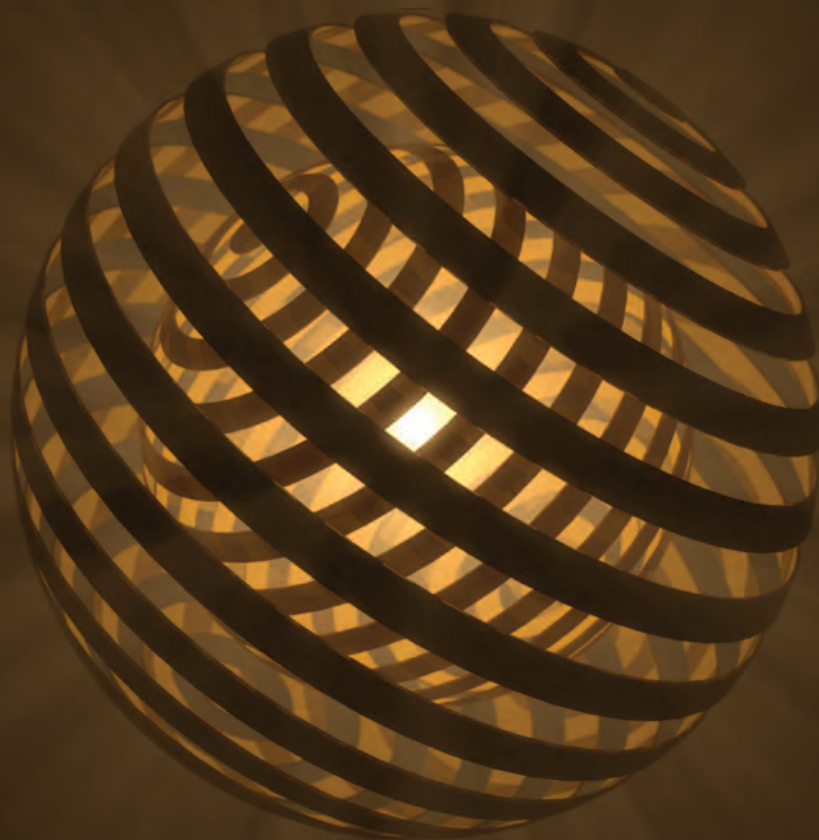


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October 2015 Vol 15 No 8

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Thomas Gold, PhD
Zero-Order/Near
Zero-Order Release
Profile of Low-
Dosage Strength
Tablets



Matt Wessel, PhD
How to Choose
the Right
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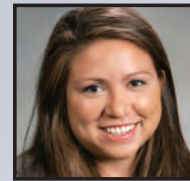
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This user-independent device is able to deliver excellent dose consistency exceeding the most stringent regulatory requirements. Moreover, with its anti-clogging technology, the system ensures spray delivery even with formulations that tend to crystallize. As a result, patients are not required to clean the actuator after each use.

The extended prime retention of up to several months offers a unique solution for drugs for which treatment needs are infrequent; hence patients do not have to re-prime the pump to ensure full delivery of the dose after several weeks of non-use; this also limits drug waste (no spray loss). All these features improve patient compliance. Advancia offers several major advantages: user-independence, excellent dose consistency, long prime retention, mechanical closing tip to prevent problems due to clogging, no metal part in contact with the formulation, and compatible with FEA 20-mm crimp-on neck finish bottles (plastic or glass).

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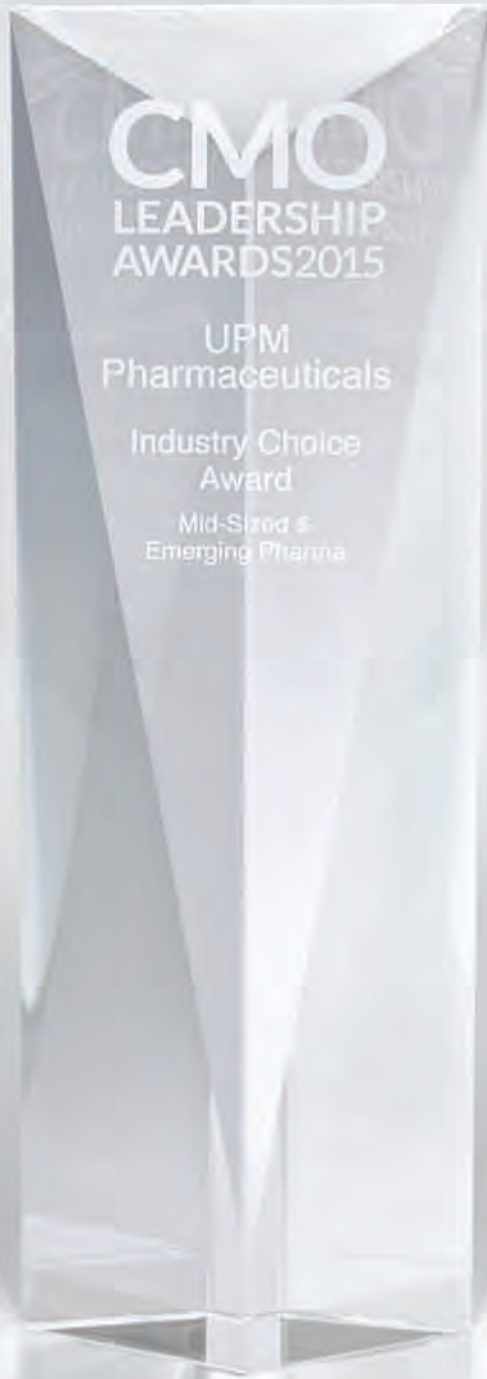
Nemera's Next-Generation Nasal Spray Now in Production

Nemera has invested more than 10 million euros in R&D and manufacturing to launch the only user-independent multi-dose nasal spray system on the market. So far, the drug product packaging for Advancia is approved in one European country.

Advancia represents a major breakthrough in nasal drug delivery by providing patients with a user-independent system ideal for topical and systemic preserved drugs in a user-friendly package.



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BIND Therapeutics Announces Pfizer Exercises Option

BIND Therapeutics, Inc. recently announced Pfizer Inc. exercised its option to obtain an exclusive license to develop and commercialize an Accurin drug candidate for the treatment of solid tumors under the companies' global collaboration agreement. The actively targeted Accurin is designed to impart cellular targeting capability and was engineered by BIND using one of Pfizer's proprietary kinase inhibitors and one of BIND's proprietary ligands. As a result of the option exercise, BIND will receive a \$2.5-million option exercise fee from Pfizer. In parallel with exercising its first option, Pfizer informed BIND that it will not exercise its option for the second compound in the collaboration.

Under terms of the original collaboration agreement, which was established in April 2013, Pfizer was granted options to obtain exclusive licenses to pursue development and commercialization of two Accurins that incorporate specified Pfizer small molecular targeted therapies. For the Accurin that has been selected, both companies will work together on preclinical research; Pfizer will have responsibility for development and commercialization, and BIND will conduct chemistry, manufacturing, and control activities.

In addition to the \$2.5-million option exercise fee, BIND received an upfront payment of \$4 million in 2013 and achieved a \$1-million preclinical development milestone for the selected Accurin in December 2014. BIND has the potential to receive additional milestone payments for the selected Accurin of up to \$86 million in aggregate upon the achievement of

additional specified development and regulatory events under the Pfizer collaboration agreement. BIND may also receive additional milestone payments for the selected Accurin of up to \$110 million in aggregate for specified commercial events as well as royalties in the low single to high single digit percentages on potential future sales of the selected Accurin, if any.

BIND Therapeutics is a clinical-stage nanomedicine company developing a pipeline of Accurins, its novel targeted therapeutics designed to increase the concentration and duration of therapeutic payloads at disease sites while reducing exposure to healthy tissue. BIND is leveraging its Medicinal Nanoengineering platform to develop a pipeline of Accurins targeting hematological and solid tumors and has a number of strategic collaborations with biopharmaceutical companies to develop Accurins in areas of high unmet need.

BIND is also developing Accurins designed to inhibit PLK1 and KSP, both of which BIND believes are promising anti-mitotic targets that have been limited in the clinic due to myelotoxicity at or below therapeutic doses.

BIND has announced ongoing collaborations with Pfizer Inc., AstraZeneca AB, F. Hoffmann-La Roche Ltd., Merck & Co., or Merck (known as Merck Sharp & Dohme outside the United States and Canada) and Macrophage Therapeutics (a subsidiary of Navidea Biopharmaceuticals) to develop Accurins based on their proprietary therapeutic payloads and/or targeting ligands.

Xcelience & Powdersize Add Delta Vita Nano-Milling

Xcelience and Powdersize recently announced the addition of the Netzsch Delta Vitamedia mills, a nanoparticle milling solution, to their arsenal of capabilities. For the first time, one CDMO can provide solutions for a full range of particle size reduction solutions, from milling and micronization through cGMP manufacturing and global clinical supplies packaging and logistics.

Xcelience announced a structured cash investment in Powdersize in July of this year, adding milling and micronization capabilities to its Suite of Services. The addition of the Delta Vita complements Powdersize's micronization capability as a primary enabling technology for improving solubility. It provides additional size reduction to nano-scale particles. The Delta Vita is used for wet grinding of batches ranging from 15 mL to approximately 60 L. This technology allows for ample milling energies (or tip speeds) to generate sub 1 µm particles and stabilize them into a suitably formulated solution.

"Most of our formulation projects are BCS class II and need solubilization improvement," says Derek Hennecke, President and CEO, Xcelience. "We bought into Powdersize and its micronization tools to provide the simplest and most applicable solution. Now with wet bead milling, we can go after the sub 1-µm particle size. It is a rare tool, and Xcelience is proud to continue to offer novel, useful solutions like this."

"With the market-leading Netzsch Delta Vita media milling equipment, we can tackle some of the most problematic API insolubility problems out there," adds TJ Higley, Vice President of Business Development for Powdersize. "Nanoparticles are a cutting-edge formulation solution, and with this piece of equipment, we can offer a scaleable and regulatory established pathway with the use of wet media milling."

The Powdersize/Xcelience combination maximizes the potential for API success by creating a smooth client experience from milling and micronization through formulation development to small-scale commercial manufacturing. This combined expertise under one corporate roof allows for maximum cross-collaboration and results in a fluid, efficient pathway that is tailor made for each API.

Xcelience offers a suite of services enabling clients to partner with a single CDMO for all of their global clinical outsourcing needs. Services include preformulation, analytical services, formulation development, cGMP manufacturing, small-scale commercial manufacturing, and global clinical supplies packaging and logistics. Xcelience takes pride in delivering the highest standards in science and service with an emphasis on quality, cost, and speed. For more information, visit www.xcelience.com.

Established in 1993, Powdersize, Inc is a privately held company with the vision to "set the benchmark" in the cGMP marketplace. Powdersize is a customer service-driven contract manufacturer, providing expertise in particle size reduction and particle size control technologies intended for powders used within the pharmaceutical industry. With two decades of manufacturing experience, Powdersize can develop a robust process at any scale of development, including Research & Development, pilot scale, or commercial scale. Powdersize combines extensive experience and their unique ability to design custom jet milling systems appropriate for their clients' needs. They are one of the leading contract manufacturers offering milling and micronization services in the United States. Powdersize is located in Quakertown, Pennsylvania, approximately 1 hour north of Philadelphia. For more information, visit Powdersize's website at www.powdersize.com.

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RegeneRx Announces First Patient Enrolled in Phase III Trial

RegeneRx Biopharmaceuticals, Inc. recently announced the first patient has been enrolled in a Phase III clinical trial with RGN-259 (designated GBT-201 in Korea), its sterile, preservative-free eye drop formulation developed for patients with dry eye syndrome, neurotrophic keratopathy (NK), and other corneal disorders. The clinical trial is being sponsored by ReGenTree LLC, a joint venture between RegeneRx and GtreeBNT Co. Ltd. a Korean biopharmaceutical company and is being conducted by Ora Inc., an established contract research organization specializing in the field of ophthalmology.

This is the second late-stage ophthalmic clinical trial with RGN-259 that has begun recently. On September 17, RegeneRx announced that it began enrollment of a 350 patient multicenter Phase IIb/III clinical trial in the US in patients with dry eye syndrome.

The NK trial is a double-masked, placebo-controlled trial being conducted at eight sites, which include major US medical centers. The trial will enroll approximately 46 patients with chronic stage 2 and 3 NK, and is expected to be completed by the end of the first quarter of 2016, or shortly thereafter. The primary endpoint is complete corneal healing in patients using RGN-259 compared to those using placebo. Patients will use the eye drops five times daily for 28 days and will be assessed periodically during treatment, upon completion of treatment, and at 1 week and 2 weeks post-treatment. There

will be numerous secondary endpoints that will also be evaluated pursuant to the trial protocol.

Thymosin beta 4 (TB4), the active ingredient in RGN-259, is a first-in-class, naturally occurring molecule that has been the subject of numerous published animal studies in the fields of ophthalmology, dermatology, cardiology, and central nervous system disorders, among others. In addition to the animal studies, the molecule has been tested in three unique formulations in approximately 350 patients and has an excellent safety profile.

Neurotrophic Keratopathy (NK) is a serious degenerative disease of the corneal epithelium (the outside layer of the eye) that is designated an "orphan" disease in the US and EU due to its relatively low prevalence. A reduction in corneal sensitivity or complete corneal anesthesia is the hallmark of this disease and is responsible for producing corneal ulceration, perforation, pain, and impaired vision.

RegeneRx is focused on the development of a novel therapeutic peptide, Thymosin beta 4, for tissue and organ protection, repair and regeneration. RegeneRx currently has three drug candidates in clinical development for ophthalmic, cardiac, and dermal indications, three active strategic licensing agreements in China, Pan Asia (Korea, Japan, and Australia, among others), and the US, and has an extensive worldwide patent portfolio covering its products. For more information, visit www.regenerx.com.

