of immediate-, controlled-, and delayed-release systems, and these products are further tailored to meet specific customer project needs.

The Controlled Release Alliance with The Dow Chemical Company is an integral part of our modified-release product and service offering. Dow's polymers for controlled-release

matrices, barrier membrane coating of multiparticulates, and osmotics are now represented globally and exclusively by Colorcon. Our combined product and service offering targets an enhanced partnership with the pharmaceutical formulator in controlled release, in the same manner as Colorcon has provided the industry historically in film-coating systems.

Inherent to our business model are continuing processes for understanding and responding to the needs and comments of our customers. This feedback is incorporated into our product and applications development plan on a regular basis. Confidentiality agreements with our customers facilitate an interactive loop, while protecting both parties' proprietary information. Our ultimate goal is to enable our customers' success in their solid oral dose development and speed their products to market.

Q: Tell us more about the Controlled Release Alliance and what it means for the pharmaceutical customer.

A: We believe the Controlled Release Alliance with The Dow Chemical Company offers tremendous value to the pharmaceutical formulator. As part of the Alliance, Colorcon and Dow have an exclusive relationship for three of the primary polymers used in oral controlled-release applications: high-viscosity hypromellose (METHOCEL™), ethylcellulose (ETHOCEL™) and poly (ethylene oxide) or PEO (POLYOX™). These polymers have established brand position, global acceptance, and high utility in solid oral dose matrix, barrier membrane coating, and osmotic applications. Indeed our market analyses suggest that these polymers, along with methacrylic acid co-polymers, in either direct use or blends, form the preferred approach to achieving modified release.

Dow provides these polymer products, unequaled production capability, and the polymer chemistry expertise to the Alliance. Colorcon's complement includes tailored formulations and systems, formulation capability, application expertise, and a global technical service and distribution network. Together, the companies bring a powerful partnership for optimized customer project design and support.

The companies are also collaborating on product development as it relates to new products, tools, and applications for METHOCEL™, ETHOCEL™, and POLYOX™, as well as industry-supporting initiatives such as Quality-by-Design.

Q: Can you provide our readers with an overview of your product platforms?

A: Colorcon is currently organized into Film Coatings and Formulation Technologies strategic business units (SBU), with focus on all stages of the pharmaceutical product development value chain, particularly Phase II forward.

Our Film Coatings SBU provides tailored immediate-release film-coating solutions for all aesthetic and functional coating applications. The Opadry® platform is the clear industry leader with optimized products for highest productivity, moisture barrier, gloss, taste-mask, etc., using a range of polymers and blends. We have tailored systems for key segments, eg, pharmaceuticals, nutrition/vitamin supplements, and Traditional Chinese Medicine.

Our Formulation Technnologies SBU provides formulated coating systems for controlled- and delayed-release applications, as well as functional excipients and expertise for matrix, multiparticulate, and osmotic applications.

Integral and distinctive components of our service and product platforms include extensive applications data, training programs for our customers in the use of our products, and brand-enhancement services for tablet formulations utilizing shape/coating/logo for optimal product positioning.

We have further enhanced our film coating portfolio with investment in physical-chemical identifiers (PCIDs) for use in preventing solid oral dose counterfeiting.

Q: What is meant by applications data, and how does this offering bring value to your customers?

A: : An intrinsic aspect of our business model is facilitating the use of our products and formulated systems in pharmaceutical solid oral dosage forms. To achieve this, we must develop such expertise in-house, which generates a vast amount of valuable reference material. We investigate and develop solid oral dose formulations utilizing our products and systems with model actives, as well as key actives in the marketplace today. These actives represent a full range of dosing and solubility parameters, as well as various processing approaches. This helps us position our products better, and therefore, our customers use our products more effectively. Conversely, these in-house studies highlight product limitations, so customers benefit from our experience and learn from our mistakes.

With all its uncertainties and commercial pressures, drug development is tough enough. First-Time-Right, a Colorcon guiding principle, is crucial to maintaining trust and confidence in our formulation partnerships. Allow me to illustrate the extent of applications data available for customer reference. For example, though hypromellose use as a matrix former is well understood, there remain many challenges facing the formulator. Formulating in the more extreme areas of dose and solubility is one such challenge, and we have developed capability and applications data for reference in all quadrants.

As previously mentioned, an area where we have and continue to develop capability is dissolution profile modulation, inclusive of minimizing burst effect, accelerating terminal phase release, ensuring exhaustive release, and optimizing upper gastro-intestinal tract release. Best practice guidelines for all of our products and systems are also developed and published highlighting optimal processing parameters using a range of equipment.

Q: What differentiates Colorcon from other pharmaceutical excipient companies?

A: We believe our model allows the best flexibility to truly deliver. Our unique position permits Colorcon to understand our customer's formulation and application needs in depth, and also work closely with major polymer suppliers in helping to meet these needs. Though we certainly ensure business continuity planning for all of our products, we are purposely not back-integrated in our key polymers. We focus on not only providing solutions, but options and flexibility within those solutions, tailoring our formulated products to a formulator's specific need in terms of dosage range, API solubility, and targeted dissolution profile.

We continue to invest heavily in subject matter expertise to enhance Colorcon's know-how in any solid oral dose application of our products. Our drug dissolution profile modulation capability extends across all applications from multiparticulates to tablets, inclusive of mini-tab and osmotic applications.

And, because Colorcon has always had a global interest, we have identical formulation and operating service models whether a customer's development is in the Americas, Europe, India, China, or Japan.

Q: What are the key areas of investment for Colorcon going forward in the drug delivery arena?

A: : Our investments are aligned with the opportunities and challenges facing the pharmaceutical industry: increasingly challenging APIs in terms of bioavailability, optimization/life cycle management of formulations utilizing existing APIs, and further globalization.

As mentioned earlier, to effectively assist the pharmaceutical formulator, we strive to be involved early in the development cycle and, of course, have in-depth application knowledge firmly established in-house. To facilitate early involvement, the ability to improve solubility and bioavailability is increasingly a prerequisite. Effectively achieving a solid dispersion of drug in our polymer products, aimed at improving

solubility and bioavailability, is a current area of investment to meet this key industry challenge.

Expanding and enhancing our capabilities in drug dissolution modulation continues in earnest, both in formulation expertise and tailored polymer blends. Ensuring that these technologies offer novelty as well as being cost-effective and scaleable is inherent to this work. Other key areas include osmotics and multiparticulate formulation options and capability.

Though Colorcon currently has a premier infrastructure of Technical Service Labs, we continue to evaluate additional investment in key population centers that will drive pharmaceutical consumption, ie, Middle East, Eastern Europe, South Asia, and Latin America.

All of these investments are aimed at partnering with the pharmaceutical industry to successfully bring new drug formulations to market and help our customers achieve their financial objectives.

Q: From your perspective, what are some of the key challenges facing the pharmaceutical formulator in solid oral dosage forms?

A: Robust formulation is a big challenge - achieving the desired drug dissolution profile (in vitro and then in vivo), scalability, and meeting exacting quality and regulatory standards on a day-to-day basis. A trend we have seen with new chemical entities is low solubility and resultant poor bioavailability and formulation robustness. Development time is extended, and the final formulation is often complex or involves specialized processes.

