

Drug Delivery[®] Technology

April 2010 Vol 10 No 3

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Increasing Bioavailability of Poorly Soluble Drugs

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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 multicompartiment, 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.

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

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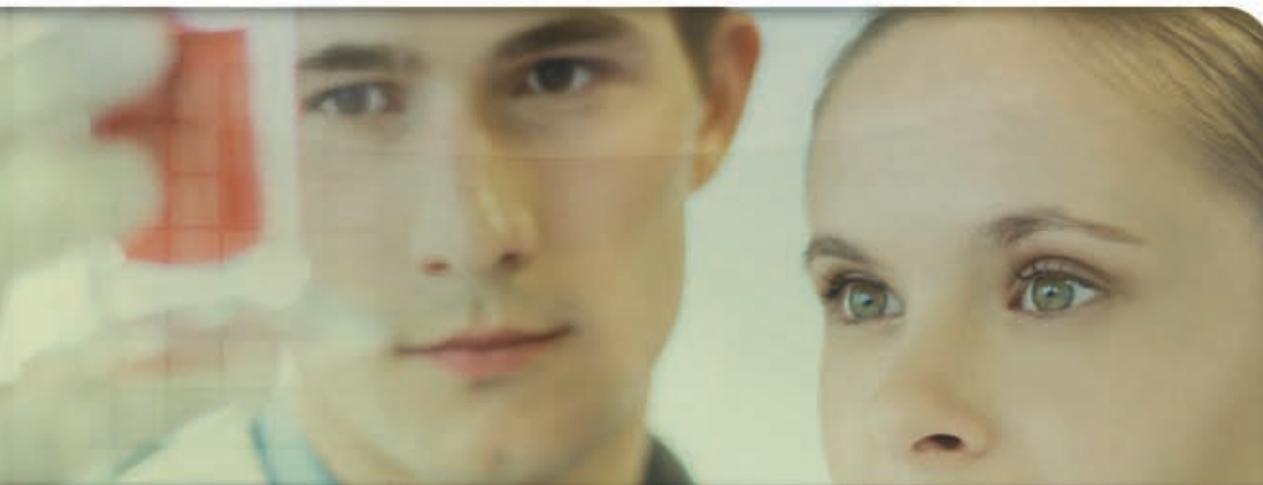
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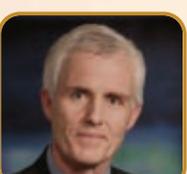
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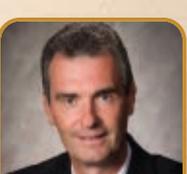
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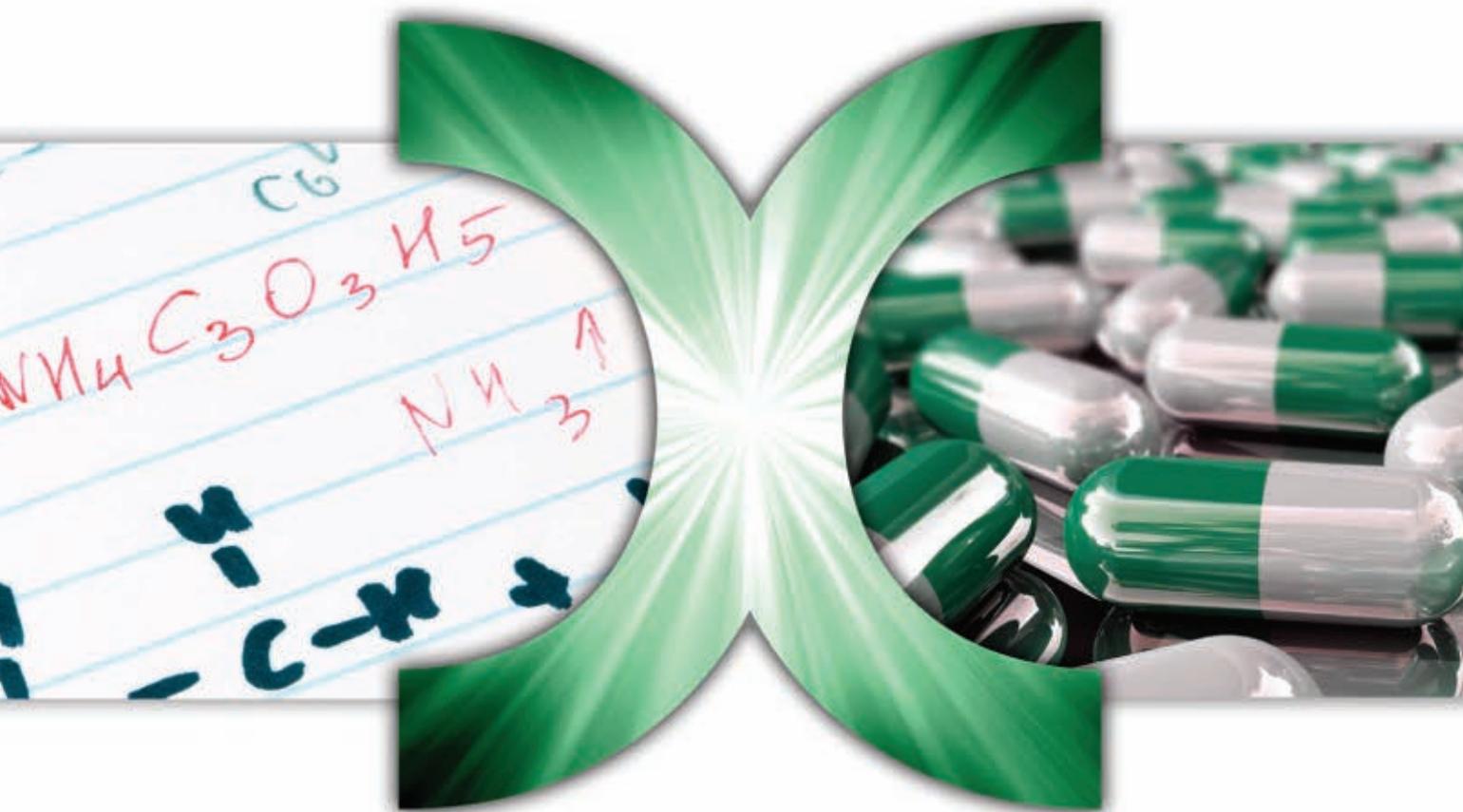
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MARKET NEWS

AND

TRENDS

BENEO GmbH Enters Japan With Multifunctional Bulk Excipient

The manufacturer BENE0, member of the Südzucker Group, recently announced that the Pharmaceutical and Medical Devices Agency (PMDA) in Japan has granted the first license for the manufacture and distribution of a pharmaceutical product utilizing the benefits of galenIQ. Having already been approved in the US and Europe, the granted license is seen as a reference approval for galenIQ in Japan.

“We are delighted to be present with galenIQ in one of the most important markets for the pharmaceutical business,” said Bodo Fritzsching, Head of Sales & Technical Services PHARMA. “The approval is a considerable step forward for galenIQ since its launch in 2005, and confirmation of the product’s technological and physiological properties. Because manufacturers located in Japan as well as global manufacturers with international drug formulations can now benefit from galenIQ, we are confident that more market products will follow.”

galenIQ (pharmaceutical grade isomalt) is available in different grades. All grades are characterized by their very low hygroscopicity, excellent chemical and physical stability, as well as their technological benefits. The multifunctional excipient especially facilitates the development and formulation of specific solid-dosage forms, such as tablets, sachets, capsules, coatings,

or lozenges. galenIQ is a white, odorless, water-soluble, crystalline substance of non-animal origin and GMO-free. Furthermore, it shows a low glycemic response and is non-cariogenic.

The multifunctional excipient combines the advantages of other well-known fillers and binders. Manufactured in different grades, it is used in a very wide range of different solid dosage forms. The galenIQ range includes grades 720 and 721, which are excellent filler/binders for direct compression and powder mixture applications, and the 800 series, which offers special ground grades for wet granulation, compaction, and other agglomeration processes. Besides its application in granulation, galenIQ 801 is used as a co-polymer in film-coatings to improve film adherence and reduce coating time. The 900 series is highly suitable for capsule fillings, sachets, sugar-free coatings, and high-boiled lozenges.

galenIQ is listed in the US FDA’s inactive ingredient database under its generic name Isomalt. It complies with the isomalt monographs of the current Ph Eur, BP, and USP-NF. BENE0-Palatinit is a member of the International Pharmaceutical Excipients Council, and produces galenIQ under cGMP conditions for pharmaceutical excipients.

INNERCAP Technologies Granted US Patent on Multi-Phase, Multi-Compartment Capsular Delivery Apparatus & Methods for Using the Same

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

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



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MARKET NEWS AND TRENDS

Compugen Announces Discovery Platform to Predict Cell-Penetrating Peptides for Drug Delivery

Compugen Ltd. recently announced the development and validation of its Intracellular Drug Delivery (IDD) discovery platform for identification of cell-penetrating peptides. Compugen also announced that as part of the validation process for the new platform, more than 20 novel peptides, predicted and selected in silico, demonstrated the predicted cell-penetrating properties in initial experimental validation studies.

The delivery of biological molecules across selectively permeable cell membranes and into the cells represents a major challenge for the pharmaceutical industry. Furthermore, important classes of biological drugs now under development, such as therapeutic peptides and siRNA, need to enter the cell to be effective. Because most are unlikely to cross the surrounding protective membranes of cells on their own, they will require some type of delivery methodology. Cell-penetrating peptides offer the opportunity to provide the required intracellular targeting of therapy, either by delivery of a therapeutic molecule as “cargo,” or by the peptide itself.

Compugen’s newly developed IDD discovery platform enables the in silico identification of novel peptide sequences that are predicted to have the potential to penetrate the cell membrane. This new platform consists of various components from Compugen’s existing computational biology infrastructure and a series of proprietary machine-learning algorithms specifically designed for this platform. In a validation run of the platform, a number of peptides having various physico-chemical properties potentially relevant for different specific uses were predicted and experimentally evaluated. Their ability to penetrate into cells was assessed by two independent well-accepted in vitro assay systems. In these evaluations, more than 20 of these peptides were shown to possess cell-penetrating activity both by visual image analysis through confocal microscopy and quantitative measures performed by flow cytometry analysis.

The past 2 decades have seen an increasing research interest in cell membrane penetration and the discovery of various cell-penetrating peptides. In addition, the potential “cargo-carrying” capability of certain of these known cell-penetrating peptides has been demonstrated in the lab by various experimental techniques; however, this capability was only recently introduced to the clinic. Looking to the future, it is forecasted that the availability of a much wider portfolio of cell-penetrating peptides with improved properties will be required in order for this delivery methodology to meet the needs of the large number of biological molecules now being evaluated industry wide for therapeutic purposes. In this regard, Compugen intends to utilize its IDD platform to create a library of cell-penetrating peptides with properties specific to different cargos and/or tissues.

In addition to the substantial opportunity represented by “therapeutic cargo-carrying,” Compugen intends to integrate its IDD discovery platform with its other in silico therapeutic peptide discovery capabilities, such as the DAC Blockers platform, in order to create dual function peptides. These dual-function peptides will be designed to both penetrate the cell membrane and provide the required therapeutic intervention.

FDA Clears GeNO LLC Investigational New Drug Application for Nitric Oxide Delivery System

GeNO LLC, a privately held, advanced development-stage technology company, recently announced that the US FDA has granted clearance of its Investigational New Drug (IND) application for its stand-alone gas cylinder Nitrosyl Delivery Platform (NDP). The initial indication to be studied for nitric oxide delivered via the GeNO Nitrosyl delivery system is as a diagnostic agent for administration as an adjunct to right heart catheterization in patients with Pulmonary Arterial Hypertension (WHO Group 1) to add information to improve clinical decision making. No agents are currently approved for this indication.

Prior to conducting a pivotal study later this year, GeNO LLC will first conduct a 10-patient Pilot Study to obtain preliminary safety and feasibility data from short-term (15 minutes) administration of inhaled nitric oxide via this GeNO Nitrosyl delivery system.

GeNO's stand-alone gas cylinder stores premixed nitric oxide as nitrogen dioxide in either air or oxygen. The gas is allowed to flow through a proprietary cartridge containing ascorbic acid, which generates nitric oxide immediately prior to inhalation. A second cartridge is provided for redundancy.

"Having our IND application accepted in the 30-day period is an important accomplishment for GeNO, given that we are working on a novel inhaled nitric oxide generation and delivery system," said GeNO LLC Founder and President David Fine. "This marks an critical milestone for the company and completes our rapid transition to a clinical-stage organization. Furthermore, this milestone enables us to move our other novel, patent-protected technology development programs toward clinical trials."

"There are hundreds of clinical studies and thousands of published papers that have evaluated the use of inhaled nitric oxide in treating patients with a variety of indications," added Dr. Lewis J. Rubin, MD, Professor of Medicine, and head of the Pulmonary Hypertension Program at University of California San Diego and a Medical Advisor to GeNO. "But despite its promise, widespread use of inhaled nitric oxide has been limited by cost, complexity, and lack of portability of the delivery equipment. The GeNO Nitrosyl Delivery Platforms offer an elegant solution, and if shown to be effective, could greatly expand the use of inhaled nitric oxide to treat a larger patient population."

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DPT Executes Strategic Initiative to Create New Centers of Excellence

DPT Laboratories, Ltd., a pharmaceutical contract development and manufacturing organization, recently announced a restructuring of its facilities to create three new Centers of Excellence to support clients' pharmaceutical development programs and manufacturing needs, each focusing on a different area of expertise: Sterile & Specialty Products, Semi-Solids & Liquids, and Research & Development.

"We believe each of these Centers of Excellence will provide our clients with access to experienced personnel who are experts in their field and who will provide comprehensive development and manufacturing services," said Paul Johnson, President & COO of DPT.

DPT Laboratories in Lakewood, New Jersey, is home to The Center for Sterile & Specialty Products. This center specializes in the development and aseptic manufacturing of clinical trial material and commercial-scale products to meet sterile requirements. The 175,000-square-foot site recently underwent a multimillion-dollar transformation to provide state-of-the-art aseptic processing suites and filling equipment.

The Center for Semi-Solids & Liquids in San Antonio, Texas, will provide cGMP pilot, clinical and commercial-scale manufacturing for prescription and OTC products. The center also includes a dedicated cGMP aerosol and pMDI manufacturing facility. A multimillion-dollar investment was also made to this center to improve efficiency and increase capacity.

DPT's Center for Research & Development also in San Antonio provides pharmaceutical development services to include preformulation and formulation development as well as analytical development services. This center will perform research and development activities and support technical transfers to the applicable manufacturing center of excellence.

"We are committed to excellence and investing in our future. Our goal is to provide our clients the most efficient and the best development and manufacturing services," said Mr. Johnson. "These strategic changes reflect our mission of providing enhancements to service, innovation, and technology for our customers as we move into our next strategic plan."

Polyplus-transfection Licenses ZNA Oligonucleotide Technology to Metabion

Polyplus-transfection SA, a company developing innovative solutions for molecular and cellular biology, recently announced that Metabion GmbH, a company specializing in custom synthesis of biopolymers, has signed a non-exclusive agreement to manufacture and commercialize Polyplus-transfection's Zip Nucleic Acid (ZNA) oligonucleotides, a new technology that increases affinity for nucleic acids. Under the terms of the license, Metabion GmbH has acquired rights to manufacture and commercialize custom ZNA oligonucleotides for research and in vitro diagnostic applications.

ZNA are novel modified oligonucleotides that offer increased affinity for nucleic acids without reducing specificity. This brings several advantages, including improving the performance of molecular hybridization techniques, such as PCR assays when used as primers or probes; increasing the sensitivity of tests and the detection of mutations; performing favorably compared with the best modified oligonucleotides available in the market today; and having the distinct advantage of being easy to design and cost effective to produce.

"We are truly delighted to sign this agreement with Metabion, a well-established dynamic oligonucleotide company in Europe," said Mark Bloomfield, CEO of Polyplus-transfection. "This licensing agreement will enable more members of the life science community to access our innovative ZNA technology."

"In line with our approach to intelligently and deliberately expand our oligonucleotide custom synthesis portfolio to bring ever increasing value to our customers, we see great potential for ZNA modified oligonucleotides due to the inherent (chemical) advantages they offer for state-of-the-art molecular biological applications," added Dr. Regina Bichlmaier, CEO at Metabion. "Combining our own and our customers' expertise, this new technology will contribute to increase R&D flexibility and progress."

ZNA are oligocation-oligonucleotide conjugates that demonstrate an increased affinity for their complementary sequence without reduction in specificity. Increased affinity derives from the molecules' cationic moieties (functional groups), which reduce the charge repulsion between the two nucleic acid strands. Thanks to the non-directive nature of the electrostatic interactions, this affinity gain is independent of the base sequence and is therefore predictable, thus making the design of ZNAs extremely easy. ZNAs are produced using a standard oligonucleotide synthesizer allowing fast, cost-effective production as well as the ability to add further useful modifications, such as fluorescent markers.

Polyplus-transfection SA is a biotechnology company researching, developing, manufacturing and marketing innovative solutions for scientists working in molecular and cell biology. The company has been producing and selling its proprietary range of transfection reagents and technologies since 2001.

Metabion is one of the globally leading suppliers of custom nucleic acids renowned for its focus on reliable supplies of consistently high-quality products and services. Metabion's core business is the production of synthetic DNA and RNA oligonucleotides according to customers' needs.

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MARKET NEWS

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Pantec Biosolutions Successfully Delivers Largest Protein Transdermally

Pantec Biosolutions AG, a privately owned company developing innovative transdermal drug delivery products, recently announced it has achieved excellent results in a Phase I clinical trial of a FSH (follicle stimulating hormone) patch used in conjunction with the company's novel P.L.E.A.S.E. (Painless Laser Epidermal System) technology. Although smaller peptides and some proteins have previously been delivered transdermally, this is the first time a molecule as large as this protein (32 KDa) has been successfully delivered in this way.

The purpose of the study was to investigate the primary pharmacokinetic characteristics as well as the safety and tolerability of the newly developed FSH protein patch in healthy male volunteers. Due to its size and physicochemical properties, FSH, a 32-KDa protein hormone, cannot permeate passively across intact skin. Therefore, prior to patch application, the skin was microporated using Pantec Biosolutions' P.L.E.A.S.E. laser device. This pre-treatment creates microchannels in the skin's stratum corneum, facilitating FSH transport through the skin and accelerating its entry into the systemic circulation.

The serum profiles further demonstrated the P.L.E.A.S.E.-FSH patch combination was able to achieve reproducible pharmacokinetics with negligible inter-individual variability. All of the volunteers considered the method to be convenient and easy to use, and there were no reports of any adverse events.

"This FSH patch Phase I trial represents a key milestone achieving proof-of-concept and demonstrating for the first time that P.L.E.A.S.E. enables delivery of large proteins, such as FSH, efficiently in therapeutic amounts from a stable patch," said Christof Boehler, CEO of Pantec Biosolutions. "This validation of P.L.E.A.S.E. is an extremely important milestone that moves the company forward and significantly closer to commercialization."

Currently, FSH is self-administered by the patients for 10 to 12 days by daily subcutaneous or intramuscular injection stimulating follicle growth during an In Vitro Fertilisation (IVF) protocol. FSH is used in all major IVF procedures. The patch will avoid these multiple injections, improving ease of use and convenience. As a consequence of these excellent results, Pantec Biosolutions is now planning a future Phase II study with the new P.L.E.A.S.E.-FSH patch.

Elan Drug Technologies Announces Pivotal Phase III Trial for Hydrocodone Controlled-Release Formulation by Licensing Partner Zogenix

Elan Drug Technologies, a business unit of Elan Corporation, plc, recently announced that Zogenix Inc, its licensing partner, has initiated a pivotal Phase III clinical trial with ZX002, a novel, oral, controlled-release formulation of hydrocodone without acetaminophen. ZX002, which was developed using Elan Drug Technologies' SODAS technology, is being studied for the treatment of moderate-to-severe pain in individuals who require around-the-clock opioid therapy for the control of pain. Currently, there are no products available with hydrocodone only, or with controlled-release formulations in the US. Using Elan Drug Technologies proprietary SODAS technology, ZX002 offers a unique controlled-release profile that utilizes both immediate-release and extended-release properties designed to enable twice-daily dosing.

"We are delighted to see the initiation of Phase III trials for this much needed treatment in patients with moderate-to-severe pain," said Shane Cooke, Executive Vice President and Head of Elan Drug Technologies. "We look forward to ZX002 progressing successfully through clinical trials and seeing it being manufactured in our DEA-approved site in Gainesville, GA, in the US."

The ZX002 Phase III clinical trial is designed to enroll approximately 600 patients with chronic low back pain. The trial is a US-based multi-center, randomized, double-blind, placebo-controlled

study to evaluate the efficacy, safety, and tolerability of ZX002. This product could potentially allow for less-frequent dosing with a customized controlled-release profile and the ability to titrate to higher hydrocodone doses than currently recommended for hydrocodone products burdened by combination formulations. ZX002 treatment in chronic pain could possibly avoid some of the serious side effects associated with the use of combination opioids that contain acetaminophen, or non-steroidal anti-inflammatory drugs (NSAIDs).

Elan Drug Technologies developed the controlled-release formulation of hydrocodone, using one of its Oral Controlled Release Technologies, the SODAS (Spheroidal Oral Drug Absorption System) technology. Elan Drug Technologies offers clients drug delivery expertise with a suite of commercially launched, proprietary, technology-driven solutions. Products enabled by EDT technologies are used by millions of patients each day. Zogenix, Inc. is a privately held pharmaceutical company focused on the development and commercialization of medicines to treat neuroscience disorders and pain. The company is commercially focused on the SUMAVEL DosePro (sumatriptan injection) needle-free delivery system, which launched in January 2010.

Unilife & sanofi-aventis Agree to Exclusivity List for Unifill RTF Syringe

Unilife Corporation recently announced it has agreed to a list of therapeutic drug classes within which sanofi-aventis has the exclusive right to purchase the Unifill ready-to-fill syringe. Sanofi-aventis has secured exclusivity for the Unifill syringe within the full therapeutic classes of antithrombotic agents and vaccines until June 30, 2014. These two therapeutic classes together represent the majority of all prefilled syringes consumed globally. Sanofi-aventis has also secured Product exclusivity in an additional six smaller sub-groups that fall within other therapeutic classes that Unilife believes represent new market opportunities in the pharmaceutical use of prefilled syringes.

The scope of the Exclusivity List allows Unilife to commence formal discussions with other pharmaceutical companies relating to the potential use of the Unifill syringe within a number of significant therapeutic classes that fall outside of those areas retained by sanofi-aventis. In accordance with the Exclusive Agreement, sanofi-aventis will receive a 10-year extension on its Period of Exclusivity within a designated therapeutic class should sanofi-aventis purchase commercial quantities of the product prior to July 1, 2014. This extension will be reduced on a per therapeutic class basis to 5 years in the event that sanofi-aventis does not sell a minimum of 20 million units of the Unifill syringe for use with an injectable drug product to be marketed for this therapeutic class in at least one of the first 5 years of the Additional Period.

During the Period of Exclusivity, sanofi-aventis may also nominate additional therapeutic sub-groups to be placed onto the Exclusivity List should the company not have already signed a commercial arrangement within this sub-group with a third party. Before an additional therapeutic class can be added to the Exclusivity List, both parties will need to be reasonably satisfied that a target drug suitable for use with the Unifill syringe is likely to generate a commercial order.

“The agreement of an exclusive list of therapeutic drug classes with sanofi-aventis for the purchase of the Unifill syringe is a significant business milestone for Unilife,” said Unilife CEO Alan Shortall. “The confined nature of the therapeutic sectors defined within the Exclusivity List considerably expands our commercial opportunities with additional pharmaceutical companies. In return, sanofi-aventis retains the opportunity to nominate the placement of additional therapeutic drugs onto the Exclusivity list provided they are commercially favorable and do not infringe upon any future agreements we may sign with other pharmaceutical companies. This is indicative of the strong collaborative relationship that has been established between both parties. We look forward to commencing supply of the Unifill syringe after the scheduled completion of the industrialization program.”

The Unifill syringe is targeted for use by pharmaceutical manufacturers who utilize prefilled (ready-to-fill) syringes as a preferred drug delivery device for injectable drugs and vaccines. More than 50 drug products used within healthcare facilities or by patients who self-administer prescription medication are currently available in a prefilled syringe format. Unilife has designed the Unifill syringe so that it is compatible with the drug validation and manufacturing systems currently used by target pharmaceutical customers to fill and package standard prefilled syringes.



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EXCIPIENT UPDATE

Combining HME & Solubilization: Soluplus® - The Solid Solution

By: Hendrik Hardung, PhD; Dejan Djuric, PhD; and Shaukat Ali, PhD

INTRODUCTION

Drug solubilization has drawn attention in recent years because large numbers of NCEs often fail in development due to their poor solubility and bioavailability.¹ To circumvent these challenges and bring the compounds to the market, the pharmaceutical industry has a desire for novel solubilizers that can provide better opportunities for poorly soluble APIs by (1) lending better solubilization capacity than known solubilizers, (2) having unparalleled safety and toxicological standards, and (3) reducing time and cost in the drug development process.

Classical solubilizers are usually polyethylene glycol-based surfactants that are well suited for liquid formulations (oral, parenteral). In addition, only a selective class of solubilizers has been developed for solid oral dosages.² For instance, polyoxyethylene and polyoxypropylene copolymers (Poloxamers) have been used as solubilizers for oral dosage forms, but their application as a matrix (e.g., in solid dispersions) is limited due to their low melting temperatures. Likewise, other polymers, such as povidone, copovidone, and cyclodextrins, have been used in various solubilization technology platforms, but their applications are limited because of poor solubilization capacity of insoluble molecules.^{3,5}

Hot melt extrusion (HME) technology has gained a significant interest in recent years. Even though this technique has been used in the plastics and food industries for decades, it is relatively new in the pharmaceutical industry, and only a few drug products (based on polyethylene glycol or copovidone) are currently available on the market.^{6,7} Hot melt extrusion technology shows numerous benefits over traditional/classical methods, including shorter processing times due to continuous downstream processes, environmental advantages due to elimination of solvents, and increased efficiency in delivery of drugs to the patient.⁸

BASF has introduced a new polymeric solubilizer, Soluplus®, a graft copolymer composed of polyethylene glycol, polyvinylcaprolactam, and polyvinylacetate. Its unique chemistry (Figure 1) coupled with granular and solubilization characteristics are important in the development of solid solutions by hot melt extrusion.⁹ Significantly greater lipophilicity in the polymer is a prerequisite for solubilization of poorly soluble molecules in solid solutions as illustrated by complexation of the active with the lipophilic portion of the Soluplus molecule (Figure 2). Soluplus outperforms many of the well-known surfactants and solubilizers for poorly soluble compounds and is potentially applicable to solid oral dosages. The low hygroscopicity and glass transition temperature of about 70°C makes it different from other polymers used as solubilizers.

