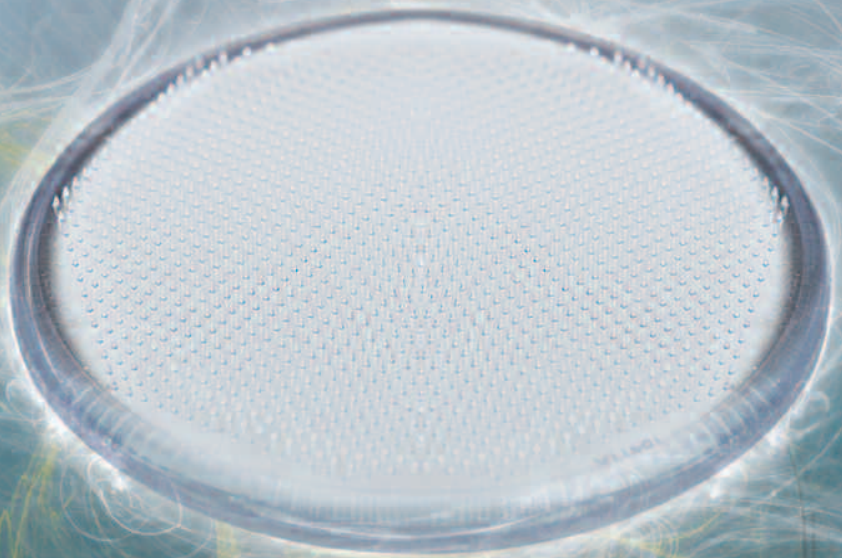
Drug Delivery® Technology

September 2008 Vol 8 No 8 www.drugdeliverytech.com

Transdermal Delivery of Biopharmaceuticals



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

David Fairhurst, PhD
Aggregation, Agglomeration – How to Avoid Aggravation When Formulating Particulate Suspensions

Kris Hansen, PhD
A Solid Microstructured Transdermal System (sMTS) for Systemic Delivery of Salts & Proteins

Tark Bunch
CMOs: Serving the Specialty Pharma Sector to Mitigate Risk & Maximize Profit

IN THIS ISSUE

INTERVIEW WITH CIRRUS PHARMACEUTICALS' PRESIDENT & CEO

ANTHONY HICKEY, PhD

Finalizing The Deal 20
Derek G. Hennecke, MBA

Hand-Held Injection 28
Cindy H. Dubin

Skin-Penetration Studies 44
Daniel Bucks, PhD

Cancer Nanotechnology 54
Geeta M. Patel
Madhabhai Patel, PhD

FEATURING

SPECIALTY PHARMA Strategies For Business Development

Testosterone Gel for HSDD 72
Stephen M. Simes

Parameters for Success 78
Josef Bossart, PhD

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

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

Drug Delivery Technology

September 2008 Vol 8 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
Malcolm A. Teasdale

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
Cheryl S. Stratos - Account Executive
103 Oronoco Street, Suite 200
Alexandria, VA 22314
Tel: (703) 212-7735
Fax: (703) 548-3733
E-mail: vgeis@drugdeliverytech.com
E-mail: cstratos@drugdeliverytech.com

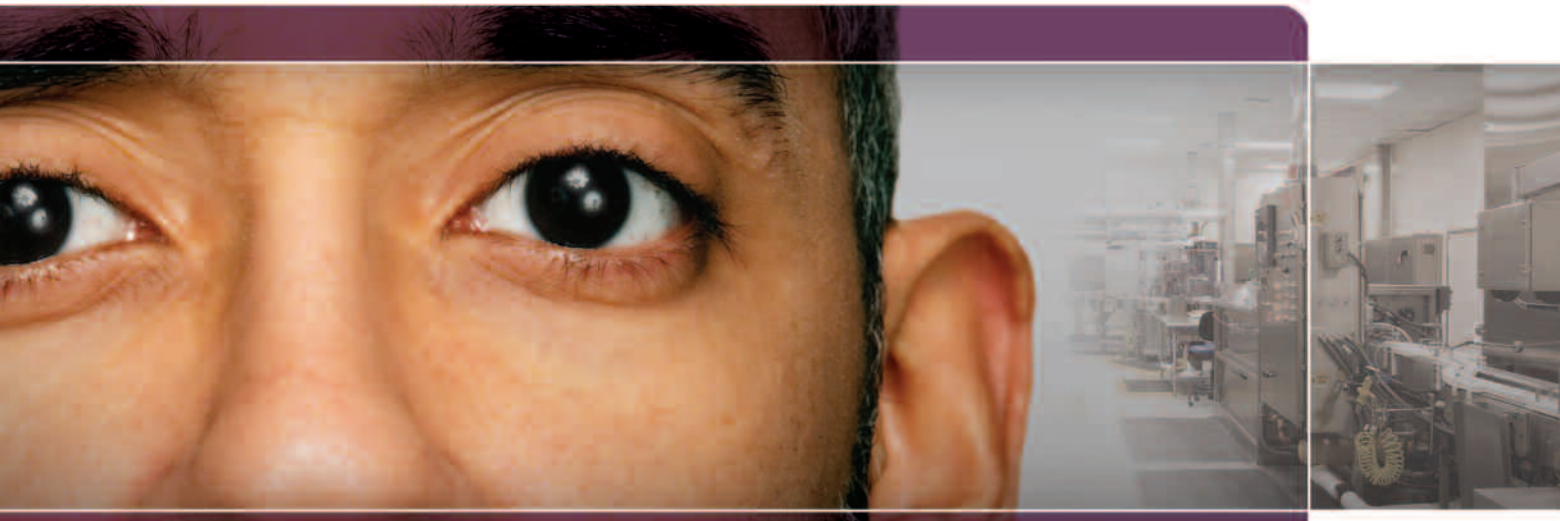
West Coast
Warren De Graff
Western Regional Manager
818 5th Avenue, Suite 301
San Rafael, CA 94901
Tel: (415) 721-0644
Fax: (415) 721-0665
E-mail: wjdegraff@drugdeliverytech.com

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

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

Table Of Contents

20 *The Deal*
Derrek G. Hennecke, MBA, concludes his 7-part series chronicling the challenges, issues, and more importantly, the opportunities he faced throughout his successful Management Buy-Out.

28 *Today's Hand-Held Injectors - Differentiation is King*
Contributor Cindy H. Dubin discovers that while all hand-held injection device companies strive to accommodate patient compliance and keep costs down, they also are vying to bring unique and innovative technologies to the market.

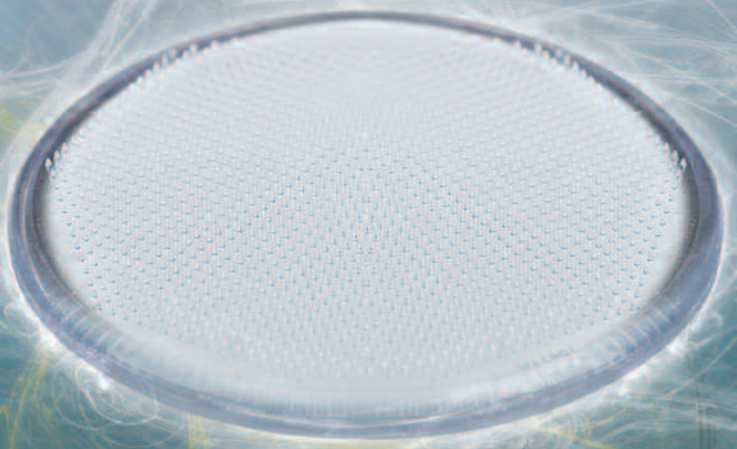
38 *A Solid Microstructured Transdermal System (sMTS) for Systemic Delivery of Salts & Proteins*
Kris Hansen, PhD, and Bret Haldin, MBA, review sMTS and how it embodies the patient-friendly characteristics of a transdermal patch with the versatility and application times more akin to subcutaneous injection.

44 *Rationale & Design of Studies to Screen & Identify Promising Topical Formulations*
Daniel Bucks, PhD, discusses the rationale for conducting skin-penetration studies, appropriate test systems, the importance of the source of the skin, and typical study design variables and deliverables.

48 *Aggregation, Agglomeration – How to Avoid Aggravation When Formulating Particulate Suspensions*
David Fairhurst, PhD, and Robert W. Lee, PhD, describe the steps involved in formulating particulate systems. Knowledge of this process coupled with an understanding of the physicochemical properties of the API is necessary to produce pharmaceutically acceptable particulate systems.

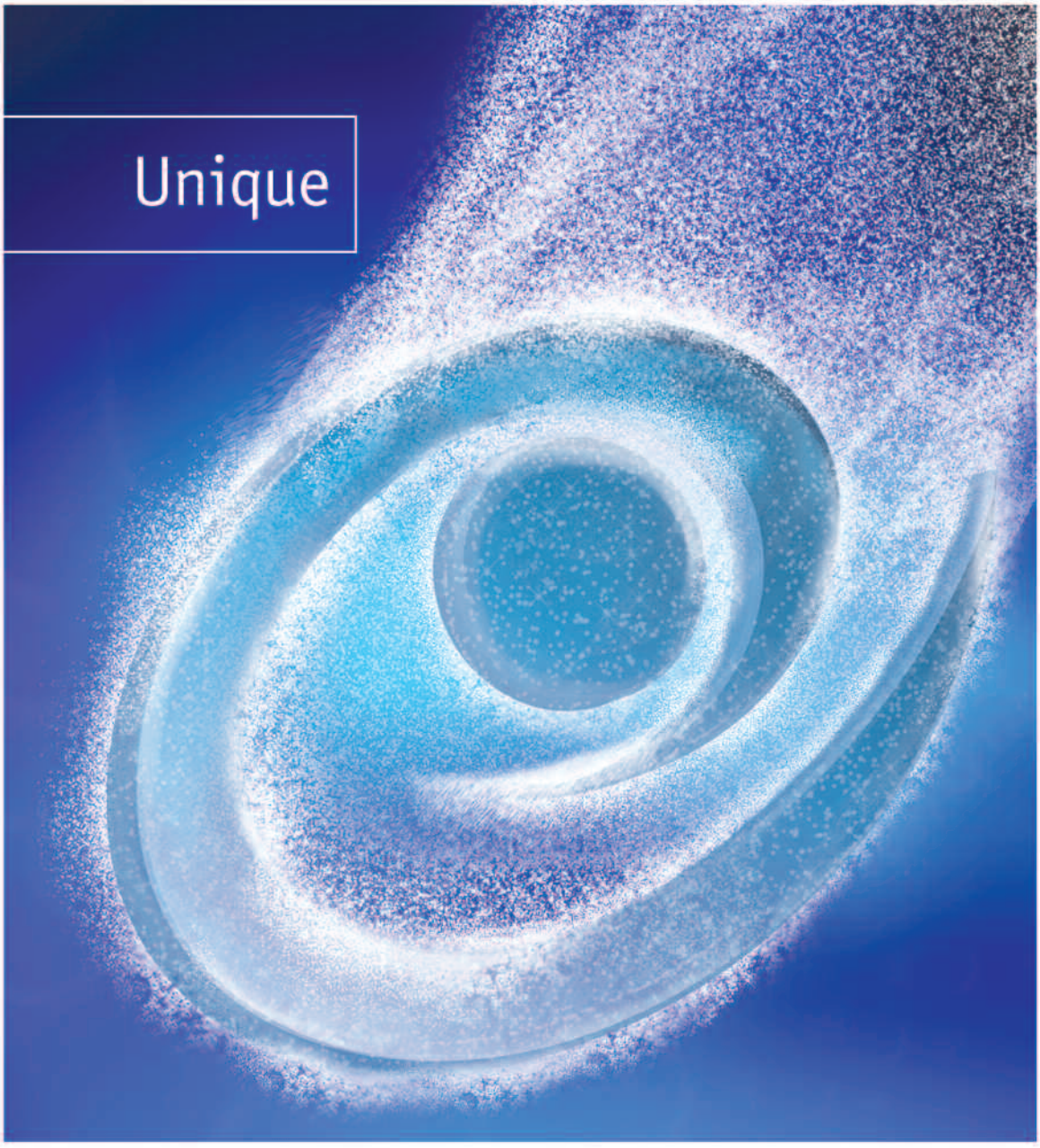
54 *Cancer Nanotechnology: Small, but Heading for the Big Time*
G.M. Patel and M.M. Patel, PhD, outline the use of nanostructures for cancer therapy, which has experienced a tremendous investment and an explosion of research and development efforts in recent years.

Delivering Biopharmaceuticals



"Drug coated on the sMTS prior to application is efficiently delivered into the systemic circulation within the 10-minute intended wear time of the patch, typically within the first 30 seconds, after which the patch may be removed and discarded. In addition to offering a minimally invasive route to systemic delivery, the sMTS eliminates the risk of accidental needlesticks before and after application."

p.38



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

USA +01-937-898-9669
EU +39-02-95428-309

ODT CUSTOMIZED RELEASE TASTE MASKING ENHANCED BIOAVAILABILITY

Risk & Profit

"Pharmaceutical companies look for prospective CMO partners with a strong record of on-time delivery. Most emerging and small pharmaceutical companies are funded by venture capital or private equity, and on-time delivery of their clinical trial materials is absolutely necessary to help them manage their cash burn rate or until they get their next round of funding."

Table Of Contents

60 *Cirrus Pharmaceuticals: Combining Excellent Service & Scientific Expertise*

Drug Delivery Executive: Dr. Anthony Hickey, Co-founder, CEO, and President of Cirrus, explains how his firm is collaborating with the industry as a CRO and how its drug delivery expertise will expand in the future.

64 *Pantec Biosolutions: Laser-Based Delivery Solutions*

Drug Delivery Executive: Dr. Christof Böhler, CEO of Pantec, discusses overcoming limitations with the P.L.E.A.S.E. platform and sheds light on the company's own pipeline as well as its strategy to penetrate new markets through strategic partnerships.

68 *Serving the Specialty Pharma Sector to Mitigate Risk & Maximize Profit*

Contributor Cindy H. Dubin speaks with three CMOs about how they are trying to appeal to the Specialty Pharma sector and the services they are providing to meet those companies' unique needs.

72 *Testosterone Gel for HSDD: Technology Tackles an Unmet Medical Need*

Stephen M. Simes talks about the development of what Biosante Pharmaceuticals expects will be the first FDA-approved medication indicated specifically for hypoactive sexual desire disorder in menopausal women.

78 *Bionumbers, LLC: Turning Insight Into Action*

Executive Summary: Dr. Jo Bossart, Managing Director of Bionumbers, shares how a better understanding of history can ensure a future product success story.

Departments

Market News & Trends 12

Excipient Update 22
Copovidone – A Copolymer With Unique Formulation Properties

Technology Showcase 62

Facts & Figures 76

External Delivery 82
Rome Is Burning!

With Our Sustained Delivery System

Our suite of patented self-correcting oral delivery systems provide precision controlled delivery and can handle your most challenging drug or nutritional ingredient. CDT's simple but elegant technology provides partners with rapid product development and the highest possible success in clinical trials.

- Our "**Electrolyte**" platform is capable of custom tailored release profiles, including zero order, that can emulate complex delivery systems. (i.e. osmotic pumps, bead systems, layered tablets)
- Our "**Amino Acid**" platform can enhance solubility to allow precision controlled delivery in simple monolithic dosage forms.
- Our "**Dual Polymer**" platform allows production of novel Matrix tablets and capsules regardless of their initial flow properties.

SCOLR Pharma, Inc.
Self Correcting Oral Delivery Systems

3625 132nd Ave S. E. • Suite 400
Bellevue, WA 98006
425.373.0171
www.scolr.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

James N. Czaban, JD
Partner, FDA Department
WilmerHale

John Fraher
President, North America
Eurand

Philip Green, PhD
Director of Business Development
Advanced Drug Delivery
BD

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

James S. Bernstein, PhD
President
Live Oak Pharmaceutical Consulting, Inc.

Philip L. Smith, PhD
General Partner
S.R. One, Limited,
GlaxoSmithKline

Ronald L. Smith, PhD
Director of Exploratory Biopharmaceutics & Drug Delivery
Bristol-Myers Squibb Research Institute

Cornell Stamoran
VP, Strategy & Business Process
Catalent Pharma Solutions

Tom Tice, PhD
Executive Vice President and Chief Scientific Officer
Brookwood Pharmaceuticals

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
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 discuss how PharmaForm can help you, please contact:

Michael M. Crowley, Ph.D., (512) 834-0449 ext. 202
Viviana Hetherington, B. Sc., MBA, (714) 274-9918

Market News and Trends

MicroDose Technologies Announces Achievement of Phase I Clinical Milestone Triggering First Milestone Payment Under Merck Collaboration

MicroDose Technologies Inc. recently announced the first clinical milestone in its collaboration with Merck & Co., Inc., through a Merck affiliate, has been achieved, triggering the first payment under the global license agreement for MicroDose's dry powder inhaler (DPI) technology announced in March 2008. This milestone signals the initiation by Merck of a Phase I clinical study of an investigational compound using the MicroDose DPI technology.

As previously announced, Merck will fund development and commercialization of products that employ MicroDose's DPI technology for the administration of Merck compounds. In addition to the up-front payment received upon commencement of the collaboration, MicroDose is eligible for additional milestone payments on this product and for the development of other products and royalties on revenues from all products developed under the license.

"MicroDose is proud to announce the start of the study by Merck which, in fact, represents the second human clinical study to be initiated under a US Investigational New Drug Application using our inhaler technology in the past 18 months" said David Byron, Vice President of Research and Development, MicroDose. "Achieving this milestone with Merck so quickly is a strong indicator of the excellent working relationship that underpins this collaboration."

The MicroDose DPI is among a number of key proprietary drug delivery platforms developed by MicroDose. By employing piezo electronics, the MicroDose DPI has the potential to deliver enhanced performance for efficient and reproducible delivery independent of patient coordination, inhalation rate, and posture, all features MicroDose hopes will be confirmed through clinical trials. MicroDose believes the flexibility of the inhaler makes it a true platform technology, able to support a broad pipeline of products across the spectrum of patient populations and therapeutic categories.

MicroDose Technologies, Inc., based in Monmouth Junction, NJ, is a leading privately held drug delivery systems company, developing advanced pulmonary, fixed-dose-combination oral dosage, and other technologies for the pharmaceutical and biotechnology industries. In addition to the collaboration with Merck, MicroDose's other partnerships include a multi-product development and licensing agreement with Novartis, the development of an inhaled insulin product through MicroDose's QDose joint venture, and an inhaler for the systemic delivery of a nerve agent antidote for the US Department of Defense in collaboration with the University of Pittsburgh. MicroDose has ongoing feasibility programs with other major pharmaceutical companies and is also conducting internal development programs for products employing its inhaler technology, and for combination oral dosage products employing its PolyCap technology in the areas of diabetes, hypertension, and hyperlipidemia.

PharmaForm to Expand Facilities in Texas to Meet Increasing Demand

PharmaForm, a provider of drug development and manufacturing services to the international pharmaceutical industry, recently announced it will expand its facilities in Austin, Texas, to meet growing demand. PharmaForm has leased 69,872 square feet at the Davis Springs Corporate site in northwest Austin, which will become the company's new headquarters.

The new facility includes 11 manufacturing and development suites, including four suites dedicated to high-potency compounds, expanded analytical laboratories, and increased vault space for controlled substances. The facility will enable PharmaForm to expand its product development, analytical characterization, technology transfer, bulk production, bulk packaging, and storage services. Construction is planned to be complete by the end of July 2009. PharmaForm has first right of refusal on 22,500 square feet of adjacent space.

"The facility expansion is part of our strategy to satisfy the existing and future development and manufacturing needs of our customers," stated Michael Crowley, PhD, Vice President of Business Development. "The new site expands our capacities to develop and manufacture various drug products, including high-potency compounds and controlled substances. This facility helps us continue to attract top talent from the industry and represents another step toward our vision of being the best provider of development and manufacturing services to the pharmaceutical industry."

PharmaForm has an international reputation for delivering novel solutions to challenging problems in pharmaceutical product development, manufacturing, and analytical services. Each member of the PharmaForm team shares a common mission: delivering unmatched excellence and innovation to clients by offering internationally recognized expertise in drug product development; completing each project in a timely and cost-effective manner; and maintaining a customer-focused operational infrastructure. PharmaForm has provided contract services with client groups varying from small virtual companies with no manufacturing facilities to large pharmaceutical organizations.

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

DSM Biologics & MorphoSys AG to Manufacture Fully Human Antibody

DSM Biologics and MorphoSys AG recently announced the signing of a Biopharmaceutical Manufacturing Agreement covering process development and cGMP manufacturing of MOR202. MOR202 is a fully human HuCAL antibody directed against CD38, a promising target for the treatment of multiple myeloma. DSM Biologics will manufacture MOR202 in its cGMP facilities in Groningen, the Netherlands. Further financial details on this agreement were not disclosed.

"Based on the positive experiences we have gained with the PER.C6 cell line and DSM's manufacturing capabilities within our MOR103 lead program, we have chosen to continue to use this platform for MOR202," said Dr. Marlies Sproll, Chief Scientific Officer of MorphoSys.

"We are very pleased that MorphoSys is extending its business partnership with DSM Biologics as their preferred manufacturing partner after our highly successful collaboration on the MOR103 program," added Marcel Lubben, VP Marketing & Sales at DSM Biologics. "It is exciting how well the combination of our two strong platforms works for fully human antibodies."

Crucell's PER.C6 technology platform has been developed for the large-scale manufacture of biopharmaceutical products, such as recombinant proteins, including monoclonal antibodies. Compared to conventional production technologies, the strengths of PER.C6 technology lie in its excellent safety profile, scalability, and productivity under serum-free culture conditions.

DSM Biologics, a business unit of DSM Pharmaceutical Products, is a leading provider of manufacturing technology and services to the biopharmaceutical industry. In addition to offering world-class biopharmaceutical manufacturing services, DSM Biologics has co-exclusive rights, along with Dutch biotech company Crucell N.V., to license the high-producing PER.C6 human cell line as a production platform for recombinant proteins and monoclonal antibodies. DSM Biologics' FDA-approved facility in Groningen was established in 1986 and has a strong track-record in using a broad range of cell lines (PER.C6, CHO, hybridoma, etc) in biopharmaceutical manufacturing and has a wide-range of experience using multiple manufacturing (batch, fed-batch, and continuous perfusion) and purification techniques. The combination of the PER.C6 human cell line and DSM's manufacturing services provides companies with a turnkey biologic manufacturing solution reducing cost, risk, and time to market.

MorphoSys is a publicly traded biotechnology company focused on the generation of fully human antibodies as a means to discover and develop innovative antibody-based drugs against life-threatening diseases. MorphoSys' goal is to establish HuCAL as the technology of choice for antibody generation in research, diagnostics, and therapeutic applications. The company currently has therapeutic and research alliances with the majority of the world's largest pharmaceutical companies, including Boehringer Ingelheim, Centocor/Johnson & Johnson, Novartis, Pfizer, and Roche. Within these partnerships, more than 50 therapeutic antibody programs are ongoing in which MorphoSys participates through exclusive license and milestones payments as well as royalties on any end products.

KV Signs Expanded Worldwide Partnership With Acrux

KV Pharmaceutical Company, a fully integrated specialty pharmaceutical company, recently announced a significant expansion of its commercial collaboration with Australian drug delivery company Acrux, under which KV will incorporate Acrux's unique spray technology for delivering drugs through the skin in up to six additional new branded products to be designated by KV for future development.

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

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

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

"The collaboration with KV not only allows us to proceed immediately with the commercialization of our estradiol product in the major markets outside the US, but just as importantly, it aligns us strongly with a very capable and committed marketing partner," added Acrux CEO Richard Treagus. "I am delighted that following the launch of Evamist, KV has seen the value and potential in our unique spray technology."

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

Under the new agreement, Acrux will gain the right to use the data contained in KV's filing with the US FDA to enable it to seek approvals for Evamist outside of the US. KV will select the products to be developed and fund all clinical development costs for each KV product utilizing Acrux's transdermal spray technology, and Acrux will receive royalties on KV's sales plus milestone payments. Evamist was originally licensed by Acrux to VIVUS Inc., which subsequently sublicensed rights to KV. With Acrux's consent, VIVUS has assigned the license to KV, so that KV is now Acrux's direct licensee.

Shire Will Pay Noven $25 Million as Sales of ADHD Patch Have Crossed Final Milestone

Noven Pharmaceuticals Inc. recently announced it will receive a $25-million payment from Shire Ltd. because annual sales of the Daytrana ADHD patch have reached $75 million. Daytrana is a patch designed to treat attention deficit hyperactivity disorder in young children who have difficulty taking pills. Shire will pay Noven $25 million because annual sales exceeded $75 million for the 12 months ended June 30.

UK-based Shire developed the drug, which is developed with Noven's technology. Daytrana was launched in June 2006, which resulted in a $50-million payment to Noven. The latest payment is the final milestone payment for the drug, although Noven will continue to receive royalties.

The $25 million will be paid in the third quarter. Noven said it will recognize the money as license revenue over time, as a deferred payment. Sales of Daytrana have been hurt by problems with the back lining of the patch. The Food and Drug Administration warned Noven in January that some patients were having trouble removing the lining, and in June, Noven recalled hundreds of thousands of patches to deal with the problem.

Noven Pharmaceuticals, Inc. is a specialty pharmaceutical company engaged in the research, development, manufacture, marketing, and sale of prescription pharmaceutical products. Noven's business and operations are focused in three principal areas: transdermal drug delivery, the Novogyne joint venture, and Noven Therapeutics, Noven's specialty pharmaceutical unit.

Mallinckrodt Baker & Rubicon Research Sign Agreement for Performance Excipient Development

Covidien, a leading global provider of healthcare products, recently announced its Mallinckrodt Baker business has entered into a licensing and commercialization agreement with drug development research specialist Rubicon Research. Following the July 2008 launch of its PanExcea performance excipient, Mallinckrodt Baker is teaming with Rubicon Research to expand its performance excipient platform. The two companies will develop and launch additional products under the PanExcea brand through 2009.

"This partnership allows Mallinckrodt Baker to take a global leadership role in the development and commercialization of performance excipients," said Paul Smaltz, Vice President, Global Marketing for Mallinckrodt Baker. "As Mallinckrodt Baker expands its presence as a supplier of performance excipients throughout the pharmaceutical landscape, we believe Rubicon Research's industry-leading expertise in formulation and drug delivery technology will assist us in providing leading-edge products that enable faster, more cost-efficient drug development and manufacturing."

Under the agreement, Rubicon Research will provide technology development and formulation expertise to Mallinckrodt Baker. An established contract research organization with an extensive network of customers in the global pharmaceutical industry, Rubicon Research is focused on oral solid dosage forms and dispersed systems. It also has expertise in the design and implementation of customized delivery systems.

"This collaboration with Mallinckrodt Baker enhances our position as a global comprehensive solution provider for diverse drug development challenges," said Pratibha Pilgaonkar, CEO of Rubicon Research. "Mallinckrodt Baker's understanding of the global pharmaceutical markets will spur Rubicon's research in areas of performance excipients and related technologies and its extensive expertise in pharmaceutical manufacturing and commercial know-how helps add value and worldwide access to Rubicon's technologies."

As a leading global manufacturer of fine chemical process intermediates and excipients for the pharmaceutical and biopharmaceutical markets, Mallinckrodt Baker has two highly respected global brand names in the pharmaceutical industry, J.T.Baker and Mallinckrodt chemicals. Offering Beaker-to-Bulk packaging flexibility and consistently high-quality products supported by ICH-Q7A systems design, Mallinckrodt Baker excels in application-based technology innovations and product solutions.

Mallinckrodt Baker is a manufacturer of high-purity chemicals and related products and services sold under two well-known and respected brand names - J.T.Baker and Mallinckrodt Chemicals. These products are widely used in research and quality control laboratories, microelectronics, environmental testing laboratories and universities, and for manufacturing in the pharmaceutical, biotechnology, and other industrial markets. Based in Phillipsburg, NJ, Mallinckrodt Baker is part of Covidien.

Covidien is a leading global healthcare products company that creates innovative medical solutions for better patient outcomes and delivers value through clinical leadership and excellence. Covidien manufactures, distributes, and services a diverse range of industry-leading product lines in four segments: Medical Devices, Imaging Solutions, Pharmaceutical Products, and Medical Supplies. With 2007 revenue of nearly $9 billion, Covidien has more than 42,000 employees worldwide in 57 countries, and its products are sold in over 130 countries.

Market News and Trends

Tekmira Pharmaceuticals Announces RNAi Research Collaboration With Bristol-Myers Squibb

Tekmira Pharmaceuticals Corporation recently announced a research collaboration with Bristol-Myers Squibb using Tekmira's stable nucleic acid-lipid particles (SNALP) technology to deliver small interfering RNAs (siRNAs) to specific organs and tissues outside of the liver. The relationship between Tekmira and Bristol-Myers Squibb builds upon earlier work conducted at Bristol-Myers Squibb using siRNA delivery technology provided by privately held Protiva Biotherapeutics Inc. In May 2008, Protiva and Tekmira combined their businesses to create a leader in the field of RNAi (RNA interference) therapeutics.

"Our relationship with Bristol-Myers Squibb is consistent with our strategy to work with global pharmaceutical leaders to expand the therapeutic potential of our leading RNAi delivery technology," said Dr. Mark J. Murray, Tekmira's President and CEO. "At the same time, this work complements our internal product development initiatives as we advance our own RNAi therapeutics to treat serious human diseases."

The initial collaboration between Bristol-Myers Squibb and Protiva focused on validating certain gene targets using small interfering RNAs provided by Bristol-Myers Squibb and employed a number of different stable nucleic-acid lipid particle (SNALP) formulations. SNALP is Tekmira's proprietary lipid nanoparticle technology for the delivery of RNAi drugs, including siRNAs.

RNAi drugs have the potential to treat human diseases by "switching-off" disease-causing genes. The technology, representing one of the most promising and rapidly advancing frontiers in biology and drug discovery, was awarded the 2006 Nobel Prize for Physiology or Medicine. RNAi drugs, such as siRNA, require delivery technology to be administered systemically. In preclinical studies, Tekmira's SNALP technology has been shown to be a safe and effective way to deliver RNAi drugs to disease sites. Tekmira believes it has a leading intellectual property position in the field of siRNA delivery.

Tekmira Pharmaceuticals Corporation is a biopharmaceutical company focused on advancing novel RNAi therapeutics and providing its leading lipid nanoparticle delivery technology to pharmaceutical partners.

Metabasis Therapeutics Announces Collaboration With Roche to Develop Liver-Targeted Compounds for Hepatitis C

Metabasis Therapeutics, Inc. recently announced it has entered into a 2-year research collaboration agreement with Roche to apply Metabasis' HepDirect liver-targeting technology to Roche's proprietary lead nucleosides in order to develop new treatments for hepatitis C virus (HCV).

Under the terms of the agreement, Roche will provide a $10-million up-front payment. In the event a development candidate is identified, Roche will assume development responsibility, and Metabasis will be eligible to receive up to $193 million in additional payments upon achievement of predetermined preclinical and clinical development events, as well as regulatory and commercialization events for each product. For any marketed products that result from the collaboration, Roche will retain full commercial rights and pay Metabasis a royalty on net sales.

"The HepDirect technology has shown significant promise in delivering the activated form of certain antiviral nucleosides to the liver and therefore has the potential to both enhance the antiviral activity of these nucleosides, as well as to lower the effective dose," said Dr. Mark Erion, Metabasis' Chief Scientific Officer and Executive Vice President of Research and Development. "A partnership with Roche enables Metabasis and Roche to combine their respective strengths in liver-targeting and hepatitis C research with the hope that this combination will lead to a drug candidate for HCV in the near future."

"We are very pleased to form this alliance with Roche, a global healthcare company that is a leader in the discovery and development of drugs and tests for HCV," added Dr. Ed Baracchini, Senior Vice President of Business Development for Metabasis Therapeutics. "Evidence of the ability of our HepDirect technology to target drugs to the liver has been seen with the three internally generated product candidates that we have put in the clinic that employ this technology. As evidenced by this collaboration, the HepDirect technology platform has garnered considerable attention within the pharmaceutical industry over the past several years. This collaboration is just one of several business development initiatives that we are currently pursuing with respect to Metabasis' many assets."

Metabasis is a biopharmaceutical company using its proprietary technologies, scientific expertise, and unique capabilities for targeting the liver and liver pathways. The company has established a broad pipeline of product candidates and advanced research programs targeting large markets with significant unmet needs. Metabasis' core area of focus is on the discovery and development of drug candidates to treat metabolic diseases, such as hyperlipidemia and diabetes, among others. Although not a core focus of the company, Metabasis has also discovered and developed drug candidates indicated for the treatment of liver diseases, such as hepatitis and primary liver cancer, which it now intends to license or partner. All product candidates were developed internally using proprietary technologies.

Archemix Expands Collaboration With Ribomic for Rights to Develop Aptamer Therapeutics for Multiple Drug Targets; Total Potential Payment Worth $200 Million

Archemix Corp., a biotechnology company focused on discovering, developing, and commercializing aptamer therapeutics, recently announced it granted Ribomic Inc., a worldwide, non-exclusive license to certain of its intellectual property rights to develop aptamers against multiple targets.

Under the terms of the agreement, Archemix will receive an up-front payment of $6 million. Ribomic has the option, upon payment of a further fee, to convert the licenses from non-exclusive to exclusive on a target-by-target basis. When the option is exercised, Archemix is eligible to receive milestone payments and a royalty on any marketed products developed under the agreement. Total milestone payments for the products combined could exceed $200 million. Other financial and business terms were not disclosed.

"Following last year's one target deal with Ribomic, we are pleased to expand our collaboration with Ribomic. This collaboration is further validation of the broad interest in aptamer technology and exemplifies our strategy of leveraging our leading intellectual property position in aptamer therapeutics to generate cash flow for Archemix," said Dr. Errol De Souza, President and Chief Executive Officer of Archemix. "Deals such as this contribute to an increase in the numbers of aptamers in development without encumbering our internal resources."

The collaboration joins the interests of Ribomic and Archemix in focusing on the development of aptamer therapeutics. Ribomic is a bioventure company based in Tokyo, Japan, formed based on the research from the Medical Institute of Science at the University of Tokyo, and focused on the discovery and development of new aptamer products. Archemix has a broad patent portfolio of fundamental patents for aptamer therapeutics, and a component of the company's business strategy is to license its intellectual property to third parties, like Ribomic, to develop their own aptamer product candidates.

