Drug Development® & Delivery

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The Challenges of Nucleic Acid Delivery

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

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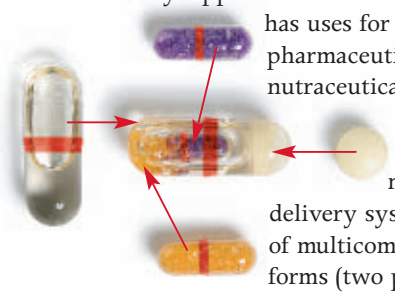
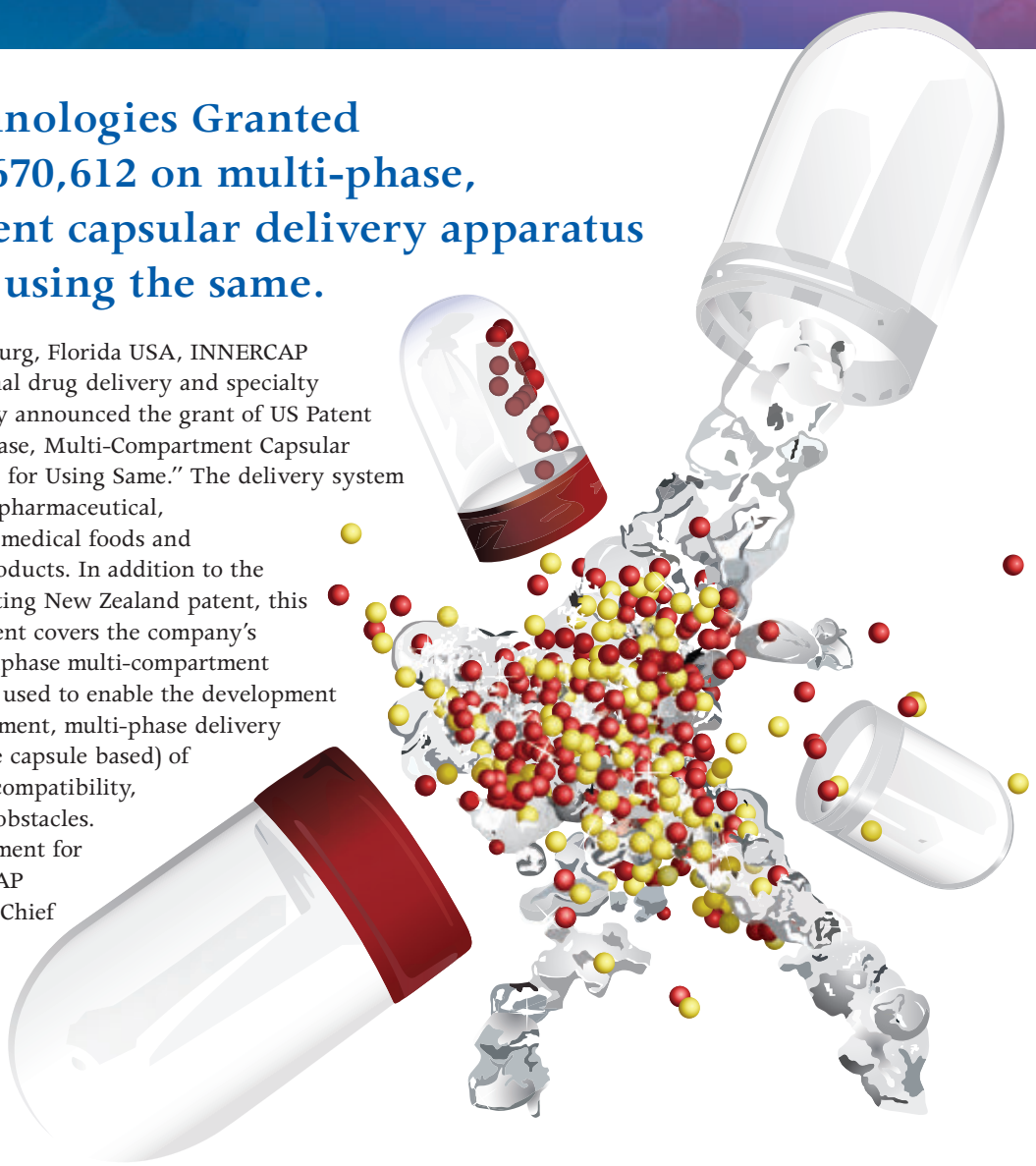
THE ADVANTAGES

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
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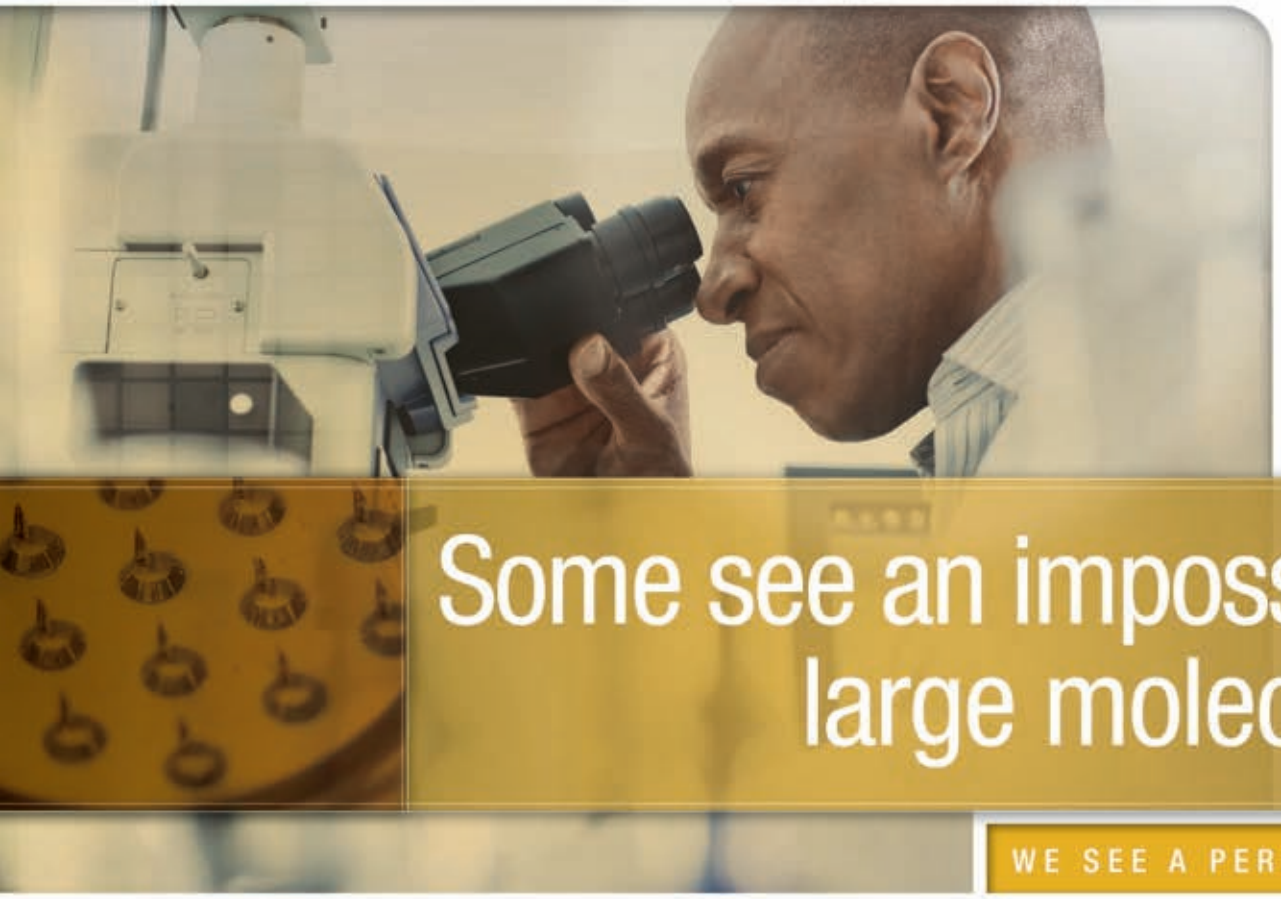

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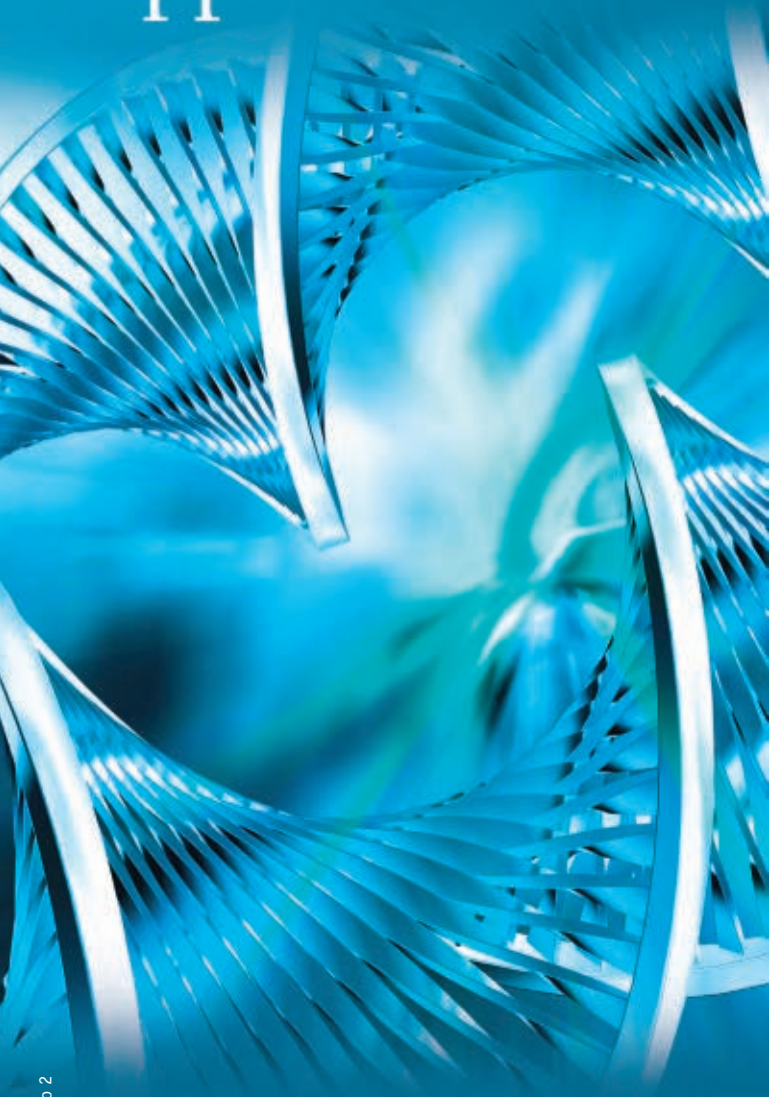

"One class of polymer-based delivery vehicle relies upon electrostatic complexation of RNA to the cationic polymer. Cationic peptides may be complexed to the negatively charged siRNA in a similar way and may be chosen to provide targeting or cell-penetrating characteristics to the complex. In one report, a peptide derived from rabies virus that targets neurons was bound to polyarginine, complexed to siRNA through electrostatic interaction with the protonated polyarginine, and penetrated the blood-brain barrier."

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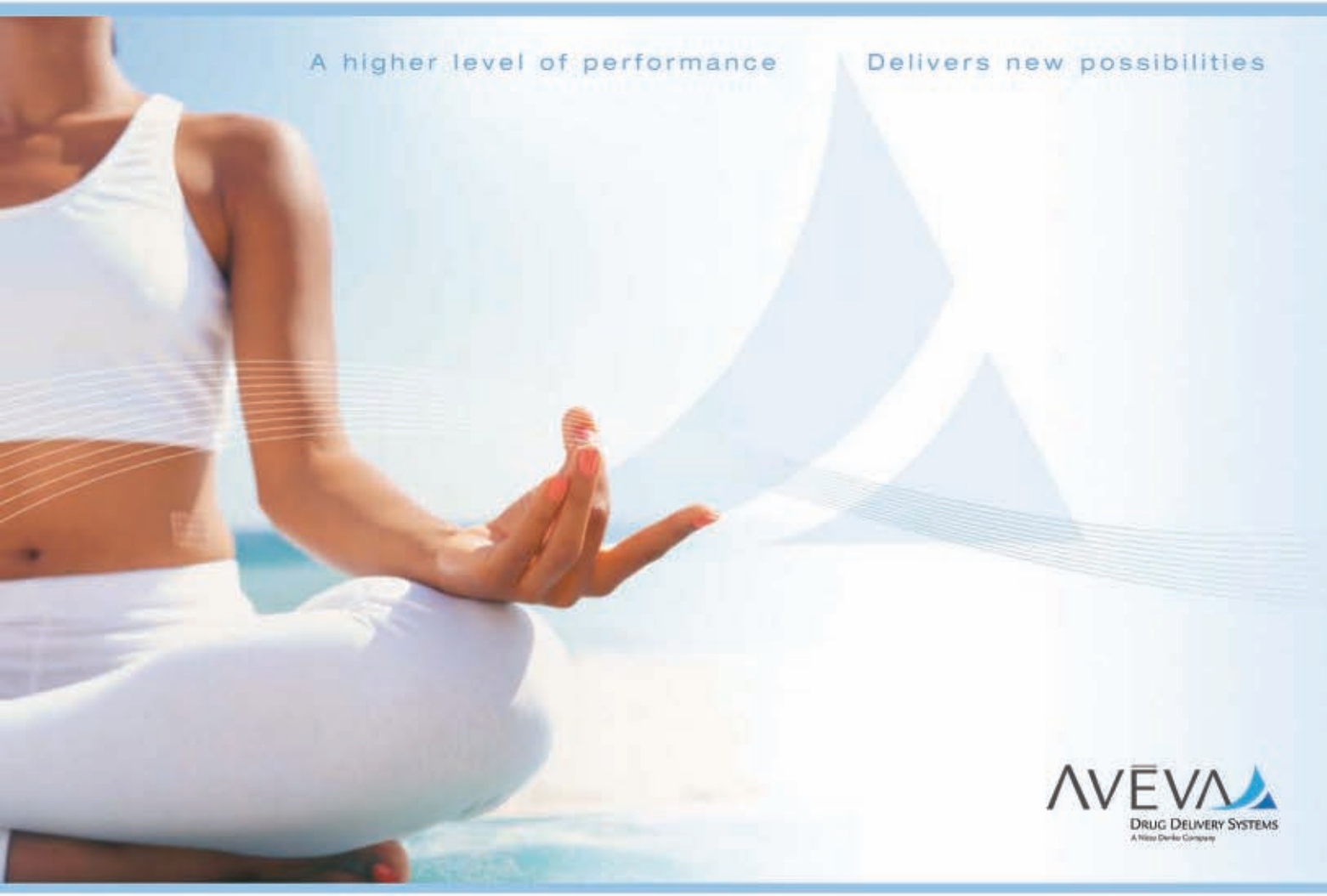
TRANSDERMAL TRANSCENDENCE



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"And the market numbers concur. In 2009, an estimated 2 billion prefilled syringe units were sold, and the market for the technology was estimated to be worth up to $2.5 billion. The biologics sector is being credited with having the most influence on the prefilled syringe market, as there is an increasing need for self-administration of these drugs for chronic conditions."

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Market News and Trends

Particle Sciences & HORIBA Instruments Form Strategic Relationship

Particle Sciences, Inc., a leading pharmaceutical CRO, recently announced the establishment of a strategic alliance with HORIBA Instruments of Irvine, CA, which is the US sales and marketing division of HORIBA Limited of Kyoto, Japan. This alliance ensures that both client bases are provided with a total solution, combining the most up-to-date physical characterization tools with operational expertise in a fully GLP/GMP compliant setting. Under the arrangement, the full array of HORIBA characterization tools will be available at Particle Sciences.

"The need for particle size analysis and physical characterization in general is growing rapidly within this highly regulated environment," said Dr. Robert Lee, Vice President of Pharmaceutical Development at Particle Sciences. "Particle Sciences is a world leader in particulate formulations and drug/device combination products. We looked for a partner that shared the same commitment to quality and innovation, and HORIBA fit the bill."

With this in place, HORIBA clients will have a resource that can both develop and perform characterization under cGLPs and cGMPs. "Our client base ranges from start-ups to the largest multinational Pharma and Biotech companies," said Dr. Mike Pohl, HORIBA's Vice President. "For a variety of reasons, we are often asked if we can recommend a site familiar with pharmaceutical development at which they could have work performed. We have worked with Particle Sciences for some time and have been impressed with their facility and their team. By entering into this relationship, we can ensure that our clients not only gain access to the most advanced technology, but also that the operators are highly trained to use the instruments to their fullest capability."

"Particle Sciences is committed to remaining one of the premier drug delivery development services providers," added Dr. Lee. "We offer a broad array of drug delivery technologies and routinely work on atypical dosage forms. It's critical that our analytic and characterization capabilities keep pace with our formulation expertise. Additionally, as our clients scale to clinical and ultimately commercial processes, we need to ensure the methods we develop are phase appropriate and based on readily available techniques. HORIBA is the world's largest instrument manufacturer with the most complete product offering and can now provide the level of security our clients deserve."

"Many pharmaceutical customers are located along the East Coast," said Dr. Pohl. "The combination of our Edison, NJ, headquarters plus the Bethlehem, PA, location of Particle Sciences, Inc., gives HORIBA a strong one-two punch to support these customers. Services ranging from sample analysis, customer support, and full consulting services will now be readily accessible to our customers."

Particle Sciences is an integrated provider of drug development services with deep expertise in micro- and nano-particulate drug delivery technologies and drug/device combination products with additional specialized capabilities in topical and mucosal drug products. Through a full range of formulation, analytic, and manufacturing services, Particle Sciences provides pharmaceutical companies with a complete and seamless development solution that minimizes the time and risk between discovery and the clinic.

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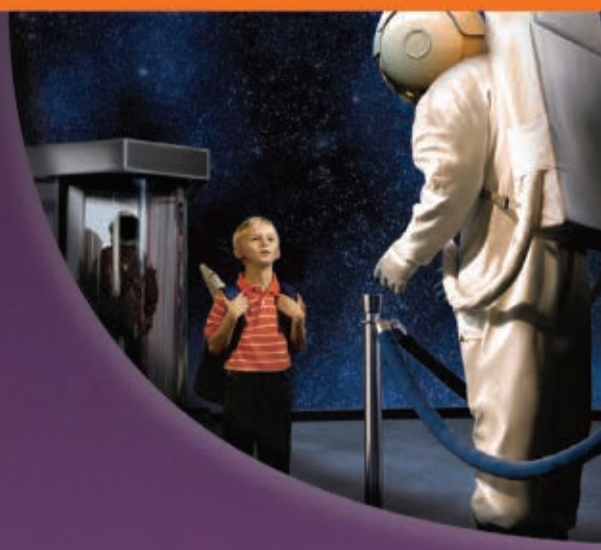

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Catalent Acquires Exclusive Worldwide Rights to Lyopan Fast-Dissolve Technology

Catalent Pharma Solutions, the world's leading provider of advanced oral drug delivery technologies and solutions, has entered into a license agreement with Pantec AG for the exclusive worldwide development rights to the Lyopan fast-dissolve technology for healthcare products.

"We are pleased to add the Lyopan technology to Catalent's oral dose technology offering, which will enable us to provide our pharmaceutical partners with an enhanced choice of drug delivery technologies to improve the performance of their treatments," said Ian Muir, PhD, President, Modified Release Technologies for Catalent. "The Lyopan technology is ideally suited to deliver a wide dose range of APIs in a fast-dissolve tablet. These are key considerations for situations in which patient adherence, ease of swallowing, and a lack of access to water are important issues to address."

Lyopan is a proprietary technology for the development and manufacture of fast-dissolve lyophilized tablets, including OTC products, such as allergy treatments or travel medications. Lyopan also requires significantly less water than existing technology, an advantage that helps reduce energy consumption, sublimation, and drying time. As a result of these advanced characteristics, Lyopan technology offers the potential for improved taste-masking capabilities and may increase the range of drugs and consumer products that can be used in a fast-dissolve dosage form.

The acquisition of Lyopan technology is the latest example of Catalent's ongoing investment in advanced oral dose solutions and novel technologies. It advances Catalent's oral dose capabilities, potentially enabling the delivery of improved, compliance-enhancing treatments across a broad range of applications, including central nervous system drugs, allergy medications, and dosage forms for pediatric and geriatric populations. Additionally, Lyopan technology lends itself easily to the development of both prescription and OTC products.

"With its long history of developing lyophilized fast-dissolve products, Catalent is the ideal partner to launch our innovative Lyopan technology," commented Hans Peter Rohrer, Chairman of Pantec.

The acquisition of Lyopan technology also has clear synergies with several of Catalent's existing technologies, such as Zydis fast-dissolve, a unique, freeze-dried oral solid dosage form that disperses instantly in the mouth without requiring water.

Zogenix Announces Completion of Enrollment for ZX002 Phase III Efficacy Study

Zogenix, Inc. recently announced the completion of enrollment in its pivotal Phase III efficacy study (Study 801) of ZX002. ZX002 is a novel, oral, single-entity, controlled-release formulation of hydrocodone for the treatment of moderate-to-severe pain in patients requiring around-the-clock opioid therapy for an extended period of time.

Study 801 is a randomized, 12-week, double-blind, placebo-controlled trial evaluating ZX002 in opioid-experienced adult subjects with moderate-to-severe chronic lower back pain. The primary efficacy endpoint is the mean change in average daily pain intensity scores between ZX002 and placebo.

Initial top-line data from Study 801 and an open-label Phase III safety study (Study 802) are anticipated to be available during the second half of 2011. As previously announced, Zogenix has completed enrollment of Study 802 to evaluate overall safety of ZX002 in patients for up to 1 year.

Pending positive Phase III clinical results, Zogenix expects to submit an NDA for ZX002 with the US FDA by early 2012. If approved, ZX002 has the potential to be the first controlled-release version of hydrocodone and also the first hydrocodone product that is not combined with another analgesic. This novel formulation has the potential to address safety concerns outlined by the FDA regarding the use of certain combination prescription pain products that contain acetaminophen, which can cause liver toxicity at high doses over time. In January 2011, the FDA announced that manufacturers of certain prescription pain products containing acetaminophen will be required to reformulate or discontinue making these products within 3 years.

"After completing enrollment in both Phase III studies, ZX002 remains positioned as the first potential single-entity, controlled-release hydrocodone product," said Stephen J. Farr, PhD, President and Chief Operating Officer. "Because it does not contain acetaminophen and allows for convenient twice-daily dosing, ZX002 may fulfill a beneficial treatment option for both patients using immediate-release hydrocodone combination products on a chronic basis and an alternative for patients already using extended-release opioids for the management of their moderate-to-severe pain. We look forward to obtaining top-line safety data from Study 802 and efficacy and safety data from Study 801 during the second half of this year to support a potential NDA submission by early-2012."