MATERIAL & METHODS

The model drugs used were: estradiol, piroxicam, clotrimazole, carbamazepine (all Pfannenschmidt, Germany), griseofulvin, cinnarizine, itraconazole, danazol (all Selectchemie AG, Germany), ketoconazole, and fenofibrate (Sigma Aldrich, Germany). Soluplus, Solutol® HS15, Cremophor® EL, and Cremophor® RH40 were obtained from BASF SE (Germany). Vitamin E-TPGS and Tween® 80 were obtained from Eastman and Croda, respectively.

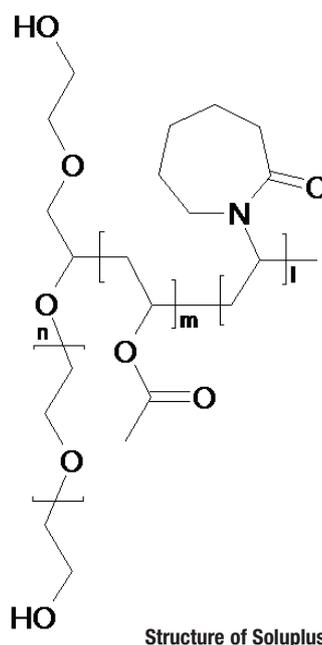
Solubilization capacity was determined in duplicate by means of saturation solubility in various buffer media (Figure 3). A 10% (w/w) polymer solution was oversaturated with an individual drug and stirred for 72 hours at room temperature. Different buffer solutions with

pH 1.2 (HCl buffer) and pH 7 and 9 (phosphate buffers) were used to investigate the effect of pH on the solubilization capacity of Soluplus. The resulting suspension was filtered through a 0.45 micrometer filter, and the amount of dissolved active was detected in the filtrate by UV spectroscopy (Hewlett Packard 8452A). Saturation solubility was expressed as a mean value in g/100 mL.

Extrusion trials were performed on a PolyLab PTW 16 extruder (ThermoFisher) equipped with 16-mm co-rotating twin-screws at a feed rate of 1 kg/h, and a barrel temperature of 150°C for itraconazole and 100°C for fenofibrate, respectively.

The degree of crystallinity of the resulting extrudates was determined by x-ray diffraction (D8 Advance, Bruker,

FIGURE 1





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Germany). Dissolution studies of fresh and stored extrudates, each containing 100 mg of active, were carried out and compared with pure crystalline active. Determination was performed in triplicate using USP apparatus 2 at 50 rpm in 700 mL hydrochloric acid (0.1 molar). The resulting data are mean values \pm standard deviation.

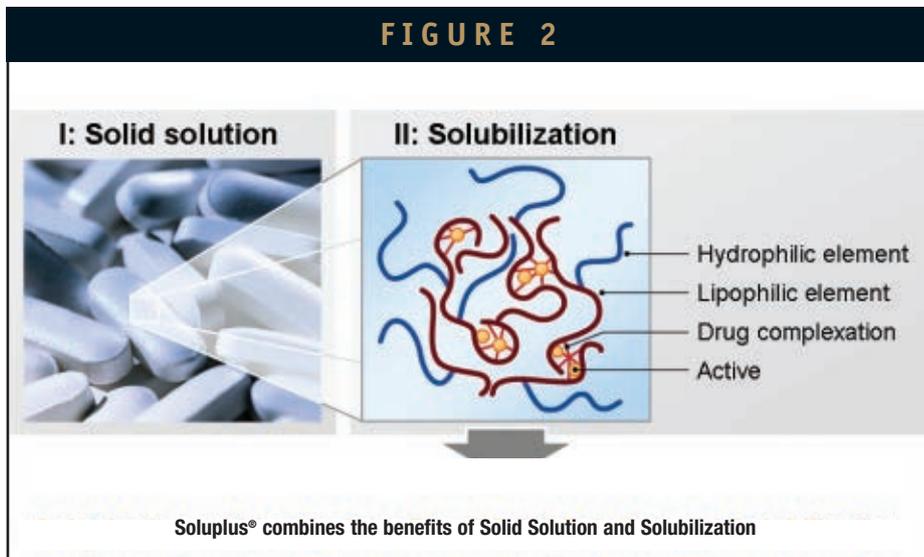
Stability of solid solutions was tested at three storage conditions (25°C/60% RH, 30°C/70% RH, and 40°C/75% RH) in glass bottles with a polyethylene lid. After 3 months, the extrudates were analyzed for degree of crystallinity and drug-release profile.

Bioavailability studies were performed in beagle dogs in the fasted state with itraconazole and fenofibrate dosed at 10 mg/kg body weight. For each active, three formulations filled in hard gelatin capsules containing the drug and disintegrant (Ac-Di-Sol[®], FMC Biopolymers) were tested. The formulations were (1) crystalline drug substance (95% active, 5% disintegrant), (2) a physical mixture of active and Soluplus (15% active, 80% Soluplus, 5% disintegrant), and (3) solid solution of active and Soluplus manufactured by hot melt extrusion (95% solid solution, 5% disintegrant; 15% itraconazole, 85% Soluplus; 20% fenofibrate, 80% Soluplus).

RESULTS

Solubilization

For all actives examined, an increase in the saturation solubility was observed with Soluplus (Figure 4). The saturation solubility in 10% solubilizer solution ranged from 0.013 g/100 mL for itraconazole to 0.35 g/100 mL for carbamazepine compared to the saturation

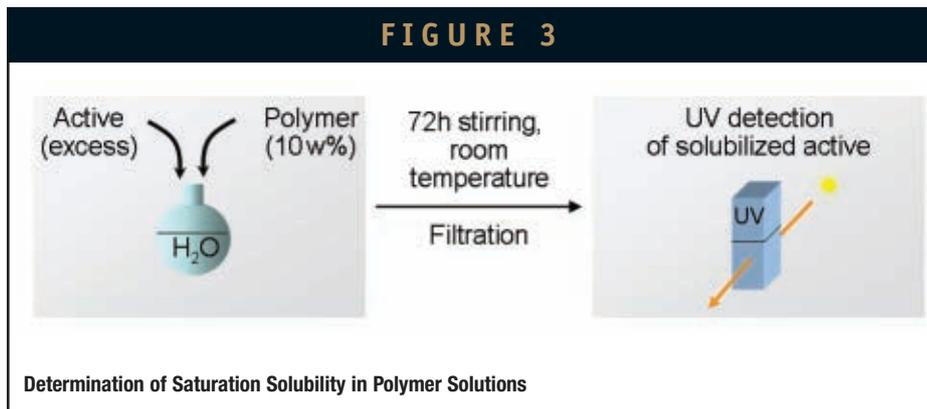


solubilities for the pure actives in water that were < 0.08 g/100 mL. In certain cases (eg, estradiol, danazol, or fenofibrate), the saturation solubility increased > 100 -fold in polymer solution.

The impact of pH on solubilization using different buffer media is presented in Figure 5. Soluplus was capable of acting as a solubilizer and increasing the saturation solubility of various actives at all pH values examined. However, actives with basic functionalities, such as clotrimazole, cinnarizine, and ketoconazole, showed an

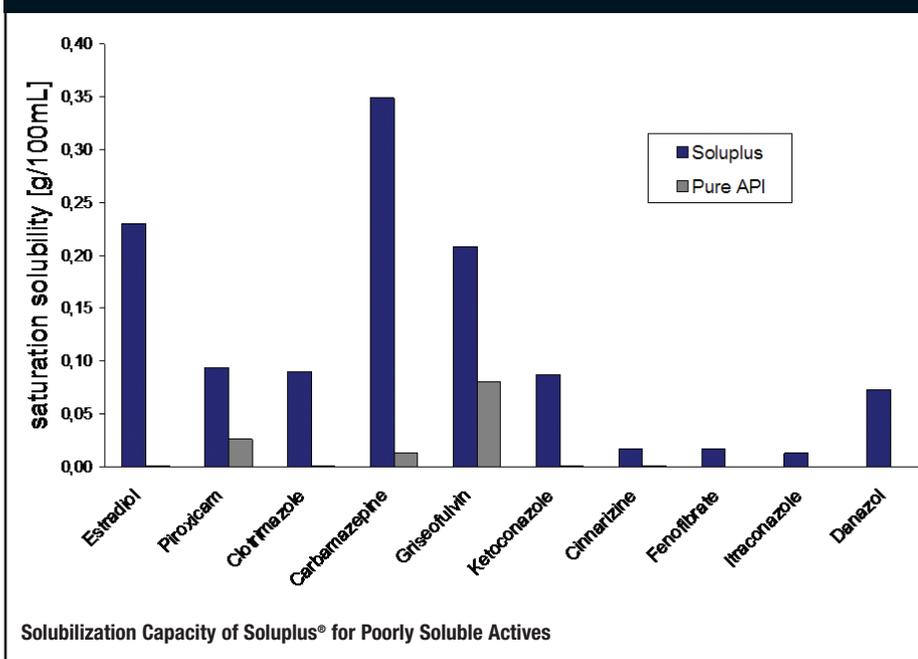
increase in saturation solubility at pH 1.2 due to salt formation in the acidic environment. Likewise, the actives, such as piroxicam among others with acidic functionalities, showed a slightly higher solubility in alkaline condition at pH 9.

The solubilization benchmark in phosphate buffer pH 7 showed a significant solubilization effect with Soluplus for all actives examined (Figure 6). In four model drugs studied, Soluplus outperformed the other solubilizers and achieved the best result.



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FIGURE 4



Extrusion

The extrusion trials conducted in this study led to transparent and clear extrudates for itraconazole and fenofibrate. Figure 7 shows the solid solution of itraconazole with Soluplus.

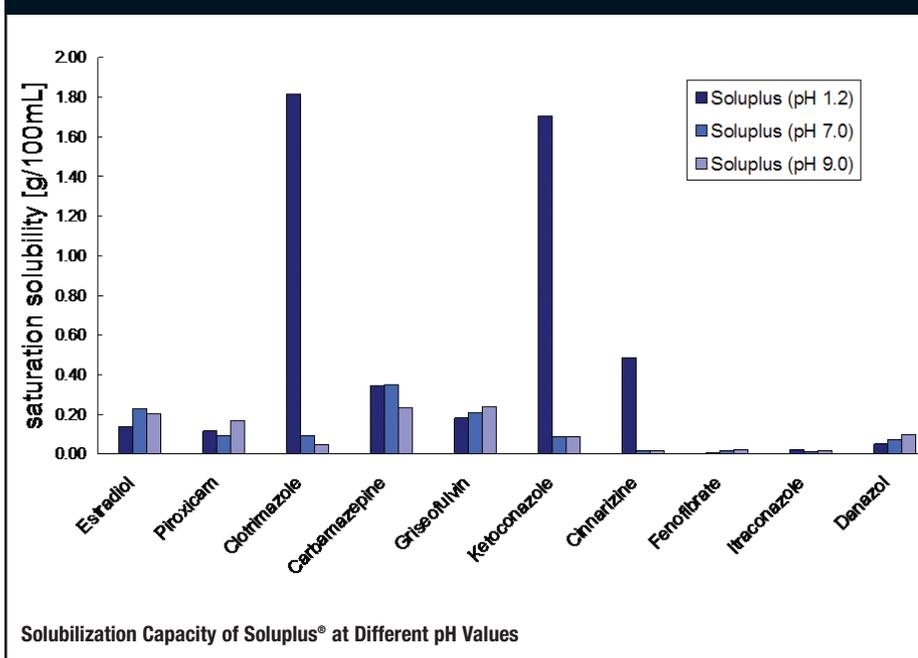
X-Ray powder diffraction (XRPD) analysis revealed no crystallinity in the freshly extruded solid solutions of both actives examined. Furthermore, the extrudates stored for 3 months at different storage conditions were clear and transparent, suggesting the drugs were completely miscible in the solid solutions and remained stable under the accelerated conditions (40°C/75% RH) with no apparent crystallization.

Dissolution

Dissolution testing of crystalline itraconazole in 700 mL HCl showed about 4% release in 2 hours, which approximates the saturation solubility of active (Figure 8). In comparison, the fresh extrudates showed a complete release and achieved oversaturation in 2 hours. Likewise, the extrudates stored for 3 months under accelerated conditions showed an identical release profile as the fresh extrudates.

Dissolution testing of 100 mg crystalline fenofibrate showed no release of drug in 2 hours in HCl due to the extremely low solubility of fenofibrate (Figure 9). In comparison, the solid solution of Soluplus and fenofibrate showed a complete release and reached several folds higher than saturation limit in the dissolution media. After storage for 3 months at accelerated conditions, the release of fenofibrate was complete in 2 hours and comparable to fresh extrudates, suggesting the drug remained in

FIGURE 5



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the amorphous state and did not change its dissolution profile.

Bioavailability Study

The solid solutions of itraconazole and fenofibrate in Soluplus prepared by hot melt extrusion were administered to beagle dogs at 10 mg/kg body weight. In comparison, the APIs as crystalline compounds and as physical mixtures of active and Soluplus were also administered at the same dose levels. Figures 10 and 11 illustrate the plasma concentrations over the time following oral administration of a single dose formulation.

The solid solution of itraconazole in Soluplus led to > 20 to 30-fold increase in the area under the curve (AUC) compared to crystalline or physical mixture formulations. Soluplus in the pure physical mixture did not influence the AUC of itraconazole, and the curve progression was comparable to the progression following the administration of the crystalline active.

Fenofibrate behaved differently than itraconazole. While the formulation with the crystalline active revealed the least concentration of the active in the plasma, the solid solution and physical mixture showed an identical concentration gradient with approximately 5-fold increase in AUC compared to crystalline fenofibrate formulation. Such effect could be related to the lower melting point of fenofibrate, which could help increase the API solubility in the physical mixture.¹⁰

DISCUSSION

Soluplus, a polymeric solubilizer with an amphiphilic chemical structure, has been designed and developed for solid solutions.

FIGURE 6

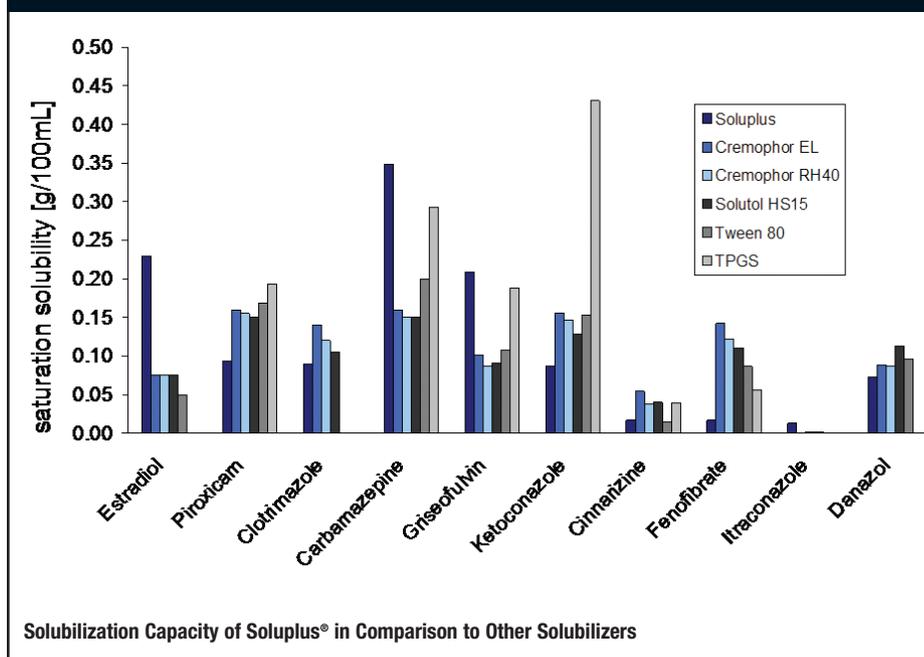
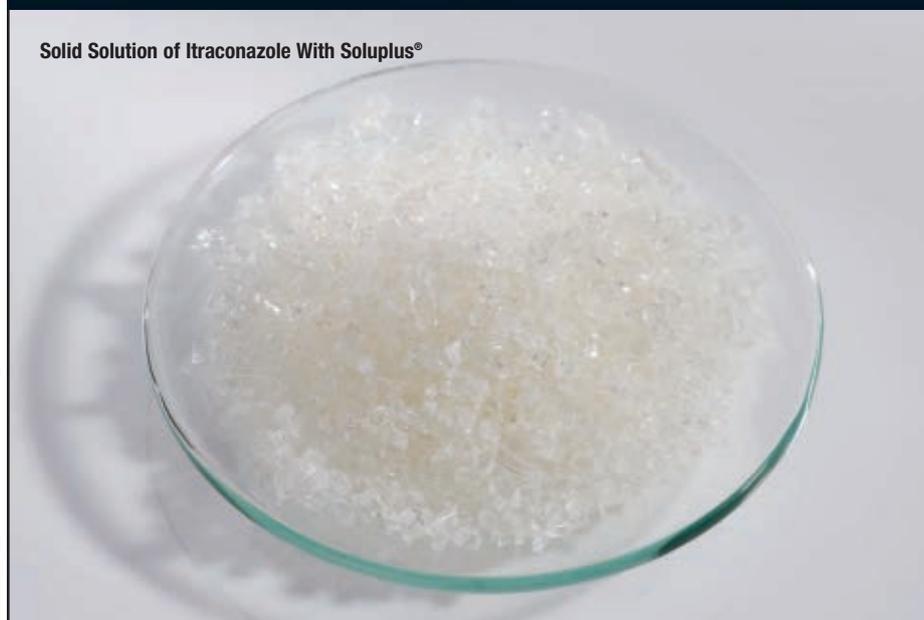


FIGURE 7



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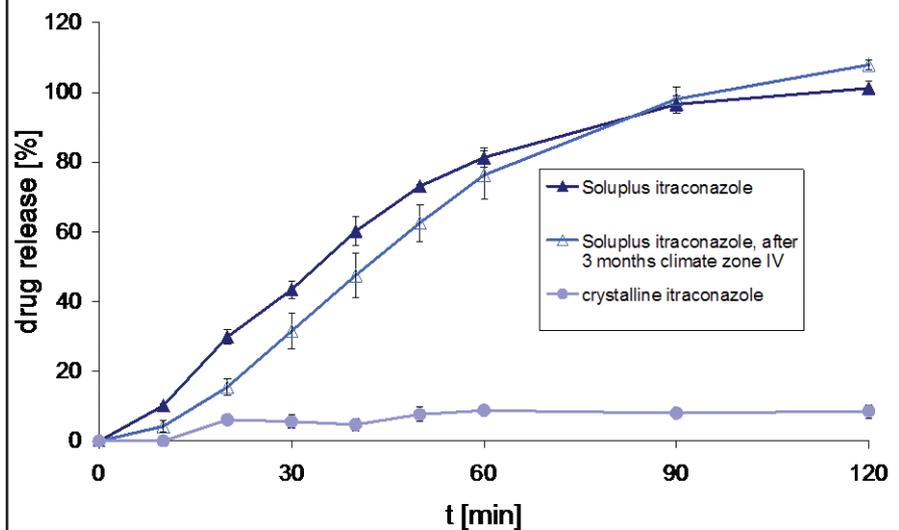
An ideal method for processing this new polymer is hot melt extrusion technology because it is highly extrudable and easily processed due to its low glass transition temperature and thermal stability at higher temperatures.

Soluplus is a polyethylene glycol-polyvinylcaprolactam-polyvinylacetate graft copolymer. Due to its bifunctional character, it is able to act as a matrix polymer for solid solutions and is also capable of solubilizing insoluble drugs in aqueous solution. This is in contrast to classical solubilizers like Cremophor RH40, Solutol HS15, or Tween 80 because Soluplus not only exhibits solubilization properties, but also combines the characteristics of a solubilizer and a matrix polymer for solid solutions.

Soluplus is capable of solubilizing various actives bearing a variety of chemical structures with different hydrophobicity and/or lipophilicity. A general trend for solubilization for individual molecules cannot be established because a variety of different drugs were solubilized successfully. Hence, Soluplus can be used as a solubilizer for many poorly soluble molecules with different chemical structures. Soluplus can also be used at a broader pH range because of its non-ionic characteristic without compromising its solubilization capacity.

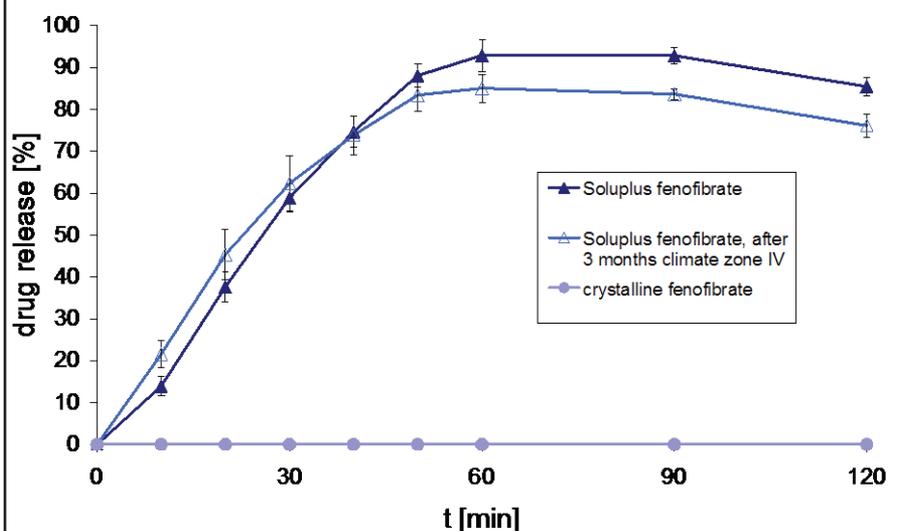
The poor solubility of drugs often leads to poor or significantly less bioavailability. Soluplus could increase the solubility and enhance the bioavailability of actives in solid solutions. Itraconazole and fenofibrate showed a significant increase in the bioavailability with Soluplus. The results also demonstrate that in certain cases, the physical blending or mixing of an active with Soluplus may enhance the bioavailability.

FIGURE 8



Drug Release of Itraconazole Compared to Crystalline Substance & After Storage at 40°C/75% RH for 3 Months

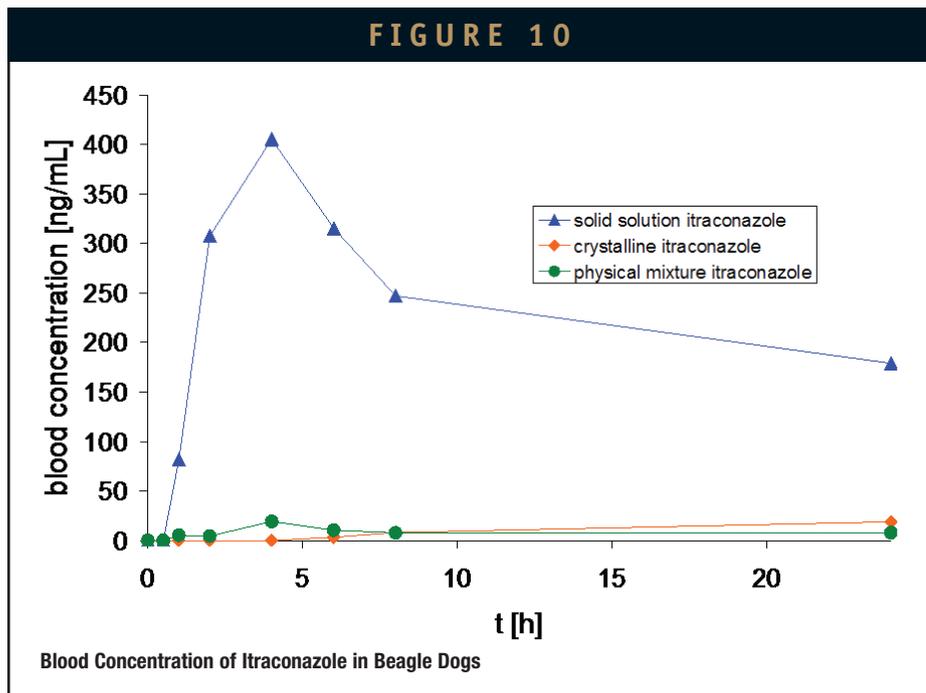
FIGURE 9



Drug Release of Fenofibrate Compared to Crystalline Substance & After Storage at 40°C/75% RH for 3 Months

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FIGURE 10



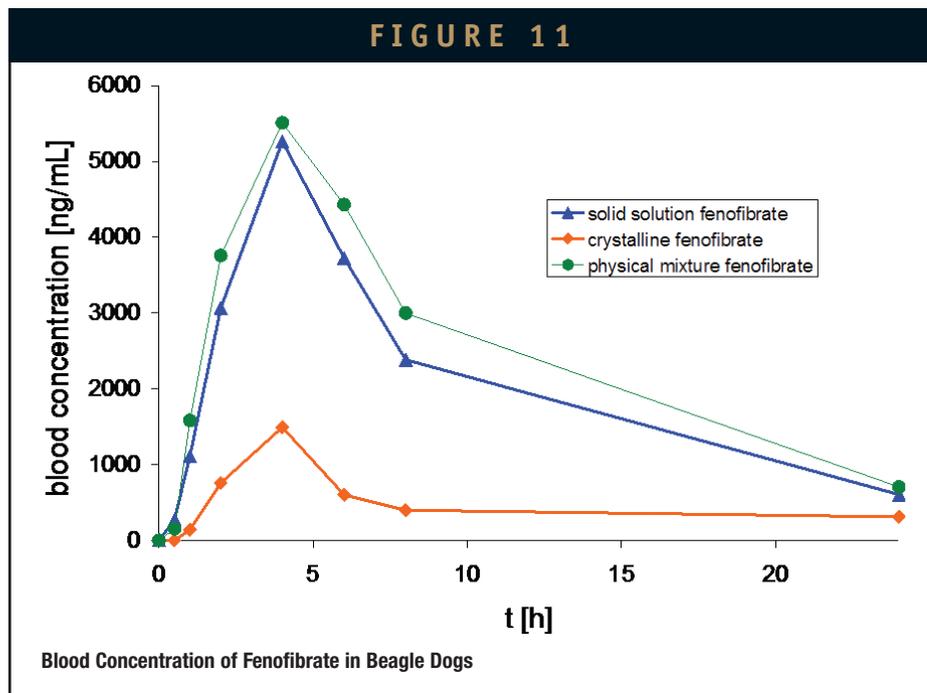
Such an effect could be observed with fenofibrate but not with itraconazole. Taken together, the data suggests that for certain individual actives, the physical mixture could be an alternative to the solid solutions to observe an enhanced bioavailability. It is therefore conceivable to use Soluplus as a binder and to achieve the solubilization effects in parallel. Soluplus also possesses appreciable wet and dry binding characteristics like PVP and Copovidone (data not shown).

CONCLUSION

Soluplus is especially designed to solubilize poorly soluble APIs and has demonstrated an excellent capability to form solid solutions with many crystalline APIs. Soluplus combines the advantages of solid solutions and solubilization in one, which can help to increase the bioavailability of insoluble actives.

The low hygroscopicity and low glass transition temperature of Soluplus makes it particularly suitable for hot melt extrusion due to its high extrudability at relatively low temperatures. The addition of a plasticizer is not required, and the low extrusion temperature provides the opportunity to extrude actives that are thermally unstable and moisture sensitive. The safety and toxicology of Soluplus have been demonstrated by comprehensive studies in animal models. The NOAEL value of Soluplus is > 1000 mg/kg.