"This deal combined with Ribomic's proprietary skills will substantially enhance the chances of brining novel aptamer therapeutics into reality. It should be good news to many people who are suffering from diseases that have no effective treatment at present." said Michi Nishiyama, President and CEO of Ribomic.

Aptamers are synthetically derived oligonucleotides, or short nucleic acid sequences, that bind to protein targets with high affinity and specificity and can be designed to have a specified duration of action. Aptamers represent an emerging class of potential therapeutic agents that Archemix believes may have broad application to treat a variety of human diseases.

Archemix is a biotechnology company focused on discovering, developing, and commercializing aptamer therapeutics. Using Archemix's proprietary processes for discovering aptamers, which are protected by its broad patent portfolio, Archemix is developing aptamer product candidates for rare hematological diseases. In addition, Archemix has licensed its intellectual property to third parties to develop their own aptamer product candidates. Currently, Archemix and its licensees are evaluating four different aptamer product candidates in human clinical trials; two in Phase II and two in Phase I. To date, Archemix has licensed its intellectual property to discover and develop aptamer product candidates to nine biotechnology and pharmaceutical companies, including Pfizer, Merck Serono, and Takeda Pharmaceuticals.

Antares Pharma & Teva Announce Filing of sNDA for Needle-Free Injector With Human Growth Hormone

Antares Pharma, Inc., a specialty pharmaceutical company focused on improving pharmaceuticals through advanced drug delivery systems, and its partner, Teva Pharmaceutical Industries Ltd., recently announced the filing of a Supplemental New Drug Application (sNDA) in order to add needle-free injection to the product drug label. This submission is the result of clinical testing and drug-device interaction studies performed over the past 18 months. The sNDA filing also references the 510(k) previously filed by Antares in 2006. The FDA has required this supplemental filing because needle-free injection is a new route of administration for this product; a needle and syringe is the current route of administration. The FDA review cycle generally takes 4 to 6 months to complete with potential FDA approval in the fourth quarter of 2008.

"Our experience and proven track-record in needle-free administration of this important biologic product underscores our strategy of focusing on the emerging biologic market place as well as our continuing commitment to the patient and the caregiver," said Jack E. Stover, CEO and Vice Chairman of Antares. "We look forward to progressing with our partners to approval, whereupon we expect to recognize important revenues based on sales of our devices and royalties on the product."

Human growth hormone is an injectable protein that is commonly used to treat children of pathologically short stature. Pediatric patients and their parents, who sometimes assist with the injections, can benefit from the elimination of needles and disposal of contaminated sharps, ease of using alternative injection sites, and the speed and quality of injections offered by needle-free devices. According to industry estimates, the market for human growth hormone in the US is approximately $1 billion, and the US market is the largest market segment for the distribution of human growth hormone globally. Antares currently markets its needle-free injection system for use in the treatment of growth hormone-deficient children through its partners in Europe, Japan, and Asia.

Antares Pharma is a specialized pharma product development company committed to improving pharmaceuticals through its patented drug delivery systems. Antares has three validated systems: the ATD Advanced Transdermal Gel Delivery system; subcutaneous injection technology platforms, including Vibex disposable pressure-assisted auto injectors, Valeo/Vision reusable needle-free injectors, and disposable multi-use pen injectors; and Easy Tec oral disintegrating tablets (ODT). Two of the systems have generated FDA-approved products. The company's products are engineered to improve safety and efficacy profiles by minimizing dosing and reducing side effects while enabling improved patient compliance. The Company's lead product candidate, Anturol, an oxybutynin ATD gel for the treatment of OAB (overactive bladder), is currently under evaluation in a pivotal Phase III trial. The Anturol trial is being conducted under an agreement reached with the US FDA under its special protocol assessment, or SPA process. Antares Pharma has corporate headquarters in Ewing, NJ, with subsidiaries performing research, development, manufacturing, and product commercialization activities in Minneapolis, MN, and Basel, Switzerland.

Azopharma Announces Additions to Clinical Research Services

Azopharma Product Development Group, Inc. recently announced plans to significantly expand its clinical research management services through its newly formed company, Acromon Clinical Research Organization. This addition complements the services already provided by the human clinical dosing unit, AvivoClin, and the bioanalytical services unit, ADMEQuant.

The new organization focuses on providing comprehensive clinical management services needed to effectively perform human clinical trials. Acromon will operate independently from other Azopharma companies to effectively design and monitor clinical trials in an unbiased fashion whether the study is performed at the AvivoClin site or another clinical facility. The staff has an extensive background in the designing, monitoring, and technical writing aspects of clinical studies with a focus on regulatory compliance. Acromon will help fill the growing need among virtual, emerging, and medium-size pharmaceutical companies for experienced teams to design and execute the clinical portion of the drug development process. The Acromon team will fill this niche using a focused, passionate approach to how clinical studies are performed.

As a leading industry expert in pharmaceutical and medical device product development, Azopharma offers the full spectrum of development services from post-discovery support through all phases of clinical development. According to Phil Meeks, Azopharma Chief Executive Officer, "This expansion will help us to meet the growing needs of the clinical design and execution market, which has seen steady growth for the past few years. This expansion will also help us more fully serve our clients' needs for total product development. Azopharma is one of the only companies in the US offering Total Product Development capabilities. There are few companies in the world that can provide the comprehensive scope of services that we offer our client base of over 1,000 customers."

New services at Acromon include Clinical Study Development, Protocol Design, Clinical Monitoring, Data Management, Biostatistical Analysis and Reporting, and Final Clinical Study Report Writing.

Azopharma Product Development Group brings together the best scientists in the field, state-of-the-art facilities, and a focus on quality that provides our client partners an unbeatable combination in total product development. Azopharma Product Development Group includes Azopharma Contract Pharmaceutical Services (integrated product development and CTM manufacturing for all dosage forms), ApiCross Drug Delivery Technologies (proprietary drug delivery platforms to solve difficult molecular challenges), Cyanta Analytical Laboratories (analytical chemistry and inhalation services from development to quality control testing), AniClin Preclinical Services (preclinical services in support of early product development), IQsynthesis (synthetic chemistry services from discovery to clinical API supplies including large-scale API synthesis), AvivoClin Clinical Services (human clinical pharmacology services for Phase I/II/III clinical trials), ADMEQuant Bioanalytical Services (bioanalytical research analysis of pharmaceutical compounds in all matrices), and Acromon Clinical Research Organization (clinical monitoring, data management, and statistical services).

American Peptide Company to be Acquired by Otsuka Chemical Company

American Peptide Company, Inc. recently announced its parent company, Ito Life Sciences (Ibaraki, Japan), will be acquired by Otsuka Chemical Company (Osaka, Japan), part of the Otsuka Group (Osaka, Japan). Otsuka Chemical Company will be the new owner of American Peptide Company and Ito Life Sciences Shanghai, both subsidiaries of Ito Life Sciences, beginning September 1, 2008. Ito Life Sciences is currently owned by Itoham Foods.

"American Peptide Company is poised to benefit greatly from this acquisition," said Takahiro Ogata, President and COO, American Peptide Company. "By operating as an enterprise of Otsuka Chemical Company, we will create new global networking opportunities as well as channel more financial resources to our production and manufacturing facilities. As a result, we will enhance our Total Peptide Management services to our customers."

The Total Peptide Management program is a customized service platform that offers a broad array of high-quality peptides, value-added services, and expert consultation. Leveraging the experience and expertise of the American Peptide Company's leadership team, the program helps pharmaceutical and biotech customers properly select peptides and follow correct procedures and compliance guidelines from research development through scale-up to full manufacturing.

As American Peptide Company continues to build its technical capabilities and customer base with its service-oriented Total Peptide Management program, it will be a critical asset to the Otsuka Chemical Company portfolio. Additionally, American Peptide Company is expanding its facilities in Vista and Sunnyvale, CA, to accommodate large-scale peptide production at the kilogram scale for the company's growing customer network.

American Peptide Company is a leading manufacturer of peptides and peptide conjugates. The company offers comprehensive selection of pre-manufactured catalog peptides, custom synthesis, and GMP generic peptide APIs. Its manufacturing facility in Sunnyvale offers research-grade peptides to customers, and its Vista facility, also in CA, provides GMP manufacturing and services. The company offers a portfolio of value-added services, including process development, scale-up production, analytical and process validation, stability studies, CMC, DMF, and regulatory support. American Peptide Company is experienced in solid-phase and solution-phase peptide synthesis, as well as organic conjugations, proteins and PEG.

The Otsuka Chemical Company is an international company based out of Osaka, Japan, with additional locations in Spain, Indonesia, India, Korea, China, Brazil, and the US. Established in 1950, its 1700-employee global workforce is dedicated to developing new materials, industrial chemicals, and pharmaceutical and agro-chemicals while actively protecting the global environment. Otsuka Chemical Company has garnered widespread industry recognition due to its strong client relationships, and aims to continue this approach with its strategic acquisition of Ito Life Sciences.

Ito Life Sciences, Inc., parent company of American Peptide Company, runs pharmaceutical, functional food ingredients, and peptide businesses in Japan. It is particularly strong in peptide and animal-derived APIs.

Otsuka Group currently consists of 123 corporate entities, including subsidiaries and affiliates. The Group, which is engaged in a wide range of activities on a global scale, posted consolidated sales of about 1000 billion yen for the year ended March 31, 2008. Its primary businesses are Pharmaceuticals, Foods, Beverages, Nutraceuticals, Cosmedics, Fine Chemicals, Agro-Chemicals, Consumer Products, and Logistics.

Cytos Biotechnology & Pfizer Enter Into Research, Option & License Agreement

Cytos Biotechnology AG recently announced it has entered into an exclusive global research, option, and license agreement with Pfizer Vaccines LLC (Pfizer) to research, develop, manufacture, and commercialize novel vaccines for a defined number of human diseases.

After completion of the research programs and exercise of its options, Pfizer will acquire world-wide exclusive rights to commercialize certain vaccines, which are based on Cytos Biotechnology's Immunodrug technology and that will incorporate specific disease targets, which are outside the scope of Cytos Biotechnology's own programs. Cytos Biotechnology retains its rights to develop, manufacture, and commercialize vaccines against different disease targets in the same human diseases. Preclinical and clinical development, manufacturing and commercialization of the vaccines will be the responsibility of Pfizer. In return, Cytos Biotechnology will receive an up-front payment of around $9 million from Pfizer and is eligible to receive up to almost $128 million in pre-commercial milestone payments and manufacturing technology transfer fees. In addition, Cytos Biotechnology will receive research funding and royalty payments, which may reach a double-digit percentage depending upon levels of annual net sales of products.

"The vaccine market, including therapeutic vaccines, represents an increasingly attractive segment of the healthcare market. This collaboration with Pfizer further establishes Cytos Biotechnology's Immunodrugs as the vaccines of choice for top-tier pharmaceutical companies and complements our ongoing collaboration with Pfizer Animal Health," said Dr. Mark Dyer, Executive Vice President of Business Development of Cytos Biotechnology.

Cytos Biotechnology's Immunodrug technology represents a versatile means to induce specific immune responses against disease-associated target molecules from a wide variety of sources, including the body's own as well as foreign molecules. The Immunodrug technology brings the targets of choice into a highly repetitive format by chemically attaching them onto the surface of virus-like particles. The resulting Immunodrugs mimic a virus through this repetitive and particulate structure and are able to induce potent antibody responses against the selected targets with the goal of modulating or interfering with an ongoing disease process.

Cytos Biotechnology AG is a public Swiss biotechnology company that specializes in the discovery, development, and commercialization of a new class of biopharmaceutical products, the Immunodrugs. Immunodrugs are therapeutic vaccines intended for use in the treatment and prevention of common chronic diseases, which afflict millions of people worldwide. Cytos Biotechnology has established a diversified pipeline of Immunodrug candidates in various disease areas, of which five are currently in clinical development. The Immunodrug candidates are developed both in-house and together with Pfizer, Pfizer Animal Health, and Novartis. Founded in 1995 as a spin-off from the Swiss Federal Institute of Technology (ETH) in Zurich, the company is located in Schlieren (Zurich) and currently employs 130 people.

MBO Discussion Series

The Deal

Part VII of The Born-Again Entrepreneur (February 2008)

By: Derek G. Hennecke, MBA

Our buy-out was scheduled to become official on May 6, 2006. The old company would cease to exist, the funding would fall into place, and the new company would be born…. party to follow. But let's leave the grand theories to Steven Hawkings. The reality was nothing like that.

We financed the purchase through something called a sale and leaseback arrangement. Basically, it was supposed to work like this. On the day of the deal, we would purchase the facility from the mother company and sell it on the same day to a third party. The money accruing from the sale would then be handed over to the mother company, paying a significant portion of the contract price. We signed a lease arrangement on the same day with the third party for a 10-year rental agreement.

As well, on this same momentous day, the one bank in the universe (believe me, we scoured every corner) that was willing to offer us a substantial line of credit, was going to extend that line. It was like conducting a grand symphony in the Sydney Opera House. Only I've never conducted the symphony before, and there would be no rehearsals.

I was worried about the bank coming through in time with the line of credit, so I spent much of the last week camped out on the doorstep of the bank, trying to push it along. The rest of my time was spent signing copious documents passed through by my lawyers. I must've signed over a thousand pages worth of documents in those final days and weeks. At some points, I just had to trust my lawyers and the Almighty, because there is no way to read all of that fine print and know absolutely everything you are promising.

The line of credit, as it turned out, was not where my worries should have been. In the end, it was the third party who didn't come through on time. It wasn't until the day of the transaction that I learned that he hadn't yet secured his own funding. So on May 6, 2006, the mother company ceased to exist. They took our names off the payroll. We no longer used their systems. The photocopy rental agency rolled the photocopiers out of the building. The old company no more. But Xcelience didn't exist yet either!

We call the days that followed our 3 days of faith. They were without a doubt the longest days of my life. My time was now spent camping on the doorstep of the purchaser. My thoughts were dominated by questions as persistent and unanswerable, such as which letterhead should we use? In my head, I was wondering if I should still be signing these commitments, but rationally, I knew it would come through and it would just take time.

You cannot imagine the relief when on May 9, 2006, the funding came through, and all the pieces fell into place. At last we could turn our head to the future and the course we had set for ourselves. Right after a good stiff drink.

With the new photocopiers in place (at one third the cost of what head office had paid for them), new letterhead and business cards, a new HR framework, and accounting system, we were off. Our sponsors had known for almost a year that something like this would happen so at least that went well. The only hiccup was our move to the new e-mail server that required our IT manager to go without sleep for 2 days.

Randall Guthrie, my VP of Sales, hit the ground running. If there was anyone who had complete confidence in our new entity, it was Randy, and it was a great boon to me to be able to leave this most essential part of the business under his stable piloting, while the rest of my management team and I put our house in order.

We had a few questions and a lot of problem-solving. Permits had to be reissued with our new name. We were visited by the FDA again that summer (visit No. 483). We had to buy from a wide variety of suppliers to meet each sponsors' needs, so our people spent a lot of time with new vendor credit checks. I could go on. Our SOPs had to be rewritten with the new name and, of course, if you are going to change that then you might as well make other suggestions. Now we needed our own IT backbone to be self-supporting, and we are fortunate to have a resourceful IT manager. Through it all, we kept cool and waited for the other shoe to drop…it just never did.

A new company with high morale, a new mission, and a sense of group ownership is a wonderful thing. We made our first profit our first month in business, and have been growing consistently since.

There are some things that I miss from the old company, but not many. I would like to have a Blackberry instead of a Motorola Q for my travels, but not enough to pay for a dedicated Blackberry server and service. More importantly, I've found my dream job. I love coming to work everyday. I enjoy the camaraderie of a really neat group of people. We are all dedicated to the work we do, and excited about what we are building. I love the challenge of directing our growth and looking for new ways of doing things. I don't waste a minute thinking about how to "sell" my ideas to the boss. I just consult with my colleagues and know that they'll tell me I'm crazy, come up with a better idea, or back it. Either way, we'll take action on the outcome immediately. It was our dream to become the very best at what we do, and you know what? I think we are. There is nothing holding us back.

I would like to take a moment here and thank everyone who committed to reading my special discussion series this year. I would also like to express my sincere gratitude to *Drug Delivery Technology* for affording Xcelience this platform to present the challenges, issues, and opportunities of our Management Buy-Out. I hope the 7-part series has provided some valuable insight for those who may be in the same unique position. ◆

BIOGRAPHY

Derek G. Hennecke, MBA
President & CEO
Xcelience

Mr. Derek G. Hennecke is a founding member of Xcelience. From 2004 to 2006, he served as Vice President and General Manager, Pharmaceutics and Biopharmaceuticals of MDS Pharma Sciences, Inc. In this capacity, he was responsible for the business and operations of MDS' CRO formulation development, including capsule development, tablet formulation, modified-release tablets, suspensions, solutions, suppositories, creams, ointments, and gels. Prior to joining MDS, Mr. Hennecke held various drug development management positions for DSM in Canada, Egypt, The Netherlands, and Mexico. In these roles, he built the operations or businesses to introduce various drug products for Europe and the US. Mr. Hennecke has also worked for Roche's research activities in Germany and Canada. He earned his BSc from the University of Alberta (Canada) and his MBA at the Erasmus University in Rotterdam, (The Netherlands).

Copovidone – A Copolymer With Unique Formulation Properties

By: Hubertus Folttmann, PhD, and Anisul Quadir, PhD, MBA

In the June 2008 issue of *Drug Delivery Technology*, the properties of the homopolymer polyvinylpyrrolidone (Povidone, PVP) and its applications were discussed. Copovidone, like Povidone, is a derivative of the acetylene chemistry founded by Walter Reppe, known as "Reppe-Chemistry." Copovidone is a linear random copolymer based on N-vinyl-2-pyrrolidone and vinyl acetate in the ratio of 6:4 by mass. Alternative designations are Copolyvidone and VP/VAc copolymer 60/40.

As in the case of homopolymer PVP, the VP/VAc copolymer 60/40 was first used in the cosmetics industry as a constituent of hair care products. The first experiments on its use as an excipient in tablets were carried out in the 1960s. During the 1970s, BASF further developed the copolymer into a pharmaceutical product; this then became a commercial pharmaceutical excipient from the mid-1970s. Copovidone per definition is pharmaceutically pure VP/VAc copolymer 60/40.

The addition of vinyl acetate to the vinyl pyrrolidone polymer chain lowers both its hydrophilicity and glass transition temperature (T_g) in comparison with polyvinylpyrrolidone (PVP). The advantages of Copovidone over Povidone K 25 or K 30 are related to its lower hygroscopicity, its excellent dry binding properties, and its higher plasticity. Films made of Copovidone show low hygroscopicity, high elasticity, and low adhesiveness.

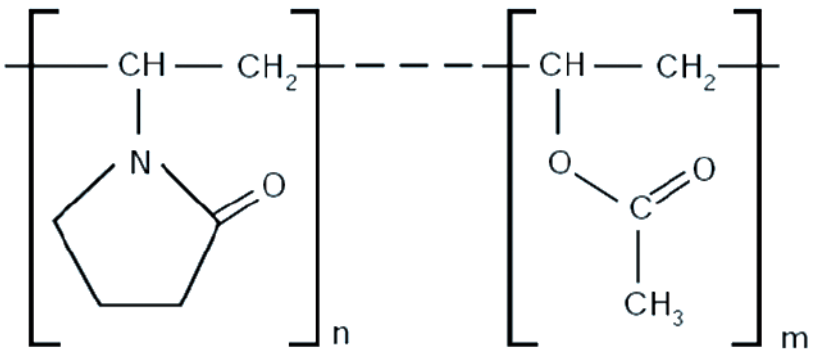
Copovidone is now being used increasingly in melt-extrusion processes for the manufacture of solid dispersions/solid solutions of poorly soluble drugs for solubility and bioavailability improvement.

COPOVIDONE

Structure, Products & Properties

Copovidone is produced by radical polymerization of 6 parts of

FIGURE 1



Structural Formula of VP/VAc Copolymer 60/40 (Copovidone) $M_r = (111.1)_n \times (86.1)_m$

TABLE 1

Product	Manufacturer	Brand	Typical Average Particle Size
Copovidone	BASF	Kollidon® VA 64	65 to 75 microns
Copovidone	BASF	Kollidon® VA 64 Fine	10 to 20 microns
Copovidone	ISP	Plasdone® S-630	65 to 75 microns

Copovidone Products

TABLE 2

Brand	Bulk Density	Tap Density
Kollidon® VA 64	0.2 to 0.3 g/ml	0.30 to 0.45 g/ml
Kollidon® VA 64 Fine	0.08 to 0.15 g/ml	0.14 to 0.20 g/ml
Plasdone® S-630	0.3 g/ml	0.4 g/ml

Bulk & Tap Densities According to Manufacturers' Data

MARK YOUR CALENDARS TODAY!

2008 AAPS Annual Meeting and Exposition

November 16–20, 2008

Georgia World Congress Center
Atlanta, Georgia, USA

aaps
American Association of Pharmaceutical Scientists

FOR UP-TO-DATE INFORMATION, LOG ON TO: www.aapspharmaceutica.com/annualmeeting

vinyl pyrrolidone and 4 parts of vinyl acetate in 2-propanol (Figure 1). Copovidone is a white or yellow-white spray-dried powder with a relatively fine particle size and excellent flow properties. It has a typical but weak odor and little taste in aqueous solution. To date, the monographs on Copovidone can be found in the European Pharmacopoeia Ph. Eur., in the US Pharmacopoeia USP-NF, and in the Japanese Pharmaceutical Excipients JPE.

BASF markets two types of Copovidone under the designations Kollidon® VA 64 and Kollidon® VA 64 Fine, the difference being in particle size. ISP markets Copovidone under the name Plasdone® S-630. The products listed in Table 1 fulfill the requirements of the aforementioned pharmacopoeia monographs.

Depending on the ratio of vinyl pyrrolidone to vinyl acetate in Copovidone, the resulting solubility is almost as universal as that of Povidone (eg, Povidone K 30). It extends from an extremely hydrophilic liquid such as water to more hydrophobic solvents such as butanol. Copovidone dissolves to more than 10% in the following solvents: water, methanol, ethanol, propanol, 2-propanol, butanol, chloroform, methylene chloride, PEG 400, 1,2-propylene glycol, 1,4-butanediol, and glycerol.

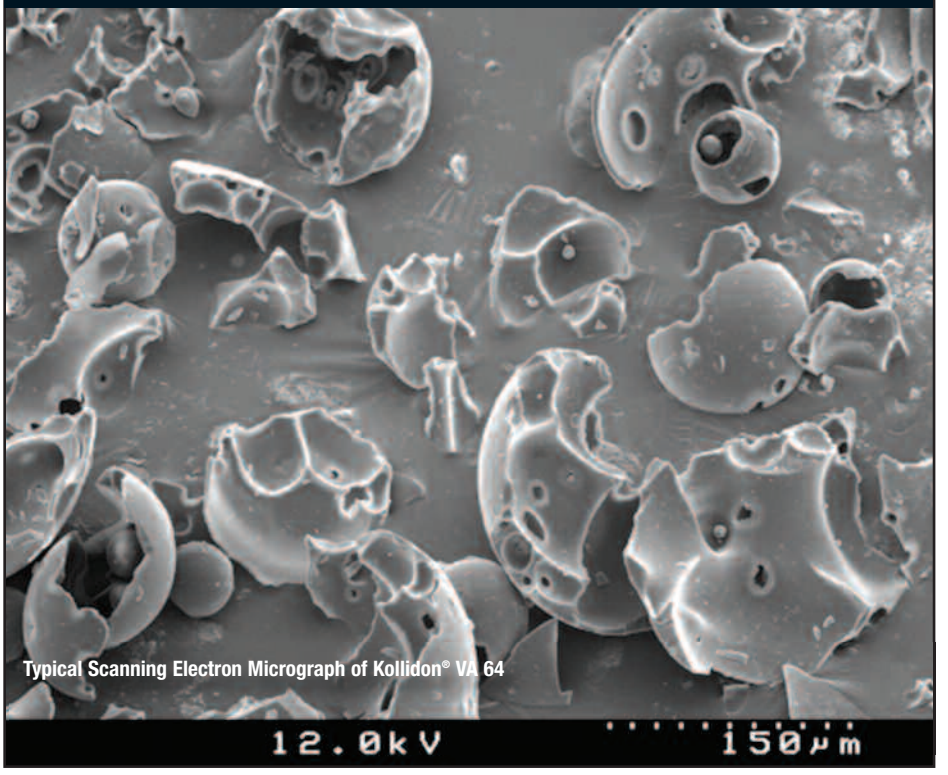
The viscosity of an aqueous solution of Copovidone is similar to that of Povidone K 30 homopolymer. This low viscosity facilitates the use of Copovidone in wet granulation and coating formulations.

The K-value of Copovidone that characterizes its mean molecular weight, is 25 to 31 and hence also similar to that of Povidone K 30 (27 to 32). The mean molecular weight (Mw) of Copovidone products is usually in the range of 45,000 to 70,000.

Table 1 shows that Copovidone is available in two particle sizes. The established standard products Kollidon VA 64 and Plasdone S-630 are characterized by close particle size distribution, a low proportion of fines and very good flow properties. The flowability of Kollidon VA 64 Fine, introduced some years ago, is inferior to that of the standard products due to its smaller particles. However, when used in the usual concentration of 2% to 6% in tablets, it shows excellent miscibility and, due to the spherical nature of its particles, improves the overall flowability of the mixture to be compressed to tablets.

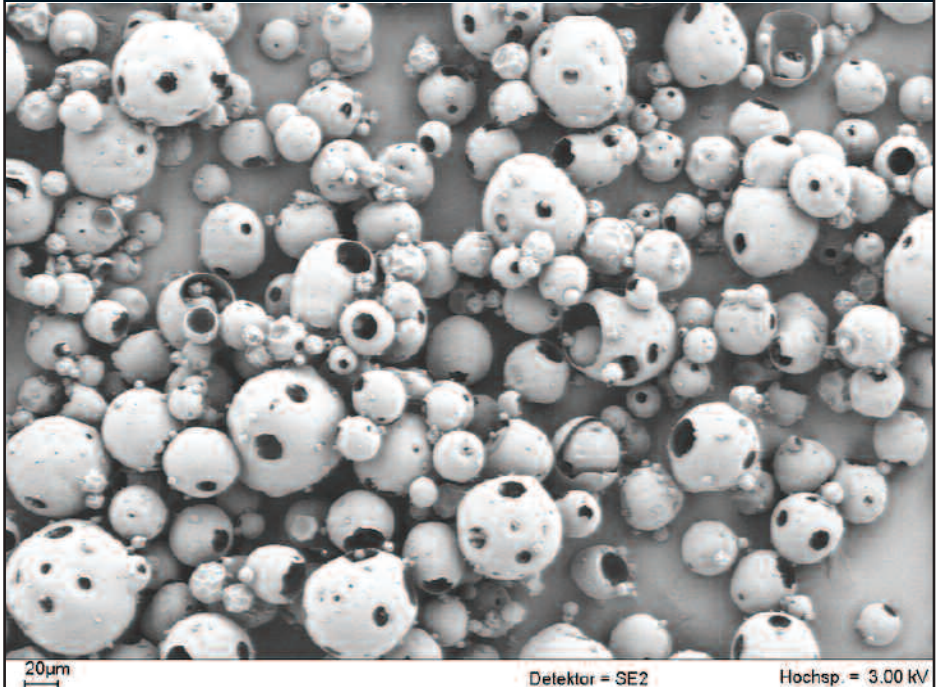
While the particles of standard products Kollidon VA 64 and Plasdone S-630 have almost always a structure comparable to broken hollow spheres, Kollidon VA 64 Fine consists of very much smaller but intact hollow spheres.

FIGURE 2



Typical Scanning Electron Micrograph of Kollidon® VA 64

FIGURE 3



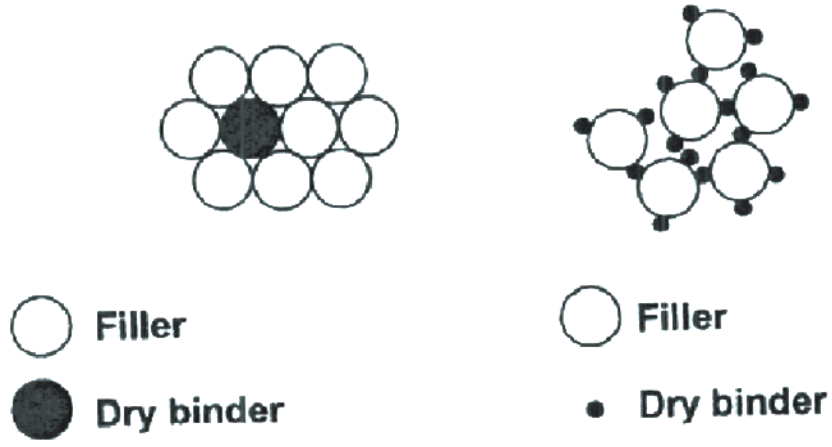
Typical Scanning Electron Micrograph of Kollidon® VA 64 Fine

TABLE 3

Function/Dosage Form	Copovidone (Standard Grade)	Copovidone (Fine)
Dry Binder in Tablets (Direct Compression)	+	+
Binder in Tablets, Pellets & Granules (Wet Granulation)	+	–
Dry Binder in Granules (Roller Compaction)	+	+
Film Former for Tablet Film Coating & Sugar Coating	+	–
Film Former for Subcoating Tablets	+	–
Matrix Former for Melt-Extrusion of Tablets	+	–
Film Former in Sprays	+	–

Summary of the Main Applications of Copovidone Grades[1]

FIGURE 4



Influence of Particle Size on the Number of Particle Contacts

The incorporation of vinyl acetate groups into the vinyl pyrrolidone polymer chain lowers the hydrophilicity and hygrocsopicity of the copolymer compared to polyvinylpyrrolidone (PVP). When used as a tablet binder and granulation enhancer, a certain degree of hygroscopicity is needed for robust granulation. In the case of film coatings, it may impact negatively. In simple terms, one can say that Copovidone absorbs only about one third of the water as Povidone at the same relative humidity. The lower hygroscopicity of Copovidone is of advantage when water-sensitive active ingredients are formulated or if production takes place in a humid atmosphere.

The applications of Copovidone are based on its excellent binding and film forming properties, its affinity to hydrophilic and hydrophobic surfaces, and its relatively low hygroscopicity. Advantages of Copovidone over Povidone K 30 in solid dosage forms are related to its low hygroscopicity, excellent dry binding properties, and higher plasticity. Table 3 summarizes the various applications of Copovidone.

As a Binder in Tablets, Granulates & Capsules

The principal application of Copovidone is as a binder in tablets and granulates, independent of whether wet granulation, dry granulation, or direct compression is involved.

In wet granulation, Copovidone does not differ significantly from Povidone K 25 or K 30. However, due to the higher plasticity of Copovidone, the granules for compression are less susceptible to capping and produce less brittle tablets during production. Due to their lower hygroscopicity, tablets produced using Copovidone adhere less to the punches when produced in a humid atmosphere.

The advantages of the Copovidone grades are evident in dry granulation and direct tablet compression. In these processes, the higher plasticity of Copovidone means that it flows better under pressure (compression force); the interstitial space between filler and particles of active ingredient is filled and thus more points of adhesive contact are generated.

Copovidone Fine Grade is tailor-made for roller compaction applications due to its particle morphology and distribution. Due to its smaller particle size, Copovidone Fine Grade is able to cover a large area and form numerous solid bridges within the tablet structure.

Figure 4 illustrates the influence of particle size on the number of contacts between binder and filler or between binder and active ingredient. On the left, the binder particle has fewer contact points with filler or active ingredient. In contrast, the reduced particle size of the binder enables each filler or active ingredient particle to adhere to three binder particles. In practice, this enables harder and more mechanically stable tablets with lower friability.

Kleinebudde et al compared Copovidone Fine Grade, Copovidone Standard Grade, and some others commonly used in dry granulation with respect to their dry binding properties.[2] Copovidone Fine Grade, with the highest tensile strength values for tablets made from powder mixtures and granules, proved to be superior.

Although many active ingredients do not fulfill all the necessary criteria for direct tablet compression, they can normally be compressed directly using Copovidone. The reasons for this excellent compressibility of the Copovidone grades are the lower glass transition temperature compared to Povidone, the higher plasticity of the polymer, and its special particle structure. Copovidone also improves the compressibility of so-called filler binders, such as lactose, dicalcium phosphate, microcrystalline cellulose, sorbitol, mannitol, etc. Kolter et al described the influence of physico-chemical aspects on the performance of dry binders.[3] According to this study, the hollow sphere structure of Copovidone is responsible for the excellent flowability and compressibility of the substance. Tablet strength is a result of bond types and the available contact surface area between particles in tablets. The binding surface area can be increased by reducing the particle size of the dry binder. Table 4 Figure 5 illustrate that a reduction in the particle size of Copovidone has a positive effect on tablet hardness.

Copovidone Fine Grade, already at a concentration of 2%, demonstrates excellent dry binding properties. This is an advantage with formulations containing a high concentration of active ingredient as it enables the tablet weight to be kept low, eg, with multivitamin tablets. Copovidone is also used in the manufacture of effervescent tablets using direct compression instead of solvent-based anhydrous wet granulation.

The aforementioned properties of Copovidone in reference to wet granulation are also suitable for use in the manufacture of granulates and pellets in hard gelatine capsules. The most important functions of Copovidone in this case are to increase the size of the granulate particles, to ensure good flowability, and to prevent the formation of dust. This facilitates the filling of hard gelatine capsules.

Improvement of the Release & Bioavailability of Active Ingredients

The most important new technology in the use of Copovidone is melt-extrusion.[4] Copovidone mostly acts as a matrix former or solvent in instant-release dosage forms. The Copovidone structure (Figure 1) links the hydrophobic elements (polyethylene backbone; vinyl acetate groups) with the hydrophilic groups (pyrrolidone rings). In addition, the pyrrolidone rings can form hydrogen bondings that facilitate the dissolution or interaction of sparingly soluble active ingredients. The polymeric matrix disperses the drug uniformly and enhances its bioavailability by preventing the API from recrystallizing when in contact with gastrointestinal fluid. By selecting the polymer or polymer combination or by combining with other excipients (eg, surfactants), a number of different active ingredient release profiles can be achieved. These can extend from those that attain peak blood levels within minutes to once-a-day formulations.