The challenge to the excipient or formulated system supplier is to help meet these challenges through the enhanced use of existing excipients. Bringing a new excipient to market is typically cost and time-prohibitive. Colorcon focuses on the use of blends of existing excipients, in terms of both application know-how as well as tailored formulated systems, in enhancing their collective functionality.

Other broader challenges include ensuring against tamper resistance, anti-counterfeiting, illegal extraction of narcotics from certain drug formulations, ensuring robust formulations in the presence of ethanol, and ensuring acceptable formulations to meet the needs of elderly and pediatric patient populations. Colorcon is investing in all of these areas in partnership with the pharmaceutical industry.

Q: What regulatory changes do you see affecting the excipient business and Colorcon?

A: The regulatory environment is becoming increasingly stringent by necessity. Excipient contamination issues have led to illness and death. IPEC guidelines are becoming increasingly stringent and global. Excipient choices, and ensuring business continuity planning of these choices, will necessarily demand more attention. This tightening regulatory environment will continue to impact not only prescription, generic, and OTC categories, but also vitamins and mineral supplements.

Additional testing requirements in other areas are also impacting the industry. New pediatric regulations in the European Union obligate market authorization applicants to submit results according to a pediatric indication plan. The objective is to improve the safety and availability of medicines for children, and the successful applicant receives additional marketing exclusivity. The FDA will establish similar requirements over the short-term, which is likely to drive increased use of multiparticulate formulations that can be dose adjusted for pediatric and adult use. Colorcon's multiparticulate portfolio in terms of spheres, barrier membranes, specialized coatings, fluidized bed equipment, and specialists throughout the world, is well positioned to partner with formulators to meet these regulatory requirements.

Another area of regulatory change is aimed at anticounterfeiting. The counterfeit drug market is estimated at over $50 billion today.

FDA guidelines for physical-chemical identifiers (PCIDs) using inks, pigments, flavors or molecular taggants have recently been issued. Colorcon's unique portfolo, inclusive of taggants, positions us well to assist our customers' efforts in addressing this growing issue. ◆

Technology Showcase

MDI Components

Enabling your success

3M Drug Delivery Systems

3M Drug Delivery Systems has been a major supplier of metered-dose inhaler valves and canisters for more than 50 years. As the developers of the first CFC-free MDI, we are experienced at overcoming the challenges that designing components for use with CFC-free propellants presents. 3M is the only MDI component supplier that manufactures both valves and canisters, allowing optimization of these components simultaneously, ensuring compatibility, while delivering the convenience of a single source. For more information, contact 3M Drug Delivery Systems at (800) 643-8086 or visit **www.3M.com/dds**.

Licensing Opportunities

Aveva has numerous products for license from its development pipeline along with a full compliment of R&D capabilities to produce transdermal drug delivery systems that fortify R&D pipelines and maximize product life cycles. Aveva Drug Delivery Systems is one of the world's largest manufacturers of and a pioneer in transdermal drug delivery systems of providing pharmaceutical partners with fully integrated, controlled-release transdermal products that fulfill unmet market needs. Products for licensing include Sufentanil, Fentanyl, Clonidine, and Nicotine. For more information, contact Robert Bloder, VP of Business Development, at (954) 624-1374 or visit **www.avevadds.com**.

Development Services

Azopharma Product Development Group, The Total Product Development Company™, is dedicated to providing clients with comprehensive product development services from discovery through commercialization. Azopharma maximizes communication and minimizes downtime by bundling services from key sections of the drug development process, including the Preclinical, CMC, and Clinical phases. Our capabilities include Full NCE Development, Full IND Development, Full NDA Development, Full ANDA Development, and Full Medical Device Development. Whether it's a stand-alone service or a comprehensive program, Azopharma has the solution to fit your needs! Our group of companies includes Azopharma Contract Pharmaceutical Services, AniClin Preclinical Services, and AvivoClin Clinical Services. For more information, contact Azopharma Product Development Group at (954) 433-7480, development@azopdogroup.com, or visit **www.azopodogroup.com**.

Prefillable Delivery Systems

BD Medical - Pharmaceutical Systems is dedicated to developing prefillable drug delivery systems designed to fit the needs of the pharmaceutical industry. BD offers a range of products, including glass and plastic prefillable syringes, a nasal spray system, and a variety of self-injection systems. We deliver cost-effective alternatives to conventional drug delivery methods, which differentiate pharmaceutical products and contribute to the optimization of drug therapy. With a broad range of innovative systems and services, BD provides pharmaceutical companies with support and resources to help them achieve their goals. Our worldwide presence, market awareness, and pharmaceutical packaging know-how allow us to propose suitable solutions for all regional markets and parenteral drug delivery needs. Only BD offers the range and depth of expertise and packaging solutions to guide your drug from early phase development through product launch and beyond. For more information, contact BD at (201) 847-4017 or visit **www.bd.com/pharmaceuticals.**

Technology Showcase

Liquid Medication Delivery

COMAR®

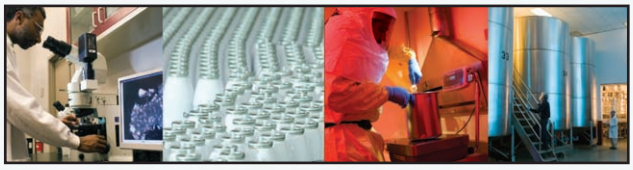
60 years of Quality, Innovation, and Service

Comar is on the cutting edge of technology and is a premier provider of innovative, high-quality liquid medication delivery devices. We are a true leader in providing safe packaging in the oral medication market with a focus on pediatric medication. Our Engineering group is committed to the design and development of the Next Generation in child-resistant packaging. Comar has been providing quality plastic packaging to the Rx, OTC, Bio, and Healthcare Markets for over 60 years inclusive of Plastic Bottles, a full line of Closures, Ophthalmic Packaging, Dropper Assemblies, Oral Dispensers, and Printed Dosage Cups. Comar is committed to providing quality products and superior customer service. For more information, contact Comar at (800) 962-6627 or visit **www.comar.com.**

Specialty Pharma

CyDex Pharmaceuticals, Inc. is a specialty pharmaceutical company focused on the development and commercialization of drugs specifically designed to address limitations of current therapies in selected established markets. We have developed a portfolio of product candidates utilizing our drug formulation technology (Captisol® cyclodextrins),which are a patent protected, specifically modified family of cyclodextrins designed to improve solubility, stability, bioavailability, safety, and/or dosing of a number of APIs. To maximize our internal resources, experience, and technology, we are focusing on the development and commercialization of product candidates for use in the acute care hospital setting. For those product candidates that likely will entail more extensive development and commercialization efforts, we partner with established pharma companies. We also outlicense our Captisol technology to third parties. For more information, contact CyDex at (913) 685-8850 or visit **www.cydexpharma.com.**