FIGURE 11



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REFERENCES

1. Mehta M. AAPS/FDA Workshop on Bio-pharmaceutics Classification Systems. September 2002, 25-27.
2. Hauss D. Oral Lipid Based Formulations: Enhancing the Bioavailability of Poorly Water-Soluble Drugs. Vol. 170. Informa Healthcare, USA, Inc.: New York, NY;2007.
3. Foltmann H, Quadir A. Polyvinylpyrrolidone (PVP) - One of the most widely used excipients in pharmaceuticals: an overview. Drug Del Tech. June 2008;8:22-27.
4. Foltmann H, Quadir A. Copovidone: a copolymer with unique formulation properties. Drug Del Tech. September 2008;8:22-27.
5. Wang L, Ruffner D. Cyclodextrin grafted biocompatible amphiphilic polymer and method of preparation and use thereof. US Patent No. 7141540; 2006.
6. Breitenbach J, Wiesner B. The use of polymers in pharmaceutical melt extrusion. ExAct. 2008;20:8-11.
7. Kolter K, Maschke A. Melt extrusion for pharmaceuticals. ExAct. 2009;22:2-5.
8. Repka M, Battu S, Upadhye S, Thumma S, Crowley M, Zhang F, Martin C, McGinity J. Pharmaceutical applications of hot melt extrusion: part II. Drug Dev Ind Pharm. 2007;33:1043-1057.
9. Djuric D, Hardung H. Soluplus - the solid solution. ExAct. 2009;23:2-5.
10. Chu K, Yalkowsky S. An interesting relationship between drug absorption and melting point. Int J Pharm. 2009;373:24-40.

BIOGRAPHIES



Dr. Hendrik Hardung is the Technical Product Manager for Soluplus®. The pharmacist by education earned his PhD in Pharmaceutical Technology from the University of Freiburg im Breisgau, Germany. Since joining BASF SE as Manager Global Technical Service Excipients in 2008, he is responsible for technical support for several excipients.



Dr. Dejan Djuric is a Laboratory Manager in the R&D Project Management Excipients at BASF SE focusing on solubilizers and hot melt extrusion processes. As an engineer for pharmaceutical technology, he previously worked in the development for solid oral dosage forms at Abbott GmbH & Co. KG. Dr. Djuric obtained his PhD in Pharmaceutical Technology from the University of Duesseldorf and joined BASF in 2008.



Dr. Shaukat Ali pursued his interest in the pharmaceutical industry and worked at the Liposome Company, Penwest, and Lavipharm before joining the BASF technical team in 2004. He earned his PhD in Chemistry from the City University of New York, NY, and carried out his post-doctoral work at the University of Minnesota and Cornell University. He is an esteemed member of the Editorial Advisory Board of Drug Delivery Technology and a member of panel of experts for Pharmaceutical Technology-Sourcing and Management.

ATTORNEY REVIEW

Designing Your Generic Pharmaceutical Product: How Close to the Branded Product is Too Close?

By: Leslye B. Davidson, Esq.

Although, generic companies often want their products to look similar to that of the corresponding brand product, copying the trade dress of a brand pharmaceutical product (ie, the physical characteristics of its visual appearance, such as its shape, size, color, coating, graphics, and texture) can lead to unwanted litigation based on claims of trademark infringement, trade dress infringement, unfair competition, or even passing off. The more distinctive a brand product looks and the more money spent on marketing and promotion, the stronger the trademark/trade dress will be. The closer a generic product gets to the look of a strong brand name product, the more likely it is to be found infringing on the trade dress of that brand product. The test for finding infringement is a fact-intensive one, and therefore, it pays to carefully consider the various design elements of a generic product, while keeping the risk of infringement in mind.

HOW TO PROVE TRADE DRESS INFRINGEMENT

Trade dress protection secures the goodwill of a trade dress owner's business and protects the ability of consumers to distinguish among competing producers. Protection for trade dress under US trademark law is available when the physical characteristics of the product (eg, color and/or shape) are distinctive and non-functional. To prove infringement of an unregistered trade dress, a plaintiff must prove that (1) the allegedly infringing feature is non-functional, (2) the feature is inherently distinctive or has acquired secondary meaning, and (3) consumers are likely to confuse the source of the plaintiff's product with that of the defendant's product.

A Plaintiff Must First Show the Trade Dress is Not Functional

Under the "traditional" definition of functionality, "a product feature is functional and cannot serve as a trademark, 'if

it is essential to the use or purpose of the article or if it affects the cost or quality of the article.'" A second "newer" test of functionality considered by courts considers a feature functional when its exclusive use "would put competitors at a significant non-reputation-related disadvantage."

A Drug's Color and/or Shape May be Non-functional: Generic companies for years have asserted that the color and shape of a pharmaceutical product is functional and argued that generic products need to have the same the color and shape as the branded product to prevent drug confusion, particularly for the safety of elderly patients. The Supreme Court took up this issue in 1982 in *Inwood Laboratories, Inc. v. Ives Laboratories, Inc.* and upheld a district court decision finding capsule colors functional because "elderly patients associate the appearance of their medication with its therapeutic effect," because "some patients co-mingle their drugs in a single container and then rely on the appearance of the drug to follow their doctors' instructions," and because "to some limited extent, color is also useful to doctors and hospital emergency rooms identifying overdoses of drugs." However, District and Circuit courts after *Inwood* veered away from this finding of functionality in the *Inwood* decision. For example, in *SK & F, Co. v. Premo Pharmaceutical Laboratories, Inc.*, Premo's generic product had the same hard gelatin capsule and same color scheme as the brand name product, but had a different logo. The court lambasted Premo for copying the brand product and disagreed with Premo's functionality rationale for why it should be able to copy the brand product despite the fact that Premo's argument closely resembled the rationale cited by the Supreme Court in *Inwood*. In *Boehringer Ingelheim G.m.b.H. v. Pharmadyne Laboratories*, the court followed the rationale of SK&F closely and also found the trade dress of the tablet at issue to be non-functional.

The issue of functionality of pharmaceutical products took



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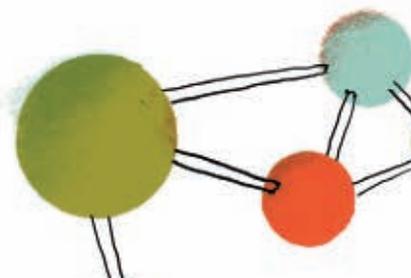
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- Continuing professional development opportunities
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yet another turn in the more recent decision in *Shire US Inc. v. Barr Laboratories, Inc.*, in which the Third Circuit found that color-coded strength serves a medical purpose for a drug for treating ADHD and therefore is functional. The Shire court distinguished the earlier Third Circuit decisions by explaining for example that the shape of the respective products were different (round versus oval), the markings were different, and “[j]uxtaposed against one another, the products are similar though not identical.” The court also pointed out that Adderall, the drug at issue, differed from the drugs in earlier cases in that it is a control substance and also cited the specific needs of patients having ADHD.

It is important to note that the Shire case was decided after two seminal Supreme Court decisions on functionality in *TrafFix and Wal-Mart*, which caution against the over extension of trade dress protection. It was also decided after change in the law to place the burden of proving non-functionality of unregistered trade dress on the plaintiff. Thus, the pendulum is currently swinging toward functionality of trade dress, at least for now.

A Plaintiff Must Also Prove the Trade Dress is Inherently Distinctive or Has Acquired Secondary Meaning

The Shire decision stopped at its decision of functionality and did not even address issues of secondary meaning, but it is important to understand that some of the same elements used to find functionality could also be used to find secondary meaning. To show that the trade dress of a product is distinctive, a plaintiff must show that the trade dress is “inherently” distinctive or that the trade dress has acquired secondary meaning in the minds of the purchasing public (ie, identifies source).

It Takes Time, Money, and Energy for a Color or Shape to be

Considered Distinctive: An example of a color acquiring secondary meaning is found in the robin egg blue of a Tiffany’s box, which identifies the source of the box as the famous Tiffany’s jewelry store.

The court in *Boehringer Ingelheim G.m.b.H. v. Pharmadyne Laboratories* found a brand drug distinctive where a good deal of time, money, and energy were expended in developing the brand drug’s sales and the Brand company’s promotion efforts “were designed not only to

familiarize doctors and pharmacists with the name Persantine but also with Persantine’s appearance. The court cited an advertisement reading “Persantine brand of dipyradamole is available as round orange sugar coated tablets.”

In more recent years, Pfizer has put much effort into getting similar source recognition for the blue color and diamond shape of its Viagra® tablet. By claiming distinctiveness under Section 2(f) of the Trademark Act [15 U.S.C. 1052(f)], Pfizer was able to obtain a US Trademark Registration covering the color blue and a completely shaded diamond shape in association with a “pharmaceutical preparation for the treatment of sexual dysfunction.” Pfizer has also associated its advertisements with the descriptive “the little blue pill,” and an internet search of this phrase immediately pulls up multiple articles about Viagra.

Factors Used to Evaluate Whether Trade Dress is Distinctive:

To evaluate whether the trade dress of a brand pharmaceutical product is distinctive, a generic company should consider a number of factors. First, the generic company should research whether trademark protection has been sought for the color and/or shape of the brand product and whether any US Trademark Registrations exist. It should also consider how long the branded product has been sold in interstate commerce; how much marketing/promotion has been conducted by the brand owner concerning aspects of the trade dress; and how distinctive the color, shape, and size of the brand name product are and the look and coloring of any identifying imprints on the product. For OTC products, the generic company should also consider the look of the product packaging. A company may further wish to evaluate third-party uses of one or more elements of the brand product trade dress, particularly for the same class of drugs. These factors all go to whether the entire trade dress or aspects of the trade dress (eg, shape or color) are distinctive enough in the minds of the purchasing public to attain trade dress protection.

A Plaintiff Must Prove Likelihood of Confusion

The third element necessary for proving trade dress infringement is likelihood of confusion. When considering likelihood of confusion,

Courts have looked at (1) the strength of the trade dress, ie, the type of trade dress and the extent of third party use; (2) the similarity of design; (3) the similarity of the products; (4) the similarity of retail outlets and purchasers; (5) the similarity of advertising media used; (6) defendant's intent; and (7) actual confusion.

Courts Look to all Aspects of a Drug's Trade Dress to Evaluate Confusion: In *Florida Breckenridge, Inc. v. Solvay Pharmaceuticals, Inc.*, a prescription pharmaceutical case concerning the Estratest caplet, the court found that a generic tablet using the same dark green color as the Estratest brand product was not likely to cause confusion. The court distinguished the generic tablet by noting it had a different shape tablet, a different size, a shiny versus dull finish, and a different stamping, and there was extensive third-party use of the trade dress elements in a combination similar to the branded product.

In *American Home Products Corp. v. Barr Laboratories, Inc.*, the color shared by trade and generic tablet was found only to have one aspect of the overall trade dress of the tablet, with the tablets being overall quite dissimilar; so much so that no confusion regarding their separate commercial sources is likely to arise.

Trade Dress Confusion is More Likely for Capsules: When considering the issue of likelihood of confusion for the pharmaceutical trade dress of capsules, companies should also be aware that use of the same or a similar color on a capsule is more likely to be found infringing because the remainder of the trade dress of all capsules is similar (eg, same shape, same texture). Thus, capsules are less distinguishable on grounds other than the color. For example, in *SK&F Co. v. Premo Pharmaceutical Laboratories, Inc.*, the court enjoined a generic product using same hard gelatin capsule and same color scheme as the brand name product, but having a different logo. Similarly, in *McNeil-PPC, Inc. v. Granutec, Inc.*, the court held that trade dress of the manufacturer's capsules had likely acquired secondary meaning and granted a preliminary injunction because the defendant copied the color of the branded capsule. An injunction against the sale of the generic product was also granted in *Ciba-Geigy Corp. v. Bolar Pharmaceutical Co., Inc.*, because the generic product copied the color/size/shape of branded capsules.

Likelihood of Confusion Test Can Differ for OTC Drugs: The analysis of trade dress also differs for OTC products where the product is not visible and the packaging looks different. For example, in *Smithkline Beckman Corp. v. Pennex Products Co., Inc.*, the court found an OTC generic pharmaceutical product not infringing despite the fact that the generic tablets looked the same as the branded tablets. In this instance, the tablet, though similar in appearance to the branded product, was not visible, and the product packaging did not resemble that of the branded product. The court therefore found that the generic product was not confusingly similar. However, the same court found that when a related generic product was visible through the packaging, a likelihood of confusion could exist. ♦

BIOGRAPHY



Leslye B. Davidson is a Founding Partner at Davidson, Davidson & Kappel, LLC, an Intellectual Property law firm in New York City. Ms. Davidson earned her law degree from New York University School of Law and her BS in Pharmacy from Rutgers University. Ms.

Davidson practice includes patent prosecution, freedom to operate and infringement opinions, due diligence, and patent litigation, with particular emphasis on pharmaceutical patent-related matters. She also practices trademark law and has significant experience in trademark prosecution, opinion work, and trademark litigation. Ms. Davidson has counseled many companies on how to create significant and valuable trademark portfolios, while avoiding the peril of litigation with competitors.

REFORMULATING SUCCESS

Industry Layoffs: Recessionary Medicine That's Worse Than the Disease

Part 1 of a 6-part series on business models & best practices for navigating the new normal.

By: Derek Hennecke, President & CEO Xcelience LLC

In the Middle Ages, doctors used leeches in a practice called bloodletting as a “cure” for many diseases. It was seen as a means of allowing the demons in the body to flow out. Today, employers throughout the country are applying the same logic to our struggling industry. Persistent and repeated layoffs are being touted as a means to bring back corporate health. It's a massive industry-wide blood-letting, and it makes about as much sense as the medieval practice. How can we let go of our own lifeblood as a means to ensure growth?

The hemorrhage has been massive. Pharma and biotech cut more than 60,000 jobs last year. That's up from 45,000 in 2008, the year the Great Recession began. Five companies alone eliminated 25,000 positions. And the carnage continues in 2010 with more layoffs announced every month. At the time of writing, the website Fierce Biotech, which tracks industry layoffs, shows nine companies cutting staff and one hiring since the new year started.

Clearly, our industry is not alone in this rampage. Employers in the US took 1,761 mass layoff actions in January of this year that resulted in the separation of 182,261 workers. It's an economy-wide obsession, and it's not limited to this recession either. In fact, over the course of the last quarter century, it has become common practice to downsize during the tough times and rehire when conditions improve. Paradoxically, many companies even continue to downsize after the profits begin to roll in again.

Layoffs are messy, unpleasant, and hugely damaging to the individual and the organization. So why do they do it? To improve the bottom line and raise share prices, of course. They cut off

a limb to save the whole. And yet, if I may take the analogy one step further, new research shows that in the vast majority of cases, cutting off a perfectly healthy limb does not make the body function better. Go figure.

I'll admit, when the recession entered into its darkest days around this time last year, when Armageddon was in the air and the stock market was plunging, the topic of layoffs came up in our management meetings. Everyone was doing it. Should we? We decided as a team that even if it hurt, we wouldn't go there. You can't really mean that your people are the lifeblood of your organization if you're willing to slit the corporate wrist just to increase this month's profits.

Since then, I have watched competitor after competitor undertake round after round of layoffs. And you know what? Every time another one does, it helps my business. Their decreasing capacity makes my capacity more valuable. I just can't understand why they do it. Layoffs are disastrous for the employee, bad for the economy, immeasurably damaging to the company itself, and if that isn't enough, there is increasing evidence that they're even bad for the bottom line. The following is why.



LAYOFFS ARE EXPENSIVE

First come the obvious costs, like severance pay, accrued vacation and sick leave payouts, and outplacement services. Don't forget higher unemployment insurance taxes, potential lawsuits, or even sabotage. Then come the less quantifiable costs like loss of institutional memory and knowledge, loss of trust in management, and declining productivity. Finally, as business returns, with lost capacity there are lost customers, and eventually - one step behind the trend - the resulting costs of hiring. In the end, layoffs are actually substantially more expensive than simply riding through a tough period. Of course public companies also have shareholders to please. So why not downsize to improve stock performance? Don't public companies enjoy a surge in share prices when downsizing? In the February Newsweek article, Lay off the Layoffs, Jeffrey Pfeffer writes that "A study of 141 layoff announcements between 1979 and 1997 found negative stock returns to companies announcing layoffs, with larger and permanent layoffs leading to greater negative effects. An examination of 1,445 downsizing announcements between 1990 and 1998 also reported that downsizing had a negative effect on stock-market returns, and the negative effects were larger the greater the extent of the downsizing."

The upshot is that layoffs actually reduce company value. Not just down the road, but immediately as well.

EMPLOYEES HATE LAYOFFS

I shouldn't have to say this, but employees don't like watching their colleagues head out the door. These are, after all, in-human trials we're dealing with. In addition to the personal tragedy, there is the anxiety and fear of those left behind. Who's next? You can't put a cost price on lower morale and its affect on productivity. But you can see its effects when fear of losing jobs leads employees to look for a more positive working environment. And you can bet it will be your best employees who find new work the fastest.

THERE'S A LINK BETWEEN CUTTING EMPLOYEES & LOSING CUSTOMERS

Research by Bain and Company fellow Fred Reichheld shows that employee and customer loyalty are directly linked. It makes sense that if you're buying from a company that treats its people badly - particularly if it's the people you were used to dealing with - you're probably going to start shopping elsewhere. At the very least, you're going to feel less loyalty, now that the face you're used to seeing is gone.

The customer/employee retention link is especially solid in the CRO industry where entry barriers are relatively low. CROs can pop-up and disappear in a period of a few years. Customers can get left mid-project. When a lab vanishes, there are even consequences for all the lab's previous clients since the FDA will be justifiably concerned about the quality of work done there.

Our customers are easily spooked. In addition to quality and reputation, longevity (past and future) is and should be something our customers look for in a CRO lab. And major layoffs are often the first step in a corporate death spiral.

HOW TO MANAGE WITHOUT LAYOFFS

This rampage - this cannibalistic killing of our own - has to stop. If layoffs are medicine for the Great Recession, then the medicine is surely worse than the disease. It's disastrous for the employees. It's strangling the recovery. And if that's not enough, it's hurting the companies doing the layoffs most of all.

Granted, there are times when layoffs are the only option. These are cases where the industry itself is in permanent decline, and capacity needs to adjust to meet the shrinking market. Think buggy whips. Photographic film. Corner movie-rental stores. Newspapers. But not retail. Not banking. Not computers. Not cell phones. And certainly not pharma and biotech. Many have argued - particularly with the unlocking of DNA sequencing - that this could be the industry's greatest decade yet.

The key to survival when sales are down is restructuring. Cut costs where they can be cut, and if a function is no longer valuable to the company, repurpose the employees. At Xcelience, when a project is delayed or the recession makes sales slow for a month, we spend more time on equipment maintenance and facility improvement, take the time for cross-training and in-house education, and move more people into sales or customer support. Then when we have a month of above average sales (and this has been a roller-coaster year), we have every man and woman on deck in a heartbeat.

So enough with these bulimic business practices. As employers, we need to put our people first. Put our economy first. Put our industry first. And if that's not motivation enough, then put our own bottom line first. You just can't downsize your way to success. ♦

BIOGRAPHY



Derek G. Hennecke, MBA
President & CEO
Xcelience

Derek G. Hennecke is a founding member of Xcelience and its current CEO and President. He has a long history of growing strong businesses around the world. He balances a scientific and business background with nearly 2 decades of international experience in the healthcare industry and a track record as a highly successful international turn-around manager in the global drug development community. Xcelience is the first company Mr. Hennecke has managed as an owner, having launched a management buy-out from MDS Pharma Services in 2006. The newly formed company immediately embarked on a robust pattern of strong growth. This growth was recognized in May 2008, when Mr. Hennecke was selected as a finalist for the coveted 2008 *Ernst & Young Florida Entrepreneur of the Year* award, a nomination based on the demonstration of extraordinary success in the areas of innovation, financial performance, personal commitment to community, and the company's perpetual growth since its official formation. Mr. Hennecke was also recognized as a finalist for the *Ultimate CEO* awards by the Tampa Business Journal in 2008. This is in addition to Xcelience's nomination for *Small Business of the Year* by the Greater Tampa Bay Chamber of Commerce, also this year. Before founding Xcelience, Mr. Hennecke managed the same Tampa-based business while also overseeing a Seattle and a Montreal-based plant as Vice President and General Manager, Pharmaceuticals and Biopharmaceuticals. Prior to that, he spent more than 10 years abroad working for the Dutch-based conglomerate DSM. In Montreal, he was GM of a 250-staff Biologics plant for more than 2 years. In Cairo, Egypt, as GM, he oversaw a radical turn-around in an anti-infectives plant that was originally slated for closure. He also spent 2 years in Holland developing new Pharma intermediates, and two years in Mexico as Commercial Director covering Central and South America. He also worked for Roche, both in Canada and Germany. Mr. Hennecke earned his BSc in Microbiology from the University of Alberta in Canada and his MBA from the Erasmus University in Rotterdam, The Netherlands.

SPECIAL FEATURE

Inhalation: Going Beyond Asthma!

By: Cindy H. Dubin, Contributor

Advances in drug formulation and inhalation device design are creating new opportunities for inhaled drug delivery as an alternative to oral and parenteral delivery methods. Much of the interest in pulmonary delivery of systemic drug therapies is focused on chronic diseases and refractory conditions, ailments that require frequent drug administration for a protracted period of time.

The role of device design and development in defining and driving emerging opportunities in this sector cannot be overstated. Nebulizers, metered dose inhalers (MDIs), and dry powder inhalers (DPIs) have each found a niche in the quest for optimal treatment and convenient use.¹ While nebulizers have evolved relatively independently of the drug formulations they deliver, the current generation of MDIs and DPIs have been developed or tailored for the specific pharmaceutical being delivered, resulting in improved performance. Advancements in formulating technology are expected to push sales of DPIs, replacing metered-dose inhalers to a larger extent. Dry powder



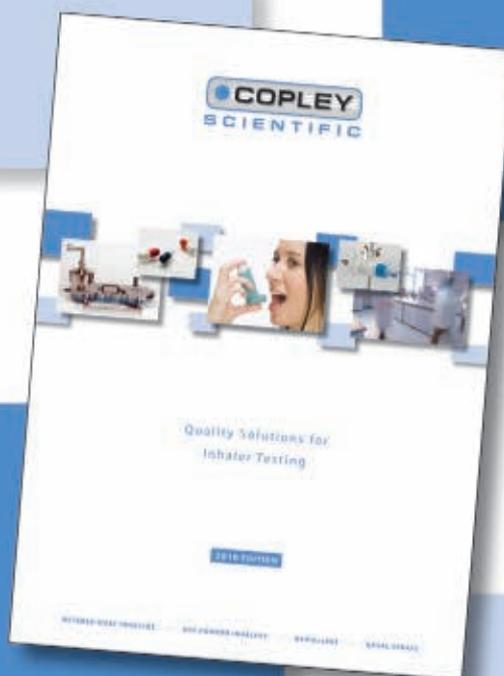
FIGURE 5
Hovione's TwinCaps®

New Quality Solutions for Inhaler Testing Brochure 2010 *available now!*

Quality Solutions for Inhaler Testing 2010, the new and significantly expanded brochure from Copley Scientific, provides a comprehensive guide to characterising orally inhaled and nasal drug products (OINDPs). Describing in detail how to use an extensive range of inhaler testing equipment it is the perfect reference document for those seeking to interpret regulatory guidance and apply *in vitro* test methods.

As a world leading supplier of inhaler testing equipment Copley Scientific is able to review and describe best practice in this field. Participation in expert groups and a network of industrial contacts, ensure the company's product offering reflects and anticipates the very latest requirements of the sector.

The new brochure makes reference to the changing regulatory environment and describes pharmacopoeial monographs in relation to device technology in detail, allowing users to establish a framework for testing. The brochure showcases new additions alongside established products, including: abbreviated impactors for rapid screening, dissolution testing equipment for inhaled products and a series of semi-automated devices that streamline impactor measurements, amongst many others.



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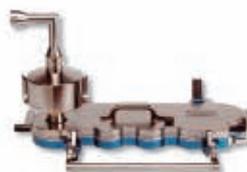
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inhalation, an enabling concept in non-invasive drug delivery, is progressively emerging as an important contender among pulmonary drug delivery methods. This importance is being fueled by the latest developments including sophisticated device architectures, growing research activity in powder formulations, and innovations in particle engineering.²

Until recently, respiratory conditions such as asthma, chronic obstructive pulmonary disease (COPD), and emphysema represented the sole therapeutic areas of the pulmonary sector. However, current technological advancements have spanned the application of pulmonary devices to the treatment of non-respiratory conditions such as diabetes and migraine. Gilead's recent approval of Cayston for use with cystic fibrosis patients is indicative of the current landscape for pulmonary drug approvals.

Despite the commercial failure of Pfizer's inhaled insulin, Exubera, alternative methods of delivering insulin to patients remain of interest to developers. Of particular interest are Mannkind's Afrezza, an inhaled insulin product that has recently completed Phase III trials. If the product gets approval and can demonstrate meaningful sales, protein and peptide delivery could again become a driver in the inhalation market. Eyes are also on Generex Oral-lyn from Generex Biotechnology, a buccal spray formulation in Phase III in the US, which has recently been approved for marketing in Ecuador, India, and Lebanon.

Asthma and COPD represent the largest market segment (65%) of the inhaled drug market worldwide (Table 1), according to SafetyNet, Inc., with asthma sales expected to reach \$21 billion by 2011 and \$11 billion for COPD.

Boehringer Ingelheim's success with inhaled Spiriva (tiotropium) for COPD is an indication that asthma is not the only

major market for inhaled drug products. The product is expected to attain sales of approximately \$2.8 billion in 2013. According to some, Spiriva represents the resurgence of the inhaler as a differentiator.

"Given the scarcity of new drug classes approved in asthma and COPD in the past decade, the number of players and intensity of competition in asthma in particular, and no near-term disease-modifying treatments, companies have to differentiate their products through new and improved devices. We see this with BI transitioning Spiriva from its HandiHaler to its Respimat™ soft-mist inhaler," says Scott Fleming, Senior Vice President, Sales and Marketing for MicroDoseTherapeutx, Inc.

Experts predict that the market potential for inhalation therapies represents significant opportunities for drug delivery developers. The total respiratory market was approximately \$25 billion in 2009 and is projected to grow beyond \$30 billion by the year 2014, and added to this are the many potential markets for non-respiratory acute treatments and systemic delivery of biologicals. In this annual Inhalation Device report, *Drug Delivery Technology* spoke with several of the industry's leading technology companies to find out what inhalation developments they have in store for the pharmaceutical industry.

ACTIVAERO—CONTROLLING THE UNCONTROLLABLE

This past October, Activaero secured its first round of outside financing in its 11-year history. Through this capital, the company is branching from a pulmonary drug delivery company to a Specialty Pharmaceutical company developing its own high-value compounds to treat pulmonary diseases with its patented controlled inhalation technologies, explains Activaero GmbH's CEO Gerhard Scheuch.

FIGURE 1



Activaero's AKITA Jet

William Zimlich, CEO of Activaero America, says the inhalation market is divided into two segments: (1) treating pulmonary diseases through drug inhalation and (2) delivering drug substances for systemic uptake through the lungs.