Market News and Trends

ICIG Announces Agreement to Acquire Genzyme's Pharmaceutical Intermediates Business

International Chemical Investors Group (ICIG) recently announced it has entered into a purchase agreement under which an affiliate of ICIG will acquire the pharmaceutical intermediates business from Genzyme Corporation.

Under the terms of the agreement, ICIG will purchase substantially all of the pharmaceutical intermediates business, excluding the drug delivery technologies portion of the business. ICIG has agreed to offer employment to the unit's approximately 120 employees upon closing and plans to maintain operations at its primary location, a manufacturing facility in Liestal, Switzerland. The acquired pharmaceutical intermediates business will be renamed Corden Pharma Switzerland LLC and will operate as part of ICIG's pharmaceutical business within the Corden Pharma platform. The companies' goal is to close the transaction during the first quarter of 2011. Financial terms are not disclosed.

As part of the agreement, ICIG will enter into a 5-year supply contract to provide Genzyme with materials needed for the production of eliglustat tartrate, an investigational treatment for Gaucher disease Type 1 that is currently in Phase III clinical trials. ICIG will also supply materials needed for the manufacture of other treatments in earlier stages of development, including neo-GAA, currently in preclinical development as a potential next-generation Pompe disease therapy.

ICIG is a privately owned industrial holding company focusing on mid-sized chemicals and pharmaceutical businesses. It has acquired 15 businesses, all of which have origins in major global chemical or pharmaceutical corporations and are independently managed. ICIG companies currently employ more than 3,000 people and operate 15 manufacturing facilities in Europe and the US. Corden Pharma group companies offer contract development and contract manufacturing for advanced pharmaceutical intermediates, APIs, and drug product formulations with more than 1,500 individuals supporting their customers with specialized technologies in all international markets.

Capsugel Acquires Novel FlexTab Delivery Technology

Capsugel, the world's leading hard capsule manufacturer and an innovator in drug delivery systems, recently announced its acquisition of the FlexTab™ technology, a novel dosage form developed throughout the past 8 years within GlaxoSmithKline (GSK). The technology uses injection-molding processes to produce unique capsule-shaped dosage forms that offer a new platform for formulating a wide range of new pharmaceutical and consumer health products. The deal between Capsugel and GSK was brokered by SR One, GSK's corporate venture fund.

"Capsugel is very excited to have this innovative technology as part of our suite of offerings", said Keith Hutchison, Vice President of Research and Development at Capsugel. "We believe the FlexTab technology's unique performance characteristics and novel presentation will enable us to formulate the next generation of pharmaceutical and biotech products for our customers. With fewer new drug entities coming to market, our customers are looking for other ways to improve the therapeutic effectiveness of existing APIs for patients and consumers, for example, through better patient compliance and convenience."

The FlexTab technology allows for a variety of fill materials, including powders, pellets, liquids, micro-tablets and tablets, and can even deliver separate liquid and powder APIs in one dose. This innovation opens the door to novel product designs and customization options. It extends Capsugel's capsule technology beyond the well-established dip-molding process used today, expanding into higher value segments and offering enhanced value for customers.

Capsugel is moving forward immediately to bring the technology and assets in-house with plans of making the new dosage form available to customers as soon as possible.

Amgen & Xencor to Co-Develop Novel Antibody; Deal Worth $500 Million

Xencor, Inc. and Amgen recently announced they will collaborate to develop XmAb5871, an Fc-engineered monoclonal antibody dually targeting CD19 and CD32b. XmAb5871 is currently in late-stage preclinical development for the treatment of autoimmune diseases.

Under the terms of the agreement, Amgen has the option to an exclusive worldwide license following the completion of a predefined Phase II study. Xencor will lead all clinical development until that time. Xencor will receive up-front and early development milestone payments. If Amgen does exercise its option, Amgen will assume responsibility for future development, Xencor will receive an option-exercise fee, which combined with the up-front and early development milestones, will total $75 million, and Xencor could receive up to an additional $425 million in clinical, regulatory, and commercialization milestone payments. Xencor will receive tiered royalties on future sales of XmAb5871.

Xencor's CD32b technology is a novel immunomodulatory platform consisting of engineered Fc domains with selective high affinity binding to FcyRIIb (CD32b), a receptor with dominant inhibitory activity on B cells and other immune cells. The CD32b pathway has never been therapeutically exploited and applied to high affinity antibodies targeting immune cells.

"XmAb5871 provides a novel approach to suppress B-cell function, which will enhance Amgen's internal efforts in inflammatory diseases," said Joseph P. Miletich, MD, PhD, Senior Vice President, Research & Development at Amgen. "We are delighted to have the opportunity to partner with Xencor in exploring their novel immunomodulatory approach."

"Amgen's long-time leadership in antibody development for oncology and inflammatory diseases aligns seamlessly with Xencor's pipeline development," said Bassil Dahiyat, PhD, CEO of Xencor. "We expect that XmAb5871 will soon become the fifth XmAb-engineered antibody in clinical development. This program is a testament to the progress we've made expanding the XmAb platform into autoimmune disease with our CD32b technology, which is at the core of the XmAb5871 compound. The option deal structure allows us to continue to lead the development of XmAb5871 while also leveraging Amgen's experience in developing novel biologics for unmet medical needs."

Progenics & Salix Announce Worldwide License Agreement

Progenics Pharmaceuticals, Inc. and Salix Pharmaceuticals, Ltd. recently announced they have entered into an exclusive worldwide (except Japan) agreement by which Salix has licensed rights to RELISTOR® (methylnaltrexone bromide). RELISTOR Subcutaneous Injection is indicated for the treatment of opioid-induced constipation (OIC) in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. Use of RELISTOR beyond 4 months has not been studied.

RELISTOR is a peripherally acting mu-opioid receptor antagonist that counteracts the constipating effects of opioid pain medications in the gastrointestinal tract without affecting their ability to relieve pain. The methylnaltrexone license includes intellectual property from the University of Chicago, Progenics Pharmaceuticals, and Wyeth Pharmaceuticals, including patents and applications with expiration dates that will range from 2017 through 2031. RELISTOR was approved in the US in 2008, and currently, the drug is approved for use in over 50 countries worldwide. In 2010, RELISTOR single-use, prefilled syringes were approved for use in the US, Canada, and the European Union. Worldwide net sales of RELISTOR totaled $16 million in 2010.

Financial terms of the transaction include a $60 million up-front payment and development milestones totaling $90 million, contingent upon the achievement of certain US regulatory milestones. Salix also will pay sales-based milestones of up to $200 million plus royalties on product sales in the US, as well as 60% of all revenue received from non-US sublicensees. Salix will fund all development, registration, and commercialization activities for RELISTOR in markets worldwide other than in Japan, where Progenics has licensed to Ono Pharmaceuticals the rights to develop and commercialize subcutaneous RELISTOR.

Salix will market RELISTOR directly through its specialty sales force in the US, and outside the US, RELISTOR will be marketed with sublicenses to regional companies. The parties plan an April 2011 transition of RELISTOR commercial and development responsibility to Salix from Pfizer Inc, which acquired Progenics' former RELISTOR partner, Wyeth Pharmaceuticals. While Salix effects a country-by-country transition of ex-US commercialization rights, Wyeth will remain the Marketing Authorization Holder for RELISTOR and will continue to supply product. In the interim, Wyeth remains responsible for all manufacturing, clinical, medical, and regulatory activities for RELISTOR outside of the US and Japan.

Merck Serono & Domain Therapeutics Announce to Develop Drugs for Parkinson's Disease

Merck Serono, a division of Merck KGaA, Darmstadt, Germany, recently announced an exclusive development and licensing agreement with Domain Therapeutics, Strasbourg, France, to develop metabotropic glutamate receptor 4 (mGluR4) Positive Allosteric Modulator (PAM) drugs targeting Parkinson's disease and other neurodegenerative diseases.

Domain Therapeutics will contribute optimized compounds that have been developed from their proprietary chemical series. Under the terms of the agreement, the company will receive EUR 2 million in up-front payment and research funding and is eligible for up to EUR 132 million in milestones for the first two products, as well as undisclosed royalties.

"We are pleased to have the opportunity to work with Domain Therapeutics, which has developed great expertise in the G-Protein Coupled Receptor area," said Bernhard Kirschbaum, Executive Vice President for Global Research and Development at Merck Serono. "This partnership with Domain Therapeutics reflects our long-term commitment to develop new treatments for neurodegenerative diseases."

"This agreement is a validation of Domain Therapeutics' business model of addressing difficult GPCRs and partnering compounds, with a significant deal, at an early stage of development," said Pascal Neuville, CEO, Domain Therapeutics. "Merck Serono is known to set very high standards for the compounds they are licensing, and this deal is a demonstration of the quality of our work. We anticipate that this agreement will enable us to sign further deals of this kind." mGluR4 is a glutamate receptor, member of the G-Protein Coupled Receptor (GPCR) family, and is believed to be a potential therapeutic target for Parkinson's disease.

Allosteric modulation of mGluR4 receptors is thought to exert regulatory activity on glutamate-mediated neurotransmission.

EXCIPIENT UPDATE

Permeability Study on the Coating Film Consisting of CA-398-10 NF/EP & CA- 320S NF/EP

By: Jinghua Yuan, PhD; Doug G. Dunn, Nancy M. Clipse, Ray J. Newton, Jr., PhD

INTRODUCTION

Cellulose esters form the most suitable semi-permeable membranes for osmotic drug delivery systems. Eastman produces several types of cellulose esters, in which CA-398-10 NF/EP and CA-320S NF/EP are the most commonly used for the application. CA-398-10 NF/EP and CA-320S NF/EP could be used alone or combined to form the membrane.[1-4] CA-398-10 NF/EP and CA-320S NF/EP have different acetyl content (CA-398-10 NF/EP, 39.8% vs. CA-320S NF/EP, 32.0%) and physical properties.[5] These differences in properties result in different permeability of the coating films. One would expect that the permeability of the coating films could be tailored by adjusting the ratio of two polymers in the coating solution to fit particular needs.

The objectives of this study were to investigate the effects of the ratio of CA-398-10 NF /EP to CA-320S NF/EP on the permeability of the coating films, to investigate the effects of plasticizer level and molecular weight on the permeability of the coating films, and to address the effect of acetyl content variation in CA-398-10 NF/EP polymer on the permeability of the coating films.

MATERIALS

To determine the permeability of coating films, the designed coating solution was coated on model tablets. The model tablets consisted of POLYOX water-soluble resins with a molecular weight of 5,000,000 (Dow Chemical, Midland, MI), colorant (Sensient Technologies Corp., St. Louis, MO), and magnesium stearate (Mallinckrodt Baker Inc., Phillipsburg, NJ). For coating solutions, CA-398-10 NF/EP with an acetyl content at 39.4% (CA-NF, Eastman Chemical Company, Kingsport, TN), CA-398-10 TG (technical grade) with an acetyl content at 40.3% (CA-TG, Eastman Chemical Company) and CA-320S NF/EP (Eastman Chemical Company) were used in the study. Plasticizers (Pz) investigated were polyethylene glycol 400 (PEG 400) and polyethylene glycol 3350 (PEG 3350) (Sigma Aldrich, St Louis, MO). High purity acetone (B&J Brand, Burdick & Jackson, Muskegon, MI) and de-ionized water (NANOpure water system, Barnstead, Van Nuys, CA) were used as the solvent systems. All of the materials were used as received.

METHODS

Experimental Design of Coating Formulation

Four groups of coating formulations were designed. Table 1 lists one group (Group 1) of formulations having CA-320S NF/EP and low acetyl content of CA-398-10 NF/EP with PEG 400 as the plasticizer. The table is color coded so that one color region has the same ratio of CA-398-10 NF/EP to CA-320S NF/EP with changing plasticizer concentration. Group 2 is the formulations having CA-320S NF/EP and low acetyl content of CA-398-10 NF/EP with PEG 3350 as the plasticizer. The water concentration is kept at 10% in the total solution for all formulations. The other two

TABLE 1

Sample ID	CA	Total CA (g)	PEG 400(g)	Water (g)	Acetone (g)	PEG/CA
1	50% NF + 50% CA 320S	80.00	0.00	133.33	1120.00	0.00
2	50% NF + 50% CA 320S	72.00	8.00	133.33	1120.00	0.10
3	50% NF + 50% CA 320S	64.00	16.00	133.33	1120.00	0.20
4	75% NF + 25% CA 320S	80.00	0.00	133.33	1120.00	0.00
5	75% NF + 25% CA 320S	72.00	8.00	133.33	1120.00	0.10
6	75% NF + 25% CA 320S	64.00	16.00	133.33	1120.00	0.20
7	90% NF + 10% CA 320S	80.00	0.00	133.33	1120.00	0.00
8	90% NF + 10% CA 320S	72.00	8.00	133.33	1120.00	0.10
9	90% NF + 10% CA 320S	64.00	16.00	133.33	1120.00	0.20

Formulations having CA-320S NF/EP and low acetyl content of CA-398-10 NF/EP with PEG 400 as the plasticizer.

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groups of formulations were the same compositions as Groups 1 and 2, except high acetyl content of CA-398-10 TG was used to replace the low acetyl content CA. There were 36 formulations in total.

Preparation of Model Tablets & Coating Solutions

The model tablets and coating solutions were prepared according to the procedures described in a previous study.[6]

Procedures of Performing Coating

A quantity of 800 g of tablets was coated with one coating solution in each run. All of the coating runs, with a theoretical coating weight of 10 wt% relative to the tablet weight, were performed in a pan coater (COMPU-LAB, Thomas Engineering, Inc., Hoffman Estates, IL) with one spray gun under the processing conditions indicated in a previous study.[6] The inlet temperature was controlled at 25°C, and the bed temperature was 21°C. All of the coating formulations were repeated twice.

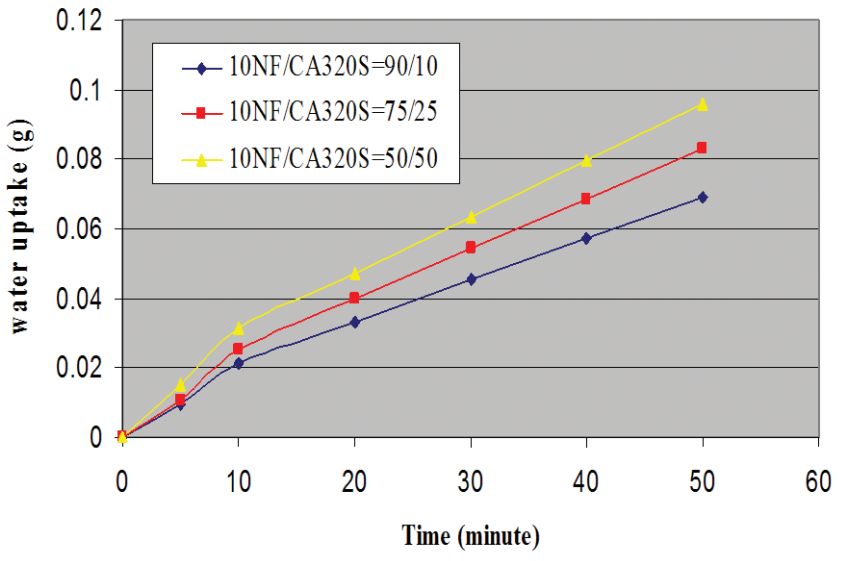
Determination of the Permeability of Coating Films

The permeability of coating films was determined by a water uptake test.[7] The test was terminated when the water uptake by the tablet caused the internal pressure to increase to a point at which the film coating ruptured. The average weight gain of eight tablets was used in the data analysis.

RESULTS & DISCUSSIONS

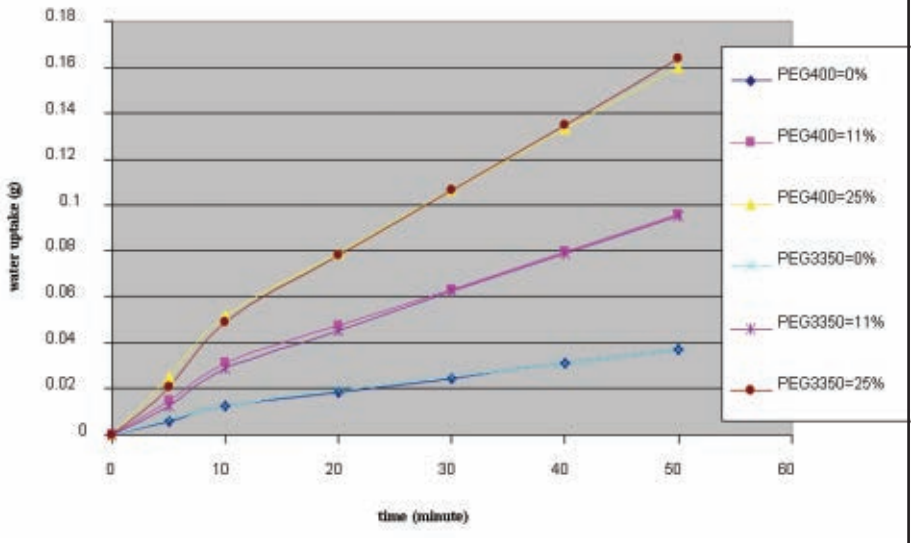
Permeability of the coating films is determined by water uptake experiments. The faster water uptake rate indicates the film is more permeable. It was observed that the water uptake rate changed from fast to slightly slower around the first 5 minutes during a water uptake experiment. The shift in uptake rate may be due to the change in mechanism

FIGURE 1



The ratio of CA-398-10 NF/EP to CA-320S NF/EP effect on the permeability of the coating films. (PEG400 = 11.1% in the formulations)

FIGURE 2



PEG level and molecular weight effect on the permeability of the coating films. (CA-398-10 NF/EP/CA-320S NF/EP = 50/50; acetyl in 10 NF/EP = 39.4%)

of water transporting through the film. In the beginning of the testing, by capillary action, water will occupy the pores or small channels formed during coating; after that water will penetrate through the membrane by diffusion. Because the diffusion step is slower, the water uptake rate governed by diffusion is slower.

Water uptake results were analyzed with statistical tools. Design Expert® software (Design Expert V7., Stat-Ease, Inc., Minneapolis, MN) was employed to establish models to predict water uptake rates. Because water uptake rates changed during the course of testing, two models were obtained to describe the water uptake rates for one group of formulations. There are eight models developed for four groups of formulations. The models are displayed in Table 2.

TABLE 2

Acetyl Content of CA-398-10 (%)	Plasticizer	Water Uptake Rate Model	
		To 5 Minutes	Beyond 5 Minutes
39.4	PEG 400	0.001231032 + 5.65762E-05 * CA320S +1.71733E-05* CA_NF +0.000375182 * PEG -1.07434E-06* CA320S * CA_NF -2.72024E-07* CA320S * PEG -4.09833E-06 * CA_NF * PEG	0.000622234 -7.68814E-06 * CA320S +1.84631E-06 * CA_NF +0.000182026* PEG +5.34942E-07*CA320S * CA_NF -1.11611E-06* CA_NF * PEG
40.3	PEG 400	0.001377644 +5.71842E-05 * CA320S +2.02306E-05 * CA_TG +0.00040116 * PEG -1.07434E-06 * CA320S * CA_TG -2.65677E-06* CA320S * PEG -4.09833E-06* CA_TG * PEG	0.000622234 -7.68814E-06 * CA320S +1.84631E-06* CA_TG +0.00014694* PEG +5.34942E-07* CA320S * CA_TG -1.11611E-06* CA_TG * PEG
39.4	PEG 3350	0.001326205 +5.89555E-05* CA320S +1.71733E-05 * CA_NF +0.000373997 * PEG -1.07434E-06* CA320S * CA_NF -2.15027E-06 * CA320S * PEG -4.09833E-06 * CA_NF * PEG	0.000617775 -7.68814E-06 * CA320S +1.73484E-06* CA_NF +0.00023638 * PEG +5.34942E-07 * CA320S * CA_NF -2.50565E-06* CA_NF * PEG
40.3	PEG3350	0.001820165 +6.82472E-05* CA320S +2.02306E-05 * CA_TG +0.000376468* PEG -1.07434E-06 * CA320S * CA_TG -1.02092E-06* CA320S * PEG -4.09833E-06* CA_TG * PEG	0.000617775 -7.68814E-06* CA320S +1.73484E-06* CA_TG +0.000201294* PEG +5.34942E-07* CA320S * CA_TG -2.50565E-06* CA_TG * PEG

CA_NF: CA-398-10 NF/EP; CA_TG: CA-398-10 TG

Established models to predict water uptake rates.

The Ratio of CA-398-10 NF/EP to CA-320S NF/EP Effect on the Water Uptake of the Coating Films

To study the ratio of CA-398-10 NF/EP to CA-320S NF/EP effect on the permeability of the coating films, three ratios of CA-398-10 NF/EP to CA-320S NF/EP - 90/10, 75/25, and 50/50 (wt%), were investigated. Figure 1 shows the results having CA-398-10 NF/EP with 39.4% acetyl and 11.1% of PEG 400 relative to the CA polymers' weight in the formulations.

It is known that the permeability of a CA film increases with decreasing acetyl content in the polymer.[5] CA-320S NF/EP has acetyl content at 32%; its film is more permeable compared to a CA-398-10 NF/EP film with acetyl content at 39.8%. Thus, the more CA-320S NF/EP in the formulation, the faster the rate of the water uptake. The trend maintains the same when PEG 3350 was used in the formulation.