Using the melt-extrusion technique, it has become possible to develop dosage forms for active ingredients that, due to their lack of solubility or poor bioavailability, otherwise cannot be formulated satisfactorily using conventional methods. Abbott's anti-HIV protease inhibitor combination (Kaletra®) comprising Lopinavir and Ritonavir is an example.[5] SOLIQS, the drug delivery business of Abbott GmbH & Co. KG, has developed melt-extrusion to a very high level and offers this service to other pharmaceutical companies under Meltrex® technology in the form of feasibility studies, development programs, and commercial manufacture.

Other Applications

FILM COATING: Copovidone forms water-soluble films that are less hygroscopic and elastic than corresponding films of Povidone (eg, Povidone K 30). However, Copovidone is rarely used as the only film former as it prones to water absorption. It is thus recommended that Copovidone be used along with less hygroscopic excipients, such as cellulose derivatives, shellac, PEG, etc. In combination with cellulose derivatives, Copovidone reduces the brittleness of films and increases their solubility. With spray suspensions based on HPMC, the viscosity of the suspension is reduced if part of the HPMC is replaced by Copovidone. This enables spray suspensions of higher polymer concentration to be processed, hence rendering the coating process short and more economical.

SUB-COATING: Today, tablet cores are predominantly coated with aqueous polymer solutions or suspensions. If such tablet cores contain active ingredients that are very sensitive to moisture or a large proportion of highly effective disintegrants, a sub-coating is recommended as a moisture barrier. In such a case, the tablet cores are coated with a 10% organic solution of Copovidone (eg, 2-propanol or ethanol). Sub-coating with Copovidone moistens the tablet core and reduces the generation of dust. Both factors

TABLE 4

Ingredient	[mg]
Ascorbic Acid	200
Ludipress®	231.25
Dry Binder	50
Kollidon®CL	15
Aerosil® 200	1.25
Magnesium Stearate	2.50

Formulation for Evaluating the Dry Binding Capacity of Excipients at a Concentration of 10%

facilitate subsequent coating with aqueous polymer solutions or suspensions. Due to its hydrophilic and hydrophobic components, Copovidone acts as a layer between the waxy tablet core and the HPMC-based coating.

Sugar Coating: Copovidone is used in sugar coating to improve the adhesion of the coating to the surface of the tablet core and to increase the capacity of the coating solution for pigments; it also improves their dispersibility. Copovidone helps in the application and automation of sugar-coating processes.

Film Forming Agent in Topical Sprays: Due to its film-forming and bioadhesive properties and water solubility, Copovidone (alone or in combination with cellulose derivatives) is used as a film former in aqueous sprays and as a final dosage form for human or veterinary topical administration.

Transdermal & Transmucosal Systems: Due to its plasticity, lower hygroscopicity, and bioadhesion, the film former Copovidone could be more suitable than Povidone for transdermal or transmucosal systems. The crystallization inhibitory effect of Copovidone has been documented for several APIs in such systems.

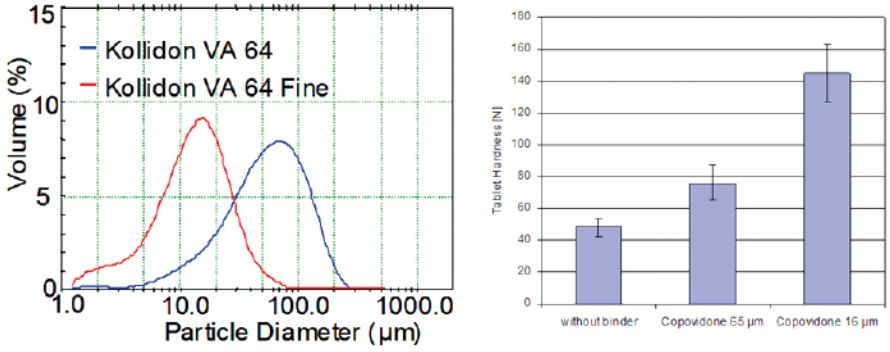
SUMMARY

Like Povidone, Copovidone is a highly versatile excipient and is used in a wide range of pharmaceutical applications. Its properties as a binder in both wet and dry granulation and in direct tablet compression processes exceed the expectation compared to other dry binders. Copovidone's ability to form solid dispersions or solid solutions with sparingly soluble active ingredients, hence improving their solubility and bioavailability, will render it increasingly important in the future in such applications. ◆

REFERENCES

1. Bühler V. Kollidon® VA64. In: Kollidon® Polyvinylpyrrolidone for the Pharmaceutical Industry. 9th ed. BASF SE;2008:205-252.
2. Herting MG, Kleinebudde P. Comparison of different dry binders for roll compaction/dry granulation. Pharm Dev Tech. 2007;12:525-532.
3. Maschke A, Meyer-Böhm K, Kolter K. Dry Binders Used in Direct Compression. PMPS. Spring 2006.
4. Breitenbach J. Melt extrusion: from process to drug delivery technology. Eur Pharm Biopharm. 2002;54:107-117.
5. Breitenbach J. Melt extrusion can bring new benefits to HIV therapy: the example of Kaletra tablets. Am J Drug Delivery. 2006;4(2):61-64.

FIGURE 5



Influence of the particle size distribution of Copovidone grades (left) on tablet hardness at a binder concentration 10% (right: tablets were prepared using the formulation shown in Table 4).

BIOGRAPHIES

Dr. Hubertus Folttmann is a pharmacist by education. After 12 years of experience in different functions in the pharmaceutical industry, he joined BASF in 1998. His current position at BASF SE is the Head of Global Marketing, Pharmaceutical Excipients. His areas of expertise include binders, disintegrants, coatings, and solubilizers. He can be reached by e-mail at hubertus.folttmann@basf.com.

Dr. Anisul Quadir is the Technical Development Manager of BASF Corporation in Roxbury, NJ. He earned his PhD in Pharmaceutics from the University of Rhode Island and his MBA from Rutgers University at New Jersey. In his current position, he leads the BASF Care Chemicals, North America development group for new applications of pharmaceutical excipients and to provide technical support to the pharmaceutical industry. The group developed various technologies like taste-masking, intra-oral film, soft gelatin coatings, floating technology, and drug solubilization, which can be used in different drug delivery systems. Before joining BASF, he worked at American Cyanamid and Catalytica Pharmaceuticals as a Development Scientist. He has been invited by the FDA to speak about the development of high-functionality excipients, is author of 7 publications in peer-reviewed journals, and holds 5 patents. He can be reached by e-mail at anisul.quadir@basf.com.

Special Feature

Today's Hand-Held Injectors – Differentiation is King

By: Cindy H. Dubin, Contributor

Improving the convenience and ease of administration of parenteral therapeutics is becoming a common strategy to augment product marketability in the biotechnology and pharmaceutical industries. The growth of the injectable market, increased competition in the industry, and regulatory requirements for end-user safety have driven product improvements, according to a July 2007 report by Donna French, Executive Director, Commercialization, Amgen, Inc., *Market Trends in Injection Devices for Pharmaceuticals*. Injection devices that facilitate preparation, ease administration, and ensure safety are increasingly prevalent in the marketplace. Because most injection devices are proven technologies that can be commercialized within 1 to 3 years, these systems are an attractive option for differentiating a product in a competitive marketplace.

In addition to their use in diabetes, injection systems can be applied in the treatment of anemia, hepatitis, infertility, osteoporosis, psoriasis, rheumatoid arthritis, thrombosis, growth disorders, and other hormone therapies, says Ian Thompson, Manager, Business Development at Ypsomed. "Many pipeline drugs are complex biotech molecules and consequently have to be administered, in most cases, by injection. This means that the need for customer-specific injection systems will continue to increase in the future."

INJECTION DEVICES

Pen injectors have been widely used in the diabetes market for the past 25 years and in the hGH deficiency market for the past 20. Throughout the past decade, these devices entered the reproductive health, osteoporosis, and hepatitis markets. Traditionally used for frequent self-administration of preserved multi-dose drug formulations requiring weight-based dosing, recent commercial introductions include fixed-dose and single-use pens. Initially, pens were re-usable, and disposable pen injectors were introduced in the 1990s for insulin and more recently for other indications. Pen injectors can accommodate liquid or lyophilized formulations, which is an advantage over some other types of devices that are limited to liquids. Newer developments in pen devices include the use of needle safety devices, automated needle insertion and injection, smaller dosing capabilities, and electronics.

"A key advancement related to needle-based auto-injector systems expected within the next year is the evolution of primary containers (glass syringes) from the original designs intended for manual use, to new designs that are intended specifically for use in auto-injector devices," says Mike Kasprick, Vice President Business Development, Parenteral Products, Antares Pharma, Inc. "This will include changes to syringe designs and manufacturing tolerances to improve the compatibility with injection devices.

The aforementioned French report also points out that auto-injectors have been co-marketed with drug products in the MS, RA, reproductive health, anemia, and oncology markets in the past 5 years. Re-usable auto-injector systems have become particularly well established in the MS market; second- and third-generation auto-injectors have recently been commercialized.

Re-usable systems are a cost-effective option for frequently administered products. These auto-injectors require a significant amount of end-user manipulation to perform an injection, and the complexity of use has potentially limited their popularity. Current trends are toward single-use disposable auto-injectors, which are easier to use than re-usable systems and have integrated needle-stick protection.

"We see auto-injector, single-dose, disposable technology as an interesting and rapidly changing market segment," says Michael Mesa, Director, Applied Product Development, King Pharmaceuticals, Inc. "Looking over the horizon, we see the possibility that the biotechnology sector will have growing needs for auto-injection systems."

However, the biotech sector does present some new challenges for auto-injection technology. Auto-injectors that strictly conserve these very expensive drug products will need to be designed appropriately. It is quite likely that such biological drugs will have limited shelf-life in a liquid form, thereby requiring consideration for strictly protecting the drug against breakdown during storage and

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

use, notes Mr. Mesa. “The doses of many biotech drugs may well be less than 0.1 mL and may require shallower injection depths than what has been traditional with emergency-use auto-injection systems,” he says.

On the needle-free side of the equation, the industry expects to see the first prefilled disposable needle-free injector product launched by Zogenix in 2009. “We are proud to set the standard for how needle-free delivery systems will need to perform to be successful — they must be both simple to use for patients and easy for healthcare professionals to teach,” says J.D. Haldeman, Chief Commercial Officer, Zogenix. “We believe we have that winning combination in DosePro.”

“There is definitely strong interest in needle-free injectors, and I believe the pharma industry is anxious to see the response to Zogenix from patients and physicians. If successful, I would expect to see other single-dose needle-free products developed,” says Mr. Kasprick.

ANTARES PHARMA ADDRESSES DELIVERY CHALLENGES

According to Mr Kasprick, Antares is focused on solving challenging delivery needs and providing compelling patient benefits. Working from three technology platforms (mini-needle auto-injectors, needle-free injectors, and new pen injectors), the company hopes to provide custom delivery solutions on an exclusive basis to licensees.

“There is great interest coming from new drugs in development that have unique delivery challenges, such as high viscosity and reconstitution, which our devices are able to address successfully,” says Mr. Kasprick. “There is also a growing recognition of the need to differentiate products based on the delivery system, both in branded innovator products as well as generics, and our devices are recognized for their compelling set of patient benefits.”

The most recent platform introduction, the pen injector device, is a fixed-dose, disposable device, but Mr. Kasprick says the company anticipates merging its technology platforms with the opportunity to offer a mini-needle pen injector as a future offering.

Antares’ needle-free injection system, the Medi-Jector VISION is currently commercialized in the fields of insulin and growth hormone administration; however, efforts are focused on expanding use of the technology.

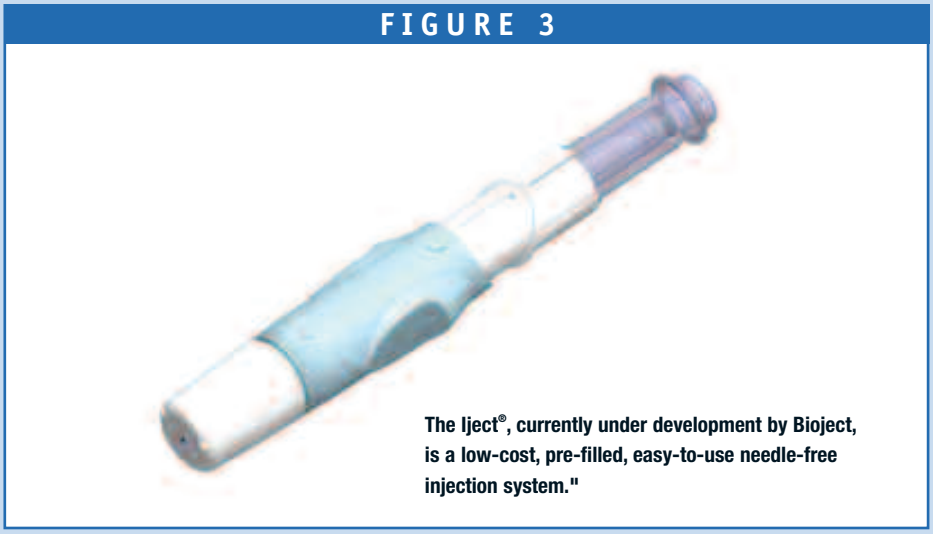
FIGURE 1

The Vibex device from Antares, now in commercial scale-up, ensures subcutaneous delivery via the shallow needle insertion.

FIGURE 2

The Biojector® 2000 is a versatile needle-free injection system that has been used to deliver millions of injections in a range of healthcare settings.

FIGURE 3



The Iject®, currently under development by Bioject, is a low-cost, pre-filled, easy-to-use needle-free injection system."

FIGURE 4

BD TSCF packaging helps ensure the safe transfer of stoppers into sterile filling areas.

The Vibex device (Figure 1) is currently in commercial scale-up. Vibex benefits patients by ensuring consistent subcutaneous delivery via the shallow needle insertion. The current version of the device is a fixed-dose, single-dose disposable injector, but Antares is currently presenting next-generation concepts that add variable dosing and reconstitution systems to this platform. The Vibex system is suited for delivering viscous materials.

In July, Antares and its partner, Teva Pharmaceutical Industries Ltd., filed for a Supplemental NDA for a needle-free injector with human growth hormone. Estimated at a $1 billion market in the US, the largest market segment for hGH globally, Antares currently markets its needle-free injection system for hGH use in children.

BIOJECT FOCUSES ON DRUG & VACCINE DEVICE DELIVERY

Bioject, Inc. has spent the past year changing its business model and moving in a new direction. "We are changing from a technology/device manufacturing company to developing a drug/device platform with patient and clinician benefits, which translates into greater value for our customers," says Ralph Makar, RPh, MBA, President and CEO at Bioject. "The company is now well positioned to begin the transformation into an organization that delivers new therapeutic options in the specialty injectable pharmaceutical marketplace."

Mr. Makar says the new business strategy includes creating focused partnerships in areas where Bioject's Needle Free Injection Therapy (NFIT) systems add value, and securing injectables for Bioject to create its own drug/device combinations for the market. "We believe there are several growth drivers that position Bioject quite well to expand our leadership by offering our own drug/device therapeutics in the future," says Mr. Makar.

In the biotech industry, there is a significant increase in the number of large-molecule therapeutics and a growing emphasis on self-administration. There is also a positive trend in providing drug/device combination offerings for new therapeutics. Several compounds have been successfully tested using Bioject's NFIT systems.

"Our new strategy incorporates feedback from our customer base, as well as positioning Bioject as a strategic solution in this era of rapidly changing pharmaceutical industry restructuring, where cost-effective therapeutic solutions are needed," he says. "With our product offerings, injectable drugs that may be typically given in expensive acute care hospital settings can be delivered in outpatient settings, often at home."

"Bioject is the only needle-free company that has been on the market for more than 15 years with an FDA-released product for the delivery of injectables subcutaneously and intramuscularly," says Dr. Richard R. Stout, Chief Medical Officer and Executive Vice President of Bioject. "We understand the needs of patients, clinicians, and the pharmaceutical industry to offer an alternative to the needle and syringe for parenteral delivery of many therapeutic injectables and vaccines in the clinic, as well as the home environment. We manufacture a product that is currently on the market today for the intramuscular or subcutaneous delivery of 0.1 mL to 1.0 mL using the Biojector 2000 device (Figure 2). We also manufacture two devices for the delivery of Human Growth Hormone in the pediatric and adult market."

The future product offerings for needle-free delivery at Bioject are growing with the announcement of a new spring device that will deliver intramuscular, subcutaneous, and intradermal injectables with an auto-disable syringe to avoid cross-contamination.

"This device will be lower cost, more reliable, durable, and easier to use than previous products," says Dr. Stout. "We look forward to offering this device to deliver vaccines in the developing world, where the need for an alternative to the needle and syringe is very important."

Bioject also has a device that is completing the final stage of development and has a very significant potential for additional patient benefits. The Iject (Figure 3) is a single-use, prefilled device. Dr. Stout believes it will set the standard of such systems.

Bioject is very focused on its target markets (chronic diseases or therapeutic treatment regimens) in which multiple injections are needed daily, weekly, or monthly. "There are several high-value therapeutics that represent a significant segment of the commercial opportunity in which Bioject can add value, such as vaccines, hematopoietics, anti-inflammatory, MS, hGH, reproductive, and other injectables," says Mr. Makar.

The company is currently collaborating to prove that lower dosages delivered via needle-free devices are as effective as a full dose delivered with a needle and syringe. "This has tremendous potential to reduce the cost per dose of expensive biologicals, or to allow a limited quantity of vaccine to cover a larger population," adds Mr. Makar. "We believe there will be a trend toward dose sparing and intradermal delivery of vaccines. With therapeutic drugs, single-use prefilled systems, in which the drug and needle-free delivery are combined in a single product, is where the market is heading."

BD LEANS TOWARD PREFILLED SYRINGES & SELF-INJECTION SYSTEMS

Throughout the past 5 years, the growth of prefilled syringes has been more than double the growth of the overall parenteral market (approximately 9% versus 4%). Several key factors are driving this trend: simplifying the preparation of an injectable drug and the desire by drug companies to have packaging differentiation in their marketplace. Perhaps the most compelling reason remains reducing medication risks, including minimizing the risk of cross-contamination.

"Becton, Dickinson and Company (BD) has been a leader in the prefilled industry for nearly 40 years and is an established drug delivery systems manufacturer for prefillable products worldwide," says Brian Lynch, Senior Product Manager, BD Medical–Pharmaceutical Systems.

The company's BD Hypak SCF glass prefillable syringe system offers many features that can be customized, allowing pharmaceutical companies to deliver products that meet the needs of the customers.

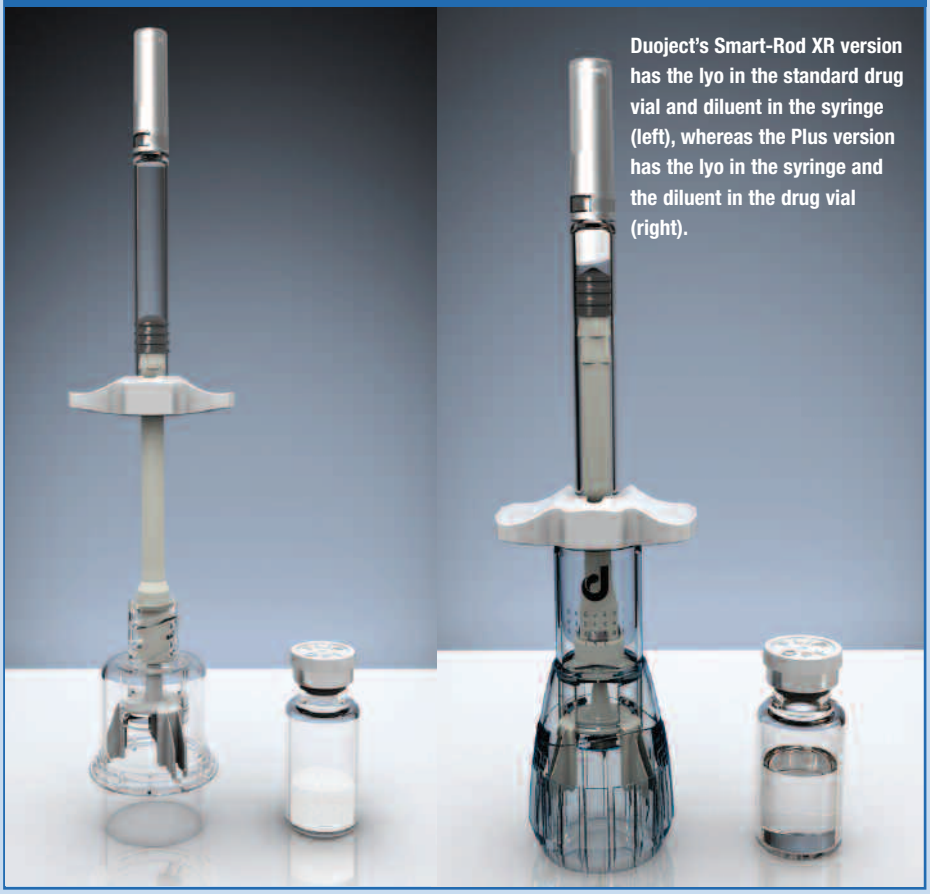
The surge in the manufacture of biotechnology drugs in recent years led BD to create the BD Sensitive Drug Initiative (SDI), an undertaking aimed at developing new technologies to meet the current and future needs of the biotechnology and biovaccine industries. The BD SDI team works closely with customers to assess the sensitivity of their particular drugs, with container packaging components, and develops new solutions that ensure product integrity.

And, as the interest in barrier isolation technology continues to grow, BD is responding with solutions that allow safe and efficient introduction of sterile components into a sterile filling environment, explains Janice Fajarito, Senior Product Manager, BD Medical-Pharmaceutical Systems. The BD TSCF packaging (Figure 4) helps ensure the safe transfer of stoppers into sterile filling areas, while the e-beam-compatible BD Hypak SCF syringe packaging allows for e-beam sterilization of the outer surface of the tubs before entry into the filling environment.

To meet specific customer needs, BD has a renewed focus within the self-injection platform. This focus includes building capabilities in concept design, prototyping, and in-house manufacturing. BD also plans on commercializing its BD Physioject, a disposable auto-injector using a 1-mL BD Hypak prefilled syringe, as well as an infusion system that uses a BD CCP (Crystal Clear Polymer) collapsible container as the primary container within the system.

"BD continues to do extensive market research on unmet pharmaceutical, clinician, and patient needs in order to have a full understanding of the market, while providing the optimal solutions for our partners," says Michael Ratigan, Business Platform Leader Self-Injection, BD Medical–Pharmaceutical Systems.

FIGURES 5 & 6



Duoject's Smart-Rod XR version has the lyo in the standard drug vial and diluent in the syringe (left), whereas the Plus version has the lyo in the syringe and the diluent in the drug vial (right).

DUOJECT MAKES RECONSTITUTION & RESUSPENSION EASY

This past year, Duoject has been focusing its efforts on developing new resuspension and reconstitution devices to better serve the pharmaceutical industry. The company received FDA 510k approval earlier this spring for its Smart-Rod reconstitution system (Figures 5 & 6) and is taking necessary steps to provide sufficient quantities to clients for clinical trial studies.

According to Dan MacDonald, Vice President, Engineering Services, the company is currently focusing its development efforts on syringe-based reconstitution devices in which the solid-form drug is found in the syringe rather than in the standard drug vial.

"We believe the best place to fill or lyophilize the drug product is in the actual container from which the drug will be delivered to the patient," he says. "Not only does this reduce the number of steps required by the end user to perform the reconstitution, it greatly reduces potential drug waste as the drug never leaves the syringe until injection."

There are no exposed needles during the reconstitution or resuspension steps when operating Duoject's devices; only the injection needle is exposed at the moment of delivery. Third-party safety devices, such as SSI's UltraSafe Passive and BD's Preventis can be added to enhance the safety of the syringe and Smart-Rod combination. Additionally, the Smart-Rod family of devices can be connected to the 1-mL staked-in needle syringe, which is the most widely accepted self-injection syringe on the market today, says Mr. MacDonald. Duoject is currently working with Hyaluron Contract Manufacturing to optimize the lyophilization

process in ISO-standard prefillable syringes for use with its reconstitution devices.

With more focus being given to long-acting release drugs, Duoject developed the Airless DC resuspension device (Figure 7) to answer the need for a system capable of resuspending microspheres with viscous diluents, while eliminating air before performing high-shear mixing of the solution between two syringes. This year, Duoject has added an actuator feature to its Airless DC system that controls the speed of plunger displacement during resuspension and improves overall operation of the device. "We are also pursuing a single-chamber version of our Airless DC system, which will reduce cost of manufacturing," adds Mr. MacDonald.

"We see the market moving toward simpler and safer reconstitution devices, which are also less costly to fill," he continues. "These devices must be 'fail-safe' and offer the same benefits to the end user as would a simple liquid-filled syringe. We believe our line of products follows this trend very nicely, offering ease of use and safety."

FIGURE 7

Duoject has developed the Airless DC resuspension device for long-acting release drugs.

GLIDE PHARMA DELIVERS INJECTIONS IN SOLID DOSES

Glide Pharma, previously known as Caretek Medical, is a specialty pharmaceutical company developing products based on its proprietary Glide Solid Dose Injector (SDI) technology. Glide SDI is a needle-free drug delivery system for the injection of drugs and vaccines in solid doses (Figure 8).

In its simplest form, the needle-free Glide technology contains a tiny, pointed rod of pharmaceutical material that is pushed against, pierces, and penetrates the skin. The pharmaceutical material comprises the active drug and any required excipients to produce a formulation that has the desired release kinetics for the drug. The drug formulation is stored within the disposable drug cassette and is pushed into the skin using the reusable spring-powered Glide actuator.

The drug component is smaller than a grain of rice, with the injection process completed in a faction of a second. "In the clinic, volunteers have been shown to prefer the Glide SDI to a standard injection with a needle and syringe," says Glide CEO Charles Potter, MA, PhD.

The formulation may contain one or more drugs and may be formulated to provide immediate and/or sustained release/controlled release of the drug to the systemic circulation. As the actuator is removed from the skin, the drug cassette is pushed from the actuator, and the actuator is automatically reset and ready for reuse. For some applications, such as the administration of emergency medicines, the drug cassette may be supplied attached to the actuator, ready for immediate and rapid use. In this case, the whole system would be disposable.

Due to its simplicity, the Glide SDI is ideally suited to the injection of drugs in the home environment," says Dr. Potter. "The solid formulation may avoid the need for refrigeration and, as there is no reconstitution steps, administration is much more convenient for patients."

In vaccine studies, the Glide SDI has demonstrated enhanced efficacy when compared to a standard needle and syringe injection, continues Dr. Potter, and in conjunction with the needle-free aspects of the technology, it offers a new vaccine delivery system for immunizations in industrialized countries, developing nations, as well as pandemic situations.

Glide Pharma is developing its own portfolio of products, including injectable formulations for fentanyl for acute pain, octreotide for acromegaly, and sumatriptan for migraines. "In addition to the in-house product development, Glide Pharma is working with five pharmaceutical companies, three of which signed feasibility study agreements in the first half of 2008, for the delivery of their proprietary biopharmaceuticals or vaccines," says Dr. Potter.

KING PHARMACEUTICALS & MERIDIAN AUTO-INJECTORS: FOCUSING ON PATIENT CARE

"King is constantly evaluating new technologies that can meet the future demand for simple-to-use, reliable, automatic injection of a range of medicines," says Mr. Mesa. "We use both internal development and acquisition strategies in this process."

King has active programs aimed at innovative drug delivery, including a wet-dry binary auto-injection system that will store

sensitive drug product separately from its diluent until it is needed for injection. This injector automatically mixes the sterile powder drug substance and diluent during the injection sequence, so it essentially protects the drug from breakdown by keeping it in stable form until injected.

Mr. Mesa says the company is also evaluating new ways to control and deliver small-volume parenteral medications. "Patient safety is a major focus for the drug delivery market. Home healthcare and self-administration of parenteral medications is becoming much more important as the industry looks to reduce medical care costs and improve quality of life," he says. "An auto-injector has to be intuitive and simple-to-use, regardless of whether the patient is in a medical crisis or administering routine medications. It must also withstand the riggers of a 12-year-old's backpack. We are ever diligent about ways to enhance the safety of these technologies and routinely employ human factors testing into our programs to better understand the user/device interface."

The King technology is comprised of a single-dose, prefilled syringe that contains sterile pyrogen-free drug product. The current systems are capable of delivering drug volumes from 0.5 mL to 3 mL. The technologies are capable of subcutaneous or intramuscular delivery. King's auto-injectors are all disposable, single-use, pressure-activated systems that are used for treating a range of acute and emergency medications. These auto-injector systems may also be adapted for use in chronic applications.

Pressing the tip of the auto-injector against the injection site activates the injector. Only two user steps are required: remove the safety and apply pressure against the injection site. "So, they are exquisitely simple for patients to use even under emergency situations," says Mr. Mesa.

The King auto-injection systems were originally designed for use by the military to speed the administration of life-or-death rescue medicines. "The US military and its allies still use our delivery systems to treat those exposed to organophosphorus nerve agents and to deliver pain medication on the battlefield."

Several of the military products have been adapted for use in homeland security applications, such as the DuoDote Auto-Injector (Figure 9). King also expanded on its military rescue applications to develop the EpiPen and EpiPen Jr. auto-injectors for use by patients who experience anaphylaxis. In each of these applications, the auto-injector may be self-administered quickly and through clothing to speed drug delivery.

According to Mr. Mesa, King is currently focused on drugs to treat pain and neurologic disorders. A Phase III clinical trial is underway to evaluate a diazepam-filled auto-injector product as a treatment for acute, repetitive epileptic seizures. "We are also working to complete design development of SoluJect, the antidote system that employs our binary wet-dry auto-injector technology," says Mr. Mesa.

Looking ahead, Mr. Mesa sees an increasing acceptance of at-home therapies by the medical community, thereby opening opportunities that may not have been available in the past. "These opportunities will come as a result of new applications for existing drugs, as well as additional opportunities for compounds still under development."

SAFETY SYRINGES: PHARMA PARTNERSHIPS PROVE SAFETY COMES FIRST

Since 1991, Safety Syringes, Inc. (SSI) has specialized in developing anti-needle-stick devices. The company is now developing and marketing its delivery systems for prefilled pharmaceutical glass syringes for vaccines, low-molecular-weight heparins, and many of the newer biotechnology drugs (Figure 10). The company is also aggressively attacking the threat of drug counterfeiting by offering an overt deterrent system, which helps prevent, or make evident, attempts to adulterate or counterfeit unit-dosed prefilled pharmaceutical presentations, says Christer O. Andreasson, Chairman and CEO of SSI.

"Counterfeit drugs are a big global business and as such, have attracted interest from organized crime," he says. "The number of investigations by the FDA has tripled throughout the past few years. We are actively attacking the threat of drug counterfeiting with our tamper-evident version of the UltraSafe Passive Delivery System. The system makes it more difficult for counterfeiters to copy brand name drugs

FIGURE 8

Glide SDI is a needle-free drug delivery system for injecting drugs and vaccines in solid doses.

FIGURE 9

The DuoDote Auto-Injector from Meridian has been adapted for use in homeland security.

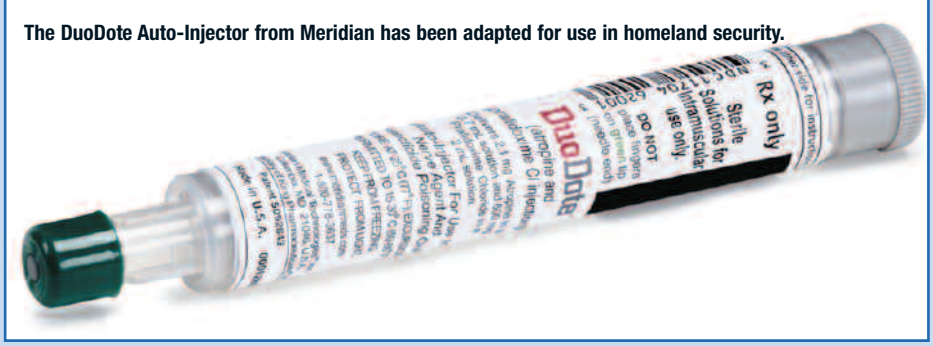
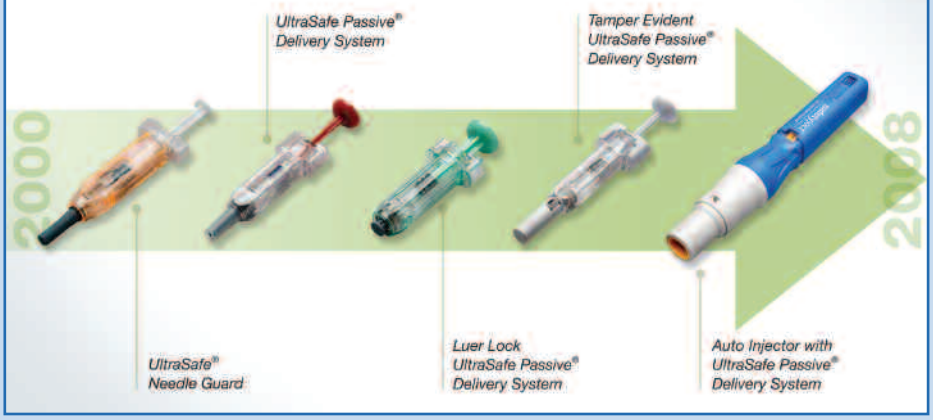


FIGURE 10

SSI is developing its delivery systems for prefilled pharmaceutical glass syringes for vaccines, low-molecular-weight heparins, and many of the newer biotechnology drugs.



packaged in the system. It provides another layer of protection and is at the unit-of-use level, which is what the FDA recommends for the counterfeiting solution. I believe these counterfeiting issues will be with us for some time. SSI has made a good first effort, but this will be a long-term battle."

