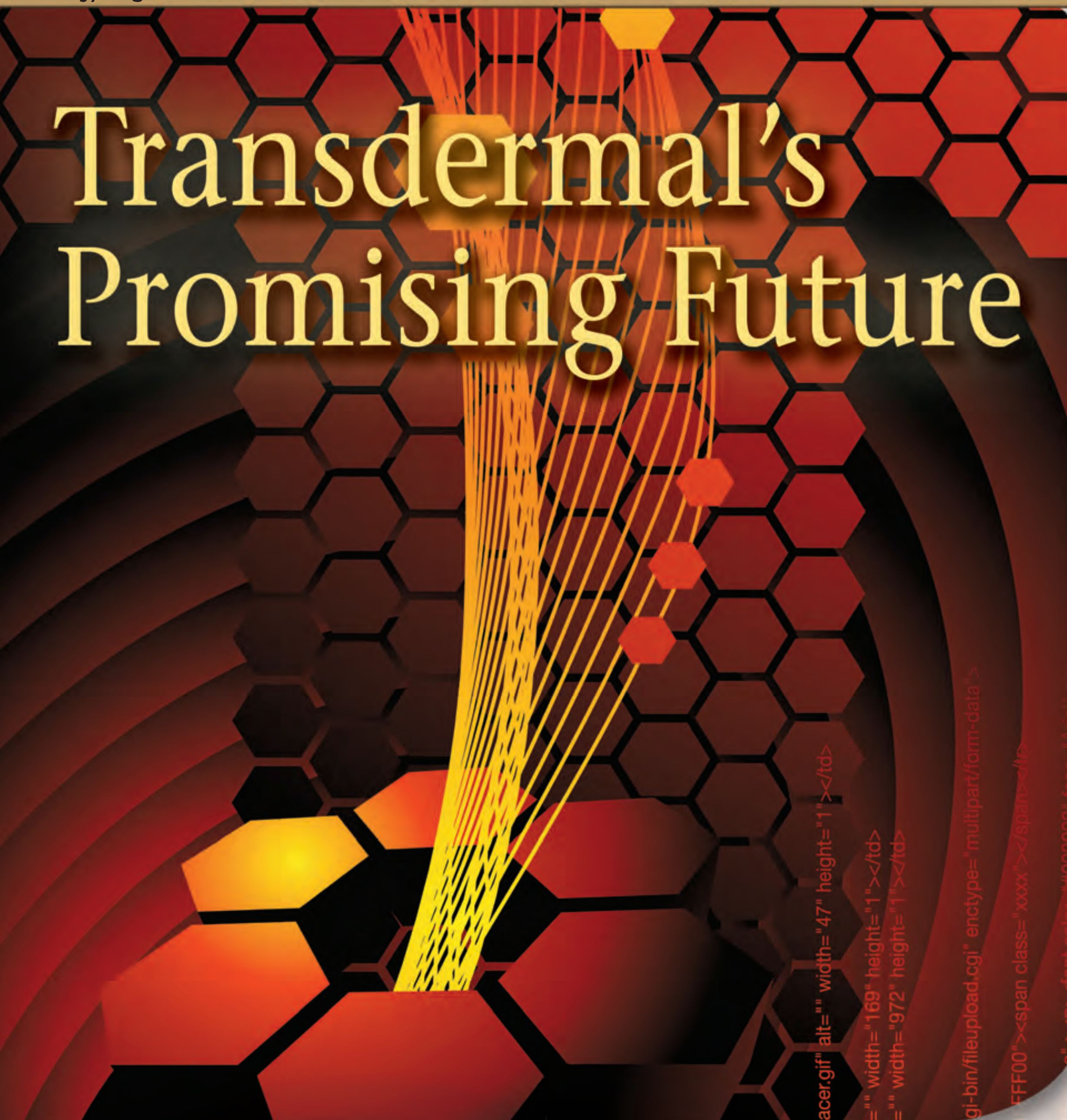
Drug Delivery Technology®

July/August 2010 Vol 10 No 6

www.drugdeliverytech.com



Transdermal's Promising Future

IN THIS ISSUE

INTERVIEW WITH PARTICLE SCIENCES' VP, DRUG DELIVERY

ROBERT W. LEE, PHD

FEATURING

SPECIALTY PHARMA
Strategies For Business Development

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

Mark Copley
Optimizing Cascade Impactor Testing for Characterizing Orally Inhaled & Nasal Drug Products

Cindy Dubin
Transdermal Delivery - Making a Comeback!

John Fort, MD
Creating Safer Pain Relievers Using Proton Pump Inhibitor Drug Delivery Mechanisms

Drug Delivery Technology

July/August 2010 Vol 10 No 6

PUBLISHER/PRESIDENT
Ralph Vitaro

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

CREATIVE DIRECTOR
Shalamar Q. Eagel

CONTROLLER
Debbie Carrillo

CONTRIBUTING EDITORS
Cindy H. Dubin
Debra Bingham
Jason McKinnie

TECHNICAL OPERATIONS
Mark Newland

EDITORIAL SUPPORT
Nicholas D. Vitaro

ADMINISTRATIVE SUPPORT
Kathleen Kenny

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

Advertising Sales Offices

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

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

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

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

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

3M DRUG DELIVERY SYSTEMS

TRANSDERMAL SYSTEMS

3M microneedle technology delivers the widest range of API's in a transdermal format scalable to your needs.

3M Microstructured Transdermal Systems (MTS) combine the efficiency of a syringe with the convenience of a transdermal patch.

- Local or systemic delivery for a wide variety of molecules, including proteins, peptides and vaccines
- Microneedles bypass barrier properties of stratum corneum with delivery efficiency that matches or exceeds injection
- Provides competitive differentiation and lifecycle management solution

3M's team of formulation, development and manufacturing experts are ready to ensure your needs are met from clinical to commercial scale. **Find out more at www.3M.com/MTS.**

US: 1 800 643 8086
UK: 44 (0) 1509 613626
ASIA: (65) 6450 8888

ENABLING YOUR SUCCESS.

Making a Comeback!

"Through the continued innovation and evolution of these various transdermal delivery methods, the global market for transdmeral formulations is estimated to reach $12.7 billion this year, and one-third of US drug products will rely on transdermal delivery."

p.25

Table Of Contents

TRANSDERMAL TRANSCENDENCE

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

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

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

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

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

NITTO DENKO GROUP

Table Of Contents

Choosing the Right Path

"rxRNAs take advantage of a unique design of modifications that provide stability, partially block off-target effects, and prevent detection by the innate immune response while supporting specific and extremely potent gene silencing. Because toxicity issues, including sequence-mediated off-target effects or delivery vehicle-related side effects, are likely dose dependent, the use of the GeRP oral delivery technology to administer low doses of rxRNA drugs provides an opportunity for a wide therapeutic index delivered via a patient-friendly route of administration."

p.66

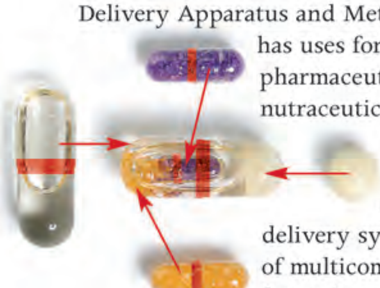
DEPARTMENTS

THE ADVANTAGES

OF MULTI-PHASE, MULTI-COMPARTMENT CAPSULES ARE CLEAR

INNERCAP® Technologies Granted US Patent No. 7,670,612 on multi-phase, multi-compartment capsular delivery apparatus and methods for using the same.

March 23, 2010, Saint Petersburg, Florida USA, INNERCAP Technologies, Inc., an international drug delivery and specialty pharmaceutical company, recently announced the grant of US Patent No. 7,670,612 entitled "Multi-Phase, Multi-Compartment Capsular Delivery Apparatus and Methods for Using Same." The delivery system has uses for bio-pharmaceutical, pharmaceutical, medical foods and nutraceutical products. In addition to the existing New Zealand patent, this patent covers the company's multiphase multi-compartment delivery system used to enable the development of multicompartment, multi-phase delivery forms (two piece capsule based) of combination products that have compatibility, formulation or targeted delivery obstacles.



"This is a significant development for INNERCAP Technologies NOVACAP technology," said Fred H. Miller, Chief Executive Officer at INNERCAP. "The continued growth of our patent portfolio establishes INNERCAP as one of the leading companies in this space."

The delivery system and combinations covered by the patent have the ability to deliver therapeutic entities that have never been combined previously and now can be administered together, via an oral, implanted, or suppository capsule, in the most advantageous pharmacokinetic profile, utilizing different physical phases. This technology can therefore be used to enable capsule administration of compounds that are not normally administered as a combination product. The efficacy, safety, and side-effect profiles of drugs can be substantially improved using this delivery technology. It will also provide very significant quality-of-life improvements for patients and substantial economic savings for hard-pressed healthcare systems.

"INNERCAP's multi-phase, multi-compartment technology has been commercially manufactured and validated in several products, demonstrating that INNERCAP's delivery system creates real value to consumers and branded manufacturers," added Mr. Miller.

INNERCAP was represented by Cliff Davidson, Esq. of the patent firm Davidson, Davidson & Kappel, LLC (www.ddkpatent.com) based in New York City.

For more information contact us at the telephone number and email address below:

INNERCAP® TECHNOLOGIES, INC

United States Patent No. 7,670,612
US and International Patents Pending

9216 Palm River Road, Suite 203 • Tampa, FL 33619 USA • (813) 837-0796 • www.innercap.com • busdevelopment@innercap.com

The Editorial Advisory Board

MARKET NEWS AND TRENDS

Valeant & Biovail Agree to Merge, Combination Creates Leader in Specialty Pharmaceuticals

Valeant and Biovail recently announced that both companies' Boards of Directors have unanimously approved a definitive merger agreement under which the companies would combine to generate enhanced value for stockholders. The combined company will be called Valeant Pharmaceuticals International, Inc.

Valeant and Biovail believe the new Valeant's scale, financial strength, and complementary product lines will enable it to pursue substantial growth opportunities. The combined company will have a significantly expanded presence in North America and operations in eight other countries, working across four growth platforms. The new Valeant will be able to leverage its complementary product lines and operations in specialty Central Nervous System (CNS), dermatology, Canada, and emerging markets/branded generics. In addition, the combined company will have limited patent exposure and enjoy strong and stable cash flows from legacy products that will support future growth. The new Valeant, on a 12-month trailing basis as of March 31, 2010, would have experienced double-digit revenue growth.

Under the terms of the agreement, Valeant stockholders will receive a one-time special cash dividend of $16.77 per share immediately prior to closing of the merger and 1.7809 shares of Biovail common stock upon closing of the merger in exchange for each share of Valeant common stock they own. The transaction is intended to qualify as a tax-free reorganization for Valeant stockholders. Upon the completion of the merger, which is expected to occur before the end of the year, Biovail stockholders will own approximately 50.5%, and Valeant stockholders will own approximately 49.5% of the shares of the combined company on a fully diluted basis. For Biovail stockholders, this transaction represents a 15% premium based on a calculation of the stock prices over the last 10 trading days. It is anticipated that by December 31, 2010, contingent upon the closing of the merger and subject to approval by the new Valeant's Board of Directors and to applicable law, the combined company will pay an additional one-time $1.00 per share dividend to all stockholders of the new combined entity, after which the new Valeant does not intend to pay dividends. To finance the transaction, the companies have secured a commitment of $2.8 billion through a term loan facility provided by Goldman Sachs Bank USA, Morgan Stanley & Co. Incorporated, and Jefferies & Company, Inc. Existing Valeant 7.625% and 8.375% senior unsecured notes will be refinanced as part of the transaction.

J. Michael Pearson, currently Chairman and Chief Executive Officer of Valeant, will serve as the new Valeant's Chief Executive Officer, residing in Barbados, and Bill Wells, currently Chief Executive Officer of Biovail, will be the non-executive Chairman. The new Valeant's Board of Directors will consist of 11 members, including five Biovail representatives, five Valeant representatives and one additional independent Canadian resident director to be identified through a search process and nominated by Valeant and agreed upon by Biovail. Robert A. Ingram, currently lead director of Valeant, will serve as lead independent director of the new Valeant's Board. Michael Van Every, currently Chairman of Biovail's Audit Committee, will serve in the same function for the combined Board.

The new Valeant will retain Biovail's corporate structure and related financial efficiencies, leading to enhanced financial performance. Following the completion of the merger, it is anticipated that the transaction will be cash EPS accretive to both companies' stockholders within the first 12 months post-close. On a trailing 12-month basis as of March 31, 2010, the combined company would have had pro forma revenues of $1.75 billion and pro forma cash flow from operations of $575 million. The new Valeant expects to generate at least $175 million in annual cost synergies in the second year.

Intellipharmaceutics Files ANDA for Generic Protonix

Intellipharmaceutics International Inc. recently announced it has filed an ANDA with the US FDA for a generic of Protonix (delayed-release pantoprazole sodium). Protonix inhibits gastric acid secretion and is prescribed for the short-term treatment of conditions such as stomach ulcers associated with gastroesophageal reflux disease as well as the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome. Sales of pantoprazole sodium delayed-release tablets in the US were approximately $1.8 billion in 2009. Pantoprazole delayed-release tablets is the fourth ANDA product candidate that Intellipharmaceutics has disclosed from its 15-product pipeline, which includes both ANDA product candidates and the development of new drugs through the S.505(b)(2) NDA regulatory pathway.

"I am extremely pleased with the progress we continue to make with the advancement of our product pipeline," said Dr. Isa Odidi, CEO of Intellipharmaceutics. "Protonix is the second ANDA we have filed with the FDA this year and, together with Focalin XR and Effexor XR, it represents another potential source of future revenue from our company's ANDA pipeline."

Intellipharmaceutics International Inc. is a pharmaceutical company specializing in the research, development, and manufacture of novel controlled- and targeted release oral solid dosage drugs. The company's patented Hypermatrix technology is a unique and validated multidimensional controlled-release drug delivery platform that can be applied to the efficient development of a wide range of existing and new pharmaceuticals. Based on this technology, Intellipharmaceutics has a pipeline of products in various stages of development in therapeutic areas that include neurology, cardiovascular, GIT, pain, and infection.

Avista Capital Partners Commits $48.5 Million to OptiNose to Develop Nasal Delivery Technology

Avista Capital Partners, a leading private equity firm, recently announced it has committed to invest $48.5 million in OptiNose, which has developed an innovative nasal drug delivery technology that enables administration of drugs deep in the nasal cavity, enabling the treatment of both local and systemic disease. In conjunction with this investment, OptiNose will reincorporate in the US and move its headquarters from Oslo, Norway, to Yardley, PA.

OptiNose, which was founded by Dr. Per Djupesland in 2000, has extensively tested its nasal drug delivery device under the leadership of the current CEO, Helena Kyttari Djupesland. The company recently completed Phase II clinical studies for chronic rhinosinusitis with polyposis, chronic rhinosinusitis without polyposis, and migraine therapies with positive results. Avista's investment will support Phase III trials and enable OptiNose to build out its clinical development and commercialization infrastructure. WFD Ventures, a New York-based venture capital firm specializing in medical technology investing, will also maintain a significant stake in the company and continue to actively support the development program.

Peter Miller, the President and former Chief Executive Officer of Take Care Health Systems, a business Mr. Miller co-founded and sold to Walgreens, has been appointed the new Chief Executive Officer of the company and will serve on the OptiNose Board of Directors. Prior to joining Take Care Health Systems, Mr. Miller spent over a decade at Johnson & Johnson in senior executive positions.

"OptiNose's technology is extremely promising for the indications slated to begin Phase III trials and for a wide variety of other applications," said Larry Pickering, an Avista healthcare industry executive who will become the new Chairman of OptiNose. "We look forward to supporting the company as it enters these trials with a low risk development pathway. I have known Mr. Miller since his time at Johnson & Johnson, and am convinced he is the ideal executive to lead this company."

"I am very excited about the opportunity to lead a company that has core technology with such strong potential, and to work with the talented OptiNose team and a group of investors with such a history of success," added Mr. Miller. "OptiNose's devices deliver intranasal drugs in a completely new way to targeted regions of the nasal cavity, including the sinuses and the olfactory region, without lung deposition. I believe this technology provides a broad platform for delivering significant value to patients, physicians, and payers, with potential applications in pharmaceuticals, vaccines, and OTC products."

"We are delighted to welcome Peter Miller and Avista Capital Partners to the OptiNose team," said Dr. and Ms. Djupesland. "We strongly believe in our technology, which solves many of the common problems associated with current nasal drug delivery techniques. With Mr. Miller's leadership and healthcare background, and the support and deep healthcare experience offered by Avista and WFD Ventures, we are confident in our ability to leverage our device's potential with many compounds."

OptiNose is a drug delivery company with breakthrough technology set to transform the static nasal drug delivery market. The company was founded in 2000 to commercialize a novel nasal drug delivery system that achieves targeted delivery to sites that are poorly accessed by existing nasal sprays. The technology is unparalleled in its ability to effectively deliver drugs to specific sites within the nose, while uniquely preventing drug distribution to the lungs.

Aradigm Announces Private Placement for $5 Million

Aradigm Corporation recently announced it has entered into a definitive agreement for the sale of common stock and warrants to three existing shareholders and one new investor in a private placement for aggregate gross proceeds of approximately $5 million. The closing of the private placement is subject to the satisfaction of customary closing conditions.

Under the terms of the agreement, Aradigm has agreed to sell an aggregate of 34,702,512 shares of common stock at a price of $0.1184 per share and warrants to purchase an aggregate of 7,527,215 shares of common stock, which become exercisable at an exercise price of $0.1184 per share upon the company's receipt of shareholder approval to increase the number of authorized shares of the company's common stock. The warrants include a mandatory exercise provision whereby the company has the right to require the holder to exercise the warrant following the company's receipt of such shareholder approval. After deducting for fees and expenses, the net proceeds from the sale of the shares of common stock are anticipated to be approximately $3.7 million, and the net proceeds from the exercise of the warrants following the company's receipt of such shareholder approval are anticipated to be approximately $0.9 million.

Aradigm will be required, among other things, to file a resale registration statement within 30 days following the closing that covers the resale by the purchasers of the shares and the shares issuable upon exercise of the warrants.

"We are very pleased with the support of our shareholders in this private placement, and we welcome our new investor," said Igor Gonda, President and Chief Executive Officer of Aradigm. "These proceeds will enable us to take further steps in the development of our lead product candidate, inhaled liposomal ciprofloxacin, required for Phase III studies and filing an NDA."

Aradigm is an emerging specialty pharmaceutical company focused on the development and commercialization of a portfolio of drugs delivered by inhalation for the treatment of severe respiratory diseases by pulmonologists. The company has product candidates addressing the treatment of cystic fibrosis, bronchiectasis, inhaled bioterrorism infections, and smoking cessation.

Market News and Trends

BD Launches World's Smallest Pen Needle

BD (Becton, Dickinson and Company), a leading global medical technology company, recently announced the launch of BD Ultra-Fine Nano, the world's smallest pen needle. The BD Nano pen needle is proven to be as effective as longer needles for patients of all body types and proven to offer a less painful injection experience for the more than 5 million people in who inject insulin or GLP-1 to manage their diabetes.

"BD is committed to helping improve the injection experience for the millions of people who live with diabetes, as demonstrated by our long history of innovative firsts - the first insulin syringe in 1924, the first 5-mm pen needle in 1999, and now the world's first 4-mm pen needle, the BD Nano," said Linda Tharby, President, BD Medical - Diabetes Care. "We are confident this tiny needle can have a big impact by easing diabetes patients' transition and ongoing adherence to injectable drug therapy regimens, a key element in helping reduce the disease's deadly, debilitating, and costly complications."

Studies suggest that as many as one-fifth to one-third of people with diabetes are hesitant or unwilling to give themselves insulin injections for reasons that include needle anxiety. Patients who reported injection-related pain or embarrassment intentionally skipped insulin injections. The short length (4 mm) and thin gauge (32 G) of the BD Nano pen needle may help people with diabetes adhere to an insulin injection regimen and improve outcomes with its comfort and ease of use.

"Diabetes tools have just gotten a lot better with the release of BD's new 4-mm insulin pen needle," said Kris Swenson, RN, CDE, and Co-owner and Co-founder of the Diabetes Management and Training Centers, Inc., Phoenix, AZ. "The latest science shows that insulin injections with these new short and fine pen needles are just as effective in the delivery of insulin, and also much less frightening. This should help people get started on insulin much sooner, before long-term health problems occur."

Clinical trials demonstrated that insulin injections with the BD Nano pen needle provide equivalent glucose control to longer insulin pen needles. It effectively delivers an insulin dose to subcutaneous tissue, the recommended site for insulin injections, while reducing the risk of injecting into muscle. Intramuscular injection can accelerate absorption and increase the risk of hypoglycemia. Subcutaneous injection allows the insulin to be absorbed at an appropriate rate, resulting in better glycemic control.

BD is a leading global medical technology company that develops, manufactures, and sells medical devices, instrument systems, and reagents. The company is dedicated to improving people's health throughout the world. BD is focused on improving drug delivery, enhancing the quality and speed of diagnosing infectious diseases and cancers, and advancing research, discovery, and production of new drugs and vaccines.

New Mountain to Acquire Mallinckrodt Baker

An affiliate of New Mountain Capital, LLC has recently entered into a definitive agreement to acquire Mallinckrodt Baker, Inc. (MBI) from Covidien. MBI is a leading global manufacturer and supplier of high purity chemicals used in the laboratory,

Pharmaceutical, and microelectronics industries. Its product line consists of over 12,000 products sold to research and development laboratories and manufacturers of pharmaceuticals, semiconductor chips, solar cells, and flat panel displays.

New Mountain identified MBI through a proactive focus on the specialty chemicals and materials space. New Mountain is providing MBI with significant financial and strategic resources to support future growth initiatives, which include expansion of its activities in current end markets as well as acquisitions.

"For over a year, New Mountain has been working closely with Raj Gupta and other industry executives to find a new platform to build into a leader in high-growth, high value-added niches of the specialty chemicals and materials industries," said Steve Klinsky, Founder and CEO of New Mountain. "As CEO of Rohm and Haas, Mr. Gupta helped build that company to $19 billion of enterprise value, and we look forward to working with him and MBI's managers to build the company."

"After the sale of Rohm and Haas, I chose to join New Mountain over a year ago because of NMC's unique track record of building great businesses and employing sound capital structures," added Mr. Gupta, Senior Advisor at New Mountain Capital. "With New Mountain as its partner, MBI can be positioned as a leading global player in the pharmaceutical, laboratory, and electronic segments of the specialty chemicals and materials industry. We look forward to supporting an accelerated growth plan that builds upon the current strengths of the company."

Headquartered in Phillipsburg, NJ, MBI 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 Laboratory Chemicals. These products are widely used in research and quality control laboratories, microelectronics, environmental testing laboratories, universities, and for manufacturing in the pharmaceutical, biotechnology, and other industrial markets.

Market News and Trends

Multistage Nanovector System Provides Sustained Delivery of siRNA Cancer Therapeutic in Mice

New research by scientists at The University of Texas Health Science Center at Houston (UTHealth) and The University of Texas M.D. Anderson Cancer Center could make it easier for patients to use a family of promising experimental cancer therapeutics known as small interfering RNA (siRNA). siRNA is a part of an innovative strategy to disrupt the activity of cancer-related genes that has broad applications to other diseases.

In the May issue of Cancer Research, the scientists reported that a multistage nanovector system for the delivery of siRNA significantly lengthened the therapeutic effects of the treatment in two independent mouse models of advanced ovarian cancer. The researchers reported that a single intravenous dose of siRNA targeting the EphA2 oncoprotein provided the same tumor shrinkage for 3 weeks as that now achieved by six doses over the same period.

"The multistage delivery system is revolutionary in that it allows the therapeutic payloads to cross the biological barriers in the body and reach their target. It further helps release agents over long periods of time directly into the bloodstream, which is unprecedented," said Mauro Ferrari, PhD, Chairman of the Department of NanoMedicine and Biomedical Engineering at The University of Texas Medical School at Houston, which is part of UTHealth. "We are very excited about the results of this paper as it provides the first validation of the therapeutic advantages of the multistage delivery system in animal models of cancer."

The multistage nanovector system is composed of nanoporous silicon carrier particles that are about 100 times smaller than a strand of hair, which can be loaded with tiny bubbles of fat called nanoliposomes containing siRNA. The system provides for the release of the nanoliposomes and their contents.

"This is an exciting development because RNA interference has worked well in an animal model but has such a short half-life that it requires frequent delivery," said Anil Sood, MD, Professor in M.D. Anderson's Departments of Gynecological Oncology and Cancer Biology. "A 3-week dosing period is much closer to the sustained dosing needed to properly test this therapy in clinical trials." The multistage nanovector system was developed in Dr. Ferrari's laboratory, and the liposomal siRNA was developed at M.D. Anderson.

"We have provided the first in vivo therapeutic validation of a novel, multistage siRNA delivery system for sustained gene silencing with broad applicability to pathologies," wrote Takemi Tanaka, PhD, a co-first author and a research assistant professor of nanomedicine and biomedical engineering at the UT Medical School at Houston, and the other investigators in the paper.

"EphA2 is an important target because it's overexpressed in 70% of ovarian cancers and is strongly associated with poor survival and a higher likelihood of advanced or metastatic disease," said Gabriel Lopez-Berestein, MD, Professor of Experimental Therapeutics at M.D. Anderson. "It's also overexpressed in melanoma, breast, and lung cancers with the same poor prospects for patients."

The protein is not present in normal tissue and cannot beattacked using more traditional drug approaches.

BioDelivery Sciences Announces Commercial Partnership for BEMA Fentanyl

BioDelivery Sciences International, Inc. (BDSI) recently announced it has entered into a license and supply agreement with Kunwha Pharmaceutical Co., Ltd., for the exclusive rights to develop and commercialize BEMA Fentanyl (marketed as ONSOLIS in the US) in the Republic of Korea. The agreement results in potential milestone payments to BDSI of up to $1.275 million, which includes an up-front payment of $300,000. In addition, BDSI will receive an ongoing royalty based on net sales.

"We are very pleased to partner with Kunwha on the continued global commercialization of BEMA Fentanyl," said Dr. Mark A. Sirgo, President and Chief Executive Officer of BDSI. "Kunwha has a long history in Korea and a strong market presence, as demonstrated by their sales force of 150 well-trained and experienced medical and sales representatives and is, we believe, ideally suited to address the specific needs of the Korean marketplace."

Kunwha will be responsible for the regulatory filing of BEMA Fentanyl in South Korea as well as future commercialization in that territory. BEMA Fentanyl is approved in the US and Canada, under the trade name ONSOLIS, for the treatment of breakthrough pain in opioid-tolerant adult patients with cancer, and BDSI anticipates approval in the EU later this year. BEMA Fentanyl is licensed to Meda AB for all territories with the exception of Taiwan and South Korea.

BDSI is a specialty pharmaceutical company leveraging its novel and proprietary patented drug delivery technologies to develop and commercialize, either on its own or in partnerships with third parties, new applications of proven therapeutics. The company is focusing on developing products to meet unmet patient needs in the areas of pain management and oncology supportive care. BDSI's pain franchise currently consists of two products utilizing the company's patented BEMA buccal soluble film technology.

Market News and Trends

PPD & Furiex Announce Completion of Spin-Off

PPD, Inc. and Furiex Pharmaceuticals, Inc. recently announced the successful completion of the spin-off of Furiex. As previously announced, PPD received a private letter ruling from the Internal Revenue Service that the dividend of common stock of Furiex to PPD shareholders qualifies as a tax-free distribution for US income tax purposes. On June 14, 2010, shareholders of record of PPD as of June 1, 2010, received a pro rata dividend of one share of Furiex common stock for every 12 shares of PPD common stock they held. Fractional shares were paid in cash.

PPD and Furiex now operate as two independent companies. PPD has no ownership of Furiex. PPD will continue as a leading global contract research organization, and Furiex will advance the former compound partnering business of PPD.

To facilitate the advancement of the development programs, PPD transferred $100 million in cash to Furiex prior to the spin-off. In addition, Furiex has assumed current accounts receivable and payable associated with the compound partnering business. As previously announced, Takeda Pharmaceutical Company Limited recently received pricing approval for NESINA (alogliptin) in Japan, triggering a $7.5-million milestone payment to PPD. PPD will recognize this milestone payment as revenue in the quarter ending June 30, 2010, but PPD is transferring the account receivable for this payment to Furiex. The accounts receivable Furiex is assuming from PPD consist primarily of the $7.5 million Takeda milestone payment. The assumed accounts payable, which are predominantly to third-party vendors, should substantially offset the assumed accounts receivable, resulting in approximately $100 million of net working capital as of June 14, 2010.

PPD common stock will continue to trade on the NASDAQ Global Select Market under its current ticker symbol, PPDI. Furiex common stock begins trading on a "regular way" basis on the NASDAQ Global Market under the ticker symbol FURX.

Furiex Pharmaceuticals is a drug development collaboration company using innovative clinical development design to accelerate and increase value of partnered drug programs by advancing them in a cost-effective, efficient manner.

PPD is a leading global contract research organization, celebrating 25 years of providing drug discovery, development, and life-cycle management services. Clients and partners include pharmaceutical, biotechnology, medical device, academic, and government organizations.

Regulus Therapeutics & Sanofi-Aventis Form Largest microRNA Therapeutics Alliance to Date

Regulus Therapeutics Inc. and sanofi-aventis recently announced they have entered into a global, strategic alliance to discover, develop, and commercialize microRNA therapeutics. The alliance represents the largest microRNA partnership formed to date, valued at potentially over $750 million, and includes a $25-million up-front fee, a $10-million future equity investment subject to mutual agreement on company valuation, and annual research support for 3 years with the option to extend 2 additional years. Alnylam Pharmaceuticals and Isis Pharmaceuticals formed Regulus in 2007, with each company currently owning approximately 50% of the preferred stock.

The alliance will initially focus on the therapeutic area of fibrosis. Regulus and sanofi-aventis will collaborate on up to four microRNA targets, including Regulus' lead fibrosis program targeting microRNA-21. sanofi-aventis also receives an option for a broader technology alliance that provides Regulus certain rights to participate in development and commercialization of resulting products. If exercised, this 3-year option is worth an additional $50 million to Regulus. microRNAs are a new class of small non-coding RNAs that regulate gene expression by interfering with translation or stability of target messenger RNA transcripts. Endogenous microRNAs regulate the expression of over one-third of all human genes, and the association of microRNA dysfunction with disease phenotypes has given rise to an entirely new class of pharmaceutically relevant targets. In preclinical studies, Regulus has demonstrated that modulating microRNAs can effectively regulate disease pathways and produce therapeutically beneficial effects.

"This new partnership continues to illustrate sanofi-aventis' commitment to develop innovative therapies," said Marc Cluzel, MD, PhD, Executive Vice-President, Research & Development, sanofi-aventis. "microRNAs are believed to be extremely important in human development and physiology. Together with Regulus, we will develop therapeutics that could potentially open a new paradigm in the treatment of major diseases and could offer an attractive new therapeutic approach for patients."