Development & Manufacturing



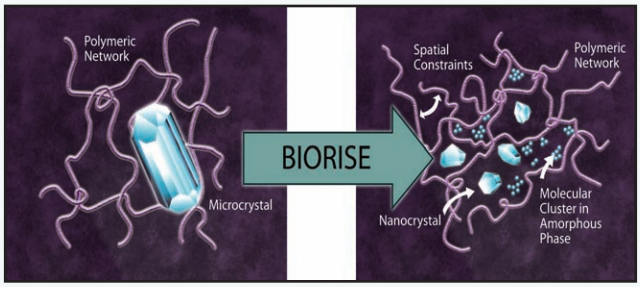
DPT is a contract development and manufacturing organization (CDMO) specializing in semi-solid and liquid dosage forms. DPT provides fully integrated development, manufacturing, and packaging solutions for biopharmaceutical and pharmaceutical products. DPT is the industry source for semi-solid and liquids — from concept to commercialization and beyond. Drug development services range from preformulation, formulation and biopharmaceutical development, analytical development, and validation through process development. Production capabilities include four cGMP facilities, clinical trial materials, full-scale commercial production, controlled substance registration Class II-V, and complete supply chain management. Packaging services encompass engineering and procurement resources necessary for conventional and specialized packaging. For more information, contact DPT at (866) CALL-DPT or visit **www.dptlabs.com.**

New Auto-Injector Line

Elcam Medical recently launched its Flexi-Q line of auto-injectors for self-medication - the only fully disposable auto-injectors designed for life-cycle management. Flexi-Q DV is designed for drugs in vials in liquid or lyophilized form, and the Flexi-Q PFS is for drugs in prefilled syringes. Both incorporate our unique platform with flexibility in customization: dosage between 0.3-1.0 ml, needle length & gauge, viscosity, injection force, and injection time. Elcam Medical is a leading worldwide OEM supplier of Fluid Management, Drug Delivery, and Vital Signs Monitoring systems and devices. As an OEM partner, we have significant experience in partnering with pharmaceutical companies in many disease states and therapeutic classes. Our dedicated team of auto-injector engineers and technical staff has worked with many leading companies in the field. For more information, contact Elcam Medical at (201) 457-1120 or visit **www.elcam-medical.com.**

Technology Showcase

Bioavailability Enhancement

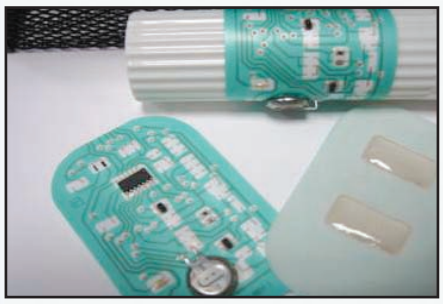


Biorise® increases the "intrinsic dissolution rate" of poorly water-soluble drugs, thereby enhancing their bioavailability and/or onset of action. Eurand's proprietary Biorise and Diffucaps® technologies can be applied to enable formulation of insoluble drugs and to improve the rate and extent of absorption of drugs from oral dosage forms. Diffucaps is a multiparticulate system that provides flexible dosage strength, required PK profile, and optimal release profiles for single drugs and drug combinations. The Diffucaps drug-release system can also be used in combination with other Eurand technologies to enhance drug solubility in the GI tract. For more information, visit Eurand at **www.eurand.com** or email us at partners@eurand.com.

Combination Capsule Technology

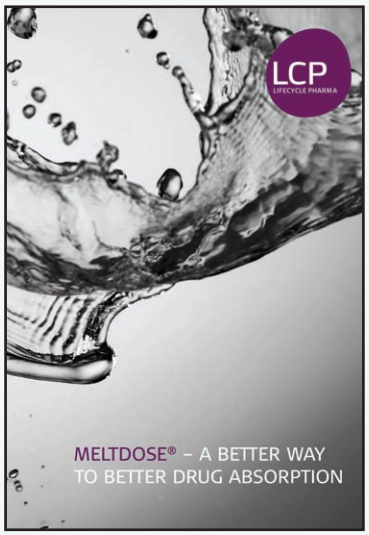
InnerCap offers an advanced patent-pending multi-phased, multi-compartmentalized capsular-based delivery system. The system can be used to enhance the value and benefits of pharmaceutical and biopharmaceutical products. Utilizing two-piece hard shell capsules, the technology offers the industry solutions to problems affecting pharmaceutical companies, patients, and healthcare providers. The delivery system will be licensed to enhance pharmaceutical and biopharmaceutical products. It is a very effective way to deliver multiple active chemical compounds in different physical phases with controlled-release profiles. The delivery system provides the pharmaceutical and biopharmaceutical industries with beneficial solutions to the industry's highly publicized need to repackage and reformulate existing patented blockbuster drugs with expiring patents over the next 5 years. For more information, contact InnerCap Technologies, Inc., at (813) 837-0796 or visit **www.innercap.com.**

Iontophoretic Patch



Isis Biopolymer, Inc. is expanding the capabilities of active transdermal drug delivery with its breakthrough product, the Isis Patch. The first compact, wireless, active iontophoretic patch to be fully programmable by healthcare professionals, the Isis Patch enables physicians to control activation, monitor use, and adjust drug delivery to each patient. Proprietary hydrogels allow dosing of multiple drugs, as well as a wide variety of drugs. A smaller, softer, and more flexible design resembles a band-aid, while hypoallergenic, skin-friendly polymers eliminate irritation and enable the patch to be worn for up to 7 days with superior adherence to the skin. Isis Biopolymer's lower cost, environmentally friendly manufacturing process reduces the cost of conventional iontophoresis by much as 50%. For more information, contact Isis Biopolymer at (401) 921-6873 or visit **www.isisbiopolymer.com.**

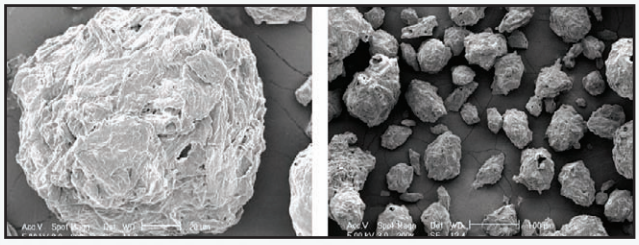
Absorption Enhancement



LCP is an emerging specialty pharmaceutical company focused on certain cardiovascular indications and organ transplantation. It currently has one product on the market, seven clinical development programs covering five product candidates, and three product candidates in preclinical development. Its first commercialized product, LCP-FenoChol, has received FDA approval for sale in the US under the brand name Fenoglide™ and is marketed in the US by Sciele Pharma. Fenoglide and its other development compounds are based upon its unique drug delivery technologies. The proprietary MeltDose® platform enhances the absorption of poorly soluble drugs. Applying MeltDose technology creates new versions of existing drugs with improved oral bioavailability, improving efficacy, allowing for lower dose, and in some cases, reducing food effect and/or potential side effects. For more information, visit LCP at **www.meltdose.com.**