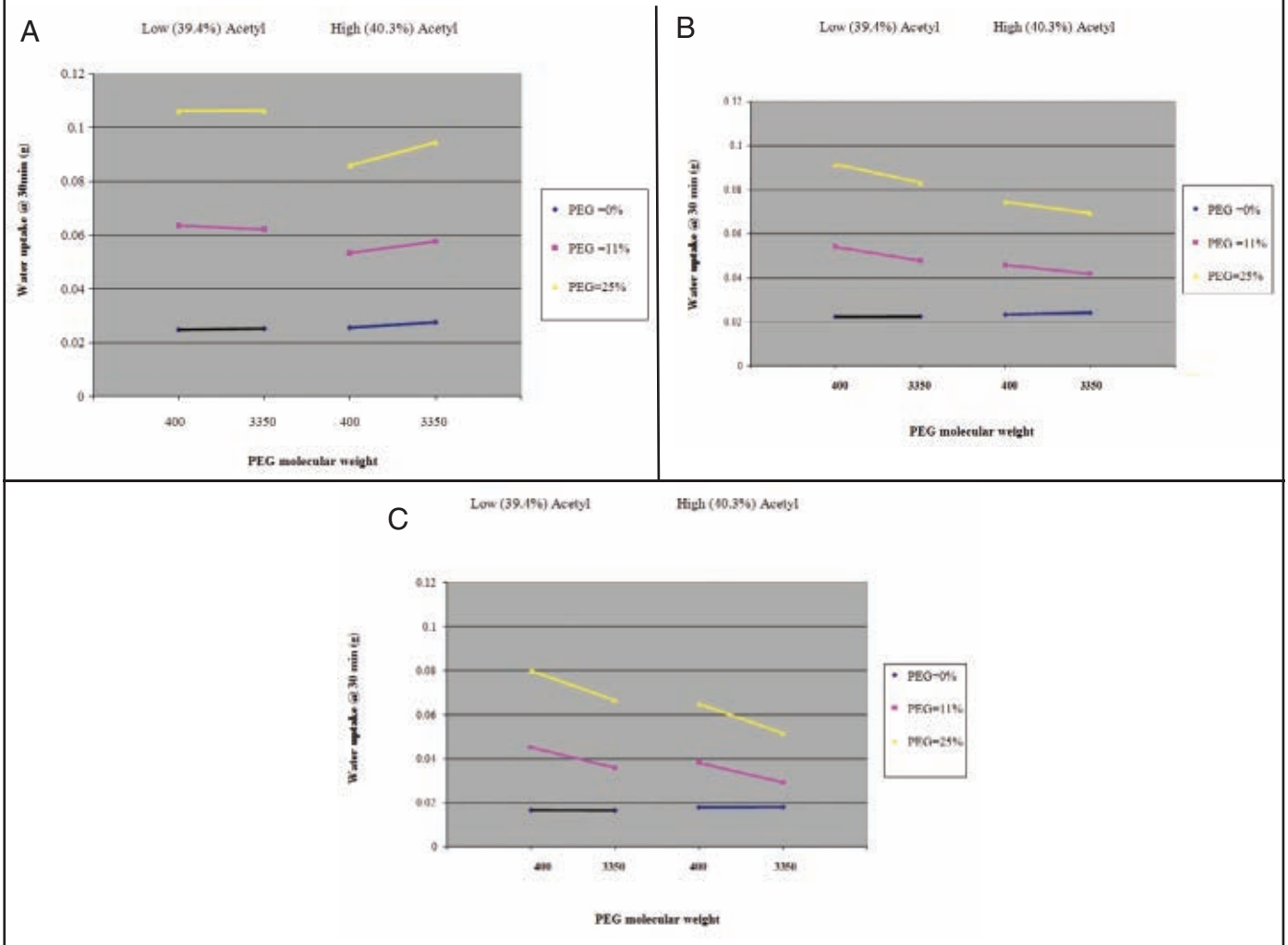
The significant implication of this finding is that one can readily adjust the desired rate of water uptake in an osmotic drug delivery system by selecting the appropriate ratio of CA-398-10 NF/EP to CA-320S NF/EP to use in the coating formulation. Thus, one can control the rate at which a drug is released from an osmotic tablet by controlling the rate of internal osmotic pressure build-up, which is a direct function of the rate of water uptake by the tablet. Indeed this concept is already used commercially.[8]

Effect of PEG Level & PEG Molecular Weight on the Water Uptake of the Coating Films

PEG 400 and PEG 3350 at 0%, 11.1%, and 25% relative to total CA polymer weight were studied to investigate the effect of PEG level and PEG molecular weight on the water uptake of coating films.

Figure 2 displays the effect of PEG level and PEG molecular weight on the water uptake, while the ratio of CA-398-10 NF/EP to CA-320S NF/EP was maintained at 50/50%. The results of this study show that PEG molecular weight has little, if any, impact on the rate of water uptake. However, PEG level has a significant effect as is seen from the eight-fold increase in the water uptake when the PEG is increased from 0 to 25% of the total CA polymer weight. Based on past research with cast films, it is expected

FIGURE 3 A, B & C



Predicted water uptakes at 30 minutes to show the effects of PEG level and PEG molecular weight, and acetyl variation in CA-398-10 polymer on the water uptake of the coating films. (3A) CA-398-10/CA320S = 50/50, left lines: low acetyl CA-398-10 was used; right lines: high acetyl CA-398-10 was used. (3B) CA-398-10/CA320S = 75/25, left lines: low acetyl CA-398-10 was used; right lines: high acetyl CA-398-10 was used. (3C) CA-398-10/CA320S = 90/10, left lines: low acetyl CA-398-10 was used; right lines: high acetyl CA-398-10 was used.

TABLE 3

Ratio of NF/CA320S	PEG Type	PEG Level (%)	Water uptake (g)@30 min, 39.4% acetyl	Water uptake (g)@30 min, 40.3% acetyl	% Difference in water uptake due to acetyl
90/10	PEG400	0	0.0167	0.0179	7.2
		11	0.0451	0.0381	15.5
		25	0.0799	0.0648	18.9
	PEG3350	0	0.0166	0.0181	9.0
		11	0.0359	0.0292	18.7
		25	0.0664	0.0515	22.4
75/25	PEG400	0	0.0223	0.0233	4.5
		11	0.0541	0.0459	15.2
		25	0.0914	0.0744	18.6
	PEG3350	0	0.0224	0.0242	8.0
		11	0.0478	0.0419	12.3
		25	0.0830	0.0693	16.5
50/50	PEG400	0	0.0248	0.0256	3.2
		11	0.0636	0.0534	16.0
		25	0.1062	0.0859	19.1
	PEG3350	0	0.0252	0.0276	9.5
		11	0.0621	0.0577	7.1
		25	0.1063	0.0945	11.1

Difference in water uptake at 30 minutes due to acetyl variation.

that increasing the level of a hydrophilic plasticizer such as PEG would increase water uptake because these types of plasticizers make the chains of polymers more flexible and more permeable.

The effect of PEG molecular weight on the rate of water uptake of coating films is more complicated; it depends on other formulation factors, such as ratio of CA-398-10 NF/EP to CA-320S NF/EP, and the acetyl content in CA-398-10 NF/EP. To better address the effect, consideration of the ratio of CA-398-10 NF/EP to CA-320S NF/EP must be included, which is discussed further on.

Effect of Acetyl Variation in CA-398-10 NF/EP Polymer on the Water Uptake of Coating Films

In this study, two acetyl contents of CA-398-10 were used - 39.4% (CA-NF) and 40.3% (CA-TG). Design Expert software was employed to establish models to predict water uptake rates (Table 2). Based on the models, water uptake at 30 minutes for each formulation is predicted. The results are presented in Figure 3.

It is observed that at a fixed ratio of CA-398-10 to CA-320S and without PEG in the formulations, a 1% acetyl variation (low to high - introduced by the CA-398-10) does not have a significant impact on the rate of water uptake, which is supported by the straight lines in Figures 3A through 3C. When PEG is present in the formulations and the ratio of CA-398-10 to CA-320S is greater than 50/50, the water uptake from PEG 400 plasticized films is slightly higher than those plasticized with PEG 3350. This is consistent with prior published results.[3] It is surprising that PEG molecular weight doesn't show significant influence on the water uptake when the ratio of CA-398-10 to CA-320S is at 50/50. In this case, the water uptake is influenced mainly by the presence of the high level of CA-320S; therefore, it is impossible to distinguish any additional effect from PEG 400 versus PEG 3350.

The results in Figure 3 suggest that when PEG was present in the formulations, lower acetyl CA-398-10 results in higher water uptake; the differences due to acetyl variation are shown in Table 3.

The data in Table 3 indicate that acetyl content variation in CA-398-10 polymer over 0.9% (within CA specification) range could influence the rate of water uptake of the coating films to a certain degree; especially the formulations that have higher levels of CA-398-10 NF/EP and PEG 400 as the plasticizer. At the 11% PEG 400 level and when the ratio of CA-398-10 to CA- 320S was 50/50, the data suggest that on average, one would expect a 1.5% increase in the rate of water uptake for each 0.1% decrease in the acetyl content in the CA-398-10.

CONCLUSIONS

This study demonstrates that one can readily adjust the desired rate of water uptake in an osmotic drug delivery system by selecting the appropriate ratio of CA-398-10 NF/EP to CA-320S NF/EP to use in the

coating formulation. Thus, one can control the rate at which a drug is released from an osmotic tablet by controlling the rate of internal osmotic pressure build-up, which is a direct function of the rate of water uptake by the tablet. Additionally, it has been confirmed that plasticizers also play a very important role in determining the permeability of the coating films with higher levels of plasticizer in the formulation, resulting in increased permeability. Finally, variation in acetyl content of the CA-398-10 can also contribute to the film permeability with the lower acetyl levels giving increased permeability in formulations that also include a plasticizer. All of these factors should be considered when designing an osmotic drug delivery system for tablets coated with a mixture of these two cellulose acetates.

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BIOGRAPHIES

Dr. Jinghua Yuan is Principal Technical Service Representative at Eastman Chemical Company, responsible for pharmaceutical excipient products. Dr. Yuan has more than 20 years experience in formulation development and drug delivery systems. Prior to joining Eastman, Dr. Yuan worked as a Research Associate at Purdue University and University of Virginia. She earned her PhD from Tianjin University, China in 1989.

Doug Dunn joined Eastman Chemical Company in 2005 and has more than 25 years of laboratory experience, 18 of those in the pharmaceutical industry. Prior to joining Eastman, he worked as a Development Scientist for GlaxoSmithKline Pharmaceuticals in an R&D analytical laboratory. Mr. Dunn earned an Associate of Science degree in Chemical Technology from Northeast State Technical Institute, Tennessee in 1981.

Nancy Clipse is a Lab Analyst and has been with Eastman Chemical Company for more than 40 years. She has more than 20 years experience in formulation and drug delivery. Ms. Clipse attended East Tennessee State University in 1968 and 1982.

Dr. Ray Newton is retired and was the Group Leader of the Formulation Products Lab. His career at Eastman included a wide range of duties, including R&D, manufacturing technical support, manufacturing supervision, and new business development. Dr. Newton earned his BS in 1974 from Lee University and his PhD in 1978 in Organic Chemistry from the University of Tennessee, Knoxville.

FDA Regulatory Update: Top 10 Policy Development Issues for 2011 & What May Stand in the Way of Advancing Them

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

The FDA's Office of Combination Products (OCP) has for many years engaged on policy issues and how best to serve patient needs with respect to drug delivery and other combination product products in a thoughtful and patient-focused manner. However, it seems that in recent years, the significant increases in the OCP's workload have created a need for additional resources specifically devoted to supporting the OCP and combination product policy development, while at the same time preserving the OCP's other functions, including the informal dialogue in which the OCP engages with industry and the public. This discussion will summarize that resource quandary, and then will turn to highlighting the top 10 policy issues percolating in the drug delivery and combination product area.

Drug delivery and other combination products - products that involve the convergence of two or more different types of FDA-regulated articles (drugs, medical devices, and biological products) - represent promising advances in patient care. Patients suffering from serious diseases and conditions have already benefited from innovative drug delivery technologies, and many more are currently being researched and developed. Industry estimates reflect this growth and development.

In turn, as Agency data demonstrate, increases in the development and marketing of combination products have significantly impacted the OCP's workload, leading to more things like Requests for Designation, inter-agency consultations, and individual requests from industry for Agency meetings. The OCP has done a great job rising to the occasion, executing these regulatory responsibilities in a timely and thoughtful manner.

At the same time, though, in spite of the tremendous industry growth and consequent impact on the Agency, the resources the FDA has been able to devote to combination products has remained nearly static. Indeed, the first annual report of the OCP reported that the Office was staffed by 6 individuals, with one vacancy. At that time, the eventual projected staff was 10 individuals. Today, 7 years later, there is just 1 more staff member.

As a consequence of the growth in this field (and without corresponding growth in its staff), the OCP increasingly has had to focus primarily on its regulatory responsibilities, which the Office continues to perform timely and efficiently. Of late, policy-making has had to take a back seat. Although the OCP has initiated work on several guidance documents and other policy issues, many of these await the next step of publication, finalization, response to industry comments, and the like. We have considered what the most significant issues are and indentified the 10 most critical to drug delivery regulation.

(1) GOOD MANUFACTURING PRACTICES (GMPS) FOR COMBINATION PRODUCTS

We ranked this issue at the top of the list for several reasons. In September 2009, the OCP published a proposed rule on GMPs for combination products. As described in the March 2010 Combination Update in Drug Delivery Technology, many issues implicit in these rules impact drug delivery products and the entities that manufacture them. As such, drug delivery product developers and manufacturers are anxious to understand the final content of these rules. Recently, the Agency has publicly predicted that the proposed rules will not be finalized until the end of 2011. The Agency announced its intent to publish rules on combination product GMPs in early 2006; however, prior to the proposed rule published earlier this year, the only interpretation offered by the Agency was a draft guidance document issued in September 2004. Waiting until the end of 2011 continues to put a strain on manufacturers that need to move forward with new technologies to improve patient care, and the wait also leaves critical regulatory issues in a state of ambiguity and flux.

(2) POST-MARKET SAFETY REPORTING

As with GMPs, we understand the Agency is predicting the proposed rule on post-marketing safety reporting for combination products will not be finalized until the end of 2011. Although most developers and manufacturers probably would agree that the GMP regulations should have a higher level of priority, the post-market

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safety reporting requirements nevertheless are an important priority. Ideally, finalizing these rules also would be accomplished prior to the end of next year.

(3) IMPLEMENTING GUIDANCE DOCUMENTS ON COMBINATION PRODUCT GMPS & POST-MARKET SAFETY REPORTING

The Agency has acknowledged that implementing guidance will be critical to ensure a successful and timely implementation of both of the aforementioned proposed rules. Publishing these guidance documents, at least in draft form, prior to issuing the final rules would be extremely helpful to ensure stakeholders can comply with the final requirements within the effective date of the rules. These guidance documents will undoubtedly be complex and will require a fair amount of Agency manpower in order to issue them in a timely manner.

(4) REPORTING MANUFACTURING & DESIGN CHANGES TO MARKETING APPLICATIONS

The FDA has reported they have been working on a guidance document on this topic since 2006. This is an extremely complex issue that no doubt requires a significant amount of Agency resources, both from OCP and the Centers. It is also a topic on which industry has an acute need for guidance. In an industry survey conducted a few years ago, post-market modification issues were among the topics industry rated highest as needing Agency guidance. Along with the proposed rules on GMPs and adverse event reporting, rules or guidance on the reporting of design and manufacturing changes to marketing applications should be one of the highest ranking priorities in terms of combination product policy development.

(5) AUTOINJECTOR GUIDANCE

The Agency issued a draft guidance on Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products in April 2009. The September 2009 Combinaton Update in Drug Delivery Technology discussed and analyzed this draft guidance. As you may remember, industry had a number of concerns with this draft guidance. Partly in response to those comments, the OCP has explained in public forums that they are working on a second, companion autoinjector guidance that should clarify the numerous ambiguities in the draft guidance published nearly 2 years ago. Many members of the drug delivery technology industry are anxious to obtain clarification on the issues raised by the first guidance and with respect to autoinjector issues generally.

(6) NUMBER OF MARKETING SUBMISSIONS

The Agency published a Concept Paper on the number of marketing submissions required for a combination product in 2005. The Agency has not produced a guidance document or responses to the comments raised in the industry comments. Incidentally, we are also not aware that a docket was established for this issue, so the public is unable to access any comments submitted. Hopefully, the Agency will be able to make some progress on a guidance document or a Concept Paper revised in response to comments at some point this year.

(7) REGISTRATION & LISTING

Currently, there is no published guidance on registration and listing requirements for combination product manufacturers. We understand the OCP has been working on a draft guidance document for quite some time, and that registration and listing questions are among the most frequently asked of OCP.

(8) CLINICAL STUDY REQUIREMENTS

In recent times, drug delivery and other combination product developers also have ranked clinical trial requirements for combination products very highly among current guidance document needs. These clinical trial issues may include such topics as bioequivalence studies for autoinjectors, human factors as part of Phase III studies, patient numbers required to demonstrate device effectiveness, clinical trial designs for combination products, and number of clinical studies required for medical devices. The Agency has not issued guidance on these issues since the high level guidance on Early Development Considerations for Innovative Combination Products in September 2006.

(9) CHEMICAL ACTION

This is another topic on which we understand the Agency has been developing a guidance document for quite some time; however, the Agency has not yet published a draft for comment. Although it's difficult to offer a prediction without better understanding what the Agency has in mind, the content of this guidance could be fairly far-reaching across the combination product spectrum and could well impact drug delivery technologies.

(10) CONTRAST IMAGING AGENT

Finally, adding to all of these competing priorities is the recent debate and controversy surrounding the contrast agent and imaging guidance, which the OCP published in accordance with the Medical Device User Fee Amendments of 2007 (MDUFA) Commitment for the Performance Goals and Procedure. This particular guidance document directly impacts the drug delivery industry very little, if at all. However, participating in the discussion concerning this guidance could further consume resources within the OCP and could impact the timing of the drug delivery policy issues.

SUMMARY

At the time of this writing, the OCP was staffed with just 7 individuals. And as previously mentioned, in addition to these fundamental policy issues, the OCP has on its plate a number of day-to-day functions, such as reviewing and responding to Requests for Designation, consulting with other Agency personnel who are responsible for marketing submissions, and participating in industry meetings. Importantly, the OCP also engages regularly with members of industry to discuss questions concerning individual combination products.

With these significant issues on the horizon, the time is right for the FDA to review the Agency's prioritization of and resources allocated for combination product issues. The Agency needs to consider how it can support the advancement of combination product policy development without jeopardizing the OCP's other functions and the current level of informal discussions with the industry on individual product issues. At minimum, the OCP seems to need additional personnel devoted to the policy-making function and who are formally tasked with ensuring the advancement of regulatory policy concerning combination products.

These top 10 issues are at the heart of advancing drug delivery and other combination product policy development and regulation, as moving policy development forward will help provide the clarity and regulatory predictability that is needed to provide patients with safer and more effective healthcare. We eagerly await progress on these issues and hope the Agency finds a way to support them in the coming year. ◆

BIOGRAPHIES

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

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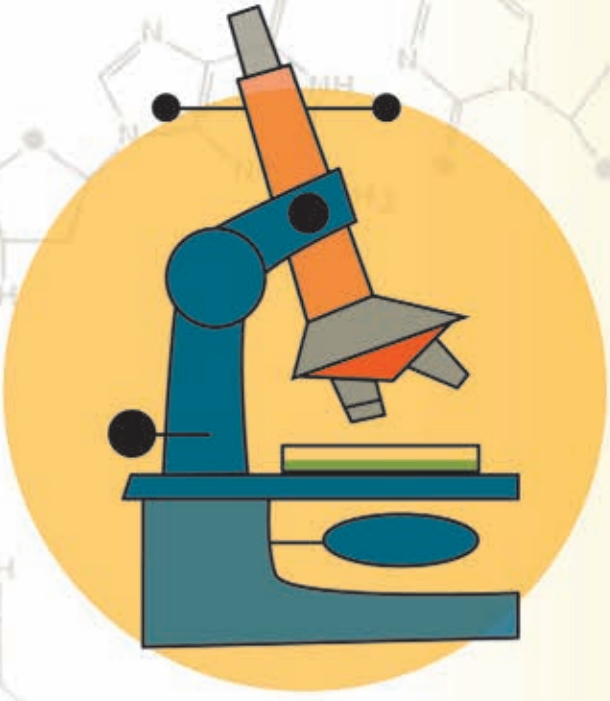

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Fast-Dispersing Dosage Forms for the Pediatric Market

By: Susan Banbury, PhD; Karen MacGregor, PhD

INTRODUCTION

Recent recognition and industry acceptance of the unique therapeutic needs of pediatric patients has led to regulatory activity and development programs that are re-defining this market segment. The result has been a push by developers and formulators emphasizing pediatric drug delivery–the creation of formulations engineered and packaged specifically for children to meet the needs of pediatric patient populations.[1] Several factors are driving the growth of the pediatric drug delivery as a business strategy. The pediatric sector is forecast to be one of the fastest growing drug markets throughout the next decade, according to Greystone Research Associates.[1] The growing availability of drugs targeted for childhood illnesses is focusing efforts on child-friendly delivery methods.

Throughout the past few years, the pharmaceutical industry has seen patent expiries for major blockbuster drugs, resulting in losses worth billions. More blockbuster drugs are about to lose patent protection in the coming years. In such a situation, pharmaceutical companies are increasingly adopting various drug delivery systems to enhance their product efficacy and patient compliance, and extend patent protection through innovative repositioning and reformulations of existing drugs. This has resulted in recent significant growth in the drug delivery market.

The oral drug delivery market, in particular, remains the largest segment of the overall drug delivery market, presently valued at $49 billion, and is expected to reach $92 billion by 2016.[2] Growth in the oral drug delivery market is being driven in part by innovative oral formulations like orally disintegrating tablets (ODTs) and fast-dissolving oral thin films (OTFs), which offer the stability, dose accuracy, and convenience of solid oral dosage forms with the dosing ease of a liquid to facilitate patient compliance, an important consideration in pediatric drug delivery.

COMPARING THE FAST-DISPERSING FAMILY

ODTs and OTFs have continued to expand in sales as the pharmaceutical industry addresses the need for patient compliance and convenience across a broad range of indications and patient types. ODTs gained early interest in the pharmaceutical community because they help overcome difficulties in swallowing or chewing conventional solid oral dosage forms.

Generally, an ODT is a solid dosage form that disintegrates rapidly in the mouth (either on or beneath the tongue or in the buccal cavity) without the need for chewing or drinking liquids. The 2008 FDA Guidelines on ODTs recommend a disintegration time of 30 seconds or less (*in vitro*) and maximum tablet weight of 500 mg. Recent market studies indicate that more than half of the patient population prefers ODTs to other dosage forms, such as conventional tablets or liquids, and according to Technology Catalysts International, a technology-transfer and business consulting firm based in Virginia, the market for ODTs could exceed revenues of $13 billion by 2015.[3]

ODTs may be categorized into two main groups: lyophilized formulations and loosely compressed tablets (Table 1). Loosely compressed ODTs are based on conventional tableting technology and achieve the rapid disintegration by varying degrees of compaction in combination with water-soluble excipients and/or super

FIGURE 1

Product utilizing loosely compressed technology

disintegrants (Figure 1). Lyophilized ODTs, on the other hand, exploit the highly porous structure that results from lyophilization processes to achieve the rapid disintegration (Figure 2). In the case of Catalent Pharma Solutions' Zydis® ODT, a lyophilized formulation, disintegration occurs in less than 5 seconds. A Zydis fast-dissolve can be formulated to incorporate up to 400 mg of insoluble drug and up to approximately 60 mg of soluble drug compared to approximately 500 mg drug for loosely compressed ODTs.

As an alternative, the OTF has evolved. OTFs consist of a thin polymeric film (50 to 150 microns thick) incorporating drug, which dissolves rapidly on the moist mucosal surface of the oral cavity or rapidly hydrates and adheres to the site of application. The films can be produced with a manufacturing process that is competitive with the manufacturing costs of conventional tablets. Film production may use industrially feasible and scalable solvent cast methods or hot-melt extrusion technologies, though the solvent cast method suffers the disadvantage of solvent residues within the film and environmental risks in the case of organic solvent.[4] In addition to manufacturing issues, OTFs are somewhat limited in the unit dose they can offer to patients, potentially making dosing more frequent or limiting the application of the technology. Nevertheless, according to Technology Catalysts, more than 15 companies are actively developing OTF delivery technologies, leading the research to forecast the market for drug products in OTF formulations to have reached $2 billion last year.[3] Examples of commercially available fast-dispersing dosage forms are seen in Table 2.