"Regulus is very pleased to form this landmark alliance with sanofi-aventis, a leading visionary company developing important new medicines," added Kleanthis Xanthopoulos, PhD, President and Chief Executive Officer of Regulus. "The significant support from sanofi-aventis in this new alliance will strengthen our efforts as we continue to build the leading microRNA therapeutics company through our commitment to scientific excellence and advancement of our pipeline of innovative new medicines. Indeed, this landmark alliance will significantly extend our capabilities and resources to lead the discovery and development of microRNA therapeutics."

Prefilled Syringes: Injecting the End-User's Perspective

By: Misty Hughes, Research Analyst, Pharmaceuticals & Biotechnology, Frost & Sullivan

INTRODUCTION

The FDA recognizes 111 routes of administration for drugs. Of these, the most commonly used are topical, oral, ocular, nasal, pulmonary, and injectable. Although the majority of products in development and on the market in the US are oral formulations, injectables are an integral part of the pharmaceutical market.

In 2009, there were 309 new injectable compounds in clinical development for treating over 100 diseases (Figure 1). Their ability to bypass the digestive system and deliver therapies locally or systemically makes them ideal for treating a large variety of diseases. With ever-increasing numbers of Americans suffering from diseases like diabetes, cancer, and autoimmune disorders, the patient population requiring treatment via injection is steadily escalating. According to a 2007 report in the Journal of Oncology Practices, the number of US cancer patients or survivors is expected to increase by 55% to 18.2 million by 2020, from 11.7 million in 2005. Similarly, according to the American Diabetes Association, 8% of Americans (23.6 million) have diabetes, and 1.6 million new cases are diagnosed each year.

For compounds with poor bioavailability, like the majority of biopharmaceuticals and cancer medications, injection is the only viable and effective delivery route. A large number of FDA-approved injectable medications are biopharmaceuticals. Biopharmaceuticals are derived from living sources and may be composed of living cells, tissues, sugars, proteins, or nucleic acids. As these large and complex molecules are easily denatured or altered with harsh handling or processing, in most cases, oral drug delivery is not an option. When a drug is taken orally, several key factors affect its absorption into the bloodstream. For example, macromolecules taken orally tend to have poor bioavailability because they are broken down by the gastrointestinal tract or are unable to pass through the epithelial cells that line the tract.

Nevertheless, when compared to oral and inhaled modes of delivery, the injectable route can be complicated, expensive, uncomfortable, and inconvenient. It is estimated that 50% of all long-term medications are discontinued in the first year. For injectables, the non-compliance rate is particularly high. Most patients find self-injection challenging, especially those who have to inject medications that come in vials.

As part of the Frost & Sullivan customer research survey on preferences, usage patterns, and opportunities in US drug delivery, 450 patients with diabetes, chronic pain, or inflammation were presented with four drug delivery regimens (dose/time combinations): once-daily injection, twice-daily inhalation, twice-daily patch, or twice-daily oral. When asked to rank the desirability of the four choices to treat their disease, a once-daily injection was selected most frequently as the least desirable choice (Figure 2). In response to the rising demand from patients, physicians, and managed care providers for cost-effective injectable delivery modes that improve self-administration, compliance, and safety, manufacturers are moving away from traditional vial-disposable syringes to self-injectable prefilled syringes.

BEYOND CONVENIENCE

The dosage preparation from vials and ampoules can be daunting and complicated. It requires multiple steps, including reconstitution or dilution if needed, placing the needle on the syringe, drawing the correct amount of medication into the syringe, and performing the injection. In addition, because the glass vials that injectable drugs are packaged in are typically overfilled by 25% to 30% to ensure the end-user can withdraw the required dose, more drug is often drawn than required. When the excess drug is purged out in efforts to reach the correct dosage, many times the final volume of drug in the syringe does not match the dosage requirement.

Ultimately, the complications associated with self-injecting

medications supplied in vials often promote non-compliance. As part of the aforementioned Frost & Sullivan customer research survey, 206 physicians were asked to rate in order of importance the top five factors considered when selecting a drug delivery type. Ease of use, patient satisfaction, patient convenience, and patient comfort were ranked as four of the top five most important factors by more than half the physicians polled (Figure 3).

Prefilled syringes make injectable medications safer and easier to use. Containing an exact dose of medication and a fixed needle, using a product packaged in a prefilled syringe typically involves nothing more than removing the syringe's packaging and injecting. By essentially eliminating the tedious steps required before using a drug in a vial, parenteral packaging innovations like prefilled syringes can help physicians tackle tough compliance barriers they face with patients on injectable drug regimens.

Beyond convenience are the cost savings. With the advent of expensive biotech drugs, eliminating overfilling is especially advantageous. Less waste can equate to significant cost savings all around.

Furthermore, as medication errors are a key area of concern in drug administration, prefilled syringes reduce the risk of misidentification and improper dosage delivery. Prefilled syringes are filled mechanically and checked electronically as a part of quality control at the manufacturing level. Eliminating human involvement helps ensure patients receive the correct dose, and clear labeling on the syringe and packaging diminishes the risk of busy, multi-tasking healthcare professionals administering the wrong product.

An additional benefit to healthcare professionals is that prefilled syringes also reduce the risk of needlestick injuries. In traditional formats, the needle tip remains exposed while the user performs a series of actions that require dexterity and concentration. Similarly, because prefilled syringes are single-use devices, the possibility of cross-infection arising from needle re-use is eliminated.

FIGURE 1

Injectable Drug Pipeline: Number of Injectable Compounds by Classification (U.S.), 2009

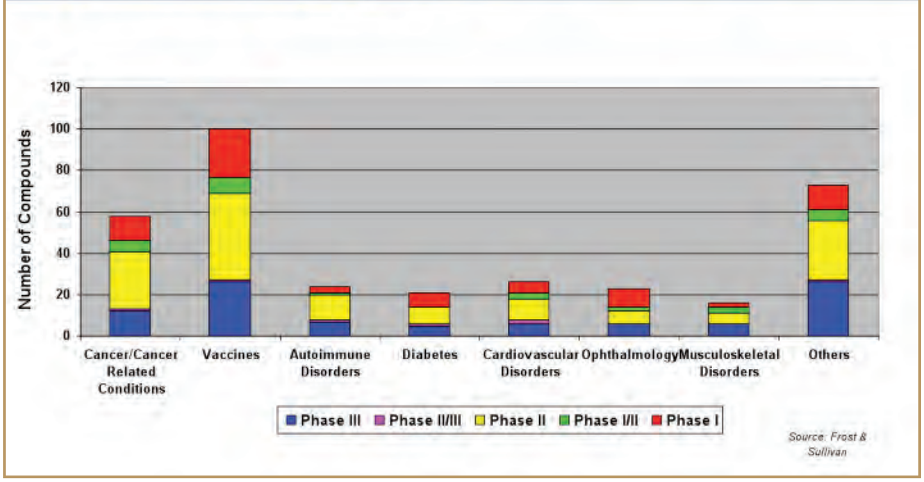
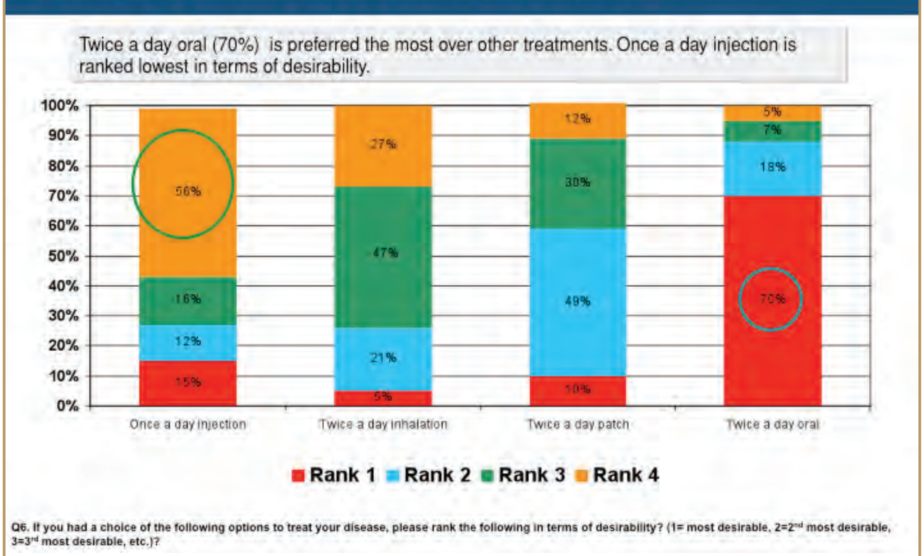


FIGURE 2

Drug Regimen Desirability - Patient



FEEDBACK ON INJECTABLE DRUG DELIVERY

Feedback from patients and physicians on factors such as perception, desired attributes, compliance, and drivers of adoption/non-adoption for different drug delivery types is valuable to companies developing or seeking to utilize novel drug delivery technologies. In terms of usage and satisfaction, patients with rheumatoid arthritis, type 1 diabetes, and type 2 diabetes were asked to select and then rate the presented methods of injectable drug delivery devices.

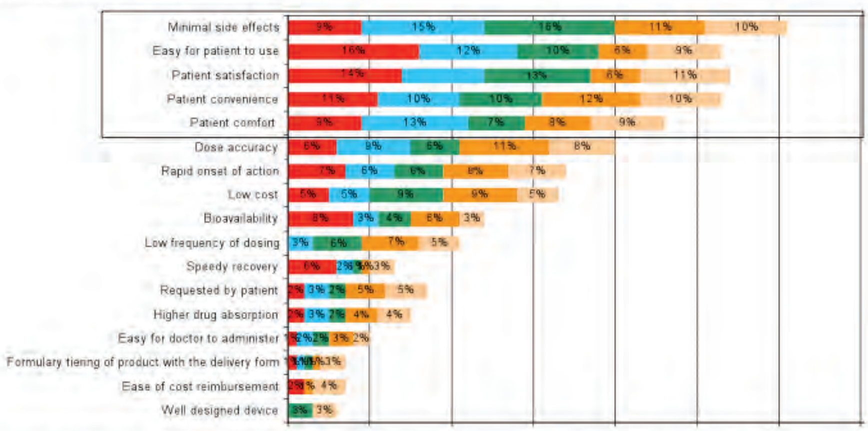
For survey participants with rheumatoid arthritis, 36% use prefilled syringes. Of them, half are very satisfied/satisfied with the device, while the balance rated their satisfaction at using the device to administer medication as neutral (Figure 4). Of the 29 type 1 diabetics surveyed, 25% of the respondents who use injection use prefilled syringes. Among those using prefilled syringes, half are very satisfied/satisfied with this device, while the other half are neutral with their use of the device in administering their medication. None expressed dissatisfaction (Figure 5). For type 2 diabetics, 22% of the 161 surveyed use prefilled syringe as their injection delivery device. Satisfaction is highest among prefilled syringes, with 75% noting they are very satisfied/satisfied. Interestingly, only the type 2 diabetics (16%) expressed any dissatisfaction with prefilled syringes (Figure 6).

In a separate 2009 Frost & Sullivan customer research survey in which cancer patients (n = 150) with breast, colorectal, prostate, and lung cancer were asked about their willingness to use autoinjectors and prefilled syringes as delivery mechanisms for their oncology treatment, 41% of patients said they were willing or very willing to use an autoinjector, while 31% were willing or very willing to use a prefilled syringe. Approximately one-third of patients were neutral for both delivery types. This could yield an education opportunity to developers if product benefits can be translated to the patient. Furthermore, a segment of patients were unwilling but would comply if prescribed by their

FIGURE 3

Factors for Selecting Drug Delivery Type - Physician

The top 5 factors considered by a majority (over 50%) of doctors are: minimal side effects, patients' ease of use, satisfaction, convenience, comfort.

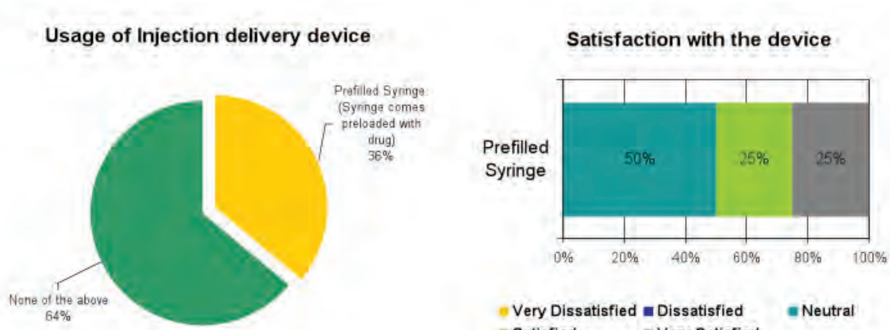


Q5. In order of importance, please select the top 5 factors that you consider when selecting a drug delivery type? (1= most important, 2=2nd most important, 3=3rd most important, etc.)

FIGURE 4

Injection Delivery Device: Rheumatoid Arthritis - Patient

About 36% of the Rheumatoid Arthritis patients who use injection use a prefilled syringe. About half of the respondents are satisfied with the device.



Q2c2 For injection delivery do you currently use either of the following Q2c3. How satisfied are you with your use of this method in administering your medication for rheumatoid arthritis ?

physician (13% for autoinjector, 17% for prefilled syringes). Overall, platforms that allow patients to self-inject at home and improve or make easier their injection experience is something that is beneficial and often sought after by them in their treatment (Figure 7).

PRODUCT DIFFERENTIATION: VALUE-ADDED MARKET OPPORTUNITY

Commercial advantages are key to a product's success. Medicines within therapeutic categories are increasingly hard to differentiate, making market conditions difficult for industry participants. Pharmaceutical companies are employing novel modes of drug delivery to overcome this challenge and get a leg up on the competition.

Prefilled syringe devices represent a growing, value-added market. The vast improvements in drug delivery devices like pen injectors and prefilled syringes not only make injections easier and safer, but the product differentiation they can provide gives products a competitive edge over similar medications that do not come in prefilled syringes or another self-injection system. For example, the SoloSTAR prefilled disposable pen is projected to be the major growth driver for Sanofi-Aventis' billion dollar Lantus franchise. With one and a quarter times greater capacity than other insulin pens, SoloSTAR is the only disposable prefilled insulin pen that offers patients a dosing range of as little as 1 to as much 80 units in one injection. Lantus racked up roughly $4.3 billion in sales in 2009, making it the leading branded insulin in the US and much of Europe.

Pharmaceutical companies invest millions of dollars to develop and patent a new drug; however, when a patent expires, the drug faces increasing competition from generic manufacturers selling the same molecule at a fraction of the brand's price. Innovator companies can prolong their compound's patent life by launching the same molecule in a prefilled syringe, which they can then sell at a premium price.

For example, in 2002 Teva Pharmaceuticals was able to salvage its multiple sclerosis therapy

FIGURE 5

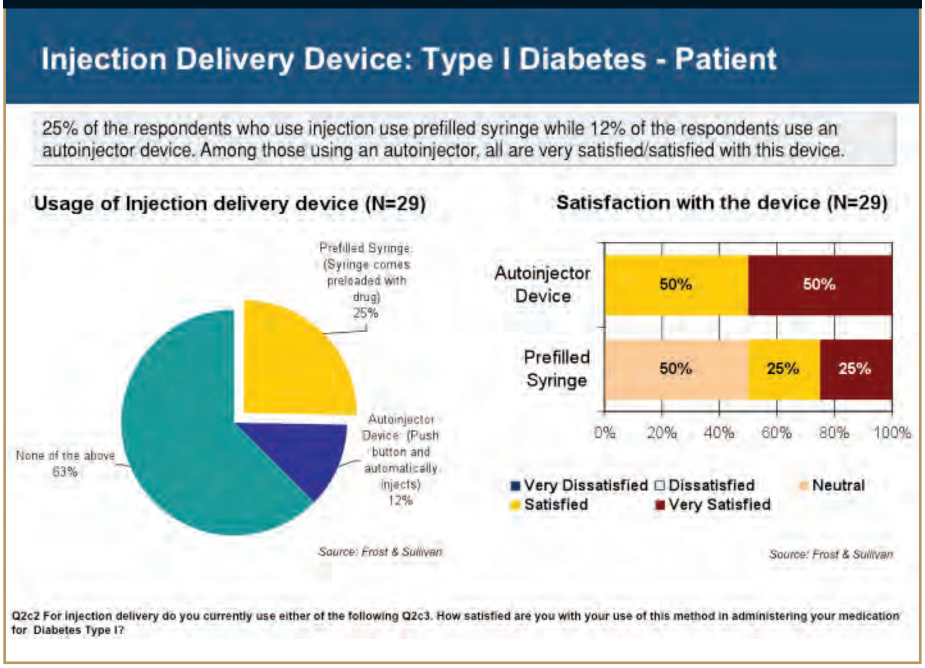


FIGURE 6

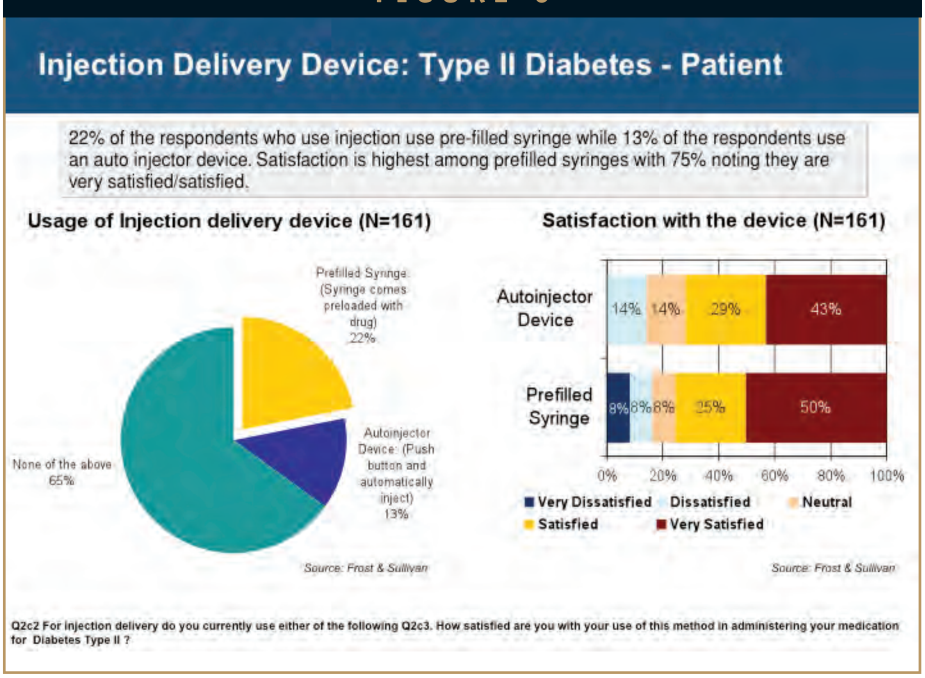
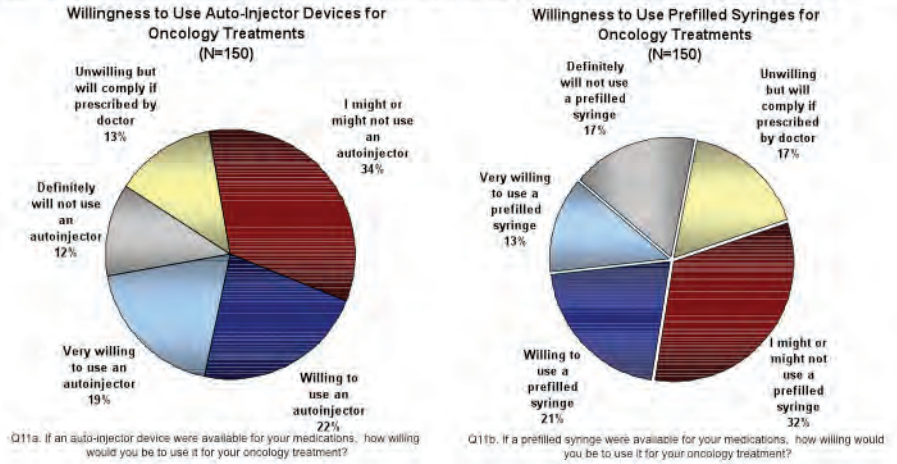


FIGURE 7

Willingness to Use Auto-injector & Prefilled Syringe: Cancer - Patient

Respondents indicated various degrees of willingness to use auto-injectors and pre-filled syringes. Roughly four out of ten (41%) were willing or very willing to use auto-injectors, while 31 percent were willing/very willing to use a prefilled syringe. About one-third of each group in each category indicated uncertainty ("might or might not use") which could represent an education opportunity.



Copaxone's declining market share by converting it from a lyophilized vial presentation into a stable liquid offered in a prefilled syringe. In spite of being offered at a premium price, over two-thirds of patients had converted to the prefilled version within its first 3 months on the market. An additional 3 months later, the conversion rate was 100%. The rapid uptake of the pricier, prefilled alternative is a testament to the role convenience and quality-of-life play in patients' and physicians' decisions to adopt novel drug delivery technologies. The market's acceptance of prefilled syringes has grown throughout the past decade, further encouraging pharmaceutical companies to employ them as a means to extend product life cycles and differentiate existing and new products from the competition.

SUMMARY

As managed care providers have uncovered ways to cut healthcare costs, the range of treatments completed on an outpatient basis has expanded, making at-home treatment, especially for injectable drugs, a key area of opportunity for many companies. The large product pipeline for injectables and prefilled syringes not only helps ensure the future potential of this market, but also provides a steady stream of innovation. Utilized in treating a variety of serious diseases ranging from diabetes to cancer and autoimmune disorders, injectable drugs and prefilled syringes have and will continue to play an integral role in the future of the pharmaceutical and biotechnology markets.

An in-depth report on this and other related topics can be obtained by contacting Frost & Sullivan at www.frost.com.

BIOGRAPHY

Misty Hughes is a Research Analyst for Frost & Sullivan's North American Pharmaceutical & Biotechnology practice. She focuses on monitoring and analyzing emerging trends, technologies, and market dynamics in the pharmaceutical and biotechnology industry in North America. Since joining Frost & Sullivan in April 2007, Mrs. Hughes has completed several research studies and consulting projects in oncology (breast cancer), vaccines, ophthalmic diseases/drug delivery, hyperlipidemia, and Alzheimer's disease. Prior to joining Frost & Sullivan, Mrs. Hughes worked as a pharmaceutical sales representative for Schering-Plough, Synthon Pharmaceuticals, and JDS Pharmaceuticals, where she covered the cardiovascular, allergy, and central nervous system markets. She earned her BA in Biology from Southwestern University in Georgetown, Texas.

SPECIAL FEATURE

Transdermal Delivery – Making a Comeback!

By: Cindy H. Dubin, Contributor

The interest in transdermal delivery in the 1980s was owed to the advantages of bypassing the traditional liver metabolized route, increased patient compliance, and reduced adverse events. However, the promise was short lived as several problems emerged upon development of transdermal drugs that included dose limitation, skin irritation, delayed time of action, and site-dependent absorption, says Barath Shankar, Research Analyst–Pharmaceuticals & Biotechnology, Frost & Sullivan. The waning of interest from Big Pharma resulted in a limited number of transdermal delivery-based drugs entering the market.

However, with thinning pipelines and fewer blockbusters, pharmaceutical companies are increasingly looking to innovative drug delivery routes to extend patent life. The success of transdermal drugs, especially nicotine-based transdermal products in the 1990s, brought back interest amongst pharmaceutical companies and has resulted in a significant upward trend that is likely to drive the market in the future, says Mr. Shankar.

While the passive transdermal delivery systems are "patch" based, the emerging "active" transdermal drug delivery platforms that incorporate innovative technologies include iontophoresis for non-invasively delivering drug molecules via a small electric current to enable charged drugs to permeate through the epidermis, electric patch-based systems that deliver a range of drug molecules; microneedle technology for targeted delivery of drug molecules across the skin membrane; and sonophoresis for the application of low-level ultrasound energy to increase permeability of the stratum corneum by creating reversible channels through the skin, permitting the delivery of drug molecules through the transdermal route.

Through the continued innovation and evolution of these various transdermal delivery methods, the global market for transdmeral formulations is estimated to reach $12.7 billion this year, and one-third of US drug products will rely on transdermal delivery.[1] *Drug Delivery Technology* recently spoke with some companies that never gave up on the idea that transdermal delivery is indeed an area with great potential now and for the future.

3M–MICRONEEDLES OVERCOME DELIVERY OBSTACLES

3M Drug Delivery Systems is focused on keeping pace with the drug delivery needs of its customers. With regard to transdermal technology, that means researching new technologies as well as continuing to bolster the efficacy of existing technologies through rigorous testing, explains Kris Hansen, PhD, MTS New Technology and Product Development Manager, 3M Drug Delivery Systems. Currently, 3M offers transdermal systems and components for small molecules, proteins, or peptides.

Traditional transdermal patch technology has been limited to the delivery of smaller, lipophilic molecules that can, in the presence of an adhesive patch, diffuse though the stratum corneum and pass into systemic circulation. Given the whole of the pharmaceutical market, and especially the biopharmaceutical market, there are few

FIGURE 1

3M Drug Delivery Systems' Solid Microstructured Transdermal System (sMTS) can provide a faster, more robust immune response than IM injection.

APIs compatible with this technology, says Dr. Hansen.

"The transdermal patch offers convenient, controlled release of a therapeutic through a continuous, diffusion-controlled delivery system. A patch is easy to use, and the comfort and convenience associated with a patch rank higher than either pulmonary, injection, or intranasal delivery amongst patients. A drug delivery platform that can provide the efficiency, versatility, and speed of delivery associated with a syringe injection with the comfort and convenience of a transdermal patch offers the opportunity to differentiate an existing product in a crowded market space or enhance the utility and acceptance of a new molecule in an emerging biopharmaceutical market," she says.

That's where 3M has overcome obstacles with its Solid Microstructured Transdermal System (sMTS) (Figure 1) and hollow microstructured transdermal systems (hMTS) technologies. 3M has developed a method of solid microneedle delivery that expands the range of medications that can be delivered transdermally to patients, using biocompatible, polymeric microneedles to bypass the barrier properties of the stratum corneum and deliver previously undeliverable molecules, including vaccines, proteins, and peptides to the system.

3M's microneedle platform is targeted to biologics, including vaccines, hormones, treatments for autoimmune diseases, anemia/neutropenia, and osteoporosis. A key advantage of 3M's microneedle system is that the company has found a way to manufacture and dry onto the microneedles in such a manner that the drug doesn't require cold storage.

"If you can eliminate the need for cold storage, the distribution and access to that drug or that dosage form can be widened quickly because it can be distributed a lot faster and less expensively," says Dr. Hansen. "In the case of vaccine delivery, the sMTS technology can actually provide a faster, more robust immune response than can be achieved by IM injection."

As 3M has secured partner contracts for its sMTS, the company has shifted some of its R&D focus into expanding research into hMTS, which allows liquid forms of protein-based drugs and vaccines to be delivered, expanding the range of medications that can be delivered transdermally.

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

To better understand the potential of the hMTS to deliver non-traditional therapeutics as efficiently as a syringe, a number of pharmacokinetic (PK) studies have been conducted. Studies were conducted in swine using the hMTS device. A human growth hormone (hGH) formulation (1 mg/mL) was administered to anesthetized swine using the hMTS device or by subcutaneous injection. Blood samples were collected at intervals over an 8-hour period. Results showed the average bioavailability associated with hMTS delivery is equivalent to that determined by syringe administration; peak blood levels associated with hMTS delivery exceeded those resulting from traditional injection.

Additionally, an hMTS tolerability study was conducted in humans using a placebo formulation administered with the hMTS proof-of-concept (POC) device. A total of 48 deliveries between 0.75 to 1 mL were administered to the upper arm or upper thigh of healthy subjects between the ages of 18 to 40 years. Phase III clinical trials are expected to commence with a partner within the next 3 years.

"With study data continuing to show that the hMTS technology can provide similar bioavailability to that of subcutaneous injection, but in a patient-friendly delivery method, the future for this technology is very bright indeed," says Dr. Hansen. "Both the sMTS and hMTS technologies continue to have significant potential in the marketplace and will remain a featured focus for this company well into the future."

FIGURE 2

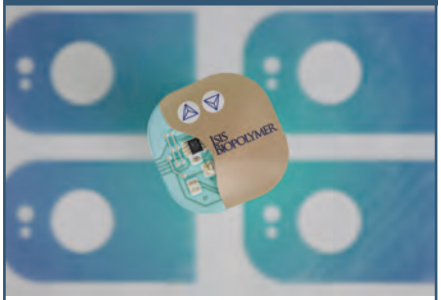
With a small, easy-to-apply skin patch, the PassPort® system enables bolus or sustained delivery of water-soluble biologics and small drugs for acute or chronic conditions.

ALTEA THERAPEUTICS–NEEDLE INJECTIONS REPLACED BY SAFE AND CONVENIENT SKIN PATCH

In April 2009, Altea Therapeutics announced it entered into an agreement with Eli Lilly and Company and Amylin Pharmaceuticals, Inc. to develop and commercialize a daily transdermal patch delivering sustained levels of exenatide using its proprietary PassPort® Transdermal Delivery System (Figure 2). Exenatide, the first-in-class incretin mimetic approved for the management of type 2 diabetes, is currently available on the market as a twice-daily injectable under the brand name Byetta®.

Lilly and Amylin will fund all product development, manufacturing, and commercialization activities for the product. In addition, Altea Therapeutics received from Lilly and Amylin an up-front license payment and may receive clinical, regulatory, and sales milestones of up to $46 million, and royalties on future product sales. As part of the

FIGURE 3



IsisIQ™ is a fully programmable, single-use, "band-aid-like" active patch that controls and monitors transdermal delivery of up to three drugs.

agreement, an equity investment in Altea Therapeutics was included.

In January 2010, Altea Therapeutics announced a partnership with KAI Pharmaceuticals for the preclinical and clinical development of certain KAI proprietary peptides using the PassPort System. Under the terms of the agreement, Altea and KAI will examine the transdermal delivery of certain KAI proprietary compounds using Altea's transdermal delivery technology. Altea has also granted KAI an option to receive a worldwide technology license for the further development and commercialization of these transdermal products. Should KAI exercise the option, KAI will fund all product development, manufacturing, and commercialization activities, and Altea may receive license payments, development, and commercialization milestones and royalties on product sales from KAI.

Altea is also developing a transdermal version of enoxaparin sodium (currently available on the market as Lovenox® injection) with Hospira. The company is in clinical development for a Transdermal Basal Insulin Patch that provides continuous delivery of insulin for people with type 1 and type 2 diabetes, and for a Transdermal Fentanyl Citrate Patch that enables rapid and safe management of moderate-to-severe pain.

"Altea's partnerships with Lilly/Amylin, KAI, and our existing partnerships with Hospira and other pharmaceutical companies are significant events that both validate our transdermal PassPort System technology and provide us with significant business opportunities," says Steven P. Damon, SVP, Business Development at Altea Therapeutics. Currently, the company is seeking to license its basal insulin patch and its fentanyl citrate patch, both in Phase I clinical development. Altea Therapeutics is also targeting pharmaceutical companies interested in leveraging the PassPort System for transdermal delivery of their proprietary compounds."