Technology Showcase

Performance Excipients

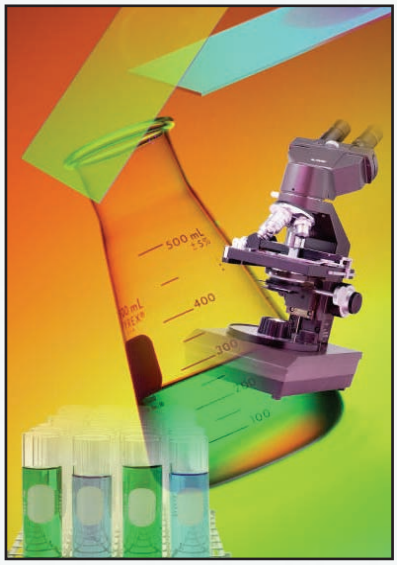


Mallinckrodt Baker recently launched PanExcea™ MHC300G performance excipient, a homogeneous particle that serves as a filler, binder, and disintegrant for immediate-release applications. Manufactured using novel particle engineering technology, the granular spherical excipient provides multifunctional performance capabilities that enable efficient and cost-effective drug development and manufacturing. PanExcea MHC300G lowers the total cost of ownership for the drug formulator by facilitating direct compression of even the most difficult APIs. It offers extensive API compatibility and variable API load capability to increase formulation flexibility. PanExcea MHC300G, which can be used as a building block or as a complete excipient, provides formulation development flexibilities and efficiencies, and enables implementation of Quality by Design (QbD) initiatives. For more information, contact Mallinckrodt Baker at (800) 943-4747 or visit **www.MallBaker.com/PanExcea.**

Silicone Materials

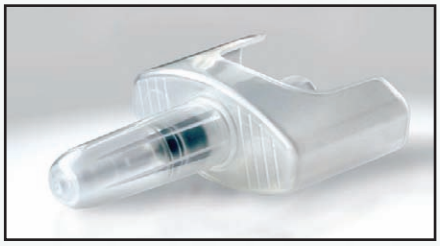
When it comes to drug delivery, NuSil provides numerous solutions that fit a variety of device needs. While most silicone products are customized for individual delivery systems, all are developed with FDA regulatory concerns in mind. In addition to its role as a supplier, NuSil offers research and development capabilities for those looking for proprietary, custom formulations. Regardless of batch size, NuSil delivers quality, high-performance silicone materials based on your unique property requirements, as well as provides precise, custom formulations. NuSil offers an even wider range of silicone material and compound options for transdermal, transmucosal, implanted intrathecal, and external delivery devices, as well as ingestible materials. For more information, contact NuSil Technology at (805) 684-8780 or visit **www.nusil.com.**

Development & Delivery Solutions



Founded in 1991, Particle Sciences is an integrated provider of both standard and nanotechnology approaches to drug development and delivery. Through a combination of preformulation, formulation, analytic, bioanalytic, and manufacturing services, Particle Sciences provides clients with a powerful, integrated solution to most efficiently take a drug from discovery to the clinic. Each project has a dedicated team and leader to manage the project from start to finish. With years of experience to draw upon, Particle Sciences can confidently handle difficult APIs, complicated intellectual property terrains, and challenging delivery goals to arrive at the simplest, most efficient solution to the client's needs. For more information, contact Particle Sciences at (610) 861-4701 or visit **www.particlesciences.com.**

Nasal Spray



In a rapidly growing market, the Pfeiffer Unitdose nasal spray device has established itself as a solution for applications as diverse as anti-migraine and anti-osteoporosis products. The Unitdose is designed to administer one accurate 100-microliter dose of a drug formulation via the nasal route. Maximum patient convenience is ensured by an integrated pressure point actuation mechanism with no need for initial priming. Years of research teamed with German engineering enabled Pfeiffer to produce this innovative nasal spray with its unique ability to protect the contents 100% until they exit the system after actuation. The Unitdose is ideally equipped to positively contribute to maximizing the contained drugs' effectiveness while minimizing their side effects. For more information, visit Pfeiffer of America at **www.pfeiffer-group.com.**

Technology Showcase

Knowledge Management

PharmaCircle™

PharmaCircle is an innovative knowledge management company specializing in the drug delivery, pharmaceutical, and biotechnology fields, with a current client base ranging from start-up life science companies to world leaders in Big Pharma. Clients choose PharmaCircle's services and content for its comprehensive technical (pipeline, products, molecule, and technology) and business (deals, acquisitions, royalty, licensing, drug revenues, market information, etc) related information and analysis, which are ideal for all segments of small and large companies. PharmaCircle helps facilitate product life cycle management (LCM), partnering, licensing, and competitive intelligence efforts as well as supplements internal efforts and costs at a fraction of the cost if performed internally. For more information, contact PharmaCircle at (847) 729-2960 or visit **www.pharmacircle.com.**

Contract Service Provider

PharmaForm doesn't just provide its clients with creative solutions; it creates successful partnerships. As a pharmaceutical contract service provider, it offers a wide range of formulation, drug product development, manufacturing, analytical testing and stability services, patent litigation support services, and product platform licensing opportunities. Its formulation scientists have core expertise and experience in improving solubility of poorly soluble compounds. One such available technique to clients is Evaporative Precipitation into Aqueous Solutions (EPAS), a process that causes the formation of nano-sized particles that can help enhance bioavailability of a poorly soluble compound. PharmaForm's state-of-the-art facility is registered with the FDA and the DEA and is cGMP/GLP Compliant. For more information, contact PharmaForm at (512) 834-0449 or visit **www.pharmaform.com.**

Global Central Labs

PPD

PPD's Global Central Labs — A 20 Year History of Success — A Future of Endless Innovation

No one gets medicine into the system faster®

PPD's global central labs fully support your drug development programs with extensive global reach; logistical expertise; highly customized and flexible services; strong and consistent science and therapeutic expertise; high-quality performance (98.5% data acceptance rate); efficient, accurate, and rapid sample collection; and state-of-the art laboratories with all relevant accreditations and certifications. Through strategically located facilities in North America and Europe, and with the use of sophisticated logistics and courier services, PPD provides clinical laboratory services to investigator sites in virtually every country of the world. PPD recently announced it has expanded its global central lab services into China through an exclusive agreement with Peking Union Lawke Biomedical Development Limited. For more information, contact Rob Danziger at (859) 442-1300 or visit **www.ppdi.com.**

Auto-Injector System

Designed to provide an optimum solution for self-injection of a fixed-needle prefilled syringe, West's ConfiDose® disposable auto-injector system offers a safe, convenient, easy-to-use solution for a wide range of drug products. With the press of a button, the syringe needle automatically extends to deliver a precise dose. After use, the needle is permanently and completely shielded within the system, averting the risk of needlestick injury and making the system safe for disposal. Ideal for home injections, ConfiDose® accepts a 1-mL long prefilled syringe format that can be used with a Daikyo Crystal Zenith® or glass syringe. Pharmaceutical companies can market the ConfiDose® two-component auto-injector system as a finished drug/device combination. For more information, contact West Pharmaceutical Services, Inc. at (732) 946-2929 or visit **www.ConfiDose.com.**

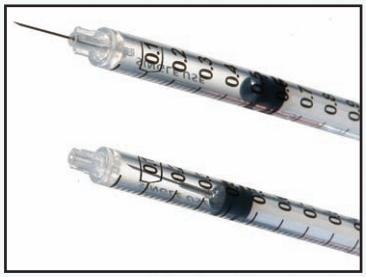
Technology Showcase

Contract Manufacturing

Stason Pharmaceuticals, Inc.