WHAT IS THE ZYDIS ODT?

In December 1996, Zydis fast-dissolve was the first ODT form of a drug to receive approval from the FDA and effectively defined this dosage form category. Catalent Pharma Solutions' Zydis technology involves the preparation of an aqueous solution or suspension, from which individual units are dosed into pre-formed blister pockets, cryogenically frozen, and lyophilized. The formulations are generally simple, typically incorporating two structure-forming agents with the API, in a ratio optimized for each product, plus any additives specifically required, such as flavors, sweeteners, or pH-modifying agents. The liquid-dosing process ensures excellent dose uniformity and facilitates containment of the active ingredient. The freezing process results in a network of ice crystals that are sublimed during lyophilization to produce the highly porous structure. This facilitates the penetration of moisture and quick dissolution of the Zydis excipients, resulting in the extremely rapid dispersion characteristics of the product.

Following dispersion in the mouth, the formulations are typically swallowed, and the drug is absorbed in the same way as conventional solid-oral dosage forms. In other applications, Zydis fast-dissolve products have been used to achieve buccal or sublingual absorption of certain pharmaceuticals. The ability to achieve such "pre-gastric" uptake is becoming increasingly desirable for drug developers seeking to enhance bioavailability or to avoid first-pass metabolism. The potential benefits of pre-gastric absorption may include reduced dose, less frequent dosing, faster onset of action, and reduction of adverse effects.

Taste and palatability are also important, particularly when dealing with pediatric patients and chronic conditions in which repeated administration is required. In the case of Zydis fast-dissolve, flavors and

FIGURE 2

Product utilizing Zydis® fast dissolve technology

TABLE 1

Feature	Zydis Fast-Dissolve Technology	Loosely Compressed
Dispersion Speed	~3 Seconds	15-60 Seconds
Mouthfeel	Smooth	Gritty
Dose Size	< 400 mg (Insoluble) < 60 mg (Soluble)	< 500 mg
Taste-Masking	Yes	Yes

TABLE 2

Fast-Dispersing Dosage Form	Technology Platform	Proprietary Technology	Technology Company	Examples of Commercial Products (API)
Orally Disintegrating Tablets	Lyophilized	Zydis®	Catalent Pharma Solutions	Claritin® Reditabs® (loratadine) Zyprexa® (olanzepine) Zofran® (ondansetron) Minirin® Melt (desmopressin)
		Lyoc	CIMA Labs	Lopéramide-Lyoc (loperamide) Paralyoc (acetaminaphen) Spasfon-Lyoc (phloroglucinol)
	Compressed Tablets	AdvaTab®	Eurand	Lamictal ODT® (lamotrigine) Unisom® SleepMelts® (diphenhydramine HCl)
		Orasolv®	CIMA Labs	Clarinex® Reditabs® (desloratidine) Orapred ODT® (prednisolone) Tempra® FirsTabs (acetaminophen)
		Durasolv®	CIMA Labs	Alavert® (loratidine) NuLev® (hyoscyamine)
		Flashtab®	Ethypharm	Nurofen® Meltlets (ibuprofen) Calpol™ Fast-Melts (acetaminophen)
		Frosta®	Akina	FortéCal™ (calcium carbonate)
Oral Thin Films		Dissolvable Film Technology	ARx	TheraFlu Thin Strips® (cough/cold ingredients) Triaminic Thin Strips® (cough/cold ingredients) Gas-X Thin Strips® Anti-gas (simethicone)
		Buccal Wafers	LTS Lohman Therapie-Systeme	Sudafed PE® (phenylephrine) Benadryl® Allergy (diphenhydramine) Listerine PocketPaks® (breath-freshening wafers) Listerine Whitening®
		Rapidly Dissolving Oral Film	KyuKyu	Amlodipine OD Film (amlodipine) Tomedain OD Film (loperamide)
		PharmFilm®	Monosol Rx	Zuplenz® (ondansetron HCl) Pedia-Lax® (sennosides) Chloraseptic® (benzocaine)

Source: Technology Catalysts International / Company Information[3]
Trademarks are the property of their respective owners.

Examples of Commercial Products Available as Fast-Dispersing Dosage Forms

sweeteners are typically used to optimize the taste of the finished product. Ion-exchange resins, such as amberlite, or microencapsulation polymers, such as celluloses, can also taste-mask particularly bitter drugs. In addition, a smooth mouthfeel contributes to product palatability. This is affected by the rate of dispersion and dissolution of the ODT matrix and particle size and content of insoluble components. Any insoluble components required in Zydis formulations are micronized, which, in combination with the fast dispersion and dissolution of excipients, typically results in a smooth "melt" sensation in the mouth.

ODTS & LARGE MOLECULES

In addition to conventional small molecules, the Zydis lyophilization process has also been shown to be suitable for the formulation of peptide and protein drug molecules. Protein and peptide molecules are physically and chemically sensitive, and lyophilization processes are typically used in their manufacture owing to the relatively low stresses applied during processing (eg, low temperatures).

Typically, protein- and peptide-based therapeutics have limited bioavailability when administered by conventional oral dosage forms. The molecules have low permeability and degrade rapidly in the gastrointestinal tract. Should next-generation drugs be predominantly protein or peptide based, tablets may no longer be the dominant form for dosing such moieties.[5] However, development of enhanced oral protein delivery technology using ODTs, with the potential to release these drugs in the oral cavity for transmucosal absorption, is very promising for the delivery of high molecular weight protein and peptides.

PACKAGING

Special packaging requirements are often necessary for ODTs because of their relative fragility. In the case of the Zydis ODT technology, the blister pack is an integral part of the product, forming the molds for the individual unit doses. The size, shape, and depth of the blister mold can be changed, depending on dose and weight requirements. Blister pockets can also be debossed with letters, numbers, or simple logos, which are then re-created on the base of the Zydis units for unique identification and brand differentiation.

Following freeze-drying, the blister packs are sealed, and the units are not removed until the point of administration, thereby providing physical protection throughout the manufacturing and distribution process. The use of all-aluminum blister packs also provides effective moisture protection throughout the product's life cycle and typically gives the Zydis units 3-year shelf-life stability.

The blister packs are also a small, convenient, and discrete packaging option for drugs taken as needed. Moreover, child-resistant features can be built into the blister design, to a range of access levels, thereby avoiding unintentional exposure.

PEDIATRIC ODT FORMULATIONS

The portability of ODTs and ease of administration to children make these a potentially valuable aid to children's health, and the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) described orally dispersing dosage forms as having "great promise for children."[6]

Tablet size and disintegration time are particularly important in this patient group. A fast disintegration time will reduce any potential choking hazard and will make it harder for less-motivated patients to spit out the dose. Taste and texture are clearly critical, and specific consideration needs to be given to the level of excipients, including flavors and sweeteners, if artificial ingredients are used or where there are established limits for children or lack of safety data in the required age group. For pediatric applications, formulations may need to be adapted to a wide range of doses to accommodate the potential age/weight variations, particularly at the lower end of the dose range and technologies, such as Zydis ODT, that offer low-dose accuracy are particularly beneficial. Ultimately, clinical trials in the pediatric age group are required to confirm acceptable safety and efficacy, but selection of an orally dispersing dosage form would help reduce the risk of long-term compliance problems.

ODT formulations are now available for several indications, including those applicable to the pediatric market, such as allergy, nausea, vomiting (including motion sickness), and nocturnal enuresis. In the treatment of nocturnal enuresis, the use of an ODT offers a specific advantage by enabling administration of the bedtime dose without water, thereby avoiding additional fluid intake, which would otherwise be counterproductive to the treatment.

In the treatment of nausea and vomiting, a study conducted by Pediatric Emergency Medicine, Hospital for Sick Children, University of Toronto, found that in children, ages 6 months to 10 years old, with gastroenteritis and dehydration, a single dose of oral ondansetron (administered as an ODT) reduced vomiting and facilitated oral rehydration, and may be well suited for use in the emergency department.[7]

SUMMARY

The tablet remains the most widely used method of drug delivery in medicine. Fast disintegrating tablets and thin films dissolve quickly in the mouth and do not need to be taken with water or fluid. This makes them particularly suitable for pediatric patients.

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BIOGRAPHIES

Dr. Susan Banbury is currently Project Manager within Zydis Product Development at Catalent Pharma Solutions, Swindon, UK. She is a graduate of pharmacy from the University of Bath, UK, and earned her PhD from the University of Nottingham, UK, where she studied the mechanisms of intranasal peptide and protein delivery. Dr. Banbury began her industrial career in formulation development with Cyanamid GB Ltd (subsequently Wyeth, now part of Pfizer) in 1991, supporting a range of new product developments, including topical, powder, and encapsulation technologies. Dr. Banbury joined R.P.Scherer in 1995, leading the development of soft gelatin capsule formulations, from feasibility studies through to technology transfer with international project teams. She subsequently transferred to the Zydis ODT development group as formulation manager with particular focus on initial product feasibility and supported the development of several, now commercial products. Dr. Banbury has co-authored several articles on ODT formulations, and, in her current role, provides technical support to the Catalent Business Development team, including the evaluation of physico-chemical data to identify potential candidates for the Zydis technology, in addition to R&D project management.

Dr. Karen MacGregor, as a pharmacist with a PhD in topical cytotoxic drug delivery, has more than 17 years experience in the pharmaceutical industry with the past 10 years being in outsourcing pharma services and a provider of innovative solutions to the industry. Dr. MacGregor has had functional and leadership roles in Rhone Poulenc Rorer, Aventis, CCL Pharmaceuticals, and Cardinal Health, involved in oral, topical, and inhalation dosage forms. Throughout this time, Dr. MacGregor has led technical teams both in the areas of formulation and process development and in operational technical support. Working for Catalent Pharma Solutions for more than 7 years, as Director Product Development, she is responsible for leading multifunctional teams in the development of new and existing ODT products.

NUCLEIC ACID DELIVERY

Tackling the Challenge of Nucleic Acid Delivery: Progress & New Approaches

By: James J. Cunningham, PhD; Louis S. Crocker, PhD; Anthony Leone, PhD

INTRODUCTION

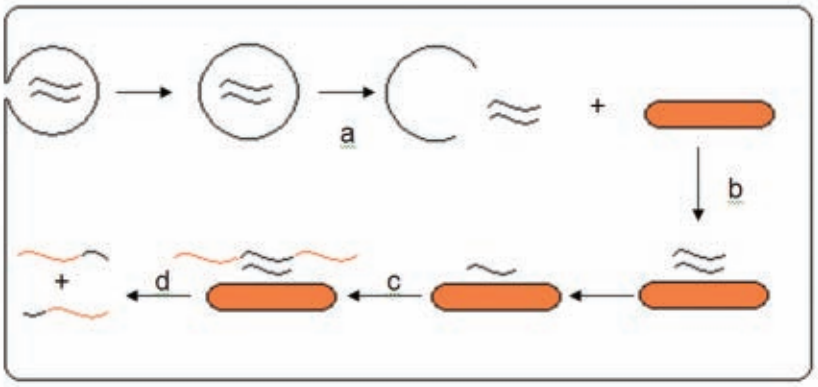
It is broadly accepted that nucleic acid delivery, particularly targeted intracellular delivery following systemic administration, remains one of the most difficult challenges facing pharmaceutical scientists today. Nucleic acids are large, hydrophilic, charged molecules, and as such, are not easily transported across the cell membrane. Add to this the poor stability of unmodified nucleic acids in circulation, and the desire to direct delivery to specific cell types in specific tissues, and the complexity multiplies. Efforts to achieve such delivery have enjoyed a resurgence of interest following the discovery of RNA interference (RNAi) in mammalian cells, which has the potential to revolutionize drug discovery and development and provide an entirely new therapeutic modality.[1,2] Despite the significant challenges facing this endeavor, major progress has been made throughout the past several years, and the following aims to highlight some of the most promising approaches.

NUCLEIC ACID THERAPEUTICS & MODALITIES

Therapeutic interest in nucleic acid delivery now spans many decades, dating back to the advent of gene therapy, as investigators began to explore viruses, calcium phosphate, and other methods to deliver DNA to restore missing or deficient gene function.[3] The field continued to expand with the discovery that short, single-stranded synthetic oligonucleotides could inhibit gene expression by hybridizing with the target mRNA, creating new opportunities for antisense therapeutics that lead to the approval of Fomivirsen (Vitravene, ISIS) by the FDA in 1998.[4,5] Selective oligonucleotide design created further opportunities with the discovery of aptamers, oligonucleotides with the ability to bind to target molecules with high specificity.[6,7] Pegaptanib (Macugen, Gilead/OSI/Pfizer), a PEGylated aptamer, was approved by the FDA for treatment of AMD in 2004. DNA vaccines, involving the delivery of plasmid DNA to express antigens, comprise another area of active investigation.[8]

In specific circumstances, such as local delivery, where direct administration to the site of action is feasible and a localized effect is desired, nucleic acids can be successfully delivered naked, without a delivery vector.[9] Ocular delivery is perhaps the best example of this: Fomivirsen and Pegaptanib are both delivered via intraocular injection, and numerous siRNA therapeutics have been evaluated preclinically and clinically for indications such as age-related macular degeneration, choroidal

FIGURE 1



A representation of the mechanism of RNA interference. (a) Endocytosis and endosomal escape are thought to be critical steps in the introduction of siRNA to the cytosol. (b) Combination of either naturally occurring or synthetically introduced siRNA with enzymes forms the RISC (RNA Induced Silencin Complex). (c) RISC binds to complementary mRNA in the cytosol, resulting in its destruction (d).

neovascularization, and diabetic macular edema.[10,11] Other examples of local siRNA delivery include direct administration to brain, respiratory system, and tumor.[12,13] A major concern of systemic administration of nucleic acids is their instability in circulation, unprotected by a delivery system.[14] Liver delivery via IV administration has been demonstrated in rodents using the technique known as hydrodynamic injection; however, applicability of this approach would appear to be limited to the laboratory.[15] Successful systemic delivery typically requires a specialized delivery vector, and such vectors can generally be classified as viral or non-viral. As viruses have evolved specialized mechanisms to efficiently deliver their genetic material to target cells, they can be highly effective vectors. Adenoviruses, adeno-associated viruses, and retroviruses have all been successfully employed to deliver nucleic acids.[16] Their clinical utility has, however, been limited due to safety concerns, including disruption of cellular DNA upon viral gene insertion, mutations that restore replication competence, and immune stimulation. As a result, in recent years, much effort has focused on non-viral delivery vectors, including lipid-based, polymeric, and other delivery approaches. The remainder of this article will focus on the application of these tools to systemic administration of siRNA therapeutics.

SIRNA MECHANISM & UTILITY

RNA interference (RNAi) is a highly conserved cellular mechanism for regulating gene expression. RNAi utilizes small interfering RNA (siRNA), which are short (approximately 21 base pairs) double-stranded RNA molecules, to induce specific degradation of messenger RNA (mRNA). siRNAs are produced via the Dicer pathway, or are introduced therapeutically into the cell. Once in the cytosol, an siRNA molecule interacts with Argonaute and other proteins to form the RNA-induced silencing complex (RISC), and the complex then catalytically cleaves the complementary mRNA.

FIGURE 2

Barriers to Effective Gene Delivery

Therefore, the RISC complex with siRNA provides a way to regulate the synthesis of a single protein in a cell. The goal of therapeutic RNAi is to regulate gene expression by means of delivery of specific synthetic siRNA to the cytosol. A schematic of the mechanism of RNAi is shown in Figure 1.

BARRIERS TO EFFECTIVE SIRNA DELIVERY

To achieve safe passage of siRNAs to the cytosol of target cells, multiple hurdles must be overcome.[17] These challenges are summarized in Figure 2. Interaction of the siRNA or delivery vehicle with whole blood components can result in inflammatory responses, such as cytokine elevation or complement activation. These responses can serve both to alter the biodistribution of the siRNA and result in dose-limiting toxicity. Interaction with other whole blood components, such as fibrinogen, transferrin, lipoproteins, or nucleases, can also affect potency by manipulation of the delivery vehicle and/or components. These interactions and alterations may heavily influence biodistribution or degrade the delivery vehicle (eg, nuclease activity). Chemical modifications of oligonucleotides, such as 2' O-methylation, can be effective at dampening immune stimulation as well as reducing kinetics of nuclease activity. If efficient and specific distribution of the siRNA to the therapeutic tissue is achieved, successful uptake is typically accomplished through an endocytosis mechanism. Reliance on this cellular trafficking mechanism for uptake requires efficient escape from the endosome and unpackaging of the cargo for presentation to the RNA-silencing complex (RISC) in the cytosol.

LIPID-BASED SIRNA DELIVERY SYSTEMS

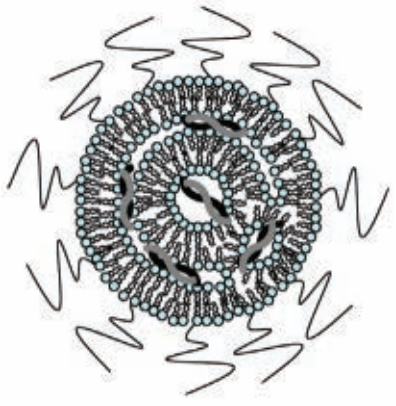
Lipofection with cationic lipids has been in common use for many years to transfect cells in vitro. Cationic lipid-based systems were later developed for plasmid DNA delivery in vivo and have since been adapted to siRNA delivery, making them the most mature of the non-viral technologies currently used for systemic in vivo nucleic acid delivery.[18,19] The SNALP technology developed by Tekmira (formerly Protiva) demonstrated robust silencing of ApoB mRNA in non-human primates and has since been evaluated in three clinical trials (ApoB SNALP, ALN-VSP, ALN-TTR01).[20] Another lipid nanoparticle technology, the AtuPlex platform from Silence Therapeutics, is also currently in clinical development for solid tumors, and the lipid nanoparticle approach is used in much of our work at

Merck/Sirna.[21]

Cationic lipid nanoparticles (LNPs), such as liposomes, form a complex with nucleic acids, often termed a lipoplex.[22] Although these are often depicted in the context of classical liposomes, with nucleic acid encapsulated in the aqueous core of the liposome, lipoplexes tend to form more complex, though still ordered, structures (Figure 3).[23] In addition to the nucleic acid cargo, these systems typically contain a cationic lipid, neutral helper lipids, cholesterol, and a PEGylated lipid. The cationic lipid drives encapsulation of anionic nucleic acids and is hypothesized to interact with anionic lipids in the cell membrane or endosome to promote cell association and endosomal escape. Helper lipids, such as phospholipids, can be selected for bilayer-forming or fusogenic properties, and cholesterol modulates the fluidity and phase behavior of the lipid phase.[24-26] It is hypothesized that upon mixing of the LNP lipids with lipids of the endosomal membrane, a phase change from lamellar to inverted hexagonal occurs, driving disruption of the endosome and escape of the siRNA.[27] The inclusion of a low molar percentage of a PEGylated lipid sterically stabilizes lipid nanoparticles by inhibiting intra-particle aggregation and interactions with plasma proteins.[28,29]

Many of the cationic lipids typically used in lipoplex formations, such as DOTAP and DOTMA, contain quaternary amines, and positive lipoplex surface charge has been implicated in mechanisms of toxicity, such as complement activation.[18,30] Significant medicinal chemistry efforts have since been invested to address this issue and improve the in vivo tolerability of vectors containing cationic lipids.[31] One successful approach involved replacing the quaternary amines with titratable amines, and tailoring the lipid pKa such that the lipid is uncharged at physiologic pH, but protonated at acidic endosomal pH.[32] Further optimization of lipid alkyl groups, linker, and headgroup, as well as lipoplex formulation, have been reported to further improve potency and therapeutic margin.[33] In another approach, a library of "lipidoids" was synthesized via conjugation of alkyl acrylates or alkyl acrylamides to amines, formulated in LNPs, and screened in multiple models to identify potent and well-tolerated molecules.[34,35] There are numerous reports in the literature of lipid-based siRNA delivery systems that do not include a cationic lipid component, but instead rely solely on fusogenic neutral lipids.[36,37] Although intriguing based on the potential for improved tolerability, efficient siRNA encapsulation could be a challenge without siRNA modification, and none of these systems have advanced to clinical testing.

FIGURE 3



Schematic of a lipoplex.

POLYMERIC SIRNA DELIVERY SYSTEMS

Polymer-based delivery can broadly be divided into two major approaches: 1) polyplex particle delivery and 2) polymer conjugate macromolecular delivery.[17,38] There are merits and disadvantages to both approaches, as well as some unsolved challenges that remain common to both. These will be addressed briefly in the ensuing section.

Polyplex delivery exploits the highly efficient condensation characteristics of polyamines for encapsulating polyanionic oligonucleotides. Mixtures of the two macromolecules at controlled amine-to-phosphate ratios result in self-assembly of spherical particles approximately 100 nm in diameter. This encapsulation provides safe passage of the oligonucleotide from nucleases in circulation. Systemic administration of these particles results in very rapid and efficient tissue uptake by lung, liver, spleen, and kidney. Polyethyleneimine (PEI) and Poly-L-Lysine (PLL) are the most widely studied polymeric systems, with the former representing a benchmark for the field. Recent advances in development of dendritics, biocompatible, and biodegradable polymers have offered substantial promise. The greatest limitation to this approach is improving transfection efficiency. Endosomal escape and efficient release of the oligonucleotide cargo from the polyplex into the cytosolic compartment of action is widely viewed as a limiting factor.[39,40] This inefficiency of delivery demands relatively high polymer doses to achieve efficacy and translates to increased toxicity. Additional challenges include the ability to definitively reproduce and characterize the complex polymer raw material as well as polydisperse polyplexes. Additional challenges associated with polyplex delivery include potential for complement activation and tissue access limited to tissues with irregular fenestration.

Conjugation of oligonucleotides to polymers results in macromolecules presenting a unique opportunity to engineer functionality, such as fusogenicity, tissue targeting, and pH-dependent endosomolytic properties.[38,41,42] This approach is less likely to impart immunogenic properties to the delivery vehicle than peptide- or particle-based approaches, and is less dependent on high cationic character, a property that is typically cytotoxic or results in substantial interaction with blood components.