SSI has also made great strides in partnering with some of the industry's leading pharmaceutical companies. "Pharmaceutical companies are very careful in selecting their partners, and SSI is keenly aware that those relationships can be significant for the long-term. But it takes a real commitment on our part in dealing with the problems these companies must address," says Mr. Andreasson.

To that end, SSI is expanding and bringing its manufacturing and assembly capabilities in-house to meet anticipated customer needs. "We are working diligently on significant product launches in two new and exciting drug segments — vaccines and biosimilars," he says. "Simultaneously, we are in the late stages of two additional product indications, one with a leading biotech company and another with a global top-10 pharmaceutical company."

Furthermore, the company recently entered into a development agreement for a custom product based on the UltraSafe Passive Delivery System for another top-10 pharmaceutical company.

"We have some exciting new products in the pipeline that (even for us) are beyond what the market has been able to predict, let alone produce, says Mr. Andreasson. "Decisions by pharmaceutical companies to convert to safety systems will continue to be based on fundamentally sound business economics, either to gain a competitive advantage and gain market share, or to prevent or slow down market share erosion."

YPSOMED UNDERSTANDS PATIENT NEEDS

"We are having broad success with our new spring-driven insulin pens, dual-chamber monodose devices, and disposable auto-injectors," says Ian Thompson, Manager, Business Development at Ypsomed. "These devices have all been developed with the patient in mind and have gone through objective handling studies. Regardless of their fear of injection, patients generally want to understand how the injection is taking place and have control over how the injection is performed. Self-injection devices have reached a high level of user-friendliness with more focus on patient-appealing, easy-to-industrialize designs."

Ypsomed insulin pens are reusable or disposable multi-dose injectors for frequent injections. Insulin pens are used with dedicated 3-mL cartridges and pen needles. All of the pens include easy dose-setting and clear last-dose indication.

Ypsomed also has a range of pen devices for non-insulin therapies. Dose-memory pens simplify handling so that the patient only needs to set the required dose once. For all subsequent injections, the patient only needs to "pull-push" the dosing knob until the cartridge is empty. This pull-push principle also applies to Ypsomed's fixed-dose pens. All Ypsomed pen systems for liquid-stable drugs can be adapted to accommodate dual-chamber cartridges. Safety pen needles developed for insulin injections, performed in care-giving situations, are ideal for use in other pen therapies, such as treatments for infectious diseases, in which potential needle-stick injuries pose a special threat, says Mr. Thompson.

The use of dual-chamber cartridges puts special demands on the pen system in terms of intuitive reconstitution, priming, and dose-setting steps (Figure 11). It is very important for the patient that these steps are easy to learn and always performed in the correct order. Ypsomed has developed a family of four device platforms for dual-chamber cartridges.

Disposable auto-injectors (Figure 12) are usually single-dose delivery devices for the infrequent injection of larger doses of drugs, explains Mr. Thompson. Ypsomed's standard device is designed for 1-mL long, prefilled syringes. The complete injection process (needle, insertion, injection, and subsequent needle shielding) is performed automatically.

"The device's easy activation, obvious visual and audible signals, and needle safety have been favorably compared in handling studies against currently marketed devices," says Mr. Thompson.

Needle safety is also an issue when delivering protein therapeutics, which are generally injected with conventional needle-based systems. "Advances in finer needles and needle-safety systems have reduced the interest in needle-free devices for such therapies," says Mr. Thompson. "Needle-free systems are associated with the issues of immunogenicity, bioequivalence, and increased cost of goods. The interest in needle-free injection is focused mainly on vaccines and small molecules, such as sumatriptan, in which immunogenicity and bioequivalence may not be such issues; whereas the issue of cost of goods often remains."

ZOGENIX: TO MARKET WITH KEY TECHNICAL DIFFERENTIATORS

If approved by the US FDA as expected in February 2009, sumatriptan DosePro (Figure 13) will be the first prefilled, single-use, disposable, needle-free delivery system for liquid medication. The drug/device combination is expected to challenge tablet versions of triptans, the most commonly used

migraine medications, by delivering sumatriptan subcutaneously, thereby providing migraine relief in as little as 10 minutes, all without a needle. In the case of DosePro, the subcutaneous delivery is propelled by compressed gas.

"Our market research shows an intense desire on the part of migraine patients to find new treatment options that can provide faster relief, and sumatriptan DosePro provides that relief in a user-friendly, needle-free system that patients prefer over needle auto-injectors," says Ms. Haldeman. "Our clinical studies have unequivocally shown that sumatriptan DosePro is bioequivalent to sumatriptan delivered by the leading needle-based auto-injector. And, 98% of patients were able to accomplish the three-step delivery on the first try with simple illustrated and written instructions, testimony to the product's exceptional ease of use."

However, sumatriptan is just the beginning for DosePro. Zogenix is actively working with several companies to put their drugs into the DosePro delivery system. DosePro may have an advantage because of some unique technical features. First, the patented drug capsule is type 1 borosilicate glass, a uniquely friendly container closure material for pharmaceuticals and biologics not commonly found in other needle-free products, says Ms. Haldeman.

Zogenix uses no silicone in the glass drug capsule, which can eliminate issues of silicone-related glide forces that can lead to underdosing. Further, the needle-free DosePro system uses no tungsten to form the nozzle; tungsten being another negatively reacting material in other systems. Finally, the company has generated data showing it can deliver highly viscous solutions with extremely short injection times due to the single-aperture nature of the system.

Zogenix has also demonstrated protein integrity after actuation and correlated this with a lack of immunogenic response in animal models. "While sumatriptan DosePro is an important first milestone for our company, we expect the DosePro system use to extend broadly within the biopharmaceutical business," says Ms. Haldeman. "We offer the combination of both a technically unique system, with one that is also extremely friendly to the end user, and this is what the industry is seeking."

SUMMARY

Experts agree that there is clear interest in both needle-based and needle-free injection systems. And while some argue that many are intrigued by the faster market approval of needle-based systems, others posit that drug delivery decisions go well beyond that. "The role of injection systems has evolved. They are no longer viewed as packaging or convenience items; they are now recognized as adding compelling product differentiation and substantial value to injectable products," says Mr. Kasprick of Antares Pharma. He believes pharma partners are now recognizing that the selection of an optimal injection device can have significant impact on the success of a product, whether it is due to enabling features of the device (the ability to deliver viscous materials), blocking intellectual property, or patient benefits. And, pharma companies are making sure that the device selection is made with input from all the necessary constituencies, rather than simply looking for the least expensive device. ◆

FIGURE 11

Ypsomed dual-chamber pen Lynx

FIGURE 12

Ypsomed disposable autoinjector Silberhorn

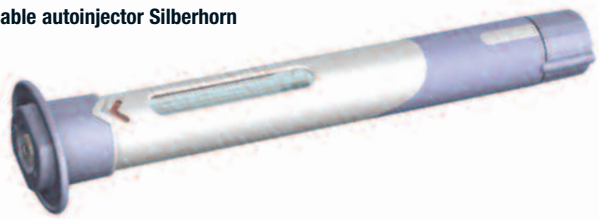
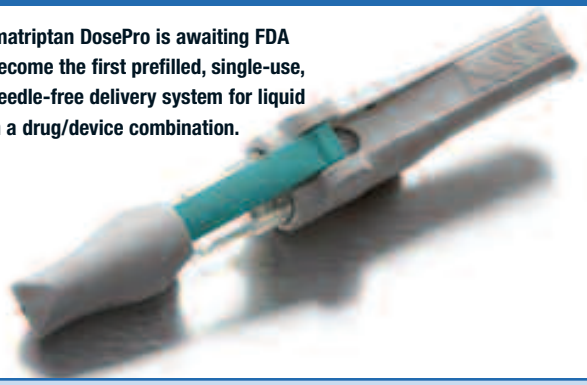


FIGURE 13

Zogenix's sumatriptan DosePro is awaiting FDA approval to become the first prefilled, single-use, disposable, needle-free delivery system for liquid medication in a drug/device combination.



BIOGRAPHY

Ms. Cindy H. Dubin has been a professional journalist since 1988. She is currently a Contributing Editor to Drug Delivery Technology as well as Editor of its Specialty Pharma section. Prior to these positions, she spent several years focusing her writing on pharmaceutical formulation and development. She has been recognized by the American Society of Business Press Editors for an article she wrote on nanotechnology, and her writing has been awarded by the prestigious Neal Award Committee for Journalistic Excellence. Ms. Dubin earned her BA in Journalism from Temple University in Philadelphia and her certificate in Business Logistics from Pennsylvania State University.

ONE STOP

service for product development & licensing decisions

www.pharmacircle.com

The Only Knowledge Management Service integrating complete drug delivery information into the broader analysis of the Pharma/Biotech Pipeline, Products and Deals

- Complete, comprehensive and up-to-date drug delivery information and analysis for better product decisions
- Detailed scientific and business related information on Pharma/Biotech, Drug Delivery, Specialty Pharma companies, including technologies, pipeline & products acquisitions & deals to facilitate licensing and competitive intelligence efforts
- Interactive and powerful search engine with user customized filters displays strategic information & analysis just the way you want to see them
- Web based service also provides phone & e-mail support

new

Please visit our free contract pharma section which provides detailed listings and comparison of services

For more Information please visit, www.PharmaCircle.com or contact tkararli@pharmacircle.com at (847) 729 2960

TRANSDERMAL DELIVERY

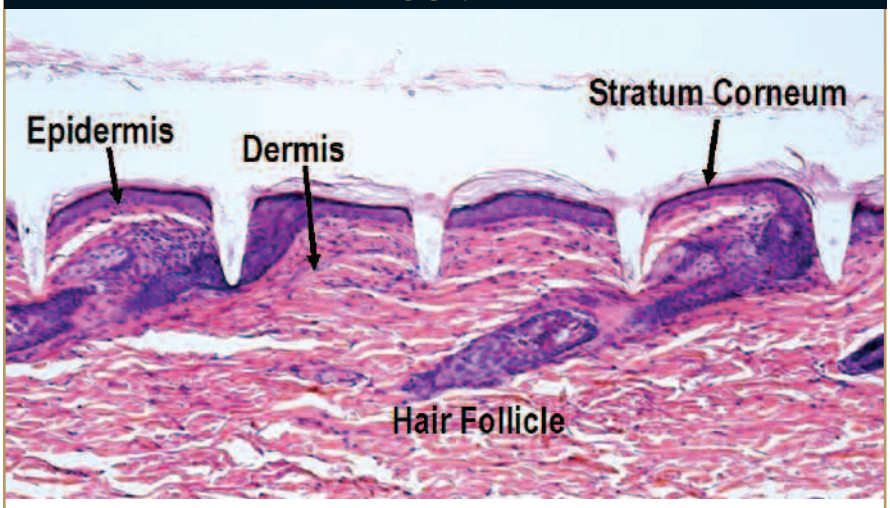
A Solid Microstructured Transdermal System (sMTS) for Systemic Delivery of Salts & Proteins

By: Kris Hansen, PhD, and Bret Haldin, MBA

INTRODUCTION

As the $80-billion drug delivery market expands to accommodate growing requirements from physicians, patients, and regulatory bodies, there is a desire to see more options for easy-to-use, self-administration delivery technologies.[1,2] A key reason for this expansion in requirements is the focus on biopharmaceuticals and their delivery, which has raised overall interest in non-invasive drug delivery systems in general. The solid microstructured transdermal system (sMTS), which uses small microstructures that painlessly penetrate the stratum corneum and increase the permeability of the skin, embodies the patient-friendly characteristics of a transdermal patch with the versatility and delivery times more akin to subcutaneous injection.

FIGURE 1



Magnified Cross-section of HGP Skin After sMTS Application & Removal

BIOPHARMACEUTICALS & TRANSDERMAL DRUG DELIVERY: A GROWING CHALLENGE

Traditional transdermal patch technology is generally limited to the delivery of smaller, lipophilic molecules. When placed in close contact with the skin and in the presence of an adhesive patch, these select molecules are able to diffuse though the stratum corneum and pass into systemic circulation, offering slow, continuous delivery throughout the wear time of the patch. Transdermal patches have a long and successful legacy for extended release of hormones, along with other small molecules, such as nicotine, to aid in smoking cessation and fentanyl, for long-acting pain relief. Although an elegant system, given the whole of the pharmaceutical market, there are relatively few APIs compatible with this diffusion-based technology, and drug-in-adhesive transdermal delivery is limited when viewed in the context of current and future large-scale trends in the pharmaceutical industry, more specifically, those related to biopharmaceuticals.

The biopharmaceutical industry continues to show signs of robust growth with an historic annual growth rate of 17%, revenues for 2007 exceeding over $80 billion, and industry net loss shrinking to $2.7 billion - the closest the industry has come to profitability since its inception.[3] By 2014, 6 of the top 10 pharmaceutical products are forecasted to be biologics, accounting for over 65% of revenue from the top 10 products in that year.[4] This rise of biopharmaceutical drugs within the overall pharmaceutical industry provides a growing supply of NCEs and marketed drugs that, at best, significantly challenge the capabilities of existing transdermal drug delivery systems, and at worst require that delivery of them be by injection only.

Transdermal drug delivery is by definition non-invasive, and from both patients' and doctors' perspectives, is second only to oral in terms of preference.[2] Typical reasons for transdermal drug delivery preference include patient convenience, ease-of-

use, and satisfaction with transdermal patches.[5] Conversely, injection systems are valued for their speed of delivery and high bioavailability. A platform offering both of these characteristics would be well suited to meet the need for enhanced delivery systems that provide a method to both extend pharmaceutical product life and lower patient risks associated with therapy administration in emerging biopharmaceutical markets.

Ideally, a system such as the one described earlier would be no more complex than existing pen injection systems, which have evolved considerably throughout the past several decades. Today, these systems have proliferated and now exist in a large portion of biopharmaceutical markets. They have evolved from the standard Luer syringe to relatively sophisticated devices using needle-covers, electronics, automated needle covers, and automated injection capability.[6] This evolution has been dictated by both the perceptions and realities of using needles in drug delivery systems across a broad array of markets and users.

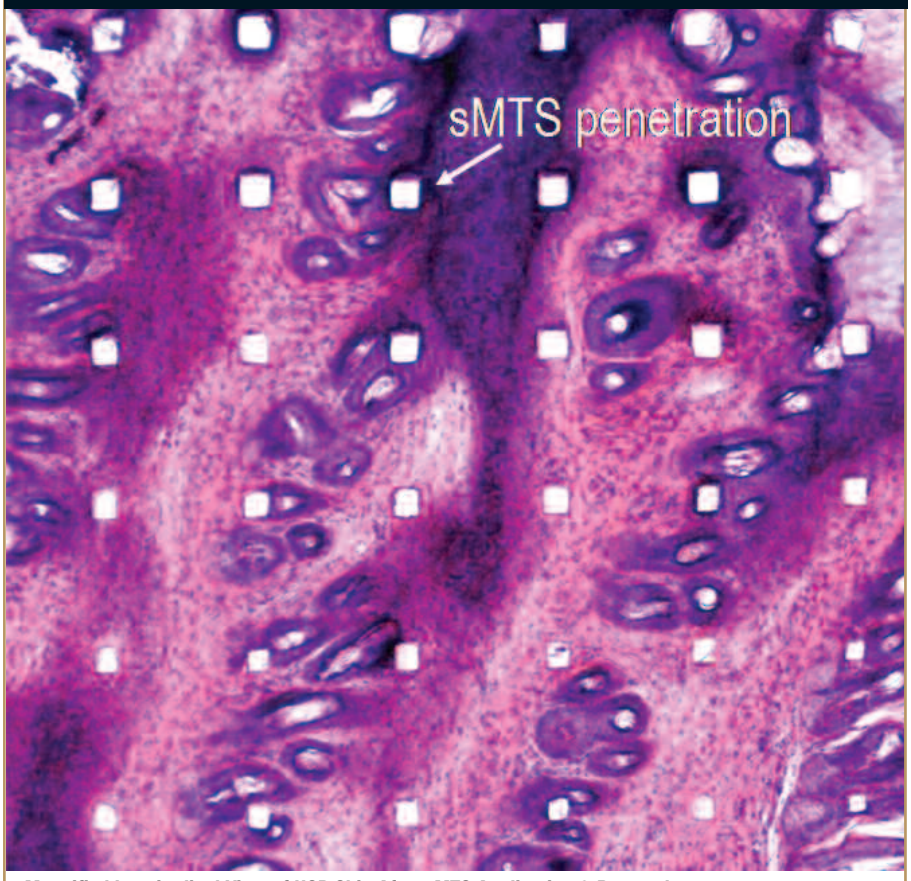
3M'S SOLID MICROSTRUCTURED TRANSDERMAL SYSTEM (sMTS)

The sMTS is composed of microprojections less than 0.5 mm long. These microstructures can be used to puncture the stratum corneum and increase the permeability of the skin. Figure 1 provides a cross-sectional view of hairless guinea pig (HGP) skin after application of the sMTS showing penetration of the stratum corneum; note that for these images, the skin has been fixed to retain the channels and impression of the microstructures.

The microstructures allow for direct communication through the skin to the interdermal tissue and may significantly increase the versatility afforded transdermal delivery. An API coated on the microstructures, for example, may enter the interdermal space and dissolve off the microstructures, offering an efficient and effective route into systemic circulation. Because the microstructures overcome the protective barrier of the stratum corneum, delivery is not limited to those few molecules that can diffuse through the skin. Figure 2 shows a longitudinal view of HGP skin after application and removal of the sMTS array. Again, the skin has been fixed to retain the impressions created by the microstructures.

Because sMTS 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

FIGURE 2

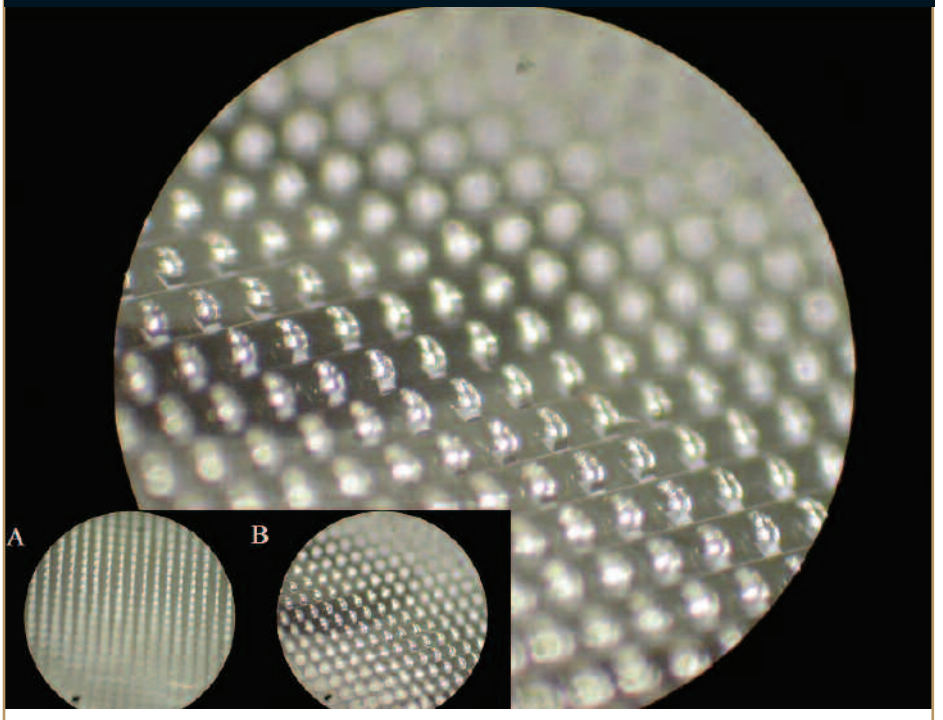


Magnified Longitudinal View of HGP Skin After sMTS Application & Removal

FIGURE 3

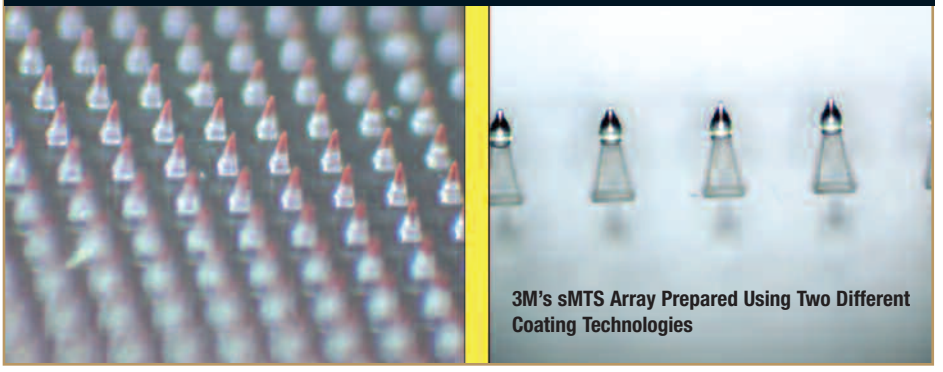
3M's sMTS Array for Systemic Delivery

FIGURE 4



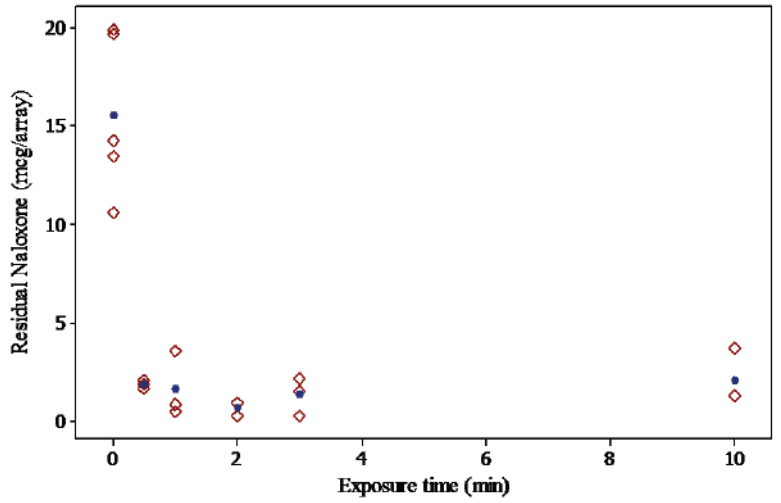
3M's sMTS Array Before & After the Application of 245N of Force Applied Against a Rigid Surface

FIGURE 5



3M's sMTS Array Prepared Using Two Different Coating Technologies

FIGURE 6



In Vivo Release of Naloxone From sMTS Array

disposable syringes and injection pens. The survey was conducted in 24 French public hospitals and included reported accidental needlestick injuries received over the period of 1 year. Injection pens accounted for a disproportionate number of accidental needlestick injuries (six times higher than with disposable syringes), likely due to the additional handling required to assemble, and then disassemble, the needle on the injector. 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.[7]

A survey conducted in Egypt and published in 2003 found that over 35% of healthcare workers received at least one needlestick injury within the previous 3-month period with an estimated annual needlestick injury rate of 4.9 needlesticks per worker per year. Using a model based on this rate and coupled with the vaccination rate for Egyptian healthcare workers, the authors estimate over 24,000 hepatitis C and over 8,500 hepatitis B viral infections occur each year as a result of occupational exposure in the healthcare environment.[8]

3M's sMTS is a single-use system that cannot be reloaded and thus cannot be reused, eliminating disease transmission associated with use of a used delivery system. Despite the development of single-use syringes, millions of injections are administered every year with used and unsterile needles. In the 1990s, surveys tracking vaccination activities in developing nations indicated that up to one third of the 1 billion immunizations delivered in these countries, and half of the other 9 billion injections, were unsterile.[9] The World Health Organization estimates that every year, unsafe injections result in 80,000 to 160,000 new HIV-1 infections, 8 to 16 million hepatitis B infections, and 2.3 to 4.7 million hepatitis C infections worldwide.[9]

sMTS ARRAY

The sMTS consists of a Class VI polycarbonate array containing over 1000 microstructures integrated into a simple applicator/patch system (Figure 3).

Drug coated on the sMTS prior to application is efficiently delivered into the systemic circulation within the 10-minute intended wear time of the patch, typically within the first 30 seconds, after which the patch may be removed and discarded. In addition to offering a minimally invasive route to systemic delivery, the sMTS eliminates the risk of accidental needlesticks before and after application. The sMTS can be disposed in a medical waste stream and requires no special accommodations for sharps disposal.

The strength of the sMTS array is attributable to the high flexural modulus (2300 MPa, as per ISO 178) and high tensile strain at break (70%, as per ISO 527) of the polycarbonate. The sMTS 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, HGPs, and humans. Under extreme force, the microstructures will bend rather than fracture or break (Figure 4), as might be expected from microstructures made of glass or metal.[10]

sMTS API APPLICATION & RELEASE

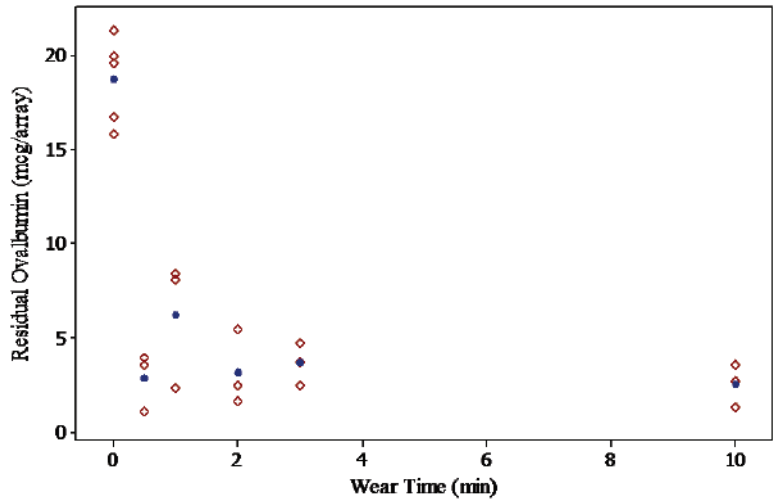
Historically, a variety of technologies have been employed to coat API on the surface of the microstructured array. For example, the arrays may be dipped in formulation or the formulation may be brushed onto the surface. Alternatively, small aliquots of liquid formulation may be applied to the array and dried, leaving a stable API residue for delivery. Figure 5 shows examples of sMTS arrays prepared according to two different coating technologies.

After coating and drying, the sMTS array is affixed into an adhesive patch and fit into a delivery device for self-administration. Tested in domestic swine and HGPs, the microstructures have been shown to penetrate approximately 120 micrometers into the skin, deep enough to provide a suitable release environment for the API.

In a study designed to determine wear time, sMTS arrays were coated with naloxone, a small molecule salt, or ovalbumin; the amount of API on the arrays was quantitatively characterized using HPLC-UV. After coating, the arrays were applied to HGPs and allowed to remain in place for a set amount of time between 3 seconds and 10 minutes. After the specified wear time, the sMTS arrays were removed and assayed for residual API. Results from the wear time studies are presented in Figures 6 and 7.

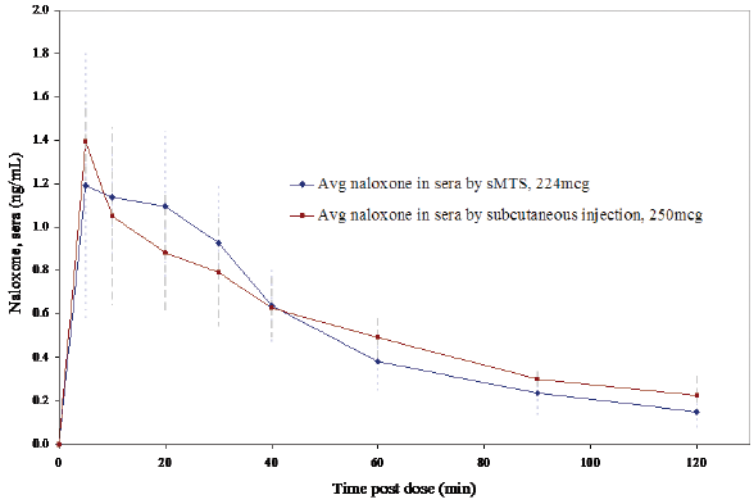
At 3 seconds (data not shown), only small changes in the drug level measured on the array were observed, indicating that the API penetrates the stratum corneum along with the microstructures and does not wipe off on insertion. As evident in Figures 6 and 7, when the microstructures are inserted, the API is readily released with residual

FIGURE 7



In Vivo Release of Ovalbumin (MW = 45 kDA) From sMTS Array

FIGURE 8



PK Profiles for Naloxone Delivery in Swine Using sMTS or Subcutaneous Injection

levels measured at 30 seconds being no different from those measured after 10 minutes of wear time.

sMTS FOR SYSTEMIC DELIVERY OF SALTS & PROTEINS

Given the experimentally determined depth of penetration (DOP) associated with the sMTS, API coated on the sMTS array will be delivered into the epidermis, the upper most region of the skin. Although the epidermis contains neither blood vessels nor nerve fibers, drug deposited there may diffuse through interstitial fluid into capillaries in the dermis for systemic distribution. Figure 8 shows the pharmacokinetic (PK) profile obtained when sMTS arrays coated with naloxone were applied to 25- to 35-kg domestic swine. The PK profile obtained following a subcutaneous injection of a similar amount of naloxone is shown for comparison.

This dataset demonstrates similar PK profiles for the naloxone delivered by sMTS or subcutaneous injection. In both cases, the Cmax is at 5 minutes. The bioavailability and the elimination kinetics associated with the two delivery routes appear similar, suggesting the absence of a depot in the epidermis for sMTS delivery.

The sMTS has been used to deliver molecules as large as ovalbumin (approx 45 kDa) and human growth hormone (approx 22 kDa) and is an ideal choice for delivery of highly potent therapeutic proteins, peptides, or small molecule salts.

SUMMARY

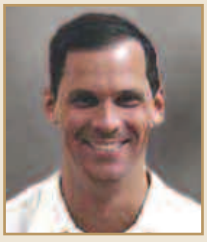
The combination of ease of use, painless delivery, and no sharps hazard, all in a platform that offers a new paradigm for select self-administered small and large molecule drugs typically requiring subcutaneous injection, speaks to an exciting technology with the ability to significantly change the standard for drug delivery in emerging therapy areas. Drug delivery via 3M's sMTS provides systemic delivery of APIs not typically compatible with transdermal delivery. By painlessly penetrating the stratum corneum, the coated microstructures provide a fast entry into the systemic circulation, even following a wear time as short as 30 seconds. APIs may be delivered via the sMTS with a bioavailability and a pharmacokinetic profile similar to those observed using subcutaneous injection. The sMTS delivery route embodies high-performance delivery with administration characteristics most desired by patients and doctors, potentially enhancing standards of care, particularly for chronic diseases with therapies requiring systemic delivery, and improving treatment compliance levels among patients.

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 Industry Report Vol. 1-2; January 2008.
3. Beyond Borders: Global Biotechnology Report 2007. Ernest & Young; June 2008.
4. Decision Resources Product View; March 2008.
5. US Drug Delivery, Usage Patterns, Preferences and Opportunities in the US. Frost & Sullivan Industry Report Vol. 2; January 2008.
6. Thompson I. New generation auto-injectors: completing the scale of convenience for self-injection. Drug Delivery Report. 2005(Autumn/Winter):47-49.
7. Pellissier G, Migueres B, Tarantola A, Abiteboul D, Lolom I, Bouvet E. Risk of needlestick injuries by injection pens. J Hospital Infection. 2006;63:60-64.
8. Talaat M, Kandeel A, El-Shoubary W, Bodenshatz C, Khairy I, Oun S, Mahoney F. Occupational exposure to needlestick injuries and hepatitis B vaccination coverage among healthcare workers in Egypt. Amer J Infection Control. 2003;31:469-474.
9. Kane A, Lloyd J, Zaffran M, Simonsen L, Kane M. Transmission of hepatitis B, hepatitis C and human immunodeficiency viruses through unsafe injections in the developing world: model-based regional estimates. Bulletin of the WHO. 1999;77(10):801-807.
10. 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 Biomechanics. 2004;37:115-1163.

BIOGRAPHIES

Dr. Kris Hansen is the MTS Technical 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. Dr. Hansen has more than 20 publications in technical journals.



Bret Haldin is the MTS Business Manager for 3M Drug Delivery Systems in St. Paul, Minnesota. He earned his MBA from The Wharton School of the University of Pennsylvania, and his BS in Aeronautical Engineering from Rensselaer Polytechnic Institute. He also served as an officer in the United States Navy. His business interests include the commercialization of new technologies in drug delivery and biopharmaceutical markets.

www.frost.com

What do you *really* know about end-users of drug delivery technologies?

Drug delivery technologies are an important part of the changing Pharma & Biotech industry. Feedback from patients and physicians, in terms of factors such as perception, desired attributes, compliance, and drivers of adoption/non-adoption for different drug delivery types, is therefore vital to developers. Is your company positioned to understand and take advantage of these opportunities for growth?

Frost & Sullivan's Pharmaceutical & Biotechnology group can provide your organization with the research and support it needs to fully understand end-users of Drug Delivery Technologies, and to identify and take advantage of the best opportunities for growth in this market.

Our expert Healthcare analysts:

- Provide objective, 3rd party analysis
- Identify a range of growth options
- Evaluate which options will produce the best Return on Investment
- Work with clients to develop effective implementation strategies

For more information on growth opportunities in the Drug Delivery market, please contact Johanna Haynes at johanna.haynes@frost.com.