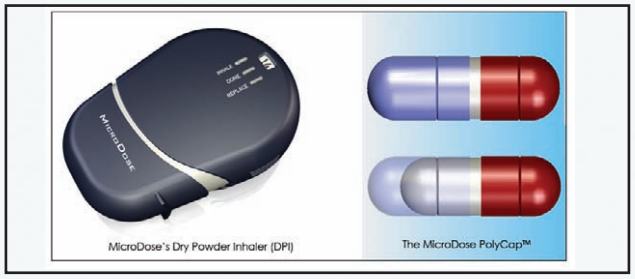
Stason Pharmaceuticals, Inc. has the experience and capabilities to manage the most challenging solid dose formulations. The company is a fully integrated cGMP contract development organization that provides complete turn-key drug development services for oral products. We offer services for both non-High Containment and High Containment Products. Stason offers a range of services for New Chemical Entities (NCEs), generics, and upgrades to existing formulations, and provides development and manufacturing services in its FDA-inspected facilities. We currently produce finished products at all scales through to commercial scale. All solid and semi-solid dosage forms are covered, including immediate- and delayed-release tablets and capsules, fast disintegrating tablets, creams, and lotions. For more information, contact Stason Pharmaceuticals at (949) 380-4327 or visit **www.stasonpharma.com.**

Prefilled/Clinical Safety Syringes



Unilife Medical Solutions has a range of prefilled and clinical safety syringes suitable for pharmaceutical companies, healthcare facilities, and patients who self-administer prescription medication. Our products incorporate passive and fully integrated safety features that can help customers comply with needlestick prevention laws and encourage single-use and safe disposal practices outside of healthcare settings. The products feature a passive (automated) needle retraction mechanism allowing operators to control the speed of needle retraction directly from the body into the barrel of the syringe. The Unilife Ready-to-Fill Syringe features a glass barrel and is compatible with the manufacturing procedures used to fill standard prefilled syringes. The Unitract 1-mL Insulin Syringe is FDA certified and now being manufactured in the PA facility. For more information, contact Unilife at (717) 938-9323 or visit **www.unilife.com.**

Next-Generation Products



MicroDose Therapeutx is pioneering the creation of next-generation products utilizing its proprietary technologies. MicroDose's Dry Powder Inhaler (DPI) and PolyCap™ combination oral dose capsule system promise to dramatically improve efficacy and compliance. MicroDose's next-generation DPI is a state-of-the-art electronic inhaler providing superior delivery for both small and large molecules to the lungs. It provides a platform technology that is low cost, reusable, and environmentally friendly, which can support a full pipeline of products. MicroDose's PolyCap System is a proprietary approach that enables the rapid development of FDC therapies in a single dose, but separated by a physical barrier. Utilizing the proven strengths of capsules and the advantages of a barrier system, it allows for more rapid development timelines and lower regulatory requirements. For more information, contact MicroDose Therapeutx at (732) 355-2100 or visit **www.mdtx.com.**

Nanotechnology Platform

SoluBest

Performance through NanoTechnology

SoluBest has developed a proprietary nanotechnology platform (Solumer™) for significantly improving the bioperformance of poorly soluble and insoluble. The versatile solubilization technology is widely applicable to numerous off-patent (or soon to be off-patent) drugs and NCEs. Rapid screening times allow the identification of suitable candidates in a few short weeks. Feasibility studies to clinical batch preparation can proceed in under 6 months. A significant advantage of the technology stems from its use of readily available equipment for a process consisting of a few simple steps, making scale-up safe, robust, rapid, and inexpensive. The company's strategy focuses on the development of novel drug formulations that can be performed in collaboration with API manufacturers, generic and brand pharmaceutical companies, biotechs, and drug delivery firms. For more information, visit SoluBest at **www.solubest.com.**

SPECIALTY PHARMA
Strategies For Business Development

Contract Manufacturing

Gaining Access to Global & Specialized Services

By: Cindy H. Dubin, Contributor

Marc Iacobucci

VP, Marketing & Project Management, DPT Labs

Marcelo Morales

CEO, HollisterStier-Draxis Pharma Contract Manufacturing

Diana Wood

VP, Business Development, Stason Pharmaceuticals, Inc.

Eric P. Neuffer

VP of Sales & Business Development for North America, Cambrex

The global pharma industry faces numerous challenges in the form of increasing competition in generic markets, rising costs of new product development, declining research and development productivity, shrinking average patent life, and mounting governmental pressure to reduce drug prices. Given the backdrop of such a competitive landscape, the decisive factors for growth and sustainability are faster new drug development and cost containment, with pharmaceutical contract manufacturing (PCM) emerging as a strategic option offering several advantages, according to Global Industry Analysts, Inc. Thus, the global market for PCMs is projected to reach close to $40 billion by 2012, up from $26 billion in 2007.

As stated by Global Industry Analysts, Inc., the US is the single largest market for PCM, with revenues projected to be $12.8 billion in 2012. However, Asia has immense manufacturing capacity and is projected to emerge as the fastest growing region in the global PCM market. Contract manufacturing in India and China is forecast to expand at a CAGR of 20% through to 2011. Big Pharma is increasingly outsourcing manufacturing to low-cost destinations due to cost and margin pressures, and India and China offer skilled manpower and a robust manufacturing infrastructure.

The PCM sector is three tiered. Tier 1 companies offer end-to-end services ranging from clinical trials to commercial manufacturing, logistics, packaging, and marketing assistance. Tier 2 companies provide services ranging from early stage project development to commercial level manufacturing. Tier 3 companies are conventional manufacturing companies, which address the needs of the generic drugs industry.

A major factor driving the upward trend in the number of manufacturing projects being outsourced is that specialized production, ie, sterile manufacturing; biopharmaceutical manufacturing; and specialized processes, such as chiral chemistry and improvements in catalyst activity, are often not included in the core competency of pharmaceutical and biotechnology drug makers. Biopharmaceutical manufacturing is forecast to have increased by 15% in 2008, driven by sales growth of biologics.

Specialty Pharma magazine recently asked key players in the PCM market to discuss the value they offer specialty pharma companies, the unique services they bring to the table, and how they are competing in this very competitive outsourcing environment. Participants include Marc Iacobucci, Vice President, Marketing & Project Management, DPT Labs; Diana Wood, Vice President, Business Development, Stason Pharmaceuticals, Inc.; Marcelo Morales, CEO, HollisterStier-Draxis Pharma Contract Manufacturing; and Eric P. Neuffer, VP of Sales and Business Development for North America, Cambrex.

Q: What strategic opportunity does PCM offer today's Specialty Pharma company?

Mr. Neuffer: PCMs offer companies the strategic opportunity to access established assets with existing cGMP quality systems that employ a highly skilled workforce in facilities with the appropriate regulatory approvals. Contract manufacturers typically have the knowledge and experience to avoid project/product production pitfalls. In addition, Specialty Pharma can access the contractor's unique capabilities, significantly reducing cost, time, and risk versus establishing these capabilities themselves.

Mr. Morales: They can offer a combination of speed to market, lower total cost to commercialization, and enhanced quality output. CMOs that have a corporate culture dedicated to process improvements, such as Lean and Six Sigma that adhere to a "right-first-time" mentality, present the most efficient and cost-saving means of bringing a product to market. In support of a robust process improvement system, CMOs must have detailed procedures that clearly articulate executing a method, provide required training, detail necessary project management, and define effective change control management to ensure an efficient manufacturing process. Specialty Pharma companies that partner with a CMO will find a manufacturer that has an innate understanding of the entire transfer and manufacturing life cycle and possesses the ability to absorb the associated complexities at an earlier stage than has been done in the past by CMOs.