"Activaero has always focused on pulmonary conditions such as asthma, COPD, alpha 1 antitrypsin deficiency, and cystic fibrosis, and unfortunately, none of these diseases are on the decline. Activaero may branch out into systemic delivery if the compound being delivered was a strategic fit."

Currently, Activaero is focused on the uncontrolled asthmatics market. Through its drug development and intelligent devices, Activaero plans to help a large percentage of asthmatics get their condition partly controlled or permanently controlled, says Mr. Zimlich. "The American Lung Association reports that asthma affects nearly 23 million Americans, including 7 million children. More than half of them have uncontrolled asthma."³

In addition to raising money this year to carry out its plans, Activaero launched the Watchhaler children's spacer device in the US and received 510(k) clearance for its AKITA Jet (Figure 1). AKITA offers

FIGURE 2

Bang & Olufsen Medicom's Asmair®



high lung deposition, explains Mr. Zimlich.

“Activaero was founded on the principle of guiding the patient’s inhalation maneuver to optimize drug deposition. We do this through active controlled inhalation volume and flow rate programmed on an individualized SmartCard.”

The SmartCard looks like a credit card that fits into the front of the AKITA, and it programs the machine. At Activaero, the SmartCard is programmed for each patient by using data provided by the patient’s physician. The doctors provide the drug dose and schedule as well as the patient’s pulmonary function, and this patient-specific programming is like personalized medicine, says Mr. Zimlich.

In some applications, the drug dose does not need this much attention, and the doctors can simply select one SmartCard out of a notebook based on the patient’s FEV1. The SmartCard is read/write, thus it records all the events of the AKITA, giving Activaero compliance/adherence monitoring.

“Doctors find this incredibly useful especially in clinical trials,” he says. “We believe the AKITA technology is most valuable in severe pulmonary diseases with high unmet medical needs.”

BANG & OLUFSEN MEDICOM— A RENEWED FOCUS ON ASTHMA & COPD

Bang & Olufsen Medicom has been active in the inhalation development range for the past 15 years, developing several pressurized metered dose inhalers (pMDI) that can be used for asthma and COPD. The latest addition to the inhaler range, Insulair®, a disposable breath-actuated device, is designed for use with liquid drug formulations suitable for pMDIs. The inhaler offers improved pulmonary drug delivery for systemic treatment of diseases, including diabetes. The company has also developed Asmair® (Figure 2), a pMDI for asthma and COPD.

Asmair features a patented single increment dose counter, which reduces over-counting and under-counting. Additionally, the unit requires 50% less force than conventional inhalers to release a single dose.

“After the massive interest in inhaled insulin delivery a few years back, almost all of our focus has returned to asthma and COPD,” says Soren Jacobsen, vice president, R&D. “We still hope that inhaled insulin will become a success one day and revitalize this marked as well as let us capitalize on our vast knowledge around systemic delivery. We also have new concepts including proprietary technology in the pipeline not restricted to usage only with insulin and including compliance enhancing features. These concepts can rapidly be taken to market due to the fact that all necessary skills and experience is currently within Medicom”.

Another major focus for B&O Medicom is service and consulting on its customers’ intellectual property. Mr. Jacobsen explains that B&O Medicom offers its expertise from concept design to commercial production. Many of the

projects with which the company is currently consulting on are expected to reach the market in the next 7 years. It has become clear to Medicom that the combination of development capabilities with in house GMP manufacturing offering fast time to 1st clinical, is becoming more and more important to clients.

CATALENT PHARMA SOLUTIONS—FILLING CAPABILITIES

Most of Catalent’s business today is with companies that are either early-stage firms looking for efficacy of candidate compounds or larger companies that are new to the inhalation space and don’t have the in-house capabilities for feasibility and product development activities, explains D. Dean McKinney, Vice President of Business Development for the respiratory and analytical business at Catalent Pharma Solutions.

In January, Catalent announced it had acquired advanced fine powder filling capability to solidify its position in inhalation development and manufacturing services. With the purchase of Harro Höfliger’s Omnidose filling equipment, Catalent now offers its customers fully scaleable DPI filling capability. Housed in Catalent’s Research Triangle Park, NC, facility, this capability provides a flexible platform to support all clinical manufacture through Phase II/III and a scaleable path to higher volume late-stage clinical and commercial manufacturing.

Complementing Catalent’s pre-existing automated pMDI infrastructure (Figure 3), the new equipment is designed for powder filling for microdosing, in the 1 to 300 mg of powder range, into an array of DPI formats to include both capsule-based and pre-metered blister device formats.

“We saw a void in capabilities in the

industry for first-in-man studies that take programs further,” says Mr. McKinney. “This capability will enable us to do early studies and leverage that development as the program progresses.”

Catalent’s clients cover the gamut of therapeutic focus areas: COPD, asthma, cystic fibrosis, pain treatment, and even bioterrorism products. While a small portion of Catalent’s business involves companies interested in changing a delivery method to become an inhaled delivery, most clients are interested in improving performance and reducing dosing regimens for existing compounds.

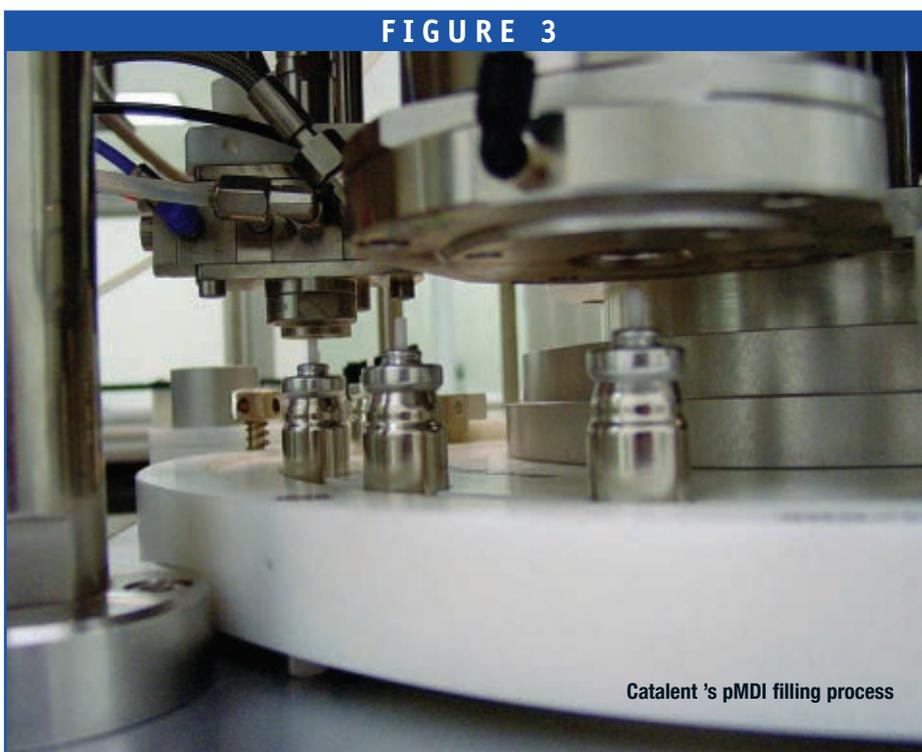
“Inhalation is a healthy market right now and keeps growing,” says Mr. McKinney. “We see Catalent as being in the unique position to develop all inhaled dosage forms and serve a variety of markets.”

CIRRUS PHARMACEUTICALS— MULTIPLE FOCUS AREAS

Cirrus Pharmaceuticals, Inc. is a contract product development company assisting biotechnology and pharmaceutical companies with dosage form development projects (Figure 4). Like other contract product developers, Cirrus faces driving market undercurrents. These include upcoming patent expirations, the prospects of systemic delivery in a post-Exubera environment, increasing focus on the treatment of COPD and cystic fibrosis, and the debate on how to approach generic DPI products.

“Inhalation products are a multibillion dollar industry, and the market still shows great potential for growth, such as in emerging markets and for underserved disease states (eg, COPD),” says Michael Branciforti, Director, Business Development.

Cirrus provides product development services worldwide for all major dosage forms and a variety of delivery systems,



including, but not limited to, nebulizer, MDI, and DPI products. The scope of Cirrus’ work includes dosage form selection, preformulation studies (including salt selection), analytical method development and validation, formulation development, process development, tech transfer, release testing, stability studies, device evaluation and selection, and life cycle management.

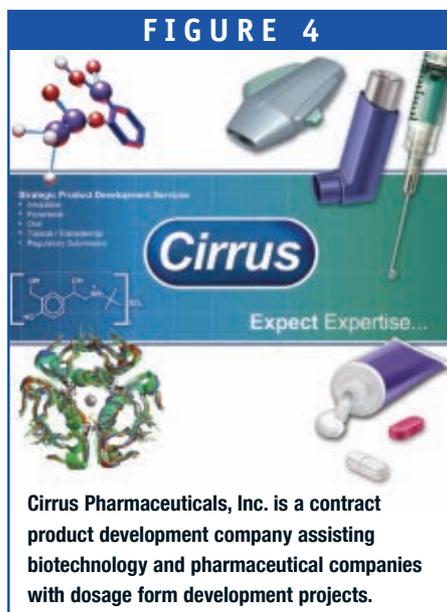
Cirrus develops inhalation products for all therapeutic areas. A few examples are asthma, COPD, cystic fibrosis, smoking cessation, antibacterials, and antivirals. The company routinely works with small and large molecules.

“We’ve been involved in an interesting mix of generic and new molecule development, including both single entities and combination products,” says Jay Holt, Director, Inhalation. “We also continue to do quite a bit of device evaluation, for example, for MDI spacers and valved holding chambers. We’ve developed a strong expertise for the application of breathing simulation to *in vitro* testing, and

we saw that work continue to grow throughout the past year.”

Mr. Branciforti adds that inhalation products are special with regard to the higher level of chemistry, manufacturing, and controls (CMC) development required to bring a product to market, compared to other routes of administration. Cirrus is registered with the FDA as a cGMP testing facility and can generate QA-reviewed, regulatory submission-ready CMC documentation.

“Cirrus was founded based on its inhalation expertise,” says Mr. Branciforti. “We have developed a reputation for solving challenging development problems, as well as for handling more routine testing programs. However, the primary driving force behind our business remains: Focus on our clients’ needs and assist them in bringing a quality product to market at a reasonable cost and within a tight timeline.”



HOVIONE—BUILDING INHALED PRODUCTS

Hovione has understood that inhaled drug products need to be developed from the ground up, and that means starting at the API. Hovione is building a development strategy that encompasses the molecule, the crystal, the powder, and the unit dose, as well as the delivery device, to make sure that all drug product components work together efficiently.

“Only with integrated development can we be sure of efficient delivery and a stable product,” says Peter Villax, Vice President, Pharma Business Unit, Hovione.

Hovione’s capabilities range from developing API and formulation processes that create engineered particles with optimal lung delivery and deposition, to DPI devices. An important part of its expertise is making drug substance, formulation, and device work together effectively. Hovione’s work in 2009 was supporting Daiichi Sankyo and Biota’s new product for influenza, CS-8958, a pro-drug of laninamivir, which is delivered using Hovione’s DPI, TwinCaps® (Figure 5). Trials indicate the product is effective in

treating asthma with one course of treatment. Daiichi Sankyo filed the NDA in Japan in January, while Biota is seeking licensees worldwide. Hovione is also working on formulation development and manufacturing supplies for clinical trials for an inhaled protein.

“As an independent and integrated service provider, Hovione encompasses all aspects of inhalation formulation development and takes responsibility for the work it performs with regard to suitability for the next project step. We do not resort to subcontracting, and share the same goal as our client: a successful product application and registration (NDA, MAA, etc),” says Mr. Villax.

TwinCaps is suited to acute inhaled treatment for delivering antivirals and antibiotics for treating lung disease. Hovione is able to provide formulation and particle engineering services for such drug substances. In addition, Hovione uses particle engineering technologies to target specific particle size profiles of powder formulations (drug only or drug/excipient combinations) for developing multidose inhalation drug therapy for chronic conditions, explains Jason Suggett, PhD, Hovione’s Director of Pharma Operations.

“One of the major challenges in this area is to develop a product with the ability to consistently deliver a high proportion of the dose to the target area of the airways (thereby optimizing efficacy while minimizing the chance of systemic side effects),” says Dr. Suggett. “This is a challenge both to the innovators developing new drug products as well as generic companies trying to match the performance (show therapeutic equivalence) to existing products.”

MICRODOSE THERAPEUTX—SMART INHALATION

MicroDose had a very busy and productive year in inhalation, both in development of its own proprietary products and with its partnered programs with Merck, Novartis, and the US Department of Defense. Throughout the past 18 months, the MicroDose inhaler has been in two successfully completed US clinical trials and is currently in a third trial still ongoing. Two evaluation studies have been completed with potential partners, one for a novel peptide for asthma. In the past 6 months, the company acquired a clinical stage, novel, inhaled antiviral for the treatment and prevention of RSV disease (MDT-637) and initiated the development of a patented LAMA (long-acting muscarinic antagonist) for COPD (MDT-006). MicroDose is currently seeking option and evaluation partners for both MDT-637 and for MDT-006. On the device development front, the company completed a commercial design of a multidose inhaler platform suitable for Phase II studies and demonstrated the incorporation of cell phone uplink technology into its inhaler that can send dosing and compliance information from the inhaler, in real time, to a web-based data management system for compliance tracking.



“The MicroDose electronic DPI (Figure 6) represents a ‘game changing’ technology shift in dry powder inhalation,” says Scott Fleming, Senior Vice President of Sales and Marketing at MicroDose. “Through the innovative use of off-the-shelf, state-of-the-art electronics, MicroDose has created the ideal inhaler that meets all of the ‘holy grails’ in inhalation. Using a high-frequency piezo transducer and other electromechanical elements, the MicroDose inhaler achieves superior dose delivery efficiency that is patient flow rate, orientation, and coordination independent. Our reminder features and wireless real-time compliance tracking ability should improve patient compliance and allow a reduction in the size and cost of clinical trials while improving efficacy in the clinic and patient outcomes in the market.” Mr. Fleming says this puts MicroDose in a position to deliver all manner of drugs (both small and large molecules) for local or systemic delivery to all patient populations in all potential pulmonary markets.

MDT’s current therapeutic focus in inhalation is in respiratory diseases, such as asthma, COPD, cystic fibrosis, and respiratory syncytial virus (RSV), and is also developing an inhaled antidote against nerve agents. In addition, MicroDose is contemplating an acute inhaled treatment for an auto-immune disease as well as inhaled anti-infectives.

Mr. Fleming sees much over-crowding in the asthma market, which has led to the emergence of development programs for the pulmonary delivery of acute treatments for non-respiratory diseases, such as agitation, migraine, acute pain, viruses, and infections and even insomnia. This strategy, he says, can allow companies like MicroDose to create products with more manageable clinical trials and lower costs than those needed for chronic diseases.



REXAM HEALTHCARE—MEETING THE CHALLENGES OF INHALATION

The inhalation market is a challenging one, and one that Rexam Healthcare is meeting head-on, explains the company’s Global Marketing Director, Patrice Lewko. “Devices have a strong influence on the efficacy of the drug and on patient compliance. Indeed, the device will impact the way the drug gets to its intended destination; in many cases, it will also create the therapeutic dose. In addition, inhalers are very often difficult to use properly for patients, and this can jeopardize compliance and patients’ health. To make it even more complex, the lungs are a sensitive organ, and we need to be very careful with what is inhaled; leachables should be very well controlled. In order to help our customers develop the best device for their drug, Rexam has developed a strong network of regional Technology Centers in Europe, Asia, and North America. We can participate in the whole development and industrialization process, working as a team with our customers to ensure successful project developments.”

On the pMDI side, Rexam recently

introduced a metering valve platform (Inhalia™, Figure 7) a proprietary technology that has demonstrated

performances in dose consistency and prime retention. As for DPI, Rexam develops and manufactures devices for customers interested in pulmonary and nasal spray applications. In nasal delivery, Rexam has finalized the design of Advancia™ which Mr. Lewko says will bring a unique combination of features to the market, from preservative-free to user independence. While allergic rhinitis is the key nasal spray therapy, Rexam is also involved in programs for systemic administration, including protein delivery through the lungs.

Looking ahead, Mr. Lewko predicts the value of the inhaled products market will stagnate due to the increasing amount of generics. “However, we should see the return of a more dynamic market with the introduction of once-daily treatment and new combination drugs. The market is going to be more diverse and maybe less predictable. Rexam is well positioned in that environment, with strong development capabilities to participate in the rise of new devices in combination with our proprietary platforms for nasal and pulmonary applications.”

3M DRUG DELIVERY SYSTEMS—IMPROVING HEALTH THROUGH INHALATION

Currently, more than 50% of all metered-dose inhalers worldwide use 3M drug delivery technology, says Robert Odenthal, Vice President, Inhalation Business, 3M Drug Delivery Systems (Figure 8). New components for 3M's aerosol MDIs include a non-priming face seal valve and an interior canister coating that protects the formulation to ensure a more reliable dose.

In the area of DPIs, 3M has introduced the Conix™ DPI and the Taper DPI. The 3M Taper DPI stores APIs on a microstructured carrier tape. The DPI uses 3M microreplication and extrusion technologies to create a “dimpled” tape upon which one or more APIs are coated, enabling it to provide up to 120 pre-metered doses. This dimple design allows the use of API only, eliminating the need for lactose or complex powder formulations. The device works via a mechanical process. Upon opening the mouthpiece, a dose is ready for use. The air flow of the patient's inhalation releases an impactor that strikes the tape and releases API into the airstream. API particles are further deagglomerated as they pass through the device, helping to ensure effective delivery.

The Conix DPI is designed with a patented reverse-flow cyclone technology that effectively uses the patient's inhalation to aerosolize the drug. As the patient inhales, air is drawn into the cyclone chamber, where a vortex is established. At the bottom of the chamber, the airflow reverses direction and travels up through the circular outlet. The swirling airflow deagglomerates and aerosolizes fine, respirable particles



(API) from larger particles (lactose).

“DPIs offer several important benefits over aerosol-based inhalers,” says Mr. Odenthal. “They may be used to deliver medicines that may not be deliverable in an aerosol propellant formulation. MDIs require the medicine to be combined with propellants and possibly other materials in order to function properly, a process that may be unsuitable for some drugs. With DPIs, however, no propellant is necessary.”

He adds that 3M DPI devices deliver more of the respirable-sized drugs deeper into the lung. “Their ability to be used in both lung-specific and systemic applications gives them important flexibility for pharmaceutical developers.”

Common features of 3M's devices include Plasma Coating Technology, which helps ensure technical success with inhalation components for challenging hydrofluoroalkaline (HFA) formulations by creating a layer that protects against degradation, deposition, and corrosion. Additionally, a 3M Face Seal Valve eliminates the need to prime an inhaler by firing an uninhaled shot before use; an extra step, Mr. Odenthal says, can lead to loss of prime or loss of dose over time.

Finally, the 3M Integrated Dose by Dose counter offers a precise counting mechanism to eliminate under- and over-counting.

3M's pMDIs are primarily indicated for asthma, COPD, and seasonal allergies, while the DPIs are also suited for mass immunizations and vaccines. “Our current and future delivery inhalation systems are designed to play a vital role in improving public health,” concludes Mr. Odenthal. ♦

REFERENCES

1. Greystone Associates, Delivering Drugs by Inhalation, August 2009.
2. BizAcumen, Inc., Pulmonary Drug Delivery Technologies: A Global Market Perspective, November 2009.
3. Peters S, Jones C, Haselkorn T, Mink D, Valacer D, Weiss S. Real-world Evaluation of asthma control and treatment (REACT): Findings from a national Web-based survey *J Aller Clinical Immunol.* 2007;119(6):1454-1461.

ONCOLOGY DELIVERY

Perspectives in Oncology Drug Delivery

By: Daniel Ruppar, Industry Manager, Pharmaceuticals & Biotechnology, Frost & Sullivan

INTRODUCTION

Overall, the pharmaceutical and biotechnology industry is in a state of transition. Reorganization, M&A, consolidation, and portfolio changes are being evaluated to maintain growth centers in the face of a myriad of serious challenges. Many companies are seeking interest in oncology as an area to provide revenue streams and product opportunities. This sector has not only been a key area for start-up companies, but it has also increasingly become a talking point for Big Pharma as an area of investment and future value. Many of the key points of recent highly visible M&A deals in the industry were oncology centered (eg, BMS-Medarex, Pfizer-Wyeth, Eli Lilly-ImClone).

Furthermore, many leading companies are touting their position in this space as key to their future business. For example in 2009, Pfizer announced its desire to be third in oncology drug sales by 2018. Sanofi Aventis has launched a dedicated website to its oncology portfolio. Also, at an industry level, "cancer and cancer-related conditions" are the leading area of development in the biotech pipeline (Source: PhRMA) (Figure 1).

In addition to developers/sponsors, or areas such as diagnostics, contract outsourcing service providers are also tied to the sector. Contract Research Organizations (CROs) and Contract Manufacturers (CMOs), for example, are both expected to benefit from the continued high interest in cancer pipeline development. In a recent Frost & Sullivan assessment of the CRO market in the US by therapeutic area, oncology was the leading area of revenue for CROs through the end of that assessment in 2016. For contract manufacturing of pharmaceuticals, small volume parenterals (SVP) is a leading area of revenue growth. Within the SVP market, cytotoxics are expected to be the key driver of growth given the robust demand for oncology and other high-potency drugs in the market (Figure 2). There is a significant amount of investment being made by CMOs both in the primary and secondary manufacturing facilities to augment their capacities for these drugs. Ben Venue, Catalent, Patheon, and Pharmatek are some of the CMOs that have made investments in building new plants and augmenting existing capacity to support the manufacturing of high-potency drugs and cytotoxics.

FEEDBACK ON ONCOLOGY DRUG DELIVERY & TREATMENT

As developers design future drugs for oncology, they seek to uncover and understand opportunities. Given these factors, companies are trying to assess new pathways for development, market opportunity, and new areas for future drugs and treatment. Even for companies already established in this space, they are asking a variety of questions about what delivery and

treatment of cancer drugs could be like in the future. In healthcare overall, dynamics are changing in how people imagine treatment in many areas. New operating models are being conceptualized, springing up, and morphing into current practice, with many having the potential to become standard-of-care. Cancer treatment is a different target than many other areas companies look to for drugs. There are many complex layers, not only of the long list of different sub-diseases that make up the entire area, but

differences including where patients receive treatment, reimbursement, how drugs are administered, the goal of drug therapy, and how that connects with other parts of the treatment paradigm, such as surgery or radiotherapy.

Understanding feedback from patients, nurses, and physicians on factors such as perception, desired attributes, compliance, and drivers of adoption/non-adoption for different drug delivery types is important to developers as they seek to offer new product solutions to the market. As companies

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look to utilize innovative drug delivery technologies in product designs, an understanding of these opportunities could lead developers in new directions and result in products that significantly improve the lives of patients.

In oncology, developers are interested in understanding the opportunities and parameters for drug delivery in outpatient settings. This is important for products used in this area as companies seek to design new products and evaluate new opportunities for targeted therapies and other cancer treatments. Furthermore, insight into different drug delivery technologies within the scope of cancer treatment is critical in terms of portfolio decisions, as new platforms or enabling technologies evolve cancer treatment.

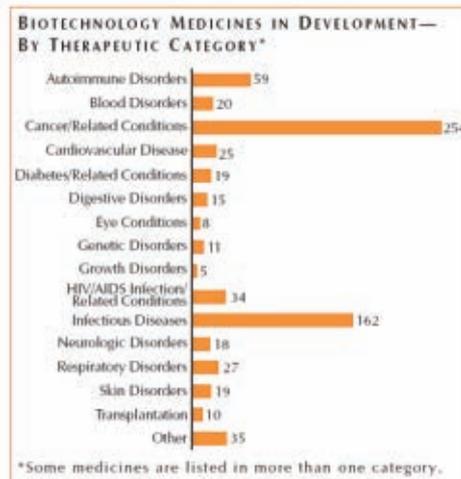
In Frost & Sullivan customer research surveys of oncologists, infusion nurses, and cancer patients, 11 different drug delivery types were compared: intravenous infusion, oral (pill/capsule), intravenous injection, subcutaneous injection, intramuscular injection, implant, external infusion pump, implantable infusion pump, rectal, transdermal patch, and topical gel/cream. This research contained a variety of issues relating to oncology treatment, including attributes, drivers/barriers, and parameters particular to delivery of drugs for cancer in different settings (eg, home, office).

SATISFACTION & CURRENT CLASS PREFERENCES

In terms of satisfaction, oncologists were asked to rate the presented methods of drug delivery for cancer treatment. Overall, oncologist satisfaction was

FIGURE 1

Biotechnology Pipeline - 2008



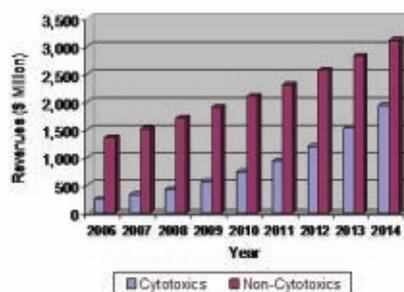
Source: PhRMA

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FIGURE 2

SVP Contract Manufacturing Market: Revenue Forecasts by Cytotoxic Status (U.S.), 2006-2014



- Cytotoxics contract manufacturing is one of the fastest growing market segments
- Several old and new products expected to drive volume and revenue growth

Year	Cytotoxics (\$ Million)	Non-Cytotoxics (\$ Million)
2006	\$258.1	\$1,355.0
2007	\$331.0	\$1,508.0
2008	\$425.9	\$1,703.5
2009	\$568.1	\$1,902.0
2010	\$733.8	\$2,099.4
2011	\$939.1	\$2,310.5
2012	\$1,199.3	\$2,560.3
2013	\$1,527.9	\$2,826.3
2014	\$1,941.8	\$3,107.3
CAGR (2009 - 2014)	27.9%	10.3%

Source: Frost & Sullivan

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highest for intravenous infusion, with 84% of responses being satisfied/very satisfied for that delivery type. The majority were also satisfied with intravenous injection and oral delivery. In terms of dissatisfaction, rectal was the worst with 47% uncomfortable with that delivery mechanism for oncology treatment (Figure 3).

Three drug treatment types in cancer therapy are cytotoxics, hormone, and targeted therapies. All three treatment types are diverse and used in different capacities. Discussions with oncologists regarding drug delivery preference, where they assumed all 11 drug delivery approaches were available for use, revealed the following.

For cytotoxic therapies, intravenous injection is the most preferred oncology drug delivery mode by 44% of surveyed oncologists. Across hormone and targeted therapies, oral is most preferred (59% and 49%, respectively). Oncologists have some preference for both intravenous infusion and for cytotoxics and targeted therapies - the second leading response in both drug categories (22% for both). However, for hormone therapy, intramuscular injection is the second leading method (15%) (Figure 4).