FROST & SULLIVAN

SKIN PENETRATION STUDIES

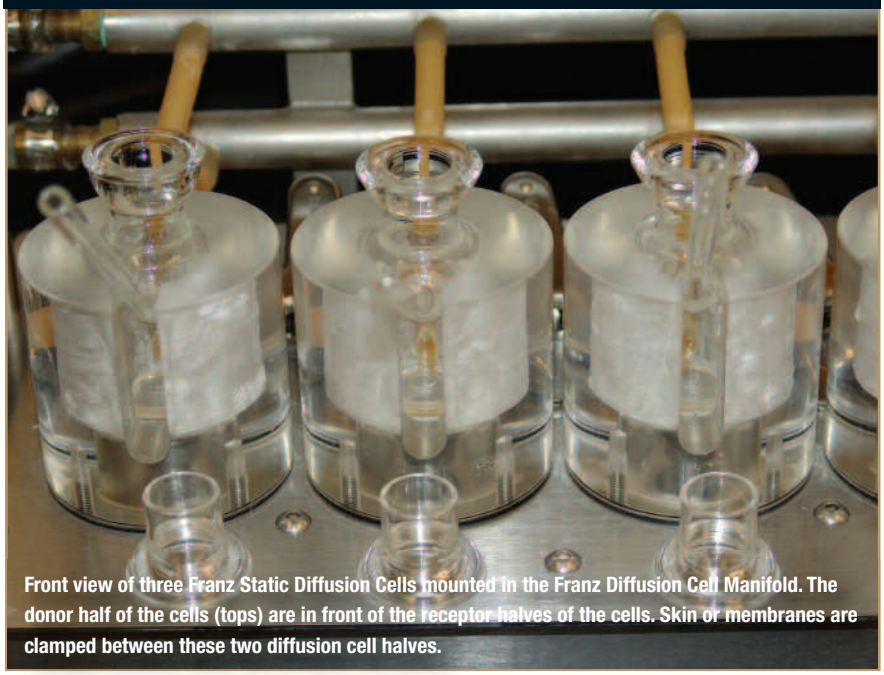
Rationale & Design of Studies to Screen & Identify Promising Topical Formulations

By: Daniel Bucks, PhD

INTRODUCTION

One of the unique opportunities that Dow Pharmaceutical Sciences, Inc. (DPSI) offers to clients is the evaluation of drug permeation into and through human skin and the role that formulation excipients play on this process. This is achieved with well-designed and appropriately executed in vitro percutaneous absorption (skin penetration) studies. The following discusses the rationale for conducting skin penetration studies, appropriate test systems, the importance of the source of the skin, and typical study design variables and deliverables.

FIGURE 1

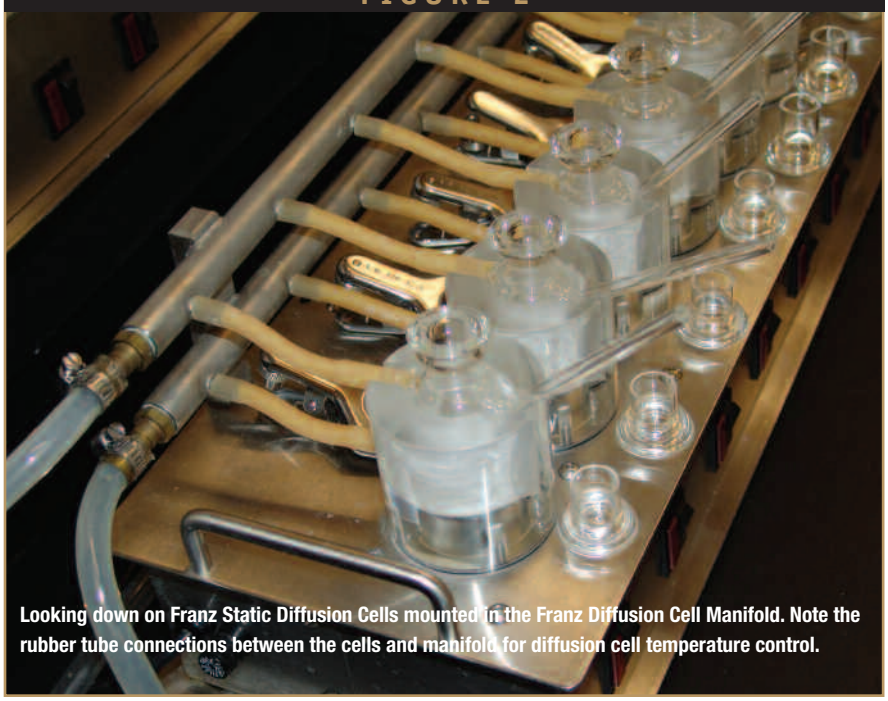


Front view of three Franz Static Diffusion Cells mounted in the Franz Diffusion Cell Manifold. The donor half of the cells (tops) are in front of the receptor halves of the cells. Skin or membranes are clamped between these two diffusion cell halves.

OPTIMIZING FORMULATIONS TO MEET YOUR DESIRED DRUG DELIVERY PROFILE

In vitro percutaneous absorption studies are routinely conducted during topical drug formulation development to identify promising prototypes. These studies allow for the characterization of several critical formulation attributes: drug release from the formulation, drug deposition in the targeted skin tissues, and drug permeation through the

FIGURE 2



Looking down on Franz Static Diffusion Cells mounted in the Franz Diffusion Cell Manifold. Note the rubber tube connections between the cells and manifold for diffusion cell temperature control.

Take Your Stand

at the 36th Annual Meeting & Exposition of the Controlled Release Society

July 18-22, 2009 • Bella Center • Copenhagen, Denmark

Contact Debby Woodard today for more details.

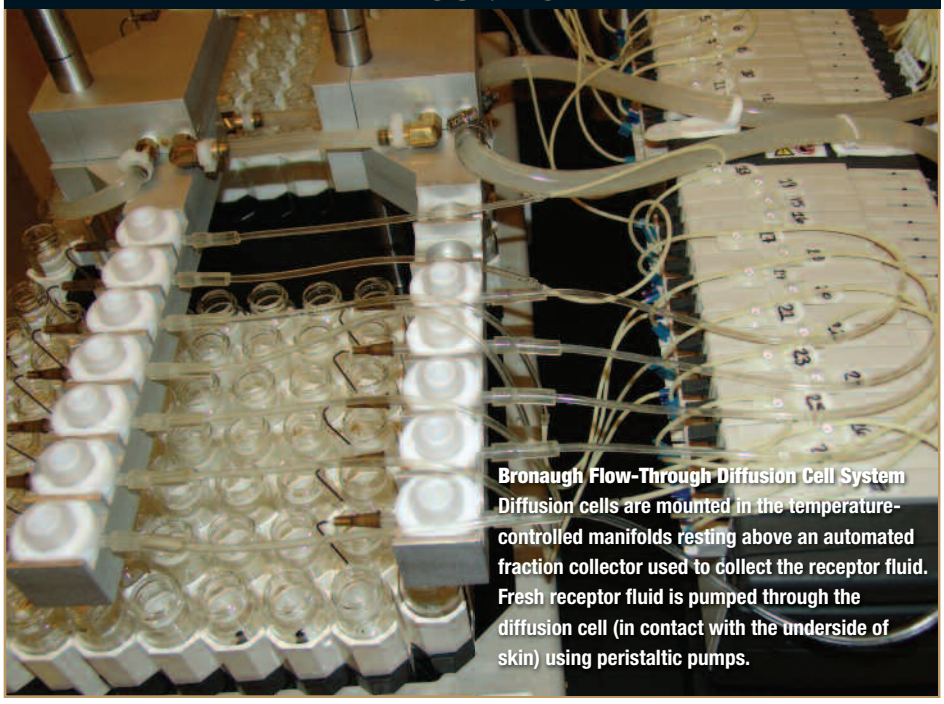
dwoodard@scisoc.org • +1.651.994.3817

skin. These attributes combine to form a formulation-specific, drug delivery profile. The optimal drug delivery profile is defined by the intended use of the drug product as well as the particular disease state. A profile with enhanced drug retention in the outermost layer of the skin, the stratum corneum, is desired with sunscreens, keratolytics, and antifungals. On the other hand, enhanced deposition in the viable epidermis and dermis (and receptor fluid when using dermatomed skin) is the profile best suited for a promising formulation under development to become a product intended to modify the physiology of the skin. The purpose of screening is to optimize formulation composition to enhance the desired delivery profile. A formulation optimized for skin deposition and drug penetration is more efficient, requires less drug and thus offers the advantage of less potential irritation (if the drug is irritating), lower drug cost for manufacture, and maximum opportunity for clinical efficacy. In summary, in vitro percutaneous absorption studies are a powerful tool for selecting the dermatologic formulation that will progress to the clinic.

ADVANTAGES & PROPER USE OF TWO DIFFUSION CELL SYSTEMS

When evaluating the in vitro percutaneous absorption of a drug from potential formulations, two types of diffusion cell systems are available: the static diffusion cell systems and the flow-through diffusion cell systems. These diffusion cell systems are available from several manufacturers. Often in vitro percutaneous absorption studies are conducted using a finite, clinically relevant dose of formulation. In this situation, both the Franz static diffusion cell system and the Bronaugh flow-through diffusion cell system have proven to be very effective. Manual collection of receptor fluid samples, large skin area for topical application, and large area for drug diffusion make the Franz static diffusion cell an excellent choice when characterizing skin deposition and penetration of drugs from formulations with very low drug permeation rates. By contrast, the Bronaugh flow-through diffusion cell system offers the advantages of continuous perfusion of the underside of the skin, the dermis, with fresh receptor fluid to maintain sink conditions when evaluating more readily penetrating drugs. The Bronaugh system also allows for more cells to be run within a study, and the automated receptor fluid sample collection allows for easy kinetic profiling of drug permeation. This system is also most suited for high volume characterization of multiple formulations.

FIGURE 3



Bronaugh Flow-Through Diffusion Cell System Diffusion cells are mounted in the temperature-controlled manifolds resting above an automated fraction collector used to collect the receptor fluid. Fresh receptor fluid is pumped through the diffusion cell (in contact with the underside of skin) using peristaltic pumps.

IMPORTANCE OF SKIN SOURCE & QUALITY OR SUCCESSFUL PERCUTANEOUS ABSORPTION STUDIES

While formulation selection and cell design can be decisive elements in the success of an in vitro percutaneous penetration study, the source and quality of the skin used are also essential.

Because the purpose of the development process is to generate a

product intended for human use, human skin is naturally the ideal in vitro model. Additionally, there typically exists a large variation in skin barrier properties across species. Although human cadaver skin can be used, cadaver skin obtained from tissue banks can be highly variable with respect to its permeability to drugs. This variation is due in part to the lack of standardized methods for collection and preparation of human cadaver skin obtained from morgues in addition to variation in the "health" of the skin at the time of death. The use of fresh human tissue removed from healthy, but overweight, people who have undergone an elective "tummy tuck" (abdominoplasty) surgery is the best tissue for an in vitro percutaneous absorption study. By standardizing the methods of skin collection, processing, and storage, DPSI can preserve the normal barrier properties of the skin. To further control variation in study data, human skin from a single donor and a single anatomical site should be used. These conditions allow for comparable results across the various formulations tested within a study and eliminates the variability that occurs when multiple donors or skin from various anatomical sites are used.

PERCUTANEOUS ABSORPTION STUDY DESIGN

In a typical in vitro percutaneous absorption study, a clinically relevant dose of each prototype formulation is applied to excised human skin mounted in either Franz static or Bronaugh flow-through diffusion cells. Skin should be exposed to the formulation no longer than 24 hours because of deterioration of skin integrity with time. Receptor fluid samples are collected at regular intervals. At the end of the exposure period, residual formulation can be removed from the skin surface by washing, wiping, tape-stripping, or combinations thereof. After removal of the residual formulation from the skin surface, the epidermis is separated from the dermis by blunt dissection. The epidermis, dermis, and receptor fluid samples are then analyzed for drug content by use of radiolabeled drugs or use of sensitive analytical methods like LC/MS, and the profile of drug delivery is assessed. The turn-around time for a typical in vitro percutaneous absorption study is 4 to 6 weeks.

SUMMARY

In vitro percutaneous absorption studies have become an important tool in the evaluation of potential drug candidates and prototype topical formulations for drug release and cutaneous delivery. Selection of the appropriate diffusion cell system, proper study design, and skin source and quality all are critical components for success.

BIOGRAPHY

Dr. Daniel Bucks is the Founder and Director of the Skin Biology & Drug Transport Department at Dow Pharmaceutical Sciences, Inc., where he is responsible for this department consisting of the drug transport laboratory and personnel utilized for the in vitro and in vivo evaluation of new drugs and prototype topical formulations. He also functions as the resident expert in skin biology and pharmacokinetics to help guide topical product development efforts. Dr. Bucks earned his PhD in Pharmaceutical Chemistry from the University of California, San Francisco. He has worked in the field of dermatological product development for over 25 years and authored over 70 publications. Dr. Bucks can be reached at (707) 793-2600 or dbucks@dowpharmsci.com

PARTICULATE SUSPENSIONS

Aggregation, Agglomeration – How to Avoid Aggravation When Formulating Particulate Suspensions

By: David Fairhurst, PhD, and Robert W. Lee, PhD

INTRODUCTION

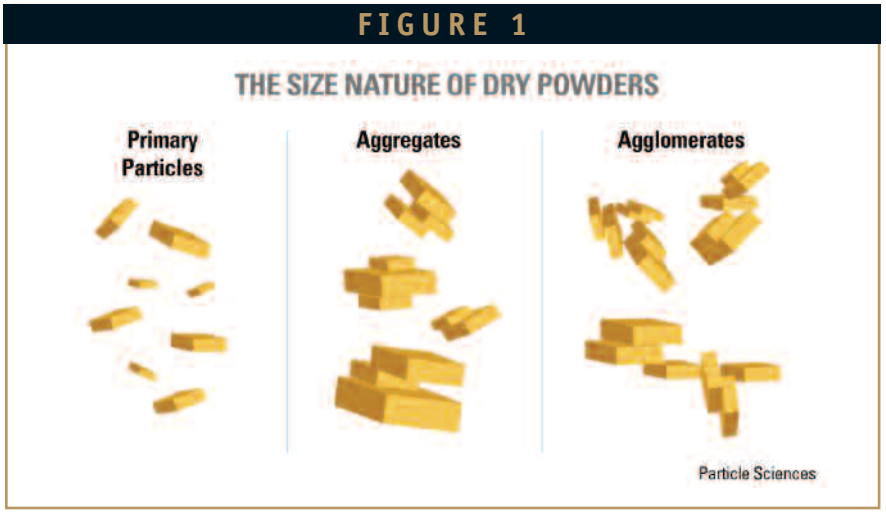
Life cycle management is of increasing interest and importance to pharmaceutical companies.[1-4] Drug delivery technologies that offer positive differentiation over first-generation commercial products provide an important means for staying competitive in today's challenging business environment. A cursory glance through the scientific and patent literature reveals that it is replete with examples in which reducing the particle size of an API results in increased bioavailablility.[5-9] In the case of formulations intended for oral administration, poorly water-soluble APIs may suffer from an inadequate or highly variable rate and/or extent of drug absorption (sometimes as a function of food in the stomach, ie, fed/fasted variability). Particle size reduction of the API prior to formulating will significantly increase the specific surface area and subsequently the rate of dissolution of the drug in the gut milieu. Therefore, in the case of poorly water-soluble, highly permeable APIs, classified according to the Biopharmaceutical Classification System as Class II (BCS class II) for which absorption is dissolution limited, particle size reduction may result in significant improvement in the rate and extent of drug absorption such that the bioavailability requirements of the drug are met.[10-14]

Leading drug delivery technologies employing proprietary milling processes (coupled with steric stabilization techniques) that have produced nanotechnology-enabled products are NanoCrystal® technology from élan Drug Technologies, Insoluble Drug Delivery (IDD®) technology from SkyePharma, Biorise® technology from Eurand, and NanoEdge® technology from Baxter BioPharma Solutions.[15-18] NanoCrystal technology has been the front runner that forms the technology platform for four marketed products in the US. Reduction in particle size can be achieved by various means but, subsequently in formulation, the API is usually dispersed in either aqueous or non-aqueous media depending on the pharmaceutical application.[13] Preparation of the formulation requires that a stable (non-agglomerating) and reproducible particle size distribution (PSD) be achieved. This implies not only proper dispersion of the particulates but also subsequent prevention of any re-agglomeration. Proper dispersion greatly enhances final product performance and, in addition, maximizes efficiency and provides increased product value from raw materials.

As good as formulation skills, experience, and testing may be, difficulties can still sometimes be encountered in achieving stable, effective, and elegant formulations containing particulates. Dispersing powders in liquids is, however, simply a matter of proper technique based on an understanding of a few key principles. By considering each component of the suspension in relation to the whole, logical choices can be made that will result in the desired product.

All powders consist of three groups of particles: primary particles, aggregates, and agglomerates (Figure 1). These three distinct species constitute what is known as the

FIGURE 1



particle size distribution (PSD) of any powder (Figure 2). A detailed discussion of what is implied by PSD can be found in Particle Sciences' Technical Bulletin No. 1. The act of dispersion entails overcoming the various binding forces between particles by use of both physicochemical and mechanical means. The final dispersed state is accomplished via three distinct steps: wetting the solid surface, deagglomeration of the particles, and stabilization of the particles.

It is critical that these three steps be viewed as distinct and are performed in the correct order. The physicochemical ways in which all three processes can be influenced are covered in textbooks of colloid and surface chemistry.[19] This is not to say that all steps always require separate procedures but, if needed, the procedures must occur in sequence. In addition, the following factors will each play a role:

- Selection of the suspension liquid;
- Selection of the type and concentration of the various dispersion aids (ie, wetting agent, deagglomerating agent, and stabilizing agent); and
- Selection of the type and duration of the mechanical dispersing treatment.

The complete dispersion process is shown in Figure 3. The following briefly discusses each step separately, while a comprehensive review has been given elsewhere.[20]

WETTING

Wetting is the act of getting the particle into the chosen liquid. It involves contact (or adhesion) of the liquid to the particle solid surface, spreading of the liquid over the surface, and finally, penetration of the liquid into the spaces between agglomerated particles. Surfaces that are easily wetted are termed lyophilic. Those that are difficult to wet are termed lyophobic; such surfaces require the use of a wetting agent. Many APIs fall into this latter category. The fundamental thermodynamic equations that govern adhesion and spreading are expressed as the Young-Dupré equations (Equations 1 & 2).[21]

Equations 1 & 2.

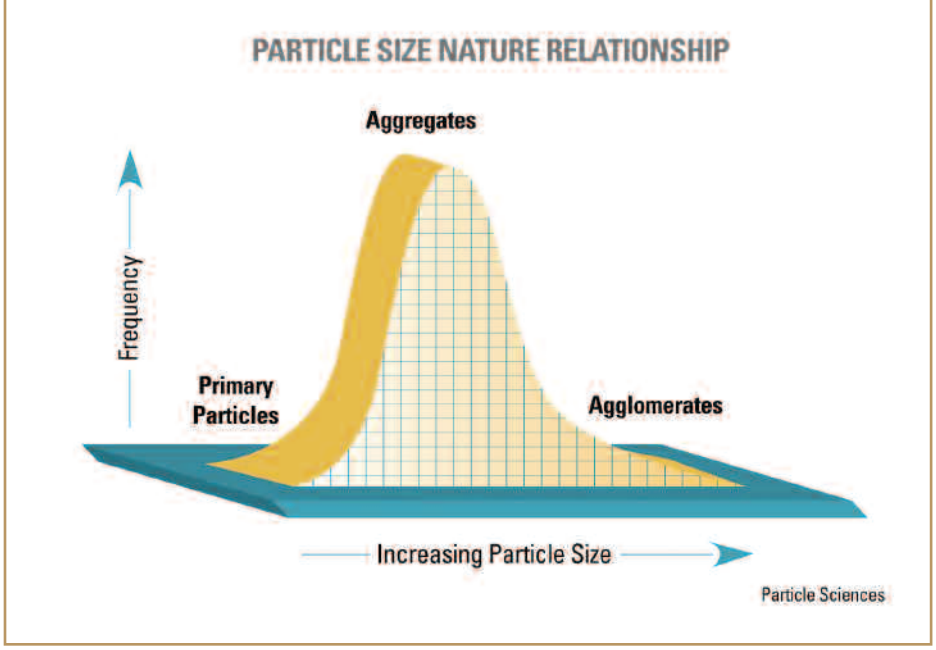
$$\gamma_{SV} = \gamma_{SL} + \gamma_{LV}\cos\theta$$
$$\omega_A = \gamma_{SV} + \gamma_{LV} - \gamma_{SL}$$

Where, γ_{SV} is the interfacial tension between the solid and the vapor, γ_{SL} is the interfacial tension between the solid and the liquid, γ_{LV} is the interfacial tension between the liquid and the vapor, θ is the contact angle at the solid-liquid interface, and ωA is the work of adhesion.

A surface will be fully wetted by a liquid as both γ_{LV} and $\cos\theta$ tend to zero (Figure 4). To achieve this condition it is necessary (for lyophobic surfaces) to add a wetting agent to the liquid. A wetting agent adsorbs at the liquid-vapor interface, reducing the interfacial tension as well as the contact angle of the liquid at the particle surface. A wetting agent, therefore, is "surface-active" – hence the term surface-active agent or, more commonly, surfactant. It is necessary to use the absolute minimum of wetting agent. One obvious downside to the use of too much surfactant is to increase the potential for foaming, and this may cause separation of the finer particles. An additional reason to use the lowest possible concentration is to minimize any potential toxicity associated with the surfactant.

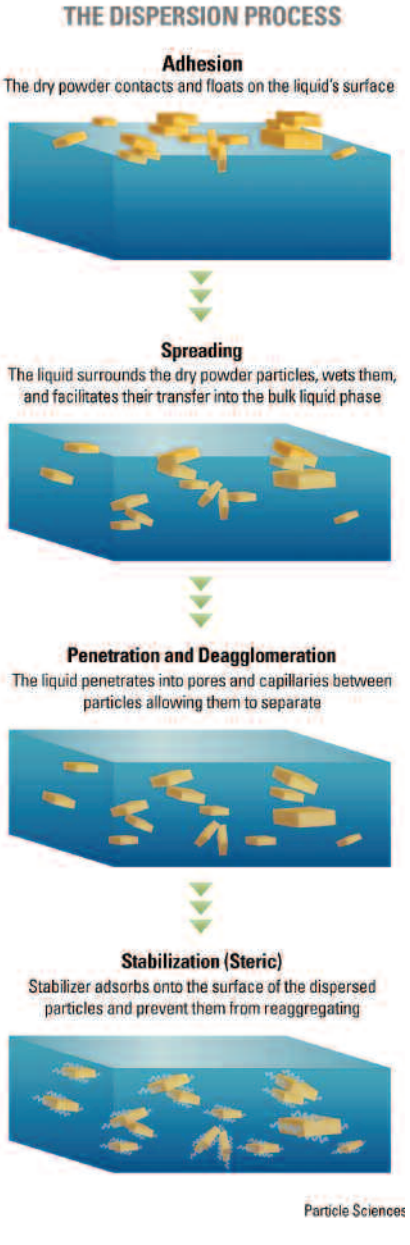
It is possible to pre-wet a surface without using a surfactant. Any liquid that has a contact angle lower than water will suffice. For example, mono- or poly-hydric alcohols (ethanol, propylene glycol) can be used. Liquid compounds

FIGURE 2



that have humectant properties (ie, glycerin) will also work and should be considered. The consequence of not achieving complete wetting is to affect the suspension properties, particularly the stability. It is equally important to realize that if a solid wets on its own (ie, it is lyophilic), then a wetting agent is not needed. Indeed, the use of one can in fact make the subsequent deagglomeration step more difficult.

FIGURE 3



The rate of penetration of liquid into the pores and capillaries between particles is an important factor. It is desirable that this be as large as possible. An indication of the major variables impacting penetration is expressed by the Washburn equation (Equation 3).[22]

Equation 3.

$$L^2 = (rt\,\gamma_{LV}/4\eta)$$

Where, L is the depth of penetration into a pore of radius (r) in a time (t) and (η) is the viscosity of the liquid. In general, the overall wetting process (adhesion, spreading, and penetration) is more spontaneous the lower the contact angle (θ) and the higher the liquid-vapor interfacial tension (γ_{LV}). Because any given surfactant affects both of these parameters, choosing the best agent for a given system is often a difficult process.

DEAGGLOMERATION

Deagglomeration is the process of separation of particles from each other once they are wetted. A deagglomerating agent adsorbs only at the solid-liquid interface. Such materials are not "surface-active." Their job is to chemically aid separation of the agglomerated particles by increasing the electrostatic forces of repulsion between the particles. This allows further liquid penetration into the interparticle spaces that, in turn, enhances the separation process. For easily wetted material, this enhanced penetration of liquid into the voids between the particles may provide sufficient force alone to bring about complete dispersion. More often than not, however, some mechanical energy is required. The choice of the correct deagglomerating agent requires consideration of both the particle's surface chemistry and the suspension medium conditions. For water as the fluid, for example, this would include pH and electrolyte concentration (see Particle Sciences' Technical Bulletin No. 2).

Again, the two processes (wetting and deagglomeration) are fundamentally different and need to be considered separately. So-called "dispersion aids" are often ambiguous as to their primary function and, consequently, are used interchangeably, often with deleterious results.

Following initial wetting of a powder (and sometimes deaeration), often termed the premix stage, some mechanical agitation is necessary. The degree of turbulence and shear vary considerably with the type of operation and design of equipment. Essentially, there are two types of processing methods: high-shear mills in which efficiency depends on the formulation viscosity and high-impact mills in which efficiency depends on the size of the grinding media. A detailed overview of processing methods for making emulsions and suspensions is provided in Particle Science's Technical Bulletin No. 9. If, however, the various steps previously outlined are followed, then the minimum of mechanical agitation will suffice. Excess mechanical energy also increases thermal energy, and together it can result in re-agglomeration, changes in the PSD, and consequently, the total available surface area. In addition, it is even possible to change the surface chemistry. All of the foregoing impinges on the specific properties of the suspension.

PARTICULATE SUSPENSIONS

STABILIZATION

Stabilization is the act of keeping the particles apart once they are wetted and deagglomerated. Importantly, stabilization is the last step. If completed too early, one just stabilizes agglomerates. Hence, the order of addition of ingredients is always of concern. Stabilization is usually accomplished via electrostatic forces (surface charge), steric forces (adsorbed layers), or a combination of the two (see Particle Sciences' Technical Bulletin No. 3). Steric stabilization is preferred when formulating suspensions in non-aqueous media.

"Thickeners" are often added to increase liquid viscosity. Although useful, this should not be viewed as a substitute for true stabilization. Increasing the viscosity simply reduces the settling rate(s) of larger and/or denser particles. In any event, thickeners should be added after the stabilization step.

As previously outlined, the dispersion process is really a series of ordered events, each dependent on the previous one. The performance of any system, including pharmaceutical preparations, is directly linked to this process. As alluded to earlier, proper dispersion can greatly enhance performance. As an example, the improved oral bioavailability of élan Drug Delivery's NanoCrystal Technology formulation approach is based on the increased surface area of the nano-milled APIs giving rise to increased dissolution rate of the NanoCrystal Colloidal Dispersions™.[14,15] However, it is necessary to keep these nanoparticles discrete in order to benefit from the enhanced surface area. This is accomplished by use of both steric and electrostatic stabilization. This technology has been commercially validated and is used in four marketed products (Wyeth's Rapamune®, Abbott's TriCor®, Merck's Emend®, and Par's Megace® ES).

Finally, wet suspensions can "age" on standing, or during storage, through a process known as Ostwald ripening (see Particle Sciences' Technical Bulletin No. 4). Ostwald ripening is an important mechanism for destabilizing all types of dispersions (suspensions, emulsions, and foams). For suspensions, a critical

FIGURE 4

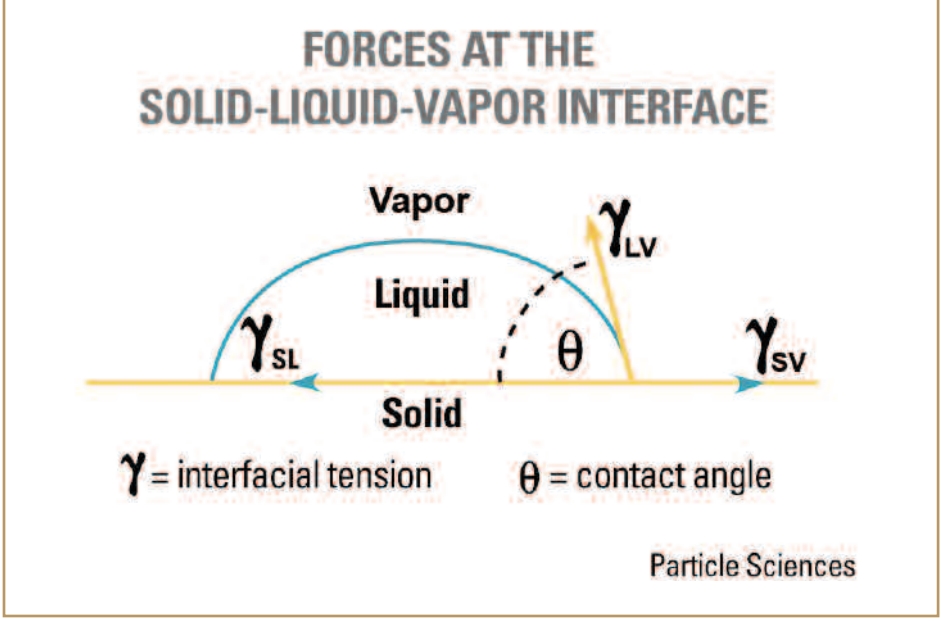
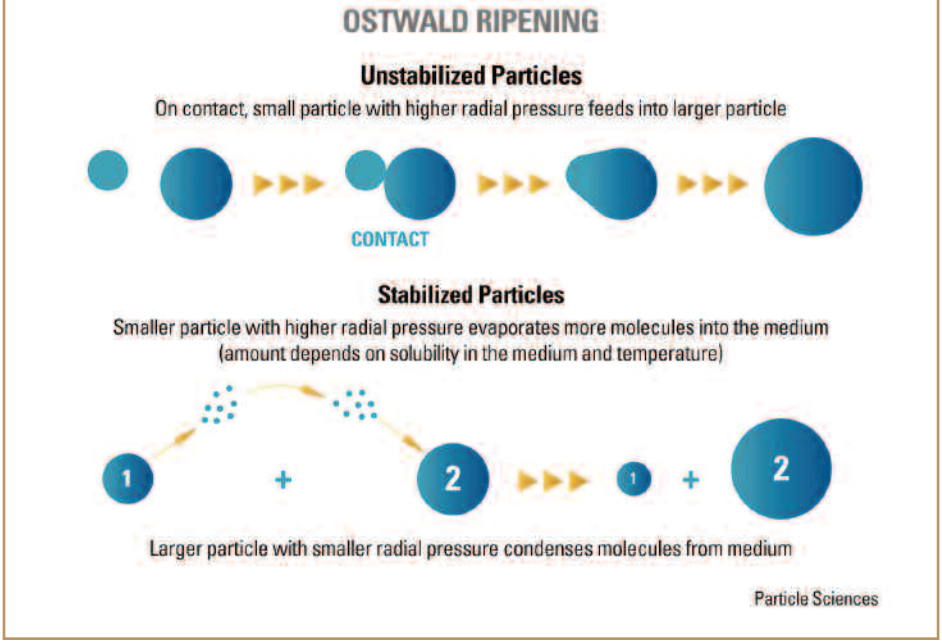


FIGURE 5



parameter that determines if Oswald ripening will occur is the solubility of the particular material in whatever liquid is chosen. Ostwald ripening only occurs for materials that are sparingly soluble; it does not occur if the material is either completely soluble (ie, salt, NaCl in water) or totally insoluble (ie, titanium dioxide, TiO_2 in water).

The consequence of Ostwald ripening of suspensions is that larger particles grow at the expense of the smaller ones.[23,24] This increase in size (Figure 5) can occur via two mechanisms. The first is that the small particles "dissolve" but because the solubility product is low, once sufficient material has dissolved and saturation is reached, any further dissolution results in nucleation followed by precipitation onto the larger particles. The second occurs at higher particle concentrations. In this case, the smaller particles simply aggregate directly onto the surface of the larger particles, which are, thermodynamically, the preferred route. Thus, Ostwald ripening is both solubility and concentration dependent; the rate of ripening obviously also depends on the viscosity of the suspending liquid.

SUMMARY

This article describes the steps involved in formulating particulate systems. Knowledge of this process coupled with an understanding of the physicochemical properties of the API is necessary to produce pharmaceutically acceptable particulate systems. The goal is to tailor the resulting formulations to target the required site of action and produce the desired physiological response, ie, getting the right amount of drug to the right place at the right time. Formulation parameters that can be explored include particle size, surface charge or zeta potential, and surface coating. At times, formulating APIs with low aqueous solubility is challenging, but there are contract research organizations available to assist in this effort.

REFERENCES

1. Slowson M, Slowson S. What to do when patients can't swallow their medications. Pharmacy Times. 1985;90-96.
2. Lindgren S, Janzon L. Prevalence of swallowing complaints and clinical findings among 50- to 79-year old men and women in an urban population. Dysphasia. 1991;6:187-192.
3. Doheny K. You really expect me to swallow those horse pills? Am Druggist. 1993;208:34-35.
4. Ali S, Quadir A. High molecular weight povidone polymer-based films for fast-dissolving drug delivery applications. Drug Deliv Technol. 2007;7(6):36-43.
5. Müller RH, Jacobs C, Kayser O. Nanosuspensions as particulate drug formulations in therapy: rationale for development and what we can expect for the future. Adv Drug Deliv Rev. 2001;23:47(1):3.
6. Patel D, Sawant KK. Oral bioavailability enhancement of acyclovir by self-microemulsifying drug delivery systems (SMEDDS). Drug Dev Ind Pharm. 2007;33(12):1318.
7. Attia IA, El-Gizawy SA, Fouda MA, Donia AM. Influence of a niosomal formulation on the oral bioavailability of acyclovir in rabbits. AAPS Pharm Sci Tech. 2007;14:8(4):E106.
8. Kesisoglou F, Panmai S, Wu Y. Nanosizing: oral formulation development and biopharmaceutical evaluation. Adv Drug Deliv Rev. 2007;59(7):631. Epub May 25, 2007.
9. Vyas TK, Shahiwala A, Amiji MM. Improved oral bioavailability and brain transport of Saquinavir upon administration in novel nanoemulsion formulations. Int J Pharm. 2008;347(1-2):93. Epub Jun 19, 2007.
10. Takagi T, Ramachandran C, Bermejo M, Yamashita S, Yu LX, Amidon GL. 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.
11. Kasim NA, Whitehouse M, Ramachandran C, Bermejo M, Lennernas H, Hussain AS, Junginger HE, Stavchansky SA, Midha KK, Shah VP, Amidon GL. Molecular properties of WHO essential drugs and provisional biopharmaceutical classification. Mol Pharm. 2004;12;1(1):85-96.
12. 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.
13. Lee RW, Shaw JM, McShane J, Wood RW, Shenoy DB. Particle size reduction in water-insoluble drug formulations. In: Liu R, ed. Water-Insoluble Drug Formulation. 2nd ed. Boca Raton, FL: CRC Press;2008;17:467.
14. Lee RW. Case study: development and scale-up of NanoCrystal® particles. In: Burgess DJ, ed. Injectable Dispersed Systems: Formulation, Processing and Performance. Vol. 149. New York, NY:Taylor & Francis;2005;149:355.
15. NanoCrystal® technology from élan Drug Technologies. Website: www.elan.com/EDT/nanocrystal_technology.
16. Insoluble Drug Delivery (IDD®) technology from SkyePharma. Website: www.skyepharma.com/solubilization_idd.html.
17. Biorise® technology from Eurand. Website: www.eurand.com/Technologies/Bioavailability-enhancement/Biorise.
18. NanoEdge® technology from Baxter BioPharma Solutions. Website: www.baxterbiopharmasolutions.com/content/formulation_tech/nanoedge.html.
19. Everett DH. Basic Principles of Colloid Science. London: RSC Publications;1988.
20. Fairhurst D, Mitchnick MA. Fundamentals of Particles in Liquid Dispersion: Lowe NJ, Shaath NA, Pathak MA. Sunscreens. 2nd ed. New York, NY: Marcel Dekker;1997.
21. Evans DF, Wennerström H. The Colloidal Domain. New York, NY: VCH Publishers;1994.
22. Washburn EW. The dynamics of capillary flow. Physical Rev. 1921;17:273.
23. Nancollas GH. The growth of crystals in solution. Adv Coll Interface Sci. 1979;10:215.
24. Higuchi WI, Misra J. Physical degradation of emulsions via the molecular diffusion route and the possible prevention thereof. J Pharm Sci. 1962;51(5):459.