Ms. Wood: Selecting a contract manufacturer that offers turn-key services can facilitate consistency and efficiency. Identifying and formulating the API and developing the product from benchtop through large-scale production with the same contract manufacturer without the need for a tech transfer saves time and money. In addition, designing a drug up-front for manufacturability or the ability to scale up at a later time ensures that, should a tech transfer be required, the potential for issues or delays is significantly reduced.

Mr. Iacobucci: Specialty Pharma companies typically carry limited or no internal development or commercial manufacturing overhead. Historically, Specialty Pharma companies outsourced formulation development to CROs. Later, they would have to find a CMO for late-stage development and product launch. Today, the concept of a CDMO (Contract Development & Manufacturing Organization) has emerged. Such organizations have comprehensive services from preformulation through clinical and commercial manufacturing. And tying world-class development together with broad commercial manufacturing capability is a key strategic opportunity. Cost savings, time efficiencies, and access to technical

Stason Pharmaceuticals, Inc., established in 1994 is a global pharmaceutical company involved in drug development, manufacturing, importation, exportation, licensing and marketing of both generic and branded products. We are actively seeking partners for products that will be introduced into the US through our Asian offices.

- Generic Division
- Branded Division
- Contract Manufacturing
- Licensing

Developing Products, Building Partnerships

STASON

11 Morgan • Irvine, CA 92618
Phone: (760) 929-0346 • Fax: (949) 380-4345
www.stasonpharma.com

Your
Where Vision Becomes Reality

expertise are the greatest advantages Specialty Pharma companies have found working with a CDMO. The benefits include a smoother transition from development to launch, one point of contact through the entire process, and decreased regulatory complexity.

Q: What issues are driving Specialty Pharma to outsource to a contract manufacturer?

Mr. Morales: Organizations focused on specialty pharmaceutical products are likely looking for opportunities to decrease costs and invest capital into R&D efforts. In-house manufacturing operations require a substantial amount of overhead to maintain the level of training and state-of-the-art equipment necessary to uphold cGMP manufacturing suites. As a result, outsourcing the compounding, filling, labeling, and shipping of a product provides Specialty Pharma the convenience of bringing the product into a facility that is adept at running a cGMP manufacturing operation and can gain the strategic edge of having the capacity for multiple batch sizes, quicker turnarounds, and a secure supply chain. Furthermore, CMOs can complement these manufacturing capabilities with method development support, protocol development support, and related enhanced testing support, allowing Specialty Pharma organizations to focus on their core activities in research, development, patient testing, and commercialization support. Specialty Pharma recognizes that many CMOs are finely tuned facilities that anticipate demand and have the capacity to accommodate it. By looking at the entire life cycle and supply chain, CMOs become a part of Specialty Pharma's cost-management solutions.

Ms. Wood: Due to the current economic challenges, many companies have downsized, sold off certain assets, or merged, which has resulted in reduced resources and expertise, and most importantly, periods of significant distraction and questions of goals or direction. Contract manufactures can offer both expertise and resources to a Specialty Pharma. This not only includes the actual development and formulation, or manufacturing, but regulatory advice and strategy. Contract manufacturers that have expanded their services into other areas directly, or through affiliations, can assist with clinical trials, product registrations, acquisition of comparator products, and exportation/importation. This results in a turn-key operation, from discovery through registration and beyond to commercialization.

Mr. Neuffer: Specialty Pharma companies choose to outsource in an effort to minimize risk if a drug product does not make it to market or has a weaker-than-expected market penetration; minimize capital outlay for manufacturing equipment; and access large-scale specialized technology platforms (ie, high potency, chiral chemistry, highly energetic processes) without which a Specialty Pharma could not commercialize a product.

Mr. Iacobucci: As stated, Specialty Pharma companies tend not to be burdened with significant internal development and manufacturing overhead. This is in contrast to Big Pharma that historically conducted virtually all development and manufacturing internally. This is actually a good thing for Specialty Pharma as it is not laden with associated overhead and are better able to focus resources on research, business development, and marketing. So, rather than Specialty Pharma being "driven to outsource," contract manufacturers are simply an excellent complement to Specialty Pharma.

Q: What specialized processes (ie, sterile manufacturing, biopharmaceutical manufacturing, chiral chemistry) do you offer to drug makers as many of these processes are often not included in their core competencies?

Mr. Iacobucci: At DPT, we focus on semi-solid and liquid dosage forms. These types of formulae can be complex, and we have incorporated virtually every API (including biopharmaceuticals) into these platforms. We offer sterile manufacturing services, manufacturing capabilities for aerosol formulations, and metered-dose inhalers. We also offer full Chemistry and Manufacturing Controls (CMC) documentation services for these products. Customers benefit by leveraging our experience early in the development process to avoid duplicative efforts in formulating their product. We have invested substantially into niche areas that are hard to commoditize (eg, pharmaceutical aerosol). And, we have enhanced our regulatory awareness and compliance to satisfy key geographies outside the US.

Ms. Wood: Stason provides cGMP high containment manufacturing for oral products, not only on a pilot scale, but commercial scale as well, distributing products in the US and abroad. In addition, our API plants provide both pharmaceutical and biologic APIs. Stason also develops new processes for synthesizing target molecules, including biotransformation processes for the preparation of chiral molecules. We also screen biocatalysts for the resolution or asymmetric synthesis of drug molecules and development of the biotransformation process. Specific to biotechnology products, we offer services that provide advantages of conventional organic syntheses and biotransformations to design specific chemo-enzymatic approaches for the synthesis of fine chemicals and

pharmaceutical intermediates. In addition, we help develop products and technologies in molecular diagnostics for cancer and screening for anti-cancer activities.

Mr. Neuffer: Cambrex possesses a handful of key core competencies that enable drug makers to bring their products to market from a technology and value perspective. These include specialized drug delivery technology, highly potent API development and production facilities, a controlled substance license, transaminase technology, Continuous Flow Microwave Assisted Organic Synthesis, and high-energy processes (ie, nitrations, fluorinations). The large-scale heterogeneous CFMAOS lead Cambrex to develop a reactor where products are manufactured on a continuous basis, giving improved productivity, quality, and thus lowering costs.

Mr. Morales: Sterile manufacturing are core strengths of both HollisterStier and Draxis, which requires complex technology, qualified facilities, and highly-trained staff. Within our global partnerships, we offer manufacturing services for sterile injectable liquid and lyophilized products, sterile ointments and non-sterile liquids, semi-solids, and solids. To complement our parenteral manufacturing services, we have world-class laboratory capabilities. As such, we offer method validation/transfer services for chemical and biological methods. Furthermore, HollisterStier has experience in processing and testing our own dedicated line of biologic-based immuno-therapeutic agents. Ultimately, our CMO clients, especially those clients with biologic or protein-based products, benefit from this expertise.

Q: How has the growing number of biotechnology-driven protein and peptide drugs affected the amount of business you are doing, and what types of services do you offer to accommodate these types of drug products?

Ms. Wood: Alhough Stason does not offer biomanufacturing, we do have fermentation API plants. Stason has also forged partnerships with other contract manufacturers that offer biomanufacturing and expects to expand into this area in the next few years. This expansion not only includes building or acquiring manufacturing facilities, but in-licensing biotechnology products, which we plan to develop internally. To further enhance our drug development capabilities, we plan to add a new division focused on compound screening, plasma protein binding, preclinical drug metabolism, preclinical and clinical study designing, and pharmacokinetic analysis.