The PassPort System offers a safe, painless, and convenient way to deliver a range of currently injected compounds via the skin. With a small, easy-to-apply skin patch, the technology enables bolus or sustained delivery of water-soluble biologics and small drugs, providing dosing flexibility and significantly extending the range of diseases that can be treated using a method of drug administration proven to lead to high patient compliance. In addition, the technology has optional features that provide for dose recording, dose lock-out, and dosing reminders, designed to further enhance drug effectiveness.

"By providing a safer, more convenient dosage form, this technology has the potential to grow the current market of transdermal patches by replacing injections and in some cases even oral agents'" adds Mr. Damon.

Altea Therapeutics PassPort Transdermal System has been shown to be safe in more than 5,500 uses in humans. The company has tested its transdermal patch across many different therapeutics areas and a range of patients and subjects in clinical trials.

"The data that we are able to share include the transdermal delivery of active insulin over 24 hours in human subjects from our patch," explains Mr. Damon. "In addition, with our fentanyl citrate patch, we have demonstrated kinetics comparable to 50 mcg/hr of intravenous infusion of fentanyl citrate over 24 hours–from a skin patch the size of a thumbnail. These data demonstrate the capability of our transdermal technology to provide continuous dosing. In addition, we have conducted some initial studies with parathyroid hormone and some other compounds that demonstrate our ability to successfully achieve a bolus dosing profile with our patch."

Altea is currently conducting preclinical feasibility studies with several pharmaceutical companies to assess the feasibility of transdermal delivery of proprietary compounds using its PassPort Transdermal System.

"We have developed a highly successful model that allows us to conduct proof-of-concept studies very quickly and cost effectively," says Mr. Damon. "We have an integrated operation at our Atlanta facility, ranging from animal testing to Phase I clinical research and everything in between. We are collaborating with various pharmaceutical companies under this feasibility model, and we hope to convert these collaborations into development and commercialization agreements."

Moving forward, Mr. Damon says that Altea's greatest challenge is the same one that all transdermal technologies must overcome. A patch must be commercially viable to succeed. In addition to safety and convenience, the patch formulation must offer efficient drug delivery and be cost effective.

"In other words, if the patch delivers 1% of the payload and/or cannot meet the required therapeutic levels, just delivering drugs transdermally does not create much or any value for the industry," he says. "With the PassPort System, our scientists work to meet and overcome these challenges. Our cutting-edge approach to advance technology and science provides the potential to make our patch commercially viable and cost effective, in addition to all the other benefits we offer."

The company plans to leverage its ability to transdermally deliver biologics. By enabling transdermal delivery of biologics, Altea Therapeutics has the potential to develop "biobetter" patches, providing differentiation from competitor biologics and biosimilar injectable drugs, he says.

ISIS BIOPOLYMER–A NEW APPROACH TO IONTOPHORESIS

The development of "active" transdermal devices has allowed for a modulated and more effective drug delivery approach, notably iontophoresis. Encompassing the technologies of electrical engineering, polymer chemistry, and fluid dynamics, Isis Biopolymer has developed an iontophoretic drug delivery device with a design that is both patient and physician friendly.

IsisIQ™ (Figure 3) is a fully programmable, single-use, "band-aid-like" active patch that controls and monitors transdermal delivery. The patch design consists of a battery-powered electrode layer, a drug-infused hydrogel layer, and a selectively permeable membrane layer. Isis is focusing its development of transdermal drug delivery patches for analgesics for pain management as well as combination delivery patches because IsisIQ can deliver and modulate up to three drugs in one patch.

"Our greatest challenge has been differentiating Isis' unique technology from the concerns associated with conventional iontophoresis," says Shawna Gvazdauskas, Chief Commercial Officer for Isis. "Due to our proprietary single-electrode design and selective barrier membrane, IsisIQ eliminates burning and stinging of the skin as well as the risk of over delivery or inadvertent delivery of drug. Both of these technologies provide a much safer and precise approach to using very small amounts of electrical current to push drug molecules through the skin."

Isis Biopolymer currently has two commercially available products, the first of which was launched this past January. These cosmeceutical delivery patches are licensed to University Medical Pharmaceuticals for anti-aging.

"Through Isis' technology, we are able to deliver ingredients such as hyaluronic acid for the improvement in the appearance of wrinkles," says Emma Durand, Isis' Chief Executive Officer and Chief Technology Officer. "Although Isis was founded to provide transdermal delivery patches for the delivery of pharmaceuticals and biologics, the agreement with University Medical Pharmaceutical has allowed us to fast-forward our revenue stream by manufacturing 12 months earlier than originally planned."

Isis Biopolymer is focused on new business development for several applications of IsisIQ. "In addition to our agreement for the development and production of cosmeceutical delivery patches, we are in discussions with several pharmaceutical companies interested in delivery of both prescription and over-the-counter drugs," explains Ms. Gvazduskas. "In addition, we continue to develop our revolutionary technology for large molecule drug delivery via an innovative approach to iontophoresis. The Isis Biopolymer MicroSpatha™ transdermal delivery patch looks very promising for delivery of drugs that are greater than 5,000 Daltons, such as insulin."

In the past 6 months, Isis relocated to downtown Providence, RI, and is building manufacturing lines.

"We did this to accomplish our objective of developing and producing transdermal delivery patches for University Medical Pharmaceutical and to become part of Providence's emerging "Knowledge District," says Ms. Durand. "Our new location provides us with proximity and access to clinical as well as research and development resources from the Brown University Medical School as well as the Lifespan Hospital network."

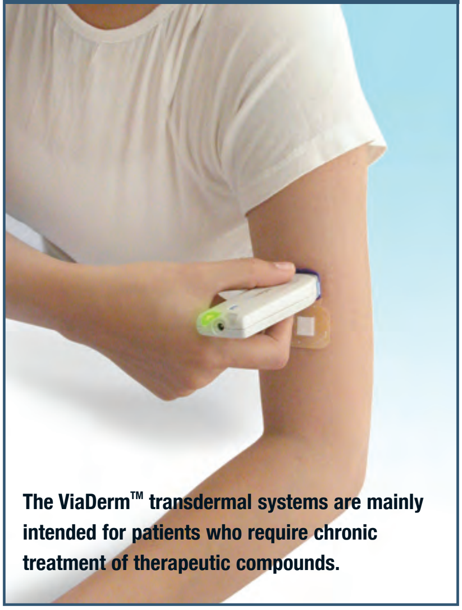
In addition to its local work, Isis Biopolymer is working with pharmaceutical and biotech companies to expand the global market for transdermal delivery of existing and drugs in development for pain management, oncology, neurology, endocrinology, cardiovascular, CNS disorders, as well as other therapies for chronic and acute conditions.

"We also have a collaboration with another life science company (EpiVax) for the development of vaccine patches," says Ms. Durand. "And we remain committed to the commercialization of a patch for the delivery of insulin."

TRANSPHARMA MEDICAL–FOCUSING ON BIOLOGICS

In the past year, TransPharma Medical has completed a 3-month Phase IIA trial for its lead product, ViaDerm-hPTH (1-34), currently in development. The product is developed in collaboration with Eli Lilly. More than 100 patients participated in the study. All of the study's primary and secondary endpoints for efficacy and safety were met. The safety endpoints included a skin safety endpoint for repeated dosing with the ViaDerm system (Figure 4). A Phase IIB study is currently on-going.

FIGURE 4



The ViaDerm™ transdermal systems are mainly intended for patients who require chronic treatment of therapeutic compounds.

"The successful completion of this Phase IIA study has demonstrated clinical capabilities of the ViaDerm system that are extremely promising and reiterate and further demonstrate the system's unique capabilities that were shown in previous studies," says Dr. Daphna Heffetz, TransPharma's CEO.

TransPharma's transdermal technology enables the systemic delivery of therapeutic doses of a range of drug molecules, including biologics.

"We have chosen to focus on delivery of biologics because it is a rapidly growing market," adds Dr. Heffetz. "The ViaDerm system offers patients in need of biologic therapeutics an administration method that avoids the need for injections, thereby increasing compliance and safety. The system also enables the maintenance of the drug-product at room temperature and a capability to control blood drug profile, thereby enabling the development of superior future products with increased drug efficacy and safety."

The ViaDerm transdermal systems are mainly intended for patients who require chronic treatment of therapeutic compounds. ViaDerm hPTH (1-34) is intended for osteoporosis patients. These patients require daily painful injections of hPTH (1-34). Currently, hPTH (1-34) is the only osteoporosis drug available in the US with anabolic properties, stimulating new bone growth that results in an increase in bone strength and a decrease in fracture risk. It is

FIGURE 5

(A) Zosano Patch & Applicator System, (B) Simply press and apply patch.

widely considered the most effective treatment for osteoporosis; however, it is currently available only as a daily injection in need of refrigeration.

According to the National Osteoporosis Foundation, approximately 10 million people in the US currently suffer from osteoporosis, and another 34 million are estimated to have low bone mass, placing them at increased risk for the disease. By 2020, the number of cases of osteoporosis in the US is expected to reach 14 million, with over 47 million cases of low bone mass. Anabolic agents are projected to be the fastest growing segment in the US osteoporosis market, reaching $1.24 billion by 2010 at an astounding compound annual growth rate of 52.3%, states Dr. Heffetz.

The company's second product in development, ViaDerm-GLP-1 analog, is currently in Phase I clinical trials. TransPharma has identified significant advantages that its future ViaDerm-GLP-1 analog product may offer over the current injectable marketed product.

"Our Phase I study results demonstrated a preferable sustained drug PK profile when the molecule is administered using our ViaDerm system," explains Dr. Heffetz.

The sustained-release profile may allow for once-daily painless transdermal administration, in comparison to two daily injections with the existing product. It also indicates that GI side effects associated with the injected peak drug blood profile may be lessened. The first GLP-1 analog, Amylin/Lilly's Byetta (Exenatide), an injectable that was approved in 2005, has already reached sales of over $670 million. Whether it's ViaDerm hPTH or ViaDerm-GLP-1, TransPharma's greatest challenge is selecting the right products to develop.

"With each product we select, we strive to make a real impact on patients' lives and disease management, and we must make careful decisions with regard to what builds our pipeline."

ZOSANO PHARMA–TAKING ON OSTEOPOROSIS

Zosano Pharma, Inc. is a privately held pharmaceutical company focusing on the development of its lead clinical program, the ZP-PTH rapid delivery patch for the treatment of patients with osteoporosis (Figure 5). ZP-PTH is being developed as an alternative to daily injections and is based on Zosano's transdermal delivery technology, which can deliver peptides, proteins, small molecules, and vaccines by permeating the skin's outer layer and ensuring significant therapeutic effect. This offers benefits such as efficacy and safety comparable to approved injectables, needle-free and pain-free delivery, a self-administered patch, rapid onset of action, and room temperature storage. Zosano's transdermal delivery technology has been clinically tested in more than 400 patients with four different peptides and a vaccine. Zosano aims to develop products both independently and through strategic licensing and co-development arrangements.

Founded in 2006 as an ALZA Corporation spin-out led by Nomura Phase4 Ventures, Zosano is funded by New Enterprise Associates, Nomura Phase4 Ventures, HBM BioVentures, and ProQuest Investments. This year, Zosano Pharma announced the closing of a $30-million financing round with existing venture investors, bringing the total investment to $120 million for the development of ZP-PTH. This investment supports Phase III clinical development and scale-up of manufacturing.

"Financing validates the significant potential of Zosano's microneedle patch system to provide a differentiated therapeutic alternative for a large underserved osteoporosis patient population," says Dr. Peter Daddona, Chief Scientific Officer.

Investors are also interested in the osteoporosis market. By 2025, experts predict that osteoporosis-related fractures will be responsible for an estimated $25.3 billion in medical costs, an economic burden comparable to other major chronic diseases.

"The severe osteoporosis market is extremely underserved with only 3% penetration, yet approaching $1 billion in annual product sales. The market is expected to grow by 5% to 10% per year. Zosano's ZP-PTH has the potential to capture a sizable portion of this severe osteoporosis market," he adds.

Zosano published results of a multinational Phase II clinical study of 3 doses of ZP-PTH in post-menopausal women with severe osteoporosis in 2009. The ZP-PTH patch delivered a consistent rapid pulse PTH plasma PK profile, and a comparable increase in lumbar spine bone mineral density (BMD), but additionally an early increase in hip BMD and effect not seen with the marketed injection product Forteo®, says Dr. Daddona. Zosano is in advanced partnering discussions for the product and is anticipating a Phase III clinical study to initiate soon thereafter. Product commercialization is anticipated in early 2014.

SUMMARY

Transdermal drug delivery holds great promise for the future as more companies show interest in the platform in the form of collaboration between drug delivery and pharmaceutical companies and development of newer technologies.

"The transdermal delivery market is rapidly evolving beyond the passive delivery boundaries to enable transdermal delivery of therapeutic products that were not possible before, says Dr. Heffetz of TransPharma.

"It's a very exciting time for transdermal drug delivery," agrees 3M's Dr. Hansen. "As more biopharmaceutical products are developed, the demand for needle-free injection systems is going to grow. Pharmaceutical companies need to find ways to differentiate their products; physicians want to see products that increase compliance and keep patients away from the clinic, and patients want administration that is convenient and painless. Transdermal drug delivery is in the best position to meet these growing demands."

REFERENCE

1. Transdermal Formulations International Market Gradually Heat, Universal-Drugs.com. May 10, 2010. Website accessed June 20, 2010. http://universal-drugs.com/fentanyl/transdermal-formulations-international-market-gradually-heat/.

CASCADE IMPACTION

Optimizing Cascade Impactor Testing for Characterizing Orally Inhaled & Nasal Drug Products

By: Mark Copley

INTRODUCTION

Cascade impaction is a core analytical technique for characterizing orally inhaled and nasal drug products (OINDPs), yielding the aerodynamic particle size distribution (APSD) data used to assess product consistency and provide a broad indication of deposition behavior. The challenge to individual laboratories is to ensure the technique is used to optimum effect to achieve maximum accuracy and productivity.

The unique value of cascade impaction lies in its ability to deliver APSD data for the active ingredient in an OINDP formulation. Particle size is of interest because it influences in vivo deposition behavior. To achieve clinical efficacy, OINDP developers tend to target a certain aerodynamic particle size profile, even though it is difficult to obtain robust in vitro/in vivo correlations. Cascade impaction data are used to increase the probability of achieving efficient delivery and to confirm dosing consistency, rather than to predict exactly how and where an active will deposit in the respiratory system.

High-quality, reliable data provide a firm foundation for decision-making throughout development and manufacture. Cascade impaction makes such an important contribution to this that it has to be used effectively. It is a lengthy and predominantly manual analytical method, and there is no doubt that understanding the factors affecting its performance ensures its better use.

HOW CASCADE IMPACTORS WORK

Although the information set out here focuses (because of their market leading positions) on the Andersen Cascade Impactor (ACI) and Next Generation Impactor (NGI), all multistage cascade impactors operate on the same principle: size fractionation on the basis of inertial impaction. Instruments such as the ACI and NGI consist of a series of stages each made up of a nozzle plate, with a specific nozzle arrangement and a collection surface. Sample-laden air is drawn into the impactor and passes sequentially through the stages; nozzle size and total nozzle area decrease with stage number.

Volumetric air flow rate through the system is constant; so as nozzle area decreases, air and particle velocities increase. As a result, smaller and smaller particles acquire sufficient inertia to impact on the collection surface rather than remaining entrained in the air stream (Figure 1). Therefore, for a given flow rate, each stage of the impactor is associated with a cut-off diameter, a figure that defines the size of the particles retained on that collection surface; any residual material is captured by a Micro-Orifice Collector (MOC) or glass fiber filter. Analyzing these size fractions, typically by high pressure liquid chromatography (HPLC), produces APSD data for the active.

This simple outline raises some of the key issues relating to cascade impactor use:

- Nozzle diameter and air flow rate through the impactor together dictate particle velocity, particle inertia, and ultimately, the size of the particles that collect on any given stage.
- The accuracy of particle size measurement depends on retaining the impacting particles on the collection surface.

- Ideally, the entire dose drawn into the impactor should be captured on the collection surfaces rather than, for example, on the walls of the impactor (inter-stage losses).

This final point is reflected in data analysis procedures. These include completion of a mass balance (MB) for each experiment, ie, comparison of the mass entering the instrument with the total mass recovered from all rinsed surfaces. Checking that the MB lies within the acceptability criteria specified by the regulators verifies to some degree the integrity of analysis. However, a good MB result does not mean that APSD measurements are correct, as material may have simply collected on the wrong surface. Developing a robust method and establishing good routine practice is the way to making certain that both MB and APSD are within specification.

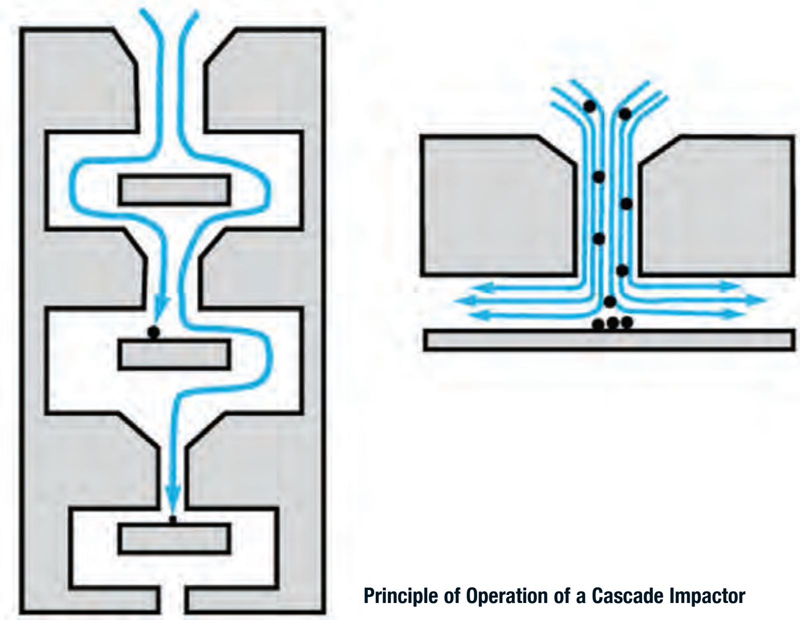
METHOD DEVELOPMENT

Developing a robust method for a specific OINDP demands consideration of the following issues:[1,2]

- Use of a pre-separator
- Solvent choice
- Number of actuations required during testing
- Collection surface coating
- Environmental and electrostatic effects
- Drug recovery and sample work-up technique
- Selection of back-up filter
- Cleaning regime

For dry powder inhalers (DPIs), a pre-separator is often installed immediately before the impactor inlet. This acts in the same way as an impactor stage, separating out any powder boluses and non-inhalable particles larger than approximately 10 microns, depending on test flow rate, prior to entry into the impactor. Failure to remove any particles in this size range has a significant impact on APSD results but little if any effect on MB, as the amount of material trapped in the pre-separator is analyzed in the same way as for any other stage.

FIGURE 1



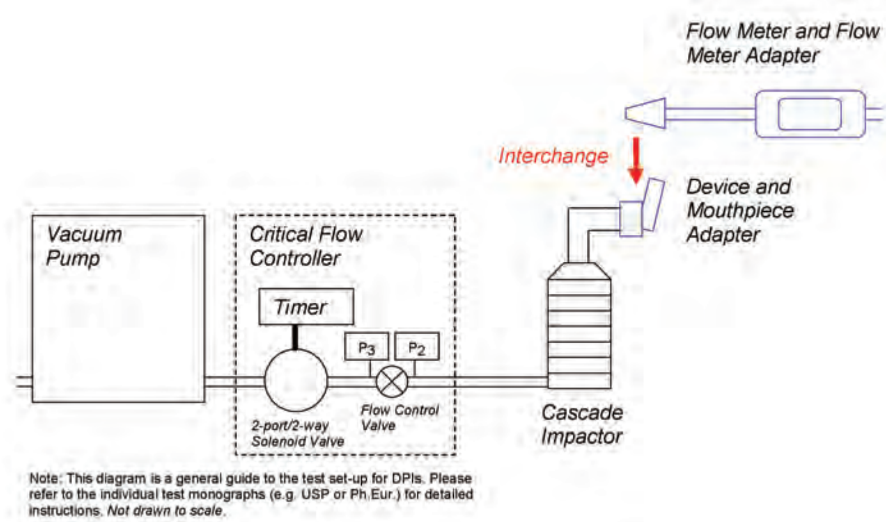
Principle of Operation of a Cascade Impactor

Solvent choice is driven largely by the solubility of the active. The number of actuations for each test then derives directly from this as it is a function of the quantitation lower limit (the lowest detectable concentration of active in the solvent) and APSD. Best practice is to minimize the number of actuations, within the constraint of ensuring that each stage collects sufficient active for reliable analysis. This reduces the risk of overloading the collection surfaces, lessening the chances of particle re-entrainment into the air stream, and reduces dose averaging effects.

Coating the collection surface, a process that potentially eliminates "particle bounce," also reduces the probability of particles collecting on the wrong stage. Applying a thin layer of glycerol or silicone oil, for example, makes the collection surface more adhesive. This practice is widespread with DPIs, due to the propensity for dry particles to bounce and, to a lesser extent, pressurized metered dose inhalers (pMDIs). For OINDPs producing liquid droplets (which are less prone to re-entrainment), the need for coating is often considered and discounted as part of method development. Application of a coating raises a number of additional questions, including which coating agent? how much? which application technique? impact on drug recovery and HPLC analysis?

With some formulations, particle collection on the wrong stage may also result from electrostatic effects. These can lead to unpredictable deposition behavior, skew APSD measurements, and affect inter-stage losses, thereby influencing MB. Equipment grounding and the use of static eliminators, amongst other anti-static precautions, can help.

FIGURE 2



A Schematic Showing a Typical Set-Up for Cascade Impactor Testing (for DPIs)

Considering the way in which temperature, humidity (especially in the case of hygroscopic formulations), and light affect the active can also help promote the development of a reliable method.

At the drug recovery stage, the aim is to dissolve sample from each collection surface before making accurate measurements of the amount of active present in each of the resulting solutions. This is the most time-consuming, manually intensive part of the technique. Successful recovery relies on the following:

- Using a suitable volume of solvent: too much compromises HPLC accuracy, too little, dissolution efficiency.
- Establishing a dissolution procedure (contact time, degree of agitation, use of ultrasonics) that ensures complete removal of the active from the collection surfaces.
- Selecting equipment and methods that avoid, for example, sample loss to vessel walls, absorption of active from the solution, and solvent evaporation.

Here, semi-automation can significantly improve productivity and reproducibility. Devices range from simple equipment to automate induction port rinsing, for example, to fully integrated solutions such as the Andersen and NGI Sample Recovery Systems (A-SRS and N-SRS) that cover the whole of sample work-up.

Another important element of drug recovery is ensuring the capture of sub-micron particles. Where there is a substantial population of such particles, such as solution MDIs for example, it is necessary to consider matters like porosity, retention efficiency, and compatibility with the selected solvent to ensure adequate particle capture by the back-up filter. In the case of the NGI, in which a Micro-Orifice Collector is routinely used instead of a back-up filter, it may be necessary to consider an additional internal or external filter arrangement.

And finally, there is impactor cleaning. It is common practice to recover drug from the collection surfaces only, in cases where validated inter-stage losses amount to less than 5% of the total drug recovery from the impactor, as this has little material affect on MB. This is typically the case with the NGI, in which inter-stage losses are low, by design, significantly speeding up analysis times. However, in such cases, it is still necessary to clean the remaining parts of the impactor, such as the inter-stage passageways and nozzle plates after a series of tests, to maintain impactor performance and reduce the risk of drug carryover. Cleaning methods should be tailored to the impactor type, the formulations being tested, and drug recovery methods used to ensure long-term impactor operation remains robust.

SETTING UP THE TEST APPARATUS

Figure 2 shows a typical test set-up for APSD measurement. Most of the ancillaries for the cascade impactor are there in order to ensure a known, constant flow of air during testing. The test apparatus clearly extends well beyond just the impactor, so it is vital to include all items for validation purposes.

The flow rate for testing, for different OINDPs, is set in accordance with regulatory guidance and pharmacopoeial specifications. For example, nebulizers are tested at 15 L/min to reflect the mid-tidal breathing flow of an average adult user. With DPIs, air flow rate is set to generate a 4-kPa pressure drop across the device, mirroring typical patient inhalation. Flow rate for DPIs varies significantly from device to device, up to a maximum of 100 L/min for low-resistance products, for practical reasons.

During testing, any differences between the actual flow rate through the device and impactor inlet, and the indicated flow rate, are a source of error when estimating stage cut-off diameters. For DPIs, this may additionally undermine device performance. Good practice here should include the following:

- Leak testing the cascade impactor to ensure flow is only entering through the inlet as intended and to determine whether acceptance criteria are met.
- Calibrating the flow meter for exiting flow rate (ie, entry flow rate to the impactor) or correctly calculating an exiting flow rate, from the entry flow rate, based on the flow resistance of the meter.
- Applying suitable correction factors to account for differences in temperature and pressure between the calibration and experimental conditions, where applicable.
- Setting the flow control valve to achieve sonic flow; a condition reached if the ratio of downstream-to-upstream absolute pressure across the valve is less-than-or-equal-to 0.5 ($P3/P2 \leq 0.5$). In these circumstances, fluctuations in downstream pressure, especially those derived from the vacuum pump, have no impact on flow rate upstream of the valve, through the impactor and device.
- Using the correct ancillaries, a fast-acting leak-free solenoid valve, for example, and tubing of appropriate size.

Poor set-up of the impactor itself is also a source of inaccuracy. Although the NGI has fixed nozzles and only one preseparator type, for the ACI, incorrect ordering of the stages and/or use of the wrong pre-separator configuration are relatively easy mistakes to make, as is mis-counting the number of device actuations. For both the NGI and ACI, misalignment at the interfaces between the device, induction port, and impactor is a common source of leaks and measurement error. Implementing procedures that ensure routine checking of the impactor stages and that avoid using bent, scratched, or otherwise damaged collection surfaces, on a day-to-day basis, is good practice. However, it is also essential to monitor the long-term performance of the impactor.

PRECISION ENGINEERING, CALIBRATED PERFORMANCE

The NGI and ACI are precision-engineered instruments. They are manufactured to defined specifications that detail acceptable tolerances for all the mechanical dimensions influencing aerodynamic performance, most notably nozzle diameter. The NGI is the most recently developed of the commercially available multistage cascade impactors, having been designed specifically for inhaler APSD testing and brought to market in 2001. Calibration of an archival NGI formed part of the development project, so data are available to accurately calculate stage cut-off diameters for any flow in the 15- to 100-L/min range, the range of interest for most OINDPs.[3-5] The ACI has a notable heritage in the air sampling industry, prior to adoption by the pharmaceutical industry, and was originally developed for use at a flow rate of 28.3 L/min (1 cubic foot per minute); conversion kits now allow its operation at 60 and 90 L/min. Despite a lack of rigorous reference calibration data for the ACI, it remains popular due to extensive industry and regulatory experience gained in its use over many years. This can be attributed, in the most part, to its successful implementation as a relative, rather than absolute, measure of product performance and quality.[6]

APSD measurements are generated by calculating stage cut-off diameters at the test flow rate, using the appropriate equations for the impactor. The underlying assumption is that the nozzle diameters still meet the manufacturing specification. Unfortunately, with repeated use, the nozzle diameters tend to change, most usually occluding due to metallic salt extraction as a result of constant contact with corrosive solvents. The speed of this process varies, and today’s use of more corrosion-resistant construction materials, such as 316 stainless steel, reduces the problem in most cases.

Regular stage mensuration, which involves the re-measurement of all critical mechanical dimensions, is an efficient way of monitoring impactor performance.[7] It also obviates the expensive, time-consuming, and inherently variable method of calibration with particles. Precise measurement of each nozzle results in an “effective diameter” (a theoretically derived parameter that considers a multi-nozzle stage as if it were a single nozzle) that correlates directly with the aerodynamic performance of the impactor. Comparing effective diameters with the nominal diameter for each stage allows the determination of the “in-use margin,” a figure that describes the extent to which performance lies within the acceptance tolerances defined by the manufacturing specification.

Stage mensuration therefore indicates the rate of deterioration of an impactor, flagging up the point at which the results are likely to fall out of specification. In some cases, it also highlights an inadequate cleaning regime. When in-use margin falls below an acceptable limit, the instrument must be refurbished to return it to productive use or taken out of service.

OPERATOR-TO-OPERATOR VARIABILITY

Every step of cascade impactor testing requires manual intervention, so there is great scope for operator-induced variability.[8] Certain parts of the analysis, drug recovery being a prime example, are laborious and time-consuming. Other tasks, such as the calculation of stage cut-off diameters and flow rate setting and control, require appropriate knowledge and understanding. The following help reduce operator variability:[9]

- Good training
- User-friendly ancillary equipment that guides the operator
- Simple tools, such as actuation counters, that reduce the risk of error
- Automating routine tasks to avoid repetitive strain injury, monotony, and stress

SUMMARY

Optimizing cascade impactor use is vital because of the unique value and importance of the resulting data. While optimization relies on developing a robust methodology based on a thorough understanding of the workings of the technique, attention must also be paid to human factors; routine good practice is essential. Investment in training ensures a well-educated team with operators less likely to introduce error, while semi-automation drives down workload and monotony. Both approaches support the goal of optimizing productivity and data quality.

REFERENCES

1. Bonam M, et al. Minimizing variability of cascade impaction measurements in inhalers and nebulizers. AAPS PharmSciTech. 2008;9(2):404-413.
2. PQRI Working Group. Considerations for the development and practice of cascade impaction testing, including a mass balance failure investigation tree. J Aerosol Med. 2003;16(3):235-247.
3. Marple V, et al. Next generation pharmaceutical impactor (a new impactor for pharmaceutical inhaler testing): part II, archival calibration. J Aerosol Med. 2003;16(3):301-324.
4. Marple V, et al. Next generation pharmaceutical impactor: a new impactor for pharmaceutical inhaler testing: part III, extension of archival calibration to 15 L/min. J Aerosol Med. 2004;17(4):335-343.
5. Marple V, et al. A proposal for the use of the next generation pharmaceutical impactor (NGI) at flow rates between 15 and 30 L/min. Respir Drug Del IX. 2004:701-704.
6. Van Oort M, et al. Verification of operating the andersen cascade impactor at different flow rates. Pharmacopeial Forum. 1996;22(2):2211-2215.
7. Byron P, et al. Selection and validation of cascade impactor test methods. Respir Drug Del IX. 2004:169-178.
8. Adamson J. Investigating analyst error in andersen cascade impaction. DDL. 2008:147-150.
9. Copley M. Process improvement and troubleshooting for cascade impactor testing. Paper presented at Respir Drug Del Eur workshop;2007.