BIOGRAPHIES

Dr. David Fairhurst is a Corporate Research Fellow at Particle Sciences Inc. He earned his PhD in Physical Chemistry in 1968 from Liverpool Polytechnic, UK, where he was also a Lecturer (in Physical Chemistry) for 4 years. Trained in the discipline of colloid and surface chemistry, Dr. Fairhurst has spent the past 40 years solving problems in industrial and pharmaceutical applications and has published more than 100 technical papers, scientific articles, and book chapters in the open literature. Prior to joining PSI in 1993, he was, for 7 years, Director of Applications at Brookhaven Instruments Corporation and is an internationally recognized authority on dispersion and emulsion technology and in the assessment and characterization of particle size.

Dr. Robert W. Lee is Vice President of Pharmaceutical Development at Particle Sciences Inc. His responsibilities include product development as well as supporting clinical manufacturing operations and business development. He earned his PhD in Physical Bioorganic Chemistry from the University of California, Santa Barbara. He has more than 17 years of experience in the pharmaceutical industry, including senior management positions at Novavax, Inc., Lyotropic Therapeutics, Inc., and Imcor Pharmaceutical Co. Prior to this, Dr. Lee held positions at élan Drug Delivery, NanoSystems, and Sterling Winthrop. Dr. Lee has published articles in numerous peer-reviewed journals and 3 book chapters, plus holds 11 issued patents and 14 provisional or PCT patent applications.

THE NUMBERS ARE OUT. WILL YOU BE READY TO RESPOND?

Announcing publication of the first in the Parameters of Performance Series from Bionumbers: Drug Delivery 2008 - Product Success Rates and Development/Approval Times.

Drug Delivery 2008 - Product Success Rates and Development/Approval Times for the first time quantifies drug delivery product success rates and development times. The results will surprise you.

Based on an in-depth analysis of more than 430 clinical stage drug delivery product candidates, Bionumbers provides critical insight into development and approval times for drug delivery products along with their success rates. More than an estimation of times and rates, the report analyzes product performance in terms of multiple variables including therapeutic area and delivery mode that yield insights into how they influence approval performance.

These numbers will reshape how everyone looks at the drug delivery business.
Will you be ready to take advantage?

Bionumbers™
Critical numbers. Remarkable insight.

The report is available at www.bionumbers.com.

NANOTECHNOLOGY

Cancer Nanotechnology: Small, but Heading for the Big Time

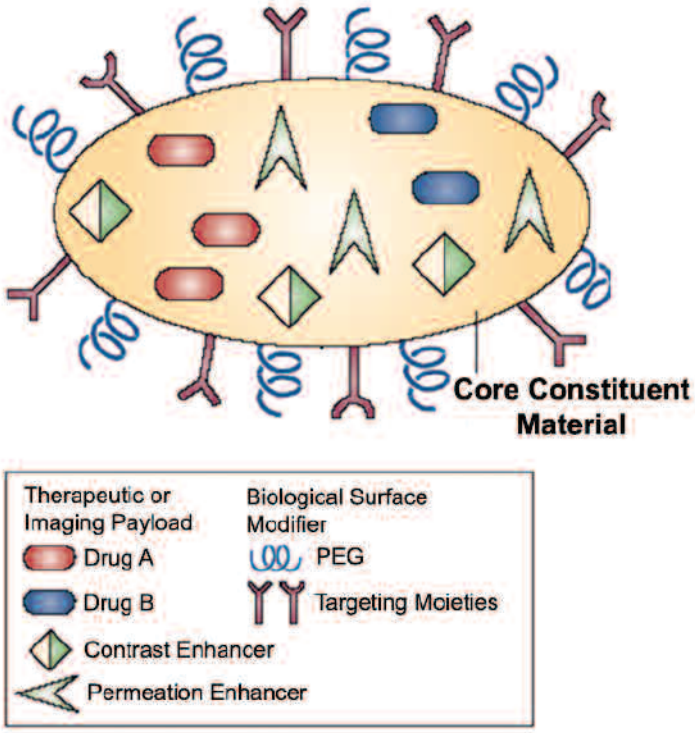
By: G.M. Patel (PhD student) and M.M. Patel, PhD

ABSTRACT

Cancer is the leading cause of death, and this fact accentuates the need for a new generation of more effective therapies for cancer. Recent research in nanotechnology has developed new ideas that could lead to the future cure for cancer. Radiation therapy and chemotherapy are the usual treatments for cancer, but each causes problems for the body. Radiation damages the skin, mouth, throat, and bowel cells. Chemotherapy can produce hearing loss and damage to a number of organs, including the heart and kidneys. It is hoped that nanotechnology can reduce the side effects produced by the present treatment for cancer.

Nanotechnology has considerable promise for the detection, staging, and treatment of cancer. This discussion outlines one such promising application: the use of nanostructures for cancer therapy. There has been tremendous investment in this area and an explosion of research and development efforts in recent years, particularly in the area of cancer research.

FIGURE 1



Multifunctional Nanoparticle

WHAT IS CANCER NANOTECHNOLOGY?

Nanotechnology is a broad term covering the building of structures and "machines" on an atomic or molecular scale in the range from 1 to 100 nanometers. A nanometer is one billionth of a meter or about the size of 10 hydrogen atoms. The techniques range from various chemical and biological processes used to "construct" structures (in some cases atom by atom) to the etching methods used to produce computer chips. The emerging field of nanotechnology involves scientists from many different disciplines, including physicists, chemists, engineers, and biologists. In the past 5 years, the applications of nanotechnology have been realized in clinical laboratory analysis, imaging, and therapeutics.[1-8]

Cancer-related examples of nanotechnologies include injectable drug delivery of nanovectors (such as liposomes for the therapy of breast cancer); biologically targeted, nanosized magnetic resonance imaging (MRI) contrast agents for intraoperative imaging in the context of neuro-oncological interventions; and novel, nanoparticle-based methods for high-specificity detection of DNA and protein.[9-12] In his definition of nanotechnology, George Whitesides places less stringent limitations on the exact dimensions, and defines the "right" size in bionanotechnology in an operational fashion, with respect to addressable unmet needs in biology.[13]

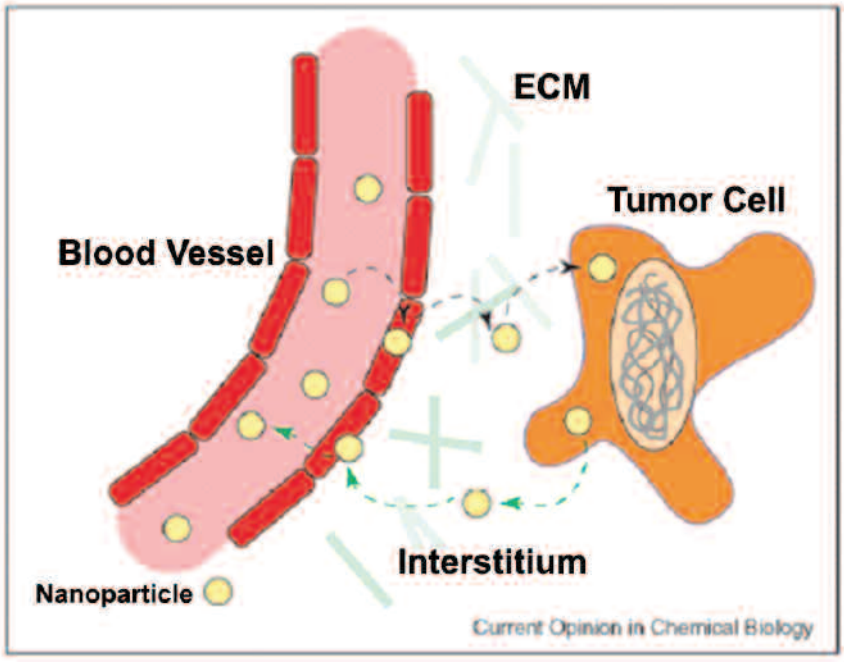
Nanotechnology is being applied to cancer in two broad areas: the development of nanovectors (such as nanoparticles that can be loaded with drugs or imaging agents and then targeted to tumors) and high throughput nanosensor devices for detecting the biological signatures of cancer. Combining such technologies could lead to earlier diagnosis and better treatment for patients with cancer.[14]

The "war on cancer" is now in its fourth decade since the National Cancer Act was passed in 1971. Although much progress has been made in cataloging the environmental causes and cellular and molecular biological basis for this dreaded disease, we still do not have a precise understanding of the differences between a cancer cell and its normal counterpart. If we do not understand cancer, we cannot control, conquer, and eliminate it. The completion of the human genome sequence in 2001 and subsequent improvements in the sequence data are important steps toward our goal to fully comprehend cancer cell biology.[15-17] We are now closer to being able to fully characterize the differences between normal and tumor cells. Coupled with the use of microdissection techniques,

it is also possible to interrogate the genetic make-up of individual cell types.[18] The hope is that use of such technologies will accelerate the progress in identifying the differences between normal and tumor cells, which in turn, will lead to development of new therapies that will specifically target the cancer. The ultimate goal of these strategies is to eliminate the tumor with limited effect on normal tissue.

Perhaps the greatest immediate impact of nanotechnologies in cancer therapy will be in the realm of drug delivery. The therapeutic index of nearly all drugs currently being used would be improved if they were more efficiently delivered to their biological targets through appropriate application of nanotechnologies.[19,20] Some drugs that have previously failed clinical trials might also be reexamined using nanotechnological approaches. A number of obstacles may be overcome with various novel applications of nano drug delivery.

FIGURE 2



Nanoparticle Distribution in Tissue.[75]

AN IMPORTANT TOOL FOR CANCER RESEARCH?

The following are several reasons nanotechnology could help transform cancer research and the clinical approaches to cancer care:

- Most biological processes, including those processes leading to cancer, occur at the nanoscale. For cancer researchers, the ability of nanoscale devices to easily access the interior of a living cell affords the opportunity for unprecedented gains on both clinical and basic research frontiers.
- The ability to simultaneously interact with multiple critical proteins and nucleic acids at the molecular level will provide a better understanding of the complex regulatory and signaling patterns that govern the behavior of cells in their normal state as well as the transformation into malignant cells.
- Nanotechnology provides a platform for integrating research in proteomics with other scientific investigations into the molecular nature of cancer.

Nanotechnology offers the unprecedented and paradigm-changing opportunity to study and interact with normal and cancer cells in real time, at the molecular and cellular scales, and during the earliest stages of the cancer process. Through the concerted development of nanoscale devices or devices with nanoscale materials and components, the NCI Alliance for Nanotechnology in Cancer will facilitate their integration within the existing cancer research infrastructure.[21] The Alliance will bring enabling technologies for the following:

- Imaging agents and diagnostics that will allow clinicians to detect cancer in its earliest stages.
- Systems that will provide real-time assessments of therapeutic and surgical efficacy for accelerating clinical translation.
- Multifunctional, targeted devices capable of bypassing biological barriers to deliver multiple therapeutic agents directly to cancer cells and those tissues in the microenvironment that play a critical role in the growth and metastasis of cancer.
- Agents that can monitor predictive molecular changes and prevent precancerous cells from becoming malignant.
- Novel methods to manage the symptoms of cancer that adversely impact quality of life.
- Research tools that will enable rapid identification of new targets for clinical development and predict drug resistance.

ASSOCIATED CHALLENGES[22-25]

Today, much of the science on the nanoscale level is basic research, designed to reach a better understanding of how matter behaves on this small scale. Matter behaves differently on the nanoscale than it does at larger levels. The factors that govern larger systems do not necessarily apply on the nanoscale. Because nanomaterials have large surface areas relative to their volumes, phenomena like friction and sticking are more important than they are in larger systems.

TABLE 1

Application (In Vitro Diagnostic)	Nanostructure	Reference No.
Nanocrystal		
CdS, CuS, PbS	Single nucleotide polymorphism	[26]
Fluorescein diacetate	IgG	[27]
Nanoparticle		
EuIII-chelate-doped polystyrene	PSA	[28]
Au	Prion protein	[29]
2-methacryloyloxyethyl phosphorylcholine	C-reactive protein	[30]
Polystyrene	Single-base mutation	[31]
Silica	Calf thymus DNA	[32]
Nanopore		
Silicon nitride	DNA sequencing	[33]
Nanoprism		
Ag		[34]
Au		[35]
Nanorod		
Au/Ag/Ni/Pd/Pt	IgG	[36]
Carbon Nanotube	DNA	[37]
Nanowire		
Si	Influenza A	[38]
Au	E. coli	[39]
Polypyrrole	DNA	[40]
Liposome		
Gadolinium	MRI imaging	[41,42]
Dual-fluorescence or iron oxide	Optical & MRI imaging	[43]
Dendrimer	MRI imaging	[44,45]
Nanoparticle	MRI imaging	[46]
Quantum Dots	Near-infrared imaging	[47,48,49]
Nanoshell	Optical detection	[50]
Nanotube	MRI imaging	[51]

Nanostructure materials and their applications.

These factors will affect use inside and outside the body.

One of the key challenges in creating effective nanoparticles is targeting them to appropriate cells and tissue. Although biological targeting using aptamers or antibodies on the surface of nanoparticles is one popular option, other researches are beginning to exploit the physical characteristics of the particles to guide them to the desire location. The size, shape, physical properties, density, and charge all affect how particles travel through the body and whether they will cross biological membranes.

Other challenges apply specifically to the use of nanostructures within biological systems. Nanostructures can be so small that the body may clear them too rapidly to be effective in detection or imaging. Larger nanoparticles may accumulate in vital organs, creating a toxicity problem. Scientists will need to consider these factors as they anticipate how nanostructures will behave in the human body and attempt to create devices the body will accept.

"The future of oncology — and the opportunity to eliminate the suffering and death due to cancer — will hinge upon our ability to confront cancer at its molecular level," said Andrew von Eschenbach, MD, Director of the National Cancer Institute. "Nanodevices, invisible to the naked eye and a tiny fraction the width of a human hair, will enable researchers to probe genetic defects inside cells, detect the earliest aberrations of cellular function that lead to cancer, and correct those errant processes long before they give rise to cancers large enough to be diagnosed by today's methods."

PLATFORMS FOR CANCER THERAPEUTICS

Nanostructured materials/nanodevices may be defined as those materials whose structural elements like clusters, crystallites, or molecules have dimensions in the 1- to 100-nanometer range. The initial medical applications, using nanostructured materials, are already being tested in a wide variety of potential diagnostic and therapeutic areas and are discussed further.

There are two basic approaches for creating nanodevices. Scientists refer to these methods as the top-down approach and the bottom-up approach. The top-down approach involves molding or etching materials into smaller components. This approach has traditionally been used in making parts for computers and electronics. The bottom-up approach involves assembling structures atom-by-atom or molecule-by-molecule and may prove useful in manufacturing devices used in medicine. Some of the many types of nanostructures that have been used as components of in vitro diagnostic tests for protein markers or nucleic acid targets are presented in Table 1.[26-51]

Liposomes

Liposomes are vesicles made up of a lipid bilayer, resembling tiny cells with a cell membrane but nothing in the core. Research on using liposomes to encapsulate and deliver chemotherapeutics has been performed since the late 1970s, and in the early 1990s, they were extensively studied as potential vectors for gene therapy. At the time, they were not referred to as nanoparticles, but liposome research has gained considerable renewed momentum in association with the nanotechnology movement. Liposomes do not constitute novel nanotechnology, and their sizes (ranging from 90 to 150 nanometers) are slightly bigger than what would qualify as nanotechnology, according to the conventional definition (ie, having a dimension of < 100 nanometers), but a significant portion of what is considered nanotechnology research in biomedicine today is represented by liposome research.

Mills and Needham have constructed temperature-sensitive liposomes that can release the drug contents in tens of seconds at

clinically attainable hyperthermia (39°C to 42°C).[52] Administration of these liposomes loaded with doxorubicin, in combination with local hyperthermia, resulted in complete regressions of human tumor xenografts in all of the mice studied.[53]

Nanoparticles

Nanoparticles can be engineered to target cancer cells (Figure 1) for use in the molecular imaging of a malignant lesion.[1,54] Large numbers of nanoparticles are safely entered in to the body and preferentially bind to the cancer cell, finding the anatomical counter of the lesion and making it visible. These nanoparticles provide the ability to see cells and molecules that otherwise cannot be detected through conventional imaging. Tagged nanoparticles are particles that can track biological events by simultaneously tagging each biological component and become a new class of bioprobes for many biological applications.

Nanoparticles coupled with cancer-specific targeting ligands can be used to image tumors and detect peripheral metastases.[55] Super magnetic nanoparticles that have a metal core and are bioconjugated with antibodies against ERBB2 have shown promising results for simultaneous imaging and targeting of breast cancers therapeutically in vivo.[56] Moreover, nanoparticles conjugated to cancer-specific ligands could be used in early identification of tumors, allowing for early intervention with a chemo-preventive agent.

A long-term goal of research into nanoparticle-based biomarker harvesting is the administration of in vivo harvesting nanoparticles.[57] These particles would have access to numerous tissue microenvironments in the host, thereby enabling a thorough sampling of the proteins being expressed, and providing an overall portrait of the patient's health (Figure 2). In this system, the particles would be periodically harvested from the vascular compartment for analysis. Issues for study as this approach is developed include the tissue distribution of particles, the likelihood of retrieving the particles from the patient's blood, and the potential toxicity profiles of the particles.

Quantum Dots

Quantum dots nanocrystals are nanoscale crystals of semiconductors that behave as single super atoms.[58] They are capable of confiring a single electron (or a few) and in which the electrons occupy discrete energy states just as they would in an atom (quantum dots have been called artificial atoms).

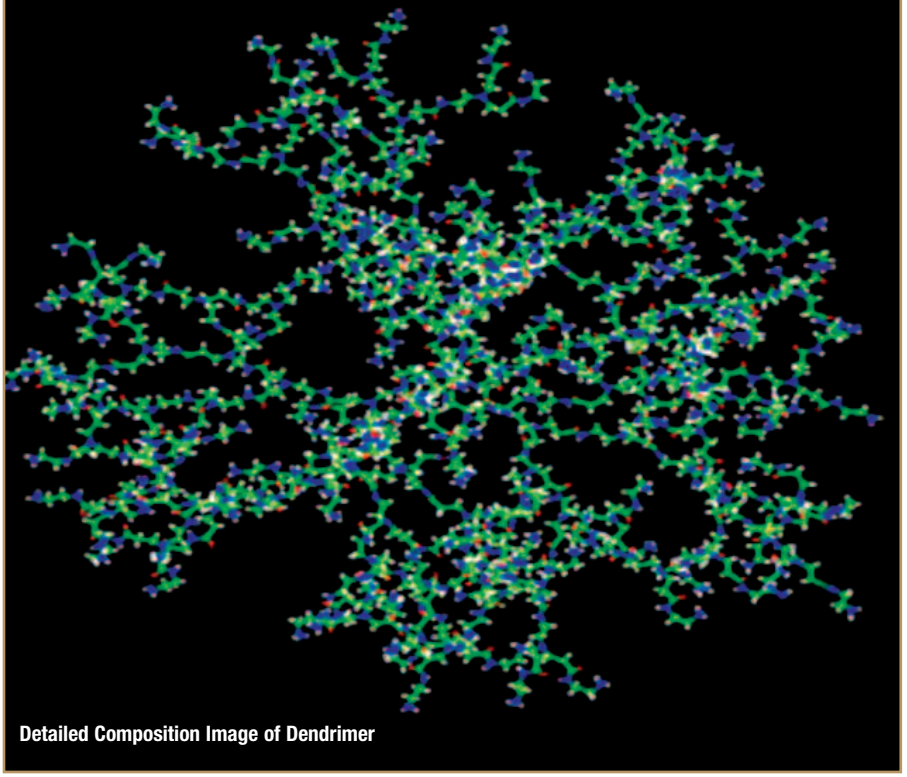
Quantum dots nanocrystals would be used to tag biological molecules and would have applications in medical diagnostics, targeted therapeutics, and high-throughput drug screening.[59] They will allow, for the first time, direct imaging of small numbers of dying cells in degenerative eye diseases and reduce the time frame for testing ocular drugs from 10 years to less than 1. They will also greatly enhance imaging during surgical removal of lymph nodes associated with cancerous tumors, thereby improving the prognosis for cancer patients and saving lives while simultaneously reducing the cost and training required for the procedures.

Dendrimers

Dendrimers are precisely defined chemical structures.[60] The name dendrimer is derived from the ancient Greek word dendron, which means tree, and from the Greek suffix mer, which means segment. Dendrimers are man-made molecules having treelike structures (Figure 3).[61] They are prepared generation by generation in a series of controlled steps that increases the number of small branching molecules around a central core molecule. Dendrimers measure between 2 and 20 nanometers across and are branching molecules with the branching beginning at the core. The core generally consists of an amine core, but sugars and other molecules can be used as well. All core molecules share the characteristic of having multiple reaction sites that are identical. The core is mixed with an excess of the first monomer molecule, which reacts with all of the core's reaction sites, giving rise to the first branches. This monomer molecule has two distinct reactive groups, one at each end. After one kind of end reacts, the other end will provide reaction sites for the next layer of the shell.

Dendrimers are ideal building blocks for creating biologically active nanomaterials

FIGURE 3



Detailed Composition Image of Dendrimer

because of their consistency of structure. The Center for Biologic Nanotechnology has been running tests of functioning biologic nanodevices based on dendrimers, especially one called an anticancer therapeutic nanodevice. These tests have been conducted in vitro on living cells and confirm that this nanodevice will work as a therapeutic agent. It will perform cancer cell recognition, diagnosis of cancer causes, drug delivery, reporting drug levels in tumors, and reporting cancer cell death.[62]

Nanoshells

Nanoshells have a core of silica and a metallic outer layer. These nanoshells can be linked to antibodies that can recognize tumor cells (PSMA).[64] When cancer cells take them up, by applying a near infrared light that is absorbed by the nanoshells, it is possible to create intense heat that selectively kills the tumor cells and not the neighboring healthy cells.

Their primary application is in thermal ablation therapy by exploiting their ability to absorb light. Meanwhile, their ability to scatter light has potential for cancer imaging. The most useful nanoshells are those that have a silica core diameter of ~120 nanometers with a 10-nanometer layer of gold shell because these strongly absorb NIR light (~800 nanometers) and can create intense heat that is lethal to cells. This NIR light can penetrate several centimeters of human tissue without causing harm because tissue chromophores do not absorb much energy in the NIR range.[63]

Nanocantilevers

Nanocantilevers are flexible beams resembling a row of diving boards that can be coated with molecules capable of binding to cancer biomarkers.

Nanowires

Nanowires are nanoscale-sensing wires that can be coated with molecules, such as antibodies to bind to proteins of interest and transmit their information through electrodes to computers. Arrays of Si nanowires have been used to detect ultralow traces of multiple cancer markers in clinical samples. The nanowire sensor array consists of up to 200 individual, electrically addressed Si nanowires devices. Monoclonal antibodies that bind distinct protein markers of cancer are attached to the surface of different nanowires. When a charged protein binds to its antibody receptor, it acts like a gate electrode in a transistor and alters the conductance of the nanowire. Nanowires were modified with antibodies for prostrate-specific antigen (PSA), carcinoembryonic antigen (CEA), and mucin-1 (MUC). Introducing solutions of the proteins resulted in conductance changes only at the nanowires with the corresponding antibody. This multiplexed detection of different cancer markers is achieved with sensitivity to concentrations at the 50- to 100-fg/ml levels and with complete selectivity.[64]

Fullerene-Based Pharmaceuticals

Soluble derivatives of fullerenes, such as C60 (a soccer ball-shaped arrangement of 60 carbon atoms per molecule), show great promise as pharmaceutical agents. These derivatives, many already in clinical trials, have good biocompatibility and low toxicity even at relatively high dosages. Fullerene compounds may serve as antiviral agents (most notably against HIV), antibacterial agents (Escherichia coli, Streptococcus pneumoniae, Mycobacterium tuberculosis), photodynamic anti-tumors and anticancer therapies, antioxidants and antiapoptosis agents (as treatments for amyotrophic lateral sclerosis and Parkinson's disease), and other applications, most being pursued by C60, the leading company in this area.[65-69]

Carbon Nanotubes

Carbon nanotubes (CNTs) are a distinct molecular form of carbon atoms that were discovered in the late 1980s. In the area of cancer therapeutics, carbon nanotubes have primarily been used for transporting DNA cargoes into the cell and for thermal ablation therapy. Carbon nanotubes consist exclusively of carbon atoms arranged in a series of condensed benzene rings rolled-up into a tubular structure. This novel non-material belongs to the family of fullerenes, the third allotropic form of carbon along with graphite and diamond. Carbon nanotubes can be classified into two general categories based on their structure: single-walled (SWNTs), which consist of one layer of cylinder grapheme, and multi-walled (MWNTs), which contain several concentric graphene sheets. Carbon nanotubes have nanometric dimensions: SWNTs have diameters from 0.4 to 2.0 nanometers and lengths in the range of 20 to 1000 nanometers, while MWNTs are bigger objects with diameters in the range of 1.4 to 100 nanometers and lengths from 1 to several micrometers.[70]

Recently, Zhang et al have demonstrated that CNTs carrying short (or small) interfering RNA (siRNA) can rapidly enter tumor cells, then release the siRNA to exert RNA interference on target gene expression.[71]

Microbivores

Nanorobotic phagocytes (artificial white cells) called microbivores could patrol the bloodstream, seeking out and digesting unwanted pathogens, including bacteria, viruses, or fungi.[72] Microbivores, each 2 to 3 micrometers, would be up to ~1000 times faster-acting than unaided natural or antibiotic-assisted biological phagocytic defenses. Related nanorobots could be programmed to recognize and dissolve cancer cells or to clear circulatory obstructions in a time on the order of minutes, thus quickly rescuing the stroke patient from ischemic damage.[73]

Nanorobot-Cancer Killers

Cancer killers, these nanorobots will be applied in chemotherapy to combat cancer through precise chemical dosage administration. These killer cells identify, target, and finally destroy cancer cells.[74]

SUMMARY

There has been a sharp growth in the pace of discovery and development of targeted nanostructures throughout the past few years. Current preclinical and clinical data support the hypothesis that targeted nanostructures can provide the means to deliver drugs at a prolonged rate to specific cancer targets. When optimized, these targeted nanoplatforms will provide the improved treatment options that are so urgently sought for cancer.

REFERENCES

1. Ferrari M. Cancer nanotechnology: opportunities and challenges. Nat Rev Cancer. 2005;5:161-171.
2. Couvreur P, Vauthier C. Nanotechnology: intelligent design to treat complex disease. Pharm Res. 2006;23:1417-1450.
3. Cuenca AG. Emerging implications of nanotechnology on cancer diagnostics and therapeutics. Cancer. 2006;107:459-466.
4. Farokhzad OC, Langer R. Nanomedicine: developing smarter therapeutic and diagnostic modalities. Adv Drug Deliv Rev. 2006;58:1456-1459.