Mr. Morales: We are seeing an increasing number of bio-driven protein and peptide drugs, and many companies who are looking to outsource require increased flexibility in the manufacturing schedule and multiple manufacturing capabilities to accommodate several different dosage forms. HollisterStier has been fortunate to have experienced substantial growth in the past fiscal year, and protein and peptide drugs represent an increasing percentage of what we manufacture. Our recent experience shows an increased trend in Phase I, II, and III biological products. Greater than 60% of the clinical trial products being produced in the past several years have been bio-driven protein and peptide drugs, and this trend continues to increase. New product submissions are an equal mix of NDAs and BLAs, and site transfers include various categories of product.

We offer specialized pharmaceutical processes and manufacturing equipment, such as lyophilizer cold-shelf loading, use of diaphragm and peristaltic pump filling technologies, aseptic compounding capability, and cold storage capacity for API and finished product.

Mr. Neuffer: Following the successful sale of the Biopharma and Bioproducts businesses in 2007, Cambrex is completely focused on small molecule API products and development/production services. As a segment of the biotechnology-driven market is focused on enhanced delivery of very potent small molecule drugs, Cambrex has invested in capacity to support the production of HPAPIs.

Q: The highly competitive nature of the pharma industry has been driving consolidation, and companies are increasing off-shoring to emerging markets to reduce costs. As a result, players in key outsourcing destinations have been improving their manufacturing infrastructure to increase their global competitiveness. Does this speak to what is happening at your company?

Mr. Morales: Our CMO organization has anticipated the shifts in our industry and understood early on the strategic opportunity in having a global presence. Both HollisterStier and Draxis have a partnership with facilities in India and Europe, allowing us to diversify our offerings, expand our capacity, and tap into resources within our parent and sister organizations that streamline the manufacturing process. HollisterStier and Draxis Pharma Contract Manufacturing are a part of Jubilant Organosys, an Indian-based multinational pharmaceutical organization. This partnership has allowed us to expand the services our combined organizations are able to offer clients–R&D through Jubilant Drug Discovery Services, clinical trial support through Clinsys, and API manufacturing through Jubilant Organosys. Since our integration with global partners, HollisterStier has expanded its facilities to include a commercial high-speed fill line,

an analytical and microbiological lab, 1,200 sq ft of lyophilizer shelf space, and we have recently invested $2 million into an expansion project in our clinical trial manufacturing suite. CMO organizations who maintain a global footprint provide access to a broad array of services and are able to offer a single point of contact to further reduce transfer and manufacturing complexity.

Mr. Neuffer: Cambrex has increased its global competitiveness by sourcing raw materials and intermediates from Asian providers to help lower overall cost of goods to our clients. In addition, Cambrex extended its footprint into Eastern Europe in 2008 by acquiring a facility with highly skilled chemists in Estonia, providing a value-added resource to support our R&D activities across in the US and Europe.

Ms. Wood: We started out offshore, so we inherited intrinsic competitiveness from the beginning. The core company, Standard Chemical & Pharma, based in Taiwan, was established in 1967 and has become a dominant player within the Asian market. Stason was set up in 1994 as part of a global expansion plan. We have since expanded in the US to three offices, and also expanded our offices and facilities into Japan and China. We are actively pursuing expansion through acquisition and partnerships into global territories that have a significant unmet medical need for the products we currently manufacture.

During the past year, Stason expanded manufacturing facilities and developed a licensing division within both the US and Japan. This division works with companies to license products into Asia through co-development agreements, which lead to marketing/distribution agreements, and at the same time, provide our clients revenue. Through our licensing office in Japan, we are working with companies that desire co-development agreements with US-based companies. This allows us to offer our clients potential new product offerings, many NCEs within the US. Contract manufacturers have to think outside of the box and provide other services where they truly partner with clients on a global basis with a long-term vision that benefits both parties.

Q: How do you see your business evolving to keep up with the Specialty Pharma industry throughout the next 3 to 5 years?

Ms. Wood: We are actively evaluating biomanufacturing opportunities and expect this to be a growing segment within our organization. Our current goal is to continue to build on our contract manufacturing expertise worldwide and at the same time ensure quality and customer satisfaction. We are also evaluating emerging markets outside North America, Europe, and Asia to introduce current products through co-development or licensing agreements to facilitate access to medicines and products that may not be available in those territories. Stason is quite diversified offering not only contract manufacturing, but we also have divisions in APIs, brand pharmaceuticals and development, medical devices, diagnostics, nutraceuticals, and animal health. Our goal over the next 3 to 5 years is to provide additional focus and resources to grow each of these areas as manufacturing is a significant component to each.

Mr. Morales: Specialty Pharmaceutical organizations will continue to see enhancements in drug development and related delivery mechanisms. It is critical that our CMO organization monitor these improvements carefully such that we can make targeted investments in infrastructure to keep pace with the changing needs of our clients.

HollisterStier has undergone significant growth in the last 5 years, and we predict that growth to maintain over the course of the next 3 to 5 years. We will continue to be a flexible and transparent manufacturer, working through the life cycle to take costs out of the supply chain and streamline manufacturing. We are a very heavily regulated industry and take training and continual process improvements very seriously. It is our belief that these investments in time and resources ultimately present our customers with the most safe, reliable, and efficient manufacturing partnership.

Mr. Neuffer: Cambrex will continue to provide innovation and value to our commercial products and services. The evolution in the next 3 to 5 years will include further expansion and exploitation of the core competencies. As an example, Cambrex is actively working with companies to taste-mask and enhance the drug delivery aspects of APIs using our proprietary resin technology. In addition, we continue to improve our transaminase technology, increasing the yields and refining the percent of enantiomeric excess.

Mr. Iacobucci: We're seeing more and more of our work shifting to development services earlier in the regulatory process, and we are building greater flexibility to meet the needs of these products. Many of these products are 505(b)2 NDAs that are looking for new indications and even new delivery systems. As such, we will continue to enhance service, innovation, and technology. While we will remain focused on our core business of semi-solids and liquids, we'll also expand into more adjacent delivery technologies that we'll offer our customers. Our strategy isn't necessarily to become the biggest, but our goal is to be the best at whatever we tackle. ◆