OTHER SIRNA DELIVERY SYSTEMS

In addition to lipid-based and polymer-based delivery, other methods have been reported, which include complexes of oligonucleotides, conjugates of oligonucleotides, and inorganic delivery vehicles. Representative examples of these delivery methods are described further; a review containing references to the various delivery methodologies has been published.[43]

COMPLEXES

One class of polymer-based delivery vehicle (described previously) relies upon electrostatic complexation of RNA to the cationic polymer. Cationic peptides may be complexed to the negatively charged siRNA in a similar way and may be chosen to provide targeting or cell-penetrating characteristics to the complex. In one report, a peptide derived from rabies virus that targets neurons was bound to polyarginine, complexed to siRNA through electrostatic interaction with the protonated polyarginine, and penetrated the blood-brain barrier.[44] Another complex is the cyclodextrin-decorated polymer described by Hu-Lieskovan et al.[45] In this work, both siRNA and a targeting ligand (transferrin) are complexed to the functionalized polycation. Successful systemic administration of siRNA in mice was observed when the targeting ligand was incorporated into the formulation. The characteristics and utility of the formulation, including evaluation in a Phase I clinical study, have been reviewed by Davis et al.[46,47]

The use of atelocollagen complexes to provide localized delivery has been reported.[48] Atelocollagen is a modified and highly purified protein derived from collagen, a fibrous protein found in connective tissue. Atelocollegen was used to form complexes with siRNA and used in both in vitro and in vivo experiments. The complexes of atelocollagen may be formed as nanoparticles intended for systemic delivery, or may be injected locally to form a solid mass that serves as a depot, delivering siRNA over time.

CONJUGATES

Conjugates of siRNA are RNA to which are attached, through covalent bonds, other molecules. These molecules are selected to confer upon the conjugate characteristics, such as the ability to target a particular receptor, protect the siRNA from degradation, or provide a particular reactivity or characteristic, such as provided by a cell-penetrating peptide, a hydrophobic molecule, or a polycation, any of which could be expected to help surmount a particular barrier to siRNA delivery. Conjugates differ from complexes in that relatively stable covalent bonds attach the siRNA to the supplementary structure, although that distinction is blurred to some extent by conjugates that are made deliberately susceptible to cleavage by certain conditions, such as acidic or reducing conditions. A conjugate between siRNA and cholesterol was shown to suppress gene expression, and subsequently other efficacious conjugates with lipophilic molecules were identified.[43,49] A review of numerous other conjugates, including those with peptides and bioactive molecules, has been published.[45]

INORGANIC DELIVERY VEHICLES

Certain inorganic materials can be used to deliver siRNA in vitro. Layered double hydroxides, which are in a class of inorganic clays that includes the natural mineral hydrotalcite [$Mg_6Al_2(OH)_{16}CO_3 \cdot 4H_2O$], form nanometer-sized crystals that can incorporate siRNA into their structure.[50] These minerals have been shown to be useful for in vitro delivery of siRNA as well as DNA. Furthermore, the shape and size of the particles have been hypothesized to direct intracellular trafficking of the payload nucleic acid. Quantum dots are semiconductor crystals of nanometer size. When decorated with targeting ligands and conjugated to RNA, they have been shown to be useful as siRNA delivery vehicles in vitro.[51] Other species, including carbon nanotubes, have been identified as novel delivery vehicles as well.[52,53]

KEY CHALLENGES & FUTURE DIRECTIONS

Key challenges facing the field are improving potency while attenuating toxicity, and accurately characterizing delivery vehicles to enable effective mechanistic studies that conclusively establish structure-activity relationships. Taking lessons from highly evolved viruses that are exquisitely efficient at cargo delivery has resulted in intense research around pH-responsive systems in which the differential pH properties of the endosome are exploited to accelerate delivery vehicle degradation, metabolism, and/or facilitate endosomal escape. Efforts to address these key challenges promise to expand the opportunities for clinical application of RNAi, and potentially enable an entirely new therapeutic modality to address a wide range of currently unmet medical needs.

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BIOGRAPHIES

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The Use of Surface-Modified Nanoparticles to Facilitate the Processing of Oral Solid Dosage Forms

By: Joseph Beaurline; John Hedenstrom, PhD; Jacqui Ganser, MS; Jimmie Baran, PhD; and Fred LaPlant, PhD

INTRODUCTION

Surface-modified silica nanoparticles (SMNs) are a non-aggregated form of colloidal silicon dioxide (CSD) that have been found to enhance physical attributes associated with the processing of powder blend formulations used for making oral solid dosage forms (OSDFs). The core material, amorphous silica, has been a standard for processing pharmaceutical powder blends to manufacture OSDFs. The SMNs can be dry-blended and readily distributed, transferring from particle to particle during mixing with minimal energy. Counter to typical flow modifiers, these materials can simultaneously enhance flow ability and increase tap/bulk density by as much as 50% in blends and raw materials. Improvements have been seen in many pharmaceutical operations, including but not limited to stability on storage, powder transfer operations, solids blending, tableting, capsule fill, and cleaning. Other excipients have been used in attempts to address these processing challenges, yet rarely are multiple benefits simultaneously seen (eg, the typical trade-off of increased flowability at the expense of increased bulk density). As a result, a reduction of processing steps, reduced capital equipment costs, increased rate of tablet/capsule production due to increased tablet flow, and a reduction in unit weight variability will reduce manufacturing costs.[1] The ease of mixing and more uniform response of materials using SMNs is also anticipated to improve process robustness.

CHARACTERIZATION OF MODEL APIS & SMNS

The initial objective of this work was to investigate and characterize how surface SMNs affect the physical attributes of a typical pharmaceutical blend, both with and without the presence of a model active pharmaceutical ingredient (API). The blends were then used to demonstrate the improved physical processing attributes due to the SMNs. Acetaminophen (APAP) was chosen for specific reasons: first, its poor flow properties are well documented and lead to many difficult manufacturing issues for both tablet and capsule formulation; second, it is present in relatively high proportion in a typical OSDF and; third, because it is still a commercially important pharmaceutical product in today's marketplace. This work has been replicated with similar results using ibuprofen as the API, but due to space limitations, those results are not presented here. The effects described herein are not due to the chemical composition of the nanoparticles themselves. Similar effects have been shown using metal oxide nanoparticles, metal nanoparticles, phosphate-based nanoparticles, and the like. For comparison purposes to CSD, the most commonly used flow aid in the industry, amorphous surface modified silica nanoparticles, were used in the studies below.

THERMOGRAVIMETRIC ANALYSIS (TGA) OF SMNS

The binding strength of the surface modification to the nanoparticle core is an important factor in estimating the stability of the SMNs. Thermogravimetric analysis (TGA) was performed on SMNs to obtain sample weight loss versus time and temperature. The powder sample was run on the TGA with the following parameters: equilibrate at 30°C, ramp at 10°C/min to 105°C, isothermal at 105°C for 10 minutes and ramp at 10°C/min to 700°C. The weight loss pattern shows negligible losses until temperatures greater than 400°C are reached. This indicates the ligands are strongly attached to the core particle.

DETERMINING DEGREE OF CRYSTALLINITY OF APAP & SMNS BY X-RAY DIFFRACTION (XRD)

XRD of APAP was performed to evaluate the form and degree of crystallinity of the APAP in comparison to established reference patterns. Different

crystalline forms of APAP and forms with incomplete crystallinity are known to perform differently in processes when making OSDFs.[2] XRD of SMNs was performed to confirm the amorphous form of the nanoparticle raw material core is not altered by the surface modification chemistry.

Sample Preparation

Samples were tested after gently milling to reduce the size of clumps present in the "as received" powder. Samples were placed on glass inserts as dry powders.

Data Collection

Reflection geometry data were collected in the form of a survey scan by use of a Bruker D8 Advance diffractometer (Bruker AXS, Madison WI), copper K radiation, and Vantec detector registry of the scattered radiation. The diffractometer is fitted with variable incident beam slits and fixed diffracted beam slits. The survey scan was conducted using a coupled continuous mode from 5° to 55° (2θ) using a 0.015° step size and 6-second dwell time. X-ray generator settings of 40 kV and 40 mA were employed.

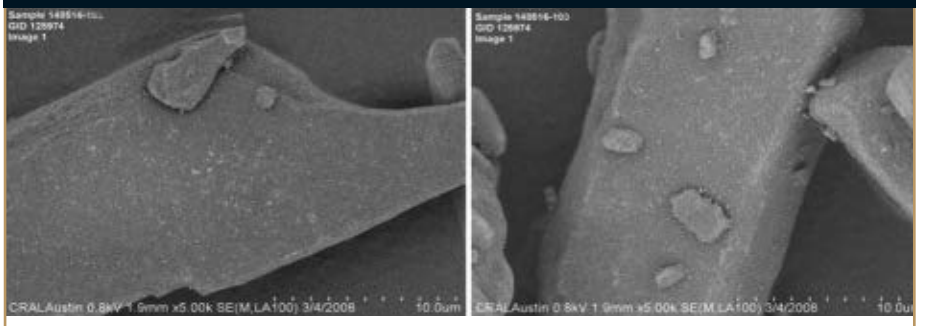
The powder XRD patterns of the APAP show it to be highly crystalline and in conformance to reported reference patterns, with peak intensity differences attributed to preferred orientation effects. The powder XRD pattern of the SMNs indicates a noncrystalline amorphous form.

ANALYTICAL CHARACTERIZATION OF POWDER BLENDS CONTAINING SURFACE MODIFIED SILICA NANOPARTICLE & ACETAMINOPHEN

Scanning Electron Microscopy (SEM)

SEM images of the SMNs blended with APAP can give some indication of the resulting distribution and a measure of the ability to dry blend SMNs. Changes in distribution of SMNs on the APAP surfaces with changing SMNs concentration can also be evaluated. APAP was dry blended with the SMNs at two concentrations of SMNs (0.25%, 0.5%). Mixing was done with a planetary mixer (1 min at 60 rpm/sieve mixture through 60 mesh screen/mix again for 1 min at 60 rpm). Samples were prepared for imaging by sprinkling/dusting on carbon paint applied to the sample holder (aluminum disc). The instrument used was a Hitachi S-4800 UHR Field Emission SEM. The untreated

FIGURE 1A&B



SMNs - 0.25% & 0.5% on Acetaminophen (5K zoomed image)

APAP crystals were imaged and are essentially smooth and featureless, showing none of the fine particle matter observed for the SMN-treated material. The SMNs in Figures 1 and 2 are clearly present and appear to be uniformly dispersed over the surface of APAP following dry blending, without any preferential localized deposition on edges, cavities, crevices, etc. There appears to be a mixture of primary and aggregated nanoparticles. Increasing the concentration of SMNs from 0.25% to 0.5% appears to proportionately increase the coverage of SMNs over the surface of APAP in a uniform fashion.

Differential Scanning Calorimetry (DSC)

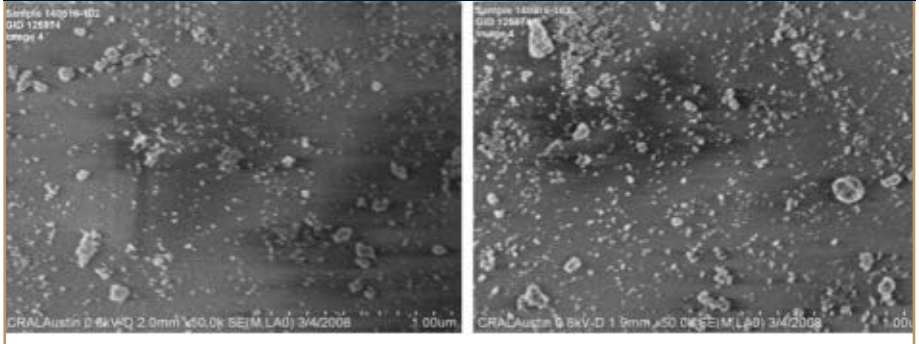
DSC of APAP/SMNs blends could give an indication of possible interaction between the APAP and SMNs such as degradation reactions. APAP was dry blended with SMNs at concentrations of 0.25% and 1%, and the blends were analyzed by DSC. Mixing was done with a planetary mixer (1 min at 60 rpm/sieve mixture through 60 mesh screen/mix again for 1 min at 60 rpm). Pure APAP and SMNs were also measured, respectively. Approximately 3 mg of each sample were heated from 20°C to 250°C at a rate of 10°C/min on a TA Q1000 (TA Instruments, New Castle, DE). Sample pans were weighed before and after thermal analysis to confirm that no change in weight occurred. Results are summarized in Table 1. The concentration of SMNs on the surface of APAP has no significant effect on the duration of the melt event with 0.25% and 1% loadings yielding traces virtually identical to those of the native APAP. The melt onset and maximum temperatures and enthalpies were also not appreciably changed upon addition of SMNs.

POWDER FLOW & DENSITY ENHANCEMENT

The APAP/SMN blends and the APAP/CSD (Aerosil 200, Evonik/DeGussa Corp., Parsippany, NJ) blends were added to a 4-quart planetary mixing bowl in separate experiments; each was blended for 3 minutes at 60 rpm. The blend was passed though a 60-mesh screen and returned to the mixer and blended for an additional 2 minutes at 60 rpm.

Powder flow and bulk density measurements were performed on blends of APAP with varying concentrations of SMNs and CSD as a comparator on a model PTGS-3 Flow Tester (Pharma Test, Hainburg, Germany) instrument. Five measurements were made for each blend and used to determine an average flow rate. Bars are used

FIGURE 2A&B



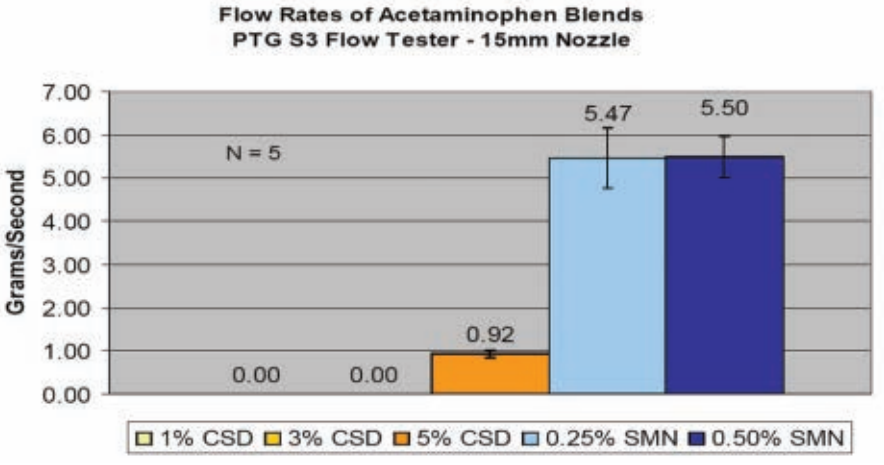
SMNs - 0.25% & 0.5% on Acetaminophen (50K zoomed image)

TABLE 1

Sample	T_{Melt} (°C)	T_{Peak} (°C)	Enthalpy (J/g)
APAP	168.75	169.87	184.2
APAP 1% SMNs	168.39	170.51	187.9
APAP 0.25% SMNs	168.42	169.43	187.9
SMNs	No Events Observed		

Summary of DSC Data on APAP & APAP with 1% and 0.25% SMNs Loadings

FIGURE 3



Comparison of Flow Rates of APAP Using Various Flow Modifiers

TABLE 2

	Compression Force @ 40RPM			Machine Speed @ 100N CF		
Formulation	50 N	100N	150 N	40RPM	60 RPM	70 RPM
Formulation A – 0.25% SMN's	75N	150N	250N	150N	125N	75N
Formulation B – 0.08% SMN's	100N	150N	300N	150N	125N	100N
Formulation C – 0.5% CSD	250N	400N	500N	400N	450N	450N

Effect of Capsule Fill Parameters on Ejection Force

TABLE 3

	50 N			100 N			150 N		
Formulation	Wt av	Std dev	% RSD	Wt av	Std dev	% RSD	Wt av	Std dev	% RSD
A- APAP/0.25% SMNs	442	17.4	3.9	429	14.9	3.5	461	12.5	2.7
B- APAP/0.08% SMNs	418	25.6	6.1	436	16.6	3.8	447	15.1	3.4
C- APAP/0.5% CSD	405	8.7	2.1	415	17.6	4.2	412	17.0	4.1

Effect of Compression Force on Fill Weight Using a 40-mm Powder Bed Height and a Constant 40 rpm Machine Speed

to indicate the range of flow rates. Cone angle and cone density were also measured.

The flow rates were measured on the PTGS-3 using a 15-mm nozzle and a stir speed of 25 rpm.

As seen in Figure 3, the flow rate for the APAP/SMNs blends is increased by more than five-fold over the APAP/5% CSD blend; no flow occurs at the lower levels of CSD blends (1% and 3%). Cone angle and density were also measured; for the APAP/SMNs blend the cone angle is about 10% less than the APAP/5% CSD blend, while the cone density for the APAP/SMNs is more than twice that the APAP/5% CSD. This demonstrates that incorporation of a 0.25% or a 0.5% loading of SMNs in a powder blend with APAP significantly increases the bulk density and could increase the flow rate five times or more than a similarly prepared blend with 5% CSD.

The tapped density was determined by loading 100 g of sample sieved through a 60-mesh screen into a 250-mL graduated cylinder. The graduated cylinder was raised 14 mm and dropped 200 times. The tapped density was determined by dividing the mass by the volume occupied by the powder in the graduated cylinder. The results of the tapped density experiment for blends of APAP and SMNs or CSD are shown in Figure 4.

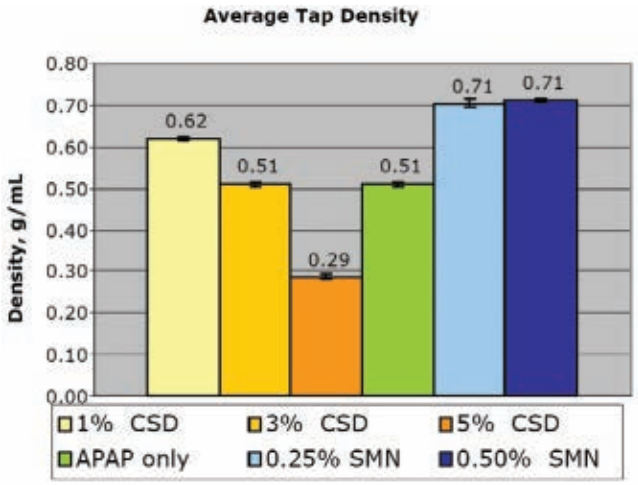
It should be noted that although the 1% and 3% CSD/APAP blends have tap densities approaching the APAP/SMN blends, the APAP/CSD blends would not flow through the 15-mm nozzle on the PTGS-3 flow apparatus.

Higher powder density is a strongly favorable parameter during processing because it can lead to higher fill levels in capsules, better tablet compaction, quicker fill times, lower flocculation, etc. However, flow enhancers typically decrease particle-particle interactions by decreasing the packing efficiency of the matrix, so that improved flow can only be achieved at the cost of powder density, and vice versa. Increasing flow and density simultaneously is therefore a fundamental advance in the capability to tune powder flow characteristics.

CAPSULE-FILLING TRIALS

A capsule-filling trial was performed at the University of Maryland, School of Pharmacy using a Harro Hoffliger-KFM/3 machine (Harro Hoffliger Packaging Systems, Doylestown, PA) and size 1 hard gelatin capsules (Capsugel, Peapack, NJ). The encapsulation machine employs a dosator disc to transfer an amount of formulation from the

FIGURE 4



Comparison of Tapped Densities of APAP/SMNs or CSD Blends

cavity to the body of the hard gelatin capsule. To study the effect of compression force (CF) on fill weight and ejection force, the machine was run at three compression forces (50, 100, and 150 N) at 40 rpm.

To study the effect of machine speed on fill weight and ejection force, the machine was run at three machine speeds (40, 60, and 70 rpm) at 100-N compression force. The fine powder APAP (Spectrum Chem.) was blended with SMNs at two levels, 0.08% and 0.25% and with CSD at 0.5%. The flow and density properties of the APAP alone did not make the encapsulation process viable without blending with SMNs or CSD. Although a capsule formulation will typically contain other components to ensure adequate plug formation and minimize plug ejection forces, this study was intended to evaluate the filling characteristics of this binary mixture in typical capsule filling equipment and to determine if the SMNs are capable of imparting favorable characteristics to this process. The effects of compression force and machine speed on the plug ejection force are shown in Table 2.

Compression force studies showed a significant decrease in ejection force values by incorporating SMNs instead of CSD in all cases. Best performance was observed with Formulation A with 0.25% SMN loading at each compression force and machine speed, although the improvement over Formulation B with three times less SMN loading was not substantial. The limiting concentration of SMNs required to optimize the flow effect will no doubt depend on morphology and particle size of the bulk materials, and rigorous prediction of this effect is beyond the scope of this paper. A particularly interesting result was that Formulations A and B exhibited reduced ejection forces even as machine speed increased.

Fill weight was measured from capsules made at a bed height of 40 mm and a machine speed of 40 rpm. The results are shown below in Table 3. Formulations A and B stand out as having a higher average fill weight with progressively lower % RSD with increasing compression force at a fraction of the concentration compared to Formulation C.

DIRECT-COMPRESSION TABLETING TRIALS

The objective of this study was to assess the compaction behavior of APAP formulations by measuring breaking strength and weight variation. A non-optimized direct compression formulation containing APAP powder, a binder, disintegrant, lubricant, and SMNs for process enhancements was prepared for these trials. The SMN concentration chosen for these tests was 1% w/w with respect to the formulation. This is higher than the levels used previously to show density and flow characteristics because the purpose of this study was to indicate whether the presence of the SMNs would have a deleterious effect on the properties of the tablets produced. Presumably lower concentrations of SMNs would have no more pronounced effects on the tablet performance. The formulation was prepared by adding 1% by wt SMNs to the APAP and mixing for 5 minutes on a planetary mixer. The remainder of the excipients, except the lubricant, were added to the dry blend and mixed for 10 minutes on a planetary mixer. The lubricant was added as a pre-mix to the formulation and mixed for 3 minutes on the planetary mixer. A similar formulation using 1% (w/w to the formulation) CSD was prepared for comparison. When CSD was used in place of SMNs, a tablet could not be made because the mixture had insufficient flow to fill the die. The samples were compressed on a 16 station Manesty Beta Press (Thomas Eng.) running at three speeds (40, 50, and 60 rpm); for these studies, all 16 punch and die sets were used. The fill weight settings were not changed as the speed of the press was adjusted in order to show the nature of the flow properties. The tooling type (Natoli Eng. Co., St. Charles, MO) is described as 5/16" standard concave with tapered dies. Tablet breaking strength was measured using a KEY HT-300 hardness tester (Englishtown, NJ). For this study, 25 tablets were compressed and tested for hardness at each speed. Unfortunately, the transducer used to measure compressional force was not operable at the time of this trial. The tableting results for a non-optimized direct compression formulation of APAP are shown in Table 4.

Based on the tablet trial results, it can be concluded that the tablets exhibited acceptable hardness. The weight variation also met USP standards for content variation (USP 32-NF 27, <905> Uniformity of Dosage Units, pp. 382). Note that for high dose drugs, the USP states that content uniformity can be measured by weight variation. APAP content uniformity was measured at 147.4 mg ± 1.9 (1.3%), or 62.7% ± 1.1 (1.7%) of the formulation using a drug content assay method similar to the USP monograph for APAP tablets.