BIOGRAPHY

Mark Copley graduated from the University of Bath, UK in 2000 with a Masters Degree in Aerospace Engineering. For 8 years he was Technical Sales Manager and product specialist for Copley Scientific's range of inhaler testing equipment and is now Sales Director for the company. Mark is considered a leading authority in testing methods and systems for metered-dose inhalers, dry powder inhalers, nebulisers and nasal sprays; authoring and contributing to more than 20 published articles. He also provides application support and consultancy, runs focused training workshops for the inhaled drug testing sector of the pharmaceutical industry and sits on the editorial advisory panel of Inhalation Magazine. An invited member of the European Pharmaceutical Aerosol Group (EPAG) impactor sub-team, Mark has also made recommendations to the Inhalanda working group, leading to subsequent revisions to Ph. Eur. and USP monographs.

PULMONARY UPDATE

Pulmonary Drug Delivery: Going Beyond Lung Diseases

By: Katheryn Symank, MS

INTRODUCTION

Pulmonary drug delivery is often thought of as being reserved for the treatment of respiratory diseases, such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis. For these diseases, inhaling medication allows for a localized treatment with fewer side effects. Although the lung's natural defense systems present obstacles to drug delivery, the lung has certain innate characteristics, such as a large blood supply, that create the perfect vehicle for delivery of medications. Recent advances make it clear that pulmonary drug delivery need not be limited to localized therapy in the lungs, but also may be used for systemic drug delivery. This is particularly true for medications, such as biopharmaceuticals and immediate-acting medications, which are traditionally delivered through injection.

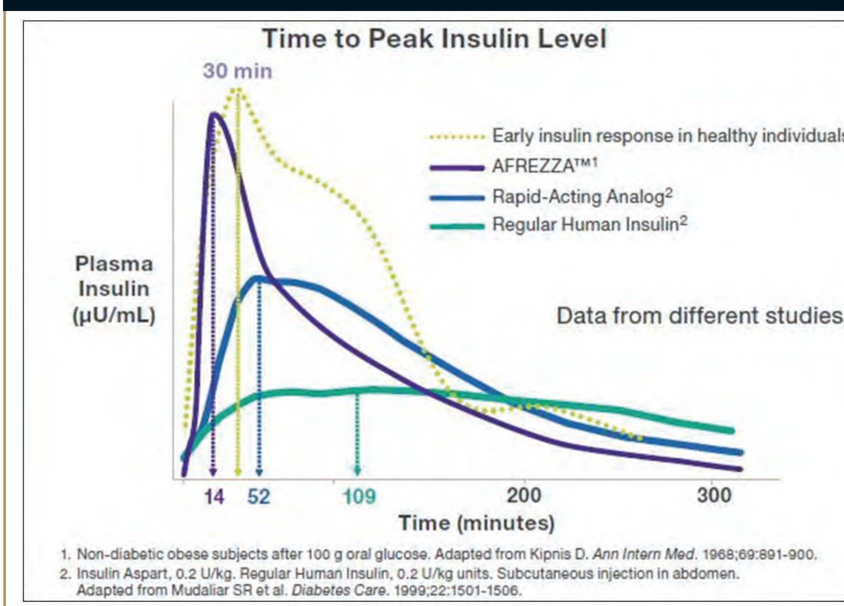
Because of their respiratory function, lungs are ideal for the delivery of medications. The adult lungs, which contain over 300 million alveoli, provide a large surface area that may be used for drug absorption. Surrounding the alveoli, the actual site for gas exchange, is an abundant network of capillaries, resulting in a rich blood supply. The alveor epithelium is very thin and highly permeable, allowing for rapid absorption. Compared to other systems, like the gastrointestinal tract, the lungs have relatively few enzymes, making pulmonary drug delivery an attractive option for medications that have poor bioavailability or need to bypass the gastrointestinal system.

While in many respects the lung is accommodating to the pulmonary drug delivery of medications, it also provides many obstacles to overcome. For instance, as a way to defend itself against harmful particles, the lungs only allow small particles that are less than 3 to 5 microns to pass. In addition, the lungs are lined with thick mucus that traps particles and prevents them from entering further. The materials enmeshed in the mucus are removed by being sent to the mouth where they are swallowed. Another deterrent to pulmonary drug delivery are macrophages that act as protectors for the alveoli. These mobile cells seek out foreign particles and bind to them. These particulates are then engulfed, killed, and digested. Within the macrophage are small amounts of peroxides that may be released or secreted. These substances are able to degrade some medications, complicating their successful administration by the pulmonary route. Despite these complications, some companies have been able to find ingenious solutions to circumvent these challenges.

PULMONARY DELIVERY OF BIOPHARMACEUTICALS

One potential application of pulmonary drug delivery is for the administration of biopharmaceuticals. These large and complex molecules are most commonly administered through injection or intravenous infusion because they are easily denatured or altered with harsh handling or processing. Many patients view these routes as less desirable than other options. For instance, intravenous infusion must be administered in a medical setting and can be time-consuming and uncomfortable for patients. Because biopharmaceuticals are delicate and elaborate, they are not able to easily utilize other drug delivery methods or formulation approaches. For instance, in

FIGURE 1



AREZZA™ Compared to Rapid-Acting Insulin Analog most cases oral drug delivery is not an option because the medication can easily be denatured by the body before it can take affect in the body. Other drug delivery methods have been used to administer biopharmaceuticals with mixed results. For example, a few biopharmaceuticals on the market, like Fortical (calcitonin-salmon) and Miacalcin (calcitonin-salmon) are administered intranasally. However, intranasal drug delivery is only a viable option for smaller drugs.

Another option tried has been transdermal drug delivery. Unlike with the oral drug delivery method, the transdermal patch bypasses the gastrointestinal tract, eliminating problems there. However, the skin itself acts as a barrier that inhibits the amount and size of the molecules that can be delivered in this way. Because of its positive attributes, pulmonary drug delivery stands out as solid option for the delivery of a wide range of medications.

MANNKIND'S AFREZZA™ – CONTINUED INTEREST IN INHALED INSULIN

One of the most well-known examples of pulmonary delivery of a biopharmaceutical is inhaled insulin. In the recent past, a variety of companies, including Pfizer, Eli Lilly, and Novo Nordisk, were all competing to lead in the potential opportunity for inhaled insulin. The only product to receive approval was Pfizer's Exubera, which has subsequently been discontinued. In addition to safety concerns, Exubera had several disadvantages that contributed to its poor uptake, including the fact that it worked the same as injected rapid-acting insulin without an additional clinical benefit. Additionally, the Exubera inhaler was large, about the size of a 16-oz water bottle, and was cumbersome to use.

Following the disappointment of Exubera, both Eli Lilly and Novo Nordisk terminated the development of their respective inhaled insulin products. The only company left developing late-stage inhaled insulin is MannKind Corporation, whose cutting-edge AFREZZA™ (Technosphere® Insulin System); an ultra-rapid-acting inhaled insulin, does not have the issues seen in Exubera, such as reduced lung function and an increased risk for lung cancer. Moreover, AFREZZA offers positive factors over current injectable versions of rapid-acting insulin that could draw the interest of doctors and patients.

MannKind's AFREZZA is made using the company's versatile delivery formulation called Technosphere. This proprietary technology allows for drugs that are normally injected to be formulated into a dry powder form that is inhaled. Technosphere formulations have many attractive attributes setting them apart from competing drug delivery methods, including rapid systemic absorption comparable to intra-arterial delivery, and the prevention of first-pass metabolism. AFREZZA is an inhaled microparticle formulation of insulin that closely mimics the release of endogenous insulin in non-diabetics. AFREZZA has certain advantageous attributes that make it a potentially important therapeutic alternative to marketed rapid-acting insulin. Specifically, AFREZZA is rapidly absorbed into the bloodstream, reaching peak levels within 12 to 14 minutes. This may offer a marked improvement over current injected rapid-acting insulin, which reaches peak levels in 1 to 3 hours. Additionally, injected rapid-acting insulin can take between 4 to 8 hours to leave the system, sometimes resulting in hypoglycemia, which is listed as a serious concern for diabetics. Clinical studies have shown that AFREZZA has reduced risk for both mild/moderate and severe hypoglycemia as compared to subcutaneous insulin comparators because it dissipates within 3 hours and showed less weight gain when compared with other insulin. Moreover, AFREZZA is inhaled into the deep lungs using a palm-sized inhaler that is anticipated to be easy and convenient for patients to use. AFREZZA has not yet received FDA approval. The company filed an NDA in May 2009 and received a complete response letter in March 2010. The FDA did not cite safety concerns but did request additional information about AFREZZA's clinical utility and comparison data of the MedTone inhaler (the one used in clinical trials) and the newer version of the inhaler.

FIGURE 2

Akela Pharma's TAIFUN® Inhalation Device

PULMONARY DELIVERY OF FAST-ACTING MEDICATIONS

Another promising application for pulmonary drug delivery is for the rapid, systemic administration of medications. Although popular with patients, oral drug delivery presents challenges of transit time, bioavailability, and degradation by the gastrointestinal tract. Commonly, drugs with a rapid drug action are administered by

FIGURE 3

Alexza Pharmaceutical's Staccato System

injection or continuous intravenous infusion. The injection route, especially intravenously, allows for rapid onset of action. However, delivering medication through this route results in a short duration, making it a poor option for long-term care. Whereas continuous intravenous infusion allows for rapid and sustained drug delivery, it also is usually limited to patients who are hospitalized. Oral transmuccosal drug delivery is another method used for delivery of medications requiring a rapid onset of action. The transmuccosal area is highly vascular and has few barriers. However, drugs delivered through this route achieve peak levels within 10 to 15 minutes, which is much slower than by injection. In contrast, pulmonary drug delivery is non-invasive and provides one of the most direct routes of entry into the bloodstream, allowing for rapid onset of action.

One company developing a fast-acting inhaled medication is AKELA Pharma whose Fentanyl TAIFUN is a formulation of free and liposome-encapsulated fentanyl delivered using the company's dry powder inhaler platform TAIFUN. Fentanyl TAIFUN is being developed for the treatment of breakthrough cancer pain, a brief and often severe flare up of pain that occurs despite the use of daily pain medications. The free fentanyl is designed to provide rapid pain relief, while the encapsulated fentanyl provides longer-acting pain relief. Results from Phase II clinical trials indicated patients using Fentanyl TAIFUN experienced significant pain relief with a median time of 5.2 minutes, faster than currently marketed non-injectable therapies used for the treatment of breakthrough cancer pain. Moreover, compared to other non-injectable rapidly acting formulations of fentanyl, patients using Fentanyl TAIFUN may require a lower dose of medication. This is an important distinction because use of high doses of fentanyl has been related to several deaths, resulting in public health advisories from the FDA.

Another company working is this area is Alexza Pharmaceuticals. The company's Staccato system is a pulmonary inhalation device allowing for the rapid delivery of a broad range of medications. This breath-actuated device works by creating a rapid vaporization of the drug, without thermal degradation, forming an aerosol made up of small particles. This aerosol is rapidly absorbed deep in the lungs allowing for fast-onset of action. Alexza has five products in clinical development using the Staccato system, including Staccato loxapine and Staccato alprazolam.

SUMMARY

With advancing technology and new innovations, the true potential of pulmonary drug delivery is only now being appreciated. The lung, with its large surface area and rich network of capillaries, has many innate characteristics that make this an attractive delivery route for many medications. For biopharmaceuticals, which are delicate and easily altered, pulmonary drug delivery offers an exceptional alternative to injection or intravenous infusion. In addition, as the pulmonary route bypasses the gastrointestinal system and provides an almost direct route to the bloodstream, it is a worthwhile delivery method for drugs requiring a rapid onset of action.

BIOGRAPHY

Kathryn Symank is a Research Analyst with the Frost & Sullivan North American Healthcare team. She focuses on monitoring and analyzing emerging trends, technologies, and market behavior in the Pharmaceutical and Biotechnology industries. Since joining Frost & Sullivan in February 2007, Mrs. Symank has completed several research studies and consulting projects with recent works focused on monoclonal antibodies, stem cells, osteoporosis, lifestyle disorders, and respiratory diseases. Prior to joining Frost & Sullivan, Mrs. Symank worked for 7 years in pulmonary pathology at the University of Texas Health Science Center in San Antonio, where she studied bronchopulmonary dysplasia. She earned her BS from Texas A&M University in Molecular and Cell Biology and her MS from the University of Texas at San Antonio in Biotechnology.

PPI

DELIVERY

Creating Safer Pain Relievers Using Proton Pump Inhibitor Drug Delivery Mechanisms

By: John Fort, MD

INTRODUCTION

In the US, more than 5 billion units of aspirin in all of its forms are sold each year, with approved indications ranging from the treatment of rheumatic diseases to the secondary prevention of cardiovascular and cerebrovascular events. Approximately 50 million adult Americans regularly use low-dose aspirin (75 to 325 mg daily) for cardiovascular disease (CVD) prevention.[1] A daily aspirin regimen is also recommended to help prevent a second or recurrent stroke or transient ischemic attack (TIA, or mini stroke).[2] Worldwide, aspirin is the most widely used drug to prevent heart attack and stroke.

Unfortunately, aspirin therapy is also associated with the development of clinically important upper gastrointestinal (GI) side effects that do not appear to be significantly reduced with dose reduction or the use of modified-release (enteric-coated/EC) or buffered aspirin.[3-6] Even in doses as low as 75 mg daily, aspirin therapy is associated with a significant risk of developing serious GI complications, such as gastric ulcer bleeding.[7] In patients taking daily aspirin for cardiovascular prophylaxis, serious ulcer complications are reported to be approximately two- to four-fold higher compared to controls.[8]

The potential for upper GI complications is even greater in individuals who are taking low-dose aspirin for cardio protection who also require other non-steroidal anti-inflammatory drugs (NSAIDs) for treatment of rheumatic diseases, such as osteoarthritis or rheumatoid arthritis.[9] Approximately 70% of Americans over the age of 65 use NSAIDs at least once weekly, and an estimated 34% of Americans in this age group take NSAIDs on a daily basis.[10] The complications of concurrent aspirin/NSAID administration include a substantially increased risk of upper GI hemorrhage compared with administration of each drug alone.[9]

MAKING ASPIRIN SAFER: COORDINATED DRUG DELIVERY TECHNOLOGY & PA PRODUCT CANDIDATES

Proton pump inhibitors (PPIs) can significantly reduce or prevent the occurrence of aspirin-related ulcer complications when taken as a co-therapy with aspirin.[11-13] Per the 2008 expert consensus document issued by the American College of Cardiology Foundation (ACCF), American College of Gastroenterology (ACG), and American Heart Association (AHA), PPIs are the preferred agents for the therapy and prophylaxis of aspirin- and other NSAID-associated GI injury, including for patients on dual anti-platelet therapy, such as aspirin and clopidogrel.[13]

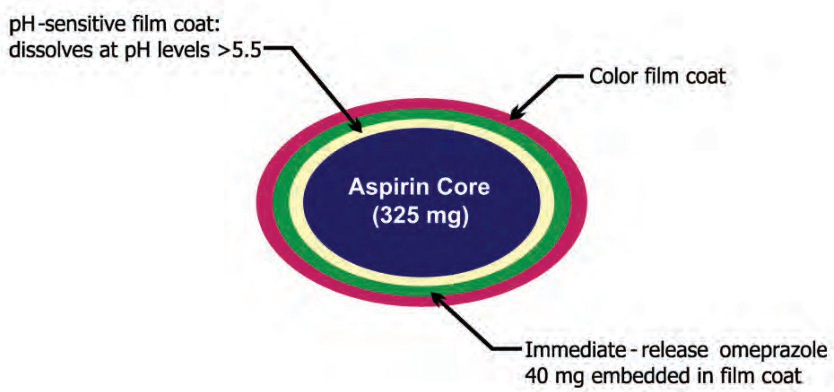
Although physicians may seek to co-prescribe PPIs with aspirin, the potential benefit of this strategy is limited by both imprecise dosing instructions and lack of patient adherence. Non-adherence has been recognized as a special risk in several patient populations, including the elderly, who are at increased risk of aspirin-associated upper GI ulcers.[14] Co-prescription of aspirin and PPIs usually involve an immediate-release aspirin and a delayed-released PPI, resulting in exposure of the GI tract to aspirin prior to onset of acid inhibition by the PPI, thus mitigating the beneficial effects of co-therapy. Thus, a combination tablet consisting of a PPI and aspirin, if successful, would clearly meet an important medical need by reducing GI side effects in at-risk patients requiring aspirin therapy.

POZEN Inc. has developed the PA franchise of product candidates to help address the problem of upper GI complications caused by long-term aspirin therapy. POZEN's investigational PA products pair an EC aspirin core with a mantle of immediate-release omeprazole to reduce aspirin-associated GI complications in individuals requiring aspirin therapy. The PA products are investigational and have not been approved by the FDA.

The first investigational PA product candidate is PA32540, a patented, multi-layer, coordinated-delivery tablet combining immediate-release omeprazole 40 mg surrounding a pH-sensitive aspirin 325 mg core, administered orally, once a day (Figure 1). The use of the PPI omeprazole in patients taking low-dose aspirin therapy who are at high risk for gastric ulcer complications has been reported to be a safe and effective therapeutic approach.[15-18]

The PA dosage form provides coordinated release of a PPI and aspirin. The gastroprotective agent, immediate-release omeprazole, is released in the

FIGURE 1



Tablet schematic showing PA32540's multilayer, coordinated delivery system.

stomach within the first 30 minutes of administration, prior to the release of aspirin (Figure 2).

PA32540 CLINICAL TRIALS

POZEN has achieved key clinical development milestones with the investigational PA franchise, with the completion of several Phase I clinical trials that demonstrate the upper gastrointestinal (GI) protection provided by PA product candidates compared to aspirin (Figure 3), as well as studies demonstrating the bioequivalency of PA32540 and EC aspirin 325 mg, in which PA32540 (325 mg of aspirin surrounded by a coating of 40 mg of immediate-release omeprazole) exhibited a similar rate and extent of absorption as EC aspirin 325 mg in terms of salicyclic acid pharmacokinetics.

The first Phase I study of a PA candidate evaluated PA32520 (containing 325 mg of aspirin and 20 mg of omeprazole). This proof-of-concept study involved 80 subjects over the age of 50 who received EC aspirin (325 mg) or PA32520 once daily. The primary endpoint was GI damage at 28 days as measured by the Lanza scoring system (a severity score for NSAID-induced erosive mucosal injuries in the stomach or duodenum, with grade 3 and 4 representing greater damage). At Day 28, endoscopy confirmed that 7.5% of subjects receiving PA32520 had Lanza grade 3 or 4 gastrointestinal damage, compared to 47.5% of subjects who had received EC aspirin 325 mg ($P < 0.001$). Furthermore, no ulcers were observed in the PA32520 group, whereas 20% of subjects who received EC aspirin 325 mg developed a gastric ulcer during the study period ($P = 0.005$).

PA32520 has also been investigated in comparison to 81 mg EC aspirin, a common dosage recommend for cardiovascular protection due to concern about the GI toxicities caused by aspirin. In this study of 80 healthy volunteers, treatment with EC aspirin 81 mg was associated with a 12.8% prevalence of Lanza grade 3 or 4 upper GI damage compared to 4.9% with PA32520 therapy.[19] In addition, PA32520 also provided greater urinary 11-dehydro thromboxane B2 (11-d-TXB2) suppression (Figure 4). Higher urinary 11-d-TXB2 levels have been associated with an increased risk of cardiovascular events.[20,21] The most common adverse events were gastrointestinal, with GI events occurring in 12% of subjects on PA32520 and 8% of subjects on EC aspirin 81 mg.

A third study investigated PA32540 compared to EC aspirin 325 mg in 80 healthy volunteers. Endoscopy at Day 28 revealed that 2.5% of patients in the PA32540 arm had a Lanza score of 3 or 4, compared to 27.5% of patients in the EC aspirin 325 mg arm ($p = 0.003$). Adverse events occurred in 25% of subjects on PA32540 and 35% of subjects on EC aspirin 325 mg.

In the pooled analysis of the three Phase I PA studies, PA32540 has demonstrated the least gastroduodenal damage and fewer overall GI adverse events compared to EC aspirin 81 mg, EC aspirin 325 mg, and PA32520. Furthermore, normal endoscopy (grade 0 Lanza score) at Day 28 was noted in 75% of patients taking PA32540 compared to 16.3% of patients taking EC aspirin 325 mg ($p < 0.001$). For these reasons, PA32540 has been selected to move forward into Phase III trials for evaluation in secondary CVD prevention.

In November 2009, POZEN began enrolling patients in two pivotal Phase III trials that will evaluate PA32540 for secondary CVD prevention. The studies will be conducted under a Special Protocol Assessment agreed with the FDA and will involve over 100 sites, enrolling approximately 500 patients per study. The primary endpoint of these studies is the cumulative incidence of gastric ulcers over the 6-month treatment period for PA32540 versus EC aspirin 325 mg. In addition to these trials, a long-term, open-label safety study will be conducted to assess the safety of PA32540 administration over 1 year.

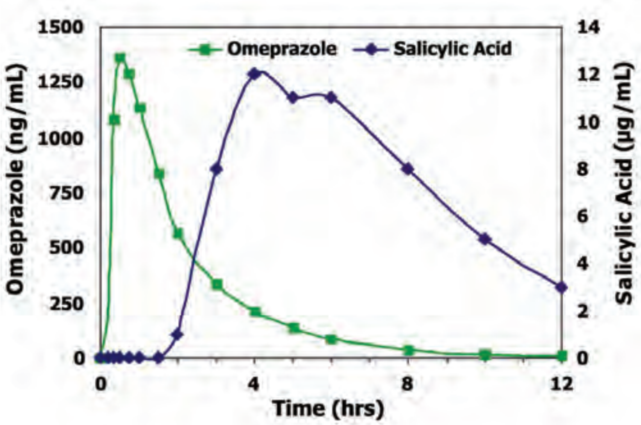
PA32540 FOR THE SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE

PA32540 is currently being investigated for the secondary prevention of CVD, including heart attack, stroke, and TIA. There is a large market opportunity for a safer aspirin product for individuals requiring long-term, daily aspirin therapy for CVD prevention. Among the various forms of CVD, coronary heart disease is the leading single cause of death in the US, affecting approximately 17.6 million people and causing over 425,000 deaths annually. In 2010, an estimated 785,000 Americans will have a new coronary attack resulting from coronary heart disease, and approximately 470,000 will have a recurrent attack. Each year, approximately 134,000 Americans die of stroke and an estimated 795,000 Americans will experience a new or recurrent stroke. The incidence of TIA in the US is estimated to be 200,000 to 500,000 per year. The estimated direct and indirect cost of CVD for 2010 is \$503.2 billion.[22]

PA32540 FOR THE REDUCTION OF COLORECTAL NEOPLASIA

In addition to pursuing an indication in CVD for PA32540, POZEN is also considering investigating this product for the secondary prevention of colorectal neoplasia, such as adenomatous polyps. More than 80% of colorectal cancers arise from adenomatous polyps, or adenomas.[23] Adenomas are found in

FIGURE 2

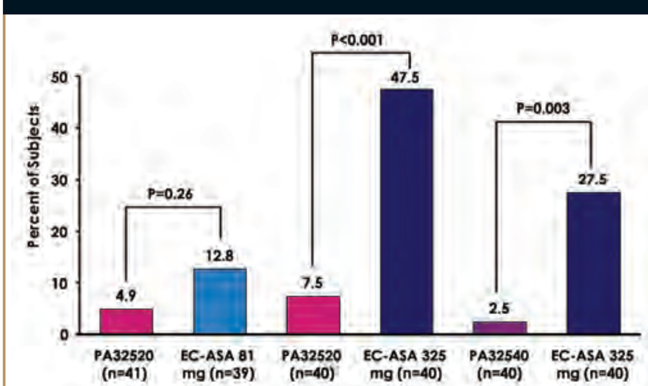


Release profile of PA32540, Day 13. On Day 13, the median time to maximum plasma concentration (Tmax) for omeprazole (from PA32540) is approximately 30 minutes and for salicylic acid (from PA32540) is 4.5 hours.

approximately 25% of screening colonoscopies and in more than 40% of colonoscopies for prior adenomas.[24] Prevention of adenomas is believed to also prevent colorectal cancers.[25] Colorectal cancer is the second most common cancer in developed countries, with a lifetime risk of 5%.[26] In 2008, there were 149,000 new cases of colorectal cancer and 50,000 related deaths in the US.[27]

Several prospective randomized controlled trials demonstrate that low dose aspirin decreases the risk of adenomas in the large bowel in patients with a history of colorectal neoplasia.[25] Recent follow-up and observational studies support that long-term aspirin use (especially > 5 to 10 years) reduces colorectal cancer risk and mortality.[28-30] These data demonstrate the need for a safer aspirin product that can provide chemoprevention of colon neoplasias while reducing the risk of GI mucosal damage with long-term use. A consensus statement resulting from the Fifth International Conference on Cancer Prevention held in 2008 stated that aspirin clearly shows a chemopreventive effect on colorectal cancer, with coadministration of aspirin and PPIs an "attractive option" to prevent upper GI bleeding.[31] However, since many physicians are not aware of research efforts showing the benefits of aspirin for this indication, the use of aspirin is rare. In addition, due to the upper GI bleeding risk, aspirin and other NSAIDs are not routinely recommended for the prevention of colorectal neoplasia.[32]

FIGURE 3



Comparison of the incidence of grade 3 or 4 Lanza scores in clinical trials evaluating the PA product candidates. At Day 28, subjects taking PA32520 (325 mg aspirin surrounded by a 20 mg coating of immediate-release omeprazole) or PA32540 had significantly less upper GI damage compared with subjects taking EC aspirin 325 mg.

PA65020 FOR ANALGESIA

POZEN has also begun to investigate analgesic doses of aspirin (650 mg) in combination with omeprazole for the PA franchise. Recent Phase I results from a randomized, double-blind study (N = 40) demonstrated that twice-daily PA65020 (EC aspirin 650 mg + omeprazole 20 mg) is associated with a significantly decreased risk of GI mucosal damage compared to over-the-counter EC aspirin (650 mg, twice daily) in healthy adults (baseline Lanza score: grade 0). Following 28 days of therapy, 85% of the EC-aspirin treatment group had a grade 3 or 4 Lanza score, in contrast to only 15% of the PA65020 treatment group (P < 0.001) (Figure 5). Additionally, at Day 28, 65% of subjects in the PA65020 group did not have any visible gastroduodenal lesions (grade 0 Lanza score), whereas gastroduodenal mucosal damage was observed in all subjects treated with EC-aspirin. Finally, no gastric or duodenal ulcers were observed at Day 28 in subjects who received the investigational product, whereas the incidence of gastric/duodenal ulcer was 40% in subjects who received EC-aspirin (P = 0.003). No serious adverse events were reported, and there were no withdrawals due to adverse events.

OTHER NSAID/PPI COMBINATIONS FOR REDUCING GI COMPLICATIONS: VIMOVO™

The risk of GI side effects is not limited to patients receiving long-term, low-dose aspirin therapy. GI complications are also a known side effect of non-aspirin NSAIDs, such as those taken for arthritis. Up to 50% of the estimated 27 million adults in the US with osteoarthritis are at risk of GI side effects related to NSAIDs.[32] Current clinical recommendations include the use of PPIs in patients at risk who are on chronic NSAID therapy.[13] Co-developed with and licensed to AstraZeneca, VIMOVO™, which combines an NSAID and PPI into one convenient tablet, was developed to address the problem of NSAID-associated ulcers.

In April 2010, the US FDA approved VIMOVO, (naproxen and esomeprazole magnesium) delayed release tablets, for the relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers. A Marketing Authorization Application (MAA) is currently under review with the European Union.

VIMOVO is a fixed-dose combination of enteric-coated naproxen, a pain-relieving non-steroidal anti-inflammatory drug (NSAID) and immediate-release esomeprazole, a proton pump inhibitor.

Positive results from two multicenter, randomized, double-blind, controlled, Phase III pivotal trials for VIMOVO were announced in 2008. In both trials, approximately 400 H. pylori-negative subjects with osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, or other conditions requiring daily NSAID therapy received either VIMOVO or EC naproxen 500 mg twice daily over a 6-month treatment period. The data demonstrated that patients at risk for developing NSAID-associated gastric ulcers who took VIMOVO experienced significantly fewer endoscopically confirmed gastric ulcers compared with patients taking EC naproxen alone. In Study 1, the incidence of gastric ulcer in patients taking VIMOVO was 4.1%, compared to 23.1% in patients taking EC naproxen ($p < 0.001$). In Study 2, gastric ulcer incidence was 7.1% with VIMOVO, compared to 24.3% with EC naproxen ($p < 0.001$).

The pivotal studies also analyzed the reduction in incidence of endoscopically confirmed gastric ulcer among patients taking VIMOVO and EC naproxen who were on concomitant low-dose aspirin (LDA) therapy. In a pre-specified pooled analysis, VIMOVO was associated with a significantly reduced risk of gastric ulcer compared to EC naproxen in patients taking LDA, with a gastric ulcer incidence of 3% for VIMOVO, compared to 28.4% for EC naproxen ($p < 0.001$). Patients taking VIMOVO who were not on LDA experienced a 6.4% incidence of gastric ulcer compared to 22.2% among those taking EC naproxen ($p < 0.001$).

Additional analyses of the Phase III studies demonstrated that VIMOVO was also associated with a decreased incidence of endoscopically confirmed duodenal ulcers and improved upper GI tolerability assessments compared to EC naproxen alone.

The most frequently reported adverse events among patients taking both VIMOVO and EC naproxen were GI disorders, including dyspepsia, erosive esophagitis, and erosive duodentis. Commonly reported treatment emergent adverse events (experienced by more than 10% patients in either treatment group) included erosive gastritis, gastritis, dyspepsia, and erosive duodentis.

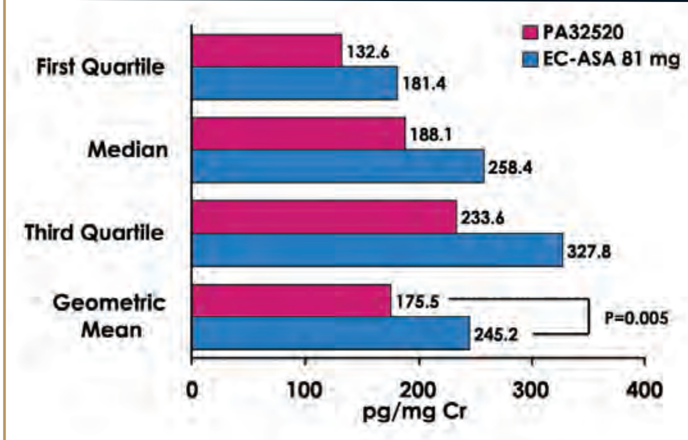
CONCLUSION

New approaches are needed to reliably reduce upper GI toxicity and its complications and better ensure treatment adherence in patients requiring long-term aspirin therapy who are at risk of upper GI events. POZEN's investigational PA franchise, a combination of aspirin and omeprazole, is intended to deliver the cardiovascular benefits of aspirin with a lower incidence of gastric ulcers than EC aspirin. In Phase I studies, the PA product candidates were associated with significantly less upper GI damage compared to aspirin alone. In addition, due to the potential for enhanced thromboxane suppression compared to standard aspirin therapy, PA may also represent an improved therapeutic option for patients who require long-term aspirin therapy for cardiovascular protection. Phase III studies on PA32540 for the secondary prevention of CVD are ongoing. The PA family of product candidates may also provide a new therapeutic option for the secondary prevention of colorectal neoplasia and for patients who require analgesic doses of aspirin.