BioCancell Advances Phase III Clinical Program for the Treatment of Bladder Cancer

BioCancell Ltd. recently announced the results of a pilot clinical trial using a combination of BC-819 and BCG in intermediate-risk and high-risk patients, in preparation for BioCancell's Phase III clinical program for the treatment of bladder cancer.

Thirty-eight (38) patients were recruited and divided into two groups. The first, composed of six patients, received sequential weekly treatments (a course of BC-819/PEI followed by a course of BCG). In the second group, thirty-two (32) patients received alternating treatments of BC-819 followed by BCG, once or twice weekly (89% were classified as high-risk and 34% were pre-treated). BioCancell plans to utilize the alternating-treatment regime in Phase III pivotal studies.

Analysis of the results received from all patients shows that the combination treatment is safe. No severe adverse events occurred related to BC-819/PEI. 77% of the alternating-treatment patients who completed three months from the commencement of treatment, were recurrence-free (up from 64% in BioCancell's Phase IIb bladder cancer trial of BC-819/PEI alone). Only one additional patient of the 12 alternating-treatment patients (8%) who have already completed 6 months from the commencement of treatment, experienced recurrence. The high rate of patient response to the combination therapy is believed to reflect this therapy's better efficacy, which BioCancell intends to investigate in its Phase III pivotal studies.

"We are very pleased with the results of this combination therapy clinical trial. These results pave our way forward to the commencement of the Phase III pivotal study next year. We look forward to developing a leading new therapy to treat the unmet need of so many bladder cancer patients," said Jonathan Burgin, Chief Executive Officer of BioCancell.

BioCancell's lead product candidate, BC-819, is a double-stranded DNA plasmid construct that uses the H19 gene to activate the synthesis of diphtheria toxin after entering a cell in which H19 transcription factors exist, destroying only that cell. The result of this mechanism is highly selective tumor cell destruction. BioCancell has successfully completed Phase I/IIa and Phase IIb clinical trials for BC-819 as a treatment for bladder cancer, as well as a pilot study of combination therapy using BC-819 and the current standard of care, Bacillus Calmette-Guérin (BCG). BC-819 is a Phase III-ready asset for the treatment of bladder cancer. In 2016, BioCancell plans to initiate two Phase III trials in intermediate- and high-risk non-muscle-invasive bladder cancer (NMIBC). The first Phase III study will be performed under an FDA Special Protocol Assessment, and will use BC-819 in combination with BCG for patients who have failed at least one course of BCG. The second Phase III study is designed for patients who are unresponsive or intolerant to BCG and will be treated with BC-819 as monotherapy. These indications cover about 70% of all NMIBC patients and received fast track designation from the FDA. Although most patients respond well initially to BCG treatment, its efficacy diminishes upon repeated administrations, leaving patients with no effective treatment and in danger of disease progression.

BioCancell is a clinical-stage biopharmaceutical company focused on the discovery, development, and commercialization of novel therapies to treat cancer-related diseases. BioCancell is also developing a second-generation drug, BC-821 for the systemic treatment of advanced malignant neoplasms. Preclinical studies of BC-821 have showed significant efficacy in different cancer animal models such as metastatic lung cancer and metastatic liver cancer. BioCancell's third product candidate, BC-830, is a "liquid biopsy," which is intended to replace invasive and costly cystoscopies for the follow-up of NMIBC patients. BioCancell's R&D activities build upon the research of Professor Abraham Hochberg of the Hebrew University of Jerusalem. Professor Hochberg isolated the human H19 gene and determined that the gene is expressed in over forty different forms of cancer.

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West & Healthprize Announce Self-Reporting & Barcoding Capabilities for Self-Injection Technology

West Pharmaceutical Services, Inc. and HealthPrize Technologies, LLC, recently announced the completion of the first two phases of their four-phase strategic collaboration. The companies are working to integrate HealthPrize's Software-as-a-Service (SaaS) medication adherence and patient-engagement platform with West's injectable drug delivery systems to provide an end-to-end connected health solution for pharmaceutical companies and the patients they serve. The combined offering will provide voluntary, electronically connected drug delivery systems that track when patients take their medication. The HealthPrize system engages and educates patients to increase adherence and medical literacy, rewarding interaction and compliance with prescribed treatment plans, and contributing to better health outcomes.

Phase I of the platform allows for patient self-reporting once the medication has been injected. Phase II simplifies the self-reporting process through bar coding or QR coding of self-injection systems, which, when scanned, reports use of the injection system to the HealthPrize patient-engagement system via a secure cloud environment. Bar coding allows for the recording of other medication details, including manufacturing information, pedigree, expiration date, dosage, and more.

The final phases of development that are currently in progress are fully integrated injection systems with onboard monitoring and built-in wireless communication capability (integrated connected health) and the connection of legacy, mechanical injectors to the HealthPrize platform via an adaptive attachment (legacy connected health). In all four

phases, data captured over time will afford pharmaceutical companies insight into valuable trends and analytics regarding the actual use of their products.

Medication non-adherence is a leading cause of poor clinical outcomes and increased healthcare costs. Industry analysts estimate that poor medication adherence costs the US healthcare system more than \$290 billion in otherwise avoidable medical spending. According to a recent study performed by Capgemini Consulting and HealthPrize Technologies, the pharmaceutical industry's global revenue loss due to non-adherence to medication for chronic conditions is estimated to be \$564 billion.

As a leader in drug packaging and delivery systems, West provides solutions for self-injection technologies that provide new options for higher-dose volumes and drug viscosities. West currently offers pharmaceutical customers several unique drug delivery systems, including the SmartDose electronic wearable injector—the first wearable bolus injector to be studied in a clinical setting, the SelfDose injector system, and the ConfiDose autoinjector. West is also one of the largest contract manufacturers of injection pens and autoinjectors globally, producing more than 100 million of these devices each year.

HealthPrize's Software-as-a-Service (SaaS) medication adherence and patient-engagement platform provides an innovative approach to addressing the problem of medication nonadherence with an online- and mobile-based program that is fun, educational, and rewarding.

Scholar Rock Presents First Data, Announces Lead Drug Development Candidate

Scholar Rock recently announced that SRK-015 is the company's lead drug development candidate, a niche modulator inhibiting activation of the latent myostatin precursor. The announcement of this program coincides with the presentation of preclinical data for SRK-015, which demonstrated for the first time that therapeutic targeting of the latent complex of myostatin is an important mechanism for enhancing muscle growth in disease. The data were presented at the European Molecular Biology Organization's Workshop on Molecular Mechanisms of Muscle Growth and Wasting in Health and Disease taking place on September 20-25 in Ascona, Switzerland.

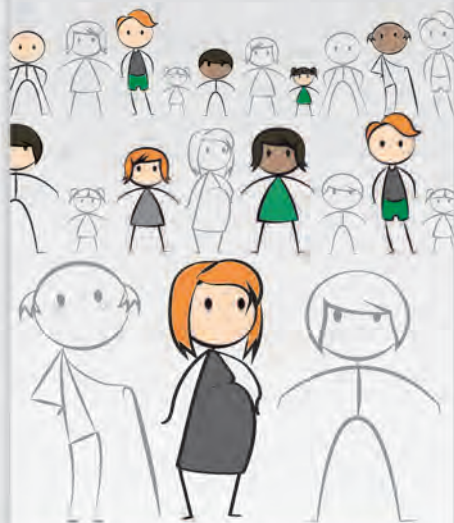
"We are excited to announce SRK-015 as the first development candidate from our niche modulator platform. The data we presented demonstrate the exceptional selectivity that is achieved by targeting the latent, inactive forms of myostatin compared to the traditional approach of targeting the mature, active form of myostatin or the myostatin receptor," said Nagesh Mahanthappa, PhD, President and Chief Executive Officer of Scholar Rock. "We look forward to advancing SRK-015 for the treatment of primary myopathies and believe it will be the first of many novel niche modulators that target protein growth factors with unprecedented specificity and localization of effect."

The preclinical data demonstrated that SRK-015 can selectively block the activation of myostatin in vitro and enhance muscle growth in vivo. These data suggest that SRK-015 may be useful in treatment of muscle wasting disorders while avoiding the undesirable, systemic side effects that can result from directly targeting myostatin or its receptor with insufficient selectivity. Myostatin is a member of the TGF β superfamily of growth factors that is expressed primarily in skeletal muscle cells to inhibit muscle growth. Myostatin has been implicated in a range of muscle diseases, and Scholar Rock plans to pursue initial development of SRK-015 in primary myopathies, disease states in which restoration of normal muscle function can significantly improve patients' lives.

Scholar Rock's therapeutics are designed to target the activation mechanism of protein growth factors selectively in the microenvironment of specific types of cells and tissues. By doing so, these niche modulators are able to achieve highly specific and localized therapeutic effects at the site of disease while avoiding undesirable side effects that can result from systemic modulation of such growth factors.

Scholar Rock is a biotechnology company focused on discovering and developing niche modulators, a novel class of biologic therapies that selectively modulate the activation of growth factors in the disease microenvironment. The Company's initial proprietary and partnered drug discovery programs target specific growth factors, including members of the TGF β superfamily, and have a near-term focus on the treatment of muscle disease, fibrosis and immuno-oncology. Scholar Rock was founded based on discoveries made by its scientific founders, Professors Timothy Springer, PhD, and Leonard Zon, MD, of Boston Children's Hospital and Harvard Medical School, related to the molecular mechanisms of growth factor activation. The company is backed by leading life sciences investors, including Polaris Partners, ARCH Venture Partners, Timothy Springer, EcoR1 Capital and The Kraft Group. For more information, visit www.scholarrock.com.

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Dimension Therapeutics Announces FDA Fast Track Designation

Dimension Therapeutics, Inc. recently announced that the US FDA has granted Fast Track designation for the company's lead product candidate, DTX101, for the treatment of hemophilia B. Dimension expects to initiate a multi-center Phase I/II study to evaluate DTX101 in adult patients with moderate/severe to severe hemophilia B by the end of 2015.

DTX101 is designed to deliver blood clotting Factor IX (FIX) gene expression in patients with hemophilia B. Hemophilia B is a rare genetic bleeding disorder resulting from a deficiency in FIX. The current standard of care for patients with hemophilia B involves chronic replacement of FIX protein through intravenous infusion. In 2013, the World Federation of Hemophilia estimated there were more than 28,000 hemophilia B patients worldwide, including 4,000 patients in the US.

The FDA's Fast Track program is designed to facilitate and expedite development and review of new drugs to treat serious or life-threatening conditions and address unmet medical need. Through the Fast Track program, a product may be eligible for priority review at the time of BLA and may be eligible to submit sections of the BLA on a rolling basis as data become available. In addition there are opportunities for frequent interactions with FDA with this designation.

"We are very pleased to achieve this additional important milestone for our DTX101 program, following the

FDA's recent acceptance of Dimension's investigational new drug (IND) application and granting of orphan drug designation for our lead candidate," said Annalisa Jenkins, MBBS, MRCP, Dimension's Chief Executive Officer. "This latest development provides further momentum as we advance DTX101, with the near-term goal to initiate our clinical trial by the end of this year."

Dimension is developing its lead gene therapy product DTX101, which is expected to enter clinical development in 2015, for the treatment of moderate/severe to severe hemophilia B. DTX101 is designed to deliver Factor IX, or FIX, gene expression in a durable fashion, preventing the long-term complications of hemophilia B. Preclinical studies completed to date indicate DTX101 has the potential to be a well-tolerated, effective therapy for hemophilia B.

Dimension Therapeutics, Inc. is a rare disease company focused on discovering and developing new therapeutic products for people living with devastating rare diseases associated with the liver and based on the most advanced adeno-associated virus (AAV) delivery technology. The company is advancing multiple programs toward clinical development, including programs addressing unmet needs for patients suffering from OTC deficiency and GSDIa; a collaboration with Bayer HealthCare in hemophilia A, and a wholly owned program in hemophilia B, which is expected to enter clinical testing by the end of 2015.



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ADVANCED DELIVERY DEVICES

Implantable Drug-Eluting Devices: A Novel Approach to Patient Care

By: Samuel D. Trohman, MBA, Joey L. Glassco, Elena Draganoiu, PhD, and Carey Boyum

INTRODUCTION

Implantable drug-eluting devices (also referred to as implantable drug delivery systems) offer several unique advantages over conventional oral or parenteral drug delivery methods. For instance, they can provide localized, site-specific drug delivery, which is especially important in applications such as cardiology and oncology, where targeted delivery can improve the effectiveness of treatment and minimize side effects or damage to healthy tissue.^{1,3} The dosage requirements often are lower than alternatives, further reducing the potential for side effects.¹ Also, drug-eluting devices can improve patient compliance, one of the greatest challenges in healthcare, as about 50% of conventional medications are not used as prescribed.⁴ The treatment regimen can be simpler because it requires fewer doctor visits and dosages than traditional therapies.¹

Applications of implantable drug-eluting devices include, among others, diabetes management, contraception, HIV/AIDS prevention, chronic pain management, cardiology, oncology, and central nervous system (CNS) health.^{2,5-10} Along with subcutaneous implantation, various body regions can serve as implantation sites (eg, intravaginal, intravascular, intraocular, intrathecal, and peritoneal).^{2,6,11-13}

In this white paper, developmental and commercial examples of non-biodegradable drug-eluting devices will be presented, along with the versatile properties of thermoplastic polyurethanes, specifically Lubrizol LifeScience's Pathway™ TPU Excipients for the development of effective drug delivery systems.