5. Grodzinski P. Nanotechnology for cancer diagnostics: promises and challenges. Expert Rev Mol Diagn. 2006;6:307-318.
6. Qiang Y. Iron/iron oxide core-shell nanoclusters for biomedical applications. J Nanoparticle Res. 2006;8:489-496.
7. Sinha R. Nanotechnology in cancer therapeutics: bioconjugated nanoparticles for drug delivery. Mol Cancer Ther. 2006;5:1909-1917.
8. Yih TC. Engineered nanoparticles as precise drug delivery systems. J Cell Biochem. 2006;97:1184-1190.
9. Park JW. Liposome-based drug delivery in breast cancer treatment. Breast Cancer Res. 2002;4:95-99.
10. Kircher MF, Mahmood U, King RS, Weissleder R, Josephson L. A multimodal nanoparticle for preoperative magnetic resonance imaging and intraoperative optical brain tumor delineation. Cancer Res. 2003;63:8122-8125.
11. Neuwalt EA. Imaging of iron oxide nanoparticles with MR and light microscopy in patients with malignant brain tumors. Neuropathol Appl Neurobiol. 2004;5:456-471.
12. Nam JM, Mirkin CA. Bio-barcode-based DNA detection with PCR-like sensitivity. J Am Chem Soc. 2004;126:5932-5933.
13. Whitesides GM. The right size in nanotechnology. Nature Biotechnol. 2003;21:1161-1165.
14. News and analysis. Nature Reviews. 2007;6(3):174.
15. International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. Nature. 2001;409:860-921.
16. Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG. The sequence of the human genome. Science. 2001;291:1304-1351.
17. International Human Genome Sequencing Consortium. Finishing the euchromatic sequence of the human genome. Nature. 2004;431:931-945.
18. Player A, Barrett JC, Kawasaki ES. Laser capture microdissection, microarrays and the precise definition of a cancer cell. Expert Rev Mol Diagn. 2004;4:831-840.
19. Sahoo SK, Labhasetwar V. Nanotech approaches to drug delivery and imaging. Drug Discov Today. 2003;8:1112-1120.
20. Vasir JK, Reddy MK, Labhasetwar V. Nanosystems in drug targeting: opportunities and challenges. Curr Nanosci. 2005;1:47-64.
21. NCI Alliance for Nanotechnology in Cancer. National Cancer Institute. Website: www.cancer.gov.
22. A Workshop on Nanotechnology: Opportunities and Challenges. Workshop attended on September 10, 2001. University of California, Los Angeles.
23. X-Gu F, Karnik R, Andrew Z, Wang FA, Etgar L-N, Hong S, Langer RS, Farokhzad OC. Targeted nanoparticles for cancer therapy. Nano Today. 2007;2(3):14-21.
24. Kelly Y, Kim MA. Nanotechnology platforms and physiological challenges for cancer therapeutics. Nanomedicine: Nanotechnology, Biology, & Medicine. 2007;3(2):103-110.
25. NIH news for immediate release. U.S. Department of Health and Human Services. October 17, 2005.
26. Liu G, Lee TMH, Wang J. Nanocrystal-based bioelectronic coding of singlenucleotide polymorphisms. J Am Chem Soc. 2005;127:38-39.
27. Chan CP, Bruemmel Y, Seydack M, Sin K-K, et al. Nanocrystal biolabels with releasable fluorophores for immunoassays. Anal Chem. 2004;76:3638-3645.
28. Huhtinen P. Immunoassay of total prostate-specific antigen using europium (III) nanoparticle labels and streptavidin-biotin technology. J Immunol Methods. 2004;294:111-122.
29. Henry J. Development of a nanoparticle-based surface modified fluorescence assay for the detection of prion proteins. Anal Biochem. 2004;334:1-8.
30. Park J. Evaluation of 2-methacryloyloxyethyl phosphorylcholine polymeric nanoparticle for immunoassay of C-reactive protein detection. Anal Chem. 2004;76:2649-2655.
31. Sato K. Single-base mutation detection using neutravidin-modified polystyrene nanoparticle aggregation. Anal Sci. 2004;20:893-894.
32. Zhang D. Silica-nanoparticle-based interface for the enhanced immobilization and sequence-specific detection of DNA. Anal Bioanal Chem. 2004;379:1025-1030.
33. Li J. DNA molecules and configurations in a solid-state nanopore microscope. Nat Mater. 2003;2:611-615.
34. Jin R. Photo induced conversion of silver nanospheres to nanoprisms. Science. 2001;294:1901-1903.
35. Hao E. Synthesis and optical properties of anisotropic metal nanoparticles. J Fluoresc. 2004;14:331-341.
36. Nicewarner-Pena SR. Sub-micrometer metallic barcodes. Science. 2001;294:137-141.
37. Wang J. Ultrasensitive electrical biosensing of proteins and DNA: carbon-nanotube-derived amplification of the recognition and transduction events. J Am Chem Soc. 2004;126:3010-3011.
38. Patolsky F. Electrical detection of single viruses. Proc Natl Acad Sci USA. 2004;101:14017-14022.
39. Basu M. Nano-biosensor development for bacterial detection during human kidney infection: use of glyco conjugate specific antibody-bound gold nanowire arrays (GNWA). Glycoconj J. 2004;21:487-496.
40. Ramanathan K. Bioaffinity sensing using biologically functionalized conducting polymer nanowire. J Am Chem Soc. 2005;127:496-497.
41. Parac-Vogt TN. Paramagnetic liposomes containing amphiphilic bisamide derivatives of Gd-DTPA with aromatic side chain groups as possible contrast agents for magnetic resonance imaging. Eur Biophys J. 2005;11:1-9.
42. Saito R. Gadolinium-loaded liposomes allow for real-time magnetic resonance imaging of convection-enhanced delivery in the primate brain. Exp Neurol. 2005;196:381-389.
43. Mulder WJ. MR molecular imaging and fluorescence microscopy for identification of activated tumor endothelium using a bimodal lipidic nanoparticle. FASEB J. 2005;19:2008-2010.
44. Kobayashi H. Detection of lymph node involvement in hematologic malignancies using micromagnetic resonance lymphangiography with a gadolinum-labeled dendrimer nanoparticle. Neoplasia. 2005;7:984-991.
45. Kobayashi H. Lymphatic drainage imaging of breast cancer in mice by micro-magnetic resonance lymphangiography using a nano-size paramagnetic contrast agent. J Natl Cancer Inst. 2004;96:703-708.
46. Harisinghani MG. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. N Eng J Med. 2003;348:2491-2499.
47. Weissleder R. Cell-specific targeting of nanoparticles by multivalent attachment of small molecules. Nat Biotechnol. 2005;23:1418-1423.
48. Weissleder R. In vivo imaging of tumors with protease activated near-infrared fluorescent probes. Nat Biotechnol. 1999;17:375-378.
49. Parungo CP. Intraoperative identification of esophageal sentinel lymph nodes with near-infrared fluorescence imaging. J Thorac Cardiovasc Surg. 2005;129:844-850.
50. Loo C. Gold nanoshell bioconjugates for molecular imaging in living cells. Opt Lett. 2005;1:1012-1014.
51. Sitharaman B. Superparamagnetic gadonanotubes are high-performance MRI contrast agents. Chem Commun. 2005;21:3915-3917.
52. Mills JK, Needham D. The materials engineering of temperature sensitive liposomes. Methods Enzymol. 2004;387:82-113.
53. Needham D, Anyarambhatla G, Kong G, Dewhirst MW. A new temperature-sensitive liposome for use with mild hyperthermia: characterization and testing in a human tumor xenograft model. Cancer Res. 2000;60(5):1197-1201.
54. Kumar SS, Babu PS. Nanotechnology: a new approach in cancer therapy. Pharma Times. 2006;39(4):17-20.
55. Gao X, Cui Y, Levenson RM. In vivo cancer targeting and imaging with semiconductor quantum dots. Nat Biotechnol. 2004;22:969-976.
56. Artemov D, Mori N, Okollie B. MR molecular imaging of the Her-2/neu receptor in breast cancer cells using targeted iron oxide nanoparticles. Magn Reson Med. 2003;49:403-408.
57. Bruchez M Jr, Moronne M, Gin P, Weiss S, Alivisatos AP. Semiconductor nanocrystals as fluorescent biological labels. Science. 1998;281:2013-2016.
58. Buhro WE, Colvin VL. Semiconductor nanocrystales: shape matters. Nat Mater. 2003;2:138-139.
59. Michalet X, Pinaud FF, Bentolila LA, Tsay JM, Doose S, Li JJ, et al. Quantum dots for live cells, in vivo imaging, and diagnostics. Science. 2005;307:538-544.
60. Cagin T, Wang G, Martin R, Goddard III WA. Molecular Modeling Of Dendrimers for Nanoscale Applications, California Institute of Technology, Materials and Process Simulation Center and Division of Chemistry and Chemical Engineering, Pasadena.
61. Newkome GR, Yao ZQ, Baker GR, Gupta VK. Molecules: a new approach to micelles, A[27]-arborol. J Org Chem. 1985;50:2003-2006.
62. Klajnert B, Bryszewska M. Dendrimers: properties and applications. Acta Biochimica Polinica. 2001;48(1):199-208.
63. Konig K. Multiphoton microscopy in life sciences. J Microsc. 2000;200(part 2):83-104.
64. Wood J. Nanowires detect trace levels of cancer markers. Materials Today. 2005;8(11):20.
65. Schinazi RF, Sijbesma R, Srdanov G. Synthesis and virucidal activity of a water-soluble, configurationally stable, derivatized C60 fullerene. Antimicrob Agents Chemother. 1993;37:1707-1710.
66. Tsao N, Kanakamma PP, Luh TY. Inhibition of Escherichia coli-induced meningitis by carboxyfullerence. Antimicrob Agents Chemother. 1999;43:2273-2277.
67. Tsao N, Luh TY, Chou CK. Inhibition of group A Streptococcus infection by carboxyfullerene. Antimicrob Agents Chemother. 2001;45:1788-1793.
68. Bosi S, Da Ros T, Castellano S. Antimycobacterial activity of ionic fullerene derivatives. Bioorg Med Chem Lett. 2000;10:1043-1045.
69. Tabata Y, Murakami Y, Ikada Y. Photodynamic effect of polyethylene glycol-modified fullerene on tumor. Japan J Cancer Res. 1997;88:1108-1116.
70. Lacerda L, Bianco A, Prato M, Kostarelos K. Carbon nanotubes as nanomedicines: from toxicology to pharmacology. Adv Drug Del Rev. 2006;58:1460-1470.
71. Zhang Z, Yang X, Zhang Y, Zeng B, Wang S, Zhu T. Delivery of telomerase reverse transcriptase small interfering RNA in complex with positively charged single-walled carbon nanotubes suppresses tumor growth. Clin Cancer Res. 2006;12(16):4933-4939.
72. Freitas RA Jr. Microbivores: artificial mechanical phagocytes using digest and discharge protocol. Evol Technol. 2005;14:1-52.
73. Freitas RA Jr. Microbivores: artificial mechanical phagocytes. Research Scientist for Zyvex Corp.
74. Patel GM, Patel GC, Patel RB, Patel JK, Patel MM. Nanorobot: a versatile tool in nanomedicine. J Drug Targeting. 2006;14(2):63-67.
75. Geho DH, Jones CD, Petricoin EF, Liotta LA. Nanoparticles: potential biomarker harvesters. Curr Opinion Chem Biol. 2006;10:56-61.

BIOGRAPHIES

Geeta M. Patel is presently working as a Lecturer in the Department of Pharmaceutics and Pharmaceutical Technology at the S.K. Patel College of Pharmaceutical Education and Research, Kherva, Ganpat University, Mehsana, India. The focus of her post-graduation research has been on floating drug delivery systems. With 13 publications in various respected journals to her credit, she is currently pursuing her PhD in novel drug delivery systems.

Dr. Madhabhai Patel is currently the Principal of the Kalol Institute of Pharmacy, Kalol, India. He earned his PhD in Pharmaceutics and Pharmaceutical Technology. Dr. Patel has 25 years of academic and research experience. He has 40 national and intentional research papers to his credit. He is an approved PhD guide at Hemchandrachayra North Gujarat University, Patan and Ganpat University, Kherva, India.

DRUG DELIVERY Executive

Cirrus Pharmaceuticals, Inc.
Strategic Product Development

Anthony Hickey, PhD
CEO & President
Cirrus Pharmaceuticals

"Every new formulation raises unique questions that require a clear, efficient, and cost-effective approach to answer. Cirrus' flexible management of resources and constant attention to project needs result in rapid formulation development, quality data package, early product selection, and rapid entry to the clinic, all of which are crucial elements of successful product development."

CIRRUS PHARMACEUTICALS: COMBINING EXCELLENT SERVICE & SCIENTIFIC EXPERTISE

Cirrus Pharmaceuticals, Inc. headquartered in Research Triangle Park, North Carolina, was established in 1997 as a contract research and development company specializing in formulation and strategic product development services. Cirrus partners with biopharmaceutical companies, including start-up, mid-size, and multinational companies to provide a broad array of R&D services from physical and chemical characterization, formulation development, stability testing, container/closure selection, process development, scale-up, and technical transfer to manufacturing for inhaled, nasal, oral, topical, and parenteral products. Cirrus also provides submission-ready regulatory documentation and assistance with regulatory submission questions. With over 100 employees, the company's future growth possibilities remain opportunistic, particularly because of their ideal location within the Triangle region of North Carolina. Drug Delivery Technology recently interviewed Anthony Hickey, PhD, Co-founder, CEO, and President of Cirrus Pharmaceuticals, to discuss how his firm is collaborating with the industry as a CRO, and how its drug delivery expertise will expand in the future.

Q: Can you provide us a brief on how and why you established Cirrus Pharmaceuticals?

A: As a Professor at the University of North Carolina at Chapel Hill, I was being asked to assist in formulation development projects that realistically could only be accomplished in a commercial setting. Dr. Jean Marc Bovet, whose background in physical chemistry and analysis is of relevance to pharmaceuticals, and I had known each other for several years, and he was looking for an entrepreneurial opportunity in the pharmaceutical industry. The idea quickly evolved to partner on this project and that, with university approval for my involvement, we could find a location and begin to secure the work necessary to have the company start successfully. Indeed, we began discussions in February 1997 and incorporated in June of that year.

Q: Cirrus was founded based on expertise within the inhalation field. What other dosage forms or areas of expertise has Cirrus provided to your partners?

A: It is now clear the company not only performs research to develop nasal and inhaled aerosol products, but also works with most dosage forms, including solid

oral tablets and capsules, parenterals, topical creams and ointments, dermatologicals, and ophthalmics. Behind these products is a strong cGMP analytical capability and quality system that ensures the reliability of data with respect to regulatory standards.

Q: How has the company capitalized on its location as a CRO in North Carolina?

A: We undoubtedly benefit from the entrepreneurial activities of large and specialty pharma groups in Research Triangle Park and other locations in North Carolina. Moreover, proximity to RDU Airport and a mid-Atlantic coast location have placed us conveniently for work from the rest of the continental US. We have always had international business and continue to have strong links with European and, increasingly, Far East companies.

Q: Do you see the outsourcing trend in the industry affecting drug delivery development? If so, what impact has it had on your company?

A: Presently, business is excellent, and we are no doubt benefiting from the increasing outsourcing trends in the industry. Fortunately, there seems to be no end to this expansion in sight. It will be interesting to observe these trends throughout the next decade with respect to the ultimate structure of large pharmaceutical companies and the extent to which integrated outsourcing can address their needs while keeping down expenses. The benefits accruing from these developments may also be passed on to the consumer as we live in an increasingly healthcare-conscious society.

Q: What is Cirrus' strategy for growth going forward?

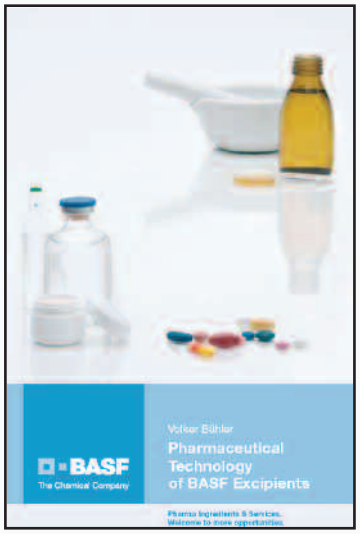
A: As mentioned previously, we have expanded our formulation opportunities in other dosage forms. In addition, our analytical services, which historically supported our product development activities, will begin to take on more independent work in the area of long-term stability, for example. Preformulation and extractables and leachables testing that require specialized instrumentation are also being expanded. There are other opportunities available in areas such as contract manufacturing, particularly clinical batch supply, that may be open to us, but our preferred course at this moment is to use strategic alliances to fulfill this need.

Q: What makes Cirrus attractive as a CRO partner for formulation and product development services?

A: Cirrus has always employed a proportionately large number of highly qualified scientists to consider both the scientific and technical problems associated with the development of particular products. Consequently, we rarely adopt a routine approach to problem-solving. Every new formulation raises unique questions that require a clear, efficient, and cost-effective approach to answer. Cirrus' flexible management of resources and constant attention to project needs result in rapid formulation development, quality data package, early product selection, and rapid entry to the clinic, all of which are crucial elements of successful product development. In addition, it has always been the Cirrus culture that employees are interested in their activities and demonstrate enthusiasm and dedication to fulfilling their personal goals and objectives and, as a result, those of the sponsor. ◆

Technology Showcase

Excipient Book



The booklet *Pharmaceutical Technology of BASF Excipients* provides an overview on the versatile functions of BASF excipients in pharmaceutical technology. Featuring 162 pages, it deals with the different dosage forms (solid, semi-solid, and liquid) and describes numerous applications of the Kollidon®, Kollicoat®, Ludiflash®, Ludipress®, Lutrol E®, Lutrol F®, Solutol®, and Cremophor® grades using typical formulations as examples for their functionality. The present third edition of this booklet includes recently launched Kollidon® (eg, -CL-F, -CL-SF, and VA 64 Fine) and Kollicoat® grades and provides more emphasis on coating applications than previous editions. You can order your personal copy of this booklet free of charge by contacting Deborah Harris, Industry Segment Manager at **deborah.harris@basf.com**.

Contract Research Organization

Cirrus Pharmaceuticals, Inc.
Strategic Product Development

Cirrus Pharmaceuticals, Inc. is a contract research organization working with start-up, mid-size, and multinational biopharmaceutical companies to provide a broad array of R&D services, including physical and chemical characterization, extractables and leachables testing, formulation development, stability testing, container/closure selection, process development, as well as scale-up and technical transfer to manufacturing. Cirrus offers expertise in the areas of inhaled, nasal, oral, topical, transdermal, and parenteral product development for small molecules as well as peptides, proteins, monoclonal antibodies, and vaccines. Cirrus also provides submission-ready regulatory documentation and assistance with government agency filings. The experienced professionals at Cirrus work side by side with clients to ensure that all research goals are achieved. Cirrus is registered with the US FDA and is a cGMP-compliant facility. For more information, contact Cirrus at (919) 884-2064, BizDev@cirruspharm.com, or visit www.cirruspharm.com.

Custom Manufacturing

DSM Pharma Chemicals, a business unit of DSM Pharmaceutical Products, is a global provider of custom manufacturing services to the pharmaceutical industry. Services include advanced intermediates, such as unnatural amino acids and derivatives, registered materials, and active pharmaceutical ingredients. Our technologies include biocatalysis, homogeneous catalysis, fermentation, and chiral technologies. DSM delivers comprehensive custom manufacturing services to the spectrum of pharmaceutical companies, including emerging pharmaceutical companies and large pharmaceutical companies. From clinical to commercial services, DSM focuses the right resources on providing the highest level of service and quality, while applying innovative solutions to satisfy customers' unique manufacturing needs. For more information, contact DSM Pharma Chemicals at (973) 257-8011 or visit **www.dsmpharmaceuticals.com**.

Ultra-Pure Chitosan

KitoZyme offers KiOmedine, the first range of non-animal ultra-pure chitosan and services for medical devices and drug delivery systems. Manufactured from vegetal source and in accordance with cGMP, KiOmedine ultra-pure chitosan exhibits excellent reproducibility, constant quality totally independent of seasonal variations, traceability, no risk of allergenicity, along with competitive price. KitoZyme's product development team (7-person staff of PhDs and engineers) provides expertise in functionalization, processing, and formulation of biopolymers applied to health sciences. KitoZyme also offers contract services, co-development opportunities, and capabilities to support customers in bringing innovative products to the market in the fields of wound care, haemostatics, surgical aids, ophtalmics, tissue engineering, drug delivery systems, adjuvants for vaccination, or cell encapsulating material. For more information, contact KitoZyme at info@kitozyme.com or visit **www.kitozyme.com**.

Technology Showcase

Packaging Solutions

MULTISORB Technologies

Multisorb Technologies provides leadership, innovation, and solutions utilizing active packaging components to manage moisture, oxygen, and/or hydrocarbons in healthcare product packaging to improve product stability. As a single-source provider of a broad range of sorbent materials, devices, and related automated insertion equipment, Multisorb supports its sorbent products utilizing SimulSorb and SimulOx pseudo-empirical modeling programs to help predict physical and chemical stability outcomes for healthcare products in their packaging. From calculations through operations, Multisorb is there for you with a seasoned team of packaging professionals, chemists, biochemists, and engineers, providing skilled resources to understand and solve virtually any product stability issues. For more information, visit **www.multisorb.com**.

Pressure-Sensitive Adhesives

National Adhesives' DURO-TAK® pressure-sensitive adhesives are approved in over 40 unique commercial transdermal drug delivery patches marketed around the world. A global leader in acrylic polymers for transdermal drug delivery with more than 35 years experience in pressure-sensitive adhesives, National offers over 25 acrylic copolymers to choose from, as well as acrylic-rubber hybrids, styrenic-rubbers, and polyisobutylenes. National's DURO-TAK PSAs ensure a good match for a multitude of drug formulations and provide the drug flux, adhesive loading capacity, and wear properties required in a comfortable, skin-compatible system. The company provides specialized technical service professionals who work in a confidential partnership with drug manufacturers, supporting them every step of the way from R&D to commercialization. For more information, contact National Adhesives at (908) 685-5462 or visit **www.transdermaladhesives.com**.

Nasal Spray System

The Pfeiffer Bidose nasal spray system offers the ideal solution when more medication is required than can be applied via one nostril. The system lends itself for example to the application of pain relief medication and vaccinations. It effectively provides the opportunity to dispense the contained amount of liquid equally into both nasal cavities so that more drug substance can be made available for absorption into the system for a longer period of time. Medication dispensed through the Pfeiffer Bidose system does not come into contact with air prior to being dispensed and therefore remains uncontaminated during the entire shelf-life. Its uniquely consistent spray performance fulfils the need for optimal dispensing efficiency. For more information, visit Pfeiffer of America at **www.pfeiffer-group.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**.

Drug Delivery Executive

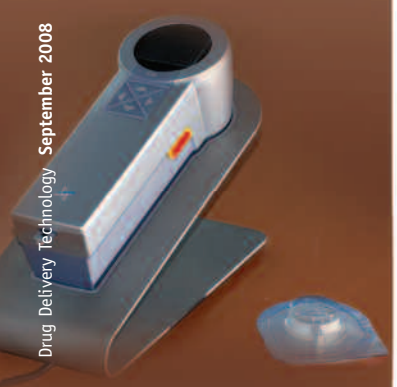
pantec biosolutions

Pantec Biosolutions: Laser-Based Delivery Solutions

Christof Böhler, PhD
CEO
Pantec Biosolutions AG

Pantec Biosolutions AG is a private drug delivery company specialized in using laser microporation technology to deliver large molecular weight drugs into the epidermis for local or systemic uptake. Its proprietary P.L.E.A.S.E.® (Painless Laser Epidermal System) platform enables efficient, needle-free, and painless administration of biopharmaceutical drugs, in varying and individualized dosages, through partnered patch technology. The technology is currently in clinical trials for the delivery of in vitro fertilization (IVF) hormone therapy, a market with an estimated value of $1.5 to $2 billion. Although transdermal delivery of drugs is a very powerful route, there are still very few patches on the market. The reason for this is that only a few molecules are able to pass the outer skin layers passively to finally reach the blood capillaries in the dermis. The stratum corneum in particular provides a strong barrier for molecules larger than 500 Daltons. Drug Delivery Technology *recently interviewed Dr. Christof Böhler, CEO of Pantec, to discuss how his company is overcoming these limitations with the P.L.E.A.S.E. platform, allowing for intraepidermal delivery of large and poorly permeating molecules. He also sheds light on the company's own pipeline as well as its strategy to penetrate new markets through strategic partnerships.*

"The combination of a 3-micron laser, beam-shaping and deflection units, as well as a skin layer detection module in the P.L.E.A.S.E. allows the highest flexibility for the control of drug dose through variation of pore properties and number - painlessly and with negligible damage to the skin. All this can be supplied at remarkably low cost per application for the end user, the patient, or the clinician."



Q: Can you provide our readers with a little more background and history on Pantec Biosolutions AG?

A: Pantec Biosolutions AG was founded in 2005 with the goal to replace the 100 daily hormone injections during infertility treatment with a smooth transdermal administration method. The initial business idea came from the internationally renowned IVF specialist Herbert Zech and pharmacist Werner Braun. They identified a strong demand among their patients to replace the painful hormone injections needed in artificial reproduction.

The problem is that the delivery of complex proteins like hormones is impossible to achieve in doses significant enough for IVF when using desired delivery technologies like transdermal patches. The initial research was carried out by our sister company Pantec Engineering AG (Ruggell Liechtenstein), led by Thomas Bragagna (now CTO of Pantec Biosolutions), Reinhard Braun (Chairman of Pantec Biosolutions), and myself.

Under Thomas' leadership, the decision to develop a laser-based skin microporation method at a 3-micron wavelength was taken. In this way, the patient's skin can be prepared for a transdermal patch in such a way that sufficient hormone delivery could occur. The team then wrote several key patents to protect the laser ablation space for transdermal drug delivery and carried out the first

successful transdermal delivery experiments, which led in turn to the foundation of Pantec Biosolutions AG.

In only 3 years, we have managed to develop the most efficient 3-micron laser of its hand-held size and grown the company to 15 employees. An additional 15 full-time equivalents work for Pantec in clearly defined outsourced projects.

Here in Liechtenstein, we focus on laser development, engineering, and laser tissue interactions, whereas our preclinical laboratory in Geneva (Switzerland) applies the laser for in vitro skin permeation studies.

The patch projects, which are partnered with a large European drug patch development and manufacturing company and a clinical CRO, are currently in Phase I clinical studies.

Q: Can you describe in more detail Pantec's core technology offering?

A: Our core technology is the proprietary laser-enhanced P.L.E.A.S.E. (Painless Laser Epidermal System), which extends the range of drugs that can be delivered transdermally. P.L.E.A.S.E. is a novel transdermal delivery method for high and low molecular weight drugs. A hand-held laser device creates controlled aqueous micropores in the patient's skin. Due to the special features of the device, the micropores do not reach the dermis, where nerves and blood vessels reside, as this would damage the integrity of the skin. The micropores are of a sufficient depth to facilitate transdermal drug delivery, and to stress, without damaging the skin. An intelligent graphical user interface guarantees simple and safe use by the medical personnel or even the patient, who can also use the device without supervision. The second piece of the product offering is a proprietary drug-containing patch, which was developed in a collaborative approach. Our marketed deliverables will be "customized package solutions" consisting of the P.L.E.A.S.E. device and an intraepidermal drug patch system for a specific therapy.

Q: For what indications and treatments are you using the P.L.E.A.S.E.-based intraepidermal systems?

A: Our initial focus is on developing our device for the clinical development and commercialization of up to three hormone patches to replace the 100 daily injections for infertility treatment. However, our preclinical department is also researching future opportunities that may lie in immunology, dermatology, neurological diseases, and vaccines. We are currently testing around five classes of molecules, and to date, all have so far reached unprecedentedly high levels of in vitro and in vivo permeation rates compared with the published data for passive and active delivery methods.

Our criteria to choose molecules for in vitro and in vivo permeation studies stem from a direct enquiry from a pharmaceutical or biotech company, which is the case for two applications, and/or existing therapies we have identified that currently require long-term injection cycles.

Our infertility hormone patches are currently in clinical Phase I. In addition, we have recently signed a contract to test intraepidermal delivery of allergens in an animal model. Last but not least, we have several preclinical programs in the aforementioned disease areas.

Q: What makes Pantec attractive and unique in the market?

A: Patches and passive transdermal delivery have been on the market for some time, and there are a number of companies in the arena that have pioneered several needle-free transdermal

technologies to make transdermal administration a much more widely used method, especially for peptide and protein delivery. However, we believe that microporation combines key advantages that together make it stand out from marketed transdermal technologies. For example, the use of medical lasers is now widely accepted in very critical treatments (eg, on the eye). The combination of a 3-micron laser, beam-shaping and deflection units, as well as a skin layer detection module in the P.L.E.A.S.E. allows the highest flexibility for the control of drug dose through variation of pore properties and number - painlessly and with negligible damage to the skin. All this can be supplied at remarkably low cost per application for the end user, the patient, or the clinician.

Finally, we can also microporate hard tissue, such as nails and bones, which has led to several business enquiries from reputable medical technology companies that are currently under negotiation.

Q: How would you characterize your strategy for ensuring the company's financial health and viability for the future?

A: Pantec Biosolutions is in a very comfortable financial situation as we have a strong group of shareholders consisting of the founders, a group of strong regional private and strategic investors, all of them with a strong entrepreneurial success record. All shareholders have participated in all financing rounds. In addition, our company is currently backed by two bank loans. Our strategy is to stay financially independent to develop the first target area for infertility treatment all the way to market in the first selected region. Our key value driver will then be the late-stage licensing for distribution of our first P.L.E.A.S.E. plus patch package solution.

In the meantime, we will sign a handful of final device, as well as OEM device, contracts under negotiation with several medical device companies. Of course, companies working on delivery devices have a shorter time to market than traditional life science companies, so we expect revenues to contribute to our financial health in due course.

Q: Where do you see the company in 5 years and beyond? What are the long-term goals?

A: Our goal is for our technology to become the gold standard for microporation-based transdermal drug delivery due to the painless process, the acceptance of lasers, and the flexibility to control the drug dose. Already next year, Pantec will generate turnover through partnered medical device/pharma projects. Five years from now, Pantec will have commercialized its own drug delivery solution composed of P.L.E.A.S.E. and one drug formulation, eg, a patch. This commercial validation and the sales that follow will make the company profitable and ready for future projects.

We see our company following two separate models: (1) As a one-stop shop solution provider that allows our partners in the pharmaceutical industry to outsource the entire process of reformulating an existing injection-based drug into the P.L.E.A.S.E.-patch and (2) As a Specialty Pharma company developing selected therapeutic areas on our own and commercializing them through licensing the distribution or through our own distribution. Finally, we anticipate our technology will also be sold into selected medical laser fields.◆

Do you find yourself stuck between

a rock

& a hard place?

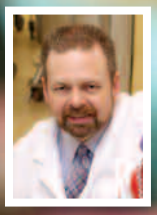
Find the right path around your obstacles at Davidson, Davidson & Kappel, LLC

Extensive pharmaceutical patent expertise:
Patent procurement | Due diligence/Opinions | Litigation

Dedication
Diligence
Knowledge

For more information, contact:
Cliff Davidson, Esq.
Davidson, Davidson & Kappel, LLC
485 Seventh Avenue
New York, N.Y. 10018
(212) 736-1940
cdavidson@ddkpatent.com
www.ddkpatent.com

SPECIALTY PHARMA
Strategies For Business Development



Tark Bunch
Senior Research Scientist for Development & Technical Services
Gilead

Michael Crowley, PhD
Vice President, Business Development
PharmaForm

Craig Mastenbaum
Vice President, Business Development
HollisterStier Contract Manufacturing

Contract Manufacturing

Serving the Specialty Pharma Sector to Mitigate Risk & Maximize Profit

By: **Cindy H. Dubin,** Contributor

The rapid growth of contract manufacturing presents both challenges and opportunities. Within the biotechnology market, there are concerns about capacity constraints as biopharma interest continues to expand. The potential for growth is huge in emerging markets, where there is already a significant amount of primary contract manufacturing of active pharmaceutical ingredients (APIs). Specialty pharmaceutical companies, which have not invested much in building manufacturing capacity, are also driving the demand for contract manufacturing organization (CMO) services.

Worldwide revenues for biopharmaceutical products is estimated to exceed $65 billion in 2007, and the proportion of pharmaceutical revenues from biotechnology drugs is estimated to surpass 10% of the total market, according to a recent study by HighTech Business Decisions (HTBD). Global spending on biopharmaceutical contract production was estimated at $2.1 billion in 2006, and according to HTBD, this level is expected to rise to $2.8 billion in 2008 and $4.3 billion by 2009.

"Understanding how outsourcers make decisions and evaluate providers is vital to services companies," notes Frost & Sullivan Industry Manager, Daniel Ruppar, who is currently working on an end-user study of outsourcing trends, perceptions, selection criteria, and other important dynamics to CMOs. "Analyzing feedback on these dynamics provides CMOs a sound basis for formulating an effective strategy to compete in the US market.

"Manufacturers that can better understand the service models and business attributes that appeal to pharmaceutical and biotechnology companies can develop and refine their operations to best serve customer demand," continues Mr. Ruppar. "With effective information partners, companies can take important steps to ensure and accelerate their future growth."

Three CMOs recently spoke with *Specialty Pharma* magazine about how they are trying to appeal to the Specialty Pharma sector and the services they are providing to meet those companies' unique needs. Participants in this discussion are: Tark Bunch, Senior Research Scientist for Development and Technical Services, Gilead; Michael Crowley, PhD, Vice President, Business Development, PharmaForm; and Craig Mastenbaum, Vice President of Business Development, HollisterStier Contract Manufacturing.

Q: *What are the pressing issues clients should be aware of in today's CMO environment?*

Dr. Crowley: The industry is steering toward a model to move new APIs into animal and human trials as quickly as possible, often through simple dosage forms, such as "powder in bottles" for reconstitution at the clinic or powder-filled capsules. Many of these studies are being conducted outside the US due to lower costs in eastern Europe and Asia. In this model, formulation and product development are conducted in parallel with these quick-exposure studies.

Pharmaceutical companies look for prospective CMO partners with a strong record of on-time delivery. Most emerging and small pharmaceutical companies are funded by venture capital or private equity, and on-time delivery of their clinical trial materials is absolutely necessary to help them manage their cash burn rate or until they get their next round of funding. Not all CMOs have the same capabilities and quality systems. Most CMOs can manufacture a tablet or powder-filled capsule, but they cannot manufacture a liquid-filled capsule, semi-solid for topical delivery, a controlled substance, or a nasal spray. Big Pharma is outsourcing manufacturing to CMOs with the expertise, facilities, systems, and equipment for these dosage forms.

Mr. Bunch: Time and flexibility: an ability to adjust to changing needs, while maintaining a state of control as required by GMP should be the hallmark of a strong CMO. This requires that there be a clear understanding of the project's requirements early in communication between both parties.

Relationships need to be grounded in trust, and trust needs to be earned, but the longer it takes to get to a point where both parties can communicate openly and effectively means the longer it will take between development and market. It is important when courting a CMO that it prove to be honest and approachable. Respect your CMO's time, but at the same time, make sure it can be reached for discussion outside of structured meetings.

Be aware of lead times. For small start-ups with limited Big Pharma experience, it can be shocking to discover how long it can take to acquire and qualify GMP-grade actives or specialty excipients, not to mention the adventure of sourcing something as seemingly trivial as a less-than-standard container-closure system. A CMO of more exotic parenterals would be expected to have a better capability of assimilating and understanding the process requirements of technically sophisticated products. Make sure the CMO's tech transfer team has a fundamental understanding of your process.

Although each client's needs are critical, the CMO's facilities and technical expertise, supply chain, and quality systems are finite. Both the CMO and the client need to plan for a long-term relationship by sharing information early with one another, so that both parties can respond as early as possible to maintain a schedule. For smaller start-ups, moving to GMP production can be alarmingly slow due to the level of documentation and control necessary for clinical and commercial production. It is important to lay out a schedule early and determine if these schedules are realistic or naive.

Mr. Mastenbaum: Clients need to be fully aware of the regulatory status at the facility that produces their product. It is an expectation that the CMO's compliance record be in good standing. If it is not, the client's ultimate approval could be put in jeopardy.

Q: *What are your tips for ensuring a customer mitigates risk and maximizes profits when using a CMO?*

Mr. Bunch: The greatest way to minimize risk to production and maximize profit is to maintain schedule adherence, and the best way to maintain the schedule is through early, clear, open communication of both the client's and CMO's needs. The client should keep the CMO informed of increasing or decreasing batch needs (both size and frequency) so that the CMO can schedule the most efficient use of the facility. In return, the CMO should keep the client informed of changes in site activity that may impact availability of the plant (maintenance shut-downs, installation, qualification of new equipment, etc).

A delay to production will impact the client's and the CMO's good names, while at the same time putting the patient's supply of medicines at risk. As a client, you must never forget that you own the product and have the right and responsibility to remain aware of your product's status at the CMO's plant.

Mr. Mastenbaum: Risk can be mitigated, and profits maximized by ensuring the CMO has employees and staff with the appropriate level of experience to handle and resolve issues when they are small, thus preventing them from becoming larger and potentially batch-impacting issues. Looking at the failure rate of a CMO will provide a window into this information.

Dr. Crowley: The most important ingredients to risk reduction and maximizing profits with CMOs are strategy and talent. Companies with a clearly defined strategy, who know and understand their plans and needs, and have the team in place to execute it are generally very successful. With these two pieces, it then boils down to communication, realistic planning and scheduling, execution, and project management with the CMO. Selecting the CMO with the right facilities, equipment, quality systems, and technical expertise for the specific drug product and manufacturing process will reduce the risks.

At PharmaForm, we recommend a technical transfer or demonstration batch to familiarize our staff with the formulation and process and to confirm equivalent results to previously manufactured product. Often, due to limited API, a smaller scale is necessary. We find this practice significantly increases success.

Q: *What should the client understand about ensuring a successful tech transfer?*

Dr. Crowley: Successful technical transfers are contingent upon the quality of the formulation and process, and providing as much information as possible on the front-end. Any missing pieces of information can result in a deviation or non-conformance. In our experience, clients with a strong in-house technical team that communicates what has been done previously and know where the challenges lie result in smooth transfers. A face-to-face visit or having the client on site during a technical transfer or demo batch always helps. Lastly, technical transfers should be manufactured in "like" equipment at a similar scale.

Mr. Mastenbaum: The client needs to understand that throughout the technical transfer process, they are as responsible for the output as is the CMO. There will be many deliverables, many of which require client input or response. Timely feedback by the client will help ensure a successful tech transfer process.

Mr. Bunch: Allow the CMO to incorporate the client's protocols into the CMO's document control system, then review to make sure nothing was lost in translation. Be aware that your procedures will need to comport with the CMO's standard controlled practices, so make sure that the final documents don't confuse the critical process parameters. If this is a technically challenging process, insist on sending some of your subject matter experts to the CMO's plant and overseeing the pilot runs. Take a fly-on-the-wall approach to tech transfer, only interceding when the CMO is struggling with the process. This will give you a better sense of the CMO's true capabilities. By stepping into the process at every opportunity to demonstrate how you would do it, you will come away with a false sense of the CMO's capabilities, namely you will have only observed your own capability. Ultimately, if the process is robust, the client should be able to leave the CMO's plant with the confidence that the CMO can manufacture the batch without the client's presence. If the process is not stable, this exercise provides a roadmap for optimization.

Keep an open mind. The innovators should be the expert at how to prepare their own products, but the CMO may have ideas how to make the process more efficient. Take advantage of the CMO's expertise, but always insist on a state of control.