VIMOVO, licensed to co-development partner AstraZeneca, was approved by the FDA in April 2010 and represents a new treatment for the millions of patients with arthritic osteoarthritis. VIMOVO may provide arthritis patients at risk for NSAID-associated gastric ulcers a new treatment option that combines EC naproxen and immediate-release esomeprazole in a single tablet.

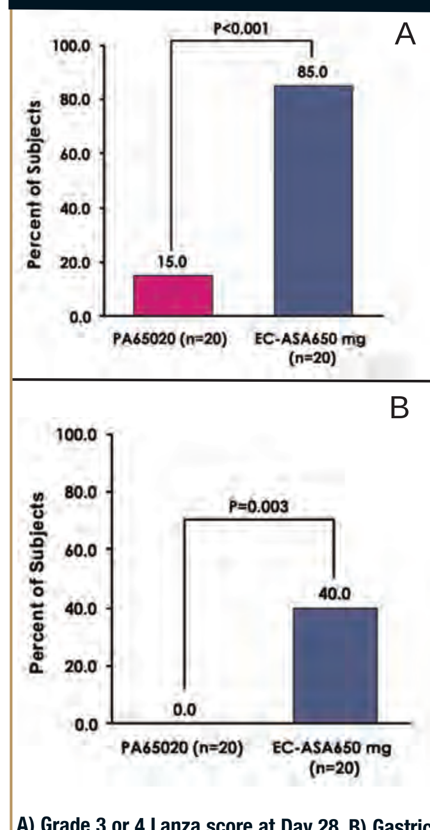
The single tablet administration of the PA product candidates and VIMOVO seeks to ensure that gastroprotection is delivered with every dose in a consistent and coordinated approach that may increase patient convenience.

FIGURE 4



Urinary 11-d-TXB2 after 28 days of treatment. PA32520 produced significantly greater inhibition of in vivo thromboxane generation, as measured by urinary 11-d-TXB2, compared to EC aspirin 81 mg.

FIGURE 5



A) Grade 3 or 4 Lanza score at Day 28. B) Gastric or duodenal ulcer at Day 28

REFERENCES

1. Campbell CL, Smyth S, Montalescot G, Steinhubl SR. Aspirin dose for the prevention of cardiovascular disease: a systematic review. JAMA. 2007;297(18):2018-2024.
2. Adams RJ, Albers G, Alberts MJ, et al. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. Stroke. 2008;39(5):1647-1652. Epub 2008 Mar 5.
3. Kelly JP, Kaufman DW, Jurgelon JM, Sheehan J, Koff RS, Shapiro S. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. Lancet. 1996;348(9039):1413-1416.
4. Derry D, Loke YK. Risk of gastrointestinal hemorrhage with long-term use of aspirin: meta-analysis. BMJ. 2000;321:1183-1187.
5. de Abajo FJ, García-Rodríguez LA. Risk of upper gastrointestinal bleeding and perforation associated with low-dose aspirin as plain and enteric-coated formulations. BMC Clin Pharmacol. 2001;1:1. Epub 2001 Feb 13.
6. García-Rodríguez LA, Hernández-Díaz S, de Abajo FJ. Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies. Br J Clin Pharmacol.

2001;52(5):563-571.
7. Weil J, Colin-Jones D, Langman M, et al. Prophylactic aspirin and risk of peptic ulcer bleeding. BMJ. 1995;310(6983):827-830.
8. McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. Am J Med. 2006;119(8):624-638.
9. Lanas A, Scheiman J. Low-dose aspirin and upper gastrointestinal damage: epidemiology, prevention and treatment. Curr Med Res Opin. 2007;23(1):163-173.
10. Goldstein JL, Lowry SC, Lanza FL, Schwartz HI, Dodge WE. The impact of low-dose aspirin on endoscopic gastric and duodenal ulcer rates in users of a non-selective non-steroidal anti-inflammatory drug or a cyclo-oxygenase-2-selective inhibitor. Aliment Pharmacol Ther. 2006;23(10):1489-1498.
11. Lai KC, Lam SK, Chu KM, et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. N Engl J Med. 2002;346(26):2033-2038.
12. Chan FK, Ching JY, Hung LC, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. N Engl J Med. 2005;352(3):238-244.
13. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risk of Antiplatelet Therapy and NSAID Use. A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2008;52(18):1502-1517.
14. Yeomans ND, Lanas AI, Talley, et al. Prevalence and incidence of gastroduodenal ulcers during treatment with vascular protective doses of aspirin. Aliment Pharmacol Ther. 2005;22:795-801.
15. Chan FK, Chung SC, Suen BY, et al. Preventing recurrent upper gastrointestinal bleeding in patients with Helicobacter pylori infection who are taking low-dose aspirin or naproxen. N Engl J Med. 2001;344(13):967-973.
16. Lanas A, Rodrigo L, Márquez JL, et al. Low frequency of upper gastrointestinal complications in a cohort of high-risk patients taking low-dose aspirin or NSAIDS and omeprazole. Scand J Gastroenterol. 2003;38(7):693-700.
17. Pilotto A, Franceschi M, Longoa MG, et al. Helicobacter pylori infection and the prevention of peptic ulcer with proton pump inhibitors in elderly subjects taking low-dose aspirin. Dig Liver Dis. 2004;36(10):666-670.
18. Ng FH, Wong BC, Wong SY, Chen WH, Chang CM. Clopidogrel plus omeprazole compared with aspirin plus omeprazole for aspirin-induced symptomatic peptic ulcers/erosions with low to moderate bleeding/re-bleeding risk - a single-blind, randomized controlled study. Aliment Pharmacol Ther. 2004;19(3):359-365.
19. Gurbel PA, Fort JG, Orlemans E, Platchetka J. Abstract 4267: PA32520 (Single-tablet of enteric-coated aspirin 325 mg + immediate-release omeprazole 20 mg): aspirin therapy combining greater thromboxane suppression and lower upper gastrointestinal damage. Circulation. 2008;118:S-855.
20. Gurbel PA, Bliden KP, DiChiara J, et al. Evaluation of dose-related effects of aspirin on platelet function: results from the Aspirin-Induced Platelet Effect (ASPECT) study. Circulation. 2007;26;115(25):3156-3164. Epub 2007 Jun 11.
21. Eikelboom JW, Hankey GJ, Thom J, et al. Incomplete inhibition of thromboxane biosynthesis by acetylsalicylic acid: determinants and effect on cardiovascular risk. Circulation. 2008;21;118(17):1705-12. Epub 2008 Oct 6.
22. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart Disease and Stroke Statistics - 2010 Update. A Report From the American Heart Association. Circulation. 2009 Dec 17. [Epub ahead of print]
23. U.S. Preventive Services Task Force. Routine aspirin or nonsteroidal anti-inflammatory drugs for the primary prevention of colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2007 Mar 6;146(5):361-364.
24. Giacosa A, Frascio F, Munizzi F. Epidemiology of colorectal polyps. Tech Coloproctol. 2004;8 Suppl 2:s243-247.
25. Cole BF, Logan RF, Halabi S, et al. Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials. J Natl Cancer Inst. 2009;101(4):256-266. Epub 2009 Feb 10.
26. Weitz J, Koch M, Debus J, Höhler T, Galle PR, Büchler MW. Colorectal cancer. Lancet. 2005;365(9454):153-165. Review.
27. Jemal A, Thun MJ, Ries LA, et al. Annual report to the nation on the status of cancer, 1975-2005, featuring trends in lung cancer, tobacco use, and tobacco control. J Natl Cancer Inst. 2008;100(23):1672-1694. Epub 2008 Nov 25.
28. Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Wu K, Fuchs CS. Aspirin dose and duration of use and risk of colorectal cancer in men. Gastroenterol. 2008;134(1):21-28. Epub 2007 Sep 26.
29. Flossmann E, Rothwell PM; British Doctors Aspirin Trial and the UK-TIA Aspirin Trial. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet. 2007;369(9573):1603-1613. Review.
30. Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. JAMA. 2009;302(6):649-658.
31. Cuzick J, Otto F, Baron JA, et al. Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. Lancet Oncol. 2009;10(5):501-507. Review.
32. U.S. Centers for Disease Control and Prevention. Arthritis: Meetings the Challenge-At a Glance 2009. Accessed January 2010. Available at: http://www.cdc.gov/chronicdisease/resources/publications/AAG/arthritis.htm

BIOGRAPHY

Dr. John G. Fort has been Chief Medical Officer at POZEN since 2003. Prior to joining POZEN, he was Vice President, Medical Affairs at Adolor Corporation and held positions with Pfizer Inc., including Vice President, Medical Affairs, and was Vice President, Arthritis and Pain at G.D. Searle & Co., Monsanto Corporation. Prior to joining the pharmaceutical industry, Dr. Fort was an Associate Professor of Medicine at Thomas Jefferson University, Division of Rheumatology. He earned his MD from the University of Valencia Faculty of Medicine and is board certified in internal medicine with a subspecialty certification in rheumatology.

ENDOTHELIAL TECHNOLOGY

The Power of the Endothelium: Novel Delivery Approaches to Promoting Vascular Healing

By: Helen Nugent, PhD

INTRODUCTION

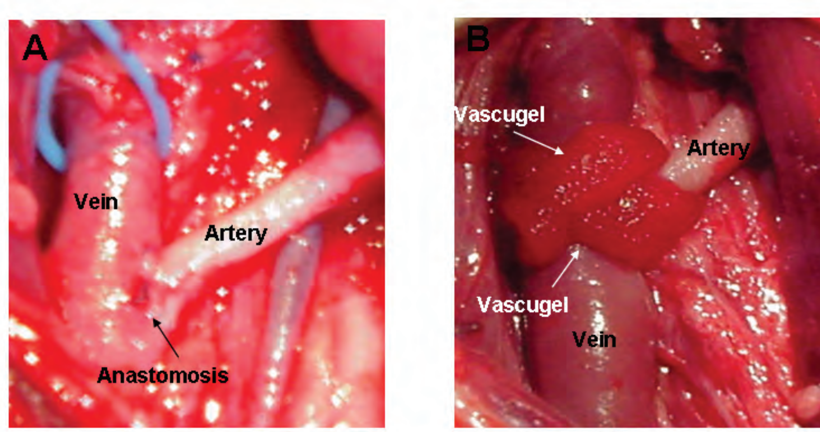
The blood vessel is a structure of extraordinary complexity. The continuity of vascular cells and tissues that make up the blood vessel contribute to its structural integrity and also maintain homoestasis through precise biochemical control, allowing the blood vessel to contract and dilate regulating blood flow. The blood vessel lining, called the endothelium, plays a key role within the vascular system, providing biological signals to the vasculature in order to maintain health and ensure normal blood flow. Vascular interventional procedures, such as bypass surgery, angioplasty, stent, or graft placement, are intended to treat diseased or occluded blood vessels, but often end up disrupting the endothelial lining triggering a cascade of unwanted events that lead to inflammation, thrombosis, and restenosis. Restenosis is the recurrence of stenosis after a vascular interventional procedure and is a major complication for patients. In order to address restenosis, patients often require repeated interventions, which are associated with significant co-morbidities and costs to the healthcare system.

Vascular access failure due to stenosis and thrombosis is a major complication in more than 300,000 patients in the US receiving hemodialysis to treat end-stage renal disease (ESRD).[1,2] The annual cost of vascular access-related complications currently exceeds $1 billion per year. Peripheral artery disease (PAD) affects greater than 7 million adults in the US and results in approximately 1.3 million procedural interventions in the US annually.[3] Although the clinical data for the use of drug-eluting stents following coronary interventions is compelling, stent placement plus drug elution has yet to show a benefit in large, randomized trials in peripheral arteries.[4,5] Clearly, new treatment modalities are needed for the treatment of peripheral vascular complications. Data compiled to date suggests that placement of allogeneic, adventitial tissue-engineered endothelial cells may decrease failure rates of these procedures and improve their long-term success.

THE POWER OF THE ENDOTHELIUM

Blood vessels are composed of three concentric tunics, the tunica intima, tunica media, and tunica adventitia.[6] The intima, located at the blood vessel wall-lumen interface, is lined with a single layer of endothelial cells (endothelium) that is supported by a basement membrane. The media, located in the middle of the blood vessel wall, consists of smooth muscle cells in lamellar units bound by elastic bands or lamina. The adventitia, located at the outer layer of the blood vessel, is composed of a loose fibrous network of fibroblasts. The vessels that nourish the blood vessel wall

FIGURE 1



Photograph of an artery-vein connection (anastomosis) from a preclinical arteriovenous fistula study (A) depicting the perivascular placement of Vascugel® (B).

and the nerves that supply neural control are also found in the adventitia.

The vascular endothelium is central to understanding vascular biology and critical to maintaining vascular health. The endothelial monolayer that normally lines blood vessels forms a continuous, selectively permeable thrombo-resistant surface that regulates local biology to prevent luminal obstructions and ensures uninterrupted blood flow.[7] This level of control is achieved throughout the blood vessel by an array of endothelial cell-derived biologically active compounds that regulate virtually every aspect of vascular biology, including thrombosis; vasomotor tone; cell proliferation and migration; lipid infiltration; and leukocyte adhesion/infiltration, and remodeling.[8-12] Endothelial state and cell density determine what compounds will be secreted. While confluence breeds quiescence, monolayer disruption signals growth promotion and accompanying phenomena.[13,14] Indeed, interventions that injure or damage the endothelium, such as angioplasty, bypass grafts, arteriovenous (AV) grafts, and fistulae or stenting, may bypass or treat blood vessel obstructions, but they also elicit a sequence of events that induces inflammation, stimulates cell proliferation, and culminates in stenosis and luminal occlusions.[15-18] Stenosis is a manifestation of the general wound-healing response expressed in tissue and is commonly observed following vascular reconstructive interventions. The mechanism of response to vascular injury or intervention is a complex, multi-factorial pathological process that involves a combination of many biological events and can be categorized into five phases: 1) platelet aggregation (thrombosis), 2) inflammatory cell infiltration, 3) release of growth factors, 4) smooth muscle cell and fibroblast modulation and proliferation, and 5) extracellular matrix deposition and remodeling.[16,19,20] This process leads to critical lumen narrowings in up to 30% to 50% of patients following vascular interventions, such as AV grafts and peripheral angioplasty or stenting.

TARGETING ENDOTHELIAL CELLS

Because the endothelium plays a key role in vascular responses and health, there have been many attempts to isolate and infuse single endothelial products to regulate vascular disease, and when this has failed, to restore denuded or repair dysfunctional endothelium.[21,22] Indeed, innovative studies have been performed in an attempt to reconstruct the structure of the blood vessel by autologous endothelial cell transplantation, implantation of endothelial cell-seeded interposition grafts, or endovascular stents.[23] Seeding endothelial cells at the luminal interface is difficult to achieve in practice, applies a limited number of endothelial cells during periods of intense injury and response, and may not be necessary for the secretion of biochemical compounds. In recent years, the adventitia has emerged as a key regulator of vascular remodeling after injury. Adventitial thickening, fibrosis, inflammation, and neovascularization all contribute to lesion formation, negative remodeling, and lumen loss after vascular injury.[24] In addition, endothelial cells reside not only at the lumen interface but also within the adventitia and throughout the vessel as vasa vasorum. Therefore, the adventitia is also a potential therapeutic target for vascular interventions.

PERVASIS' APPROACH

Tissue engineering enables the development of biological substitutes that can be implanted at sites distant to their original state, providing an opportunity to examine added benefits of cell secretory function to regulation of tissue biology. This is especially important in vascular biology, where the paracrine function of the endothelium has emerged as central to controlling vascular homeostasis. Pervasis' endothelial technology was developed based on these principals and harnesses endothelial paracrine signaling. A tissue-engineered endothelium was devised that consists of quiescent endothelial cells embedded on gelatin matrices. The embedded endothelial cells are able to maintain their identity, viability, normal growth kinetics, and biochemical activity in this milieu. These matrices are then placed on the outside (ie, perivascular) of an injured blood vessel (Figure 1). In this location, the cells provide growth factors and other compounds to the underlying cells within the blood vessel and are protected from erosive blood flow and from being in direct contact with the point of intervention.

Vascugel®, Pervasis' open surgical development candidate, is composed of allogeneic endothelial cells seeded onto a sterile absorbable sponge and is placed on the adventitia of a blood vessel at the site of intervention during open surgical procedures, such as a creation of vascular access for hemodialysis. Using insight gained during development of Vascugel, the company is developing PVS-10200, which has application in minimally invasive surgical procedures, such as angioplasty and stent placement. Perivascular placement of confluent aortic endothelial cells on gelatin matrices adjacent to injured blood vessels has been shown to be safe and provide therapeutic effects in animal models and clinical trials of vascular injury.[25-28]

Mechanism of Action

Elucidation of the exact mechanism of action of perivascular endothelial cells to promote vessel healing is ongoing. Preclinical studies suggest that perivascular allogeneic endothelial cells promote vascular healing by the release of anti-inflammatory, anti-proliferative, and anti-thrombotic compounds, such as transforming growth factor-beta1 and heparan sulfate proteoglycan, which are distributed circumferentially throughout the blood vessel. These compounds are then able to alter the bioavailability and distribution of endogenous vasoregulatory compounds such as growth factors. Preclinical studies also suggest that the perivascular endothelial cells, or factors released by the cells, provide control over vascular complications by influencing early events, such as inflammatory cell infiltration at the lumen, which in turn halts the stimulus for cellular proliferation and migration that lead to stenosis and failure.

APPLICATIONS

Vascugel for Vascular Access Failure

ESRD patients require hemodialysis approximately three times a week. AV grafts and fistulae represent the two major types of vascular access for hemodialysis. Both access types involve surgery to prepare the vascular system for repeated cannulations from the dialysis needle. AV access grafts were implanted in an estimated 50,000 ESRD patients in 2007 in the US alone.[2] This number is projected to grow at 4% annually as the number of patients requiring hemodialysis continues to grow. Vascular access failure due to stenoses and thromboses often requires costly intervention. As such, it is the most frequent contributor to morbidity in hemodialysis patients and adds roughly $1 billion to treatment costs each year. Recent data shows that graft patency rates are only about 40% after 1 year and drop to below 20% at 3 years.[29] A product that can improve patency, reduce complications, or extend the usable life of a graft could improve patient outcomes and reduce healthcare costs. Pervasis has reported positive data from Phase I open label and Phase II double blind, placebo-controlled clinical trials of Vascugel in 65 ESRD patients undergoing a new AV access surgical procedure (graft or fistula). These trials achieved the primary safety endpoints by demonstrating fewer thrombotic events, early complications, and interventions than the placebo patients within the first 30 days.[28] Additionally, positive efficacy trends were observed in secondary endpoints, which included higher patency rates and greater lumen diameters at 6 months and in the diabetic sub-population.

PVS-10200 For Peripheral Arterial Disease

PVS-10200 is being developed as a treatment of restenosis following angioplasty plus stent placement for the treatment of PAD. PAD commonly results from progressive narrowing of arteries in the lower extremities due to atherosclerosis. Previous studies have shown that PAD is associated with a significantly elevated risk of cardiovascular disease morbidity and mortality.[30] PAD affects approximately 7 to 10 million US adults and as the US population ages and diabetes become more prevalent, PAD is likely to become an increasing problem.[31] Interventions for lower extremity disease include lifestyle modification, medication (eg, antiplatelet therapy, lipid-lowering therapy, etc), angioplasty, stent(s) placement, bypass surgery, endarterectomy, or amputation, resulting in approximately 1.3 million procedural interventions for the treatment of PAD in the US with over 1 million of these being endovascular-based interventions, such as angioplasty and stenting.[30] The most significant limitation of percutaneous revascularization in peripheral atherosclerosis is the high rates of restenosis. Despite initial technical success, restenosis after angioplasty or stent implantation occurs in approximately 50% of the treated vessels, such as the superficial femoral artery (SFA), within 6 to 12 months.[18] Indeed, 1 year patency rates in the SFA range between 22% and 61% after bare metal stent implantation. Preclinical studies of PVS-10200 delivered to the adventitia of stented femoral arteries by ultrasound guidance demonstrated a statistically significant decrease in stenosis and expand the opportunity for the clinical application of PVS-10200 with minimally invasive procedures for PAD.

SUMMARY

Pervasis' platform technology of perivascular, tissue-engineered endothelial cells has provided an invaluable tool to further understand vascular physiology and vascular diseases, while also providing products that are ideally suited to enhance vascular healing after intervention. Many of the pathologic events associated with vascular disease arise from endothelial injury or dysfunction. When Vascugel or PVS-10200 is placed into experimental models of vascular intervention

ENDOTHELIAL TECHNOLOGY

and healing, they provide the maximal control over inflammation, thrombosis, proliferation, and remodeling. Phase I and II clinical trials of Vascugel in ESRD patients demonstrated an excellent safety profile. Targeted local therapy with tissue-engineered endothelial cells is a novel therapeutic approach that is safe and may be ideally suited to control the response to injury, promote healing, and inhibit clinical vascular dysfunction.

REFERENCES

1. Feldman H, Kobrin S, Wasserstein A. Hemodialysis vascular access morbidity. J Amer Soc Nephrol. 1996;7(4):523-535.
2. System URD. 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. 2008(Bethesda, MD):National Institute of Diabetes and Digestive and Kidney Diseases.
3. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. Circ. 2004;110(6):738-743.
4. Duda SH, Bosiers M, Lammer J, Scheinert D, Zeller T, Oliva V, Tielbeek A, Anderson J, Wiesinger B, Tepe G, Lansky A, Jaff MR, Mudde C, Tielemans H, Beregi JP. Drug-eluting and bare nitinol stents for the treatment of atherosclerotic lesions in the superficial femoral artery: long-term results from the SIROCCO trial. J Endovasc Ther. 2006;13(6):701-710.
5. Tepe G. Drug-eluting stents for infrainguinal occlusive disease: progress and challenges. Sem Vasc Surg. 2006;19(2):102-108.
6. Burkitt H, Young B, Heath J. Wheater's Functional Histology: A Text and Colour Atlas. 3rd ed: Churchhill Livingstone;1993.
7. Rubanyi GM. The role of endothelium in cardiovascular homeostasis and diseases. J Cardiovasc Pharmacol. 1993;22:S1-S14.
8. Casscells W. Migration of smooth muscle and endothelial cells. Critical events in restenosis. Circ. 1992;86(3):723-729.
9. Furchgott RF, Vanhoutte PM. Endothelium-derived relaxing and contracting factors. Fed Amer Soc Experiment Biol J. 1989;3:2007-2018.
10. Autio I, Malo-Ranta U, Kallioniemi OP, Nikkari T. Cultured bovine aortic endothelial cells secrete factor(s) chemotactic for aortic smooth muscle cells. Artery. 1989;16(2):72-83.
11. Cybulsky MI, Gimbrone MA, Jr. Endothelial expression of a mononuclear leukocyte adhesion molecule during atherogenesis. Science 1991;251(4995):788-791.
12. Castellot JJ, Addoniziio ML, Rosenberg RD, Karnovsky MJ. Cultured endothelial cells produce a heparin-like inhibitor of smooth muscle cell growth. J Cellu Biol. 1981;90:372-379.
13. Nabel EG. Biology of the impaired endothelium. Amer J Cardiol. 1991;68(12):6C-8C.
14. Gertler JP, Abbott WM. Prothrombotic and fibrinolytic function of normal and perturbed endothelium. J Surg Res.1992;52(1):89-95.
15. Fischell TA, Derby G, Tse TM, Stadius ML. Coronary artery vasoconstriction routinely occurs after percutaneous transluminal coronary angioplasty. A quantitative arteriographic analysis. Circ. 1988;78(6):1323-1334.
16. Castaneda-Zuniga WR, Formanek A, Tadavarthy M, Vlodaver Z, Edwards JE, Zollikofer C, Amplatz K. The mechanism of balloon angioplasty. Radiol. 1980;135(3):565-571.
17. Sullivan KL, Besarab A, Bonn J, Shapiro MJ, Gardiner GA, Jr., Moritz MJ. Hemodynamics of failing dialysis grafts. Radiol.1993;186(3):867-872.
18. Cejna M, Thurnher S, Illiasch H, Horvath W, Waldenberger P, Hornik K, Lammer J. PTA versus Palmaz stent placement in femoropopliteal artery obstructions: a multicenter prospective randomized study. J Vasc Interv Radiol. 2001;12(1):23-31.
19. Chervu A, Moore WS. An overview of intimal hyperplasia. Surg. 1990;171:433-447.
20. Phillips-Hughes J, Kandarpa K. Restenosis: pathophysiology and preventive strategies. J Vasc Interv Radiol. 1996;7(3):321-333.
21. Ellis SG, Roubin GS, Wilentz J, Douglas JS, Jr., King SB, 3rd. Effect of 18- to 24-hour heparin administration for prevention of restenosis after uncomplicated coronary angioplasty. Amer Heart J. 1989;117(4):777-782.
22. Fishman JA, Ryan GB, Karnovsky MJ. Endothelial regeneration in the rat carotid artery and the significance of endothelial denudation in the pathogenesis of myointimal thickening. Laboratory investigation; a journal of technical methods and pathology. 1975;32(3):339-351.
23. Conte MS, Birinyi LK, Miyata T, Fallon JT, Gold HK, Whittemore AD, Mulligan RC. Efficient repopulation of denuded rabbit arteries with autologous genetically modified endothelial cells. Circ. 1994;89(5):2161-2169.
24. Scott NA, Cipolla GD, Ross CE, Dunn B, Martin FH, Simonet L, Wilcox JN. Identification of a potential role for the adventitia in vascular lesion formation after balloon overstretch injury of porcine coronary arteries. Circ. 1996;93(12):2178-2187.
25. Nugent HM, Groothius A, Seifert P, Guerraro L, Nedelman M, Mohanakumar T, Edelman ER. Pervascular endothelial implants inhibit intimal hyperplasia in a model of arteriovenous fistulae: A safety and efficacy study in the pig. J Vasc Res. 2002;39:524-533.
26. Nugent HM, Ng Y-S, White D, Groothius A, Kanner G, Edelman ER. Delivery site of perivascular endothelial cells determine control of stenosis in a porcine femoral stent model. J Vasc Intervent Radiol. 2009;20:1617-1624.
27. Nugent HM, Tjin Tham Sjin RM, White D, Milton L, Manson R, Lawson J, Edelman ER. Adventitial endothelial implants reduce matrix metalloproteinase-2 expression and increase luminal diameter in porcine arteriovenous grafts. J Vasc Surg. 2007;46:548-556.
28. Conte MS, Nugent HM, Gaccione P, Guleria I, Roy-Chaudhury P, Lawson JH. Multi-center Phase I/II trial of the safety of allogeneic endothelial cell implants after the creation of arteriovenous access for hemodialysis use: the V-HEALTH study. J Vasc Surg. 2009;50:1359-1368.
29. Dixon BS, Beck GJ, Vazquez MA, Greenberg A, Delmez JA, Allon M, Dember LM, Himmelfarb J, Gassman JJ, Greene T, Radeva MK, Davidson IJ, Ikizler TA, Braden GL, Fenves AZ, Kaufman JS, Cotton JR, Jr., Martin KJ, McNeil JW, Rahman A, Lawson JH, Whiting JF, Hu B, Meyers CM, Kusek JW, Feldman HI. Effect of dipyridamole plus aspirin on hemodialysis graft patency. NEJM. 2009;360(21):2191-2201.
30. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA. ACC/AHA 2005 guidlines for the mangement of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary. Circ. 2006;113:1474-1547.
31. Peripheral Arterial Disease in People with Diabetes. Americans Diabetes Association. Diabetes Care. 2003;26(12):3333-3341.

BIOGRAPHY

Dr. Helen Nugent is a Co-Founder and Vice President, Research and Development, at Pervasis Therapeutics and also holds a Research Affiliate position in the Harvard-MIT Division of Health Sciences and Technology. Dr. Nugent earned her BS in Chemistry from Merrimack College and her MA and PhD in Organic Chemistry from Brandeis University. Her doctoral thesis concentrated on the synthesis of novel organometallic polymers. She continued her work in material science by completing a 1-year fellowship at the Institute for Polymers and Organic Solids at the University of California, Santa Barbara. Dr. Nugent joined MIT as a post-doctoral fellow and performed research on tissue-engineered endothelial cells, which resulted in numerous peer-reviewed publications and abstract presentations. Dr. Nugent has more than 10 years of experience in the biotechnology industry directing and performing critical research and developmental work and over 12 years of experience in vascular and endothelial biology. She previously held positions at Reprogenesis, Inc. and its successor; Curis, Inc. Dr. Nugent has been the recipient of a National Science Foundation Research Fellowship and served as the Principal Investigator on a National Institutes of Standards and Technology Advanced Technology Program Award.

OPHTHALMIC PREPARATIONS

Trends in Ophthalmic Preservatives: A Review

By: Megha Barot, MPharm; Mitan R. Gokulgandhi, MPharm; Jolly R. Parikh; PhD

ABSTRACT

Preservatives are an important component of ophthalmic preparations, providing antimicrobial activity in the bottle and preventing decomposition of active drug. The most common preservatives in ophthalmic preparations for glaucoma and surface eye disease - benzalkonium chloride (BAK), chlorobutanol, sodium perborate, and stabilized oxychloro complex (SOC) - were reviewed. Compared with other preservatives, SOC caused the least amount of damage to rabbit corneal epithelial cells. BAK has demonstrated cytotoxic effects in cell culture, as well as in animal and human studies. Manufacturers should consider formulations with new-generation preparations containing low-risk preservatives, such as SOC, especially for patients receiving multiple ophthalmic medications.

INTRODUCTION

Preservatives are present in most ophthalmic medications and are added to multidose containers in order to inhibit bacterial growth. A 1992 study found that multidose containers of ocular medications without preservatives often become contaminated with bacteria after 1 to 2 weeks of twice-daily usage.[1] As a result, the US FDA and US Pharmacopoeia mandated that all multidose ophthalmic preparations contain a preservative to ensure a non-hazardous degree of contamination. By providing a level of antimicrobial activity in the bottle, preservatives limit bacterial, mycotic, and amoebal ocular infections caused by contaminations of solutions and prolong shelf-life by preventing biodegradation and maintaining drug potency. The primary concern with many preservatives is not their efficacy, but rather their recognized cytotoxic side effects.[2] High concentrations of some preservatives can damage and irritate ocular tissue. Preservative-free products may prevent toxic side effects, but they are expensive, and the small unit-dose container can be difficult to use, hindering compliance.[3] Nonetheless, some patients require preservative-free products because of sensitivities or allergies. The goal of the pharmaceutical industry should be to manufacture such ophthalmic preparations of effective agents that contain preservatives with minimal effects on ocular tissues.