BIODEGRADABLE VERSUS NON-BIODEGRADABLE DRUG DELIVERY SYSTEMS

There are two categories of drug-eluting devices: biodegradable and non-biodegradable. Biodegradable drug-eluting devices (also referred to as bioerodible) use biocompatible materials such as polyesteramide (PEA) and Poly Lactic-co-Glycolic Acid (PLGA) to deliver drugs, and once implanted, decompose over time.^{1,14,15}

In contrast to biodegradable, non-biodegradable drug-eluting devices (also referred to as biodurable) use biocompatible materials like silicone rubber (polydimethylsiloxane or PDMS), polyethylene-vinyl acetate (EVA), and thermoplastic polyurethane (TPU) to deliver drugs.¹⁶ Non-biodegradable drug-eluting devices can be designed as matrix, reservoir, or osmotic systems to deliver drugs via diffusion or osmosis and are generally less costly than biodegradable devices.^{1,15} Non-biodegradable drug-eluting devices can be refilled with medication (eg, via injection), and the device's effects are almost immediately reversible upon removal.^{1,11,17}

Non-biodegradable Pathway TPU excipients are versatile and customizable to a broad range of chemical and physical properties providing variety along a number of dimensions, including drug-release kinetics (short- or long-term), active pharmaceutical ingredient selection (hydrophobic or hydrophilic APIs), processing methods (extrusion, injection molding, or solvent casting), and mechanical performance.^{16,18-22} These unique attributes provide developers with tremendous design flexibility.

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DEVELOPMENTAL & COMMERCIAL EXAMPLES OF NON-BIODEGRADABLE DRUG-ELUTING DEVICES

Non-biodegradable drug-eluting devices are finding increasing applications in the areas of contraception, hormone regulation, diabetes, oncology, pain management, abuse deterrence, and CNS health.^{5,6,8-10,23,24}

Women's Health

In women's health, for instance, transmucosal hormone contraceptives delivering progestin and/or estrogen have been developed into combination products made from silicone, EVA, and TPU. A commercial example is Pfizer's Estring[®] silicone intravaginal ring (IVR) that releases 2 mg of estradiol for 90 days to treat symptoms associated with menopause.²³ Another example is Merck & Co.'s NuvaRing[®] IVR produced from EVA that delivers 120 micrograms of etonogestrel and 15 micrograms of ethinyl estradiol per day on average for 3 weeks.⁶ The NuvaRing IVR was prescribed 5.2 million times in 2012 and generated over \$720 million in sales

revenue in 2014.^{25,26}

Merck also developed Nexplanon[®] (a new version of Implanon[®]). The Nexplanon drug-eluting device is made from EVA and delivers 68 mg of etonogestrel for up to 3 years.²⁷ Unlike the NuvaRing, Nexplanon is a rod implanted subcutaneously in the arm.

Subcutaneous contraceptive implants date back to 1966 when the non-profit organization Population Council developed the Norplant.²⁸ Launched in 1983 by Wyeth Pharmaceuticals, the original Norplant was a 5-year non-biodegradable drug-eluting device designed with six silicone capsules each loaded with 36 mg of levonorgestrel. A modern version of the Norplant, Jadelle[®], currently is marketed by Bayer Pharmaceuticals.^{28,29} Several innovative contraceptive and antiviral technologies are under development:

- CONRAD, a non-profit organization, is developing multipurpose prevention technologies with polyurethanes that combine contraceptive and microbicidal attributes into a single IVR device.⁷ The University of Utah pioneered the

development of CONRAD's IVR with the antiretroviral drug tenofovir and contraceptive levonorgestrol.^{19,20}

- The Oak Crest Institute of Science is developing an antiviral drug-eluting device with PVA-coated silicone to deliver tenofovir alafenamide subcutaneously for HIV/AIDS prevention and treatment.³⁰
- The University of Manitoba is developing a polyurethane IVR for sustained delivery hydroxychloroquine to prevent male-to-female HIV transmission.³¹
- J3 Bioscience, Inc. (formerly ViroPan) is developing an intravaginal ring with a glycerin formulation to relieve the symptoms of vaginal dryness and aims to provide relief for up to seven days without the use of drugs or hormones.³² The company has completed a pilot human trial and now is preparing for the pivotal study.

TABLE 1

Product	Company/Organization	Material	Active Ingredient	Application	Launch Status
NuvaRing	Merck & Co.	EVA	Etonogestrel, Estradiol	Contraception	2002
Implanon	Merck & Co.	EVA	Etonogestrel	Contraception	2006
Prophine	Titan & Braeburn Pharmaceuticals	EVA	Buprenorphine HCl	Abuse Deterrence	Phase III
Estring	Pfizer	Silicone	Estradiol	Menopause	1997
Jadelle	Bayer Pharmaceuticals	Silicone	Levonorgestrel	Contraception	1996
Synchromed	Medtronic	Silicone	Baclofen	Chronic pain	1998
SubQ Implant	Oak Crest Institute of Science	Silicone	Tenofovir Alafenamide	HIV Prevention	Preclinical
LiRIS Program	TARIS Biomedical, Allergan	Silicone	Lidocaine	Interstitial Cystitis	Phase II
Vaginal Ring	CONRAD	TPU	Levonorgestrel, Tenofovir	Contraception, HIV Prevention	Phase I
Vaginal Ring	J3 Bioscience, Inc. (form. Viropan)	TPU	Glycerin	Vaginal Dryness	Pivotal Clinical
SubQ Implant	Axxia Pharmaceuticals	TPU	Hydromorphone	Chronic Pain	Preclinical
Restora	SinuSys Corp.	TPU	Steroid	Sinusitis	Phase II
SubQ Implant	Endo & Braeburn Pharmaceuticals	TPU	Risperidone	Schizophrenia	Phase IIb
Vantas	Endo Pharmaceuticals	N/A	Histrelin Acetate	Prostate Cancer	2004

*References used to compile all of the information in Table 1 are located at the end of this document.

Select Examples of Non-Biodegradable Drug-Eluting Devices

Diabetes Treatment

Diabetes, a condition affecting more than 371 million people globally, is another application area where implantable systems offer unique patient solutions. Continuous glucose monitoring (CGM) involves implanting sensors subcutaneously to measure blood sugar. Commercial examples include Dexcom's G4 Platinum™, Medtronic's Enlite®, and GlySens ICGM™.³³⁻³⁶

US-based Intarcia Therapeutics is developing a non-biodegradable drug-eluting device to treat type II diabetes.⁵ Intarcia's technology, ITCA 650, is a DUROS® implant delivery technology licensed from the ALZA Corporation in 2007.³⁷ ITCA 650 is a small, matchstick-sized osmotic pump consisting of a cylindrical titanium alloy reservoir that is

implanted subcutaneously and delivers a steady flow of exenatide, a glucagon-like peptide-1 receptor agonist, for 12 months.⁵ After successfully completing two of four Phase III trials for ITCA 650, French pharmaceutical company Laboratoires Servier signed a commercialization deal with Intarcia for \$1 billion.³⁸ Other implantable diabetes treatment technologies include:

- Delpor's titanium drug-eluting device that delivers exenatide for treatment of type II diabetes.^{39,40} Delpor's system also is designed to deliver drugs for treating bipolar disorder, growth hormone deficiencies, and hepatitis C.³⁹

- NanoPrecision Medical is developing NanoPortal™, a rice-size titanium implant that delivers exenatide for type II diabetes.^{41,42}
- ViaCyte is developing VC-01™ to treat type I diabetes. VC-01 is a subcutaneous implant composed of ViaCyte's Encaptra® drug delivery system and human embryonic stem cells (pancreatic PEC-01™ cells).⁴³

Oncology

Drug-eluting devices have been developed for the treatment of, among others, brain tumors, prostate cancer, and bladder cancer.^{15,44,45} Endo Pharmaceutical's Vantas™, for example, is a hydrogel depot that delivers 50 mg of histrelin acetate subcutaneously for 12-month relief of prostate cancer symptoms.⁴⁵ TARIS Biomedical developed a non-biodegradable drug-eluting device to treat non-muscle invasive bladder cancer (NMIBC).⁴⁴ TARIS Biomedical's technology is a small flexible pretzel-shaped system that delivers drugs for several weeks through an osmotic pump made of silicone and nickel alloy wire.⁴⁶ Alternative therapies for NMIBC can cause systemic side effects and are only held in the bladder for a short period of time.⁴⁴ However, drug-eluting devices implanted in the bladder offer targeted delivery of APIs for a longer period of time in comparison to traditional methods, which may improve symptom relief for patients suffering from NMIBC.

Pain Treatment

Conventional solutions for pain, such as oral and parenteral medications, often are dangerously addictive and extremely

FIGURE 1



Intravaginal ring employing both hydrophobic and hydrophilic TPUs for the sustained co-delivery of the microbicide tenofovir and contraceptive levonorgestrel. Photo courtesy of The Kiser Lab.

“Lubrizol’s 2013 implementation of the International Pharmaceutical Excipients Council’s Good Manufacturing Practice quality system for excipients and database generation of Drug Master Files facilitate non-biodegradable drug-eluting device development. As a result of Lubrizol’s 2014 acquisition of Vesta and 2015 acquisition of Particle Sciences, Lubrizol provides complete drug product development, including pharmaceutical-grade polymer supply and contract research/analytical and contract manufacturing capabilities through to commercialization.”

expensive. From 1999-2010, the CDC reported a 400% increase in deaths from prescription pain drug overdoses among women and a 265% increase in men.⁴⁷ In order to address these issues, TARIS Biomedical and Axxia Pharmaceuticals are developing non-biodegradable drug-eluting devices for chronic pain.^{44,48}

Axxia developed a subcutaneous drug-eluting device to deliver hydromorphone continuously for 30 to 90 days with zero-order kinetics to treat chronic pain associated with cancer or HIV/AIDS induced neuropathy.⁴⁸ TARIS Biomedical’s LiRIS® program delivers lidocaine for a prolonged period of time directly to the bladder of patients suffering from interstitial cystitis/bladder pain syndrome (IC/BPS).⁴⁹ In 2014, Allergan acquired the LiRIS program for almost \$600 million.⁴⁹ Also, Medtronic’s implantable Synchroned® Infusion Pump System delivered baclofen for muscle

spasticity and was made from silicone and titanium.¹² The Synchroned system generated an estimated \$320 million in sales annually, but was recalled in 2015 due to manufacturing compliance issues and patient safety concerns.⁵⁰

In order to deter opioid abuse, Titan Pharmaceuticals developed a subcutaneous drug-eluting device called

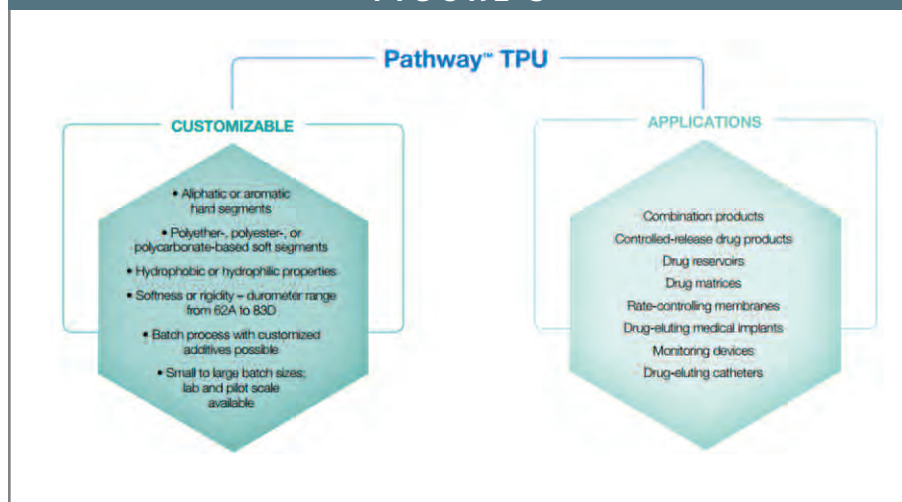
Propuphine®.^{24,51} Probuphine is an EVA matrix that delivers buprenorphine hydrochloride for 6 months following a single treatment.⁵¹ In 2012, Titan entered into an exclusive licensing agreement with Braeburn Pharmaceuticals for commercializing Probuphine.⁵²

FIGURE 2



Axxia Pharmaceuticals’ subcutaneous drug delivery system was developed to deliver an opiate continuously for 30 to 90 days with zero-order kinetics. Photo courtesy of Axxia Pharmaceuticals, LLC.

FIGURE 3



CNS Health

Endo Pharmaceuticals' MedLaunch Implant Program developed a subcutaneous drug-eluting device to deliver risperidone, and similar to Titan's Probuphine, this technology will be commercialized by Braeburn.^{10,53} Nearly 50% of patients being treated for schizophrenia are non-compliant.⁵⁴ Non-biodegradable drug-eluting devices that can deliver antipsychotics at a controlled rate for a prolonged period of time (eg, 60 to 90 days) may provide substantial therapeutic benefit for patients.

Additional therapeutic areas, such as animal health, ophthalmology, and otorhinolaryngology (ear, nose, and throat) offer ample opportunities for non-biodegradable drug-eluting devices and combination product development. Replenish, Inc., for instance, is developing an ophthalmic MicroPump™, a small, refillable drug-eluting device for glaucoma and retina disease.⁵⁵ The SinuSys Corporation is developing the Restora™ Steroid-Eluting Spacer, a transmucosal polyurethane drug-eluting device for 30-day treatment of sinusitis.⁵⁶ Zoetis developed the EAZI-BREED™ CIDR® silicone drug-eluting device to

deliver progesterone for livestock reproduction.⁵

THERMOPLASTIC POLYURETHANES FOR NON-BIODEGRADABLE DRUG-ELUTING DEVICES

Lubrizon LifeSciences partners with pharmaceutical companies from ideation to commercialization. Lubrizon's non-biodegradable Pathway TPU excipients can be tailored to suit a wide range of drug delivery applications and can be processed into a variety of shapes (eg, rods, tubes, films, and a variety of matrix-type designs) via methods such as hot-melt extrusion, injection molding, and solvent casting. Ethylene oxide, hydrogen peroxide, E-beam radiation, and gamma radiation are acceptable methods of sterilization.