CONCLUSION

These experiments have proven that surface-modified nanoparticles enhance powder processing as characterized by improved flow and increased bulk/tapped

TABLE 4

Material	Stat	Wt (mg) (RPM 60)	Hardness (kp) (60 RPM)	Wt (mg) (RPM 50)	Hardness (kp) (50 RPM)	Wt (mg) (RPM 40)	Hardness (kp) (40 RPM)
APAP	Avg	248.8	5.7	244.3	5.7	235.2	5.5
	Stdev	10.5	0.8	10.2	0.5	2.6	0.3
	%CV	4.2	13.4	4.2	8.0	1.1	6.2

Tablet Properties of APAP/1% SMN Direct-Compression Formulation at Three Press Speeds

density. This improvement has been demonstrated on model APIs, such as acetaminophen and ibuprofen. This technology possesses unique multifunctional properties that enhance the flow and bulk/tapped densities of raw materials and powder blends more efficiently than CSD. The enhanced flow will permit more efficient and faster mixing of multi-component dry blends to attain a homogenous mixture. Capsule formulations can be greatly simplified with minimal excipients used for granulation purposes to provide acceptable density and flow for manufacturing. This attribute could also eliminate the need for capital equipment and space associated with the granulation process. As a direct-compression formulation, the time in development is greatly reduced and issues with wet granulation scale-ups are eliminated.

ACKNOWLEDGEMENTS

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BIOGRAPHIES

Joseph Beaurline has worked at 3M for 37 years and with Pharmaceuticals and Drug Delivery Systems Divisions for 30 years. His R&D background spans early phase technology development as well as early and late-phase product development in solid/liquid oral dosage forms and transdermal drug delivery. He is recognized as an inventor on four patents and has received 3M corporate recognition for Technical Excellence. Mr. Beaurline is currently a Senior Product Development Engineer for Drug Delivery Systems Division.

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Jimmie Baran has worked at 3M Corporate Research in Applied Surface Science and Nanotechnology. He has BS degrees in Chemistry and Mathematics from the University of Wisconsin, Madison, and a PhD in Inorganic Chemistry from the University of Texas, Austin, with a post-doc in Surfactant Science and Microemulsion Formulation at the University of Texas, Austin. He is recognized as an inventor on 19 patents and has received multiple 3M corporate recognitions for Technical Excellence and has 25 publications in refereed journals. Mr. Baran is currently a Lead Research Specialist at 3M.

Dr. Fred LaPlant is currently the Spectroscopy Group Leader for 3M Corporate Analytical. He joined 3M after working for 10 years in the on-line monitoring and pharmaceutical industry. He has also been active in various capacities in the Society for Applied Spectroscopy, and is the current national President of the SAS. He earned his BS in Chemistry from San Diego State University and his PhD in Analytical Chemistry from Purdue.

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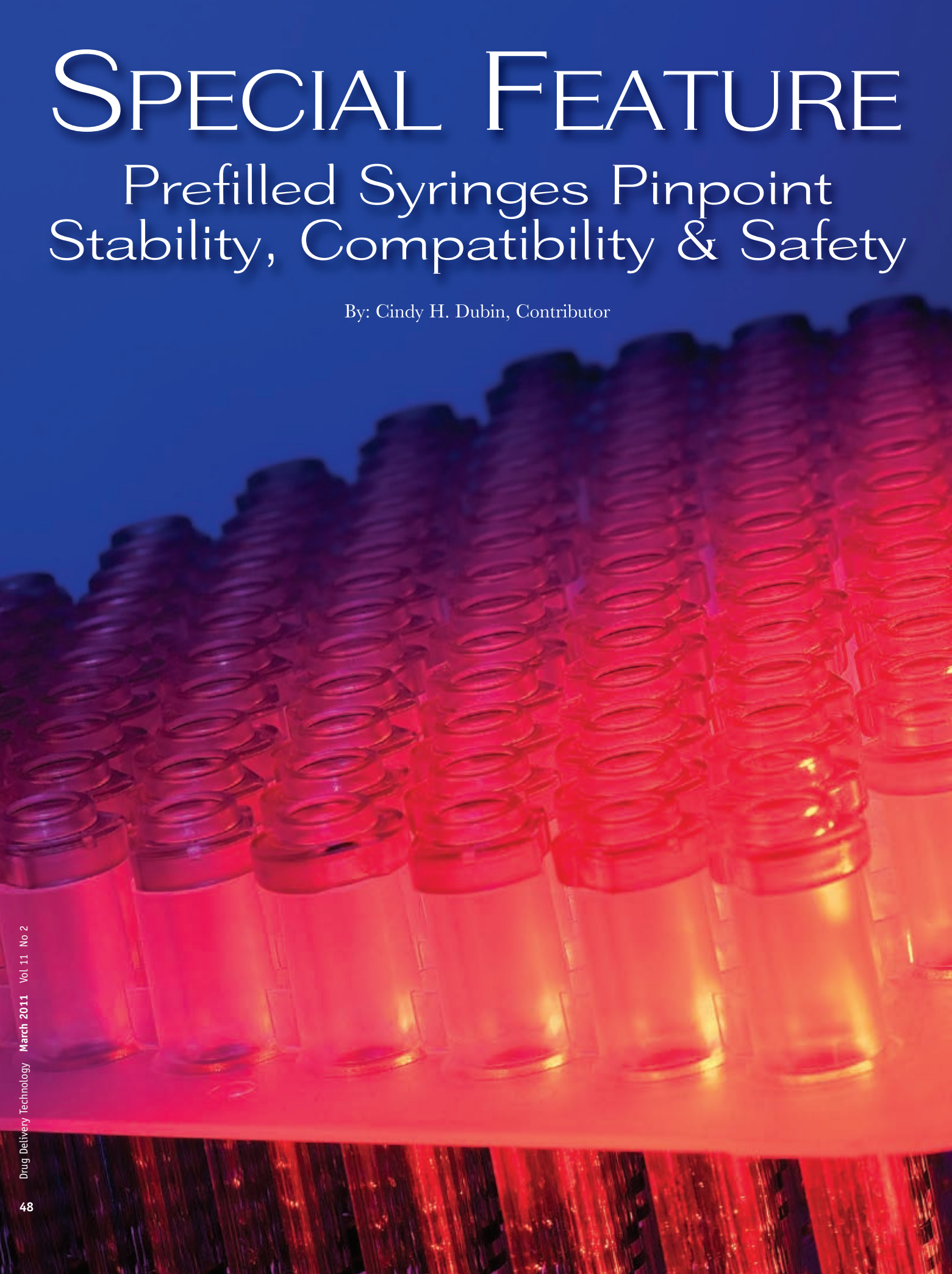
Prefilled Syringes Pinpoint Stability, Compatibility & Safety

By: Cindy H. Dubin, Contributor



Prefilled syringes and injection devices continue to grow in importance as means of improving administration, compliance, safety, costs, and accuracy of drug delivery. The market for prefilled syringes has achieved significant progression in recent years. The pharmaceutical industry accepts prefilled drug technology as a proven format of choice for many parentally administered drugs. Because a product's delivery system can affect patient compliance, easier-to-use devices have been linked to higher sales and market share.

And the market numbers concur. In 2009, an estimated 2 billion prefilled syringe units were sold, and the market for the technology was estimated to be worth up to $2.5 billion.[1] The biologics sector is being credited with having the most influence on the prefilled syringe market, as there is an increasing need for self-administration of these drugs for chronic conditions. Prefilled syringes offer numerous advantages here: Ease of administration, dosing accuracy, patient compliance, safety, and reduced pain.

However, protein-based drugs have introduced a challenge to the prefilled syringe market, eg, certain vials can have a diluting affect on a drug's potency. Both contract manufacturers and syringe developers are investing dollars and manpower to advance construction materials.

Some of these companies are featured in this exclusive, annual *Drug Development & Delivery* report. They include: Baxter BioPharma Solutions; BD Medical, Pharmaceutical Solutions; Catalent Pharma Solutions; Cook Pharmica; Gerresheimer Group GmbH; Unilife Medical Solutions; and West Pharmaceutical Services. Despite their varied approaches to prefilled syringe development, they all concur the market is one of the strongest growing segments inside the pharmaceutical primary packaging market, and the systems are an ongoing success story whose benefits will ensure commercial opportunities in the future.

FIGURE 1

Baxter BioPharma Solutions offers expanded small-scale through high-volume manufacturing of prefilled syringes.

BAXTER BIOPHARMA SOLUTIONS–TAILORED MANUFACTURING CAPABILITIES

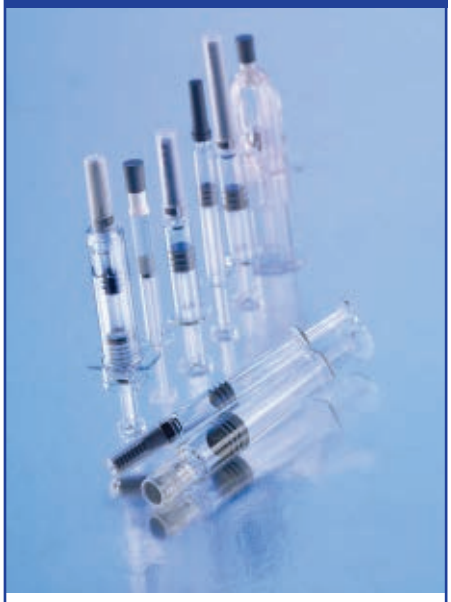
As pharmaceutical companies search for increased efficiency through manufacturing service collaborations, there is a greater need for sustainable partnerships. To this end, Baxter BioPharma Solutions, a business unit of Baxter, is investing in prefilled syringe manufacturing capabilities. Just last year, BioPharma Solutions business won the 2010 Vaccine Industry Excellence (ViE) Best Contract Manufacturing Organization Award, which recognized the company's range of services in niche and core therapeutic areas, as well as its client relationships.

"Our organizational ability to manage complex projects is particularly relevant to prefilled syringes," says Kristie Zinselmeier, Director of Marketing, BioPharma Solutions. "As we see the increased desire for, and relevance of, an enhanced delivery system, it becomes even more critical to execute on commitments, allowing the pharmaceutical company to capitalize on opportunities that may present themselves in this dynamic market."

In the area of prefilled syringe contract manufacturing, BioPharma Solutions offers expanded small-scale through high-volume manufacturing. As a parenteral manufacturing services provider, BioPharma Solutions does not focus on any one therapeutic area; however, its focus on scalable prefilled syringe manufacturing solutions is important to the company's ability to align its objectives with those of the pharmaceutical and biotech industry, explains Ms. Zinselmeier.

"Biologics, for example, require tailored manufacturing capabilities; thus, we continue to optimize our operations to make sure we are ready to serve the needs of those clients."

FIGURE 2



BD Medical offers the Hypak™ family of glass prefilled syringes.

According to Ms. Zinselmeier, the benefits of prefilled syringes to the healthcare system are driving this method of drug delivery development. From an end-user perspective, a prefilled syringe provides ease of administration and compliance benefits; from a pharmacy perspective, prefilled syringes offer a reduction in the potential for admixture-related medication errors and contamination; and from the pharmaceutical company's perspective, increased competition for scarce economic resources within global healthcare systems drives the desire to provide additional delivery enhancements to increase the likelihood that a product's commercialization objectives will be achieved.

"Many of our pharmaceutical partners are exploring the opportunity of moving a product in a vial format into a prefilled syringe presentation," she explains. "In the past, this type of development work would be difficult to invest in after a product's initial launch because of competing priorities. Additionally, we have seen an increased interest in providing prefilled syringes before Phase III clinical trials."

FIGURE 3

Catalent has the ability to handle both glass and plastic syringes to meet the changing needs of customers.

BD MEDICAL–PHARMACEUTICAL SYSTEMS–ENHANCING PATIENT OUTCOMES & OPTIMIZING INJECTION EFFICIENCY

The US predominantly uses MDVs, but PFSs have gained market share throughout the past few years. It is estimated that currently, PFSs hold approximately 30% of the market for influenza vaccines.[2] There are many factors that continue to drive the adoption of PFS in the US, such as the preparation of injectable medications, the opportunity to extend medication or vaccine supply due to the reduced overfill requirements (vs. vials), and the opportunity for pharma to differentiate its products. However, one additional factor influencing the growth of PFS is the stubbornly high incidence of bloodborne pathogen transmission due to unsafe injection practices, and the potential opportunity for unit-dose, ready-to-administer formats, such as prefilled syringes to reduce this. Human factor errors in the administration of parenteral drugs can contribute to outbreaks due to primary breaches in infection control practices. Although not as commonly reported, accidental administration of the wrong injectable medication/vaccines occurs, as in a 2010 Wellesley, MA, incident involving a school nurse giving insulin instead of H1N1 vaccine to the school staff. It was revealed that similar injection mix-ups (eg, insulin given instead of seasonal vaccine; seasonal vaccine given instead of H1N1) had been reported in nearby towns.[3] While the underlying causes of such incidents vary, the potential danger of predrawn and unlabeled vaccine syringes residing in the refrigerator at a busy clinic, side by side with other syringes is clear.

BD has been investing time and money to better understand the differences between PFS and MDVs. The company recently funded research conducted by John's Hopkins University, Bloomberg School of Public Health, to understand the efficiency, economic, and clinical best practice implications comparing PFS versus vials. In this study, several deviations from best practices were noted in the preparation for injection, including: 1) predrawing vaccine from vials into unmarked syringes; 2) using the same alcohol swab to repeatedly sterilize vials; 3) pooling vaccine remainders from multiple spent vials to assemble a full dose; and 4) saving leftover vaccine doses that were predrawn from vials for the following day.

With respect to the impact of time/efficiency/economy of different vaccine packaging, the John's Hopkins study concluded that the additional time needed for multi-dose vaccine preparation has an impact on clinic efficiency. Assuming medical assistant labor costs of approximately $14/hour, for example, the extra staff time required to administer 1,000 doses of MDV vaccine versus PFS would add about $147 to clinic costs.

"A complete cost analysis would need to factor in not only acquisition costs of the vaccines and syringes, but the opportunity cost of lost clinician or pharmacist time and, in the event of a safety mishap, any potential costs related to those events," says Brian Lynch, Marketing Manager for BD Prefilled Syringes.

As a result of its own research, BD Medical is confident that any parenteral medication can benefit from the use of a prefilled syringe as it offers greater simplicity in use versus alternative packaging forms.

CATALENT PHARMA SOLUTIONS–KEEPING PACE WITH CUSTOMER NEEDS

Catalent Pharma Solutions provides prefilled syringe fill/finish manufacturing through its recently opened Brussels, Belgium, facility, which was built specifically to provide high-volume, prefilled syringe filling. With more than 25 years of experience in filling vaccines, low-molecular weight heparins, and diluents, Catalent has expanded its focus to include biologics and therapeutic vaccines based on its customers' pipeline needs.

According to Sheila Dell, PhD, Vice President Business Development for Catalent Pharma Solutions, several of the company's customers have their pipeline products targeted for drug/device combinations, especially if the therapeutic area is for a chronic ailment that requires frequent medication. The prefilled syringe with autoinjector is meeting those therapeutic needs.

"In the next 3 to 5 years, we expect to see more syringe products filled in specific drug/device combinations," she says. "This will improve the quality of patient care and medication compliance in addition to reducing medication errors."

Changing trends in the syringe market enabled Catalent to enter collaborative agreements with customers to provide them access to a range of value-added technologies for injectables, including the ASI™ autoinjector and the Protector™ syringe safety shield.

"Last year, Catalent provided support for more than a dozen companies on more than two dozen vaccines, providing advanced solutions to accelerate product development, to speed up time-to-market, ensure adequate product supply, and provide new ways of delivering vaccines to patients," explains Dr. Dell. "Due to our substantial surge capacity and our vast experience at handling large-scale

FIGURE 4

Cook Pharmica's "one source-one location model" offers comprehensive parenteral CMO services at a single location, including this high-speed syringe line under barrier isolation.

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product launches, we were able to ensure consistent supply to our customers, despite substantial spikes in growth in market demand for these products."

Meeting customer demand is also important when it comes to meeting customers' preference for glass or plastic prefilled syringes. This is especially important for biologic compounds, which face stability and compatibility issues.

"The siliconization with glass syringes has caused sufficient concern related to stability issues with the drug for certain products," says Dr. Dell. "As a result, customers are looking at primary components that either minimize or eliminate the need for silicone in the syringe and plunger stopper."

Dr. Dell believes improvements will be made in the glass syringe format to meet the challenges faced with filling biotech drugs, thus replacing plastic syringes in certain markets.

"However, Catalent does have the ability to handle both glass and plastic syringes to meet the changing needs of our customers."

COOK PHARMICA–ONE STOP FOR DRUG SUBSTANCE, FILLING, AND PACKAGING

As a contract manufacturer, Cook Pharmica offers what it calls a "one source-one location model," which includes parenteral drug product capabilities. Ryan Hawkins, Vice President of Drug Product Operations for Cook Pharmica, explains the model consists of process development, clinical and commercial mammalian cell-culture manufacturing, as well as formulation development and clinical/commercial vial/syringe filling and finishing.

"We believe comprehensive services at a single location can minimize wasted time, redundancy, and information loss. We are also able to minimize the number of relationships and practices a sponsor has to manage. Finally, the model allows us to help sponsors better deliver life-enhancing products to patients, in a more timely manner," he says.

The one source-one location model was also designed to bridge a separation between packaging and filling. Generally speaking, says Mr. Hawkins, outsourcing teams tend to be in different departments within pharmaceutical and biopharmaceutical companies. As a result, these teams may not collaborate, thus packaging can be treated like an afterthought at times. The packaging team might go to one CMO, and the filling team might work with another, and he believes there is an opportunity for synergy here.

Last year, Cook Pharmica (parent company is Cook Medical) qualified a new high-speed syringe line, under barrier isolator, filling speeds up to 600 syringes per minute. The line is complimented by newly qualified secondary packaging equipment in the same facility. The line can handle syringe small molecule, biologic, vaccine, clinical, or commercial projects. Syringe filling and finished packaging is all performed at a single location.

GERRESHEIMER AG–THOUGHTFUL SYRINGE DESIGN

Throughout the past couple of years, quality and safety attributes of prefilled syringe systems have been adapted to evolving requirements especially from biopharmaceutical customers and regulatory agencies. For example, advanced manufacturing methods were established by Gerresheimer and others to ensure compatibility of syringes with highly sensitive biological molecules and self-injection devices.

"The increase in quality and safety requirements is caused by more demanding/sensitive drug products, increasing self-administration, and the ongoing interest of the pharmaceutical customers to improve their process yields," says Claudia Petersen Director, Business Development, Gerresheimer Tubular Glass. "This impacts all steps of the syringe manufacturing process, from glass-forming and needle assembly to ready-to-fill processing.

To address end-user safety needs, prefilled syringe suppliers, like Gerresheimer, have developed advanced syringe closure solutions like the TELC (Tamper Evident Luerlock Closure) systems. This enables syringe manufacturers to mount just one integrated component on syringes–adapter, closure, and tamper-evident seal.

Gerresheimer has also focused on the sensitivity of protein-based products. According to Ms. Petersen, medical-grade

FIGURE 5

Gerresheimer developed advanced syringe closure solutions like the TELC (Tamper Evident Luerlock Closure) systems.

silicone oils are used as a lubricant to provide glass prefillable syringe systems with the required functionality. However, small silicone oil droplets can contribute to the overall particle load of the final drug product, and in the case of protein-based drug products, may cause protein aggregation.

"Syringes siliconized using our Baked-On Ready-To-Fill process combine functional properties with significantly lowered levels of free silicone oil on the inside of the glass barrel."

Gerresheimer prefillable syringe systems are not an off-the-shelf product, explains Ms. Petersen, and therefore, customization to the requirements of various therapeutic areas is possible.

UNILIFE CORP.–A NEW APPROACH TO BRAND DIFFERENTIATION

Unilife Medical Solutions may be the new kid on the block in the pharmaceutical market for prefilled syringes, but the company has invested significant resources in building the operational capabilities to make Unilife a reliable supplier of drug delivery devices that meet the quality assurance expectations of the customer. With production of the Unifill

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FIGURE 6

Unifill's ready-to-fill syringe integrates safety into the glass barrel and meets needlestick prevention mandates.

syringe about to commence at a new facility in York, PA, Stephen Allan, Vice President, Marketing and Communications for Unilife, which expects 2011 to be a big year for the company.

"The initial production and launch this year of the Unifill ready-to-fill syringe is the start of a new generation of innovative devices from Unilife that will help empower pharmaceutical companies to harness the true competitive potential of their injectable drug products," says Mr. Allan.

Fully passive safety features have been fully integrated within the glass barrel of the syringe to virtually eliminate the risk of operators being exposed to blood-borne pathogens via potential transmission modes including needlestick injuries or splatter.

Our Unifill ready to fill syringes can function as a safe and secure primary container for injectable drugs and vaccines. Unilife syringes are designed for integration into the fill-finish systems used for equivalent standard prefilled syringes. All materials inside the fluid path are also USP-compliant materials to facilitate biocompatibility. However unlike other prefilled syringes, this is not a commodity item. Unifill syringes are unique and available only from Unilife.

FIGURE 7

West's Daikyo Crystal Zenith 1-mL Insert Needle Syringe was developed for biologics.

Obtaining special access to our devices within target therapeutic areas, as sanofi-aventis has already done for vaccines and anti-thrombotics, offers pharmaceutical companies the opportunity to generate powerful brand differentiation against their competition.

"They are a primary drug container that can be integrated into fill-finish lines and have USP-compliant materials inside the fluid path for biocompatibility. Yet, they are not a commodity item. Obtaining special access to our device within target therapeutic areas, as Sanofi-Aventis has already done for the Unifill syringe, offers pharmaceutical companies the opportunity to generate brand differentiation in competitive therapeutic drug classes," he says.

Sanofi-Aventis retained the rights to negotiate the exclusive purchase of the Unifill syringe within therapeutic classes, including antithrombotic agents and vaccines until June 2014.

One characteristic that attracts pharma companies, like Sanofi-Aventis, is the prospect for brand differentiation without industrial disruption, explains Mr. Allan.

It is this brand differentiation that will help pharma compete, he adds.

"There is a new arms race developing in the pharmaceutical market for prefilled syringes. It's no longer just about just having a new and improved drug. It's about how that drug interacts with healthcare workers and their patients to enhance the overall provision of healthcare. The pharmaceutical company that has access to the best device that is different and truly meets the needs of the patient will beat the competition."

WEST PHARMACEUTICAL SERVICES, INC.– MINIMIZING DRUG INTERACTIONS

In an industry resistant to change and challenged by many regulatory hurdles, West Pharmaceutical Services is recognizing the need to provide customers with a prefilled syringe solution in appropriate sterile formats with a demonstrated filling and handling capability, which can ease a drug's transition to market and minimize risk.

West components are used with the majority of biotech products, states Graham Reynolds, West's Vice President, Marketing, and Innovation, Pharmaceutical Delivery Systems. He attributes this to the company's FluroTec® barrier film for plungers, which act to minimize interactions between the piston and the drug.

Many drugs are packaged in a syringe with a fixed needle and can be used in combination with devices, such as autoinjectors and safety systems. Recalls of drugs packaged in glass vials and syringes, and issues of functionality between glass syringes and autoinjectors are leading companies to seek improved alternatives to glass syringes, including polymeric syringes.