NEW DEVELOPMENT

Oncology drug development is robust, so it is vital to understand delivery types most desired by oncologists and nurses. Both oncologists and infusion nurses preferred development of new oncology drugs using oral delivery over other profiled drug delivery methods. Infusion nurses would also prefer to have new oncology treatments developed using

FIGURE 3

Satisfaction with Drug Delivery Method Used: Oncologists' Perspective

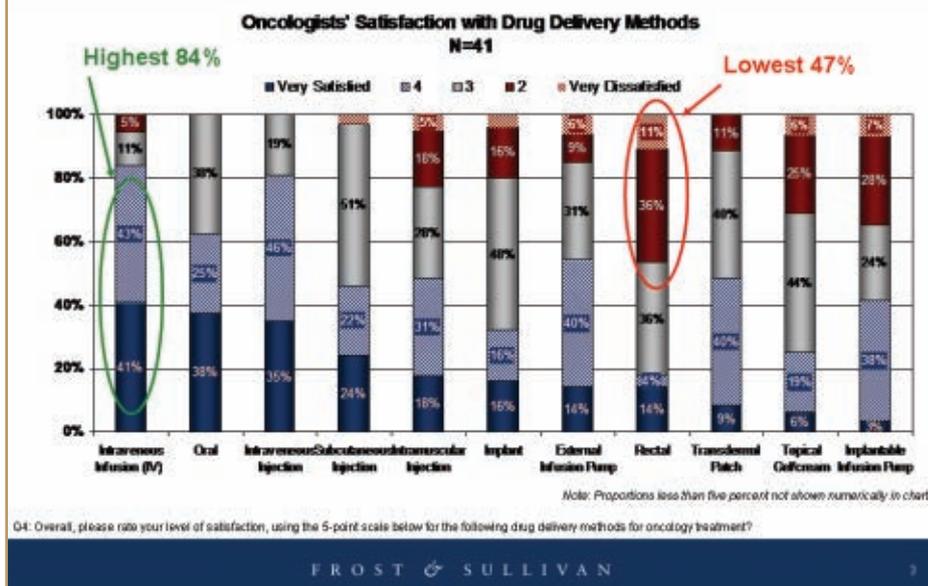
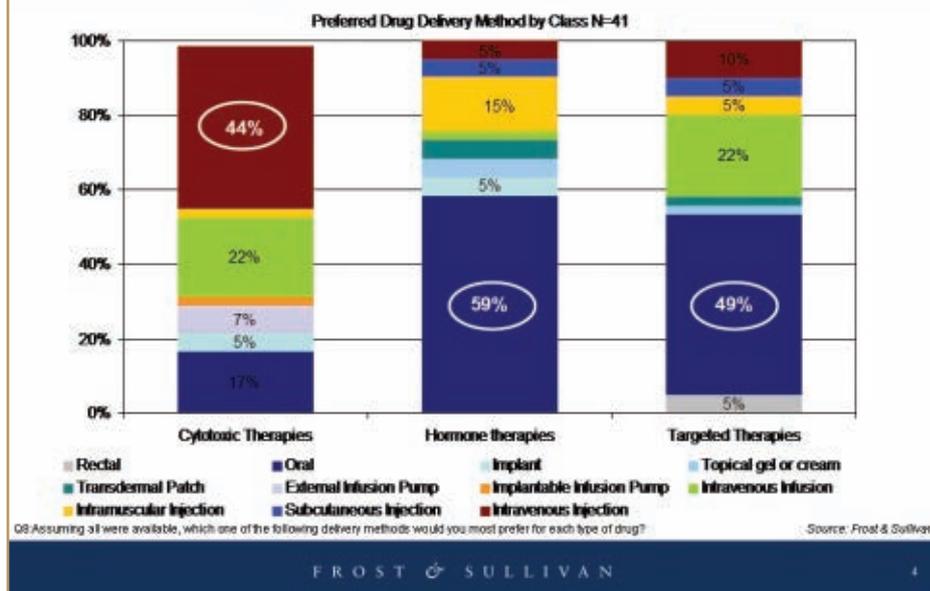


FIGURE 4

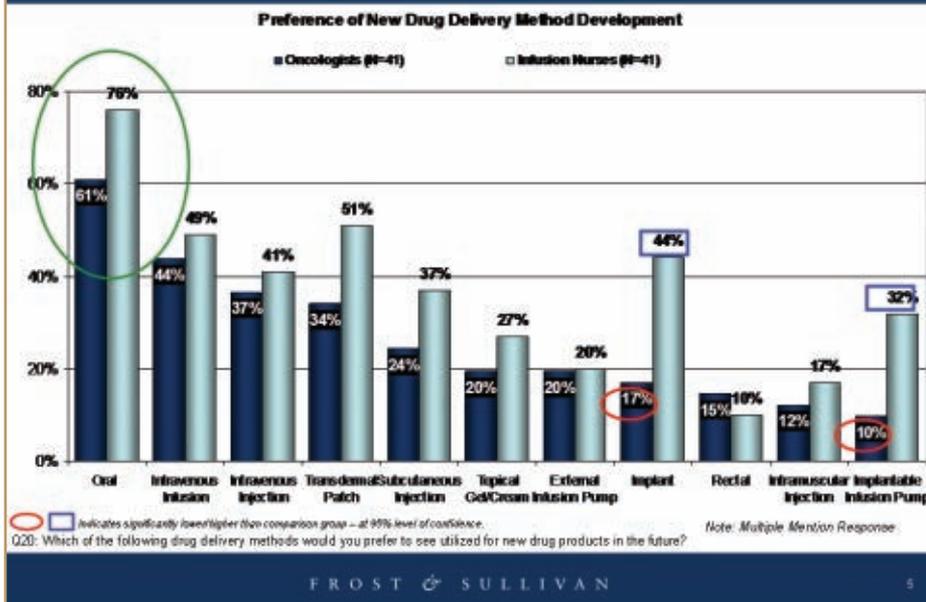
Most Preferred Drug Delivery Method for Drug Class: Oncologists' Perspective



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FIGURE 5

New Drug Development: Drug Delivery Preference



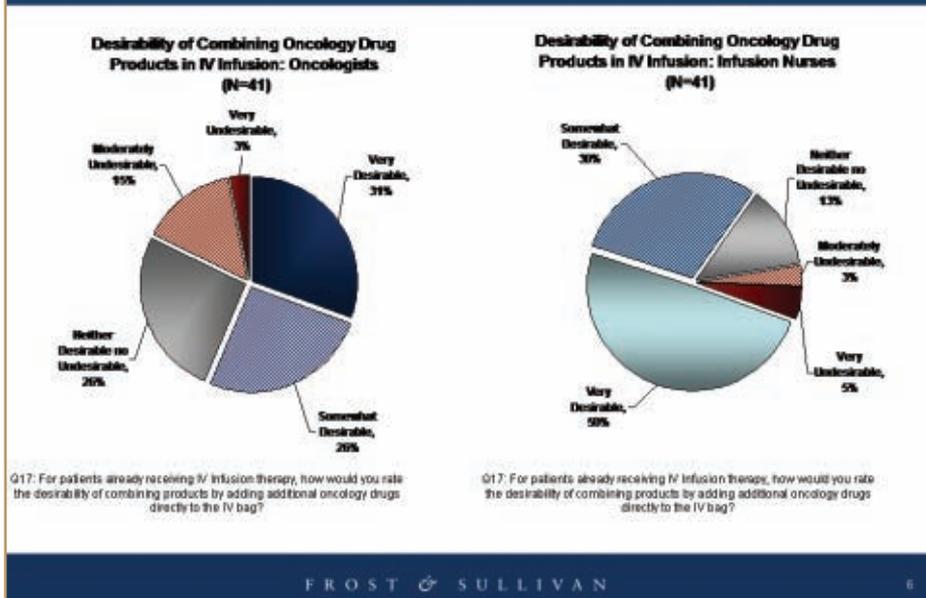
implantable drug delivery and implantable infusion pumps. Oncologists, however, did not express a significant interest (significantly lower than comparison group at 95% level of confidence) in new drug development using either the implantable infusion pump or implant. For oncologists, the other leading methods of preference for new product development were intravenous infusion (44%), and intravenous injection (37%) (Figure 5).

COMBINATIONS

In oncology, combination regimens are a key facet of treatment. Therefore, it was of interest to look at desirability of adding additional drugs directly to the IV bag for patients already on intravenous infusion therapy (Figure 6). In terms of physicians, 57% of oncologists considered it desirable to combine additional oncology drugs to an existing IV bag. Interestingly, response from the infusion nurses was far higher, with 80% of infusion nurses finding it desirable (somewhat + very desirable) to combine products in this manner. Almost half of patients with awareness of IV infusion therapy find combining products in an IV bag to be very desirable with a total of 64% of patient responses in the positive for this approach (Figure 7).

FIGURE 6

Factors in the Selection of Drug Delivery Methods: Oncology Drug Combinations



RECONSTITUTION RESPONSIBILITY & TIMEFRAME

In many areas across healthcare, home-based therapy options are being

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FIGURE 7

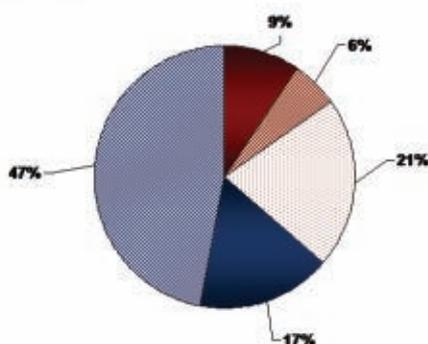
Patient

Attitudes Toward Infusion: Combinations

Almost half with awareness of IV infusion therapy find combining products in an IV bag to be very desirable.

Desirability of Combining Products in IV Bag
N=85

- Very undesirable
- Moderately undesirable
- Neither desirable nor undesirable
- Somewhat desirable
- Very desirable



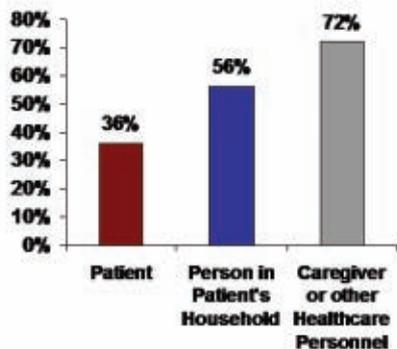
Q17. If you are already receiving IV infusion therapy, how would you rate the desirability of combining products by adding additional oncology drugs directly to the IV bag?
Asked only of respondents with awareness of IV infusion therapy.

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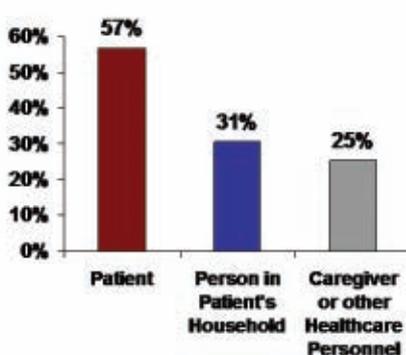
FIGURE 8

Reconstitution Parameters: Home Preparation Role Oncologists & Patients

Person to Reconstitute Lyophilized Product:
Oncologists (N=41)



Person to Reconstitute Lyophilized Product: Patient (N=114)



Who do you think would prepare a drug with this type of process for your patients in their home? Select all that apply. (Note: Multiple Mention Response)

Source: Frost & Sullivan

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evaluated. With some of these drugs, a reconstitution step is needed to properly prepare the drug for patient dosing. In this survey, differences were observed in perception of who would administer the drug in a patient's home for cancer treatment (Figure 8). When posed to oncologists and nurses, both groups believed it would be a "caregiver or other healthcare personnel" who would handle a reconstitution task in a patient's home, followed by "another person in the patient's household," and last - the patient themselves. In the minds of MDs and nurses, medically trained individuals would be handling this task in a patient's home.

Interestingly, from the patient side, the response was the complete opposite. Cancer patients believed they would be the one handling drug reconstitution in their home, followed by other family members, and caregivers/medical personnel as the last choice.

In terms of acceptable timeframes to deal with a reconstitution process, overall shorter reconstitution times were preferred by all groups (cancer patients, oncologists, and infusion nurses). 71% of oncologists and 65% of nurses indicated 10 minutes or less was an acceptable timeframe. Additionally, almost half of cancer patients would want to spend less than 10 minutes to reconstitute a liquid drug.

PATIENT PREFERENCES BY TYPE: HOME VERSUS OFFICE

In evaluation of the profiled types in this research, cancer patients answered overall preferences for drug administration either at home or in a physician office setting for cancer treatment. Overall,

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cancer patients preferred to take their oral medication at home, and that all profiled injection types and intravenous infusion be administered in an office setting. The highest office preference was for intravenous infusion, with 82% of patients preferring office treatment rather than home treatment (Figure 9)

SUMMARY

Overall, oncology is an important growth center for a variety of facets in the pharma and biotech industry. For developers, insight into physician, nurse, and patient views of drug delivery and drug treatment can play a major part in understanding how new drugs will be accepted, or enable companies to uncover

areas of opportunity. As firms continue to seek out new pathways and settings for cancer treatment, understanding feedback from patients and healthcare providers can greatly impact and change new solutions. This not only pertains to the products themselves, but also the way they are presented to the marketplace as they transition from ideas to reality.

Additionally, it can uncover gaps where value-positioned education can make a difference in potential product acceptance.

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

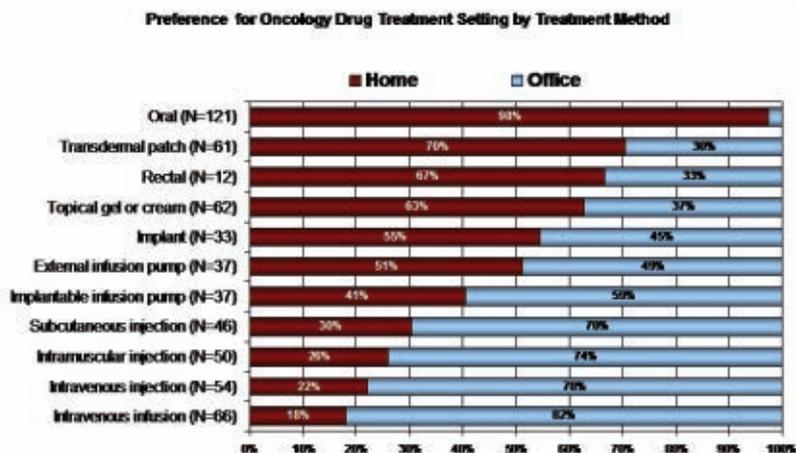
BIOGRAPHY



Daniel Ruppap is the Manager of Frost & Sullivan's North American Pharmaceutical & Biotechnology analyst team. His work since joining Frost & Sullivan in 2005 has focused on a variety of areas, including drug delivery, specialty pharmaceuticals, diabetes, cholesterol, and the anticoagulant and antiplatelet drug markets. Mr. Ruppap has also performed consulting duties for Pharmaceutical, Venture Capital, and Financial Services clients. He most recently has presented at the Next Generation Pharmaceuticals Summit. He has also spoken at other key industry events, such as BIO International and Drug Delivery Partnerships. Mr. Ruppap is interviewed frequently by the media, including NPR's All Things Considered, Fox Business News, USA Today, CNN Money, Fortune Magazine, Bloomberg, Reuters, Dow Jones Newswires, Forbes, Pharmaceutical Executive, Med Ad News, as well as other major news outlets. Additionally, he is a co-author of multiple scientific publications in peer-reviewed journals for his work in chemistry, is frequently featured in Drug Delivery Technology magazine, and is a co-inventor on 4 patents for his work in drug discovery. Prior to this, Mr. Ruppap spent 9 years in the pharmaceutical industry as a medicinal chemist working on therapeutic/drug area targets, including oncology, metabolic disease/diabetes, interferon, thrombopoietin, and the androgen and estrogen receptors. Mr. Ruppap earned his BS in Biochemistry/Economics from Trinity University.

FIGURE 9

Preferred Setting for Treatment: Home vs. Office Cancer Patients



Q15b, Q15c. Which of the following drug delivery methods would you prefer to use: at home (in an office setting) to administer your drug treatment assuming all delivery methods are available and affordable?



Drug Delivery Partnerships Exemplify Excellence, Value, & Innovation

By: Cindy H. Dubin, Contributor

Drug delivery represents a \$20-billion segment in the pharmaceutical industry. Many drug delivery companies build their own product development capabilities, but still usually turn to a pharma partner at some stage of development. Similarly, while pharma companies might be tending toward in-housing some of their delivery technologies, they cannot solve all their delivery problems alone. There will always be a requirement for the expertise of drug delivery specialists and the technologies they offer, and thus, forming partnerships will remain essential for success in the drug delivery industry. It is for this reason the 14th annual Drug Delivery Partnerships event presented the inaugural Drug Delivery Product Showcase Awards ceremony on January 26 in Orlando. The ceremony featured 15 nominees across three categories: Partnering Excellence, Pipeline Value Creation, and Technology Innovation. The awards were created to honor the best in industry innovation and success. The winning companies included Eurand (Partnering Excellence), Halozyme (Pipeline Value), and Elan Drug Technologies (Technology Innovation).

PARTNERING EXCELLENCE NOMINEES

ALTEA & PARTNERS DEVELOP BIOLOGICS PATCHES

The Altea Therapeutics PassPort® System (Figure 1) is a transdermal technology for conveniently and painlessly delivering biologics from a small skin patch that would otherwise be injected. Altea is developing and commercializing initial products using the

PassPort System with leading pharmaceutical companies and has partnered with Amylin Pharmaceuticals, Inc. and Eli Lilly and Company to develop and commercialize a daily transdermal patch delivering sustained levels of exenatide (currently marketed as Byetta®). The company also has a partnership with Hospira, Inc. to develop and commercialize a transdermal patch for delivering enoxaparin sodium (currently marketed as Lovenox®). Most recently, Altea announced a partnership with KAI Pharmaceuticals, Inc. for the preclinical and clinical development of certain KAI proprietary peptides using Altea's proprietary transdermal technology. Additionally, Altea is partnered with several pharmaceutical companies to conduct feasibility studies on certain proprietary compounds.

DICERNA & KYOWA HAKKO KIRIN TAKE siRNA TO THE NEXT LEVEL

Dicerna's patented Dicer Substrate technology is a second-generation approach to small interfering RNA (siRNA). DsiRNAs (Figure 2) enter the pathway at an upstream point. While siRNAs are generally 21 nucleotide base pairs, DsiRNA molecules are 25 base pairs or longer. The combination of properties of potency (multiple single-digit picomolar DsiRNAs against the target of choice), duration of action, and ability to manipulate the molecule for delivery purposes is what distinguishes DsiRNAs from other siRNA molecules. Dicerna has validated two approaches for delivery: nanoparticle systems and a second approach of integrated DsiRNA systems. The latter are "double-punch" molecules with an attached payload and targeting moiety that would be injected as a

molecule. In January, Dicerna and Kyowa Hakko Kirin announced their partnership to discover, develop, and commercialize drug delivery systems and siRNA medications using Dicerna's Dicer Substrate Technology for undisclosed oncology targets. The deal potentially could garner Dicerna more than \$1.4 billion and is the largest target-based RNAi deal to date. Under its partnership with KHK, Dicerna stands to gain a \$4-million up-front cash payment and up to \$120 million in research funding and development and commercial milestones for the exclusive rights to one oncology target, with the firms having the option to expand the collaboration for up to 10 targets under similar terms. The partnership also includes a 50-50 co-promotional and profit-sharing option for the initial target in the US.

EURAND & GSK DEFY DEVELOPMENT TIMELINES

Eurand and GSK have instilled optimal value in their partnership by being sensitive to the needs and timelines of one another. Extraordinary efforts were made to quickly negotiate the deal, and by Eurand to quickly execute on the development plan (Figure 3). The partnership product, Lamictal ODT, went from agreement signature to NDA submission in only 19 months. The entire process was highly iterative throughout development and the parties communicated extensively to achieve successful results in a short timeline. The companies have taken their partnership show on the road by talking at conferences about the value of drug delivery partnerships.

GENZYME VALUES LONG-TERM BENEFITS

Genzyme Pharmaceuticals has built several strong strategic relationships with

FIGURE 1



FIGURE 2

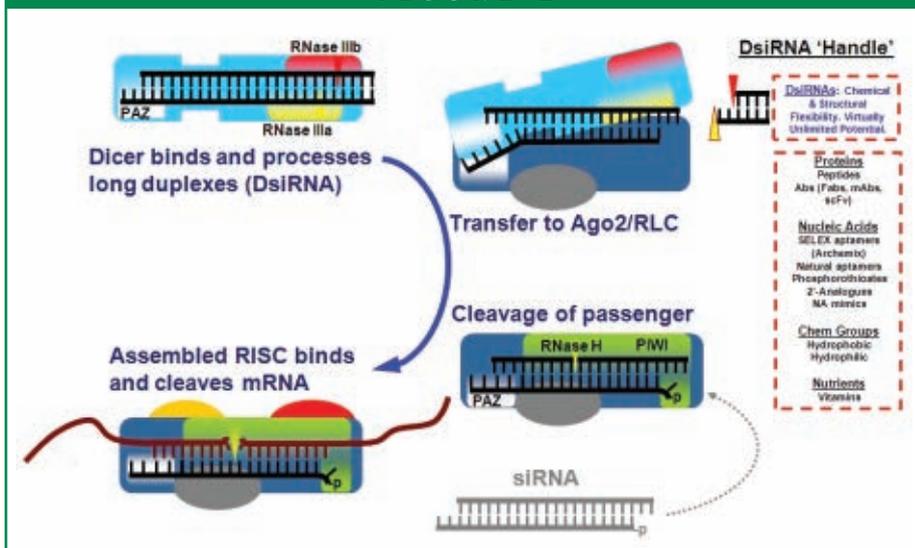


FIGURE 3



companies, such as SurModics Pharmaceuticals and Pharmidex Pharmaceuticals. The collaborations span functional areas from business development to science to marketing and draw upon available strengths and resources. This year, Genzyme and SurModics hosted an educational webinar on the collaborative service technology Design for Peptide DeliverySM with scientists from each company describing the scientific background and benefit of the service. The processes of communication and follow-up within the strategic relationships are examples of how collaborations work to create long-term value and business for both parties.

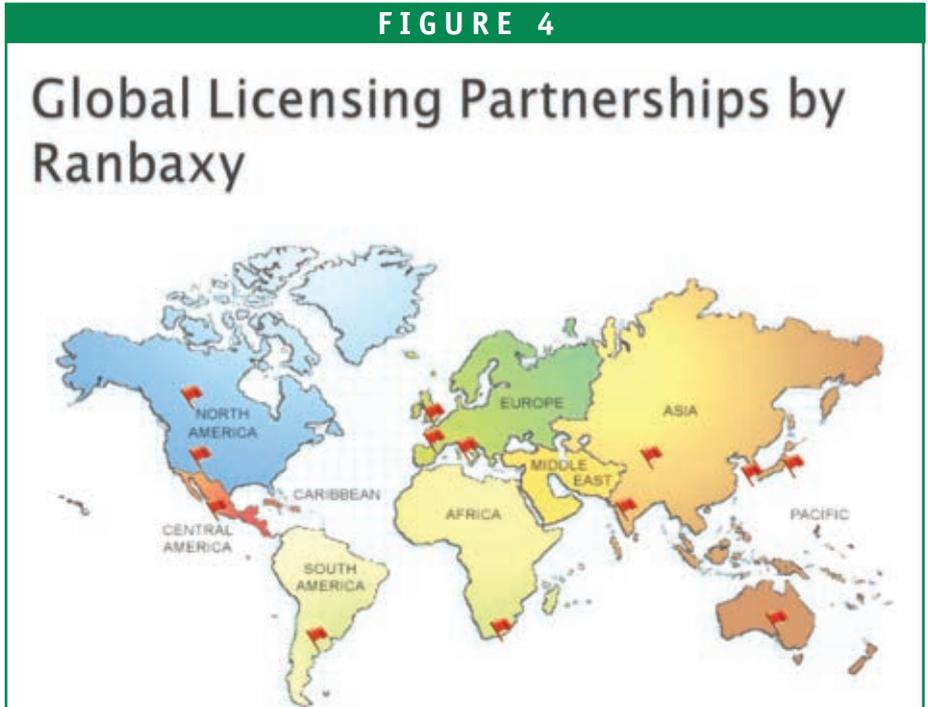
PARTNERS IN CARE STRENGTHENS HEALTH VALUE CHAIN

Partners in Care has used technology to identify gaps in care, communicate the adherence/persistence needs in chronic care to providers and suppliers, and produce exemplary results in total health management. Where others thought disease management could deliver, Partners in Care showed that patient-centered medical home care (PCMH), and Care Coordination Entities (expanded care teams armed with data and solutions), could deliver a better dividend that mattered to the patient, the employer, and the health plan. Creating replicable and sustainable results drives value and increases financial strength across the entire health value chain, promoting individual health, physician competence, and community health.

RANBAXY LABS PROMOTES IN-LICENSING

In-licensing at Ranbaxy, lead by Dr. Harvinder Popli, has resulted in 44 agreements in just the past 5 years (Figure 4).

FIGURE 4



The agreements have been signed with innovation- and technology-driven companies in the US, Europe, and Asia to address markets in India, Singapore, Malaysia, Vietnam, Cambodia, Myanmar, Philippines, Sri Lanka, and the Middle East. The therapeutic focus of these agreements include clinical dermatology, aesthetic

dermatology, CNS, urology, oncology, pain management, neutraceuticals, dental products, and respiratory. The in-licensing team has been responsible for pre-launch activities and project management associated with launching the licensed products within stipulated timelines.

FIGURE 5



FIGURE 6

PIPELINE VALUE CREATION NOMINEES

CENTRIC HEALTH RESOURCES DEFINES DISTRIBUTION MODEL

Centric Health Resources is a new-generation, Patient-Centered Health Management® organization, serving patients with rare, orphan, and ultra-orphan disorders. Centric has a deep understanding of the value of personalized relationships, helping biotech and pharmaceutical manufacturers to better serve this targeted market niche, which is typically defined as relatively small patient populations of less than 10,000. Centric pioneered the direct distribution model, which virtually

eliminates the costs and resources associated with multiple touch points for getting the specialty product into the hands of the patient. As a result, the price of the drug remains transparent and stable, without unnecessary mark-ups that inflate costs for patients and payers. Attractive pricing reflects efficiencies associated with integration as well as lower overhead. The Centric approach allows biopharmaceutical manufacturers to leverage opportunities for cost-effective drug delivery and personalized health management services. This model improves patient compliance with therapy, drives better outcomes, and provides additional long-term support for patients and their caregivers. It also offers the opportunity for pharmaceutical companies to demonstrate value to patients, physicians, and payers; adapt to a changing regulatory environment; and raise support from the patient community by engaging patient advocacy groups as partners in the provision of services.

FIGURE 7

NanoCrystal® Technology
proven innovation for poorly water soluble compounds

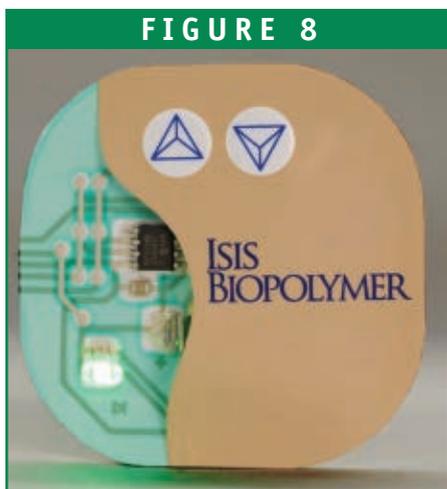
Proven
 Five products launched, US\$1.8B+ annual in-market sales.