Lubrizon's 2013 implementation of the International Pharmaceutical Excipients Council's Good Manufacturing Practice quality system for excipients and database generation of Drug Master Files facilitate non-biodegradable drug-eluting device development. As a result

of Lubrizon's 2014 acquisition of Vesta and 2015 acquisition of Particle Sciences, Lubrizon provides complete drug product development, including pharmaceutical-grade polymer supply and contract research/analytical and contract manufacturing capabilities through to commercialization.

Thermoplastic polyurethanes have exceptional safety records with over 30 years of use in medical devices, such as catheters and pacemakers.⁵⁸ The unique ability to customize TPU properties allows for the development of advanced drug delivery systems. ♦

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BIOGRAPHIES



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Management Insight

Patently Disruptive

By: Derek Hennecke, CEO & President, Xcelience

Kyle Bass and his hedge fund are challenging pharma patents for the purpose of shorting their stocks and making a fortune. Is this just industry noise or a true disruption?



We have just begun a phased move into a new, 71,000-sq-ft facility. Large swaths of clean crisp new carpet tiles create a checkered effect in an open area, where furniture will soon be. The terrain begged for life-size chess pieces. Our facilities manager, Elijah, complied.

Chess isn't the best team sport; not if you're a competitive sort. Recently, my intricate strategy for black was quickly laid asunder by a passing anonymous teammate with a different vision. I have been known to switch sides in exasperation mid-game.

A single move in chess can mean very little, or it can be hugely disruptive. Take World Champion Grandmaster Kasparov's 1997 match against IBM's Deep Blue. This was the landmark game in which, for the first time, artificial intelligence was deemed to have bested a human grand master chess player.

The truth is the tournament might have gone differently, but for a single move. Kasparov beat Deep Blue confidently on the first match, despite the computer's ability to analyze 200 million moves per second. But 44 moves into the game, Big Blue made an inexplicable move, according to Nate Silver in his recent book, *The Signal and The Noise: Why So Many Predictions Fail — But Some Don't*.

The move, a random pawn advance, spooked Kasparov. He became convinced that either he was actually up against a superior intelligence, or IBM was cheating by

allowing a human grand master to influence Big Blue's moves behind the scenes. When, in the second game, Deep Blue changed to a strategy much more like a human grandmaster, Kasparov balked. He made an unprecedented error, forfeiting a position that he could have probably drawn. He lost, drew three more games, and capitulated in the sixth.

Historians are convinced that Kasparov's demise was linked to that 44th move, and the importance he attributed to it. As it turns out, the move was a computer glitch. Big Blue froze and was unable to make a choice amongst competing possibilities so it went for a failsafe move; a random pawn shuffle.

That's it. A glitch. The world lauded (or grudgingly accepted) the triumph of artificial intelligence over human intelligence, when in fact Big Blue had goofed. But where Kasparov (and ultimately society) should have seen noise; he (and society) saw a disruptor — a game changer. It was a case of mistaken identity. It can be hard to recognize a disruption, even when it's staring you in the face.

I wrote an article recently highlighting the importance of Express Scripts' and other drug distributors as new players in the pricing of new drugs. This is a similar case in which we are forced to ask ourselves if Express Scripts influence over Solvadi's price was a signal of industry-wide change ahead, or just industry noise. I argued that the case represented a genuine disrupter. Now,

another potential disruption looms for our industry in the field of patents.

PHARMACEUTICAL PATENT CHALLENGES BEFORE 2012

Patent threats have been an issue in our industry, and in many other industries, since patents and lawyers were invented. Patent trolls are society's bottom feeders. They create broad patents and then launch lawsuits against so-called "infringers;" often for ridiculous things. Classic cases involve a company that claims to have invented wifi, another that managed to patent "internet interactivity" and now claims rights to almost everything online, and my personal favorite, a company that claims to have invented how to plug a headset into a mobile phone.

The troll's goal is rarely to take a victim to court and win a patent battle. The troll aims merely to shake out whatever it can, usually by launching a case that threatens to go into the millions of dollars — preferably a number well beyond the victim's means — and then offering to settle out of court for a slightly less extravagant sum.

In 2012, President Obama signed the Leahy-Smith America Invents Act. A major goal of the legislation was to make it hard for patent trolls to ply their trade. The legislation made several significant changes, and among them was the creation of something called Inter

Partes Review (IPR), which is designed to be quicker, more efficient, and less expensive for patent challengers. This sounds like something the trolls might like, but remember that they aren't interested in a decision; they are interested in a lengthy and costly litigation they could then offer to bypass with a settlement out of court. By creating a quick decision and inexpensive resolution, the new act did much to take the wind out of the trolls' sails. Better still, IPR results are binding and cannot be appealed.

On average, an IPR case costs about \$300,000 and takes 6 to 18 months. While this time and money is no small potatoes to many patent holders, it's a vast improvement over the \$3 million and many years involved in conventional litigation, according to Matthew Cutler, a lawyer for Harness Dickey who specializes in intellectual property (as quoted in the Ed Silverman's WSJ column *Pharmalot*, "Innovate or Else: Kyle Bass Strikes Again," April 2, 2015.)

The news, however, is not all good for patent holders. Some 2,536 challenges have been filed since the law was passed, according to Cutler. Of those challenging pharmaceutical patents, a rather stunning 87% have succeeded. This kind of patent overturning success rate is not specific to our industry. Federal Circuit Chief Judge Randall R. Rader famously called the Patent Appeal and Trial Board a "death squad" that kills property rights through administrative proceedings.

ENTER KYLE BASS

Mr. Kyle Bass was infamous long before he entered the patent arena. He is the man credited with predicting and benefiting from the subprime mortgage crisis during the Great Recession by purchasing credit default swaps on subprime securities issued by various investment banks. Featured in the non-fiction book *The Big Short* on the housing bubble collapse by Michael Lewis, Bass studied the residential mortgage market and determined which residential mortgage-backed securities were most likely to default, then essentially shorted those bonds using synthetic instruments, raking in as much as \$500 million, by some accounts.

The Recession is finished, but Bass is still on a role. His new target is pharmaceutical patents. His initial volley was directed against Acorda Therapeutics for Ampyra, a multiple sclerosis drug. He then set his sights on two Shire drugs; Lialda for ulcerative colitis and the Gattex for short bowel syndrome.

Bass claims his goals are altruistic – to lower drug prices for the masses by eliminating "invalid patents that contain no meaningful innovations but serve to maintain their anti-competitive, high-price monopoly to the detriment of Americans suffering from illness," according to a statement he sent to *Pharmalot*.

One might, then, justifiably wonder if his motivations during the

sub-prime mortgage crisis were to help the unemployed and under-employed in their underwater mortgages.

Or, he could be motivated by the huge windfalls he and his hedge fund make every time he launches a litigation on a company he has already shorted in a separate pharmacy vehicle in his fund.

On the day Bass filed his challenge against Acorda, the biotech's shares dropped nearly 10%; no small potatoes in a company with a \$1.5-billion market capitalization. It fell another 5% when he filed a second challenge on another Acorda patent.

Acorda Therapeutics revenue is almost entirely dependent on the drug Bass is challenging. If the drug lost patent protection, the company would be seriously wounded. Bass's firm, Hayman Capital Management, is threatening one of Acorda's patents on Ampyra for the obviousness of its technology. The essential molecule behind the treatment was once commonly used as a bird poison. Acorda modified the drug and found a way to use it safely and effectively.

While this challenge may succeed, Bass must know that Ampyra still has many defenses at its disposal, with four more patents protecting it against generic competition until 2027. Bass is not challenging these patents, so Ampyra will not fall. How, then, can he claim that his true goal is to fell the mighty drug for the benefit of the American people? All he has done is created a moment of doubt in

the company's market value, and benefited from that weakness.

At the time of writing, Bass has filed 13 IPR petitions with the US Patent and Trademark Office challenging the patents of six publicly traded pharma companies, according to *Business Insider* (May 7, 2015). He said earlier in the year that he was planning 15 challenges.

KYLE BASS: SIGNAL OR NOISE?

The question is then, is this a new disruption in our industry, or is it just noise? Is Bass just one man with an idea to make a quick buck, or has the new law spawned a new type of parasitic patent troll, creating nothing, advancing nothing, profiting from the labor of others, and weakening its host? The argument has been made that far from reducing overall healthcare costs, this new player is reducing the value of companies working on cures, and as a direct result, causing harm to the millions of patients who need those cures.

Mr. Bass has already achieved his goal, regardless of the outcome of his challenge. His success could encourage others to follow his example. If Ampyra's challenge succeeds, then other expensive drugs developed using molecules discovered long ago are likely to find themselves in the crosshairs. Indeed, Bass is now challenging Biogen's

Tecfidera MS drug, which earned \$2.9 billion in sales last year. Tecfidera's active ingredient, dimethyl fumarate, was first prescribed by a German physician for topical use for psoriasis in 1959. A small Swiss firm called Fumapharm studied it clinically as a cream, and the product went on the market in Germany early in the 1990s. Since dimethyl fumarate appeared to be effective by modulating the immune system, it eventually occurred to someone that it might also offer hope to MS patients. Biogen bought out Fumapharm in 2005 and continued development.

Biogen's product is a prime target for Bass, and has a decent chance of being considered unoriginal; a sad but true fact. While many could've discovered this drug's possibilities, only Biogen did. Must we now penalize Biogen for making an effective treatment of MS because someone else might have also done so but didn't? What would such a decision mean for the future of drug discovery? Think of all the drugs that might never be developed if we eliminate from research all known and somewhat understood molecules out there today.

Fortunately, like Ampyra, Tecfidera has other patents protecting it. Perhaps even better news, is the fact that Biogen's stock barely budged after the announcement of Tecfidera's patent challenge. The initial market shock that shook Ampyra seems to have worn off. Other patent challenges he has

volleyed have similarly had little effect. If Bass can't make money, perhaps he will go away.

Signal or noise? As long as Bass remains unable to make money, he is just noise. Watch for him to change his strategy soon though. He can no longer spook the market by challenging one of several patents. He may now choose to look for less-protected products, or perhaps move on to challenge another more vulnerable industry. Nonetheless, he has exposed a weakness in the patent legislation, and we should all rest easier if it were addressed. President Obama said in February 2013 that US "efforts at patent reform only went about halfway to where we need to go." Let's make sure our legislators know that challenging patents for financial gain through shorting stocks is an abuse of the system and needs to be stopped. ♦

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SOLUBILIZATION TECHNOLOGY

How to Choose the Right Solubilization Technology for Your API

By: Matt Wessel, PhD, Tom Reynolds, PhD, Sanjay Konagurthu, PhD, and Marshall Crew, PhD

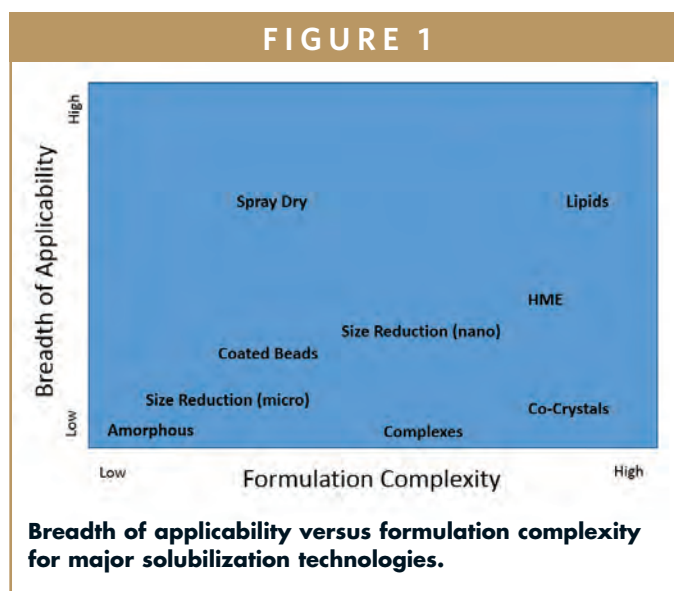
INTRODUCTION

The proportion of poorly soluble drug compounds in the development pipeline is on the rise, with 70% to 90% of current pipeline drugs falling in the two low-solubility classes of the Biopharmaceutical Classification System. With the emergence of new techniques to improve solubility, low-solubility compounds are more likely to advance to the clinic. But the large spectrum of available technologies can make it challenging for the formulation scientist to proceed in an informed and rational manner. At this point, the following questions should be addressed: what formulation technologies are available; what features of the drug might suggest one technology over another; are the technologies scalable and what are the costs; and what is the approach to making a rational technology selection? The following presents a brief overview of the various solubilization technologies, and a high-level strategy to aid in the selection of an appropriate formulation technology. Common formulation technologies available for poorly soluble drugs are listed in Table 1, with key attributes and high-level considerations.

FORMULATION OPTIONS FOR POORLY SOLUBLE DRUGS

The technologies vary in the breadth of compounds to which they can be applied, and in the complexity of their

formulations. Table 1 notes the main technologies plotted against these two factors. For example, size reduction to the micron level is relatively easy to achieve but is not applicable to a large proportion of poorly soluble compounds. On the other hand, lipid formulation technologies are more broadly applicable but more complex to formulate due to the large number of variables that must be considered. Most dispersion technologies are broadly applicable and relatively straightforward to apply; they typically involve fewer variables than lipid technologies, but more than size reduction to micron or nano-scale. The technologies shown in Figure 1 and Table 1 are briefly described below.



SPRAY DRYING

Spray drying is used to create amorphous solid dispersions (ASDs) of poorly soluble drug candidates. Depending on the drug properties, spray drying is effective because of the array of excipients that can be selected to optimize performance. The formulation approach involves co-dissolving the drug and polymeric excipient(s) in a mutually compatible organic solvent, such as methanol, ethanol, acetone, or dichloromethane. The solution is sprayed through a nozzle to form droplets from which the solvent rapidly evaporates to produce solid particles. The resulting ASD contains a homogeneous molecular-level mixture of the drug and polymeric excipients. This material can provide sustained levels of dissolved drug in targeted environments.