September 2009

Advertiser Index

Company	Pg	Phone	Web Site
3M	5	800-643-8086	www.3m.com/dds
AAPS	25		www.aapspharmaceutica.com/annualmeeting
Aveva DDS	7	954-624-1374	www.avevaDDS.com
Azopharma	Cover, 4	954-433-7480	www.azopharma.com
BD	19	800-225-3310	www.bdpharma.com
BioNetwork	39	888-482-6012	www.bionetworkus.com
Comar	15		www.comar.com
CyDex Pharmaceuticals	23		www.cydexpharma.com
DPT	2	1-866-CALL-DPT	www.dptlabs.com
Elcam Medical Inc.	9	201- 457-1120	www.elcam-medical.com
Eurand	76	937-898-9669	www.eurand.com
Innercap Technologies	75	813-837-0796	www.innercap.com
Isis Biopolymer, Inc.	51	401-921-6868	www.isisbiopolymer.com
LifeCycle Pharma	3	866-791-5715	www.lcpharma.com
Nusil	13	805-684-8780	www.nusil.com
Pfeiffer	29	609-987-0223	www.pfeiffer-group.com
PharmaCircle	31	847-729-2960	www.pharmacircle.com
PharmaForm	11	512-834-0449 Ext. 264	www.pharmaform.com
PPD	33	859-442-1300	www.ppdi.com
JT Baker	21	800-943-4747	www.mallbaker.com/PanExcea1
Mallinckrodt Baker	21	800-943-4747	www.mallbaker.com/PanExcea1
Stason Pharmaceuticals, Inc.	70	760-929-0346	www.stasonpharma.com
Unilife	49		www.unilife.com
West Pharmaceutical Services	17	732-946-2929	www.ConfiDose.com

My Theory of Relativity: $E=mc^2$

By: John A. Bermingham

With apologies to Albert Einstein, my theory of relativity has to do with hiring relatives to work in the same company. The Relativity Formula I refer to in the title of this column refers to the following: Employees = Major Concern Squared…..when related to each other!

I am dead set against the practice of hiring relatives to work in the same company and have two lasting experiences in dealing with this problem. The first was when I was Vice President & General Manager of the Telephone Answering Systems business unit at AT&T. Because it was an independent business unit, I had my own people for all functional areas, such as Bell Labs engineers, factories, finance, etc. This also included my own human resource function.

About 6 weeks after joining AT&T, I noticed one of the executives who reported to me kept submitting expense reports with an unexplained $100 charge for "other." When I questioned him on these charges, he answered that it had been his practice for years to allow himself an additional $100 per week for personal spending money. I called it embezzlement! I told him this was unacceptable conduct, and it would not be tolerated. I also did not like this person from the time I started at AT&T because he was lazy and incompetent.

So I headed down to human resources and told my HR Director what had happened and that I was terminating him for cause immediately. I also added as an aside that this was no loss for AT&T because he was also lazy and incompetent. Following the release of this person from the company for cause, I noticed my HR Director was no longer a team player and was causing problems in the business unit. So I came to find out too late that it was the practice for many AT&T people to be married, but the wife would always use her maiden name for her last name. Yep, you guessed it. She was the wife of the person I fired for cause.

The second experience was when I was the CEO of Lang Holdings, LLC leading its turnaround. Lang was headquartered in Delafield, WI, a tiny resort town west of Milwaukee. The founder and owner of Lang had a theory that if you hired most of a family to work for you, then Lang would own them and have better control of its people.

So after he sold the company to a private equity firm, I was brought in to turn Lang around as it was in serious trouble.

The company had enormous fixed overhead costs because people never got fired at Lang. So my first action was to downsize the company. I spent hours with human resources trying to figure out who was married to whom, who were the daughter's parents, which father had his son working in the company, etc. The company was a nepotism palace.

There was no way out of the mess. I had to bite the bullet and just downsize as best I could. I had my executive admin start my rental car every evening before I left (just kidding). The worst was when a few co-workers and I were in a Delafield restaurant waiting at the bar for our table and this large and scary man came up to me and said, "I just want you to know that you laid off my wife and my mother-in-law last week, and I'm upset about it." Exit left!

So the lesson that can be learned here is that while there may be the best of intentions in having family members all work at the same company, it really presents various problems and challenges to CEOs, particularly a turnaround type that has to downsize the company. ◆

BIOGRAPHY

John A. Bermingham is the President & CEO of Cord Crafts, LLC, a leading manufacturer and marketer of permanent botanicals. Prior to Cord Crafts, he was President & CEO of Alco Consumer Products, Inc., an importer of house ware, home goods, pet, and safety products under the Alco brand name and through licenses from the ASPCA and Red Cross. He successfully turned around the company in 60 days and sold Alco to a strategic buyer. Mr. Bermingham was previously the President & CEO of Lang Holdings, Inc. (an innovative leader in the social sentiment and home décor industries) and President, Chairman, and CEO of Ampad (a leading manufacturer and distributor of office products). With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona Corporation, and Rolodex Corporation. He turned around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served 3 years in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes, earned his BA in Business Administration from Saint Leo University, and completed the Harvard University Graduate School of Business Advanced Management Program.

THE ADVANTAGES

OF MULTI-PHASE, MULTI-COMPARTMENT CAPSULES ARE CLEAR

Deliver Incompatible Compounds
Deliver incompatible compounds in a single dosage form with different release profiles.

Multiple Release Profiles
Incorporate one or more release profiles into a single dosage form such as immediate, enteric, targeted, chronotherapy and pulsatile.

Higher Perceived Value
Consumers view multi-phase, multi-compartment capsules as having a higher perceived value than ordinary tablets, capsules and soft gels.

Choice of HPMC or Gelatin Capsules
With multi-phase, multi-compartment capsules you are not limited to just gelatin (animal-based product) but have the option of natural HPMC (hydroxypropyl methyl- cellulose) and alternative capsule materials.

Better Visual Appeal
Multi-phase, multi-compartment capsules have none of the dust and residue associated with powder capsules. Better visual product appearance translates to higher perceived value.

Increased Absorption and Bioavailability
Liquids naturally offer faster and increased absorption and availability of active ingredients.

Increased Profit Potential
Add up all the advantages. Expect higher sales...and high margins!

Multi-Phase System
Compounds can be delivered with the most advantageous pharmacokinetic profile such as liquids and solids

Faster Development
Multi-phase, multi-compartment capsules reduce the development time compared to bi-layer tablets to get a new product into clinical trials faster.

Smaller Capsules
Hard-shell capsules have thinner wall construction, allowing them to contain more ingredient in a smaller capsule versus thicker-shelled soft gel capsules. Hard shells have faster and more complete dissolution than soft gels.

Less Odor and Less Irritation
Reduces unpleasant ingredient taste and odor commonly found with tablets and traditional capsules. And, liquids provide less irritation than traditional delivery methods.

Tamper Proof Sealing
Band sealing reduces tampering and provides a non-permeable barrier to retard oxidation and increase shelf-life.

Unique Appearance
This new delivery system stands apart from look-alike products that crowd retail shelves.

Compounds
Deliver Pharmaceutical, bio-pharmaceutical and nutraceuticals in a single dosage form.

InnerCap™
TECHNOLOGIES, INC

Patent Pending US-2005-0008690-A1

9745 International Court • St. Petersburg, FL 33716 USA • (813) 837-0796 • www.innercap.com • fmiller@innercap.com

Unparalleled taste Flexible dose Versatile release Robust tablet

AdvaTab® The next generation ODT

Eurand's AdvaTab is an orally disintegrating tablet (ODT) technology that combines superior taste and mouth feel properties in a robust tablet. AdvaTab is unique, offering both high dose capacity and modified drug release making it the most broadly applicable ODT available. Utilization of standard tabletting processes allows for cost-efficient manufacturing and conventional packaging. The next generation ODT is here!

EURAND

www.eurand.com

+1-267-759-9340
partners@eurand.com

CUSTOMIZED DRUG RELEASE BIOAVAILABILITY ENHANCEMENT TASTE MASKING AND ODTs DRUG CONJUGATION