CLINICAL RELEVANCE

In chronic diseases, such as glaucoma or dry eye syndrome, high concentrations of preservatives or repeated exposure to preserved medications increases the likelihood of adverse effects.[4] For example, long-term use of anti-glaucoma drugs has been linked to toxic and inflammatory changes of the ocular surface because repeated doses of preserved eye drops can have a cumulative effect, and extended contact with the epithelium may lead to chronic irritation and subconjunctival fibrosis.[5,6] Patients with severe Keratoconjunctivitis sicca (KCS) may need to instill tear substitutes as often as every 20 minutes. Preservatives may worsen the condition by disrupting the precorneal tear film and damaging the epithelial surface. Many corneal specialists believe KCS may be aggravated by frequent use of preservative-containing artificial tears, especially because these patients may not produce enough natural tears to dilute harmful preservatives.[2,7] Less-frequent daily administration, lower preservative concentrations, and new formulations may help minimize this ocular surface damage.

COMMONLY USED PRESERVATIVES

Damage due to ophthalmic preservatives often goes unnoticed because it is difficult to differentiate side effects of an active ingredient from those of the preservative. The following sections review the mechanism of action and results of tissue culture and animal studies to compare toxic effects of preservatives. A spectrum of preservatives is found in nearly every type of ophthalmic solution. BAK is one of the most commonly used preservatives. Less common are benzododecinium bromide (BDD), cetrimonium chloride, thiomersal, sorbic acid, polyaminopropyl biguanide, and hydrogen peroxide. Tables 1 and 2 list commonly used products and their preservative concentrations.

Preservatives interfere with microbial organisms by causing lysis of plasma membranes, inhibiting cellular metabolism, oxidizing or coagulating cellular constituents, or promoting hydrolysis.[8] Two classes of preservatives are commonly used in ophthalmic medications: detergents and oxidants.[9]

DETERGENT PRESERVATIVES

Detergent preservatives, such as BAK and BDD have surfactant effects that disrupt cell membrane permeability. These compounds cause lipid dispersion, which in turn leads to lysis of cytoplasmic contents in microorganisms, and ultimately bacterial death.

Benzalkonium Chloride

BAK, a cationic detergent, is the most commonly used preservative in topical ophthalmic preparations and is present in concentrations ranging from 0.004% to 0.02% (Table 1). Studies from the late 1970s showed that this quaternary ammonium compound denatures proteins and causes lysis of cytoplasmic membranes. The surfactant effect of quaternary ammonium compounds, including BAK, can solubilize the intercellular cement of the corneal epithelium, thereby increasing the compound's penetration.[4,10] Moreover, because BAK can accumulate and remain in ocular tissue for relatively lengthy periods, it can induce different types of cell death in a dose dependent manner: growth arrest at low concentrations, apoptosis at 0.01%, and necrosis at higher concentrations.[4,11,12] Mammalian cells are unable to neutralize detergent preservatives, such as BAK, and ocular cells are damaged when preservatives are incorporated into them by liposomes or other intracellular vacuoles.[11] In vitro studies by De Saint and colleagues using cultured human conjunctival cells demonstrated that damage by BAK seems to be dose dependent. They showed that BAK induces cell damage ranging from growth arrest at very low (0.0001%) concentrations to apoptosis at medium (0.01%) concentrations, to necrosis at higher (0.05% to 0.1%) concentrations.[13]

In an antiglaucoma preparation, BAK does not alter the drug's ability to lower intraocular pressure but can modify the ocular surface with long-term use.[14] Patients with dry eye syndrome may have increased vulnerability to BAK-induced effects. Artificial tears containing BAK enhance corneal epithelial permeability, contributing to ocular surface disease.[15] Ophthalmic preparations that contain high concentrations of BAK interfere with the integrity of the superficial lipid layer and reduce tear break-up time, causing the duplex tear film to become unstable. This compromised stability may not be physiologically harmful, as the lipid layer of the tear film is re-formed every 15 to 30 seconds, but should be taken into account for patients with a compromised tear film. Ideally, these individuals should use products with preservatives that do not break up the tear film. At low BAK concentrations or with infrequent use, BAK-preserved preparations may pose little risk. Polyquad (polyquaternium-1) is a polymer of BAK. Polyquad has low toxicity to ocular tissues; however, a study by Way et al showed extensive superficial erosion of the epithelium and lack of protruding microvilli.[16-20]

TABLE 1

Trade Name	Manufacturer	Preservative
Alphagan	Allergan, Inc.	BAK 0.005%
Alphagan P	Allergan, Inc.	SOC 50ppm
Betagan	Allergan, Inc.	BAK 0.005%
Betoptic S	Alcon	BAK 0.01%
Cosopt	Merck & Co., Inc.	BAK 0.0075%
Lumigan	Allergan, Inc.	BAK 0.005%
Propine	Allergan, Inc.	BAK 0.005%
Rescula	CIBA Vision	BAK 0.015%
Timoptic	Merck & Co., Inc.	BAK 0.01%
Timoptic-XE	Merck & Co., Inc.	BDD 0.012%
Trusopt	Merck & Co., Inc.	BAK 0.0075%

Chlorobutanol

As an alcohol-based preservative, chlorobutanol lacks surfactant activity; therefore, unlike BAK, it does not increase penetration of additional chlorobutanol molecules into the cell.[4,10] Instead, chlorobutanol disorganizes the lipid structure of the membrane, which increases permeability and leads to cell lysis. Chlorobutanol has broad spectrum antimicrobial action. In vivo, even at concentrations 100 times that of commercial products, it did not damage rabbit corneas, including the endothelium.[4] Chlorobutanol 0.5% did not affect the stability of the tear film lipid layer in non-contact lens users and enhanced in vitro transcorneal permeation of ibuprofen.[21,22] Despite its relative safety, chlorobutanol 0.5% w/v in artificial tears caused irritation in more than 50% of patients in a double-blind crossover study, most likely as a result of cellular retraction and cessation of normal cytokinesis, cell movement, and mitotic activity.[23] Degeneration of human corneal epithelial cells and generation of conspicuous membranous blebs have also been observed.[24,25] Chlorobutanol also inhibits oxygen use by the cornea, which increases susceptibility to infection.[26] Also, compared with BAK 0.004% to 0.02%, chlorobutanol

TABLE 2

Product Name	Manufacturer	Preservative	Use
GenTeal	CIBA Vision	Sodium Perborate	Artificial tears
Hypotears	CIBA Vision	BAK 0.01%	Artificial tears
Naphcon-A	Alcon	BAK 0.01%	Vasoconstrictor
Refresh Tears	Allergan, Inc.	SOC 50ppm	Artificial tears
Tears Naturale II	Alcon	Polyquad 0.001%	Artificial tears
Vasocon-A	CIBA Vision	BAK 0.01%	Vasoconstrictor
Visine	Pfizer	BAK 0.01%	Vasoconstrictor

0.2% to 0.5% is less toxic to rabbit corneal epithelial cells in vitro.[27] In human corneal epithelial cells, the cytotoxic effects of chlorobutanol occur less rapidly and are less severe than those of BAK.[24]

OXIDATIVE PRESERVATIVES

Oxidative preservatives, such as SOC and sodium perborate are usually small molecules that penetrate cell membranes and disrupt cellular function by modifying lipids, proteins, and DNA. Their membrane-destabilizing activity is less potent than that of detergent preservatives. At low levels, oxidative preservatives have an advantage over detergent preservatives by providing enough activity against microorganism while exerting only negligible toxic effects on eukaryotic cells. This occurs because many microorganisms cannot cope with oxidative stress. In comparison, mammalian cells are equipped with antioxidants, oxidase, and catalase to neutralize the effect of low-level oxidants.[28,29]

Purite® (SOC)

SOC, an ophthalmic preservative, introduced in 1996, consists of an equilibrium mixture of 99.5% chlorite (ClO2), 0.5% chlorate (ClO3), and trace amount of chlorine dioxide free radicals. This preservative was shown to have bactericidal, viricidal, and fungicidal (Fungus-Aspergillus niger) activity. Although its mechanism of action has not been elucidated, it is known that SOC generates chlorine dioxide free radicals that oxidize unsaturated lipids and glutathione in the cell. This can likely lead to disruption of protein synthesis in bacteria, viruses, and fungi. In the eye, SOC is converted into sodium and chloride ions, oxygen, and water. SOC has been given an EPA Category II rating as a mild eye irritation.[30] Way et al studied the in vitro cytotoxic effects of Purite on cultured MDCK epithelial cells as well as the in vivo effect on rabbit corneal epithelium. No toxicity was noted in either model.[20]

Sodium Perborate

Sodium perborate is an oxidative preservative that is converted in to hydrogen peroxide when it is combined with water. Low levels of hydrogen peroxide have an effective antimicrobial action, although levels between 30 and 100 ppm have been shown to cause ocular stinging.[31,32] Sodium perborate oxidizes cell walls or membrane, affecting membrane-bound enzymes and disrupting protein synthesis. Upon entering the eye, it is rapidly decomposed to water and oxygen by catalase and other enzymes in the conjunctival sac.[33] This preservative was shown to kill the fungus Aspergillus niger. In limited testing, sodium perborate has been identified as an in vitro mutagen.[12] Mammalian cells are only minimally damaged by SOC or by sodium perborate at concentrations present in ophthalmic preparations.[30] Because these cells contain antioxidants, oxidases, and catalases, it is thought they can neutralize low doses of oxidants better than they can neutralize low doses of detergents.

SOC Compared With Other Preservatives

Relative to other preservatives, SOC is minimally toxic to the eye, as determined by one study compared with the untreated eye, the extent of corneal epithelial damage was polyquad > sodium perborate > SOC.[27] Attempts to improve drug tolerability by minimizing the toxic effects of preservatives are underway. One aim is to decrease cumulative exposure to the preservative. A once-daily form of timolol with 0.012% BDD (a preservative similar to BAK) is available; however, BDD also damages the corneal epithelium, and the gel-forming preparation may prolong contact of the preservative with the corneal surface.[3] Another approach is to reformulate existing products with better-tolerated preservatives. One such product, a brimonidine compound approved by the FDA in March 2001, has replaced BAK with SOC in the current formulation. A 12-month clinical comparison in patients with glaucoma or ocular hypertension showed that brimonidine-SOC was well tolerated and produced a significantly lower incidence of allergic conjunctivitis than brimonidine, as well as equivalent IOP-lowering efficacy.[34]

CONCLUSIONS

Many preservatives in eye drops induce histopathologic, inflammatory, and toxic changes on the ocular surface. Patients with glaucoma and/or dry eye disease who require chronic use of ophthalmic medications to control their ocular disease may benefit from formulations that are preservative-free (or contain lower concentrations of detergent preservatives) or contain oxidative preservatives such as SOC. SOC represents a new generation of ophthalmic preservative that break down into natural tear components on instillation and thus has low potential to cause toxic effects. Therefore, physicians should consider drugs containing low-risk preservatives or preservatives at concentrations least likely to cause damage.

REFERENCES

1. Schein OD, Hibberd PL, Starck T, Baker AS, Kenyon KR. Microbial contamination of in-use ocular medications. Arch Ophthalmol. 1992;110:82-85.
2. Tripathi BI, Tripathi RC, Kolli SP. Cytotoxicity of ophthalmic preservatives on human corneal epithelium. Lens Eye Toxical Res. 1992;9:361-375.
3. Pisella PI, Fillacier K, Elena PP, Debbasch C, Baodouin C. Comparison of the effects of preserved and unpreserved formulations of timolol on the ocular surface of albino rabbits. Ophthalmic Res. 2000;32:3-8.
4. Gasset AR, Ishii Y, Kaufman HE, Miller T. Cytotoxicity of ophthalmic preservatives. Am J Ophthalmol. 1974:78:98-105.
5. Baudouin C. Side effects of antiglaucomatous drugs on the ocular surface. Curr Opin Ophthalmol. 1996;7:80-86.
6. Baudouin C. Mechanisms of failure in glaucoma filtering surgery: a consequence of antiglaucomatous drugs. Int J Clin Pharmacol Res. 1996;16:29-41.
7. Berdy GJ, Abelson MB, Smith LM, George MA. Preservative-free artificial tear preparations. assessment of corneal epithelial toxic effects. Arch Ophthalmol. 1992;110:528-532.
8. Noecker R. Effects of common ophthalmic preservatives on ocular health. Adv Ther. 2001;18:205-215.
9. Spickett C. Studies of cellular response to purite and other preservatives. UK; University of Strathclyde;2001.
10. Kreiner C. Biochemical aspects of ophthalmic preservatives. Contacto. 1979; Nov; 10-14.
11. Grant WM, Schuman JS. Toxicology of the eye. Springfield, III; Charles C. Thomas; 1990.
12. Seiler JP. The mutagenic activity of sodium perborate. Mutat Res. 1989;224:219-227.
13. De Saint Jean M, Brignole F, Bringuier A, Bauchet A. Effects of benzalkonium chloride on growth and survival of change conjunctival cells. InvestOphthalmol Vis Sci. 1999;40:619-630.
14. Campagna P, Macri A, Rolando M, Calabria G. Chronic topical eye preservative-free beta-blocker therapy effect on the ocular surface in glaucomatous patients. Acta Ophthalmol Scand Suppl. 1997;224:53.
15. Gobbels M, Spitznas M. Corneal epithelial permeability of dry eyes before and after treatment with artificial tears. Ophthalmol. 1992;99:873-878.
16. Holly FJ. Surface chemical evaluation of artificial tears and their ingredients, II: interaction with a superficial lipid layer. Contact Lens. 1978;4:52-65.
17. Baudouin C, De Lunardo C. Short term comparative study of topical 2% cartelol with and without benzalkoniun chloride in healthy volunteers. Br J Ophthalmol. 1998;82:39-42.
18. Turaci E, Budak K, Kaur A, Mizrak B, Ekinci C. The effects of long-term topical glaucoma medication on conjunctival impression cytology. Int Ophthalmol. 1997; 21:27-33.
19. Morgan JF. Problem associated with current care systems for contact lenses. Practical Optom. 1990;1(1):8.
20. Way WA, Matsumoto S, Apel LJ, Wiese A, Vehige TJ. Purite as a non-disruptive preservative for lubricating eye drop solutions in comparison to alternative preservatives. Invas Ophthalmol Vis Sci. 2001;4:S223-B196.
21. Tomlinson A, Trees GR. Effect of preservatives in artificial tear solution on tear film evaporation. Ophthalmic Physiol Opt. 1991;11:48-52.
22. Gupta M, Majumdar DK. Effect of concentration, pH, and preservative on in vitro transcorneal permeation of ibuprofen and fulbiprofen from non-buffered aqueous drops. Indian J Exp Biol. 1997;35:844-849.
23. Fassihi AR, Naidoo N. Irritation associated with tear-replacement ophthalmic drops. A pharmaceutical and subjective investigation. S Afr Med J. 1989;75:233-235.
24. Tripathi BJ, Tripathi RC. Cytotoxic effects of benzalkonium chloride and chlorobutanol on human corneal epithelial cells in vitro. Lens Eye Toxicol Res. 1989;6:395-403.
25. Collin HB. Ultra structural changes to corneal stromal cells due to ophthalmic preservatives. Acta Ophthalmol. 1986;64:72-78.
26. Buestein N. Corneal cytotoxicity of topically preservatives. Surv Ophthalmol. 1980;25:15.
27. Lazarus HM, Imperia PS, Botti RE, Mack RJ, Lass JH. An in vitro method which assesses corneal epithelium toxicity due to antineoplastic, preservative, and antimicrobial agents. Lens Eye Toxicol Res. 1989;6:59-85.
28. Block SS. Disinfection, Sterilization and Preservation. Malvern, PA; Lea & Febiger; 1991.
29. Noecker RJ, Herrygers LA. Effect of preservatives in chronic ocular therapy. Clinical and Refractive Optometry. 2004;15:43-48.
30. Purite. 1-3 Bio-Cide International Inc, Norman, OK;1998.
31. Vaughan JS, Porter DA. A new in vitro method for assessing the potential toxicity of soft contact lens care solutions. CLAO J. 1993;19:54-57.
32. Paugh JR, Brennan NA, Efron N. Ocular response to hydrogen peroxide. Am J Optom Physiol Opt. 1998;65:91-98.
33. Grant R, Ajello M, Vlass E. Salt water or high tech? A look at two new rinsing solution for contact lenses. Optician. 1996;212:38-41.
34. Walters TR, Batoosingh AL. 12 Month evaluation of brimonidine-Purite compared with brimonidine in patients with glaucoma or ocular hypertension. Invest Ophthalmol Vis Sci. 2001;42:8558.

BIOGRAPHIES

Megha Barot is currently enrolled as a graduate student in the Department of Pharmaceutical Science at University of Missouri Kansas City. She has completed her MPharm in Pharmaceutical Technology from the Institute of Science & Technology for Advanced Studies & Research (Vallabh Vidyanagar, India). She earned her BPharm from Barkattullah University (Bhopal, India) and stood top most among all students.

Mitan Gokulgandhi is currently enrolled as a graduate student in the Department of Pharmaceutical Science at University of Missouri Kansas City. He has completed his MPharm in Pharmaceutical Technology from the Institute of Science & Technology for Advanced Studies & Research (Vallabh Vidyanagar, India). He earned his BPharm from A.R. College of Pharmacy (Vallabh Vidyanagar, India).

Dr. Jolly R. Parikh is currently working as an Assistant Professor and Head, Department of Pharmaceutics & Pharmaceutical Technology, at the A.R. College of Pharmacy, Vallabh Vidyanagar, Gujarat; India. She is the Chairman of the Board of Studies in Pharmaceutics & Pharmaceutical Technology at the Sardar Patel University, Vallabh Vidyanagar. She has almost 20 years of teaching experience and is currently guiding MPharm and PhD students in the research area of novel drug delivery systems.

EXTRUSION-SPHERONIZATION

An Industrial Insight Into Pellet Manufacture by Extrusion Spheronization

By: E.L. McConnell, PhD; S.R. Pygall, PhD; R. Ward, PhD; and C. Seiler, PhD

INTRODUCTION

The pharmaceutical, food, and agricultural industries have at least one common technology - pelletization. Used worldwide for the production of drug-loaded particles, non-pariels, fertilizers, or animal feeds, it could be easily assumed that such a common process would be well understood. However, despite its continued popularity, pelletization remains a complex process in which many parameters and formulation variables have an influence on the quality of the final product. Understanding and controlling this is of utmost importance for the pharmaceutical industry in particular, where uniformity, quality, and efficacy are key factors in batch production. The pay-off for addressing the complex manufacturing process is a plethora of perceived biopharmaceutical and technical advantages over other dosage forms (Table 1). The following reviews the production of pellets by extrusion-spheronization, addressing some of the major processing considerations and challenges and offering potential methods of resolution.

THE PROCESS

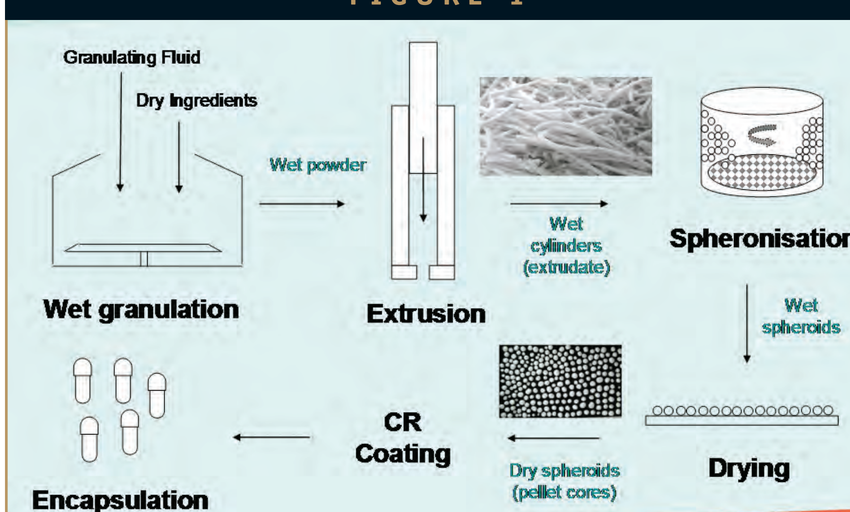
In basic terms, the extrusion and spheronization process involves four sequential steps: (1) granulation, (2) extrusion, (3) spheronization, and (4) drying (Figure 1). Each of these steps is discussed in more detail in the following paragraph.

The initial step in pellet production is mixing of the formulation components. Similar to the granulation step in the production of wet-granulated tablets, this stage involves the blending of dry ingredients followed by the gradual addition of granulating fluid. Various types of granulators can be used for this process including planetary mixers, high shear mixers, sigma blade mixers, and continuous granulators. However, the resulting mass will generally possess a higher fluid content than that used in wet granulation as it not only facilitates ingredient binding, but also provides lubrication for the extrusion process, which represents the subsequent step in pellet production. Generally, extrusion involves forcing the wet mass through a screen or a die under the force of a ram or screw feeder. The resulting compacted mass of rods (ie, strands of extrudate) are then placed into a spheronizer for the next stage of processing. A spheronizer is simply a cylindrical vessel fitted with a rotating plate. This plate has a grooved pattern that initially chops and subsequently rounds the lengths of extrudate into spherical particles. Subsequently, the spheronized particles are dried by vacuum, oven, fluid bed, or freeze drying.

THE EXCIPIENTS

As discussed earlier, one perceived advantage of pellets versus single-unit dosage forms is they can be prepared with high drug loading (up to 80% w/w has been claimed).[1] However, successful pellet formation is highly dependent upon the presence of other excipients in the

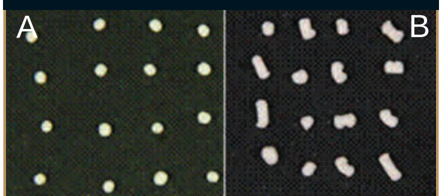
FIGURE 1



Processes involved in Extrusion/Spherionization (CR = Controlled Release)

EXTRUSION-SPHERONIZATION

FIGURE 2



Extrusion Spheronized Pellet Containing (A) MCC:Lactose:Drug (45:45:10) With an MCC:Fluid ratio of 0.8 and (B) MCC:Lactose:Drug (35:55:10) With an MCC:Fluid Ratio of 0.8

formulation composition. The wet mass, once produced, should have appropriate physicochemical properties (ie, flow, moisture content, compressibility) to facilitate the extrusion of the material, while at the same time retaining sufficient tensile strength and plasticity to enable the spheronizatino to occur. Materials facilitating this process are known as spheronization aids, with the most commonly utilized being microcrystalline cellulose (MCC).[2] The mechanism of action of MCC in the pellet extrusion process has been compared to that of a sponge.[3] Cellulose is a swellable polysaccharide, and water can be absorbed into the pores and amorphous areas of its fibers, becoming bound to its structure. When the wet mass is extruded, the water is consequently squeezed out of the structure and affords lubricant functionality throughout the extrusion process. Following extrusion, the extrudate often appears drier than the wet mass, but is still relatively soft and retains a "sponge-like" structure that can be chopped and deformed in the spheronizatopm step. Upon drying, the residual water is removed from the pharmaceutical product. Although the possibility remains to use different grades of MCC to influence moisture content and wet mass properties, much research has been carried out investigating the possible utilization of other materials as spheronization aids (to overcome the perceived shortcomings of MCC), including problematic formulation of poorly soluble drugs, chemical incompatibility with specific drugs, and drug adsorption onto MCC.[4] Examples include chitosan, starch, polyvinylpyrrolidone, and polyethylene oxide.[4-7] In another study, ranitidine pellets were successfully formulated using barium sulfate and glyceryl monostearate with and without MCC.[8] However, to date, these alternative excipients have achieved only limited success and remain on the periphery of large-scale industrial application.

One potential disadvantage of MCC with respect to the dissolution of pharmaceutical pellets is its insolubility in water. It is thus often desirable to include soluble materials to facilitate the diffusional processes that are critically involved in drug release. The commonly used pharmaceutical filler lactose (and its variants) can be employed for this purpose, formulated with or without conventional pharmaceutical super-disintegrants, such as sodium croscarmellose and sodium starch glycolate. Likewise, it is possible to substitute lactose (eg, when an incompatibility exists between this saccharide and the active pharmaceutical ingredients) for other soluble excipients, including the various grades of mannitol that are commercially available and other soluble disaccharides.

FIGURE 3

Dumbell-Shaped Pellet

CHALLENGES & POTENTIAL SOLUTIONS

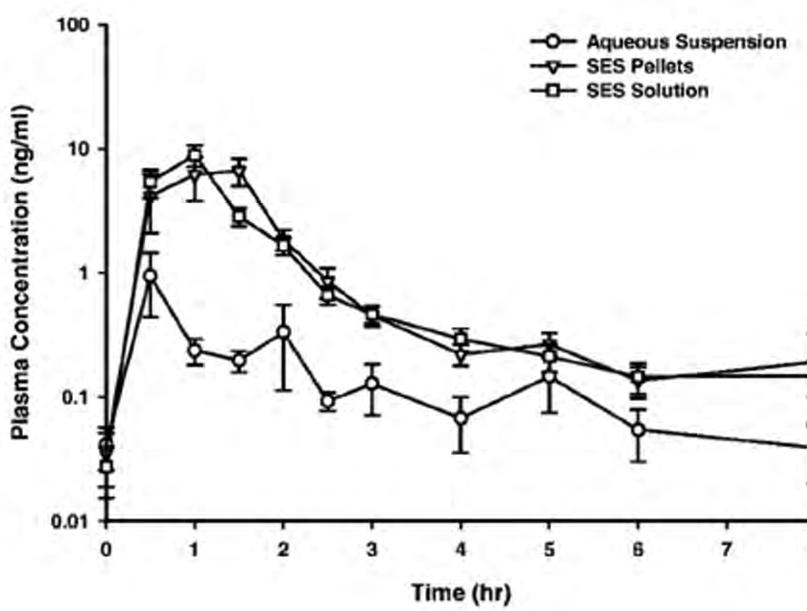
Table 2 shows the formulation and processing variables that can affect pellet quality and elegance. Given the high potential for complex interactions between formulation components during the multi-stage manufacturing process, it is not surprising

TABLE 1

Elegance	-Aesthetically pleasing -Uniform -Narrow size distribution
Biopharmaceutical Performance	-Large surface area for interaction with gastrointestinal fluids -Improved reproducibility of drug levels in the blood -Reduced risk of dose dumping -Better distribution throughout gastrointestinal tract
Regulatory	-Line extension for existing products -May have applicability for paediatric formulations

The Perceived Advantages of Pellet Formulations

FIGURE 4



Mean (± SEM, n = 5-6) Plasma Concentration of Progesterone After Administration in Self-Emulsifying Formulation of 16-mg Progesterone as Pellet (SES Pellets) and Liquid Form (SES Solution) and as Aqueous Suspension (reproduced with permission from Tuleu et al 2004)

that optimization of a pellet formulation and process can be costly, time consuming, and highly problematic. Here, we discuss some of the more common challenges encountered during pellet manufacture as well as potential solutions. It should be noted there are no general rules for pellet manufacture that can be universally applied to all formulations, pharmaceutical actives, and processing methods, but years of research and publication of data has enabled some guidelines to be gleaned from the literature.

CHALLENGE 1: DISCERNING THE APPROPRIATE FORMULATION FLUID LEVEL

The moisture content of the wet mass has a critical influence on the quality of pellets produced. As straightforward as it may seem, a simple solution for an overly wet formulation is to reduce the fluid volume used in the granulating step. However, this issue could be avoided initially through an understanding and appreciation of the fact that water-soluble drugs and excipients generally require less water than their insoluble counterparts. Solubilization of the water-soluble materials removes solids from the wet mass and therefore, less water is required to plasticize and lubricate the insoluble material. Therefore, if a formulation is being changed simply in terms of these components, then the fluid volumes should be adjusted accordingly, eg, in the case when the formulation composition is changed with respect to its MCC and lactose content. Wetter formulations may not be able to form a satisfactory extrudate, or if extrudate is formed, it will produce oversized pellets due to agglomeration of individual smaller units during the spheronization processes, owing to high surface moisture that facilitates binding.

To overcome the problem of oversized pellets, consideration should be made of a reduction of granulating fluid level in the first instance. Some authors have proposed the incorporation of non-aqueous granulating fluids, but there has been little success in this arena. Water-alcohol mixtures could be considered to tailor the solubility of individual formulation components, although this may prove potentially expensive and problematic upon scale-up and is less preferred from an environmental perspective. There has been limited success in using completely non-aqueous systems. Those using MCC and ethanol/IPA were shown to be friable and crumbly and hence unsuitable for use.[9,10] Interesting work was carried out showing pellets of good mechanical strength could be prepared using MCC and DMSO.[11] The success of this process was attributed to the similarities between DMSO and water and how they interact with the cellulosic material; DMSO also causes swelling of cellulose fibers.

If the wet mass produced in the first stage of pellet production is excessively dry, it may not adequately extrude as a consequence of insufficient available water to afford lubrication of the mass through the die. Overly

TABLE 2

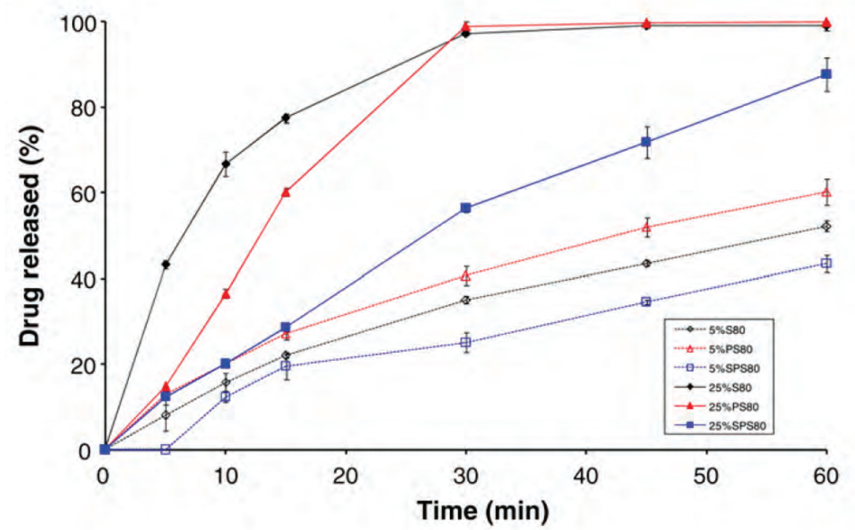
Formulation Variables	Process Variables
Drug characteristics (particle size, solubility)	Mixing speed
Drug loading	Type of extruder (ram, screw, fan)
Spheronization aid	Extrusion force & speed
Grade of microcrystalline cellulose (if used)	Batch size
Spheronization aid loading	Spheronizer size & plate
Other excipients (lactose)	Spheronising time
Fluid volume used	Drying method & time

Formulation & Processing Considerations for Extrusion Spheronization

dry formulations, which do extrude, will usually require a very high extrusion force and can often be identified at this early stage. If spheronization is carried out on an overly dry extrudate, the particles tend to be friable and undersized, reducing their usefulness in pharmaceutical applications, owing to their high degree of surface irregularity. Increasing the fluid volume in the wet mass should be attempted to rectify the propensity toward friability and small size. In line with the guidance for wet formulations, the general guideline is that water-insoluble drugs and excipients will require more granulating fluid for the production of a wet mass that will exhibit good extrusion properties. This is because there is more solid material present, which requires the wetting and lubricating properties of the water. It should also be noted that increasing the levels of MCC should be generally accompanied by a decrease in relative fluid levels (ie, a change in MCC to fluid ratio). The actual fluid levels will go up, but proportionally, the levels relative to MCC will be reduced.