West's range of plastic prefillable syringes use Daikyo Crystal Zenith® technology, which includes the recently introduced 1-mL long insert needle syringe system. This cyclic olefin polymer system offers customers a solution for packaging drugs in a clean, high-quality syringe system without the issues caused by silicone oil, aggregation, and breakage. Biologic therapies for chronic conditions, such as the various autoimmune diseases, will be the key focus for West's Daikyo Crystal Zenith systems.

"We expect the Daikyo Crystal Zenith to become the future of prefillable syringes for biologic drugs," says Mr. Reynolds. "The trend toward plastic, prefillable systems that overcome the limitations of glass will enable more novel package/device combinations to be developed and introduced, which will lead to more innovative delivery solutions for injectable drugs."

Combining a syringe with a mechanical device, such as an autoinjector, creates additional challenges of functionality. West can help customers overcome such issues through options such as the ConfiDose® autoinjector system, which has been designed for optimum performance even given the variability of glass syringes.

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INJECTABLE DELIVERY

Lifecycle Management & Differentiation Through Injectable Delivery Systems

By: Graham Reynolds

INTRODUCTION

When pharmaceutical and biotech companies begin to develop a drug, the delivery system is often far from top of mind. The growth of sensitive biologics and the plethora of recent drug product recalls, however, have encouraged drug manufacturers to start thinking about container closure systems and delivery systems early in the development process. Issues such as breakage, glass delamination, and particulate contamination have also forced the industry to rethink glass as a standard and consider novel materials, including plastics, that offer stronger, safer, and more efficient packaging options.

Ideally, drugs will be stored first in bulk containers, then move to a standard system of vial, stopper, and seal during clinical testing. As the drug moves to market, additional containment and delivery systems, including prefillable syringe systems, may be developed. Some drugs, including biologics, may require a delivery device or injection system. For each new containment system, testing is required and can often be time-consuming and costly. The development of novel materials, such as cyclic olefin polymers, can provide ideal lifecycle management solutions. Such materials, which are typically break-resistant and inert, can be used in a variety of containers, devices, and systems due to flexibility in molding. In addition to standard vials and prefillable syringes, the ability to develop a custom container in the same basic materials has significant advantages when considering an integrated system.

As the industry trends toward the use of devices or delivery systems to aid with the increased need for injection in the healthcare and home settings, the link between packaging and delivery system manufacturers and pharmaceutical manufacturers must be strong and start early. The inter-dependence of the packaging and delivery system needs to be carefully considered at an early stage, and a thorough understanding of both is key to ensuring a successful drug/delivery system combination.

AN ENVIRONMENT FOR INJECTABLE GROWTH

Growth in injectable therapies, driven by increased incidence of chronic conditions, such as diabetes and autoimmune diseases (including multiple sclerosis and rheumatoid arthritis), has resulted in the development and launch of an increasing number of new biologics designed to treat these conditions. Most of these products require regular injectable delivery, often by the patient or caregiver.

Evidence shows there is continued growth in biological products, and that most of these require delivery by injection. An analysis of the top 20 biologics on the market by revenue demonstrates that most if not all of these products are delivered through injection. These trends are driving the need for prefillable syringe systems and drug delivery devices and systems that can be used in either a clinical or home-care setting.

Because biologics are often large molecule products that do not transport well through non-injectable delivery methods, delivery devices such as auto-injectors are often the best choice for administration. While different technologies, such as inhalation and transdermal patches, have been attempted, in many therapeutic areas, injection has proven to be the most effective method of delivery. Device requirements are driven either as a means of product lifecycle management or by companies entering an established market area where devices are commonly used (such as in the treatment of various autoimmune diseases) or who often need to enter the market directly with a competitive delivery system to ensure competitive parity or additional patient benefits. Such differentiation is key to competing with established

FIGURE 1

West's ConfiDose® Auto-Injector System

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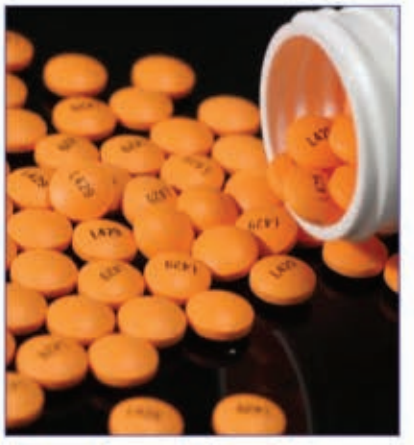

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products, and partnering with a manufacturer to provide novel technology should be an important part of the product's launch plan.

A specific example could be the planned launch of a drug for the treatment of autoimmune disease, in which the selection of a system composed of a prefillable syringe and an auto-injector (usually disposable) requires careful consideration of the primary container and the delivery system, and the performance of the two in combination with the specific drug product.

THE NEED FOR EARLY PARTNERSHIPS

Recent US FDA recalls relating to potential risks with glass prefilled syringes in auto-injectors highlight the need for vigilance when considering the interaction between device and container in the development process. In addition, documented sensitivity of certain biologics to silicone oil, tungsten, and other materials is driving the need to select systems carefully at an early stage of development.

The recalls highlight several issues that may occur when glass is used within a prefillable system. Breakage, delamination, and particulate have resulted in a significant increase in costly recalls of drug product. In 2011, lots of dexamathasone sodium phosphate and sodium bicarbonate were recalled after the drug manufacturer detected glass particulate within the vials. Particulate contamination was also cited in the recall of lots of liver injury treatment in 2010. Glass delamination, which produces siliceous flakes, was the cause of a massive recall of certain lots of anemia drugs. In 2006, certain lots of a drug product delivered by an auto-injector that contained a glass prefilled syringe were recalled in several European countries because of problems with slow or incomplete delivery of the drug. Each of these recalls may have a significant financial impact on the pharmaceutical or biotech company.

Early decisions regarding containment materials and delivery systems may help ensure compliance and increase safety once the product reaches the market. In some cases, the earliest entry of a drug to the market may be facilitated by the use of a traditional container closure system, such as a vial, with some form of reconstitution system if the product is lyophilized. This system is used for convenience and may not be the final or best delivery system for the drug. Many drugs move to prefilled syringe systems that may later be used within a device, such as an auto-injector. The drug molecule is the same, but the delivery system has changed, which may require costly testing to ensure the new container closure system does not react with the drug. There are many examples of this type of lifecycle management with established products, as well as examples of newer drugs whereby the company may choose to launch in a more sophisticated system, rather than in a vial format.

In many cases, and particularly when large molecule biologics are concerned, the prefilled syringe system may not be an adequate match for the delivery device, which can lead to safety issues, such as breakage when using glass syringes or incomplete delivery of highly viscous products. Here, early planning and a stronger focus on the lifecycle management of the containment system can be key to ensuring the earliest product launch with lower risk, no matter what format is selected by the drug company. By ensuring a good fit early in the development process, pharmaceutical companies can essentially build increased compliance and ease of transition to devices and systems once the product hits the market.

FIGURE 2

The Daikyo Family of Products

Working closely together, pharmaceutical and packaging manufacturers can look for ways to differentiate a product through the packaging and delivery systems. There are several reasons the relationship should start early. First is to ensure that packaging is right for the drug product. Packaging can be a huge factor in the success of a drug product getting through the regulatory approval process smoothly and to the market quickly. How the product is going to be delivered should be determined based on the clinical application. This will help the company understand what type of primary packaging is needed, and how that packaging will fit with the delivery system. Ideally, the same material should be used for containment from research through to commercialization.

Proper packaging can have an effect on successful development and registration. While the focus of the regulatory bodies may be on the drug itself, the reality is that when that drug hits the market, it arrives inside a container closure system. Selecting the right

system early in the process can help manufacturers not only differentiate their product in a crowded market, but also increase the chances of a successful move to market.

Often, the goal is to move from a vial/stopper system to a prefilled syringe system. Here again, early consideration to container closure and drug delivery systems can mitigate risk. Use of a consistent material throughout the drug's lifecycle can minimize risk. For example, cyclic olefin polymers, such as Daikyo Crystal Zenith® packaging systems, provide a break-resistant, silicone-free solution that can be molded in a variety of shapes and sizes. Already well established in the global market as a primary container for approved drug products, Daikyo Crystal Zenith packaging systems provide an excellent alternative to glass that can be used throughout the drug's lifecycle. Having the same material for bulk storage, vials, and prefillable syringe systems provides consistent functionality and minimizes the material contamination risk as the drug moves from research to clinical trials to commercialization. This is especially important for biopharmaceuticals, which may react with particulate from silicone-oil and tungsten contamination.

DESIGNED FOR INCREASED PATIENT COMPLIANCE & SAFETY

Many pharmaceutical companies have advanced devices capable of increasing patient compliance. Treatment for diseases, such as diabetes and multiple sclerosis, are prime for device use. In many cases, a range of device options is available to support a single drug.

For example, a single drug used to treat multiple sclerosis may be available in a ready-to-use, pre-measured, prefilled syringe. In addition, an auto-injector may be available for those with dexterity issues. Such devices may have both sight and sound signals to aid end users who may have trouble determining when the dose has been given fully, thus aiding in compliance. Recent innovations in devices have also incorporated electronics as a means of providing instant user instructions, in cases of rarely used emergency treatments, or as a means of aiding compliance.

Diabetic insulin is available in multiple formats, including syringes, pens, and pumps. As these devices become more complex, many utilize electronic feedback to ensure patient compliance. Information about the medication can be downloaded from the pen or pump directly to the caregiver. A physician can then determine quickly and easily if the patient has been following his or her medication schedule. Linking diagnosis to treatment, in conditions such as diabetes, is also becoming a more active area in terms of device development.

SAFER FOR CAREGIVERS & END USERS

Devices can be designed to aid not only in patient compliance, but also patient and provider safety. In recent years, there has been an increased focus on needlestick safety. According to the National Institute for Occupational Safety and Health (NIOSH), approximately 600,000 to 800,000 needlestick injuries occur annually in the US. These injuries carry the risk of serious infection from diseases, such as HIV and hepatitis.

New technologies include passive systems, such as West's NovaGuard™ safety needle and the eris™ safety syringe system*, that allow for safer injection without altering the caregiver's administration technique in the hospital and clinical setting.

In the home care setting, although needlestick prevention has not been a significant issue for self-injecting patients, it can be an area of concern for caregivers, family members, and downstream disposal and safety. Much of the focus for self-injection devices has been on reducing anxiety for the patient through improved needle technology and injection devices that can reduce needle phobia by hiding the needle both before and after injection (such as West's ConfiDose® auto-injector system).

Other areas of treatment require needle-free systems. For example, when treating hemophilia, needle-free systems and devices have been used extensively to eliminate needles during the reconstitution process. Use of vial adapters, needleless transfer devices, and diluent-filled Luer lock syringes have helped to eliminate dangerous needles from the reconstitution process and create a safer environment for those suffering from hemophilia.

SOLUTIONS THROUGH NEW TECHNOLOGY

New technologies and novel materials, such as Daikyo Crystal Zenith, are helping to make delivery system decisions easier and more effective for both the pharmaceutical manufacturer and the end user. By developing a thorough understanding of the drug's intended use and the patient's needs, packaging manufacturers can lend their expertise to pharmaceutical manufacturers to develop a package that differentiates the drug in the market and helps to ensure that the patient's needs are met. The key goal remains the safety and effectiveness of the drug product, and a thorough knowledge of potential interactions with packaging, combined with an intimate knowledge of the regulatory and quality environment, is key in this area.

When designing a delivery solution, pharmaceutical companies must consider the end user. This is increasingly important as

devices are designed to be safe and effective, but also easy-to-use for those patients who may have limited dexterity, and who may not be medically trained. For example, West has created an internal group that focuses on early stage concept development that works closely with outside partner Insight Product Development, a group of industrial designers who help determine a product's external look and feel and fully understand the needs of the patient and administrator (often the same person). Creative concepts can be impractical if they are not combined with a fundamental knowledge of how a device can be engineered, produced, assembled, and linked to the primary container. West provides a fully integrated process from initial patient needs through to manufacture, always with a thorough knowledge of the requirements of the drug product, which we believe is critical to ensuring that drug products can be launched effectively with an optimum packaging and delivery system.

A range of new technologies is now available to meet the many challenges of the pharmaceutical market. In the area of prefillable syringe systems, West offers the first silicone-oil-free product on the market, the ready-to-use Daikyo Crystal Zenith prefillable syringe system. One of the reasons customers choose the Daikyo Crystal Zenith syringe system is because it offers much less variability in functionality than traditional glass systems. Coupled with a plunger with Daikyo Flurotec® barrier film, the Crystal Zenith syringe system does not require siliconization, which leads to variability and can affect the gliding performance of the plunger. With a prefillable syringe system, gliding performance can have a major impact when you place the system into a device, such as an auto-injector, which relies on the complete delivery of a drug from a syringe. Gliding force, drug viscosity, and siliconization consistency can be factors in ensuring reliable dosing from an auto-injector or other device. The insert-needle version also is produced without the use of adhesives or tungsten, and a high level of built-in quality through novel manufacturing techniques supported by multiple in-line inspections, thereby ensuring the optimum container for sensitive biologic products, particularly when used with an injection device, such as an auto-injector.

In addition, cyclic olefin polymers, such as Daikyo Crystal Zenith, offer customers the benefits of low extractables, break-resistance, and high quality in a vial or syringe system. Daikyo Crystal Zenith material can be molded into complex shapes, an advantage over glass. Pharmaceutical companies can select a Daikyo Crystal Zenith containment solution for the lifecycle of their drug, from development through to commercialization. When coupled with an auto-injector, such as West's ConfiDose auto-injector system, which works well with all syringes and high-viscosity drugs, pharmaceutical companies have a unique, easy-to-use product that is safe for patients.

By working with a packaging provider who has an intimate knowledge of the regulatory and quality requirements of the medical field, pharmaceutical manufacturers will increase their ability to create a novel device that establishes the drug product as a leader in the market. Differentiation through delivery system technology, as well as advice from a partner with experience and understanding of the drug packaging industry and end-user needs will not only aid in product compliance, but also may help get products to market faster.

*The eris™ safety syringe system is not currently available in the US.

BIOGRAPHY

Mr. Graham Reynolds joined West in 1980 as a Polymer Technologist, and throughout his career with West, has held a range of positions with increasing responsibility. In his current role as Vice President, Innovation Strategic Marketing, Mr. Reynolds works within the Delivery Systems business segment, where he leads initiatives and develops strategies for future growth, including the acquisition and development of new technologies that enhance the West portfolio. His activities include work on key strategic areas involving injection devices, safety and administration systems, auto-injectors, and prefillable syringes. In 2005, Mr. Reynolds relocated to the US from Europe, where he was responsible for European Marketing and led the integration of the acquired technologies from West subsidiary, MediMop. His experience within the core West business has been complemented by several years of work in the field of devices and delivery systems. Mr. Reynolds holds a degree in Polymer Technology from Trowbridge College, UK.

DRUG DEVELOPMENT Executive

Cetero Research

CETERO RESEARCH: ADDRESSING TODAY'S CHALLENGES IN DRUG DEVELOPMENT

Troy W. McCall, PhD
Chief Executive Officer
Cetero Research

With nearly 20 years of experience in the pharmaceutical and CRO industries, Dr. Troy W. McCall has been responsible for product development, regulatory, sales and business strategies that span all phases and many functional areas of the drug development continuum. Leadership roles involving the development and implementation of services, processes, and technologies to enhance drug delivery, clinical trial conduct, and data accuracy have shaped his perspectives on opportunities to improve the efficiency of clinical research. Shortly after his appointment as Cetero Research's CEO in January 2010, the company embarked on a series of study design and operational execution approaches that focus on efficient, expedited delivery of high-quality data. Cetero Research specializes in clinical pharmacology, bioanalytical and scientific affairs for pharmaceutical, biotechnology and generic organizations. Dr. McCall recently spoke to Drug Development & Delivery about innovative advancements to address drug development challenges and how CROs must build capabilities and expertise to offer value to sponsors in a constantly evolving, yet uncertain industry environment.

"Pharmaceutical and biotechnology companies are re-examining all aspects of their businesses due to the decline in research and development (R&D) productivity, looming patent expiration, and diminishing sales of drugs. These challenges are forcing companies to work outside the traditional paradigms of drug discovery and development. Part of these changes include an increase in R&D outsourcing to drive greater productivity in a shorter period of time with fewer internal resources."

Q: What are the biggest challenges drug companies currently face?

A: Pharmaceutical and biotechnology companies are re-examining all aspects of their businesses due to the decline in research and development (R&D) productivity, looming patent expirations, and diminishing sales of drugs. These challenges are forcing companies to work outside the traditional paradigms of drug discovery and development. Part of these changes includes an increase in R&D outsourcing to drive greater productivity in a shorter period of time with fewer internal resources.

The pressure to bring drugs to market faster is greater than ever before. In turn, it is important for drug companies to narrow their focus and identify which drug candidates are the most viable early in the development process.

Sponsors can help manage these challenges by investing more wisely in early-phase clinical development, which is the most efficient stage to determine viability. More robust trial designs at this stage can significantly improve the speed and cost of the entire development process by more efficiently answering questions about the viability of a drug candidate. Efficient study conduct combined with advanced scientific

techniques can provide better decision-making and reduce the probability of costly later-stage failures.

Q: What can Contract Research Organizations (CROs) do to be better partners?

A: CROs have become an integral part of drug development as sponsors cut their internal capabilities to better control costs and improve overall R&D productivity. CROs frequently have a much wider range of scientific expertise from conducting thousands of studies, and thus can often recommend and develop protocols that accomplish sponsors' multiple goals and objectives. This improves efficiency and brings innovation to the clinical trial process.

Like any good partnership, finding the right match between the sponsor and CRO is important. Every CRO has its own unique strengths and weaknesses. It is important for sponsor companies to properly evaluate the CRO to ensure that their needs and the CRO's capabilities are aligned. Key accepted assessment criteria include relevant corporate therapeutic experience, personnel qualifications and experience, regulatory history and performance metrics.

Using an experienced CRO can expedite a drug candidate through the drug development process, gaining the necessary information needed to make key go/no-go decisions. While this is particularly true for smaller companies that may have limited resources and expertise, even large companies have seen clear and measurable advantages in outsourcing clinical trials to CRO partners. An experienced CRO can help streamline a sponsor's program, allowing multiple studies to be completed in a shorter timeline.

CROs need to think beyond the traditional fee-for-service approach and collaborate with their clients to develop innovative study designs, development approaches, and contracting agreements that help speed development and facilitate decision-making and timelines for key milestones in product development. A few brief scenarios of how contracting and design innovation can accelerate critical timelines include the following:

ACCELERATED PROOF-OF-CONCEPT: An innovative approach to cost and time-savings is accelerating the path to proof-of-concept by combining multiple studies into one protocol. For example, Cetero's Accelerated Proof-of-Concept approach offers one study design that combines a single ascending dose (SAD), a multiple ascending dose (MAD), preliminary drug-drug interaction and patient proof-of-concept into one study. This can reduce the time it takes to gain proof-of-concept in half and reduce study costs by more than 10 percent.

TIMELINES NEEDED TO ACHIEVE FIRST-TO-FILE: The rate-limiting step of first-to-file applications for a generic product is the bioequivalence studies that must be completed for most products. The typical timeline for the bioequivalence studies ranges from 56 to 63 days from dosing to final reports. Using a suite of services, dedicated lab capacity, enhanced project management, and clinic resources that are bundled together and strategically prioritized, Cetero has developed a process that can condense the standard timeline to 28 days or less. We recently began offering this timeline as a premium service offering for clients with first-to-file market opportunities.

EXPLORATORY DEVELOPMENT: Contracting flexibility and scientific collaboration in areas where standards are still evolving is critical. CROs must develop or acquire the internal expertise to work closely with sponsors in exploratory areas, such as biomarker development and applications in clinical trials. This also requires multidisciplinary collaboration across key functional

areas, scientific affairs, medical affairs, laboratory operations, and biostatistics.

Q: What trends and new developments do you see on the horizon for the year ahead?

A: Key trends that will continue to aid R&D efficiency gains in early-phase drug development include access to patients and using that access to perform early clinical studies in patients rather than healthy participants, which provides the ability to reach proof-of-concept faster. CROs must also offer the ability to develop and quickly implement protocol-specific recruitment strategies that achieve target enrollment and retention rates.

Recognizing the importance of patient access is vital. For example, Cetero has made investments in Phase I facilities that provide access to an extensive mix of populations in multiple locations across North America to meet the growing demand for more diverse study volunteer populations as well as inclusion and exclusion requirements. Across the industry, CROs and sponsors are seeking to broaden their access to patients through collaborations with medical centers, patient organizations, and specialty clinics. These efforts can be supported through maintenance of an active research database of potential participants.

Tools and approaches to improve strategic decision-making in early product development must be implemented. This includes advanced population pharmacokinetic/pharmacodynamic (PK/PD) modeling and analysis and adaptive statistical designs. Having a better understanding of the PK/PD relationship early in development will maximize the chance of success in later development.

Recent Cetero projects incorporated pharmacodynamic measurements in addition to pharmacokinetic measurements in early phase studies. Using pharmacodynamic measures, it may be possible to demonstrate that the compound should work as intended, increasing the chance of success in later development.

Technologies and standards to support vaccines and biologics development, ranging from assay development to supportive logistics for clinical studies, is paramount. Another recent Cetero project involving a vaccine has spanned more than one year based upon the novel study design. Up-front work focused on biomarker measurement, control of sample integrity, and testing of the intended clinical response.

Also important is integrated program planning – determining ways to reach the goal faster through an integrated development approach, combining clinical, regulatory, and commercial considerations to establish critical path activities and identify key milestones.

Current practices we see more often include design approaches that provide more informative data or improve study efficiency, such as accelerated proof-of-concept and adaptive designs.

Q: How do you recruit participants for clinical research?

A: Cetero's clinical pharmacology units have a proven and successful track-record of using a variety of local media for effective recruitment. Most efforts involve a targeted mix of radio, television, print advertisements, and internet. Recruitment efforts take several forms.

General advertising educates potential participants about the breadth of studies, typical duration, and associated schedules, such as availability of studies requiring weekday, multi-day, or weekend stays. Study-specific advertising targets specific groups of people with a brief message about the purpose of the study, age groups, and/or gender requirements. Advertising for special populations, such as the elderly or post-menopausal women will involve targeted media and/or select

community placements. Working with local investigator sites and physician networks to recruit and screen patients, but with the study conduct within one central clinical site. Community outreach is another method. Offering free health screenings provides an opportunity for potential participants to learn more about clinical research and specific study opportunities.

One of the keys to recruiting and retaining participants is the ability to set expectations at the beginning of a study. Participants must be clearly informed about what happens during a clinical study and what to expect in terms of their involvement. The more details that are given, the better prepared the participant will be, but the study administration team has to ensure the participant comprehends the details given. The key topics to cover include duration of the study and follow-up, how long the study will last, the timing of the visits and flexibility, if any, in the timing and the consequences for missing or being late to a visit.