Spray drying is especially useful because a wide array of excipient and solvent choices makes it applicable to a large number of potential drug candidates. It is also scalable and can be used from the early stages of discovery through to commercialization. Considerations involved with spray drying are excipient choice, solvent choice, capital expenditures on scale-up, and stability of the resultant amorphous dispersion.

HOT MELT EXTRUSION

Hot melt extrusion (HME) is a thermal fusion process used to form amorphous solid dispersions. The API and thermoplastic polymer(s) are mixed and fed into a rotating screw contained in a heated barrel. The temperature is

Formulation Options for Poorly Soluble Drugs			
Technology	Attributes	High-Level Considerations	
Dispersions	Spray Dry	Broadly applicable - similar to lipids, standard solid oral dose manufacture	Selection of excipients, solvent process, API solubility in organic solvents
	HME	Solvent-less process, continuous	Limited applicability to range of compounds and excipients, large multidimensional processing space, requires thermally stable API
	Coated Beads	Utilizes commonly available coating equipment, eg, fluid bed	Applicable to low dose formulations, selection of excipients, solvent process, API solubility in organic solvents
Lipids	Broadly applicable, available manufacturing capacity	Complex highly multidimensional formulation space, empirical development process	
Size Reduction (micronization & nanoparticles)	Retains crystal form, simple size reduction process or crystal harvesting	Limited applicability to range of compounds, formulation complexity for nano-suspensions, dosage form design	
Amorphous	No excipients required	Limited applicability to range of compounds, physical stability limitations	
Co-crystals	Crystalline API, more stable form, standard oral solid dosage forms	Limited application due to lack of standardized screening approaches, limited excipients available to form co-crystals	
Complexes	Can be a simple approach	Limited applicability to range of compounds, drug loading and dosage form design considerations may be limiting	

Available technologies for drug solubilization.

maintained such that the mixture becomes fluid, and the drug further mixes and dissolves into the molten polymer carrier. This mixture is then forced through a die and cooled to form a single-phase amorphous material. The inclusion of plasticizers in the initial formulation reduces the melting point and viscosity of the mixture.

Because the API and polymer are processed at a high temperature and shear, the possibility of thermally induced transitions, such as glass transition, melting point, thermal degradation, and high-temperature reactions, must be considered. The application of HME to APIs with high melting points can be challenging because the higher processing temperatures can degrade the polymers and possibly the API.

COATED BEADS

Coated bead technologies involve dissolving the API and a suitable polymer in organic solvents and spraying onto a substrate, such as sugar or microcrystalline cellulose beads. This approach deposits a layer of amorphous drug/polymer onto the substrate. As with spray drying, the API needs to be soluble in well-behaved organic solvent systems. Targeted dose levels of drug are a consideration when selecting this technology.

LIPID-BASED FORMULATIONS

In lipid-based formulations, lipids are used as the primary agent to solubilize and deliver the drug compound. Therefore, a critical early step is to establish the solubility range of the drug in various lipids. Once formed,

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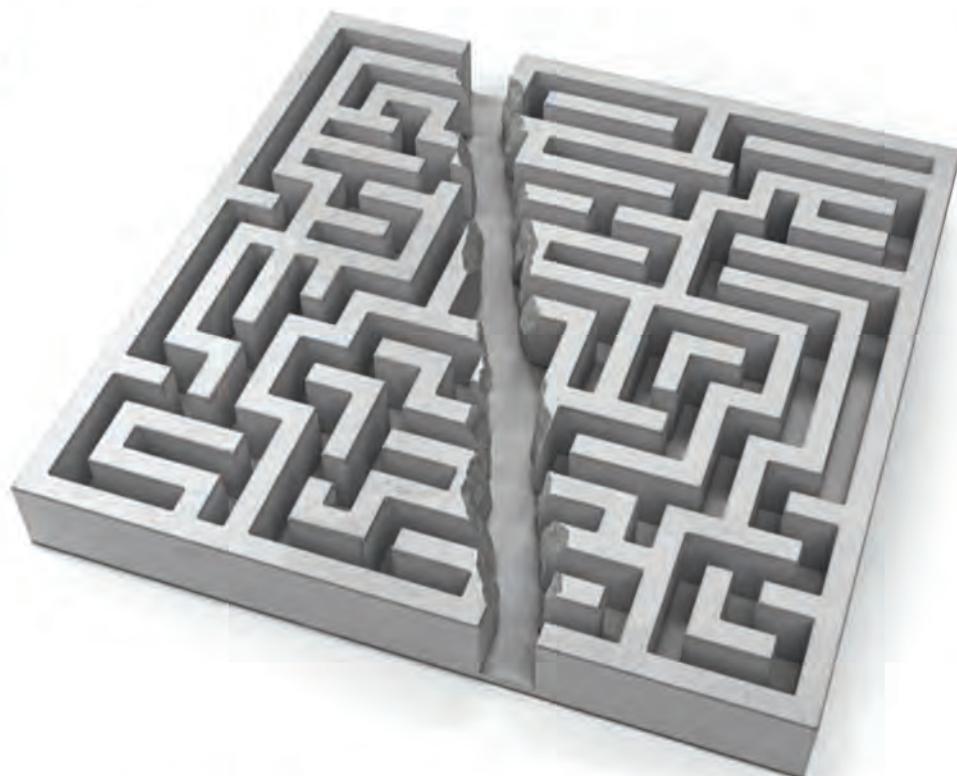
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TABLE 2

A Strategic View of Solubilization Technologies				
		Factor Range		
		Low	Medium	High
API Characteristics	Lipid Solubility	Lipids		
	Chemical Stability	Lipids		
	Partition Coefficient (aq.)	Lipids		
	Precipitation Kinetics	Lipids, Size Reduction, Amorphous		
	Water Solubility	Size Reduction		
	Melting Point	Size Reduction		HME
	Organic Solvent Solubility	Spray Dry		
	Thermal Stability	HME	HME	
	Polymer Tg		HME	HME
	Unit Dose			Coated Beads

An approach for narrowing the solubilization technology choices based on API characteristics.

the drug/lipid mixture can sustain drug concentrations in targeted environments.

Lipid formulations produce complex structures comprising micelles, micro-/nano-structures, and in some cases, liquid crystals, which are directly responsible for delivering the drug.

Lipid formulations can be complex because of the number of additives required to meet performance objectives. It is not uncommon for a formulation to contain three or more components. For instance, dietary lipids, which are known permeation enhancers, are sometimes combined with other lipids to produce a better formulation when a drug compound is both poorly soluble and non-permeable in the intestine. This adds to the complexity of the formulation and must be carefully considered during development.

SIZE REDUCTION

Particle size reduction is a strategy to increase the dissolution rate of the API by increasing its surface area to mass ratio. Particle size reduction processes are typically described as either “top down” or “bottom up.”

The top-down process involves breaking drug crystals into smaller ones by dry or wet milling. This approach can reduce particle sizes down to 1 micron; a process commonly referred to as “micronization.” However, micron-sized particles may not sufficiently enhance the solubility of many poorly soluble APIs. To further improve the dissolution or absorption characteristics, particles can be reduced to the sub-micron or nano-size ranges.

In the bottom-up approach, nano-particles are produced by solution-based drug recrystallization. The process requires careful maintenance of a supersaturated drug solution while inducing crystal nucleation, growth, and precipitation.

As particles get smaller, and surface area becomes larger, cohesive and adhesive effects can lead to particle aggregation or agglomeration, and the compound may stick to process equipment. These issues can be prevented with surface cohesion inhibitors and other surface chemical modifications.

AMORPHOUS

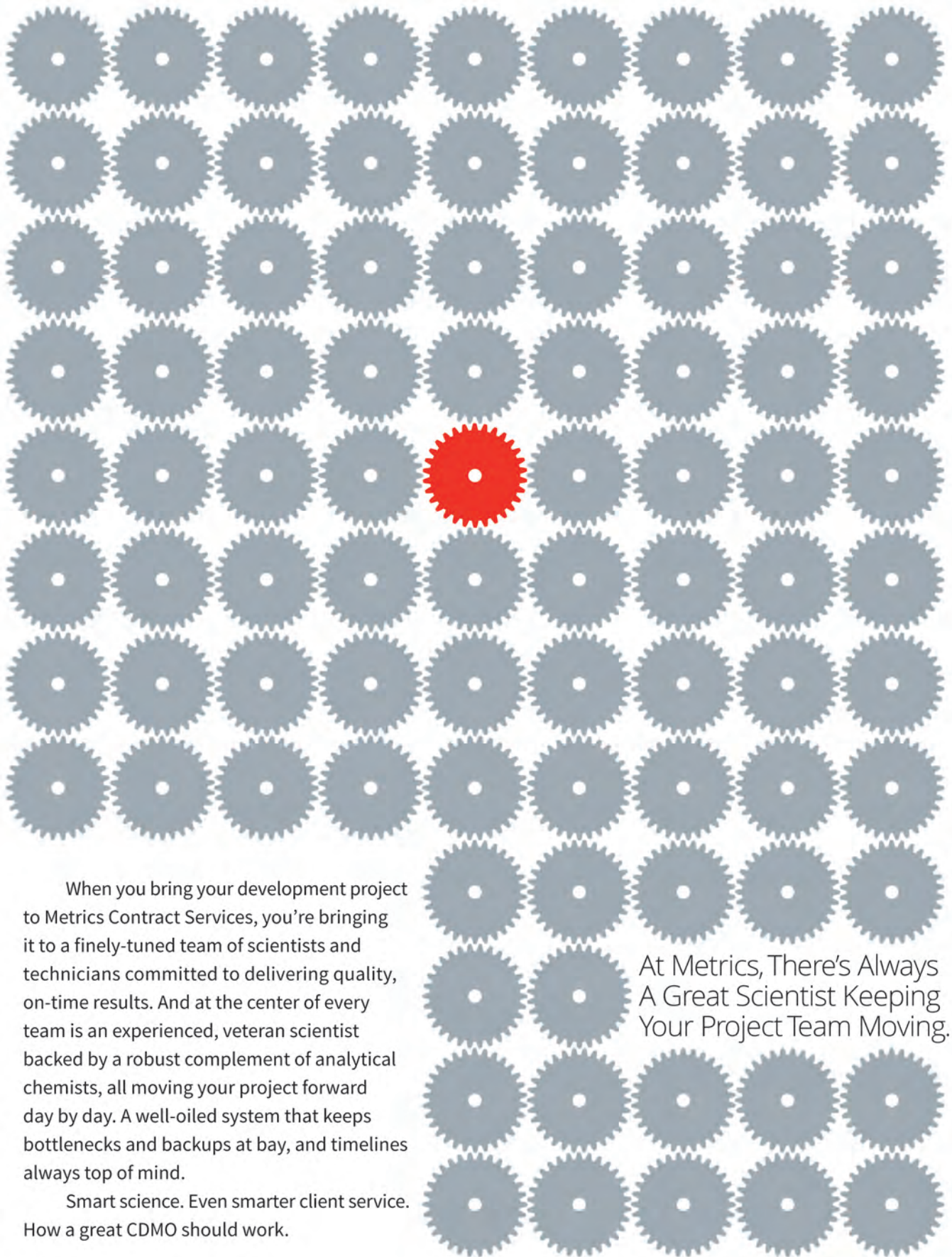
This is a simple approach that involves dissolving a crystalline API in a suitable organic solvent and then spray drying. The approach works well for some compounds; many, however, tend to recrystallize, thereby compromising the physical stability of the amorphous form.

CO-CRYSTALS

Co-crystals are crystalline structures usually comprising two or more unique components, one being the API and the other(s) being the coformer. By using suitable coformers in the crystallization process, the physical properties of the API can be improved, yielding for instance, better dissolution and stability characteristics.

COMPLEXES

In this approach, the API and a companion molecule, such as a cyclodextrin, form an inclusion complex. The API resides in cavities of the companion molecule, bound by non-covalent intermolecular forces. Because no covalent bonds are involved, the integrity of the API is preserved. The resultant formulation improves solubility



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and physical properties. API size and lipophilicity are important factors to consider.

TECHNOLOGY SELECTION STRATEGY: WHAT'S RIGHT FOR YOU?

In this section, we discuss a strategy for selection of a formulation technology based on specific characteristics of the drug. Table 2 shows a selection strategy chart with the characteristics on the vertical axis. These can be measured directly, or estimated by in silico prediction. Using the results, we can classify the drug into a high, medium, or low range for each property, and derive a shortlist of applicable technologies.

For example, if an API has poor lipid solubility, lipid formulation is excluded. If the same API also has low thermal stability, then HME may also be eliminated as an option. The remaining possibilities are then size reduction, bead coating, and spray drying. If the API has acceptable solubility in common organic solvents, spray drying and bead coating are attractive options. If the API dose is expected to be high, then bead coating is unfavorable, and spray drying remains the best choice.

THE API FORMULATION TOOLBOX

Selecting a formulation technology for a particular drug candidate can be a complicated process. There are many technologies available, each

with a set of requirements and process variables that must be considered. By understanding the available technologies and knowing the key properties of the API, we can eliminate some of the options and simplify the decision process.

The technology map shows ranges of values because there are other factors that will influence the decision, such as how an API interacts with excipients. For example, if an API has limited solubility in organic solvents, spray drying can still be a valid choice if an excipient can provide excellent sustained dissolution profiles in targeted environments. This is especially true in cases where the dose is expected to be low. Additional considerations, such as performance, manufacturability, and stability, can also greatly influence which technology is best suited to meet the specific requirements of a project.