Q: *Please explain the importance of process development when interacting with a CMO.*

Dr. Crowley: With a new formulation or early proof-of-concept formulations, process development is critical to avoid scale issues down the development path. An understanding of the critical process parameters, and their influence of drug product properties, becomes more and more important the further the product moves down the development path. The time and effort to develop a process results in a robust manufacturing process and robust product.

Mr. Bunch: A strong robust development effort at the innovator's laboratories, translated into clearly executable Master Production Records, is the best guarantee of success at the CMO. Sharing what does and does not matter in the process is critical so that the CMO knows where to focus attention and avoid distraction. Strong process understanding will be the key driver for specifying the essential engineering controls as your product requires scale-up in response to market success.

Mr. Mastenbaum: Chances are that the product being transferred to the CMO has some level of uniqueness. That is, the CMO is probably going to develop a batch record, SOP, lyophilization cycle, etc that is unique to that client and that product. Appropriate development and subsequent testing of those parts of the process utilized in generating these unique documents and systems are keys to the ultimate success of the tech transfer. Challenging these processes before regulatory submission batches or process validation batches are made will ultimately speed the entire process.

Q: *What is the key to a winning client/CMO partnership?*

Mr. Mastenbaum: The key to a winning relationship is constant communication and the desire that both parties look out for one another.

Dr. Crowley: Our formula for success at PharmaForm has been clear communication to understand and plan the manufacturing activities and set expectations, project management, and timely execution. Since we opened the doors, we have not missed a clinical ship date.

Mr. Bunch: From our experiences, honesty, respect, and transparency between both partners are keys to a long-term, successful relationship. If one partner fails to respect the other, communication is usually the first casualty. The keyword in a successful client/CMO relationship is "partnership," in which a shared synergy is experienced between both partners, and both parties are winners. A one-sided relationship may benefit one party in the short-term, but it will collapse quickly, leaving the opportunist scrambling for another partner, while at the same time trying to recover their reputation. Recognize early when a partnership isn't going to work and be prepared to part early if necessary. With these thoughts in mind, there is no reason the product and the investors need to suffer from a divorce brought about by a hasty courtship between the client and the CMO. ◆

Come See the New Face of Bilcare

Meet Vince Santa Maria, President of Bilcare GCS, Americas.
He has a fresh perspective to share on global clinical supplies.

Vince is committed to delivering service and quality beyond compliance. In research. In formulation. In packaging. In IVRS. In everything we do. And he's made that commitment part of our culture at Bilcare.

That means when you partner with us, you can count on the highest quality clinical supplies, delivered on time, every time.

Vince will see to it personally.

- New leadership
- New state-of-the-art facilities
- New global delivery capabilities

Contact us to learn how Bilcare can make your clinical trial a success.

Call 1-800-310-4445 or visit www.BilcareGCS.com.

Bilcare
Research
Global Clinical Supplies

Americas • Europe • Asia

Therapeutic Focus

Testosterone Gel for HSDD: Technology Tackles an Unmet Medical Need

By: Stephen M. Simes, CEO, BioSante Pharmaceuticals, Inc.

Introduction

A great deal of research supports the connection between low testosterone levels and diminished sexual desire in both men and women. Although testosterone traditionally is thought of as a male hormone, it also is found in women at levels that vary with their age, and in many instances at concentrations higher than that of estrogen. For example, a woman in her 40s has about half the level of blood testosterone compared to a woman in her 20s. In addition, testosterone levels fall precipitously after surgical menopause, which explains why complaints of reduced libido and other forms of female sexual dysfunction increase with age, especially in post-menopausal women.

The Implications

Studies report that as many as 43% of women experience some form of female sexual dysfunction (FSD), which is defined broadly to include lack of sexual desire, arousal, or pleasure. The largest subcategory within FSD is hypoactive sexual desire disorder (HSDD), which occurs in 31% of all women at some point in their lives.

HSDD is defined as a deficiency or absence of sexual desire, which results in reduced sexual activity, to the point of causing distress. HSDD can arise from many causes, including increasing age, certain surgical procedures, the use of prescription pharmaceuticals, disease, or chemical imbalances.

HSDD is a genuine disorder with real medical and emotional consequences. A DSM reimbursement code for HSDD dates back to 1983, and in 2000, the FDA published a guidance proposing clinical endpoints for developers of drugs to treat HSDD. To date, however, the FDA has not approved a single drug or biological to deal specifically with HSDD.

Approximately 9% of "naturally" menopausal women and 26% of women who have had their ovaries surgically removed report symptoms of (HSDD), the largest component of FSD, while 14% of women between the ages of 20 and 49 reported HSDD.

BioSante Pharmaceuticals is developing what it expects will be the first FDA-approved medication indicated specifically for HSDD in menopausal women. The product, LibiGel® (Figure 1), is a 1% testosterone gel that women apply once a day to their upper arm. LibiGel restores testosterone levels in post-menopausal women to levels that are considered necessary to restore sexual desire and activity. Testosterone used in LibiGel is in the same chemical form as the natural testosterone released by the female endocrine system. Clinical results indicate that the product can have a significant impact on sexual activity and satisfaction.

The pea-sized volume of hydro-alcoholic gel is dispensed from a metered-dose bottle to ensure delivery of the proper

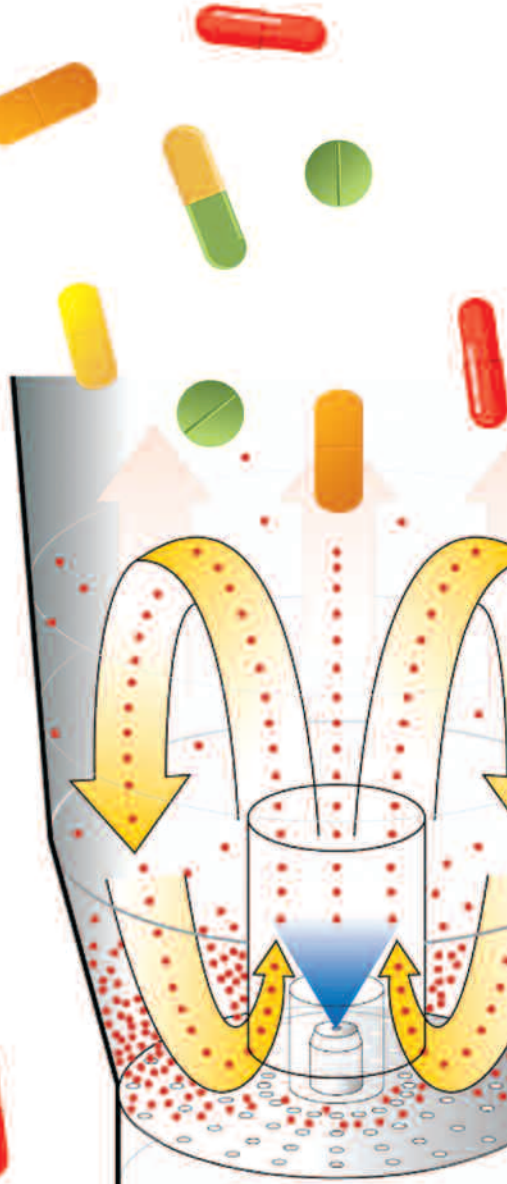
Figure 1.

Contract Modified Release Development & Manufacturing from Glatt!

- Glatt Wurster HS™ Pelletizing & Coating
- Glatt CPS™ Pelletizing
- Glatt Fluid Bed Granulation & Drying
- Glatt High Shear Granulation
- Organic Solvent Processing
- DEA Controlled Substance Capability
- From R & D to Commercial Capacities
- Unrivaled Expertise & Customer Care

Glatt Pharmaceutical Services specializes in the development and cGMP manufacture of difficult-to-craft modified and immediate release solid dosage products and is the global leader in fluid bed related product formulation, processing technology and full scale commercial manufacturing.

To learn more, contact us to schedule a visit with our accomplished staff at our newly expanded facility.



Glatt®
Pharmaceutical Services
A Division of Glatt Air Techniques, Inc.

Ramsey, New Jersey
www.glattpharmaceuticals.com
201.825.8700

Delivering Solid Experience

testosterone dose of 300 micrograms per day. Ingredients in the gel promote absorption of testosterone through the skin and into the bloodstream, in a controlled-release manner over 24 hours. After several days of dosing, women achieve a steady-state concentration of testosterone in their blood at all times, provided they keep applying LibiGel once per day.

LibiGel's open delivery system ensures there can be little or no irritation compared to patches. And because LibiGel delivers a metered-quantity of testosterone, which is absorbed slowly throughout the day, its abuse potential as a performance-enhancing substance is negligible.

An Unmet Medical Need

Physicians routinely prescribe estrogen to treat a form of FSD involving pain during intercourse due to vaginal atrophy or insufficient lubrication. Note that several over-the-counter lubricants can alleviate this condition, which has nothing to do with sexual desire. In fact, estrogen fails to address the underlying cause of HSDD, diminished testosterone levels.

Boehringer-Ingelheim is developing a fast-acting antidepressant, flibanserin, for treating HSDD in premenopausal women. Flibanserin has been called "Viagra for women" because the drug acts rapidly as a mood brightener. Drugs like flibanserin likely would not work in post-menopausal women because, as Pfizer learned when it tried to adapt Viagra for such women, libido was strongly dependent on testosterone levels.

Viagra will increase a woman's vaginal lubrication, which is sometimes associated with sexual arousal, but in 8 years of clinical studies, it was not shown consistently to increase the occurrence of satisfying sexual events, which is the FDA's primary endpoint for such drugs.

Testosterone in its natural form is FDA approved for use by men and is delivered by patches or gels for absorption through the skin. Approved doses for men are significantly too high for women and are inappropriate for treating HSDD. Methylated testosterone, a chemically modified form of the compound, is available in pill form; due to safety issues and lack of clinical data in women, however, its use for HSDD is undesirable.

Transdermal delivery of testosterone is the most desirable delivery route, but the precise dosage form matters a great deal. Procter & Gamble's testosterone patch for HSDD, Intrinsa, was approved in Europe, but not in the US, presumably because the company has declined to test the product in extensive safety trials that LibiGel currently is undergoing. This will position LibiGel, after its approval, as potentially the only testosterone product specifically indicated for HSDD and the first drug for HSDD in menopausal women.

Physicians have prescribed testosterone off-label to women for many years. Data show that in 2007, at least 2 million off-label testosterone prescriptions were written for women. This does not include prescriptions for compounded testosterone, which may add as much as 50% to the number of prescriptions.

On the basis of 2 million prescriptions, assuming a 3-month supply each, the off-label market for female testosterone products can be estimated at between $600 million and $1 billion per year in the United States. An approved product indicated specifically for HSDD could easily double or triple the market for such products to the $1.5-billion to $2-billion range, and capture a large fraction of sales as well.

Testosterone products are of course available for men in injectible, patch, oral, and gel formats. Injected testosterone has traditionally been a small market, in the $25 to $50 million per year range. Both oral and patch products have not achieved a great deal of success either. The advent of testosterone in gel form, however, transformed the market for male testosterone products, boosting sales well above half a billion dollars per year. This fact bodes well for the commercial success of LibiGel.

Testosterone may have benefits other than increasing libido. Studies have suggested it may improve a person's sense of well being, and may benefit bone and muscle function as well. However, BioSante is neither claiming any of these benefits nor testing for them. Increased sexual desire, satisfying sexual events, and a reduction in distress are the endpoints for LibiGel.

Clinical Milestones

Phase II data strongly suggest that LibiGel was significantly more effective in increasing the frequency of satisfying sexual activity than placebo. For study purposes, a qualifying event included sexual intercourse, oral sex, or masturbation that women rated as "satisfying."

A Phase II study of LibiGel examined women in monogamous, heterosexual relationships with a partner who was available at least 50% of the time. Subjects recorded sexual activity in a diary for 8 weeks before the treatment period began. The average number of satisfying sexual events for a 4-week period was 2.5 before therapy. LibiGel subjects experienced a 100% increase in satisfying events the first month; after 12 weeks, subjects reported an increase to 7.5 satisfying events per 4-week period, an increase of 238% for the final month of treatment. Women using the placebo treatment, which included gel without testosterone, reported an increase of 65%.

Safety results also were encouraging, as the incidence of acne, hirsutism, and clitoral enlargement were similar in LibiGel and placebo groups.

By comparison, women who used the Intrinsa testosterone patch, which also delivers 300 micrograms of testosterone per day, experienced a 74% increase in satisfying events. Interestingly, the placebo subjects in the Intrinsa arm of the study had only a 33% increase in satisfying events, suggesting that the patch delivery method may be less than optimal for delivering a libido-enhancing product.

BioSante currently is enrolling subjects for three Phase III studies of LibiGel. Two of the studies currently underway will include 500 women each; 250 in the placebo group and an equal number in the treatment group. Study subjects will range from 30 to 65 years of age, will have undergone hysterectomy and surgical removal of their ovaries before natural menopause, and will be on estrogen therapy. These two trials are being conducted under a Special Protocol Assessment, an agreement between

BioSante and the FDA that the studies as designed will support the eventual approval of LibiGel.

The Phase III efficacy trials have two primary endpoints (increase in sexual desire and number of satisfying sexual events) and one secondary endpoint (decrease in distress associated with low desire).

The third study, in post-menopausal women with HSDD, is a special Phase III safety study conducted at the request of the FDA. In recent years, particularly in light of controversies over estrogen therapy and the safety of non-steroidal anti-inflammatory medications like Vioxx, the FDA has become increasingly cautious regarding cancer and cardiovascular safety. The FDA seems to have adopted a more proactive policy toward drug safety. Many newly approved drugs are expected to carry post-marketing commitments (PMCs), by which approval is accompanied by the sponsor's pledge to conduct long-term safety studies. In the past, the FDA imposed PMCs but had little power to enforce them. Today, failure to comply with PMCs may carry penalties.

Despite the fact that testosterone has been used safely in both women and men for decades, the FDA has asked the industry to take a very close look at these issues in what will likely be the first large, cardiovascular event-driven, preapproval study undertaken in the absence of clear safety signals.

Incidentally, new testosterone products for men need not meet the same stringent safety criteria as those for women. All that is needed to approve a man's product is a 90-day pharmacokinetic study and no long-term safety data.

For the Phase III safety study, BioSante expects to enroll and test approximately 2,500 to 3,000 post-menopausal women between the ages of 50 and 80, with at least one cardiovascular risk factor. The primary safety outcome for this trial is the effect of treatment on the incidence of serious cardiovascular events, including cardiovascular-related death, heart attack, and stroke. The incidence of invasive breast cancer is a co-primary safety endpoint, but investigators also will look for benign breast masses and non-invasive breast cancers. Study subjects will be assessed during each study visit for hirsutism, acne, clitoral enlargement, and voice or skin reactions, as well as blood testosterone levels. The placebo-controlled study will examine the effect of LibiGel in post-menopausal women at a dose of 300 micrograms per day over 12 months at which time an NDA may be submitted seeking approval. The FDA will require BioSante to follow the study group for an additional 48 months to compare the occurrence of cardiac events and breast cancer between the treatment group and a matched group of women who receive a placebo gel.

BioSante expects to have completed recruitment for the three Phase III studies in the next year, with the trials ending some time in 2010. If efficacy expectations based on Phase II trials are fulfilled, and the anticipated safety results are achieved, BioSante will file an NDA for LibiGel in 2010.

LibiGel's initial efficacy studies are being conducted in surgically menopausal women. BioSante intends to study naturally menopausal women as well, and perhaps women who have not undergone menopause but who have medically defined, diagnosed HSDD.

The Future

With the anticipated approval of LibiGel just 2 to 3 years away, BioSante has begun to consider how to introduce this potential blockbuster product into the marketplace in a way that maximizes both patient benefit and financial returns for its stockholders.

The company has been fortunate that it has been able to develop LibiGel on its own into Phase III. By doing so, the greatest value for the investment in LibiGel should be achieved. However, BioSante may enter a business arrangement to derive the full potential from the product.

Options include selling or licensing LibiGel to a much larger pharmaceutical company with proven experience in endocrinology, women's health, or sexual dysfunction. Another possibility is to merge with, or be acquired by, a company with the sales and marketing capabilities that LibiGel will demand.

In addition to LibiGel, BioSante products include Elestrin (estradiol gel), FDA approved for treating moderate-to-severe vasomotor symptoms associated with menopause, and two development-stage drugs: Bio-T-Gel, BioSante's testosterone gel for male hypogonadism, and an oral contraceptive in Phase II clinical development.

BioSante's cash position is such that any collaboration decision will not be based on urgency. However, LibiGel's status represents an exciting opportunity to establish a solid future for these products and BioSante. Toward this end, in June 2008, BioSante engaged Deutsche Bank to assist in reviewing its strategic alternatives. ◆

Stephen M. Simes

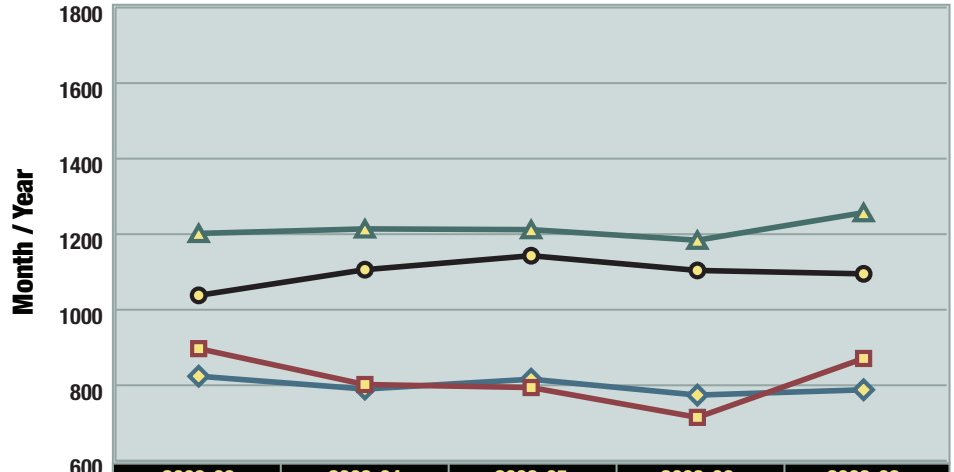
President & CEO
BioSante Pharmaceuticals

Stephen M. Simes has served as the Vice Chairman, President, and Director of the company since January 1998, and CEO since March 1998. From October 1994 to January 1997, Mr. Simes was President, CEO, and a Director of Unimed Pharmaceuticals, Inc. From 1989 to 1993, Mr. Simes was Chairman, President and CEO of Gynex Pharmaceuticals, Inc. Before that, he served as Senior Vice President and Director of Bio-Technology General Corp.

Facts & Figures

For index methodology and more detailed analysis please visit www.bionumbers.com

Bionumbers Composite Index



*The indexes refer to Market Capitalization rather than Share Price

	2008-03	2008-04	2008-05	2008-06	2008-08
CSPI	1,202	1,214	1,212	1,184	1,257
ESPI	897	802	794	715	871
DDI	4	790	816	774	788
NASDAQ	038	1,106	1,143	1,104	1,095

Index Value

CSP Index Value: 1257 | Change YTD: -2.5% | Change M/M: 1.7% | Total Index Capitalization: $50.6 Billion

Top 5 Capitalizations YTD Change		
Shire	$9.9 Billion	-23%
Hospira	$6.3 Billion	-7%
Warner	$4.1 Billion	-9%
Perrigo	$3.3 Billion	0%
Abraxis	$3.0 Billion	+8%

Top 5 Gainers YTD Change	
APP	+132%
Millbrook	+120%
Vivus	+89%
Columbia	+65%
Valeant	+62%

Top 5 Laggards YTD Change	
Indevus	-69%
Ista	-63%
Angiotech	-48%
KV	-31%
Shire	-23%

ESP Index Value: 871 | Change YTD: -30.6% | Change M/M: +1.2% | Total Index Capitalization: $2.4 Billion

Top 5 Capitalizations YTD Change		
Durect	$430 Million	-10%
Pain Therapeutics	$382 Million	-18%
Cadence	$377 Million	-13%
Nektar	$341 Million	-45%
Javelin	$170 Million	-7%

Top 5 Gainers YTD Change	
Catalyst	+22%

Top 5 Laggards YTD Change	
Keryx	-94%
Elite	-87%
Nektar	-45%
Spectrum	-35%
Alexza	-34%

DD Index Value: 788 | Change YTD: -18.6% | Change M/M: -7.0% | Total Index Capitalization: $8.7 Billion

Top 5 Capitalizations YTD Change		
Biovail	$1.7 Billion	-21%
Alkermes	$1.2 Billion	-23%
Eurand	$733 Million	+6%
Surmodics	$719 Million	-28%
Halozyme	$575 Million	+4%

Top 5 Gainers YTD Change	
Momenta	+101%
Emisphere	+43%
DepoMed	+36%
Acura	+26%
Labophram	+18%

Top 5 Laggards YTD Change	
Vyteris	-89%
Elite	-87%
NexMed	-82%
CytRx	-80%
Aradigm	-56%

Breathe Easy

with a cGMP Laboratory Market Leader

In a world where many labs can make you feel like a number, personal service is welcome refreshment. We adapt to your needs, customize your testing and reporting, and dedicate the same team to work with you personally throughout your project.

With PPD, you can count on our excellent regulatory record, state-of-the-art facilities and swift automation to deliver accurate, reliable data.

Another breath of fresh air...PPD is a market leader in inhaled and intranasal products testing.

Our high-capacity lab complex is one of the largest analytical testing facilities for pulmonary inhalation and nasal products. When you trust your respiratory product analysis to the cGMP Labs at PPD, you can breathe a sigh of relief, knowing that your testing will be done right, and right on time.

Welcome to PPD's cGMP Laboratory.

For more information, call Nick Maraveyias at +910 815 3476 or visit us at ***labs@rtp.ppdi.com***

World-class laboratories
for world-class results

PPD®

Executive Summary

Jo Bossart, PhD
Managing Director
Bionumbers LLC

Bionumbers, LLC: Turning Insight Into Action

Bionumbers, LLC is a boutique research group based in Austin, Texas, offering critical numbers and actionable insight into the parameters that impact the success and performance of products and companies in the biopharmaceutical sector. Bionumbers has a particular focus on the Drug Delivery and Specialty Pharma sectors, acting as a significant source of facts and figures useful in the preparation of biopharmaceutical plans, forecasts, and budgets. The company currently offers three biopharma indices: 1) commercial-stage specialty pharma; 2) emerging-stage specialty pharma; and 3) drug delivery. Managing Director Jo Bossart recently shared with *Specialty Pharma* magazine how a better understanding of history can ensure a future product success story.

Q: ***Why does your research primarily focus on numbers?***

A: Numbers convey the quantitative basis of our business focus. Much of the Drug Delivery and Specialty Pharma industry is based on a more qualitative approach to the business of creating and developing new pharmaceutical products. There seems almost an artisan approach to the business. Every product is treated as a one-off creation, distinct and somehow separate from all other products. The Bionumbers approach is to study the similarities between products and understand the parameters that impact their development and success. This is not to deny the artisan qualities of every product, but to acknowledge that these products are created in an environment that can have a profound influence on outcomes. It would be much like providing a mountaineering group information on the mountains they are about to climb. While they are expert climbers, they still rely on understanding the peculiarities of the mountain and the parameters that impacted the success and failure of other teams. It's all about being prepared to succeed.

Q: ***How can understanding the nature of the environment impact outcomes? Isn't product development largely dependent on execution?***

A: Understanding relevant numbers or parameters can have a profound impact on outcomes, even if they do not offer a simple "solution." For example, if a company estimates that it will require 4 years to take a product through clinical development, regulatory review, and approval, but it actually takes 6 years, what is the impact on the company and the product? Well, it is likely that the company will have significantly damaged its credibility. Pointing to a 4-year timeline and taking 6 years means that the company did not properly understand the challenge or it had poor operational performance. In addition, the funding requirements will be quite different, if only because the fixed expenses to support the product need to be covered for an additional 2 years.

There is an argument that the actual timeline can never be known and the proper approach is to work with a best "bottoms-up" estimate and then execute as efficiently as possible. A delay of 2 years then really is an unfortunate fact of life that could not have been realistically foreseen. Well, if the company had understood that other products in the same class or using a similar technology had taken 6 years on average, they would have had a strong basis to suspect that their estimate of 4 years was probably optimistic. Understanding the historical parameters, the company executives could choose to be much more aggressive in executing their plan knowing it was optimistic, or try to shorten the development period by choosing parameters associated with shorter development timelines. Let's remember that an average 6 years means that some projects were developed in less time while some required more. Understanding the parameters that provided for shorter rather than longer development times can make a big difference in the planning process. Execution is not the sole determinant of outcomes. An interesting point is that completing this program in 6 years should have been considered a success by industry standards, but promising 4 and delivering in 6, it

becomes labeled a failure. In today's financing environment, you need to deliver on any timeline you promise. Delivering on time means presenting more conservative timelines or understanding and managing the parameters that can lead to shorter development times and higher success rates.

Q: *So what kind of numbers does Bionumbers provide? There are many companies out there that provide extensive databases.*

A: We focus on defining numbers that don't drop out of commonly available data. For example, any number of databases can tell you how many CNS products are currently in Phase III development. These databases can also provide information on the companies developing these products, their clinical trial indications, and much more. Other databases can tell you what deals have been done and what the published deal terms are. This is very valuable information to define your current position in a competitive environment. This is data about the present, but an understanding of the future comes from understanding the present and the past. It's the evolution of markets that is key to developing effective strategies. It is this analysis of the environmental factors that is the focus of Bionumbers; the numbers and the derived insight they offer.

Our first report, *Drug Delivery 2008 — Product Success Rates & Development/Approval Times*, looks at the numbers, including those that impact drug delivery product development and approval. We all know, or at least suspect, that drug delivery products are developed and approved more quickly, with a higher success rate than new chemical entity products typically associated with Big Pharma. What we found was that a drug delivery product took on average 5.7 years for clinical development and regulatory approval, and the average approval rate for drug delivery products entering clinical trials was 26%. This compares with figures of 7.5 years and 20% for Big Pharma products. Yes, there is a difference in favor of drug delivery products, but how meaningful is it, and does it support the drug delivery business model? We all know that drug delivery products don't have the same kind of durable market exclusivity, so they need to provide value through higher success rates and shorter development times.

Q: *What is the benefit of this type of analysis? It seems largely defeatist.*

A: The value of analysis beyond data is the insight and opportunity it presents. If success rates and development and approval times are the outcomes, they are a function of often manageable parameters. The first Bionumbers report looked at parameters associated with drug delivery products and found that a number have an obvious impact on success rates and development and approval times. Identifying these parameters and acting upon them can impact outcomes. For example, there were important differences in development and approval times depending on the development strategy chosen, the corporate group developing the product, the platform technology, and validation status among other parameters. In many cases, there are development options available to companies that can favorably influence outcomes. But this is only the case if you understand the parameters and use them to your own advantage. Remember, if the average development and approval time for drug delivery products was 5.7 years, half the products were approved in less time. In fact, some were taken through clinical trials and approved in only 2 years. If you were going to develop a drug delivery product, you would certainly like to know what parameters were associated with the shorter development and approval times.

Q: *What other numbers are you examining?*

A: We have been publishing a stock index for about 2 years now that looks at Specialty Pharma and Drug Delivery companies. The index is different than most in that it looks at market capitalization rather than stock price. As business people, we are interested in the value appreciation of our companies. Stock prices are important for investors and our 401k, but they too often disguise the value created by companies. Significant value creation goes unrecognized when a company does financing by issuing additional shares at a modestly lower share price. To an investor, this may seem a loss, whereas the value of the company has actually increased. The two Specialty Pharma indices also track segments that are ignored by investment houses and publications. Both indices use a consistent definition that provides additional insight into the performance of these sectors. Visitors to the website (www.bionumbers.com) can also track the relative performance of the Specialty Pharma indices against the Drug Delivery index and the NASDAQ. Right now, it's not a pretty picture for any of these indexes. We are also preparing a couple of additional reports for publication before the end of the year.

Q: *What is at the core of Bionumbers?*

A: There really are two core concepts that drive our business. The first is developing actionable information. Much of the information available in the media feeds our need to be informed, but has little or no reasonable application to the business at hand. Does it make much sense to pay for data or information that doesn't suggest or support an action? Bionumbers focuses on reports that provide actionable insights.

The other core concept is providing numbers that are real and in context. Having purchased and read numerous reports while in strategic and operational roles within the Biopharma industry, I was often struck by the insight offered by certain reports in areas where I had little or no experience. But when I read a report by these same groups in areas where I was experienced, I was appalled by the inaccuracies and incomplete conclusions. I came to realize that in most cases, it was necessary to do the analysis myself. Too often, very smart people prepare reports with too little experience in the area of the report. Bionumbers will only work in areas where we have sufficient experience and expertise to ensure that we provide analysis and conclusions that are real and actionable. ■

September 2008

Advertiser Index

Company	Pg	Phone	Web Site
3M	5	800-643-8086	www.3m.com/dds
AAPS	23		www.aapspharmaceutica.com/annualmeeting
Aveva DDS	2	954-624-1374	www.avevaDDS.com
Azopharma	Cover, 4	954-433-7480	www.azopharma.com
BD	29	800-225-3310	www.bdpharma.com
Bilcare Global Clinical Supplies	71	610-935-4300	www.bilcareGCS.com
Bionumbers	53		www.bionumbers.com
Catalent Pharma Solutions	84	866-720-3148	www.catalent.com
Cirrus Pharmaceuticals	19		www.cirruspharm.com
Controlled Release Society	45		www.controllereleasesociety.org/meeting
Davidson, Davidson & Kappel	67	212-736-1940	www.ddkpatent.com
Dow Pharmaceutical Sciences	15	707-793-2600	www.dowpharmsci.com
DPT	83	1-866-CALL-DPT	www.dptlabs.com
DSM	79	973-257-8011	www.dsmpharmaceuticals.com
Eurand	7	937-898-9669	www.eurand.com
Frost & Sullivan	43		www.frost.com
Glatt Pharmaceuticals	73	201-825-8700	www.glattpharmaceuticals.com
InnerCap Technologies	3	813-837-0796	www.innercap.com
Multisorb Technologies	17	716-824-8900	www.multisorb.com
Nusil Technologies	13	805-684-8780	www.nusil.com
Particle Sciences	Insert	610-861-4701	www.particlesciences.com
PharmaCircle	37	847-729-2960	www.pharmacircle.com
PharmaForm	11	512-834-0449 Ext 201	www.pharmaform.com
PPD	77	859-442-1300	www.ppdi.com
Scolr Pharma, Inc	9	425-373-0171	www.scolr.com

EXTERNAL DELIVERY

Rome Is Burning!

By: John A. Bermingham

OK, I'm back. As our Executive Director Dan Marino told you this past month, I am now the new CEO of Alco Consumer Products, Inc. I also want to thank Dan for covering for me while I was fully engaged with Alco.

Every CEO of every company, be it public or private, has the primary responsibility of representing the shareholders' and/or investors' interests because the CEO has been "elected" to represent their interests. That leads me to what is one of the most appalling examples I have ever seen of people refusing to address what they were hired to do and avoiding their essential responsibility to the people that hired them. Yes, I am talking about our illustrious House of Representatives.

As you know, our House leadership recently adjourned choosing to leave Washington rather than address what they were elected to do….represent us in government! Nancy Pelosi, Speaker of the House, and many of her fellow members of the House followed the early vote for adjournment by heading out of town and leaving the American people to deal with rising gas prices and energy uncertainty. She and other members of Congress left to enjoy a relaxing 5-week paid vacation. Ms. Pelosi, in fact, went on a book-signing tour. The message this sends to the American people is bad enough, its ramifications, however, are far worse.

Our elected officials are chosen by us to represent our interests in government be it local, state, or federal. I don't know of one person who doesn't think we are facing a severe energy crisis and that our leaders must do something about this problem. The negative impact this crisis is having on our economy is devastating.

Putting air in your tires and tuning your engine may do some good but will never stop the $4.00 gas price. Yet, we have a trillion barrels of oil off of our coasts in Alaska and in the western states that are untapped for their shale oil. There is plenty of untapped natural gas as well. So while Congress takes its vacation and avoids its responsibility as an elected branch of government, we civilians continue on alone with multiple crises facing the nation.

The point of all of this is that if a CEO and his/her management team were facing a crisis of monumental proportions in his/her company and then left during said crisis for a vacation, what do you think the Board and/or investors would do? Yep, they would all be fired for cause. So why should we accept this irresponsible avoidance by the House of Representatives of a major crisis that must be addressed? Why should Nancy Pelosi be allowed to get away with this appalling decision to go on vacation and a book-signing tour during a major economic crisis?

Think about the ramifications of $4.00 gasoline prices on our families and our economy. I believe all Americans should wage a letter-writing campaign sending their Representatives their opinions of this irresponsible action. Or, let's do what any group of shareholders and/or Boards would do. FIRE THEM ALL! ◆

BIOGRAPHY

John A. Bermingham is the Chief Executive Officer 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. Alco also supplies many private products to several of the largest retailers in the country. 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.

CDMO *(sē-dē-em-ō)* ***n.*** a partner that provides both development and manufacturing services all under one roof.

< see DPT >

DPT provides contract development and manufacturing services for some of the world's leading pharmaceutical, biotech, and consumer healthcare companies. Through innovation, technology, and service, our capabilities go unmatched.

From pre-formulation to clinical trial materials Phase I – IV. From unique packaging solutions to validation services. With four cGMP facilities, DPT has the commercialization capabilities to get your product to market fast and with confidence.

Remember, CDMO is our MO. Contact DPT today – *The Industry Source for Semi-solids and Liquids.*℠

DPT®
A DFB COMPANY

SOURCE WITH CONFIDENCE®

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

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

Innovative solutions. Global capabilities.

Catalent Pharma Solutions offers a full spectrum of services to support pharmaceutical product development, drug delivery, manufacturing and packaging.

We have the expertise and global resources to accelerate your product's speed to market—with unmatched service and support.

For innovative solutions to help improve health care anywhere in the world, call Catalent.

Catalent

Reliable Solutions. Inspired Results.™

For more information, contact us at +1 866 720 3148, email us at sales@catalent.com, or visit www.catalent.com