Figure 2 shows an example pellet formulation with 45% w/w MCC, 45% w/w lactose monohydrate, and 10% w/w drug loading (model drug compound, solubility 1 mg/ml). An MCC:fluid ratio of 0.8 was used, and good pellets were produced with an average diameter of 1290 microns and aspect ratio of 0.92. However, when the MCC composition was reduced to 35% w/w and the MCC:fluid ratio kept the same (0.8), very dry pellets are produced (dumbbell shaped), indicating that proportionally more fluid is required relative to MCC. These pellets had a diameter of 1650 microns, aspect ratio of 0.70, and an elongation factor of 0.3, and would be regarded as pharmaceutically unacceptable.

FIGURE 5



Percentage of Ibuprofen Released From Pellet Formulations Prepared From Mixtures of Equal Parts of MCC and Ibuprofen, With 2% and 25% of PS80, S80, or SPS80 and water (reproduced with permission from Podczeck et al 2009)

CHALLENGE 2: POOR PARTICLE SPHERICITY

Poor pellet sphericity will result in poor flow properties and is particularly problematic when pellets are intended for coating in a downstream process, when coating uniformity is important to provide the desired extended-release profile. Often, this is a consequence of the extrudate being too dry, becoming friable, and breaking up excessively during the spheronization process. This can be adjusted by altering the amount of fluid used relative to the other components within the formulation. Similarly, the classic dumbbell shape is often produced by pellets that do not contain enough fluid (Figure 3). This is a result of water acting as a plasticizer, and if not enough plasticity has been imparted to the extrudate, it remains excessively rigid and will not round satisfactorily during spheronization. A rounding of the ends of the hard extrudate occurs, and the dumbbell shape results. To reduce this occurrence, additional water can be incorporated into the wet mass prior to extrusion. An alternative strategy is to increase the spheronization time; this depends on the stiffness of the formulation but in some instances, increasing the spheronization time or speed can function to round out hard material.[12]

Another reported approach to improve sphericity is the judicious use of surfactants within a formulation.[13] In this study, it was found that pellets produced using water had e_R values (a numerical descriptor of shape calculated from the aspect ratio) of 0.5 to 0.6, but incorporation of non-ionic surfactants ensured the e_R value was consistently above 0.6. The shape factor is calculated from the following equation.

Equation 1.

$$e_R = \frac{2\pi r_e}{P f} - \sqrt{1 - \left(\frac{b}{l}\right)^2}$$

Where r_e is a mean radius derived here from distance measurements between the center of gravity of the two-dimensional particle outline and the perimeter, using an angle of rotation of 5° between each line.

CHALLENGE 3: SLOW DRUG RELEASE

It has been noted in the literature that drugs formulated in MCC-based pellets often suffer from poor drug release, particularly if drug solubility is low.[14] This is due to the insolubility of MCC and the formation of a tortuous matrix through which drug must diffuse, which becomes particularly problematic for low solubility drug compounds. Several methodologies to address this have been proposed in the academic literature. For example, the levels of MCC can be minimized sufficiently to facilitate the extrusion process, and water-soluble fillers, such as lactose and mannitol, can be incorporated into the formulation composition. Attempts can also be made to alter the porosity of pellets; as the porosity of pellets can affect drug-release rates, porosity can be affected by the type of extrusion carried out (ram versus screen, by the type of drying and by the particle size of the insoluble components).[12]

There has been a significant amount of work on the influence of self-emulsifying systems on the release of drugs from pellets. Two studies have shown that the presence of the self-emulsifying system enhanced the drug release from pellets (using progesterone and methyl-and propyl-paraben as model drugs).[15,16] The second study also demonstrated that progesterone self-emulsifying pellets had comparative and improved bioavailability to a self-emulsifying liquid formulation and an aqueous suspension, respectively (Figure 4).

Other approaches that can facilitate the release of poorly soluble drugs include the use of wetting agents, such as surfactants. For example, Cremophor RH40 was incorporated into pellets and improved the in vitro release profile of hydrochlorothiazide.[17] Recently, Podczeck et al have published work which examines the drug release profiles after the incorporation of varying levels of surfactant.[18] Figure 5 shows the ibuprofen release from pellets prepared using sorbitan monoleate (S80) or polysorbate (P80) at 5 and 25%. The incorporation of 25% surfactant improves the drug release rate, although ibuprofen is still a relatively soluble drug, and it remains to be shown whether this method can prove effective for drugs of very poor solubility.[18]

SUMMARY

Depending on the pharmaceutical active, pellets may offer advantages over single-unit dosage forms, but their successful formulation and production is often problematic, and it is seldom facile to develop elegant solutions. In this discussion, we have highlighted some of the issues we have encountered in our experience of working with such systems to provide readers with some guidelines to optimize their own formulations. There is no straightforward development strategy, but combination of design space evaluation and an appreciation of the general interplay between formulation components will enable crisper execution of pellet design and processing.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Drs. S. Fitzpatrick and S. Booth for helpful comments on the manuscript.

REFERENCES

1. MacRitchie KA, Newton JM, Rowe RC. The evaluation of the rheological properties of lactose/microcrystalline cellulose and water mixtures by controlled stress rheometry and the relationship to the production of spherical pellets by extrusion/spheronization. Eur J Pharm Sci. 2002;17:42-50.
2. Newton JM. Extrusion and extruders. In: J. Swarbrick J, Boylan J, eds. Encyclopedia of Pharmaceutical Technology. Marcel Dekker Inc.: New York, NY, and Basel, Switzerland;2002:1220-1236.
3. Ek R, Newton JM. Microcrystalline cellulose as a sponge as an alternative concept to the crystalline-gel model for extrusion and spheronisation. Pharm Res. 1998;15(4);509-512.
4. Dukic-Ott A, Remon JP, Foreman P, Vervaet C. Immediate release of poorly soluble drugs from starch based pellets prepared via extrusion/spheronisation. Eur J Pharm Biopharm. 2007;67(3):715-724.
5. Jess K, Steckel H. The extrusion and spheronisation of chitosan. Pharm Technol Eur. 2007;7:21-30.
6. Liew CV, Gu L, Soh JLP, Heng PWS. Functionality of cross-linked polyvinylpyrrolidone as a spheronization aid: a promising alternative to microcrystalline cellulose. Pharm Res. 2005;22:1387-1398.
7. Howard MA, Neau SH, Jack JS. PEO and MPEG in high drug load extruded and spheronised beads that are devoid of MCC. Int J Pharm. 2006;307:66-76.
8. Basit AW, Newton JM, Lacey LF. Formulation of ranitidine pellets by extrusion spheronisation with little or no microcrystalline cellulose. Pharm Dev Technol. 1999;4(4):499-505.
9. Millili GP, Wignent RJ, Schwartz JB. The strength of microcrystalline cellulose pellets: the effect of granulating with water/ethanol mixtures. Drug Dev Ind Pharm. 1990;16:1411-1426.
10. Schroder M, Kleinebudde P. Structure of disintegrating pellets with regard to fractal geometry. Pharm Res. 1995;12:1694-1700.
11. Mascia S. Rheology and Processing of Pharmaceutical Pastes. Thesis. University of Birmingham;2008.
12. Sinha VR, Agrawal MK, Kumria R, Bhinge JR. Influence of operational variables on properties of piroxicam pellets prepared by extrusion-spheronization: a technical note. AAPS PharmSciTech. 2007;8(1):Article 20.
13. Podczeck F, Alessi P, Newton JM. The preparation of pellet containing non-ionic surfactants by extrusion/spheronization. Int J Pharm. 2008;361(1-2):33-49.
14. O'Connor RE, Schwartz JB. Spheronization part 2: drug release from drug-diluent mixtures. Drug Dev Ind Pharm. 1984;11:1837-1857.
15. Serratoni M, Newton JM, Booth S, Clarke A. Controlled drug release from pellets containing water-insoluble drugs dissolved in a self-emulsifying system. Eur J Pharm Biopharm. 2007;65:(1):94-98.
16. Tuleu C, Newton JM, Rose J, Euler D, Saklatvala R, Clarke A, Booth SW. Comparative bioavailability study in dogs of a self-emulsifying formulation of progesterone presented in a pellet and liquid form compared with an aqueous suspension of progesterone. J Pharm Sci. 2004;93(6):1495-1502.
17. Vervaet C, Baert L, Remon JP. Enhancement of in vitro drug release by using polyethylene glycol 400 and PEG-40 hydrogenated castor oil in pellets made by extrusion/spheronization. Int J Pharm. 1994;108(3):207-212.
18. Podczeck F, Maghetti A, Newton JM. The influence of non-ionic surfactants on the rheological properties of drug/microcrystalline cellulose/water mixtures and their use in the preparation and drug release performance of pellets prepared by extrusion/spheronization. Eur J Pharm Sci. 2009;37(3-4):334-340.

BIOGRAPHIES

Dr. Emma McConnell works as a Research Scientist in Formulation Development at Merck, Sharp and Dohme, focusing on developing oral drug delivery systems. This post was preceded by a PhD and Post-doctoral research fellowship at The School of Pharmacy, University of London working on site-specific targeting of oral drugs and vaccines.

Dr. Samuel Pygall is a Research Scientist at Merck Sharp and Dohme. His work is primarily focused on the utilization of product enhancement technology and oral controlled release. Prior to joining MSD, he earned an industrially sponsored PhD (Bristol Myers-Squibb) at the University of Nottingham and has worked for various companies in the form of summer placements.

Dr. Rob Ward has worked as a Research Scientist at Merck Sharp and Dohme for the past 10 years, primarily developing oral drug delivery systems. Prior to joining MSD, he earned a PhD in Surface Chemistry at the University of Cambridge and has worked for Unilever Research and Exxon Chemical in various roles in chemical research and development.

Dr. Christian Seiler is a Senior Investigator and Formulation Group Leader in the Development Laboratories of Merck Sharp & Dohme (MSD) and the Leader of the Global Controlled Release Centre of Excellence. Prior to joining MSD in 2000, he earned his PhD and Masters in Chemical Engineering at the Universities of Birmingham (UK) and Karlsruhe (Germany), respectively.

Drug Delivery Executive

CAMBREX

Dan Giambattisto
VP, Drug Delivery

Cambrex Corporation

"Cambrex focuses on the acceleration of the drug development process and product innovation. We have built our business and reputation around this philosophy. Through our Drug Delivery initiative, we are helping customers find creative ways to improve existing drug products, extending their life cycle, and offering new presentation formats."

Cambrex Corporation: Accelerating Development & Commercialization

Cambrex provides products and services to accelerate the development and commercialization of small molecule active pharmaceutical ingredients (APIs), advanced intermediates, and other products for branded and generic pharmaceuticals. Cambrex's Drug Delivery business provides innovative products that simplify the drug delivery process. The Camouflage™ drug delivery technology is a polymer-based drug delivery platform that not only masks the taste of the active ingredient, but has also been demonstrated to improve stability and modify drug release. Dan Giambattisto, Vice President of Drug Delivery, has been working with drug delivery technologies since 1995 and leading this strategic initiative at Cambrex since 2007. Drug Delivery Technology recently interviewed him to discuss how Cambrex continues to provide and enhance their drug delivery technologies for pharmaceutical preparations.

Q: What made Cambrex become interested/involved in the drug delivery business?

A: A focus of Cambrex's business is one of providing customers' tailored solutions to their pharmaceutical development. We became involved in the formulation of technology-enhanced active ingredients as a result of strong customer interest in our capabilities related to binding APIs to resins. Cambrex holds over 100 Drug Master Files for APIs and possesses a wide range of processing competencies that made the idea of manufacturing polymer-based products using our Camouflage drug delivery technology a natural fit.

Q: How is Cambrex's Camouflage drug delivery technology deployed into APIs? How does it work and what are the benefits?

A: At the heart of our technology is a process that combines an API and an ion-exchange resin. The use of ion-exchange resins in drug delivery is not new to the pharmaceutical industry and dates to the late 1950s. Since then, ion-exchange resins have been used as excipients in many orally dosed drug products because of their safety and functionality. APIs are loaded onto the ion-exchange resin as the drug ion is exchanged for an inorganic ion by an equilibrium process. Dissociation of the drug from the resin is affected by many factors and can be manipulated to suit the formulators' needs. This is not a stand-alone technology but one that can be incorporated into numerous delivery vehicles, including tablets, capsules, suspensions,gums, lozenges, and thin strips.

Camouflage resinates have many potential benefits. The use of a high molecular weight, non-systemically absorbed tasteless polymer carrier results in a resinate that masks the taste of many drugs with poor organoleptic properties. This is the most prominent feature of Camouflage products and is very important to patients, especially the young and elderly, who may have difficulty swallowing medications with strong or disagreeable flavors. In addition, resinates have been used to enhance the stability of drugs, modify their release, improve dissolution and reduce or eliminate polymorphism.

Q: Is the Camouflage technology currently being used in any products? How has the use of this technology benefited the market/industry?

A: A number of solid dose drug products containing our Camouflage drug delivery technology have been formulated and are now currently on the market. Many more, including liquid dose formulations, are in various stages of development. Some of these formulated products actually contain more than one Camouflage product. The taste-masking and drug-release properties of products manufactured using Camouflage have enabled our finished-dosage-form-producing customers to formulate innovative and distinctive products that make taking medicines more palatable and easier for consumers and caregivers to administer.

Q: Can you please explain the importance of Camouflage as a life cycle management tool for APIs?

A: The use of our Camouflage technology to enhance APIs offers the formulators the opportunity to manage the life cycle of a given product or range of products in a number of ways. Camouflage resinates, by virtue of their excellent stability profiles and compatibility with a very large number of APIs, are able to be incorporated into a variety of oral dosage forms from tablets and powders to suspensions and thin films. This is demonstrated by the increased use of resinates in rapidly dissolving tablets and powders in which taste-masking of the drug is of critical importance.

Q: Many companies offer a drug delivery platform, what makes Cambrex unique?

A: Cambrex is widely recognized in the pharmaceutical industry as a leading producer and supplier of products and services for small molecule therapeutics. Our ability to customize solutions to clients' drug development issues is in large part the driver of our success in the area of drug formulations. This, coupled with our extensive offering of APIs and track record of regulatory compliance, makes us a powerful partner for the development of new and technology enhanced APIs.

Q: As the global economy continues to struggle, how can Cambrex's drug delivery technology help control development costs?

A: Cambrex focuses on the acceleration of the drug development process and product innovation. We have built our business and reputation around this philosophy. Through our Drug Delivery initiative, we are helping customers find creative ways to improve existing drug products, extending their life cycle and offering new presentation formats. Our expertise in this field allows us to quickly determine proper dosage forms and prepare samples for customer approval, saving the customer development time and costs, allowing them to move the product quickly to the marketplace.

Q: What does Cambrex believe is the future of drug delivery technology?

A: The drug delivery market has evolved significantly in the past several years, with many new companies entering the market. This influx has led to a convergence of messages on the virtues and novelty of individual drug delivery technologies. This has made it increasingly difficult for the pharmaceutical formulator to distinguish between the benefits of different technologies and for the drug delivery providers to develop intellectual property. As a result, there is a growing tendency to focus not on the drug delivery tool itself, but how that enabling tool can be turned into a drug product with unique or improved consumer benefits. The crowding of the drug delivery space and the blurring of the message has given rise to the concept of layering, where two or more drug delivery technologies are combined.

Q: What steps is Cambrex taking to make this future a reality?

A: In order to address the demand for further innovation and novelty in the drug delivery space, Cambrex has been developing relationships with companies who offer such things as novel dosage forms. Our Camouflage resinates have been combined with partner company delivery matrices to improve drug compliance, adherence, taste, drug release, dissolution, portability, and drug efficacy. The goal of our activities in this area is to offer formulated drug products that can be commercialized in a shorter period of time. In addition, we are actively seeking to expand our technology offering through partnering and investment initiatives. ◆

TECHNOLOGY *Showcase*

MDI COMPONENTS

Enabling your success

3M Drug Delivery Systems

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

COMMERCIAL SYRINGE FILLING SOLUTIONS

ALTHEA

Althea has been filling prefilled syringes for our clients' clinical needs for years, and has recently expanded capacity for large-scale manufacturing of Phase III and commercial supplies. Our commercial line produces over 100,000 syringes per day and features "bubble-free" filling, 100% in-process control weight checks, and a fully automated system for greater speed and efficiency. Coupling prefilled syringes with our portfolio of integrated services, Althea is a true strategic partner for your drug program. For more information, contact Althea Technologies at (888) 425-8432 or visit **www.altheatech.com**.

LICENSING OPPORTUNITIES

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

PREFILLABLE DELIVERY SYSTEMS

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

Technology Showcase

Raman Chemical Imaging

ChemImage provides Raman Chemical Imaging contract services for drug formulation and development scientists needing ingredient-specific particle sizing, polymorph analysis, controlled-release analysis, content uniformity measurements, and more. ChemImage stands behind the pledge to provide our customers with the best quality information and fast sample turnaround time on every project. If you are working to develop nasal, inhalation, topical, transdermal, or controlled/sustained release systems, visit our website to learn how we can help you save time and money, raise your confidence, and lower your risk in moving forward through product development. For more information, contact ChemImage at (877) 241-3550 or visit **www.chemimage.com/branchout.**

Orally Disintegrating Technologies

CIMA LABS INC. a world leader in the drug delivery partnering business, specializes in the formulation, taste-masking, and manufacturing of pharmaceuticals utilizing our orally disintegrating tablet (ODT), oral transmucosal (OTM), tamper deterrent, solubilization, and oral powder drug delivery technologies. OraSolv®, DuraSolv®, and Lyoc™ ODTs disperse quickly in the mouth without chewing or the need for water. OraVescent® is an oral transmucosal tablet that can be administered buccally or sublingually. OraGuard™ extended release/tamper deterrent technology provides a robust extended release PK profile, even during co-administration with alcohol, and is resistant against various tampering methods. CIMA has proven commercialization success with more than 20 products marketed in more than 70 countries around the world. For more information, contact CIMA at (763) 488-4843 or visit **www.cimalabs.com**.

Combination Capsule Technology

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

Development & Delivery Solutions

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

Technology Showcase

Custom Plastics Manufacturing

Phillips Plastics Corporation's contract manufacturing services have helped create products that span all markets from drug delivery, combination/drug products, and medical devices to military communication equipment, consumer products, and beyond. Our commitment to excellence since 1964 has made us a preferred supplier to the most well-respected original equipment manufactures in the world - companies like Eli Lilly, Medtronic, John Deere, and Black and Decker, just to name a few - who turn to us for our complete services from concept design, rapid prototyping, and tooling through manufacturing and distribution. For more information, contact Phillips Plastics Corp. at (877) 508.0252 or visit **www.phillipsplastics.com**.

Polymer Processing & Fabrication

PolyMedex Discovery Group offers a variety of polymer processing and fabrication services critical to the development and manufacture of innovative medical devices. It specializes in melt-extrusion blending and forming of highly regulated materials, including implantable and bioresorbable drug delivery polymers used in combination devices and pharmaceuticals. It offers formulation, feasibility, process development, scale-up, and manufacturing in an ISO Class 8 cGMP clean room environment. Its focus on providing component finishing and assemblies within the Group offers added benefits of efficiency, traceability, and consolidated resources. Utilizing a wide variety of finishing operations, cross-functional engineering teams develop robust manufacturing processes for turnkey component solutions ready for final device assembly. Other services include Putnam Extrusions, Foster Compounds, and Polymer Distribution. For more information contact PolyMedex Discovery Group at (860) 928-4102 or visit **www.PolyMedexGroup.com**.

Contract Manufacturing

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

Impactor Test Chamber

Thermotron has developed an Impactor Test Chamber to improve accuracy and repeatability of inhaler and nebulizer testing. The test chamber includes two independently controlled test compartments: one for conditioning temperature and humidity surrounding the nebulizer or inhaler, and one for cooling the impactor. By designing a sophisticated, dual-compartment environmental enclosure, Thermotron is able to precisely control temperature and humidity conditions. The nebulizer/inhaler compartment controls temperature from 0ºC to 40ºC and humidity from 30% to 90% RH. Temperature range within the impactor test compartment can be controlled down to 0ºC. Adjustable shelving allows interface with Next Generation Impactors and Andersen Cascade Impactors. New developments in US & European Pharmacopeia testing criteria assisted in shaping this configuration. For more information, contact Thermotron at (616) 393-4580 or visit **www.thermotron.com/impactor.**

PARTICLE SCIENCES
DRUG DEVELOPMENT SERVICES

Robert Lee, PhD
VP, Drug Development

Particle Sciences, Inc.

"A key aspect of our business strategy is our initial interaction with our clients. Early in our discussions, we strive to understand exactly what our clients' goals are; we want to make sure we hear and understand their needs and design our programs to satisfy those goals."

PARTICLE SCIENCES: PROVIDING FORMULATION & ANALYTIC SERVICES TO MEET DEMANDING DRUG DELIVERY CHALLENGES

Particle Sciences, Inc. (PSI) is a leading CRO to the pharmaceutical, biotech, and drug device industries. Building on decades of experience, PSI offers expertise in nano-based approaches to drug delivery and brings this skill-set to bear on its clients' goals, independent of the dosage form, from topical to ocular to intravenous to intrathecal. Through internal development and an active in-licensing program, the company has a broad array of technologies from which to choose. This approach has resulted in an average annualized growth rate of over 25% and a very high rate of new project awards from existing clients. As Vice President of Drug Development, Dr. Robert W. Lee is responsible for overseeing PSI's scientific direction. Drug Delivery Technology recently interviewed Dr. Lee to discuss how his company is managing to thrive in such a tough business environment.

Q: 2009 was very challenging for pharma, with the top 10 lay-offs totaling 66,850. This follows several years of downsizing. How was business for PSI?

A: Particle Sciences (PSI) managed to grow 30% in revenue and increased headcount by 20%. The business model of many pharma companies is changing, and even several large Pharma companies have shifted to an outsourcing paradigm for drug development, which may include formulation development, drug delivery, analytical services, and clinical trial material manufacturing. This reduces fixed costs and helps their bottom line. However, the work still needs to get done, and this is the challenge given the reduction in internal resources. This provides growth opportunities for CROs operating in these areas. PSI is relatively unknown, but we continue to gain exposure and expand our client base. Last year, our services were in demand by both new and existing clients and in fact, we are very proud of that our existing clients continue to place additional work at PSI, a testimony to their satisfaction.

Q: Can you discuss the types of clients who seek your services?

A: Our clientele range from venture-backed start-ups to large pharma to not-for-profit organizations. We take our clients' projects with the utmost seriousness. In the case of our smaller clients, they may only be working on one project, so their success is very much in our hands. In dealing with all of our clients, our objectives are to set reasonable targets with obtainable but aggressive timelines, then delivering on-time and within the agreed to budget. This is one reason the majority of our smaller clients stick with us as their project matures. It is gratifying to see their success and to have contributed to it.

Q: How does your business strategy differ from other CROs?

A: PSI is rare in that we started as a formulation group, and that remains our core. We continue to grow deeper and deeper in our core skill set and are intentionally not trying to be all things to all people. Our goal is to solve our clients problems, and we are not wed to any given drug delivery technology. To that end, we have designed or acquired multiple drug delivery technologies in order to best serve our clients.

As our name implies, our expertise is with particulate-based systems. This encompasses both microparticles and nanoparticles. We are well versed in several technologies, including encapsulation, particle size reduction - both top-down (including high-energy milling and high-pressure homogenizers, such as Microfluidizers®) and bottom-up (solvent/antisolvent precipitation, including Microfluidics Reaction Technologies system) approaches, and particle engineering. As mentioned earlier, these techniques can be called upon when appropriate for a client's goal and have been leveraged for multiple routes of administration including, for example, non-sterile, sterile, oral, vaginal, topical, ophthalmic, inhalation, injectables, etc. It may appear that PSI has capabilities spanning almost too wide a range; however, the common thread is our deep understanding of particulate systems: solid-in-solid, solid-in-liquid, and liquid-in-liquid. We can leverage this knowledge to all routes of administration. This being the case, we opt to grow by expanding our knowledge, expertise, and capabilities in this area and not to grow in areas that are not core to us, such as in vivo or clinical testing.

Some of our service offerings, such as combination drug-eluting devices, flow naturally from our sweet spot in particulates. Our focus on particulate-based drug delivery systems and difficult to formulate API's we believe better serves our clients, and seems to be in sync with their requirements. Of course, we can and do formulate solution-based products, but this constitutes a minority of our projects. There is a tendency in times of solid revenue growth to expand as quickly as possible. This is not always the best tactic and, if there isn't a good strategic plan in place to guide that growth, it is a recipe for disaster. PSI has been and will continue to be disciplined in not over-reaching our core competencies or growing too rapidly without a sound strategy.

A key aspect of our business strategy is our initial interaction with our clients. Early in our discussions, we strive to understand exactly what our clients' goals are; we want to make sure we hear and understand their needs and design our programs to satisfy those goals. For example, an early question is whether or not our clients are interested in a formulation approach using proprietary intellectual property (IP). In some cases, our clients have strong IP surrounding their new chemical entity or use for their molecule and are interested in a straight line to some value-inflection milestone, such as in vivo evaluation or human proof-of-concept. In these cases, PSI will employ, if possible, a non-proprietary drug delivery approach. We are agnostic when it comes to using our existing proprietary or non-proprietary drug delivery technology; it is based on our clients' requirements, and often a simple emulsion or non-proprietary nanoparticulate approach works fine. In other cases, our clients may be seeking to reposition a marketed drug or may have mediocre or no IP protection for their product concept. For these clients, PSI can draw upon our existing IP or create new IP to better protect their products. It is important to understand our clients' needs, and PSI is uniquely positioned to support their development strategies from a technical as well as business perspective.

Q: What do you believe are some near-future growth areas for PSI?

A: With the current and ongoing trend in downsizing and outsourcing, I believe our clinical trial material (CTM) manufacturing services will continue to grow, especially in the areas of sterile products and drug-eluting devices. We are capable of manufacturing small-scale, aseptically processed CTM and excel at manufacturing challenging, hard-to-make products. We will continue to grow our capabilities to manufacture CTM. As a side note, whenever we work on formulation and process development, we do so with the commercial product in mind; we develop robust, scalable, commercially viable products. However, we do occasionally have a product that is transferred in from another developer that can be challenging to reproduce and may not be commercially viable. In those cases, we can execute the technology transfer and, in parallel, work on a scalable process to meet our client's requirements and stay on time.

Highly potent compounds (HPCs) are an increasing part of our business and we see this as another area for growth. There is a clear need for CRO's that are competent in handling such materials and we have invested heavily in both the needed physical and procedural infrastructure.

Another area of growth is working on challenging APIs or delivery requirements. As you can imagine, we rarely, if ever, get simple APIs to work on; those that are water-soluble, stable, and bioavailable. In most cases, the API is water insoluble. This is not too difficult a challenge, and we have several options to circumvent this issue.

However, in some cases, we are asked to formulate APIs that may or may not have low aqueous solubility, but are hydrolytically or enzymatically labile as well. These cases require work, but the challenges are not insurmountable. Another recent challenge we have been faced with has been to convert a water-soluble API into a nanoparticle formulation that is suitable for intravenous administration.

As mentioned previously, we have proprietary drug delivery technology that we have either invented or in-licensed. Our ultimate goal is a satisfied client, which leads to repeat business and a good reputation. It is in everyone's best interest to use the drug delivery approach that works best for a given API and delivery goal. It is not accurate that one size fits all, so we believe in having a good selection of drug delivery technologies, that we have demonstrated to ourselves as commercially viable, at our disposal for use on our clients' projects.

Q: What other services do you offer clients?

A: PSI has a very accomplished analytic and bioanalytic group. In addition to the traditional separation approaches, PSI offers in vitro release testing using Franz diffusion cells. We can conduct this testing to support R&D or conforming to cGMP requirements for use in regulatory filings.Our physico-chemical characterization capabilities, including optical microscopy coupled with image analysis, several different methods to measure particle size distribution, and a suite of other techniques to characterize semi-solids and particulate systems provide our clients with a one-stop shop for their CMC needs.

Q: What are PSI's future plans?