But generally speaking, the properties of the API are the primary driver of the technology choice. Knowledge of the API characteristics, as outlined in Table 2, directly leads to a more intelligent and rational decision as to which technology is most appropriate for any given drug formulation project. With this toolbox, timelines can be shortened, and more compounds can be advanced to the clinic using a solubilization technology that is well suited for clinical trials and commercialization. ♦

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BIOGRAPHIES



Dr. Matthew D. Wessel is Principal Scientist at Patheon, where he is responsible for developing predictive computational approaches for solving drug solubility and formulation problems. Prior to Patheon, he was a Solutions Architect at Schrödinger, worked for Bend Research, and was an Associate Research Fellow at Pfizer. He earned his PhD in Chemistry from The Pennsylvania State University and his BS in Chemistry from Washington State University.



Dr. Tom Reynolds is Principal Scientist at Patheon ORP, where he is responsible for development of a drug formulation and solubilization technology platform that delivers formulation options using computational methods. He has over 20 years of experience in research, development, and management of programs in nanotechnology, crystal growth, formulation, and computer modeling. He earned his PhD in Chemistry from Oregon State University.



Dr. Sanjay Konagurthu is Director, Formulation and Process Development at Patheon, where he is responsible for developing formulations and manufacturing processes for products that cover a wide range of therapeutic areas. He has extensive experience in oral solid dosage forms, including solubility enhancement and modified release. He earned his BS from the Indian Institute of Technology, Madras, and his PhD from the University of Colorado, Boulder, both in Chemical Engineering.



Dr. Marshall Crew became the VP, Global PDS Scientific Excellence at Patheon after Agere Pharmaceuticals (where he was the President, CEO & Founder) was acquired by Patheon in 2015. Dr. Crew has devoted his career to improving oral bioavailability, developing innovative technologies and approaches for the delivery of poorly soluble drugs and then managing their application to achieve client success. His scientific expertise includes formulation design and development, solid state characterization of drug substance and product, and computational modeling (predicting shelf-life and pharmacokinetic and bioavailability for oral, devices and parenteral delivery). He earned his PhD in Physical Chemistry from Oregon State University.

PRIMARY PACKAGING

Ophthalmic Squeeze Dispenser (OSD): Does One Size Fit All?

By: Degenhard Marx, PhD, and Matthias Birkhoff

INTRODUCTION

The discussion about the use of preservatives in eye drops is still controversial, but more and more evidence supports the use of unpreserved eye drops for treatment of chronic diseases. For example, dry eye, a condition in which the tear film is impaired, is increasingly more recognized as an inflammatory disease. Treatment with preserved eye drops may worsen symptoms. For the treatment of mild symptoms, the use of non-irritating or unpreserved artificial tears is recommended, while as for more severe cases, the use of an anti-inflammatory principle will become the standard treatment. The same recommendation for restricted use of preservatives applies for glaucoma, which requires a treatment for the rest of life. Baudoine et al have shown that the risks for glaucoma patients to experience severe local side effects increases with the number of preserved eye medications taken in parallel.¹ Combination products that reduce the number of necessary medications or the use of unpreserved eye drops will certainly help suffering patients and will also increase adherence to the prescribed treatment schedule. At least in Europe, the authorities have recognized the issue, and the European Medical Agency (EMA) pushes, for example, the use of unpreserved ophthalmic formulations, most recently in a guideline on pediatric medicine.²

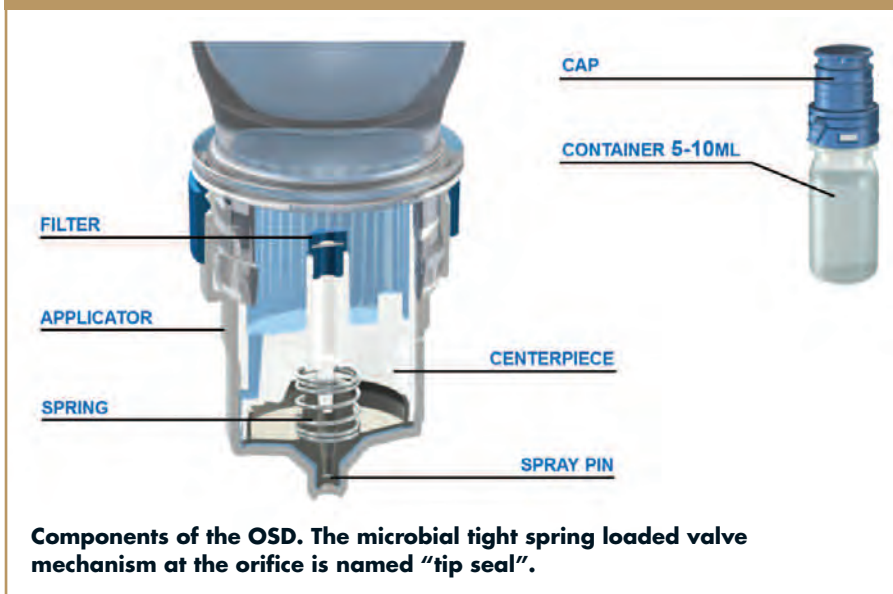
Recognizing the trend toward preservative-free topical drugs, in 2006, Aptar Pharma started the development of the Ophthalmic Squeeze Dispenser (OSD), a multi-dose device

designed for unpreserved eye drops.³ The system is designed in a common squeeze bottle shape to ensure user acceptance. The first commercial product registered under the European Medical Device Directive using the OSD as primary packaging was VISMED Multi, an artificial tear product by Swiss Eye Care expert TRB Chemedica, introduced to the market in 2011. To date, more than 25 million OSDs were sold as preservative-free multi-dose systems for several products, and many new projects are on the way. The key question we will answer in this review is how a single device can fit a wide range of formulations for different conditions and diseases?

WHERE ARE THE CHALLENGES?

Eye drops can be very different from each other, and their behavior is very difficult to predict. Artificial tears used to supplement the tear film do not contain active ingredients but vary in rheological properties, such as viscosity, depending on patients need from low to highly viscous. Eye drops containing active drugs, eg, glaucoma treatment, may contain a lot of auxiliary compounds to stabilize the formulation, and the content of active pharmaceutical ingredient may range from micrograms to few milligrams per milliliter. The dropper should always deliver the appropriate drop size, the formulation must be stable for storage and in-use period, and the forces to deliver a drop should remain in a reasonable range. What needs to be considered when putting a formulation into the OSD?

FIGURE 1



HOW THE OSD WORKS

To understand the system, its flexibility, as well as technical limits, it is useful to explain how it works. The system follows a pure mechanical approach to prevent microbial contamination of the product and uses the so-called "tip seal technology," a specifically developed outlet valve technology, and sterile filtration of the venting air. Like any other conventional dropper bottle, the OSD needs to be held in an angular or complete upside down position to deliver drops. The system is primed by squeezing the bottle until the first drop is delivered. During the actuation process (squeezing the bottle), the pressure within the system rises, and the liquid is forced through the liquid channel into the space between spray pin and applicator. As soon as the liquid pressure exceeds the valve spring force of the tip seal, the central part of the spray pin is forced backward, and the orifice opens and liquid is dispensed. The special outer geometry of the orifice allows the product to form and deliver a

drop. The tip seal outlet valve closes immediately with an outward movement when the pressure drops below a defined threshold. This function is self-regulating and prevents any backflow into the system and thus potential microbial contamination.

During the actuation in angled or upside down position, the bottle content will submerge the filter. The side of the filter membrane that faces the

formulation is highly hydrophobic, which prevents wetting of the membrane or that some part of the formulation can be forced through the filter. Dispensing drops reduces the volume inside the container; consequently, an equilibration of the container content is required. The restoring force of the bottle, which is created by returning to its initial shape, equilibrates the pressure difference by drawing air into the container through the filter, preventing microbial contamination of the formulation via the venting air. It should be recognized that the flow path for the formulation and that for the venting air are completely separated. This venting function is independent from device orientation.

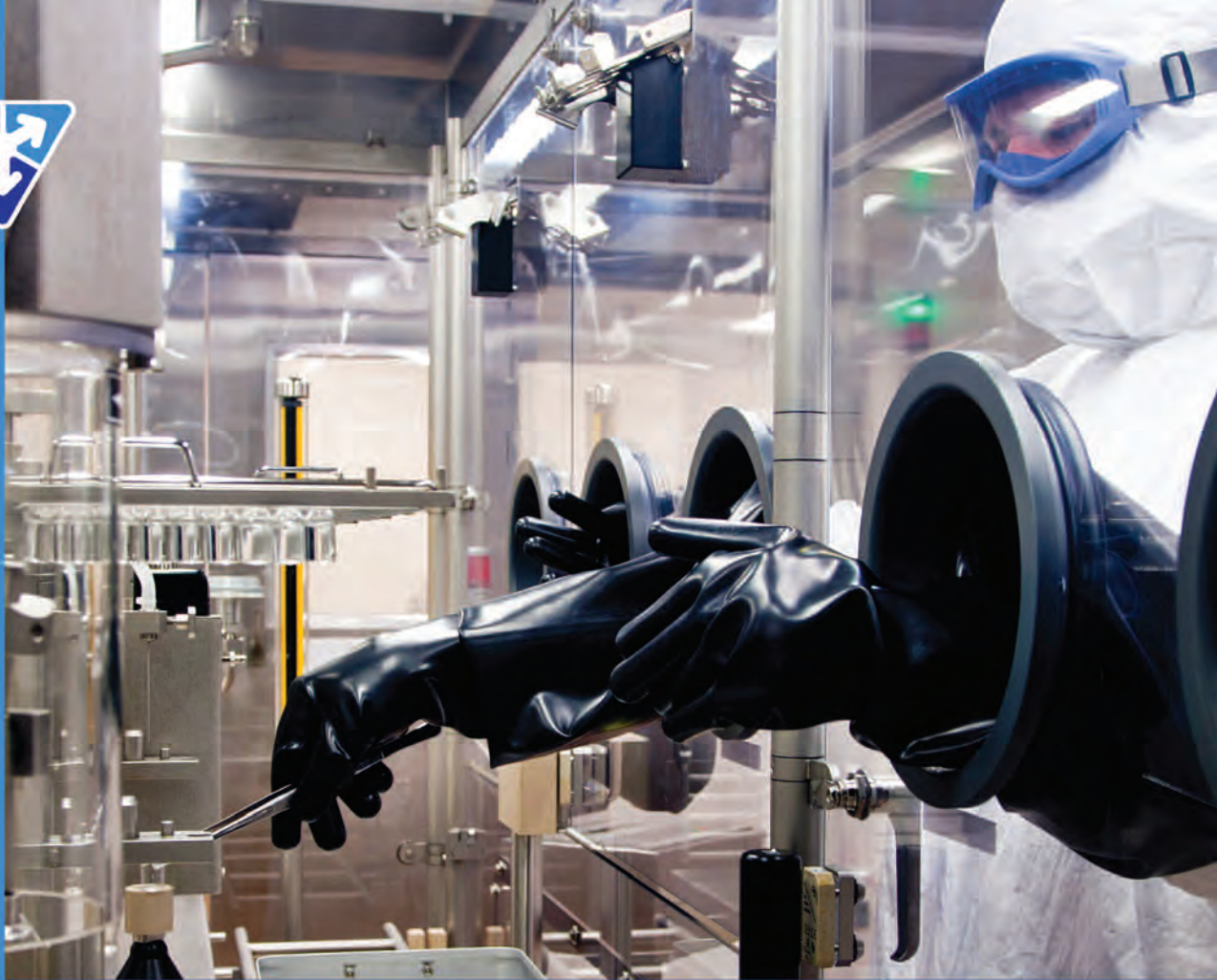
HOW TO ENSURE A SMOOTH ACTUATION?

When squeezing the bottle, the pressure will force the formulation through a specific fluid pathway into the space behind the spray tip, which subsequently

FIGURE 2



(1) The OSD is actuated like a conventional dropper: Squeezing the bottle will deliver a drop. (2) When squeezing the bottle, the formulation will force the tip seal at the orifice to open (red arrow) and a drop will be formed and delivered. (3) At the end of the actuation when the pressure in the container decreases, the spring will close the tip seal immediately with an outward movement. The restoration force of the bottle will draw the venting air through the sterile filter into the bottle.



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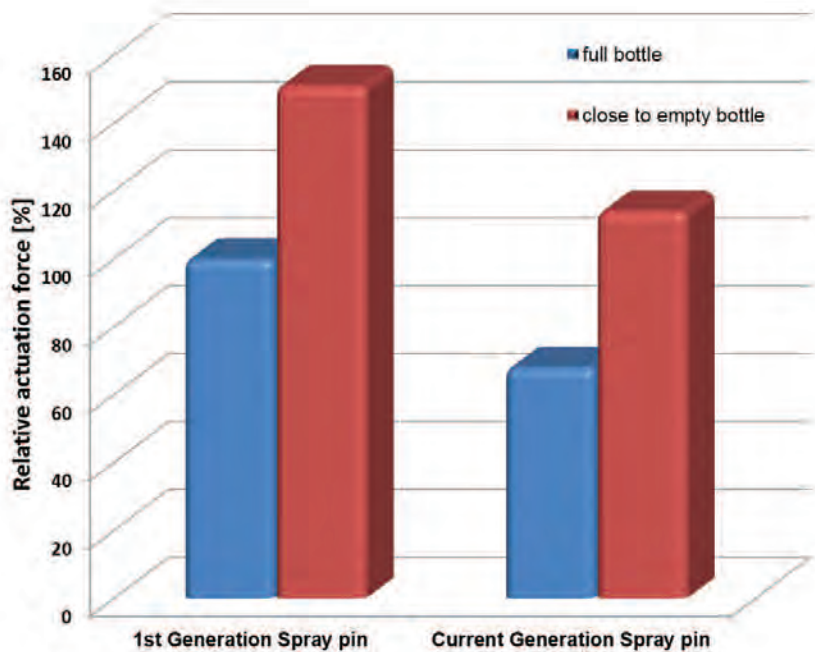


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FIGURE 3



Actuation force of initially used tip seal design compared to the improved configurations using a full (blue bars) or close to empty (red bars) 10 ml bottle.

opens the tip seal outlet valve. For a smooth actuation, the diameter and length of the flow channel between bottle and space next to the orifice are important. The length of this flow channel can be varied, thus the resistance of the system adapted to the viscosity of the formulation. The length of the internal channel can be set in multiple steps to get the best results for a given formulation. This feature is referred to as flow control. The optimum flow control for each formulation is determined by experiments in the lab using completed systems with different preset flow control values.