Study conduct. This includes the treatment and control groups, the type of procedures involved, and how the treatment will be delivered, particularly if invasive procedures will be used.

Participants need to know about the controls in place that ensure no one is put at undue risk. This includes explaining the function of the Principal Investigator and Institutional Review Board, and monitoring procedures in place during the conduct of a study.

Risks and benefits. All investigational and approved drug products have risks. This includes a full explanation of potential side effects or adverse events, even if temporary in nature, needs to be communicated clearly.

In each of Cetero's locations, we make community-based efforts to help increase public awareness and understanding of clinical trials.

Q: Do certain dosage forms (i.e., nasal sprays, patches, injections) present any special challenges (or advantages) for clinical trial testing?

A: Nearly all dosage forms present their own challenges for running successful clinical trials. A one-size-fits-all approach does not work for clinical development, especially as there is a transition between different delivery technologies. Each type of delivery system, such as a nasal spray, altered dosage form, or extended-release tablet, will alter how the clinical trial needs to be designed in order to establish safety and efficacy of the product.

As an example, a nasal spray will have a lower systemic exposure than a tablet taken orally, but the local concentration within the nasal mucosa will be higher. Therefore, the safety measure for a nasal spray will be more focused on the local effects rather than systemic effects. Also, because a nasal spray will be administered to healthy subjects as well as those with congestion, regulators often ask for the pharmacokinetics to be examined in volunteers with and without nasal congestion.

Transdermal delivery systems, such as patches, are designed to remain on the skin for an extended period of time. Due to the potential for irritation or sensitization from this long-term contact, specific studies are required to demonstrate whether this will happen with the experimental dosage form.

As one of the drawbacks for vaccine is the requirement for subcutaneous injections, many companies are looking at sublingual dosing alternatives. These studies present a variety of challenges, including the duration of the study. Just as a vaccine is intended to lead to years of benefit, the length of studies is often one year or longer.

In general, before entering into a clinical development program for a drug to be delivered via a novel technology, it is important to take the time to ensure the program is designed to address the questions that will be unique to that delivery system. ◆

Technology Showcase

Transdermal Systems & Components

Companies worldwide look to 3M Drug Delivery Systems for ingenious transdermal systems and components as well as manufacturing solutions to help accelerate development and enable success. 3M can fulfill all your transdermal delivery needs, including new microneedle technology. 3M's microneedle platform, Microstructured Transdermal Systems (MTS) leverage core 3M competencies to expand the range of transdermally deliverable drugs to include proteins, peptides, and vaccines. MTS can also deliver significant benefits over injection, including improved delivery efficiency and faster absorption of some drugs and vaccines as well as the potential to induce similar maximum drug concentrations at a significantly lower dose. Please view our latest poster presentation, *The Transdermal Delivery of Human Growth Hormone*, at www.3M.com/tddpublications. For more information, call 3M DDS at (800) 643-8086 (US) or visit **www.3M.com/MTS**.

Performance Materials

Avantor Performance Materials renamed its Mallinckrodt® Chemicals product line Macron™ Chemicals, effective March 7, 2011. The name change does not involve any product or manufacturing changes. The Macron Chemicals product line, identical to the previous Mallinckrodt line, includes high-purity solvents, acids, salts, minerals, and sugars. Macron brand products are produced in the same facilities under the same manufacturing processes, and share the same product numbers, names, and code numbers as the previous Mallinckrodt brand products. Avantor products have a legacy of safety and trust, with a 140-year tradition for delivering the highest standards of quality, purity, and consistency. Today, Macron Chemical's focus is on providing products for cGMP pharmaceutical production and everyday laboratory use in environmental testing, university research, and industrial manufacturing. For more information visit Avantor Performance Materials at **www.avantormaterials.com/macron-DDD**.

Licensing & Capabilities

Aveva has a number of products for license from its development pipeline along with a full complement of R&D capabilities to produce transdermal drug delivery systems that fortify 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 with a rich history 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**.

Drug Delivery Solutions

BD Medical - Pharmaceutical Systems provides high-quality, customized, clinically proven drug delivery systems and self-injection technologies to help pharmaceutical and biotechnology customers' injectable drugs reach their full potential. BD has over 100 years of experience in manufacturing and processing technology for parenteral drug delivery systems and has developed an in-depth understanding of the pharmaceutical industry's requirements. BD has leveraged this experience when developing advanced drug delivery systems that span from small-scale clinical through large-scale commercial programs. With a broad range of innovative systems and services, BD Medical - Pharmaceutical Systems provides pharmaceutical companies with support and resources to help them achieve their goals. For more information, contact BD at (800) 225-3310 or visit **www.bd.com/pharmaceuticals**.

Technology Showcase

Capsule Filling & Sealing

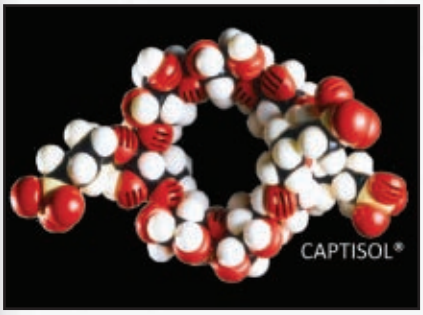
Designed to allow formulation scientists the ability to better exploit the potential of lipid-based formulations for poorly soluble compounds, the CFS 1200 helps accelerate the development timeframe and achieve Faster Time to First in Man. A fully automatic cGMP-compliant machine, it fills and seals up to 1,200 capsules per hour with liquid or semi-solid formulations without banding. It is designed for ease-of-use and high reliability, with the ability to quickly clean and change capsule sizes with available change parts. Product integrity is ensured with gentle handling of capsules before sealing and during the drying cycle. Other features include a robust filling pump with highly accurate temperature control, improved capsule manipulation before sealing and during drying using new "Cap-edge" handling system, and improved design of filling and sealing process that ensures better control and cleanability. Fore more information, contact Capsugel at (888) 783-6361 or visit **www.capsugel.com**.

Pharmaceutical Solutions

Catalent

Catalent Pharma Solutions is a world leader in patented drug delivery technologies. For more than 70 years, we have developed and manufactured advanced drug delivery systems and partnered with nearly every major global pharmaceutical company. We continually work to advance the science of drug delivery and enhance the therapeutic and market performance of our customers' drugs. Our advanced drug delivery technologies bring new options to resolve the technical challenges development scientists face every day. These patented technologies can improve the odds of successful formulation by enhancing bioavailability, optimizing the rate of release, and targeting the site of absorption. Our technologies include softgel and Vegicaps® Soft capsules; Zydis® fast-dissolve dosage form; modified-release technologies; and a range of inhaled technologies, including MDIs, DPIs, nasal sprays, and solutions/suspensions for inhalation, nebulizers, and liquid inhalers. For more information, contact Catalent Pharma Solutions at (866) 720-3148 or visit **www.catalent.com**.

Specialty Pharma



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

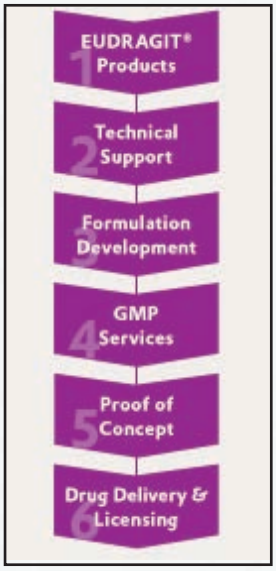
Development & Manufacturing

DPT®

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

Technology Showcase

Pharma Polymers



Evonik Industries is a global market leader in specialty chemicals, offering a broad portfolio of products and services to meet the drug delivery challenges of the pharmaceutical market. Evonik Pharma Polymers manufactures EUDRAGIT® acrylic polymers used for enteric, sustained-release, and protective formulations. The unique functionality of EUDRAGIT polymers can also meet high sophisticated drug delivery requirements (eg, pulsed drug release). We have adapted our services to meet the requirements of the pharmaceutical industry's value chain. As a result, we are able to support our customers in the development process to bring products safely and quickly to the market. From excipients supply to the development of custom tailored drug delivery solutions, our customers benefit from our knowledge and expertise. For more information, contact Evonik Degussa Corp., Pharma Polymers at (732) 981-5383 or visit **www.eudragit.com**.

Analytical Testing Services

Gateway Analytical provides quality analytical testing and consulting services to the pharmaceutical, forensics, and material science industries. Our company takes a forensic approach to scientific problem-solving, blending forensic examination practices with standard and innovative analytical methods to get to the root of pharmaceutical issues. With more than 15 years of experience, you can rely on our expertise in product and process development, non-conformance and failure investigations, foreign particulate identification, and more to help solve your toughest challenges. Trust Gateway Analytical to be an extension of your own lab, providing personal attention, high-quality results, scientific talent, and technical expertise to help you get the job done. For more information, contact Gateway Analytical at (724) 443-1900 or visit **www.gatewayanalytical.com**.

Tablet & Capsule Facility

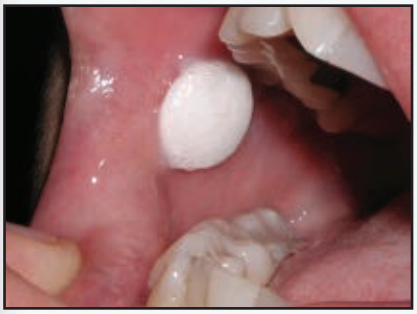
Glatt Pharmaceutical Services recently announced a new commercial-scale cGMP Contract Manufacturing capacity at its 86,000-sq-ft New Jersey facility for tablet and capsule production. High Shear Wet and Fluid Bed Granulating/Drying, Tablet Compression and Pan Coating, Wurster HS® Pelletizing and Coating, CPS Technology® Direct Pelletizing, Oven Tray Drying/Curing, Blending, Milling, and Sieving & QC production capabilities have all been added. The facility is organic solvent or aqueous and DEA-controlled substance (CII-CV) capable with unrivaled Quality, Expertise, and Customer Care. For more information, contact Glatt Pharmaceutical Services at (201) 825-6327 or visit **www.glatt.com**.

Injection Devices

Haselmeier is a leading designer and manufacturer of pens and autoinjectors for injectable pharmaceuticals with more than four decades of experience. Combining technology, function, and design, Haselmeier offers innovative and flexible platform technologies of disposable and re-usable self-injection delivery systems with many featuring a unique hidden needle design. Working with pharmaceutical companies worldwide Haselmeier develops injection devices of outstanding quality and performance to ensure comfortable and safe injections and meet the requirements of the product and patient. For more information, contact Haselmeier at info@haselmeier.com or visit **www.haselmeier.com**.

Technology Showcase

Buccal Delivery



Henkel's proprietary PROLOC™ Bioadhesive is ideal for buccal delivery and provides a superior means to deliver therapeutic agents locally or across mucosal membranes for systemic delivery. Products formulated with PROLOC Bioadhesive adhere within seconds and remain adhered until fully eroded. No backing layer is required. Additional benefits include increased bioadhesive properties and capacity for higher drug loading for hydrophilic or hydrophobic drugs, while remaining gentle to the mucosa. The material can be compressed into a tablet, utilized as a powder, cast as a film, or incorporated into a film-forming composition. PROLOC Bioadhesives provide an avenue for delivery of new drug molecules or for redirection of existing drugs, offering a viable answer to your life cycle management strategy. For more information, contact Henkel at (908) 685-5317 or **proloc.bioadhesives@henkel.com**.

Combination Capsule Technology

InnerCap offers an advanced patented 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

PARTICLE SCIENCES
DRUG DEVELOPMENT SERVICES

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**.

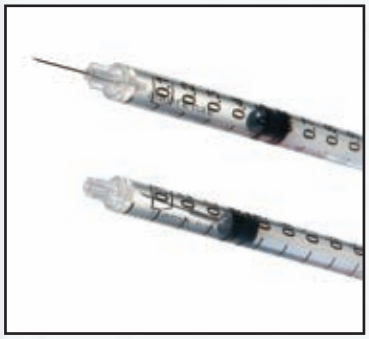
Knowledge Management

PharmaCircle™

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

Technology Showcase

Prefilled/Clinical Safety Syringes



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Partnership Spotlight

Mr. Noah Beerman
President & CEO
RXi Pharmaceuticals

RXi & EyeGate Set Their Sights on the Retinal Disease Market

By: Cindy H. Dubin, Contributor

Mr. Stephen From
President & CEO
EyeGate Pharma

Ophthalmic drugs constitute a prominent segment of the global pharmaceutical market, with sales of more than $14 billion in 2009, according to a new report, *World Ophthalmic Pharmaceutical Market 2010-2025*. Eye diseases are common worldwide and range from relatively mild conditions like allergic conjunctivitis to vision-threatening conditions, such as macular degeneration. A large prevalence rate, combined with a high unmet medical need for many sight-threatening ocular diseases, provides major opportunities in this sector as seen with the recent success of Genentech's Lucentis for macular degeneration.

According to the report, beginning in 2010, novel drugs from small-molecule anti-infectives to complex biological molecules will appear. These treatments will harness a range of drug delivery systems. Expected future benefits include restoration of vision and the cessation of vision loss, with high potential gains for developers. Success in the market will be characterized by products with superior efficacy, safety, and tolerability. Emerging technologies that increase clinical effectiveness and/or patient compliance will be particularly important therapeutically and commercially.

RXi Pharmaceuticals is a leader in RNAi-based therapeutic discovery and development with a therapeutic platform that includes both RNA interference (RNAi) compounds and delivery methods. The company is leveraging this broad and integrated RNAi therapeutic platform to build a pipeline of RNAi therapeutics for treating several disease areas, including retinal disorders. RXi recently partnered with EyeGate Pharma to evaluate administration of its RNAi compounds via the EyeGate drug delivery system, which is based on iontophoresis. This is an active method of drug delivery in which an electrical field created by a low-level of electrical current is applied to an ionizable substance or drug particle in order to increase its mobility across a biological membrane.

In a recent interview with *Drug Development & Delivery*, Mr. Noah Beerman, President and CEO of RXi Pharmaceuticals, and Mr. Stephen From, President and CEO of EyeGate Pharma, discussed why they believe their companies are well positioned to compete successfully in the ophthalmologic market. Mr. Beerman cited RXi's next-generation therapeutic platform, experienced management team, accomplished Scientific Advisory Board, including Nobel Laureate, Dr. Craig Mello, and the company's intellectual property position in RNAi chemistry and delivery.

And, Mr. From highlighted the fact that EyeGate Pharma is the only company to have successfully used iontophoresis to safely and effectively deliver medication to both the anterior and posterior segments of the human eye.

Q: *What are the unmet needs of the ophthalmic market, and how will your collaboration meet these needs?*

Mr. Beerman: There are significant opportunities in the ocular market, particularly in retinal disease, for breakthrough products. We have the potential to develop next-generation treatments and/or improve upon existing therapies, and this collaboration with EyeGate will help us explore a route of administration that satisfies the needs of the doctor and the needs of the patient. Our work in RNA interference, for which our founder won the Nobel Prize, is a natural mechanism where short, double-stranded RNA molecules interfere with the expression of genes in living cells.

Many drugs on the market today are repositioned drugs not specifically developed for ophthalmic diseases. We are developing a new class of therapy that has the potential to be broadly applicable to multiple therapeutic areas, including diseases of the eye.

Mr. From: There have been very few drugs approved in the area of retinal disease, and Lucentis is one. We want to give patients and doctors a treatment tool that as yet does not exist for retinal disease. Despite material advances in ophthalmic medicine in recent decades, there remains significant opportunity to improve patient care, lower cost of services, and treat sizable unmet medical needs. As life expectancy increases, so does the incidence of ophthalmic disease, such as glaucoma, macular degeneration, and diabetic retinopathy.

The collaboration with RXi will explore the use of our iontophoresis technology to deliver RXi's "self-delivering" rxRNA™ (or sd-rxRNA™) compounds to the eye in preclinical models.

Iontophoresis delivers a drug across a biological barrier, such as the ocular surface into the eye. Once inside the eye, we believe the sd-rxRNA compounds will access retinal cells, and by virtue of their self-delivering properties, will enter these cells and silence disease-causing genes.

Q: *What segment of the retinal disease market are your efforts being focused?*

Mr. From: We are focused on wet and dry age-related macular degeneration, diabetic retinopathy, and diabetic macular edema, which together affect tens of millions of people in the US. Macular degeneration affects 20 million people in the US. Two types exist: atrophic (dry form) and exudative (wet form). Wet-AMD is responsible for 90% of blindness and affects approximately 2 million people. The high prevalence of these diseases has created significant opportunities for companies to develop innovative medicines and technology that improve patient diagnosis and care. At the core of our approach is the understanding that for medicine to be effective, it needs to be able to get to the anatomy of the eye that is responsible for the disease.

Q: *Why is it so difficult to deliver drug to the eye to treat these diseases and how does iontophoresis overcome those difficulties?*

Mr. From: Due to natural barriers, topical (eye drops) instillations and systemic delivery of therapeutics to the back of the eye are inefficient. To overcome the low bioavailability issue associated with these delivery modalities, more aggressive treatments like intravitreal injections are performed. But as you can imagine, this is not ideal and comes with potential complications, such as retinal detachment, hemorrhaging, and endophthalmitis. The challenge has been to get compounds to the back of the eye less invasively.

EyeGate Pharma's trans-scleral (transmitted across the sclera, or white protective outer membrane of the eye) iontophoresis delivery platform, the EyeGate® II Delivery System, was designed by engineers and ophthalmologists and is based on more than 10 years of research and development, providing a strong body of scientific and proof-of-concept data.

The system consists of two parts: A reusable battery-powered generator and a disposable applicator that contains the drug. EyeGate's iontophoresis technology is coulomb-controlled, which means that it regulates each unit of drug used for treatment. The annular design and electrode composition allows for safe and effective transcleral delivery. The treatment is needle-free and requires only topical anesthesia administration.

Q: *What data can you share about your individual trials so far?*

Mr. Beerman: To date, we have seen a robust uptake of our compounds into the retina after intravitreal dosing in animal models. Most, if not all, cells take up sd-rxRNA within minutes of exposure. Intravitreal administration of sd-rxRNA shows efficient distribution and uptake of sd-rxRNA compounds to essentially all cell types with complete penetration through all layers of the retina, including retinal pigment epithelial cells. This broad cellular distribution profile allows the technology to be applied to inhibit a wide range of ocular gene targets for different therapeutic indications.

In addition to robust uptake by retinal cells, target gene silencing has been observed with sd-rxRNAs targeting two different genes following administration to the eye (MAP4K4 and PPIB). At 48 hours, 50% gene silencing was observed for both sd-rxRNAs. When compared to more conventional, chemically stabilized siRNAs, confocal microscopy shows efficient sd-rxRNA retention throughout the retina, while conventional compounds are not retained by retinal cells. While we don't yet know the length of the therapeutic effect, we have seen effective target silencing in the retina with sd-rxRNA compounds for several weeks. This critical result demonstrates that the ability of sd-rxRNAs to enter cells in the retina is significantly improved over conventional siRNAs. The use of sd-rxRNAs may change the landscape of ocular oligonucleotide-based therapeutics, enabling rapid discovery and validation of a range of novel therapeutic targets and creating the potential for next-generation therapeutics for the treatment of serious retinal disorders.

There is also opportunity to improve on existing therapies, for example, extending the time required between doses and using more effective or patient-friendly models of administration for delivery to the eye. The company intends to select a development candidate in a retinal disorder in 2011.

Mr. From: EyeGate Pharma's lead internal clinical candidate, EGP-437 (dexamethasone phosphate formulated for iontophoresis), is currently being developed to treat dry eye, uveitis, scleritis, and other inflammatory conditions. We have completed two Phase II studies (one uveitis and one dry eye), and we are currently enrolling for a Phase III dry eye pivotal study. Results of the Phase II dry eye study showed findings in multiple symptoms and signs, and had a rapid onset of action. The EyeGate II delivery system and EGP-437 have been studied in more than 300 subjects with more than 1,300 treatments performed.

Q: *As you move forward with preclinical trials and your partnership, what will be your primary objective?*

Mr. From: There are 25,000 ophthalmologists in the US and approximately 2,000 of them specialize in retinal disease cases. They need another tool for treating these diseases, and we must continue to address their needs, as well as those of their patients. We look forward to working with RXi to accomplish these goals. ◆

March 2011

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For more information on growth opportunities in the Drug Delivery market, please contact Britni Myers at britni.myers@frost.com or 210.477.8481.

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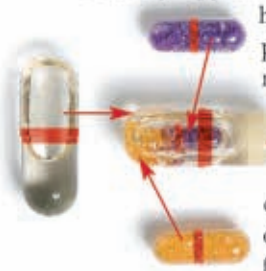
INNERCAP® Technologies Granted US Patent No. 7,670,612 on multi-phase, multi-compartment capsular delivery apparatus and methods for using the same.



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

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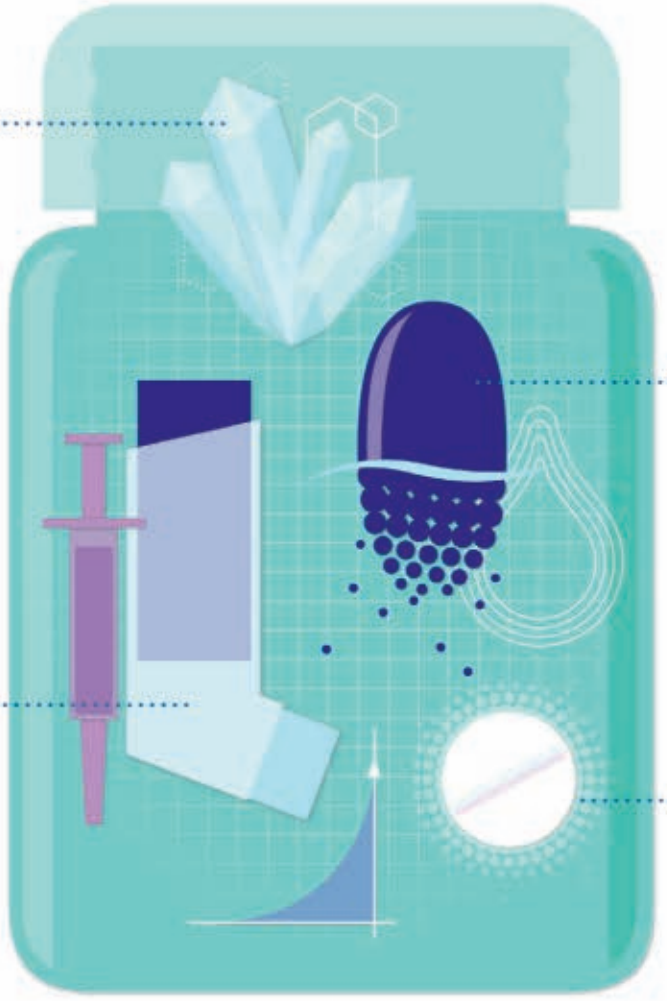

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