Patent Protected
 Over 1,000 patents/patent applications in U.S. and rest of the world.

Applicable to all dosage forms, manufactured at commercial scale since 2001.

HALOZYME THERAPEUTICS ENHANCES SUBCUTANEOUS DELIVERY

Halozyme's Enhance™ Technology is a drug delivery platform designed to increase the subcutaneous absorption of biologics and to convert biologics from intravenous to a subcutaneous route of administration (Figure 5). Two products using Enhance Technology entered Phase III studies in 2009, creating significant value for the pipelines of Halozyme's partners. One of these is the Halozyme-Roche collaboration, which involves subcutaneous formulation of Herceptin® (trastuzumab) with Enhance. Herceptin is currently administered intravenously. It is expected that Enhance will allow HER2-positive breast cancer patients to administer Herceptin themselves with or without the support of a healthcare professional. The other product, subcutaneous Gammagard® Liquid, is part of a Halozyme-Baxter collaboration. Gammagard Liquid (Immune Globulin Intravenous) 10% (IGIV) is currently

FIGURE 8

administered intravenously; subcutaneous administration with Enhance could allow patients to receive a monthly dose in a single injection within their home, compared to other subcutaneously administered immune globulin products that require weekly administration at multiple injection sites simultaneously.

ZOGENIX ALLEVIATES INJECTION FEARS

Since its inception in late 2006, Zogenix has raised \$170 million in private capital, acquired and developed a drug delivery technology, and took a drug product through full clinical development, NDA approval, and US launch. Zogenix's drug delivery technology is DosePro™, a single-use, easy-to-use, disposable, needle-free injection system that removes the anxiety associated with needles (Figure 6). In July 2009, the FDA approved the company's NDA for the first product that uses a prefilled needle-free injection technology for treating migraine and cluster headaches: Sumavel DosePro (sumatriptan for injection). In January, Sumavel DosePro was launched in the US with the Zogenix neurology sales force and the Astellas Pharma primary care physician sales force. Sumavel DosePro has been licensed to Desitin Pharma for commercialization in Europe. Desitin completed the pivotal registration study for

Sumavel DosePro and filed for approval in Europe in October 2009.

TECHNOLOGY INNOVATION NOMINEES

ELAN DRUG TECHNOLOGIES ADDRESSES SOLUBILITY

In the 10 years since its first filing with the FDA, Elan's NanoCrystal® technology has reached market sales in excess of \$7.8 billion (Figure 7). Designed to overcome issues associated with poor water solubility, five products developed with NanoCrystal are available in 100 territories worldwide. Rapamune® (Wyeth) immunosuppressant, launched in 2001, eliminates the need for refrigeration of tablet product and provides a 23% improvement in bioavailability. Emend® (Merck), launched in 2003 for nausea and vomiting, saw a 600% improvement in bioavailability. TriCor® 145, which improved bioavailability and minimal food effect, was launched by Abbott in 2004. Megace ES® for cachexia in AIDS patients was launched in 2005 with a 28% improvement in bioavailability, with a free from food effect. In August 2009, the first once-monthly schizophrenic injectable depot formulation, Invega® Sustenna™, was launched by Janssen using NanoCrystal technology.

ISIS BIOPOLYMER CONTROLS TRANSDERMAL DELIVERY

Isis Biopolymer, Inc., founded in 2006, has advanced non-invasive transdermal drug delivery with the IsisIQ™ Patch (Figure 8). The patch is a fully programmable, single-use, "band-aid-like" active patch that controls and monitors transdermal drug delivery to ensure safe and accurate administration using iontophoresis. The IsisIQ Patch features a proprietary selective barrier membrane that facilitates the transport or complete cessation of drug molecules through the skin. Drug transport can be modulated for up to three drugs per patch and is fully programmable for customized delivery and monitoring via an integrated wireless communication platform. The single electrode design eliminates variability in drug delivery that can occur with changes in the skin due to temperature, moisture, and movement, preventing inadvertent or over delivery of drug. The IsisIQ Patch is also a biosensor that can detect skin emanations, which may be indications of medical events, such as heart attacks, shock, or diabetic reactions.

Moving forward, Isis Biopolymer technology will expand the worldwide multibillion dollar market for transdermal

FIGURE 9

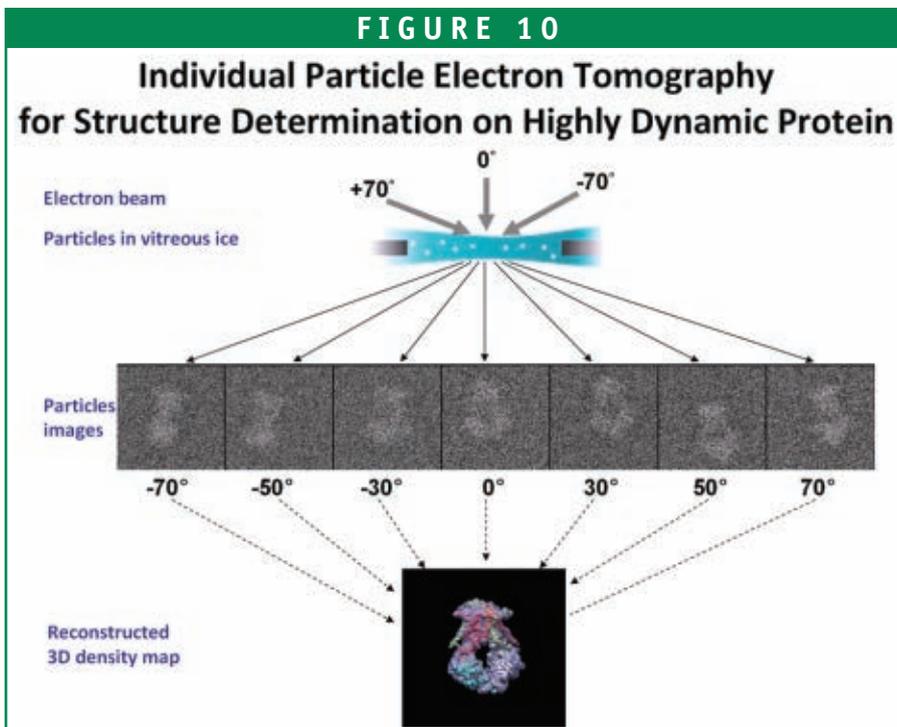
delivery of existing and drugs in development for pain management, oncology, neurology, endocrinology, cardiovascular, CNS disorders, as well as therapies for chronic and acute conditions. Isis Biopolymer developed the technology to revolutionize transdermal drug delivery, and to make it affordable with its materials and manufacturing processes.

TOPI-CLICK HANDLES TOPICAL MEDICATIONS

The patented Topi-Click topical dosing applicator (TDA) combines ease of use with dosing precision (Figure 9). Topi-Click's integrated applicator pad and metered dosing clicker aims to overcome the non-compliance often associated with having to rub topical medications onto treatment areas. Hands absorb topicals; therefore, patients wind up rubbing a large percentage of the medicine into their hands. Using the hands can also increase chances of others accidentally being exposed to someone else's prescription when holding or shaking hands. The Topi-Click audible clicker and tactile dosing feedback allow patients to dispense a metered dose in seconds, promoting compliance.

PRADAMA, INC. TARGETS BONE MINERAL

Pradama Inc. is a pharmaceutical company that creates multiple products for bone diseases and disorders using bone-targeting drug delivery technology. Bone tissue is distinguished from other tissues by the presence of bone mineral, such as hydroxyapatite. Pradama's bone-targeting agents have significant affinity for hydroxyapatite. The bone-targeting agents have several advantages over other bone-targeting approaches, including oral availability, therapeutic inactivity, stability, and flexibility.



UNIVERSITY OF CALIFORNIA AT SAN FRANCISCO STUDY DRUGS & ANTIBODIES

Antibodies have been used as a drug delivery vehicle for years, yet some conjugated antibodies may lose their function to bond to the target cell. To improve drug delivery efficiencies, the structure of the conjugate is usually needed. However, structural determination of the dynamic antibody is not available by current technology, so the University of California at San Francisco (Figure 10) developed the electron tomography and image reconstruction technology. This allows researchers to determine each individual antibody structure at a 10Å resolution. By using this technology, researchers have discovered the conformational change of the antibodies after being bound to drug. Thus, this method has a general impact to field monitor and determine the structure of highly dynamic proteins, such as antibodies, high-density lipoproteins, and low-density lipoproteins.

WHCC TRANSLATES RESEARCH

The Wallace H. Coulter Center of the University of Miami is a technology development center for biomedical innovation. WHCC acts as a catalyst for moving University of Miami research with commercial potential from the bench to industry. The WHCC has access to a scalable manufacturing platform for cellular products that is compatible with current Good Manufacturing Practice (cGMP) and current Good Tissue Practice (cGTP) regulations. The platform is ideal for genetic vaccination as it targets APC (antigen-presenting cells) and activates helper T cells. The platform also may be used to deliver nucleic acids, including siRNA, into mononuclear cells, which has broad therapeutic applications. ♦

To submit a nomination for the 2011 Annual Drug Delivery Partnerships Innovation Awards, please visit www.drugdeliverypartnerships.com.

TOPICAL DELIVERY

Biphasix™: A Topical Drug Delivery System to Deliver Large Molecules Into the Skin

By: Praveen Kumar, MPharm, PhD; Angela Perry, MSc; Ravinderjit Batta, MPharm; and M. King, PhD

INTRODUCTION

Biotechnology-derived drugs are increasingly used in the pharmaceutical industry for various indications. The majority of biotechnology drugs are large molecules (proteins, peptides, and DNA). Their large size and physicochemical properties pose a variety of challenges to the development of successful drug products. Most of the biotechnology-derived drug products on the market are available in injectable form.

In the case of treating dermatologic disease states in particular, systemic drug delivery exposes healthy tissue to the drug and can result in an increased likelihood of toxic side effects. Additionally, much larger amounts of the drug may be administered to the patient than would be required for localized delivery, adding to manufacturing challenges for the manufacturer and cost challenges for the healthcare system. Dermal or transdermal delivery would be a painless and convenient method of self-administration of drug compounds to their local target sites. Although technologies, such as iontophoresis, ultrasound, microneedles, and use of permeation enhancers, are being investigated to deliver macromolecules across the skin, there are very few topical biotechnology drug products available. Development of a flexible, easy-to-manufacture, dermal, or transdermal topical drug delivery system would help optimize a drug's efficacy, safety, and compliance while minimizing toxicity.

The skin is a particularly challenging organ for delivering drugs via a topical formulation. The stratum corneum (Figure 1), the exterior layer of the epidermis, acts as a barrier to prevent external molecules from entering the body and systemic circulation. In addition, the larger the molecule, the more difficult it is to deliver into or through the skin layers. There are currently no true topical delivery systems for large molecules commercially available.

The following describes a topical drug delivery system called Biphasix™ that enables delivery into and, with adjustments to the formulation, through the skin of an extensive variety of small and large molecules.¹⁻⁴ Compounds formulated with the Biphasix cream matrix are relatively simple to develop and manufacture and do not require unconventional equipment or novel excipients.

BIPHASIX™ TOPICAL DRUG DELIVERY SYSTEM

Liposomes and their variants, such as niosomes and transfersomes, have been shown to deliver both small molecules and, to some extent, large molecules more efficiently across the skin than traditional semi-solid products (creams, lotions, and

ointments). Biphasix is a patented drug delivery technology developed by Helix BioPharma Corp. for the delivery of macromolecules and small molecules into or through the skin or mucosa. Biphasix is based on the encapsulation of drug into vesicles. These biphasic vesicles entrap both aqueous phase and oil phase in the form of a stabilized microemulsion.

The multicompartmental lipid vesicle system is composed of aqueous, phospholipid bilayers and micellar and oil compartments (Figure 2). Biphasic vesicles differ from classical liposomes as they contain not only aqueous phase but also oil and micellar particles. Thus, both hydrophilic and lipophilic drug molecules can be entrapped into the

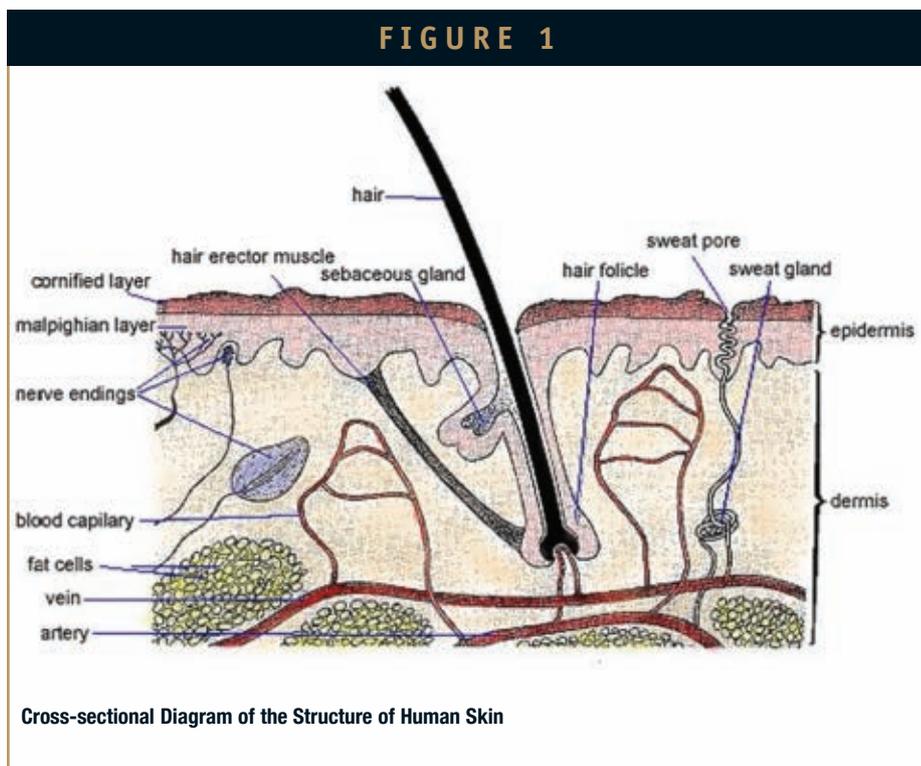
TOPICAL DELIVERY

biphasic vesicles for dermal and transdermal delivery.

The mechanism by which Biphaxis delivers macromolecules into the mucosa or skin has not been fully elucidated. However, it is hypothesized that encapsulated drug in the vesicles penetrate into the skin or mucosa via lipid channels in the skin followed by drug release from the biphasic vesicles in a controlled manner (Figure 3).

BIPHASIX™ MANUFACTURING: SIMPLE & FLEXIBLE

Traditionally, liposome preparations require the use of organic solvents, whereas the manufacture of Biphaxis products does not. In addition, commonly used pharmacopoeial excipients are employed to formulate Biphaxis products, thus enabling easier acceptance at the regulatory level. Moreover, manufacturing Biphaxis-based drug products use traditional manufacturing equipment allowing for the easy transfer of the manufacturing process from bench scale to pilot scale to commercial scale. Once manufactured, the vesicles are physically stable and help in improving the shelf life of the active pharmaceutical ingredient.⁵ Formation of vesicles and incorporation of the active drug are conducted concurrently using equipment that is commercially available today, making Biphaxis a viable technology.



CASE STUDY: TOPICAL INTERFERON ALPHA-2B USING BIPHASIX™

Interferon alpha-2b is an immune system-activating agent approved for use in the treatment of a number of malignant and viral infection indications, including malignant melanoma, hairy cell leukemia, chronic hepatitis C, condylomata acuminata, and chronic hepatitis B.⁶ Classically, interferon is administered by injection, typically intravenously, subcutaneously, or intramuscularly, but also intralesionally.^{7,8} The compound has tolerability issues, most commonly flu-

like symptoms that have an adverse effect on patient quality of life and compliance, particularly because of the months-long regimen patients may endure.⁷

Cervical dysplasia is a common disorder in women worldwide resulting from human papilloma virus (HPV) infection. These atypical cells may spontaneously resolve but may progress to invasive cervical cancer. Atypical squamous cells observed from a Pap smear of the cervix are typically managed with watchful waiting for up to 2 years.⁹ If the atypical cells do not resolve spontaneously, then a surgical intervention is required to remove them.

TOPICAL DELIVERY

FIGURE 2



Illustration of a Biphaxis™ Multilamellar Vesicle (5 micrometers)

These surgical interventions may result in an increased risk of obstetric side effects, such as pre-term labor and low birth weight.¹⁰ There are currently no pharmaceutical options for cervical dysplasia.

Interferon alpha-2b is a highly labile protein molecule that is sensitive to temperature, oxidation, peptide bond hydrolysis, aggregation, deamidation, and bacterial contamination. All of these problems encountered during formulation can lead to a substantial loss in potency of the protein and the formation of unwanted degradation products. Overcoming these constraints illustrates the flexibility of the Biphaxis drug delivery system. Aware of these particular limitations, Helix developed a process to form the vesicles at lower temperatures. Oxidation of interferon alpha-2b is a particularly challenging problem for a topical formulation.

However, the formulation was successfully modified to prevent its oxidation and consequently increase stability of the product.⁵ Any complications from bacterial contamination of the product were avoided by developing a manufacturing process to ensure a low bio-burden, using a well-designed antimicrobial preservative system, and by packaging in single-use applicators for intra-vaginal delivery.

PRECLINICAL DATA

Localized delivery of interferon alpha-2b was investigated in a guinea pig model (data not shown, manuscript in progress). The study investigated the ability of topical delivery of interferon alpha-2b formulated with Biphaxis to remain at the site of administration (ie, lack of systemic availability) compared with either intravenous or intradermal injection of interferon, and to investigate the safety of Topical Interferon Alpha-2b. Both intravenous and intradermal injections of interferon alpha-2b resulted in rapid clearance of the compound via the systemic circulation. Topical Interferon Alpha-2b remained largely contained in the skin at the site of administration, peaking at up to 12 hours post-administration then gradually decreasing in concentration over time. Systemic level of interferon alpha-2b

was < 0.1% of the peak dermal levels, even after multiple dermal applications. No pain or pronounced adverse effects were observed with Topical Interferon Alpha-2b, although mild dermal irritation was observed in a few animals that received multiple doses.

CLINICAL DATA

Topical Interferon Alpha-2b with Biphaxis technology has completed a Phase II clinical trial in 41 cytologically confirmed female patients with HPV-induced low-grade squamous intraepithelial lesions. LSIL is a mild-to-moderate form of cervical dysplasia that may progress to cervical cancer. Twenty patients self-administered Topical Interferon Alpha-2b to the cervix three times per week on alternate days, for a period of 6 weeks with a follow-up evaluation at 12 weeks. The remaining 21 patients received no treatment (ie, watchful waiting: the current standard of care). The primary end-point was the Pap response rate defined as the proportion of patients with resolution of their abnormal Pap smear LSIL cytology to normal during the 12-week study duration.

Topical Interferon Alpha-2b-treated patients showed an improved rate of normalization compared to controls. About 47% of patients treated with Topical Interferon Alpha-2b reverted to

TOPICAL DELIVERY

normal Pap smears, compared to only about 16% of controls, according to the Munich Classification System used in Europe. Employing the Bethesda Classification System used in North America (stratified recruited patients belonging to Pap smear group IIID of the Munich Classification System), about 43% of the per-protocol population reached normalization of their Pap smears compared to about 0% of controls.

Employing examination of all patients via colposcopy demonstrated similar results. Colposcopic normalization was observed in 60% of treated patients but only about 10% of controls.

Other clinical trials are ongoing and will provide additional data on the profile of the formulation of Topical Interferon Alpha-2b. A Phase II pharmacokinetic study is ongoing to confirm that Interferon Alpha-2b does not significantly access the systemic circulation of the patient. A second Phase II study in ano-genital warts patients has completed enrollment. Results are expected in mid-to-late 2010.

CONCLUSION

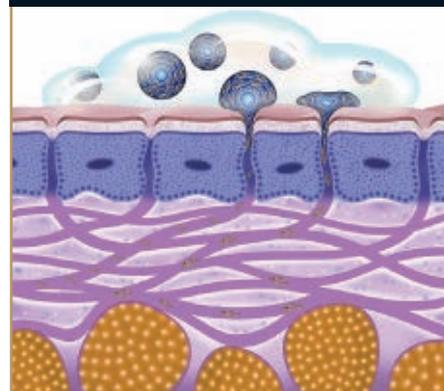
There is a need for alternatives to parenteral delivery of medications that are only treating localized sites. For skin

or epithelial lesions, topical administration is an attractive approach for both doctors and patients because of its localized activity, ease of use, and improved patient compliance. Unfortunately, until now, there has not been a topical formulation that conveniently delivers large molecules, particularly peptides and proteins, to target lesions. Biphaxis is a promising drug delivery system able to topically deliver hydrophilic and lipophilic macromolecules, with the following additional advantages:

- High efficiency of drug encapsulation;
- Improvement in the solubility of poorly soluble drugs;
- Extended shelf-life and consequently commercial viability;
- Improvement in the stability of unstable small molecules and macromolecules;
- Delivery of drugs to the targeted area, thus avoiding unnecessary side effects; and
- Painless delivery and high patient compliance.

Preclinical and clinical studies on a Biphaxis formulation of interferon alpha-2b have validated the technology as a potential drug delivery system for a

FIGURE 3



Proposed Mechanism of Drug Delivery Through the Skin

When drug (eg, interferon alpha-2b)-containing Biphaxis™ vesicles are applied to the skin or mucosa, drug in the vesicles penetrates into the skin or mucosa via lipid channels in the skin followed by drug release from the vesicles in deeper layers of skin.

wide variety of indications. The technology is promising for compounds for which localized delivery into the skin or epithelial tissues is a preferred therapeutic approach.

REFERENCES

1. King MJ, Badea I, Solomon J, Kumar P, Gaspar KJ, Foldvari M. Transdermal delivery of insulin from a novel Biphasic lipid system in diabetic rats. *Diabetes Technol Therap.* 2002;4:479-488.
2. King MJ, Michel D, Foldvari M. Evidence for lymphatic transport of insulin by topically applied biphasic vesicles. *J Pharm Pharmacol.* 2003;55:1339-1344.

TOPICAL DELIVERY

- Foldvari M, Kumar P, King M, Batta R, Michel D, Wloch M. Gene delivery into human skin in vitro using biphasic lipid vesicles. *Curr Drug Deliv.* 2006;3:89-93.
- Foldvari M, Moreland A. Clinical observations with topical liposome-encapsulated interferon alpha for the treatment of genital papillomavirus infections. *J Lipid Res.* 1997;7:115-126.
- Kumar P, Batta R, LaBine G, Shen J, Gaspar K, Docherty J, Foldvari M. Stabilization of Interferon alpha-2b in a topical cream. *Pharm Tech.* (Supplement). July 2009.
- Samuel CE. Antiviral actions of interferons. *Clin Microbiol Rev.* 2001;14(4): 778-809.
- Fent K, Zbinden G. Toxicity of interferon and interleukin. *TIPS.* 1987;8:100-105.
- Gall SA. Human papillomavirus infection and therapy with interferon. *Am J Obs Gyneocol.* 1995;172:1354-1359.
- ALTS Group. A randomized trial on the management of low-grade squamous intraepithelial lesions cytology interpretations. *Am J Obst Gynecol.* 2003; 188:1393-1400.
- Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevidis E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet.* 2006;367:489-498.

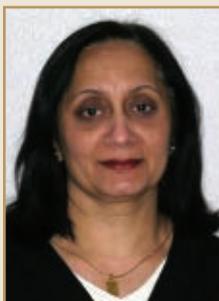
BIOGRAPHIES



Dr. Praveen Kumar is the VP of Topical Drug Product Development at Helix BioPharma Corp. in Saskatoon, Canada. He has been developing various pharmaceutical dosage forms for more than 15 years and has published several scientific research articles in the fields of drug development, drug discovery, and gene regulation.



Angela D. Perry is the Group Leader of the Bioanalytical Division of Helix BioPharma Corp. in Saskatoon, Canada. She specializes in bioassay method development and biological testing of topical formulations.



Ravinderjit Batta is the Group Leader of Formulations Division and is the Stability Studies Coordinator at Helix BioPharma Corp. in Saskatoon, Canada. She specializes in developing topical formulations for both small molecules and macromolecules and also taught Pharmaceutics at the College of Pharmacy at the University of Saskatchewan, Canada, and College of Pharmacy, Delhi, India.



Dr. Martin King is the Assistant Director, Product Development at Helix BioPharma Corp. in Saskatoon, Canada. He oversees non-clinical development and microbiological testing. He has co-authored more than 20 scientific articles in the fields of drug delivery, cancer, protein chemistry, and signal transduction.

DRUG DELIVERY

Executive

DSM Biomedical



Mr. Donato Di Biase
Business Director
DSM Biomedical

“Basically, when working with DSM Biomedical, our partners are not given a single product option (a square hole) and left to assess which drug in their portfolio happens to be the square peg that may be compatible with the delivery material. DSM Biomedical’s partners are offered access to a vast portfolio of IP-protected materials, as well as access to the full range of competencies and services of one of the world’s largest materials science companies.”

DSM BIOMEDICAL: PROVIDING SOLUTIONS FOR THE BIOPHARMA & MEDICAL DEVICE INDUSTRIES

DSM Biomedical is a global leader in biomedical materials that provides proprietary materials-based solutions, designed to enable new and more effective patient treatments for the medical device and biopharmaceutical industries. Building on the expertise and strengths of DSM and its 2008 acquisition of The Polymer Technology Group (now known as DSM PTG), DSM Biomedical’s product portfolio includes coatings, drug delivery platforms, and a wide range of biomedical materials for use in short- and long-term implantable medical devices. Leading the company’s charge in the drug delivery industry is Business Director Donato Di Biase. *Drug Delivery Technology* recently interviewed Mr. Di Biase to discuss DSM Biomedical’s drug delivery business unit, what makes its technology unique, and what the future holds for the company.

Q: Can you provide some insight into DSM Biomedical’s Drug Delivery unit?

A: DSM is unique to the world of drug delivery. Given that we are part of a leading life science and materials science company, our drug delivery business is built on the best practices in polymer science, which we have employed to develop uniquely designed systems for the biopharmaceutical and medical device industries. Through strategic alliances and co-development programs, we strive to enable our partners

to maximize value from their products by introducing novel drug delivery technology into their pipeline. DSM Biomedical seeks to partner for the co-development of next-generation products in the ophthalmology, cardiovascular, orthopedic, and pain management therapeutic areas.

Q: Can you provide more specifics about your unique product portfolio?

A: On a macro level, our Trancerta™ Drug Delivery platforms encompass both our portfolio of novel, fully bioresorbable

DRUG DELIVERY *Executive*

material platforms as well as our extensive in-house library of synthesis methods, formulation, and processing techniques. All of our materials are designed to handle specific drug payloads, to release and degrade based on a requisite profile, and are easily introduced to the target tissue alone or in combination with a device. The Trancerta Drug Delivery platforms include materials suitable for delivery of both small molecules and complex biologics.