ACTUATION FORCE

Actuation force for conventional droppers for preserved formulations with open orifice depends mainly on the stiffness of the bottle, which is

determined by wall thickness and the used material (eg, softer polyethylene or stiffer polypropylene). Compared to the open-bottle designs, the actuation force of the OSD is influenced by three factors: tip seal function, liquid level of the bottle, and stiffness of the bottle. As previously described, a certain pressure needs to be generated inside the system to open the tip seal. In a first-generation, the actuation force was quite high in order

to provide a real tight sealing of the orifice. Continuous improvement and product optimization have significantly lowered the force to actuate and as such, improved patient compliance and convenience.

An important factor influencing the actuation force is the liquid level within the bottle. A full bottle requires less squeeze force to deliver a drop than one which is close to being empty. In an almost empty bottle, more air must be compressed before the opening pressure of the outlet valve is reached. Therefore, it is recommended to use a bottle size close to the intended filling volume. Starting from the standard 10-ml LDPE (low density polyethylene) bottle, an oval-shaped (5-ml) as well as a round 7.5-ml bottle (Figure 4) is now available to meet the requirements of the market.

The bottles for the OSD are made from soft polyethylene. The wall thickness was optimized to balance between low actuation force, managing water vapor transmission rates and maintaining sufficient restoring force to enable ventilation of the system.

FIGURE 4



Bottles for the OSD made of LD-PE (low density polyethylene), the oval-shaped 5-ml (left), round 7.5-ml (middle), and 10-ml round bottle (right).

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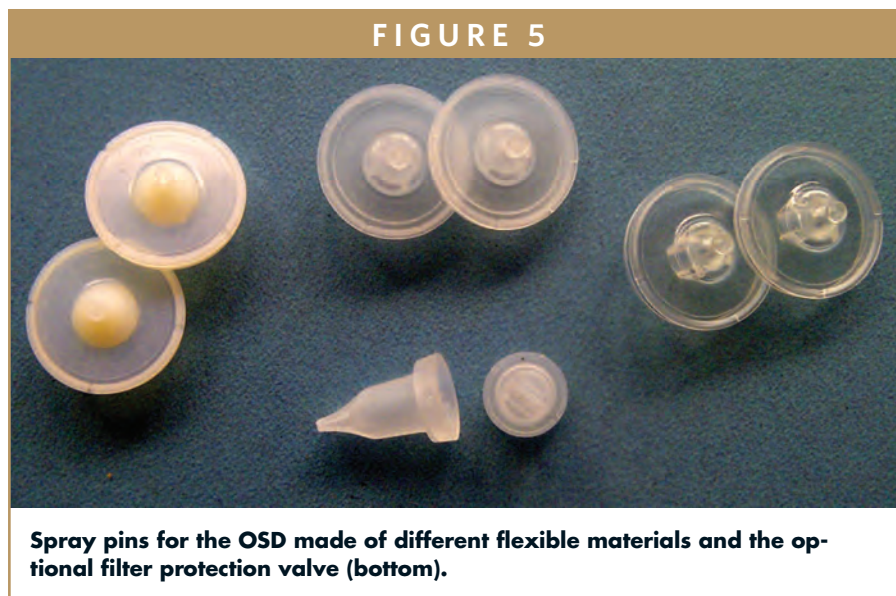
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COMPATIBILITY WITH FORMULATION

When handling liquids in delivery devices, there is always some potential risk of interactions which may impair the stability of the formulation or function of the entire systems. Any such potential compatibility issues should be considered early in development and tests addressing such issue are mandatory. The highest potential risk is sorption of active ingredients to material of the container closure system. In addition to the mentioned use of polyethylene and polypropylene, a thermoplastic elastomer (TPE) material is used for the outlet valve. This part is named spray pin (Figure 5), which comes in contact with the formulation. Aptar identified different elastomeric materials that may be used in cases when the standard material is creating compatibility concerns.

As previously described, when using the OSD, the formulation will submerge the filter. Its hydrophobic membrane will prevent formulation from impairing its proper function. This is true for most formulations. But there are also formulations known for a very low surface tension, which allows wetting the membrane or even ingress into the filter pores. If this happens, normally the venting of the system is impaired, and the restoring force of the bottle is not sufficient to bring it back into its initial shape. As a result, the required squeeze force will increase step by step for the subsequent actuations. The technical solution for such formulations is the use of a so called filter protection valve (Figure 5, bottom), a small component made of TPE resin that is slipped over the filter. This measure prevents the



formulation coming into contact with the filter membrane without affecting the venting of the system.

Another topic related to the bottle is its sterilization procedure. The standard procedure for sterilization of the low-density polyethylene bottles is gamma-radiation with more than 25 kGy. According to the literature, radiation sterilization may have an effect on the exposed material, although polyethylene is well suited for this procedure. Ethylene oxide (EtO) sterilization may be used as an alternative for the bottle.

Because of its complex design, the OSD dropper part needs to be radiation sterilized. For the OSD, a validated gamma sterilization process according ISO 11137-1 and 2 was established.

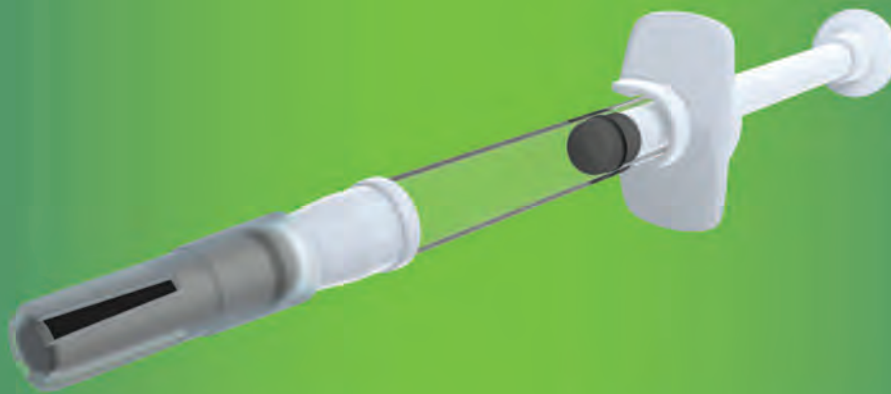
CRYSTALLIZATION AROUND THE ORIFICE

As previously described, at the end of the actuation, the tip seal valve closes with an outward movement, leaving some formulation visible at the orifice. This remaining drop (typically 3 to 7 microliters) will dry out within the next 4

to 6 hours even when the protection cap is re-attached. For some formulations, the remaining material from these liquid bears the risk of blocking the orifice due to crystallization after a few days of use. This potential risk can be tackled by introducing a porous liner material into the protection cap. When the protection cap is re-attached onto the OSD after use, the liner material will take up the remaining drop and spread the liquid within the material on a large surface. This will speed up drying and thus further reduce potential growth of microbes, preventing crystallization around the orifice. If this technical solution is suited for a particular formulation, it must be tested carefully. The impact of a potential uptake of the drop as well as the drying rate has to be understood; also the intended number of doses per day needs to be taken into consideration.

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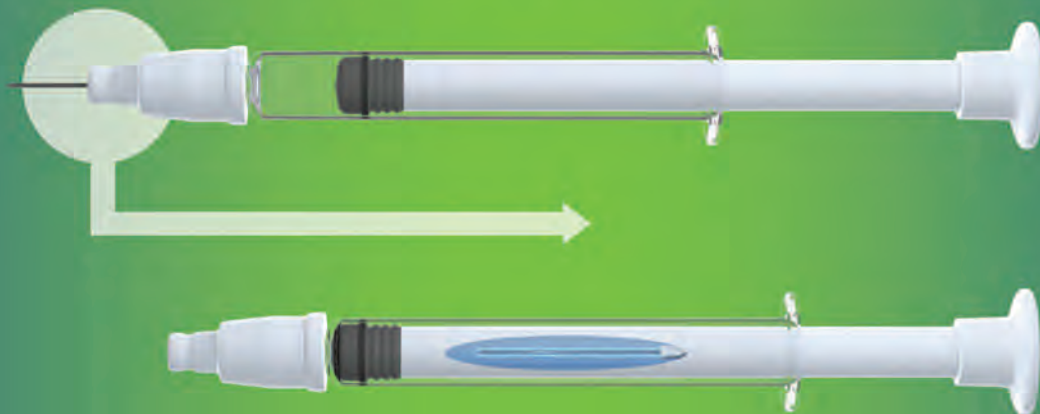


FIGURE 6



New fully automated assembly line for the OSD in a clean room ISO class 7.

SUMMARY

The wider use of preservative-free multi-dose devices for eye drops has started in Europe for artificial tears. Patients and consumers appreciate the convenient and intuitive handling of the OSD, properties which are important for the further success of this device. For pharmaceutical manufacturers, the cost effectiveness of OSD is another important aspect. The system is flexible to meet the challenge of different ophthalmic formulations. However, professional guidance is needed and provided by Aptar Pharma to find the optimum configuration. The provided technical measures were thoroughly tested with special emphasis on the mechanisms, ensuring microbial integrity of the system before the OSD was introduced to the market. Validated 100% in-process controls (IPCs) during manufacturing of the OSD ensure the reliability of the system. Although this constitutes a thorough validation of the system itself, it cannot exempt marketers from performing proper due diligence on the finished product. But the qualification work performed by Aptar Pharma helps

smooth this process significantly and allows for shorter time to market. Special attention was always paid to ensure safety, obviously with special emphasis on microbial integrity of the system. ♦

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BIOGRAPHY



Dr. Degenhard Marx, following the study of Veterinary Medicine and the successful completion of his thesis at the University of Leipzig, joined the Arzneimittelwerke Dresden/Asta Medica cooperate research in 1992. In 2001, he took over a Senior Research position at Altana Pharma/Nycomed in Constance, Germany. During this time in the pharmaceutical industry, he collected ample experiences in the drug development of anti-inflammatory and cardiovascular drugs. In 2008, he became Business Development Manager at Ing. E. Pfeiffer, Pharma Division, which became Aptar Pharma in 2010. He is now Director of Scientific Affairs within the Aptar Pharma Consumer Health Care division.



Matthias Birkhoff is Vice President, Marketing, of Aptar Pharma CHC Division. In this role, he is responsible for Aptar Pharma's Eye Care program and coordinates research and development activities, microbiological assessment, and commercial strategies. Mr. Birkhoff started his career in pharmaceutical sales in a major multinational pharma before joining Aptar 16 years ago. Before getting involved in Business Development and Marketing, he was in charge of sales in the AsiaPacific region. He studied medicine at the University of Dusseldorf, Germany and holds a nursing degree.

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The highly competitive drug development environment is a risky one, requiring enormous amounts of time and money. In fact, it can take as long as 12 years for a drug to go from research to market with an investment easily reaching between \$800 million and \$1 billion. That is why smaller biotech companies with very limited budgets must focus their efforts on their core competencies of research and development and consider partnering with a Contract Development and Manufacturing Organization (CDMO) right from the start. A CDMO can be a valuable contributor to the drug development process, providing the necessary and critical development support needed for complex compounds, including fill and finish, drug delivery systems, packaging, and product lifecycle management. The CDMO will most likely offer a better opportunity for success of the drug, helping to elevate an entire drug package's value from development on through to market. Drug Development & Delivery recently interviewed Dr. Susanne Resatz, President of Vetter Development Services USA, Inc., to discuss the many benefits to small biotech companies in utilizing a full-service CDMO, and what advanced services the Chicago-based facility offers its growing customer base.

Q: For our readers who may not yet be familiar with your company, can you briefly discuss Vetter and what service portfolio it offers?

A: Vetter is an independent CDMO headquartered in Ravensburg, Germany, and specializes in the aseptic filling of syringes, cartridges, and vials. Our state-of-the-art facilities located in the US and Europe provide support for early stage drug products, with seamless transfer to Vetter Commercial Manufacturing for large-scale production. In addition to these locations, in November 2014, taking advantage of a

rapidly growing Asian healthcare market and to better support our customers and develop new business, we announced the opening of our first Asian office in Singapore.

As a world-leading CDMO, we have extensive experience in working with biologics and other complex compounds, including monoclonal antibodies, peptides, interferons, and vaccines. And because we are a full-service provider, we can support our customers' products throughout their lifecycles, from preclinical development through global market supply. We are the originator of dual-chamber technology, which enables easier, safer lyophilized drug

administration, and we are a leader in the use of Restricted Access Barrier System (RABS) technology in cleanrooms, which mitigates risk of product contamination throughout the manufacturing process. Finally, it is important to note that as a family owned independent company, we do not manufacture our own drugs but focus solely on our customers' product success.

Q: If you were a small biotech firm, what would you see as the most important benefit for utilizing the services of a CDMO rather than a variety of service providers?

A: Due to the very nature of their size, small biotech companies face numerous obstacles, including high costs, limited budgets, and ever-increasing regulatory oversight. Executing on a well-defined product development process from the start is key and affords the biotech company the best opportunity for creating the most advanced and complete drug candidate package possible. But because small biotech companies rarely have the resources to focus beyond their core competencies of research and development of promising drugs, partnering with a CDMO right from the start can have a significant impact by elevating the entire drug package's value from development on through to market.