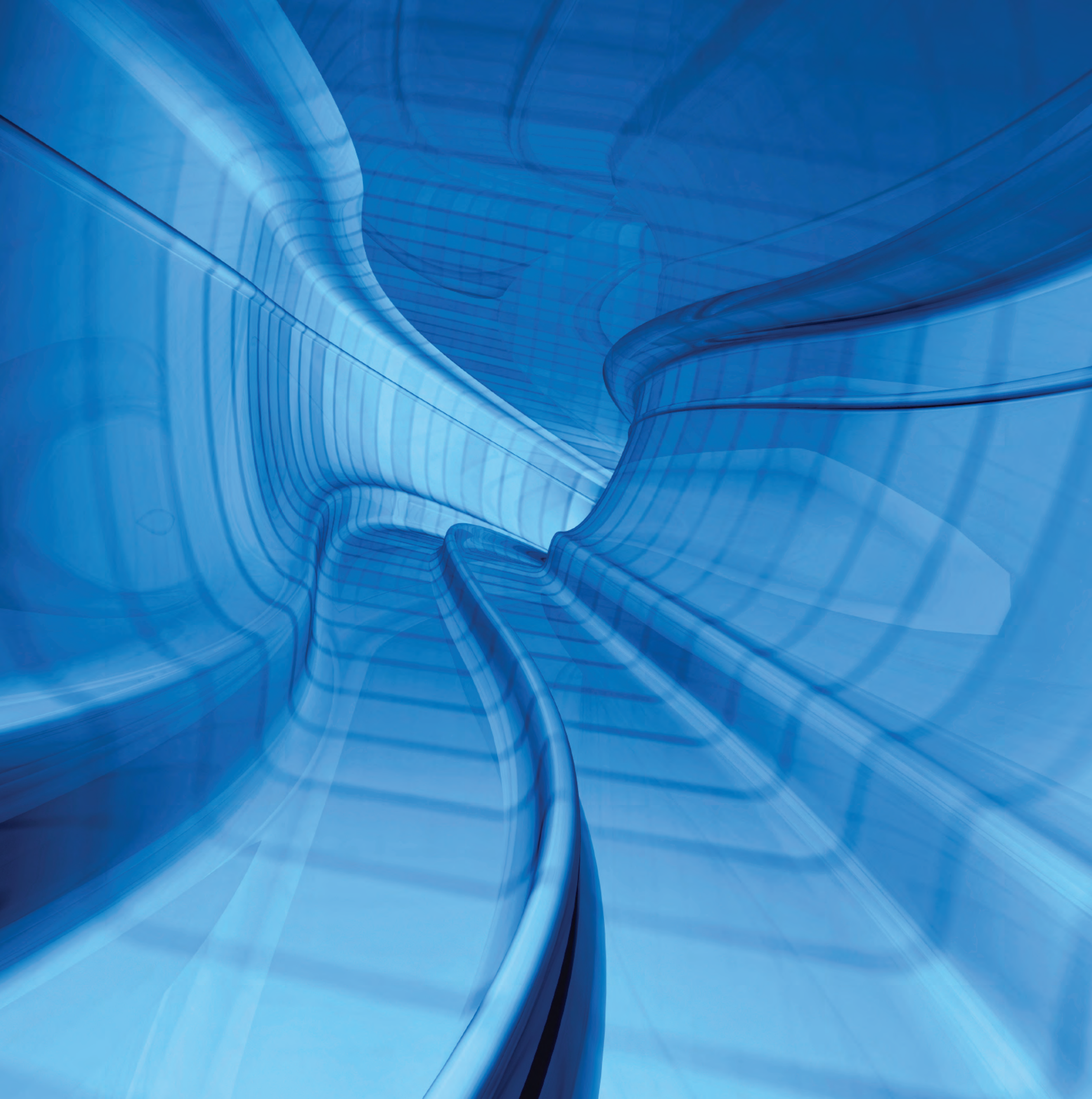
A: PSI is forming alliances with other service providers and equipment manufacturers that we consider best-in-class in order to provide our clients with seamless access to a host of services. This allows PSI to concentrate on what we do best and leverage the infrastructure of other companies to best serve our clients. An example of such an alliance is with Microfluidics Corporation. We evaluated several high-pressure homogenizers and concluded that Microfluidizers are the best-in-class. They excel at emulsions and can also be used to reduce the particle size of crystallineAPIs. This alliance provides PSI and our clients access to the Microfluidics Reaction Technology system, which is a state-of-the-art solvent/anti-solvent precipitation system. Presently, there are less than a handful of these systems in the field, and we have one. We are working closely with Microfluidics to ensure our scientists are fully up to speed and experts in this technology. Similar arrangements ranging from ADME services to large-scale commercial production will be announced in the coming months, all aimed at providing our clients the most complete set of tools possible while minimizing their administrative burden and allowing PSI to maintain its focus on developing superior drug products. ◆

SPECIALTY PHARMA
Strategies For Business Development

Therapeutic Focus

A Path to Orally Active RNAi Therapeutics

By: Joanne Kamens, PhD; Pamela Pavco, PhD; and Anastasia Khvorova, PhD, RXi Pharmaceuticals Corporation



The ability to develop drugs capable of disrupting the activity of disease-causing proteins is frequently delayed by the tedious nature of screening small molecule libraries and the time required to develop derivatives with drug-like properties. While these processes are essential to ensure drug efficacy and safety, they are costly and hinder the pharmaceutical industry's ability to respond rapidly to the changing landscape of pharmaceutical needs.

RNA Interference (RNAi) offers promise to address many of the current hurdles associated with small molecule therapeutic development. RNAi is a fundamental cellular mechanism responsible for regulation of gene expression. Mediators of RNAi, small interfering RNAs (siRNAs), can be designed to target practically any messenger RNA (mRNA), including those of previously "undruggable" targets, such as intracellular proteins with no enzymatic activity. The sequence-dependent nature of the RNAi pathway allows for relatively specific target gene silencing. This specificity can be further enhanced by the addition of a range of sequence-independent nucleotide modifications to the RNAi compound, allowing isoform-specific targeting.

In addition, certain modification patterns not only impart stability to the siRNA, but also enhance their activity. While designed as stand-alone therapeutics, the generally low toxicity profile for this class of drug enables the possibility of future RNAi-based therapeutics to be used in conjunction with complementary treatment strategies. RNAi-based drugs are viewed as a new major class of therapeutics with a market potential in the multi-billion dollar range.

While RNAi technology has matured in terms of its ability to identify and develop highly potent, specific, and stable compounds, the clinical potential has been impeded by the lack of effective, safe delivery technologies. To date, RNAi compounds in the clinic fall into two categories: (1) directly administered, unformulated siRNAs and (2) lipid- or nanoparticle-formulated compounds. Compounds dosed by direct administration are being evaluated for treatment of ocular disease (intraocular injection, Pfizer/Quark), acute kidney injury, and delayed graft function in renal transplantation (intravenous injection, Quark), infection by Respiratory Syncytial Virus (nasal administration, Alnylam),

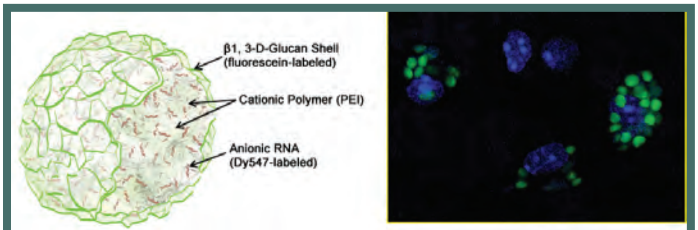


Figure 1. GeRP Structure & Cellular Uptake

(a) A schematic representation of the composition of a single GeRP. The external shell (green) represents the 2- to 4-micron, porous beta 1,3-D-glucan shell. siRNA in the GeRP (red) is retained in the shell by complexing with PEI or other cationic agents (white). (b) Efficient uptake of GeRPs by phagocytic cells. Fluorescently labeled glucan shells were administered via intraperitoneal dosing to male, C57BL6/J, wild type mice. Peritoneal exudate cells were harvested, purified by adherence to cover slips, and visualized by confocal microscopy.

and pachyonychia congenita (intradermal injection, TransDerm). Two other siRNA drugs for ocular disease have been dropped from development following unsuccessful Phase II and III trials (Allergan and Opko Health, respectively).

Work on lipid-based formulations has incorporated cationic lipids that mask the high charge-to-mass ratio of siRNAs.[1] While these formulations are effective in a range of tissue culture systems, in vivo applications have faced several challenges. Intravenous delivery of such formulations requires relatively high doses of siRNA/lipid complex (0.5-10 mg/kg siRNA), which can induce toxicity upon extended dosing.[2] Distribution of siRNAs in current lipid-based formulations is limited to tissues with discontinuous endothelium, such as liver, spleen, and bone marrow, and thus is not applicable for most other tissues. The lipid-based delivery approach is currently being tested in the clinic (liver carcinoma, Alnylam/Tekmira, and hypercholesterolemia, Tekmira/Alnylam). The clinical potential of lipid formulations is likely to be limited by the relatively low therapeutic index due to vehicle-associated toxicity, delivery to a limited number of tissues, and the requirement for an intravenous route of administration.

While direct and lipid-based delivery modalities have received the greatest attention, identification of methods that enable effective RNAi-based therapy with a more patient-friendly route of administration are clearly preferable. RNA dosing by oral delivery has been impractical to date due to the distinct characteristics of the gut. These include the highly acidic nature of the gastrointestinal track, the presence of digestive enzymes, and the relative impenetrability of the gastric mucosal barrier. Recent published collaborative work from the Ostroff and Czech laboratories at the University of Massachusetts Medical Center (UMMC) presents a promising new technique for oral delivery of RNAi compounds. This report describes a first proof-of-concept study demonstrating siRNA delivery to phagocytic cells through oral administration.[3]

Glucan Shells–siRNA Delivery to Phagocytic Cells

beta-glucan and other particulate carriers have been used extensively to effect oral delivery of a range of drugs, including antibodies, DNA, and small molecules.[4-6] Following oral administration, particles can be absorbed by at least three routes: transport between cells (paracellular transport); direct capture by dendritic cells in contact with the gut; and transcytosis. Transcytosis refers to direct transport through both enterocytes and the specialized microfold (M) cells of the follicle-associated epithelium. Particles and microorganisms are thought to be efficiently transcytosed directly through M cells to the lymphoid cells underlying the Peyer's Patches in the gut.[7,8] There, phagocytic cells (eg, macrophages, dendritic cells) expressing the dectin-1 receptor would engulf beta-glucan containing particles and traffic them to more distal tissues.[9] Thus, successful integration of the RNAi and glucan shell technologies could provide the opportunity to solve two challenges: delivery of gene targeting reagents to a limited immune cell population; and development of an oral siRNA delivery system. Such a breakthrough would allow researchers to address a range of diseases associated with the human immune system, including chronic immune conditions, such as rheumatoid arthritis, Crohn's disease, and psoriasis (Table 1). The patient population for inflammatory disease is large, estimated to be 8 to 10 million in the US alone. Although there are a number of drugs that treat these diseases in some patients, there is still a large unmet medical need for the nonresponsive patient population or those who suffer treatment-related side effects. In addition, an oral delivery technology could enable the use of siRNA-based compounds for the treatment of many diseases with an inflammatory component, such as diabetes and atherosclerosis by providing a novel in vivo drug discovery platform for diseases driven by immune cell pathology.

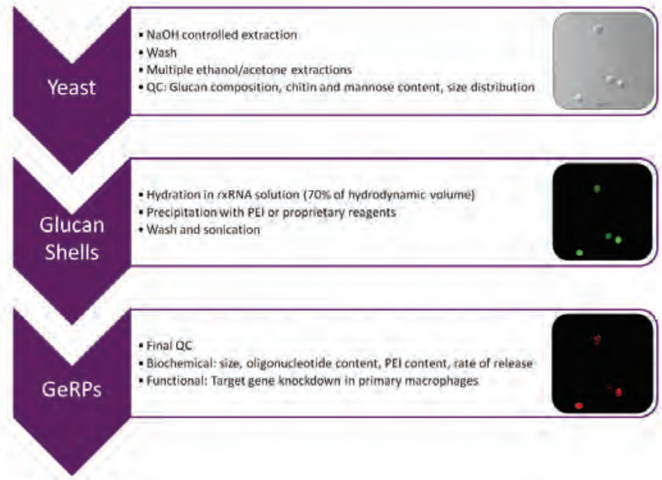


Figure 2. The GeRP Manufacturing Process

This schematic representation depicts the main steps of the GeRP manufacturing process: Glucan shell purification, RNA entrapment and extensive characterization, and quality control analyses.

UMMC scientists demonstrated that siRNAs can be packaged in glucan particles derived from baker's yeast cell wall preparations resulting in a 2- to 4-micron Glucan-encapsulated RNAi Particle (GeRP) that is recognized by the dectin-1 receptor of phagocytic immune cells (Figure 1). The manufacturing process begins with a relatively simple series of extraction procedures that lead to the generation of dried, hollow glucan-containing shells. This material can be re-hydrated with a transfer RNA (tRNA) solution and then treated with a solution of polyethyleneimine (PEI), which precipitates the nucleic acid and generates a tRNA-PEI core that is trapped within the outer shell. Subsequent consecutive treatments of these particles with the cationic peptide Endo-Porter (Gene Tools, LLC), siRNA, and PEI generates the final product (Figure 2).

In Aouadi et al, GeRPs were successfully tested under in vitro and in vivo conditions. Isolated murine peritoneal

Clinical Area	Disease	Estimated Prevalence in US population (per 10,000)
Arthritis[10]	Rheumatoid Arthritis	50-100
	Psoriatic Arthritis	10
	Ankylosing Spondylitis	13-15
	Juvenile Idiopathic Arthritis	10-20 (per 10,000 children)
Inflammatory Bowel Disease	Crohn's Disease[11]	11-20
	Ulcerative Colitis[12-14]	11-24
Psoriasis	Psoriasis[15]	250-260
Total prevalence for listed *adult* diseases:		345-429

Table 1. Estimated Prevalence of Inflammatory Disease in the US

The prevalence (number of cases per 10,000) is given as a range because estimates vary widely based on source, severity, geographical region, and ethnicity. Based on a US population of 75 million children (for juvenile idiopathic arthritis) and 232 million adults (for all other diseases), the total number of people afflicted with the listed inflammatory diseases is estimated to be at least 8 to 10 million.[10-15] Current standard of care ranges from the use of relatively inexpensive synthetic disease-modifying antirheumatic drugs (DMARDs) with an average cost of $50 to $150/month to biologic DMARDs, such as the TNF-alpha inhibitors Enbrel® and Humira®, which cost in excess of $1,200/month. The market for TNF-alpha inhibitors in the US, Western Europe, and Japan is predicted to rise from $7.1 billion in 2005 to almost $12 billion in 2014.[16]

macrophages incubated with GeRPs for as little as 12 hours (10:1 ratio of GeRPs to cells) efficiently phagocytose the particles and target specific silencing results in a dose-dependent manner. This finding is in contrast to what is observed when GeRPs are incubated with cells lacking the dectin-1 receptor (eg, HeLa cells) where no uptake can be detected. Phagocytosis of GeRPs by immune cells in culture does not observably alter the viability of these cells. Importantly, fluorescently labeled particles delivered to mice by oral gavage (20 micrograms/kg siRNA, daily for 8 days) are observed in macrophages harvested from the gastrointestinal tract and other organs (including the lung, liver, and spleen). When GeRPs were loaded with therapeutically relevant siRNAs targeting cytokine pathways, gene silencing resulted in an immune-suppressed phenotype in an LPS-induced cytokine model. Animals orally dosed with GeRPs loaded with an siRNA targeting MAP4K4 (a regulator of TNF-alpha) not only exhibited silencing of the MAP4K4 and TNF-alpha messages in macrophages recovered from the peritoneum and peripheral organs, but treated animals were also protected from LPS-induced mortality.

These studies demonstrate that GeRPs successfully protect siRNAs from the acidic environment of the gastrointestinal tract and provide a mechanism for crossing the mucosal barrier. Moreover, siRNAs delivered using GeRP technology successfully mediated cell-type specific gene silencing at unprecedented low doses and were capable of inducing a systemic phenotype associated with immune cell modulation. Thus, GeRP technology represents a completely new paradigm for targeted siRNA delivery with enormous potential for developing new therapeutic agents to combat diseases of the immune system.

Future Developments & Milestones

While initial studies identify GeRP technology as a novel and promising approach to RNAi therapeutics, this technology requires significant research and development to bring it to the level required for clinical trials and future therapeutic applications. Optimization of a range of features, including particle size, chitin and mannose content, and siRNA loading as well as characterization of release kinetics and gene silencing efficiency, will be necessary to confirm consistent manufacturing and robust performance. With respect to the RNAi component or payload, prior work in the field has focused on development of rational design algorithms and identification of nucleotide modification patterns that enhance activity, specificity, and stability of RNA duplexes. As an extension of this work, RXi Pharmaceuticals has developed a new generation of advanced RNAi compounds, called rxRNA™. rxRNAs take advantage of a unique design of modifications that provide stability, partially block off-target effects, and prevent detection by the innate immune response while supporting specific and extremely potent gene silencing. Because toxicity issues, including sequence-mediated off-target effects or delivery vehicle-related side effects, are likely dose dependent, the use of the GeRP oral delivery technology to administer low doses of rxRNA drugs provides an opportunity for a wide therapeutic index delivered via a patient-friendly route of administration.

Since its discovery, considerable hope has been placed in the contributions that RNAi can make to treat a diverse range of diseases. Identifying mechanisms for delivering therapeutic siRNAs to specific tissues represents one of the greatest hurdles in converting RNAi from a research tool to an effective therapeutic approach. It is unlikely that any single delivery technology can address the full spectrum of therapeutic challenges that would require effective delivery to a full range of diseased tissues. Because GeRPs are efficiently delivered to cells of the immune system, they represent one facet of the delivery solution. With continued research and development, the GeRP technology has significant promise for future therapeutic applications for inflammatory and related diseases and is a promising step on the path to the development of orally active siRNA therapeutics. ◆

References

1. Akinc A, Goldberg M, Qin J, et al. Development of lipidoid-siRNA formulations for systemic delivery to the liver. Mol Ther. 2009;17(5):872-879.
2. Zimmermann TS, Lee AC, Akinc A, et al. RNAi-mediated gene silencing in non-human primates. Nature. 2006;441(7089):111-114.
3. Aouadi M, Tesz GJ, Nicoloro SM, et al. Orally delivered siRNA targeting macrophage Map4k4 suppresses systemic inflammation. Nature. 2009; 458(7242):1180-1184.
4. des Rieux A, Fievez V, Garinot M, Schneider YJ, Preat V. Nanoparticles as potential oral delivery systems of proteins and vaccines: a mechanistic approach. J Control Release. 2006;116(1):1-27.
5. Soto ER, Ostroff GR. Characterization of multilayered nanoparticles encapsulated in yeast cell wall particles for DNA delivery. Bioconjug Chem. 2008;19(4):840-848.
6. Kuolee R, Chen W. M cell-targeted delivery of vaccines and therapeutics. Expert Opin Drug Deliv. 2008;5(6):693-702.
7. Corr SC, Gahan CC, Hill C. M-cells: origin, morphology and role in mucosal immunity and microbial pathogenesis. FEMS Immunol Med Microbiol. 2008; 52(1):2-12.
8. Shakweh M, Ponchel G, Fattal E. Particle uptake by Peyer's patches: a pathway for drug and vaccine delivery. Expert Opin Drug Deliv. 2004;1(1):141-163.
9. Beier R, Gebert A. Kinetics of particle uptake in the domes of Peyer's patches. Am J Physiol. 1998;275(1 Pt 1):G130-G137.
10. Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Res Ther. 2009; 11(3):229.
11. Sedlack RE, Whisnant J, Elveback LR, Kurland LT. Incidence of Crohn's disease in Olmsted County, Minnesota, 1935-1975. Am J Epidemiol. 1980;112(6):759-763.
12. Kappelman MD, Rifas-Shiman SL, Kleinman K, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. Clin Gastroenterol Hepatol. 2007;5(12):1424-1429.
13. Loftus CG, Loftus EV, Jr., Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000. Inflamm Bowel Dis. 2007;13(3):254-261.
14. Ardizzone S. Ulcerative Colitis. Orphanet. 2003: http://www.orpha.net/data/patho/GB/uk-UC.pdf
15. Koo JY. Current consensus and update on psoriasis therapy: a perspective from the US. J Dermatol. 1999;26(11):723-733.
16. Niles S. Brand of the year Enbrel. MedAdNews. 2006; 25(6): http://www.pharmalive.com/magazines/medad/view.cfm?articleID=3609.

Joanne Kamens, PhD

Director of Discovery, RXi Pharmaceuticals

Dr. Joanne Kamens completed her undergraduate work in Biology at the University of Pennsylvania. She earned her PhD in Genetics from Harvard Medical School's Division of Medical Sciences and spent 15 years at BASF Bioresearch Center, which became Abbott Bioresearch Center in 2001. While at Abbott, she led discovery research projects on small molecule and antibody approaches to immunological and inflammatory diseases serving finally as a Group Leader in Molecular Biology. Dr. Kamens directed the development of RNA interference (RNAi) methods in primary immune cells. In 2007, she joined RXi Pharmaceuticals and is now serving as Senior Director of Discovery Research. Dr. Kamens founded the current Boston chapter of AWIS (the Association for Women in Science) and is now serving on the national AWIS chapters committee. She is a member of the HBA (Healthcare Business Women's Association) Mentoring Committee and is an active Mentornet.net participant.

Pamela Pavco, PhD

Vice President of Pharmaceutical Development, RXi Pharmaceuticals

Dr. Pamela Pavco is a leader in bringing RNA drug candidates from the bench into clinical trials. During her 14-year tenure at RPI Pharmaceuticals/Sirna Therapeutics (now Merck), she was responsible for moving its first RNAi drug candidate into the clinic in less than 1 year. She also directed research and preclinical development of three other RNA drug candidates that continued into clinical trials. In addition to leading the effort to develop Sirna's first RNAi therapeutic, she managed numerous corporate partnerships and collaborations that included Allergan, Inc. for ocular disease, Targeted Genetics, Inc. in Huntington's Disease, Eli Lilly for Hepatitis C, and Elan Pharmaceuticals and Chiron Corporation in oncology. Dr. Pavco earned her PhD in Biochemistry from Virginia Commonwealth University and conducted post-doctoral research at Duke University. Dr. Pavco has authored numerous scientific articles, contributed to approximately 56 patents and patent applications in the RNA therapeutics field, and is a member of the American Association of Cancer Research and the Association for Research and Vision in Ophthalmology.

Anastasia Khvorova, PhD

Chief Scientific Officer, RXi Pharmaceuticals

Dr. Anastasia Khvorova has contributed significantly to the RNAi field. While at Dharmacon (ThermoFisher Scientific), she made major technology advances in RNAi and microRNA. Dr. Khvorova was also responsible for establishing and managing several drug discovery and development collaborations with major pharmaceutical companies, including Abbott and Alcon. Her groundbreaking work has allowed her to author more than 150 abstracts, 30 patents and patent applications, several book chapters, and over 40 peer-reviewed publications. Dr. Khvorova earned her PhD Biochemistry from Russian Academia of Sciences in Moscow in 1994 and after 10 years of working in academia and industry, she joined world-recognized RNAi leader Dharmacon in 2002, where she led R&D for 6 years.

Executive Summary

Habib Skaff, PhD

CEO, Intezyne

Intezyne: Targeting Delivery of Chemotherapeutics

While riding on a train one afternoon, friends Habib Skaff, PhD, and Kevin Sill, PhD, made the decision to leverage their expertise in polymer chemistry and start a company. The goal: Address the drug delivery problems that exist in the oncology space and treat cancer better. In June 2004, Intezyne was born. Intezyne offers a new solution to oncologists who must balance the anti-tumor activity of best-in-class chemotherapeutics with their severe toxicities. Drawing from their expertise, the company's founders created the IVECT™ method to limit chemotherapeutics' anti-tumor activity to within the tumor itself, thereby sparing healthy tissues. Ultimately, the IVECT method has demonstrated preclinical proof-of-concept in a number of therapeutic and diagnostic categories, giving the company the opportunity to monetize this asset through licensing agreements outside of Intezyne's primary oncology focus. In the past year, the pharmaceutical industry has taken notice of Intezyne. The company recently announced it has been issued new patents that cover multiple dimensions of the IVECT method in the US, Europe, and Japan. And, for his part in developing IVECT, Chief Scientific Officer Dr. Sill, a synthetic polymer chemist, has been honored as the Young Innovator of the Year. As CEO of a young company, Dr. Skaff, a synthetic chemist specializing in nanotechnology, recently spoke with *Specialty Pharma* magazine about his expectations for IVECT and how Intezyne must keep its focus in oncology to be successful.

Q: *Please describe the IVECT technology & the need it is addressing in the market.*

A: Nanoscale, drug delivery vehicles offer the potential to improve patient care, but for the most part, they have not lived up to their potential because they tend to be unstable post-administration. The encapsulated drug gets released too early because the delivery vehicle is not stable to dilution and surfactants in the bloodstream. IVECT addresses that shortcoming via a proprietary tri-block copolymer architecture. The middle block of that copolymer is the stabilizer block, which stabilizes the size of the micelle to 60 to 100 nm and increases the ability to keep the drug in the bloodstream longer. By circulating longer, our IVECT therapeutics get more passes at the tumor site. When the IVECT micelles enter the tumor, they are triggered to release their drug payload. However, as the drug is circulating, it does not interact with healthy cells even though it is circulating in the bloodstream because it is sequestered inside a stable micelle. This results in a safer and more effective treatment for the patient.

The key to this breakthrough technology is our multidisciplinary approach, integrating polymer physics and materials science with organic chemistry, polymer chemistry, biochemistry, and biology. Intezyne can improve patient outcomes significantly by amplifying the efficacy and safety profiles of best-in-class cancer drugs, whose potency is often handicapped by non-specific delivery outside of the tumor site, requiring higher dosing and resulting in severe toxicities. The IVECT Method has proven to be extraordinarily versatile, in terms of the diversity of materials that can be encapsulated securely, and its unique modular design confers unmatched adaptability at a minimal cost. Beyond chemotherapy, the company has proven the IVECT method can deliver many classes of small molecules, in addition to nucleic acids, oligopeptides, and diagnostic imaging agents.

Many promising therapeutics never reach their full potential because they are poorly soluble in the bloodstream, or they are too toxic to be administered. With the IVECT Method, Intezyne is able to bypass these issues through secure encapsulation of the active compound. Insoluble drugs previously deemed unfeasible can be sequestered safely and effectively from the bloodstream until they reach the tumor.

Q: *What are the drug delivery advantages of IVECT?*

A: We are able to significantly reduce drug toxicity by securely encapsulating the active therapeutic agent in the proprietary IVECT micelle, a polymeric nanoparticle that minimizes drug exposure to healthy tissues. Also, the IVECT micelle shields its contents from the body's natural defenses, allowing higher concentrations of the active drug to reach the tumor without being excreted or degraded. Additionally, our proprietary cross-linking technology can provide enhanced protection and increased anti-tumor activity by creating a triggered release mechanism, which actively dispenses the drug payload only at the tumor site.

The IVECT copolymer is equipped with proprietary means of attaching cell-targeting groups, which anchor the IVECT micelle to the tumor, both quickly and easily. Because of this breakthrough in modular drug design, Intezyne is able to focus the drug's anti-tumor activity to diverse tumor types without having to synthesize distinct tumor-optimized therapies from scratch.

Q: *Describe the IVECT-based products you have in the pipeline.*

A: Intezyne currently has three cancer chemotherapeutics in its pipeline: Two lead programs in final preparation for IND submission, and one other in earlier stages of preclinical development. The company's lead program, IT-141, has shown significant activity against a diverse number of cancer cell lines. Advanced preclinical studies showed IT-141 is extremely well tolerated and significantly outperforms Pfizer's Camptosar (irinotecan), which shares the same active component. Intezyne plans to file an IND for IT-141 for the treatment of metastatic colorectal cancer.

IT-143, Intezyne's drug-encapsulating doxorubicin, is being evaluated for treatment of small cell lung cancer and cancer of the head and neck. In addition to being well tolerated, IT-143 demonstrated superior pharmacokinetics versus free doxorubicin and other current formulations. Advanced preclinical studies currently are underway and will conclude this year.

Intezyne is also gaining new ground in the area of tumor-specific gene therapy. Our IT-121 program is in early preclinical testing and thus far has demonstrated *in vivo* gene expression far superior to that of commercially available gene transfection systems. Unlike other gene therapy programs, IT-121 minimizes gene expression in the liver while allowing the nucleic acid payload to accumulate in the target tissue.

Intezyne's IVECT Method is a unique and remarkably safe platform that has the potential to raise the bar in terms of what patients and oncologists can expect from chemotherapy. In addition to cancer therapeutics, IVECT could prove beneficial in treating Alzheimer's. The main problem in treating Alzheimer's and many other CNS diseases is crossing the blood-brain barrier, which is not a trivial thing to do. We believe that IVECT's engineering could make this possible.

Q: *How is Intezyne attracting investors?*

A: To date, we have been financed by high net-worth individuals. Our story to investors is simple: We offer a way to create safer and more effective therapeutics for the treatment of disease. To date, we have raised $6 million, and we are looking to raise an additional $10 to $15 million. This financing will fund the advancement of our lead product candidates through two Phase I studies and support IT-141 through Phase II clinical development.

Q: *Are partnerships and licensing part of Intezyne's business model?*

A: Our main goal is to develop proprietary therapeutics in oncology and do this in-house. But if the right opportunity presents itself, we would partner with a pharmaceutical company. We do have one pharma company interested in licensing IVECT to solve a problem it is having in delivering its drug.

The IVECT method has proven the ability to accommodate an expansive range of drugs. This versatility not only gives Intezyne a strong position in oncology, but, through strategic licensure, Intezyne can profit from the universality of the IVECT Method in an ever-expanding variety of therapeutic and diagnostic settings.

Q: *What is your long-term objective for the company?*

A: We want to be the premiere biotechnology company. We will achieve this not through small, incremental gains, but by having a major impact on the lives of cancer patients. In order to reach this goal, we must not lose focus and allow ourselves to go in too many directions at once. ■

External Delivery

Who's In Charge Here?

By: John A. Bermingham

I have been leading turnarounds for more than 20 years. Two things you can always count on in a turnaround are crises and disasters. There is a difference between the two, but both require immediate attention from the top executive.

A crisis is a situation that has reached an extremely dangerous point. A disaster is a situation that results in great damage, difficulty, or death. My belief has always been that a crisis can develop into a disaster but a disaster cannot develop into a crisis because once you have a disaster on your hands, the situation has already passed the crisis stage.

Great CEOs are very good at crisis management. That is because great CEOs are leaders and planners, and crisis management plans are a must as you have to anticipate the "what ifs" and what to do if a crisis hits. It means having a plan in place, identifying who will do what, and having already discussed amongst your people what those crisis events could conceivably be and what to do about it.

What about a disaster? Well, you have to plan for that too. I believe there are four truths in disaster planning:

1. Murphy's Law, which states that anything that can go wrong will go wrong, so a disaster is going to happen sooner or later and you need to be ready.

2. The plan has to be ready before the disaster happens, not after.

3. You must have a tremendous sense of urgency.

4. Work through it and ride it out.

When faced with a crisis or disaster (and I have experienced several in my businesses), the following needs to be executed:

1. You must quickly communicate the issue internally through town hall meetings so the people know what has happened and what you are doing about it. Leave nothing to speculation and communicate frequently. I have conducted weekly town hall meetings in these situations interspersed with company-wide e-mails. Quite frequently, the people at the company will offer excellent and practical suggestions.

2. ommunicate externally to your Board, customers, suppliers, trade,and consumer media, and others, and do it yourself as best you can. It is also a good idea to retain a consultant who is experienced in crisis communications.

3. Set up a task force composed of your people that you must lead and meet with every morning to update and see where you are on the recovery plan. You cannot delegate this responsibility.

4.If a supplier is part or the entire problem, get their CEO and his/her key people to come in to your company immediately to become part of the solution and task force. Outside experts should also be considered for inclusion.

I had a major product quality problem when I took over as CEO of Rolodex Corporation and had the supplier in China who caused the problem fly immediately from Hong Kong to Newark for a meeting when the crisis he had caused was fast becoming a disaster. I have no regrets for making him do that. So whether you have a crisis or disaster on your hands, the key is to act immediately, set your plan for recovery if one is not already in place, surround yourself with the best people you can find to include outsiders who are expert in these situations, meet quickly with the top executives from the culprit company who caused this situation, and lead with urgency, conviction, and purpose.

Sitting around for weeks studying the issue and its recovery plan is a path to failure. Time is not on your side so MOVE IT!!! ◆

Biography

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

BD Medical—Pharmaceutical Systems

Help your product reach its full potential

The world is moving to prefills and, to stay competitive, you need to move with it.

Only BD offers the range and depth of expertise and customizable packaging solutions to guide your drug from early phase development through product launch.

BD's approach can also give you an edge. Our knowledge of drug development trends and our progressive initiatives for advancing drug delivery means that you'll have a strategic advantage—both today and tomorrow.

Contact a BD expert today.

Call 800-225-3310 or e-mail BDPS_marketing@bd.com.

BD

Helping all people live healthy lives

BD Medical
Pharmaceutical Systems
1 Becton Drive
Franklin Lakes, NJ 07417
www.bd.com/pharmaceuticals