More specifically, the Trancerta Drug Delivery portfolio offers a range of material platforms, including both hydrolytically and enzymatically degrading materials, which are able to be processed into various forms from injectable nanoparticles or rods, to gels and coatings. These materials include novel proprietary linking technologies, such as polythioesters and novel polyurethanes. For example, our polythioester linking technology allows customized solutions with well-established building blocks, such as the lactic/glycolic acid polymer family. In addition to the polythioester and novel polyurethane based materials, DSM Biomedical has expanded

the portfolio with the addition of a novel amino acid-based material.

Q: Please tell us more about this new family of amino acid-based polymers.

A: In March 2009, DSM Biomedical obtained an exclusive worldwide license for a unique delivery system developed by MediVas LLC. The technology, known as PEA or Polyester amide technology, has an IP portfolio containing more than 60 issued or pending patents. The polymers are bioresorbable, biocompatible, and allow for greater control over the rate and duration of release of their therapeutic payload.

Q: How is DSM Biomedical's drug delivery technology different from other technologies on the market?

A: In addition to being backed by a strong IP portfolio, our materials (and more notably, our materials science expertise) offer flexibility from a molecular level (ie, changing monomer building

blocks to interact with a specific portion of a drug molecule) to a larger dosage form level (ie, designing a new processing technique in order to extrude a polymer into an injectable rod). Basically, when working with DSM Biomedical, our partners are not given a single product option (a square hole) and left to assess which drug in their portfolio happens to be the square peg that may be compatible with the delivery material. DSM Biomedical's partners are offered access to a vast portfolio of IP-protected materials, as well as access to the full range of competencies and services of one of the world's largest materials science companies. Instead of being offered a square hole, we ask our Partners, "What are you trying to achieve in your patient populations, and what type of delivery system would you like us to design?"

Q: What are the clinical benefits of products delivered with Trancerta Drug Delivery?

A: We are always amazed at the number of therapeutic compounds in biopharma's

DRUG DELIVERY *Executive*

arsenal, and it is a shame that many do not make it into the clinic due to safety issues. If delivery science can help bring a compound to the market because its release is being controlled, or because the new dosage form allows for an optimized administration method, then one benefit may be simply the availability of otherwise unapprovable drugs. Looking at dosing as an example, because we are able to optimize both the loading processes and the total drug loading of the material, our systems by result are ideally designed for the individual drug at hand. This then allows for smaller total doses of drug to be administered to the patient.

Q: Why should biopharma companies choose Trancerta Drug Delivery to deliver their products?

A: As part of a global life sciences and materials sciences company with leading positions not only in polymer sciences but also in pharmaceutical products manufacturing, DSM Biomedical

offers partners bench-to-bedside product and service offerings. In the development stages, we build on the expertise and strengths of DSM, extracting the top design and processing methods needed to develop superior drug delivery systems. When it's time to scale-up, we involve our DSM Pharmaceutical Products business units, who are world leaders in pharmaceutical products manufacturing, including that of the API itself, formulations development, fill and finish services, and even final packaging.

Q: The biomedical industry is a highly competitive one, with innovations constantly being developed. What sort of intellectual property is DSM building in drug delivery?

A: First, our intellectual property assets are based on very strong, internal material science competences. This results in a continuously growing patent estate on materials and processing technologies. Second, and most importantly, we develop new IP in close

cooperation with our partners, believing that these multidisciplinary innovations have the best economic impact for all parties.

Q: What do you expect to see in the way of future developments for DSM Biomedical's drug delivery portfolio?

A: Today, we will continue increasing the number of partnerships in our core strategic areas of ophthalmology, cardiovascular, musculoskeletal, and pain management. Going forward, we will expand our delivery science into other therapeutic areas where our technology can provide value in helping to improve the treatments and quality of life for patients worldwide. ♦

TECHNOLOGY Showcase

MDI COMPONENTS

Enabling your success
3M Drug Delivery Systems

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

CHILDREN'S SPACER DEVICE



Activaero Technologies has developed Watchhaler®, a novel children's spacer device with design elements that include constant volume and constant flow rate. By controlling volume and flow, the dose-to-dose variability is greatly

reduced. Current spacers are often limited by a sterile medical design, while the Watchhaler® design resembles a colorful hedgehog and is readily accepted by the child. The system incorporates an isolated folding balloon that reduces electrostatic interference on the aerosol, thus the aerosol is available for inhalation for over a minute, giving ample time for inhalation. A transparent design lets parents watch the deflating balloon and get a visible feedback of a complete inhalation manoeuvre. The Watchhaler has a valve that controls the inspiration speed during the inhalation, which helps achieve slow and even (thus successful) inhalation. The Watchhaler is easy to disassemble and clean. For more information, visit Activaero Technologies at www.activaero.com.

SOLUBILITY/BIOAVAILABILITY ENHANCEMENT

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PREFILLABLE DELIVERY SYSTEMS



BD Medical - Pharmaceutical Systems is dedicated to developing prefilled drug delivery systems designed to fit the needs of the pharmaceutical industry. BD offers

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

TECHNOLOGY Showcase

PHARMACEUTICAL SOLUTIONS



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; Zydys® 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.

NGI CUP COATER



The NGI cup coater is a new tool from Copley Scientific for use in semi-automated inhaler product testing. The Next Generation Impactor (NGI) is used increasingly for aerodynamic particle size measurement, as prescribed by the regulators for all

inhaled drug products. Applying a sticky layer to the cups of the impactor improves measurement accuracy, particularly for DPI formulations, by reducing particle bounce and re-entrainment. Copley Scientific's NGI cup coater automates this process, replacing conventional coating methods, such as spraying, dipping, or pipetting, that are often manual, messy, and time-consuming. Automating the coating process frees analysts to perform other tasks, eliminates the variability associated with a manual procedure, and reduces solvent wastage. The cup coater is easy to use and holds a full set of 8 cups for simultaneous coating of all collection surfaces. For more information, contact Copley Scientific at sales@copleyscientific.co.uk or visit www.copleyscientific.com

RAMAN CHEMICAL IMAGING



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

COMBINATION CAPSULE TECHNOLOGY

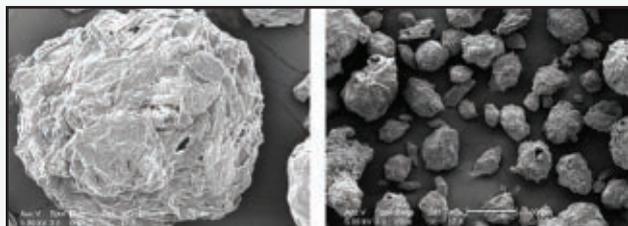


InnerCap offers an advanced patent-pending multi-phased, multi-compartmentalized capsular-based delivery system. The system can be used to enhance the value and benefits of pharmaceutical and biopharmaceutical products. Utilizing two-piece hard shell capsules, the technology offers the industry solutions to problems affecting pharmaceutical companies, patients, and healthcare providers. The delivery system will be licensed to enhance pharmaceutical and biopharmaceutical products. It is a very effective way to deliver

multiple active chemical compounds in different physical phases with controlled-release profiles. The delivery system provides the pharmaceutical and biopharmaceutical industries with beneficial solutions to the industry's highly publicized need to repackage and reformulate existing patented blockbuster drugs with expiring patents over the next 5 years. For more information, contact InnerCap Technologies, Inc., at (813) 837-0796 or visit www.innercap.com.

TECHNOLOGY Showcase

PERFORMANCE EXCIPIENTS



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

EXCIPIENTS & TECHNOLOGY



The MEGGLE Group's Excipients & Technology Business Group supplies the pharmaceutical industry with carrier substances, such as pharmaceutical lactose. With outstanding product quality and intelligent innovations, we have gained a leading global position in the field of lactose and compounds. MEGGLE pharmaceutical lactose, for example, serves as a carrier substance in medicines. It behaves completely neutrally in the human organism and causes no undesired effects due to interaction with other components of the medicine. We also have developed a diversified product portfolio in the more than 50 years that we have been active in the market that contains excipients for granulation and capsule-filling as well as special modern products for direct compaction and dry-powder inhalers. Our customers are predominantly manufacturers of pharmaceutical products and dietary supplements. For more information contact the MEGGLE Group at (914) 682-6891 or visit www.Meggle.com.

SILICONE MATERIALS



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

DEVELOPMENT & DELIVERY



Penwest is a drug development company focused on identifying and developing products addressing unmet medical needs, primarily for rare disorders of the nervous system. The company is currently developing A0001 (alpha tocopherol quinine), a coenzyme Q10 analog demonstrated in vitro to improve mitochondrial respiratory chain diseases. Penwest is also applying its drug delivery technologies and drug formulation expertise to its collaborators' product candidates under licensing collaborations. Penwest's most recent success is Opana ER, an important therapeutic option for the treatment of pain. Its drug delivery technologies include TIMERX, a flexible, approved technology for the development of patented, oral controlled-release products. Penwest's technologies can also be used for delayed release, site-specific delivery, and chronotherapeutics. For more information, contact Penwest at (845) 878-8400 or bizdev@penwest.com.

TECHNOLOGY Showcase

KNOWLEDGE MANAGEMENT



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.

PASSIVE SAFETY DEVICE



In response to the continued concern over unprotected needle exposures and the mandated Safety and Prevention regulations, Rexam has developed a fully passive safety device for prefilled syringes: the Safe'n'Sound. The Safe'n'Sound

provides healthcare industries and patients with full protection from needlesticks to avoid any contamination. Compared to a standard syringe, the Safe'n'Sound system guarantees passive protection as the syringe retracts automatically in the system after the injection without any action by the user. Compact, light, and transparent, the Safe'n'Sound has only three components (a sleeve, a body, and a spring). For more information, contact Rexam at (847) 541-9700 or visit www.rexam.com/pharma.

PERFORMANCE EXCIPIENTS



Pharmaceutical excipients produced by Stepan Company feature outstanding performance characteristics for use in the development of medical delivery systems including topical formulations. NEOBEE® Medium Chain Triglycerides are odorless, colorless, and naturally derived. Their low viscosity and polar nature facilitates handling under low-temperature processing conditions and promotes improved dispersibility, spreading, and dissolution of actives. ONAMER® M (Polyquatremium-1) exhibits unique antimicrobial activity, is extremely mild, and exhibits very low toxicity to host cells, allowing ONAMER® M to function in a wide range of medical device applications, including surgical scrubs, surgical preps, and other topical formulations requiring a broad spectrum of antimicrobial efficacy. For more information, contact Stepan at (201) 712-7642 or visit www.stepan.com.

DRUG DEVELOPMENT



Xcelience is the premier source for unsurpassed quality in drug development services. The company brings together the industry's most experienced and talented scientists, consistently and efficiently moving compounds through the research and development continuum to regulatory approval. Since 1997, the Tampa-based laboratory has been developing formulations for clients throughout the pharmaceutical industry. Xcelience's unique corporate structure creates project teams that work intensively with each client, bringing an extension of their own organization into the Xcelience lab. The lab uses only state-of-the-art equipment, highlighted by the patented Xcelodose®, which fills API directly to capsules (Xcelodose is a registered trademark of Capsugel BVBA). This and other technologies give Xcelience unparalleled speed to market without compromising its absolute commitment to quality. For more information, contact Xcelience at (608) 643-4444 or visit www.xcelience.com.

DRUG DELIVERY

Executive



Creative Partners in a Material World



Mr. Brian Nash
VP of Marketing &
Sales

NuSil Technology

“As always, we attempt to meet the needs of technically challenging applications that require a sophisticated silicone manufacturer willing to tackle difficult challenges in markets filled with potential liability. Proactive planning to meet the needs of the drug delivery industry is common sense for us and highly consistent with our historical core competencies and overarching business strategy.”

NU SIL TECHNOLOGY: FORMULATING INNOVATIONS TO MEET DEMANDS OF TODAY, TOMORROW

NuSil Technology is a formulator and manufacturer of silicone compounds for the healthcare industry, meeting the demands of new and innovative technologies by building on its extensive knowledge and expanding its products and services to provide exclusive silicone solutions for drug delivery and combination medical device products. The company offers research and development capabilities for those looking for proprietary, custom formulations and will incorporate APIs directly into silicones specifically developed for controlled release. NuSil’s materials are developed and qualified in ISO 9001-certified manufacturing facilities, ensuring consistent processes and standards across the globe. NuSil also offers testing guided by European Pharmacopeia and by the US FDA. Drug Delivery Technology recently spoke to Brian Nash, NuSil’s VP of Marketing and Sales, to discuss how his company has for more than 30 years advanced the standards for manufacturing silicone products, allowing it to offer an unparalleled consistency in its standard and custom formulations.

Q: Can you provide an example of how NuSil proactively plans to meet the needs of the drug delivery market?

A: We recently completed construction of a 2,400-sq-ft clean room designed to meet both Class 100,000 and Class 10,000 status.

Throughout the past 15 years, NuSil has sold silicones to manufacturers of controlled-release and combination products. In a number of instances, NuSil has been called upon to compound and deliver silicones that contain

APIs. In addition, in the past several years, we have seen an increase in demand for both of these scenarios. As a direct result of that spike in interest, we believed it was time to make a capital investment in a facility that would ensure all future compounding was done in a safe and controlled environment.

Q: What makes NuSil a good fit for supplying silicones to such sensitive applications?

A: NuSil’s business strategy/model has been historically centered around supplying

DRUG DELIVERY *Executive*

silicones for sensitive applications. NuSil opened its doors in 1979 because the founder of the company believed there was a need for a silicone manufacturer that was willing to custom formulate, as well as build and ship smaller quantities. The idea was to be the niche silicone manufacturer that would specialize in meeting the needs of customers that other, much larger silicone manufacturers either had no interest in serving or simply couldn't afford to do so. While NuSil remains committed to this principle, it's also true that we maintain thousands of standard products and often build 1,300-kg lots to ship via 40-ft ocean containers. Even so, it is important to remember that NuSil does not manufacture commodity silicones and never has, giving us the ability to proactively plan to meet the needs of the drug delivery industry. As always, we attempt to meet the needs of technically challenging applications that require a sophisticated silicone manufacturer willing to tackle difficult challenges in markets filled with potential liability. Proactive planning to meet the needs of the drug delivery industry is common sense for us and highly consistent with our historical core competencies and overarching business strategy.

Q: How else has the company grown and evolved since conception? Has its basic model changed?

A: While NuSil's core philosophy hasn't changed much throughout the decades, it is fair to say that NuSil redefines itself every few years. This happens organically, as the result of NuSil's response to either an industry challenge or a perceived opportunity in the marketplace. In fact, if one were to look back over NuSil's 3-decade history, it would be marked by periods of sustained growth that were occasionally interrupted by these redefining moments that expanded the definition of what NuSil is. For example, in our corporate infancy, the core of our products was intended for high-technology engineering applications, including flight and aerospace, with a small amount of healthcare silicones. It was early on in this period of the company's history that its model acquired features that it will never lose: speed and problem-solving. We made some key relationships by rapidly responding to our customers' needs - whether that meant designing new products, building or buying new equipment, adding new shifts, or designing new test methods. The first significant redefining moment came in the early 90s when the major

silicone manufacturers halted all sales of silicones for long-term human implantation applications due to the health concerns related to ruptured breast implants. At this point, the FDA created guidance for smaller manufacturers to enter the market of creating a host of silicones intended for long-term human implantation. We at NuSil were confident of the inherent bio-inertness and safety of silicones, so we moved forward. The net result was that, within 2 years, NuSil created a complete line of silicones for long-term human implantation, with many of them supported by Master Access Files (MAFs). Consequently, within 2 years, our market demographic flipped, and we became 70% healthcare and 30% engineering, aerospace, and flight. From that point forward, there were a number of acquisitions involved to further augment our vertical integration and continue with the company's core business model.

Q: To accommodate this dramatic transition, was it necessary to abandon certain products, product lines, or markets?

A: Absolutely not. It is core to our philosophy to grow without abandoning any products or

DRUG DELIVERY *Executive*

customers. We didn't shift our offerings. We simply expanded our range of products and services.

Q: What were some other redefining moments in NuSil's history?

A: The redefining moments that followed NuSil's entry into the healthcare market were so significant they resulted in the construction of additional NuSil facilities. First, in the late 90s, we were informed by a sole source supplier of a critical raw material (diphenyl cyclics) that would cease to be available within a year. We immediately bought all we could and then went to work looking for a solution. Because there was no other source of diphenyl cyclics, we looked to ourselves. Within 9 months, we designed and patented a process to manufacture diphenyl cyclics; purchased land in Bakersfield, CA; and built a facility. To this day, we manufacture our own diphenyl cyclics as well as a host of other raw materials, intermediates, and some finished products at this facility. At approximately the same time, a

major customer approached us and requested that we start a new company that would function solely as its supplier. Although the new company was owned by NuSil, it gave this customer a degree of comfort knowing that (with manufacturing sites in California and Texas) our disaster recovery posture was significantly improved. Right on the heels of this expansion, we also opened an office in Southern France to provide technical support to the European markets.

Q: This sounds like an extraordinary amount of growth in a relatively short period of time. How was this accomplished logistically?

A: Quite early in our existence, we realized that - in industries where speed to market with a quality product is essential - it was critical for our success that we have the capacity for rapid response to customer needs. One of the ways we have been able to make major adjustments so quickly is that we have an engineering department that builds or restores most of our

equipment and also builds and restores many of our buildings. This level of vertical integration has, on countless occasions, saved large amounts of money and, even more important, vast amounts of time. Consequently, it is rare that NuSil finds itself in the unfortunate position of waiting months or a year for a key piece of equipment. The other strength that allowed this expansion was our static resources. While most companies avoid excess capacity, we generally operate at 55% of our total capacity, giving us plenty of space and equipment when we need it.

Q: Please explain how the installation of your new clean room represents a moment of expansion in NuSil history.

A: We made the decision to install a clean room about 5 months ago. Since we made that decision, we've remodeled an existing facility that was largely dormant, purchased and installed a clean room that is now fully functional, and equipped it with the necessary compounding and packaging equipment. We've never had a facility like this before.

DRUG DELIVERY *Executive*

The facility will be registered with the FDA and California State Health Department, and the cleanroom will be initially rated as a Class 100,000 clean room.

Q: When and how did NuSil expand into the drug delivery market?

A: A little over a year ago, we launched our Drug Delivery Silicone line to lay the groundwork to serve the drug delivery industry. While limited in scope initially, the idea was to build some products that represent a wide variety of formulations with varied physical characteristics. The line was launched with a non-functional silicone fluid (a two-part, platinum-catalyzed, high-consistency elastomer) and a condensation-cure, low-consistency elastomer. These products can be tested in accordance with ISO 14949. Moreover, they are supported by Drug Master Files (DMFs), which include select testing per the guidance of either EP 3.1.8 or EP 3.1.9. This line of silicones was developed to showcase how we are willing to characterize and support such products. NuSil understands that most silicone

projects with an active component require extensive development work to achieve solubility; homogeneity; and, ultimately, diffusivity and elution.

Q: What are some of the challenges with incorporating active components in a silicone?

A: It isn't always easy to mix an active in a silicone. This is where NuSil's wealth of experience and vast resources really come into play. Or, taking it from another angle, sometimes an active compounds in very nicely but practically refuses to elute back out. This is where our ability to custom formulate our silicones becomes an enormous benefit. We're more than happy to experiment with various excipients and surfactants and have done so on countless occasions with success. Lastly, all of this work is meaningless unless you have the capability to analyze your experiments and your ultimate product's performance. It is for this reason that NuSil has developed methods for conducting elution rate studies and has already characterized many formulations on

various projects. It is also why we're currently evaluating other means of characterizing the diffusivity of actives through cured silicone matrices. NuSil has acquired these competencies over the course of years and, often, at customer request; but, as mentioned before, this is where NuSil is most comfortable, where there are challenges and risk. ♦

Drug Development

Ingredient-Specific Particle Sizing: Reducing Risk, Cutting Cost & Saving Time in Inhalable Formulation Development

Linda M. Batykefer, MBA, and Oksana V. Olkhovyk, PhD



The need for efficient and cost-effective means of gathering particle analysis data for pulmonary formulation is evident in today's fast growing inhalables' market. Abundant evidence indicates that currently the market for respiratory drugs and their delivery technologies are healthy, vibrant, and growing. The inhalation and nasal products had combined sales exceeding US \$22 billion in 2007 for treatment of asthma, COPD, allergic rhinitis, influenza, migraine, and osteoporosis, and for use in general anaesthesia.¹

While product pipelines have been reduced overall, and the number of new drug approval applications submitted to regulatory authorities has declined in recent years, pharmaceutical companies are pursuing alternative delivery methods for their new drug products as well as reformulating blockbuster drugs before they come off patent. Another common trend is developing respiratory drug delivery technologies for drugs currently administered via injection. Despite some initial problems, such as the failure of Pfizer's Exubera (inhaled insulin), the concept of systemic delivery via the lung is by no means dead, and many companies continue to develop inhaled drug products.²

Despite the fact many inhalable and nasal drug delivery products are limited to localized diseases, such as allergic rhinitis and asthma, continuous research and development activities are opening up opportunities in new therapeutic areas. Nasal drug delivery is becoming more common due to the potential for increased drug uptake rates, improved bioavailability for certain drugs (relative to oral dosing), and convenient administration.

A number of nasally delivered, systemically acting drugs for a number of therapeutic areas are reaching the market or are in the pipeline.³ Other areas where new nasal and inhalation drug delivery approaches could provide an alternative to current intravenous administration include seizures, heart attack, motion sickness, and psychotropic drugs.³

Ingredient-Specific Particle Sizing

In nasal spray suspension products, particle size is directly related to bioavailability. In pulmonary drug delivery, particle size also affects deposition location. When aggregates form in nasal and pulmonary drug products, they bring about an increase in overall particle size and may cause a number of potential problems, including:

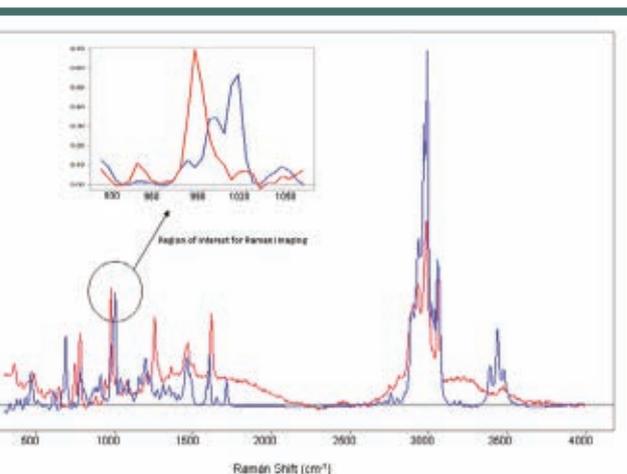


Figure 1. Raman Spectra of API Components Showing the Ability of the Raman Method to be Used to Distinguish the Two API Materials From One Another

- deposition in the wrong or unwanted part of the body;
- changes in bioavailability; and
- clogging of the medical device.

Two important parameters of particle size exist for nasal and pulmonary drug products. The first one, aerodynamic particle size (or droplet size), is the key factor for predicting whether particles will deposit in the nose, esophagus, or lung. Basic information for a given formulation about aerodynamic particle size distribution is an essential starting point in successful product development. However, traditional methods (cascade impaction followed by HPLC; laser light scattering) provide only the most rudimentary, purely physical data and cannot differentiate between chemically different particles or particle aggregates.

The second parameter, the drug particle size, will determine the rate of dissolution, dosage, and availability to sites of action within the nose (optimally approximately 10 microns) or the lungs (< 5 microns). Therefore, particle size distribution (PSD) for the drug or drug aggregates should be characterized in the formulated product both within the primary container and within the aerosolized droplets.⁴

Furthermore, the presence of more than two ingredients is becoming more commonplace as combination products (containing two APIs plus excipients) are developed. It cannot be assumed that all ingredients have similar physical characteristics, exhibit uniform particle size distribution, or do not interact. Thus, information pertaining to the particle size distribution of specific ingredients represents a significant advantage.

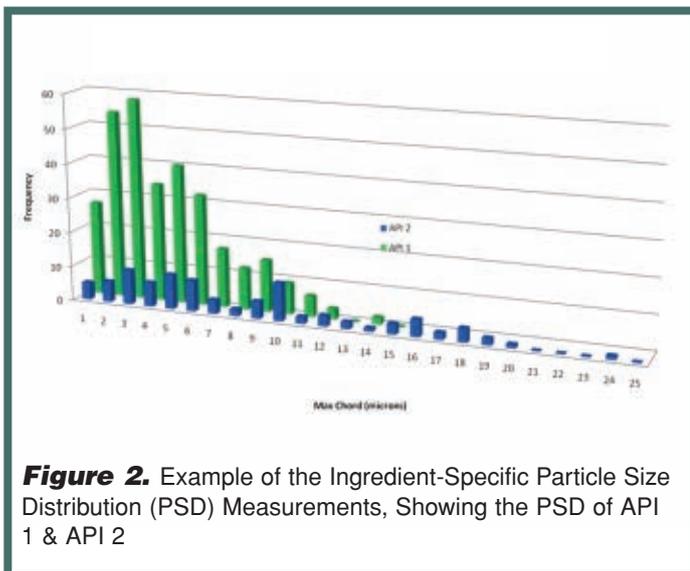


Figure 2. Example of the Ingredient-Specific Particle Size Distribution (PSD) Measurements, Showing the PSD of API 1 & API 2

Readily available, high-quality drug particle size data could provide the necessary information for conclusive *in vitro* bioequivalence (BE) comparisons of drug PSD, including PSD of dispersed and agglomerated API particles, as well as the extent of agglomeration in the product.⁵ In generic product development, if drug PSD of the generic is found to be not equivalent to (or outside of acceptable variability thresholds of) the innovative product's PSD, clinical trials can be postponed until the acceptable drug PSD is reached, saving significant time and money for generic companies.

Obtaining drug particle size information prior to entering clinical trials can provide invaluable information, raising confidence and lowering risk of failure of *in vivo* biostudies. The value and importance of gaining this information before taking the expensive step of beginning clinical development cannot be emphasized enough.

With additional information related to drug particle size and material composition at their disposal (information which was not easily accessible in the past), innovators are even better equipped to design unique, hard-to-duplicate formulations. Ingredient-specific particle sizing technology and services help innovative drug developers characterize and design their formulations better and, further on in development, as part of batch release testing.

With the increase in interest from innovative drug developers in nasal and pulmonary drug delivery, methods that characterize formulations without destroying the sample are increasingly needed. Ingredient-Specific Particle Sizing™ (ISPS™) is the technique offered by ChemImage that fulfills

this requirement for non-destructive, ingredient-specific particle size data. Chemical identification is provided by the unique Raman spectral signature based on the vibrational structure of the compound. ISPS uses ChemImage's unique approach of combining Raman chemical imaging, optical microscopy, and software to identify particles based on a unique chemistry (eg, API versus excipient) and measure their physical size or morphology.

Raman Chemical Imaging

Raman spectroscopy is a very selective vibrational technique and is often used in the pharmaceutical industry to identify drug polymorphs (different crystalline structures that are made of the same molecules, but exhibit various crystal habits or packing). With the ability to detect such small spectral differences, Raman spectroscopy is very comfortably able to differentiate between various materials in a pharmaceutical formulation, including the drug substance and various excipients (Figure 1).

Raman chemical imaging builds on the ability of spectroscopy by adding a spatial context to the chemical information provided. Raman Chemical Imaging (RCI), a method that combines the capabilities of molecular spectroscopy and advanced digital imaging, details material morphology and composition with a high degree of specificity in a non-contact, non-destructive manner. A Raman chemical image provides a Raman spectrum at each pixel in the image, providing spatially dependent Raman spectroscopic information. Interrogation of individual pixels assists in the interpretation of the data. Presence or absence of API within a field of view is determined by whether or not the Raman spectral features characteristic of the drug are present. Imaging allows one to understand size, shape, and spatial distribution of chemical components, providing a number of advantages of simple Raman spectroscopy, and in particular, drug particle sizing for nasal and pulmonary drug products.

In the wide-field RCI approach, digital images are acquired at predefined Raman spectral regions, by imaging an area through an electro-optically controlled, liquid crystal tunable filter (LCTF) that serves as an imaging spectrometer. The RCI microscope simultaneously provides diffraction-limited spatial resolution (approaching 350 nm for high signal-to-noise images) and high Raman spectral resolution. The no-moving-parts approach employed to construct Raman chemical images enables fusion of optical and Raman

chemical imaging data. Fused optical/Raman images are used to guide the size measurements, differentiation between drug aggregates, and individual particles. This approach helps eliminate problems often seen with morphologically directed, confocal Raman spectroscopy, which requires precise, repeatable stage translation.

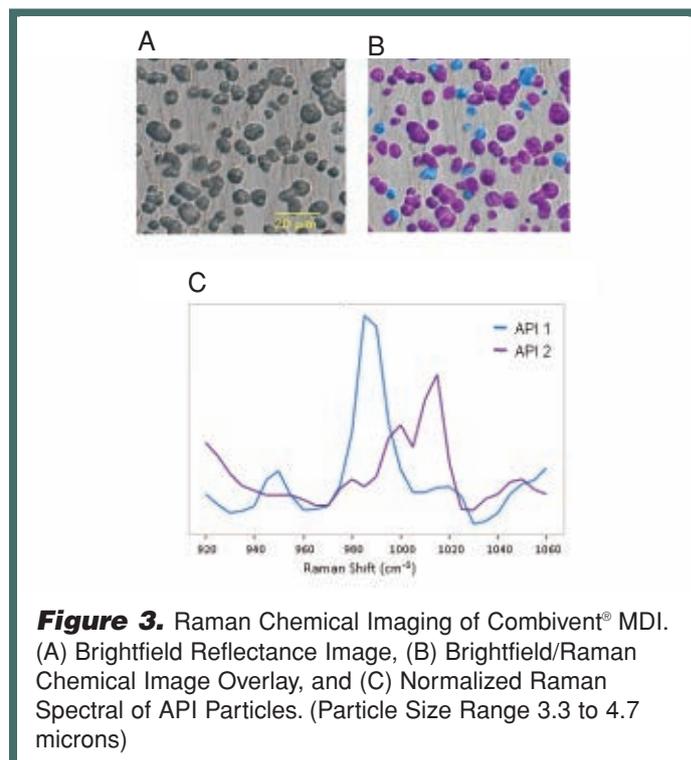
ISPS is especially useful for drug-specific particle sizing of metered dose inhalers (MDIs), dry powder inhalers (DPIs), and nasal spray suspensions. The method was initially investigated in collaboration with the US FDA to achieve drug particle size distribution measurements for nasal spray suspensions.⁵ In addition to investigating formulations for API particle size distribution, ISPS has been found to be useful for the study of drug/drug and drug/excipient aggregates. Raman imaging has also been used to investigate the structure of carrier-based DPI formulations.⁶ ISPS has proven especially useful for innovative drug developers who are interested in combining multiple drug substances in one formulation.

An example of ISPS distribution data for a sample formulation containing two APIs is shown in Figure 2. Fused optical/RCI images are used to guide the size measurements of each drug, differentiation between drug aggregates and individual particles.

Raman Chemical Imaging for Drug PSD of Two APIs in Combivent™ MDI

The MDI is the most common device for therapeutic aerosol delivery, second only to tablets among self-medicated dosage forms.⁷ The PSD of the drug substance in the aerosol plume is a very important parameter and, in regulatory terms, is a required measurement for in vitro testing of MDIs.⁷ A typical MDI formulation contains API, propellants, and surfactants. Although PSD of the drug can be easily determined prior to the formulation, it is a challenge to establish it in the finished product.

The standard traditional apparatus for the in vitro determination of PSD information is the Anderson cascade impactor (ACI). A complete ACI analysis includes introduction of the sample into the ACI, where particles are separated on the basis of their aerodynamic size. This is followed by extraction of the drug substances from the ACI plates, final filter, USP throat and mouthpiece adaptor, and finally performing



quantitative chemical analysis by HPLC or spectroscopy methods.

The procedure is time-consuming, labor-intensive, and destructive. Presence of non-volatile excipients in the formulation or a second API may complicate particle size characterization even further. Analysis of the deposition profiles may indicate formulation issues, such as agglomeration of APIs or physico-chemical stability (polymorphism, hydration) after actuation. Furthermore, a large variability in results has been observed between different operators and different ACI units. As a consequence, there is a high demand for the replacement of the ACI with an alternative technique capable of concurrently performing PSD determination and chemical identification.⁷

In a previous study, RCI was evaluated as a method for identifying two API species on cascade impaction plates and characterizing drug interaction in Combivent® Inhalation Aerosol (Boehringer Ingelheim Pharmaceuticals), an MDI sample containing two APIs.⁷ RCI successfully identified each API particle, and the total number of particles and PSD for each API and PSD of aggregated API particles were reported.⁷

ChemImage had successfully applied RCI to measure ISPS distribution in formulated nasal sprays and aerosols. This investigation was initially reported in 2005; significant progress has been made since to optimize the technique and enhance the

capabilities of RCI for the pharmaceutical industry. Issues have been addressed related to automation, image processing, and particle size analysis by applying an automated method of data collection and analysis of fused RCI and brightfield imaging.^{8,9} A new, patent-pending image processing method has been developed to evaluate each particle in the field of view individually, rather than collectively.¹⁰

Using this image processing technique, the original Combivent RCI data reported by Guo et al was revisited. API 1 (albuterol sulfate) and API 2 (ipratropium bromide) are presented as purple and blue in the brightfield/Raman binary image overlay (Figure 3). Intensity maps were developed for each API using an iterative threshold process. Once the particle map is produced, a feedback loop is initiated that confirms the chemical identity against the Raman spectrum and validates the particle size against the brightfield optical image. This individual particle approach allows for a more accurate and reliable drug PSD measurement, effectively addressing concerns of accurate size measurements in the previously publications.⁵ This combined optical approach helps avoid the issue of over- or under-sizing particles due to Raman signal intensity, which is related to size of the particle.

Acknowledgements

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References

1. Espicom. Emerging Opportunities in Inhalation & Nasal Spray Generic Drugs. s.l.: Espicom Business Intelligence, 2008.
2. Greb E. Inhalable drugs on the launch pad: will they take off? Pharm Tech Buyers Guide. 2008;4:48-55.
3. Kock M. The growing market for nasal drug delivery. Pharm Tech Touch Briefings. 2003:1-3.
4. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Draft Guidance for Industry, Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action. 2003.
5. Doub WH, et al. Raman Chemical imaging for ingredient-specific particle size characterization of aqueous suspension nasal spray formulations: a progress report. Pharmaceut Res. 2007;24(5):934-945.
6. Kinnunen H, et al. Spectroscopic investigations into the structure of carrier-based dry powder inhaler formulations. Edinburgh. Paper presented at Drug Delivery to the Lungs in Edinburgh, Scotland;2009.
7. Guo C. The potential use of Raman imaging for determination of the particle size distribution (PSD) of active pharmaceutical ingredients (APIs) in metered-dose inhalers. Paper presented at the Third International Conference on Advanced Vibrational Spectroscopy, 2005.
8. Priore R, Olkhoviyk O, Klueva O. Ingredient-specific particle sizing for batch comparison to analyze the drug particle size distribution in aqueous nasal spray formulations. Paper presented at Respiratory Drug Delivery (RDD) Europe Conference in Lisbon, Portugal;2009.
9. Priore R, et al. Ingredient-specific particle sizing for batch comparison to analyze the drug particle size distribution in aqueous nasal spray formulations. Paper presented at the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting in Los Angeles;2009.
10. Fuhrman M, Priore R, Klueva O, Olkhoviyk O. Automation of ingredient-specific particle sizing using Raman chemical imaging. 12/684,495 US, January 8, 2010. Patent Application.
11. Drug Delivery Markets, Vol III. Pulmonary delivery systems. s.l.: Kalaroma Information;2007.



Linda Batykefer

Linda Batykefer joined ChemImage in June 2003 as an Application Scientist for 4 years before moving into her current role as Marketing Manager. Ms. Batykefer earned her MBA in Business Administration & Marketing from Keller Graduate School of Business (DeVry University) and her BS in Chemistry from the University of Pittsburgh. Her current role is primarily in marketing research and corporate marketing communications, including advertising and public relations, strategy, branding, messaging, lead generation, sales, and business development support.



Dr. Oksana Olkhoviyk

Dr. Oksana Olkhoviyk joined ChemImage in September 2006. Her primary role is to advance innovative applications and assist with the development of chemical imaging technology and instrumentation. She also serves as technical support for commercial applications of spectral imaging within ChemImage lines of business. Dr. Olkhoviyk earned her PhD in Physical Chemistry from Kent State University and her MS with honors in Chemical Engineering from Lviv Polytechnic University.

Therapeutic Focus

Fast-Dissolve Technology is an Easy Pill to Swallow for Chronic Pain

By: Cindy H. Dubin, Contributor

The oral drug delivery market is a \$35-billion industry, growing at a rate of 10% each year.¹ Its popularity among the physician community can be attributed to ease of administration, accurate dosage, self-medication, pain avoidance, and patient compliance. The most popular solid dosage forms are tablets and capsules, but these can be difficult to swallow and require water. Pill-swallowing difficulty, which may lead to non-compliance, primarily affects geriatric and pediatric populations, who account for a substantial portion of prescription medicines. To eliminate this problem, fast-dissolving tablets or orally disintegrating tablets (ODTs), which disintegrate instantaneously and release the drug that dissolves or disperses in the saliva, are increasingly attracting pharma's attention.

Fast-dissolve products offer improved compliance and convenience for patients. According to Technology Catalysts International (TCI), more than 200 branded and generic products have been commercialized on ODT formulations. These ODT prescription and over-the-counter products are approaching 10% of the global oral drug delivery market with 2006 revenues of almost \$4 billion. Although the ODT market growth rate has slowed compared to previous years, products collectively increased 20% in value from 2005. TCI's fifth ODT report indicates the market is set to approach sales of \$8 billion this year, with the US holding 30% of the market share, based on current global growth trends.

Matching Fast-Dissolves to Compounds

It is these promising numbers, as well as the benefits of compliance and convenience, which fast-dissolve technology offers that drive Wilmington Pharmaceuticals to develop, commercialize, and out-license patient-friendly, fast-dissolving formulations for established medicines.

The first of these was metoclopramide HCl, which has been physicians' oral drug of choice for patients suffering from diabetic gastroparesis and refractory gastroesophageal reflux disease (GERD). In the former, the gastro muscles in the stomach stop working, leading to digestive problems, gastric distress, nausea, and vomiting.

"The idea of having to swallow a pill with water can be daunting to a patient suffering from gastroparesis," says Gene Haley, CEO of Wilmington Pharmaceuticals. "Some patients are in such GI distress from their illness that they end up at the hospital where they receive an intravenous treatment. We realized this was suboptimal delivery with serious patient and cost implications, and we knew that an ODT formulation would be superior."

The result was Metozolv™ ODT (metoclopramide HCl) 5-mg and 10-mg ODTs for the relief of symptoms in adults associated with acute and recurrent diabetic gastroparesis and for short-term therapy (4 to 12 weeks) for adults with symptomatic documented GERD who fail to respond to conventional therapy.

Patients with diabetic gastroparesis (which accounts for 50% of diabetics in the US) and symptomatic documented GERD may have trouble with the following issues:

- adhering to treatment because of difficulty swallowing;
- the need for treatment when they do not have water available; or
- the need for a portable way to take medication.

Metozolv ODT, which rapidly melts on the tongue, offers these patients a new choice that may be more convenient than traditional metoclopramide tablets.

"Metozolv promotes motility in the gastrointestinal tract, enabling patients to digest food and any other oral medications they need to take," says Mr. Haley.

Metozolv ODT received FDA approval in September 2009 and was introduced to the market in November by Salix Pharmaceuticals, which markets Metozolv ODT under a licensing agreement with Wilmington Pharmaceuticals.

"The addition of Metozolv ODT to Salix's expanding GI-specialty product portfolio provides physicians and patients an innovative treatment choice that may offer improved convenience over traditional metoclopramide therapy," says Bill Forbes, PharmD, Senior Vice President, Research and Development, Chief Development Officer, Salix Pharmaceuticals.

According to Carolyn Logan, CEO of Salix, "Wilmington Pharmaceuticals provided Salix with ready access to a late-stage, patent-protected product that complements our strategy to deliver products that meet the unmet GI treatment needs of physicians and patients." Salix anticipates Metozolv can generate peak year revenue of at least \$50 million.

Chronic Pain & ODTs

Building off the success of Metozolv ODT, Wilmington Pharmaceuticals has turned its sights to chronic pain medication and rheumatology. Approximately 46 million adults suffer from some form of arthritis, and it is the second most frequently reported chronic condition in the US.² Arthritis and rheumatic conditions cost the US economy \$128 billion in 2003, and the incidence of these diseases has increased significantly since then. By 2030, an estimated 67 million Americans aged 18 years or older are projected to have doctor-diagnosed arthritis.³ Because arthritis prevalence increases with age, the prevalence rate is 50% among adults over age 65.⁴ If prevalence rates remain stable, the number of affected persons aged 65 years and older will nearly double to 41.1 million by 2030.⁵

"When we're dealing with chronic illnesses like rheumatology,



Figure 1.

patient compliance can be poor at different points in time. The patient can be asymptomatic, but still sick," Mr. Haley explains. "Compliance drops off when they are asymptomatic. We wanted to find a way to help patients reliably take their medication, and ODT formulations are a proven way to increase compliance because of their convenience."

Mr. Haley expects a fast-dissolve alternative to have a market potential in the \$300- to \$500-million range. Without wanting to disclose which current chronic pain medication will be turned into a fast-dissolve alternative, Mr. Haley does say that the product is currently completing clinical trials, and an NDA filing is expected in early 2011. Wilmington Pharmaceuticals is interested in discussing licensing opportunities to find the best partner to take the product to market.

Lyophilized Fast-Dissolve Speeds Dosing

In both the case of Metozolv ODT and the chronic pain medication for rheumatology, Wilmington Pharmaceuticals chose Catalent Pharma Solution's Zydis fast-dissolving oral tablet. Zydis is a freeze-dried oral solid dosage form that can be swallowed without water because it dissolves instantly on the tongue in less than 3 seconds. This dissolution speed translates to dosing convenience and ease of administration, says Mr. Haley.

The production sequence begins with the bulk preparation of an aqueous drug solution or suspension and subsequent precise dosing into preformed blisters. It is the blister that actually forms the tablet shape and is, therefore, an integral component of the total product package. The second phase of manufacturing entails passing the filled blisters through a specially designed cryogenic freezing process to control the ultimate size of the ice crystals. This aids in ensuring the tablet possesses a porous matrix to facilitate the rapid disintegration function. These frozen units are then transferred to large-scale freeze dryers for the sublimation process, whereby the majority of the remaining moisture is removed from the tablets. The final phase of production involves sealing the open blisters via a heat-seal process to ensure stability and to protect the product from varying environmental conditions.

Wilmington Pharmaceuticals will commence development for a third fast-dissolve product in late summer/early fall. When there is clinical progress, Wilmington Pharmaceuticals plans to begin discussions with licensing partners in the second half of the year. This drug has the potential to reach \$700 million in US sales.

Summary

ODTs have potential advantages over conventional oral dosage forms with their improved patient compliance, convenience, bioavailability, and rapid onset of action, which have drawn the attention of many manufacturers throughout the past decade. ODT formulations obtained by some of these technologies have sufficient mechanical strength and quick disintegration/dissolution in the mouth. Many drugs can be incorporated in ODT, especially

unpalatable drugs.

According to Mr. Haley, fast-dissolve technology brings benefits to three critical audiences: (1) patients, who receive increased comfort, compliance, and convenience; (2) physicians, who see patients less often because of increased compliance; and (3) payers, who benefit from decreased total treatment costs resulting from increased compliance. Wilmington Pharmaceuticals is currently seeking highly capable marketing partners to present its pain and rheumatology product to these three critical audiences. ♦

References

1. Kalorama Information, Drug Delivery Markets: Oral Delivery, July 2009.
2. Arthritis & Rheumatism 2006;54(1):226-229 [Data Source: 2003 NHIS].
3. Benson V, Marano M. Current Estimates from the National Health Interview Survey, 1995. Vital & Health Statistics. 1998;10(199):1-428.
4. MMWR 2006;55(40):1089-1092. [Data Source: 2003-2005 NHIS].
5. CDC (2003). Public health and aging: projected prevalence of self-reported arthritis or chronic joint symptoms among persons aged >65 years - United States, 2005-2030. MMWR, 52, 489-491.

BIOGRAPHY



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

Analytical Testing Labs

Magdalena Mejillano, PhD

Vice President, cGMP Laboratory Services
PPD, Inc.



Analytical Testing Laboratories: Adapting & Responding to the Current Business Climate

By: Cindy H. Dubin, Contributor

Today's economic downturn has led to a reduction in funding for early stage projects. However, significant growth in outsourcing throughout the past several years means it is unlikely that biopharmaceutical companies will cut back on outsourcing non-core capabilities, such as analytical testing. Contract laboratories are significantly increasing these capabilities to better serve biopharmaceutical companies as they continue to seek ways to reduce cost, optimize speed, and increase the flexibility of their research and development programs.

Based on these biopharmaceutical objectives, total spending on contract analytical services is \$9.3 billion annually, distributed evenly across process/formulation development, analytical development and testing, and the manufacture of clinical trial materials, according to PharmSource.

In addition, more companies are moving their work out of the United States and into China, India, and Europe



Figure 1. PPD cGMP laboratories have more than 230 high-performance liquid chromatography (HPLC) instruments to provide analytical capabilities such as method development, validation, stability and QC testing for clients.

as biotech and pharmaceutical companies fight the effects of today's economic recession. It is expected that the global CRO market will grow 14% per year over the next 3 years, making global contract research a \$35-billion industry by 2013, according to Business Insights.

"The growth of the European CRO market is expected to be spurred by the need for pharmaceutical and biotech companies to control costs and accelerate product development," says Frost & Sullivan Industry Analyst Ranjith Gopinathan. "From early drug discovery

through post-launch services, pharmaceutical companies are moving their non-core functions to external providers,” he adds.

As a result, PPD, one of the leading global contract research organizations, is extending its presence in Europe by expanding its analytical testing services. Just two years ago, PPD acquired AbCRO, a European contract research firm offering Phase II-IV clinical services, to penetrate key Central and Eastern European markets. Additionally, PPD just opened a contract research facility in Athlone, Ireland. According to Magdalena Mejillano, PhD, Vice President of cGMP laboratory services for PPD, the facility expands the company’s global scientific expertise, laboratory capacity, and supplies network to meet growing client demand in Europe, the Middle East, and Africa. The 18,000-square-foot analytical testing laboratory and clinical supplies business will conduct testing and release of clinical and marketed products spanning all phases of drug development.

PPD has already hired 21 employees in Athlone and plans to create approximately 250 jobs at the facility to include PhD-level scientists, analytical laboratory staff, and other clinical development professionals. The company is investing up to \$19 million to develop the 35,000-square-foot campus.

To date, PPD has applied to the Irish Medicines Board (IMB) for manufacturer licenses to support both investigational medicinal products and marketed products and laboratory

certifications for quality control of medicinal products. As of March 1, PPD’s license applications have been assessed, and the quality system and premises inspected by the IMB.

Specialty Pharma magazine recently spoke with Dr. Mejillano about the future plans for the Athlone lab, the specific services it offers to US- and European-based companies, and the advantages of conducting business in Ireland.

Q: *In today’s economic environment, what trends are you seeing in analytical testing?*

A: We are seeing an increasingly competitive environment given today’s economic times, and the restructuring of pharmaceutical companies is impacting outsourcing decisions, which has delayed some projects. These changes are making analytical testing providers like PPD rethink how we can best adapt and respond to the challenging business climate. One of the primary reasons for opening our Ireland-based lab was to increase our flexibility to meet the changing needs of our clients more effectively. Outsourcing for laboratory services remains strong, and once pharma completes its restructuring, we are optimistic that outsourcing will pick up again. When that happens, we believe we are well positioned to deliver a full range of analytical testing services to our clients throughout the US and Europe.

Table 1. Global spending on analytical development and testing for large-molecule drug substances by analytical activity (US millions).

Batch Release	\$103
Stability	\$84
Methods	\$134
Viral Clearance	\$98
Microbiology	\$11
Characterization	\$221
Raw Materials	\$122

Source: PharmSource Information Services, Inc., The Market for Contract Analytical and Development Services, 2009.

Q: *What made Ireland enticing to PPD?*

A: Our decision to establish operations in Ireland was driven by several factors. First, this location creates an opportunity to offer the advantages of geographic proximity to our clients in Europe and bring streamlined program management and study oversight and ease of sample shipments. Second, European regulations require that companies looking to market products in Europe have to perform release testing at a European-based analytical lab. In addition, we needed a stronger presence outside the US to better service our growing client base in Europe and the Middle East. Finally, Ireland offers very attractive business incentives and a highly skilled, educated workforce to support our recruitment efforts. Many pharmaceutical and biotech companies have also located operations in Ireland, which creates a strong pool of potential clients for us.

Q: *What challenges and/or obstacles do you face in establishing this lab and carrying out work there?*

A: One of the challenges in establishing our Ireland lab is to make sure we have aligned our capabilities and services with what our clients are looking for. We need to maintain a certain level of flexibility in our business plan, which means we may need to accelerate offering services that were originally planned for later this year to respond to market demand and client needs. Another challenge is making sure that business opportunities are additive to what exists in the United States and our labs do not compete for the same business.

Q: *What services will the Athlone lab offer?*

A: We will offer fully integrated product and analytical development services, including method development; validation; stability, release, and quality control testing, for small and large molecules with an emphasis on inhalation products. One of our business strengths is inhalation product testing for nebulizers, nasal sprays, metered dose inhalers, and dry powder inhalers. In addition, we will also provide cGMP global clinical supplies services, including secondary packing, labeling, storage, and distribution, as well as regulatory consulting, product licensing and marketed product support, and qualified person services.

One of our near-term plans is to

establish large-molecule services for biopharmaceutical clients. Large-molecule testing is a relatively untapped and rapidly emerging business opportunity, and we have now accelerated its implementation based on client needs. In addition, we are actively assessing other client requests for various services like raw materials testing, impurity identification, and extractables and leachables.

Q: *What makes the PPD lab unique compared to others in that region?*

A: There are a handful of analytical contract labs in Ireland, mainly smaller niche facilities. PPD is unique in that we will offer small- and large-molecule testing capabilities, including inhaled products. In addition, we will provide integrated services for clinical and commercial product release testing, Qualified Person (QP) release, and a logistics center for distribution of these supplies in one location. PPD also offers the advantage of having a strong corporate presence in Europe with a global infrastructure for CMC regulatory support and clinical programs.

Q: *What are your long-term objectives for the Athlone lab?*

A: It depends on the market demand and client requirements. We will grow as the market dictates and add capabilities as our clients need them. We are optimistic the Athlone facility will enable us to capture additional market

share from European, Asian, and Middle Eastern companies needing to market their products in Europe, as well as US-based companies seeking to commercialize their products in this region.

Q: *What is the one mistake PPD must avoid as it moves forward in Athlone?*

A: We must avoid not calibrating our pricing according to what the market can bear. We are still trying to understand the competitive nature of the contract laboratory industry in Europe, the cost structure of our Ireland lab, and how to strike the right balance between being competitive while maintaining operating margins.

Q: *What do you specifically want the Specialty Pharma audience to know about the lab?*

A: The laboratory in Ireland is an extension of our US lab in terms of small- and large-molecule testing. We will take full advantage of our technical expertise and experience we have built for almost 20 years and continue to provide high-quality data and service to our clients. The Ireland lab is part of our near- and long-term vision to create “one lab, multiple locations,” wherein we can offer our clients the flexibility of using any or all of our labs operating under the same systems, processes, operating procedures, and culture. ♦

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EXTERNAL DELIVERY

Mr. Fix It

By: John A. Bermingham

People who turn around companies for a living always have a set of specific actions that they will immediately implement in the distressed company regardless of what issues are causing the problems. The following are some of my specific actions to name a few:

- Immediately establishing a formal communications process. Examples would be weekly staff meetings, company-wide townhall meetings, monthly sales performance and distribution meetings, and Stage Gate product development meetings to name a few.
- Quickly develop a new culture as to how people should act going forward and what is acceptable and unacceptable conduct.
- Make people accountable rather than allowing finger-pointing and blaming others.
- Bring back a sense of fun and increase the “laughter in the hallways.”

When a new CEO enters the company, he/she will quickly assess what additional actions will be required specific to that company. The CEO must also conduct a triage analysis so that the most critical issues are addressed first, and the least critical issues are addressed later. So what if the CEO executes all of the requisite actions that he/she determined necessary to accomplish the turnaround and the company still does not recover. What then? Well, assuming the CEO did everything correctly relative to the information that he/she received from others or discovered themselves, plus what actions they took with this information, the CEO then has to re-examine everything. I have had to do this myself on one turnaround.

I looked at this situation as the in-box and the out-box. The in-box is the information that was given to me or that I discovered on my own, and the out-box was information and/or direction I sent out for implementation based on the in-box information. Often in turnarounds, at least initially, you have a management team in place with a few people that made the mistakes and caused the problems. Obviously, they do not want the new CEO to recognize their errors, so they do not tell you things you should know, or they “spin” the information to their advantage. Already understanding this, I carefully examined all the information I acquired, albeit with a skeptical mind. From that information, I implemented the out-box information flow. When everything that was required for the turnaround was implemented and the

company still did not recover, I had to make some very quick decisions.

First, I examined the information from the out-box and then compared it to the in-box for the following three reasons:

1. Having had time in the company, I looked at the information I had acquired during my time with the company to validate it as correct or not.
2. I wanted to see who had supplied misleading information that caused a miss-fire on the action plan.
3. I wanted to determine what could be done quickly to rectify the situation.

I then moved quickly to implement the modified fixes and, while a tough go for awhile, we recovered and moved on. Maybe this is better stated as “garbage in = garbage out!” ♦

BIOGRAPHY



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



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