By contracting with a full-service CDMO, the small biotech company can keep the number of service providers to a minimum, helping to reduce the complexity of the process, including various interfaces and daily handling efforts. Additional advantages include the retention of product and process knowledge, avoiding duplication of activities, and reducing overall timelines. Also, utilizing the services of a trusted CDMO early in the drug development process will most likely offer a better opportunity for success of the drug as they will act as both a guide and a consultant during the process. A CDMO can also provide necessary and critical development support needed for complex compounds, including fill and finish operations, drug delivery systems, packaging, and product lifecycle management. They can also be a valuable contributor to the drug development process; helping to achieve an attractive, high-value drug package by lending their good reputation to the package and therefore, to the biotech company itself. This support will only increase the likelihood of getting the attention of a large bio/pharmaceutical company that might currently be following an acquisition or in-licensing

strategy. Finally, the CDMO can also act as an interface between a small biotech firm and its later bio/pharmaceutical counterpart, understanding the business situation of involved parties as well as their targets and challenges.

Q: In April 2011, Vetter revealed its Chicago facility was ready to accept client projects. Why did you decide to open a facility in Chicago? What are the services you offer here?

A: For a company like Vetter, where nearly half of its client base resides in North America, it makes sense to be located in the heartland of the United States. The Midwest and in particular, the vibrant city of Chicago, is a logical choice. Furthermore, Illinois is considered a "hot spot" in biotechnology and thus, of keen interest to Vetter.

Directly located among top-flight academic institutions, Chicago offers access to cutting-edge science and a highly skilled employee pool that is important to Vetter's success. The city also offers access to six schools of medicine, the largest concentration of physicians in the country, and major federal research labs. And when deciding on a location for situating the new facility, the Illinois Science + Technology Park in Skokie allowed Vetter flexibility to expand and easy access to the growing community of innovative pharmaceutical and biotech companies, the city's infrastructure, and the pharmaceutical and biotech hubs in the east and west of the country.

At the Skokie facility, Vetter offers top-notch flexibility and the possibility of filling various products quickly and safely. We can also react very quickly to the needs of each customer's drug substance and better respond to any changing requirements. Furthermore, the location allows the company to give all of its US customers – from the small start-up to the internationally leading drug manufacturer – uniformly high-quality and affordable services. As a leading CDMO, Vetter has created the basis for a one-stop-shop solution to assist its US customers from early drug development to long-term market supply. The close collaboration produces significant synergies in subsequent development steps, as well as more efficient transfer of substances and manufacturing processes to commercial production at its Ravensburg, Germany, facility.

Q: How has the Chicago site performed since then?

A: We are extremely pleased with our past year's performance at the Skokie facility, as well as our overall success to date. Since the full operational launch, the facility has successfully passed audits and qualifications by as many as 30 companies, including 9 of the top 20 leading (bio-)pharmaceutical companies. In addition to the US, we have contracted with a number of companies from around the globe, including Belgium, Israel, and Denmark, as well as Asian-headquartered companies, such as in South Korea.

The site has been actively releasing customer batches for clinical trials. In fact, due to our performance, many of our customers have already returned for development work for a second, third, or even fourth molecule. Furthermore, the outlook for future performance is very positive as demonstrated by a pipeline filled with high-quality customer projects for biologics. Drugs under development by our customers include treatments for blood cancer, muscular dystrophy, wound healing, and dwarfism.

Q: What is the latest news from your Chicago facility?

A: As previously stated, we announced the Chicago facility became fully operational in April 2011 and has been accepting new client projects ever since. That announcement, however, in no way signaled the end of our development work at the facility. In fact, it was only the beginning. Since that announcement, we opened a new cleanroom in December 2014, bringing the number of cleanrooms at the site to three. With the addition of the third cleanroom, filling of single-chamber syringes became available with a maximum filling speed of 3,600 units per hour, and batch sizes as large as 25,000 units. The line is constructed as a RABS, offering various filling pumps depending upon a product's unique characteristics, as well as fully automated tub processing. The other two existing cleanrooms, both operational since late 2011, provide fully automated vial filling for batches up to 10,000 liquid or lyophilized vials, as well as semi-automated filling for manufacturing prefilled syringes, cartridges, and vials in small batch sizes of a few hundred.

In 2015, we also announced initiatives that include an additional staff shift for daily clinical manufacturing operations, as well as the doubling of capacities for performing visual inspection and In-Process Control (IPC). The facility also expanded its on-site offerings by giving customers the option to

obtain secondary packaging services for small batches of frozen drug products, such as vial labeling, cartoning, and carton labeling.

To date, four customer products in development have already been successfully transferred from Vetter's US clinical manufacturing facility to the company's European sites for manufacturing of late-stage clinical supply and for subsequent commercial production. The company plans for additional product transfers from the US to Europe in the near future.

Q: You indicated that so far you transferred four customer products? How do you support a seamless transfer of products in Phase II in Chicago to Phase III in Ravensburg?

A: The secret to a seamless transfer of products is offering manufacturing resources that begin from early drug development on through to market launch and commercial supply. As a CDMO, Vetter can offer its customers a "modular service" offering in addition to a seamless transfer approach for their drug product from Vetter's US early stage facility to one of its European development and commercial manufacturing facilities. To assist in the transfer and enable consistency, the sites on both continents use similar equipment and processes whenever possible, including product contact materials, such as excipients and primary packaging materials. This flexible approach results in less overall risk of unforeseen manufacturing issues, and creates a consistency between clinical and commercial drug product handling.

In addition, the core of the aseptic manufacturing process (i.e., the filling lines themselves) are designed in the same manner at Vetter's clinical and commercial sites. The Chicago facility, designed specifically for high-yield and flexible use, employs scaled-down versions of the company's commercial filling lines. This aligned facilities approach reduces time and means less development work will be necessary to realize the transfer and scale-up process of the individual customer drug product.

Furthermore, all Vetter sites in the US and Europe are part of the same company-wide Quality System, offering a consistent quality approach over a project lifetime and avoiding non-productive time to adapt to new systems. The interaction of Vetter teams from both the US and Europe allows customers to access global expertise as necessary, an attribute that is especially valuable for projects with a very high level of complexity. ♦



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FORMULATION DEVELOPMENT TECHNOLOGY

A Novel Drug Delivery System That Offers Zero-Order/Near Zero-Order Release Profile of Low-Dosage Strength Tablets Containing Highly Soluble Actives

By: Thomas B. "Brad" Gold, PhD

ABSTRACT

The US Patent and Trademark Office awarded Dr. Thomas B. "Brad" Gold a patent for his application, Coated Tablets With Zero-Order or Near Zero-Order Release Kinetics. The intellectual property centers on formulation development technology that allows for the steady, continuous release of API over a particular duration of time to mitigate variations or spikes in therapeutic benefit.

The zero-order dissolution release profile was achieved by combining no more than five tablet excipients, one of which was the highly soluble API in very low concentration, another being the tablet lubricant, and the application of a very thin film-coat layer. Release rates of greater than 20 hours were achieved as demonstrated with in vitro dissolution testing. The following describes the technology behind that patent.

INTRODUCTION

Attempting to achieve specific modified-release rates of any API poses many challenges. These challenges may be more difficult when dealing with variables such as low-dosage

strength, highly soluble actives, and a desired zero-order/near zero-order dissolution release profile. Likewise, bioavailability of the API may be compromised when attempting to modify release of the API due to factors such as gastric retention or bypassing the absorptive "window" of the duodenum.

Many products use traditional methods of formulating for extending delayed-release actives out to 16 hours. These traditional formulation methods may be composed of a hydrophobic matrix ingredient in the tablet core and the application of a heavy tablet coating, typically methacrylate or cellulosic in composition.

Alternative traditional formulations rely on the coating layer to provide the majority, if not all, of the impact on the dissolution release rate and profile. Other products use specialty processes or patented technologies to achieve desired release rates and profiles.

Currently, there are few marketed products that achieve a zero-order/near zero-order in vitro dissolution rate. These products achieve zero-order release profiles by means of osmotic agents, ie, a bi-layer tablet in which one half controls the hydration rate of the tablet and the other contains the API - and both of which are protected by a thick film coating and physical intervention such as laser scribed holes. Moreover,



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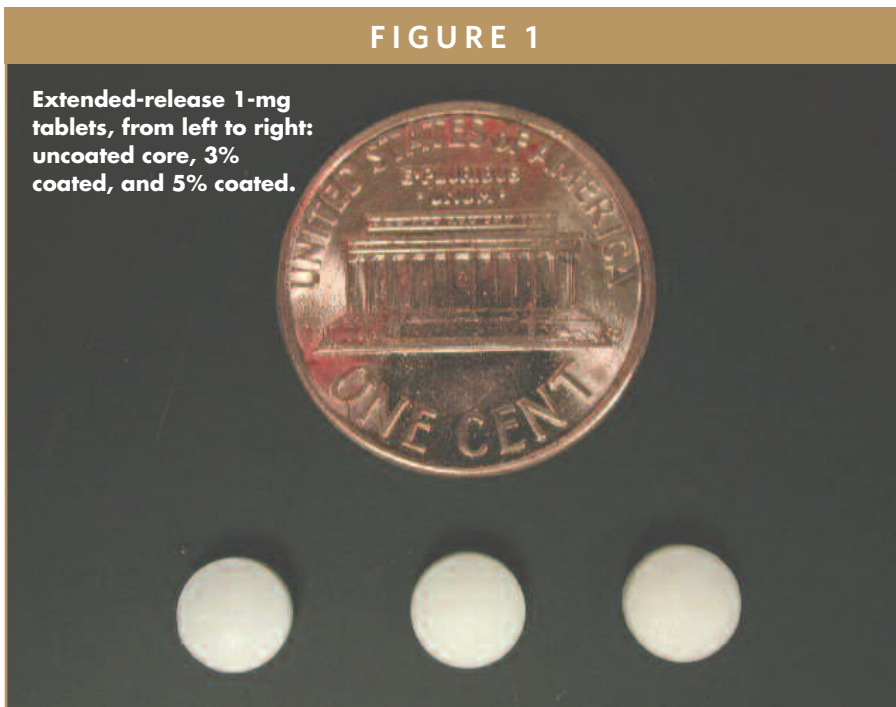
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FIGURE 1

Extended-release 1-mg tablets, from left to right: uncoated core, 3% coated, and 5% coated.



these products are costly to produce and require special equipment, and consequently, the cost is passed along to the end consumer.

BACKGROUND

There exist several means by which zero-order/near zero-order drug delivery rate has been achieved. Currently marketed products include simple matrix system tablets relying on cellulosic excipients in combination with a functional coating layer, multiparticulate systems, and osmotic systems that employ excipients, mechanical means, devices, or a combination of any.

Matrix Systems

A myriad of systems have been developed - most of which are HPMC-based - that exhibit near zero-order release rate of drug. Some of these require natural gums or waxes in the matrix to approach zero-order release, while at the same time relying on the

relative insolubility of the drug substance itself. Polyoxyethylene oxide has been used to produce an eroding tablet that releases an insoluble, high-dose drug at a near zero-order release rate, without the use of any sustained-release coating.

Multiparticulate Systems

Capsugel Dosage Form Solutions has developed osmotic-bursting multiparticulates with a barrier-coating option to approximate zero-order

release. With this, drug release is controlled primarily by manipulating coating type and weight. In this approach, one still sees a release lag based on barrier coating weight, followed by pulsatile- to short-controlled-release durations. As with most osmotic dosage forms, it is touted as having relative insensitivity to environmental pH and relative insensitivity to sweller-layer thickness or drug properties.

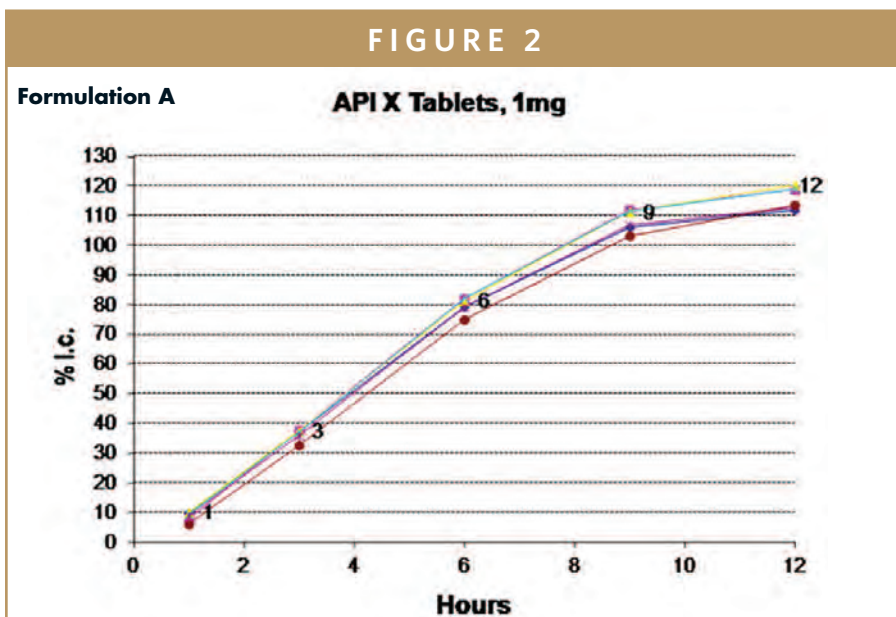
Others have developed miniaturized osmotic pumps composed of multiparticulates that possess semipermeable membranes combined with osmotic agents or "flux regulators" that push drug out of miniature pores.

Osmotic Tablets

Osmotic drug delivery systems are valuable in their ability to release API without being affected by many microenvironmental factors. Additionally, this technology is suitable for a number of types of deliverables, including solubles, insolubles, large or small molecules, lipids, and peptides, to name a few.

Pioneers for this type of delivery

FIGURE 2





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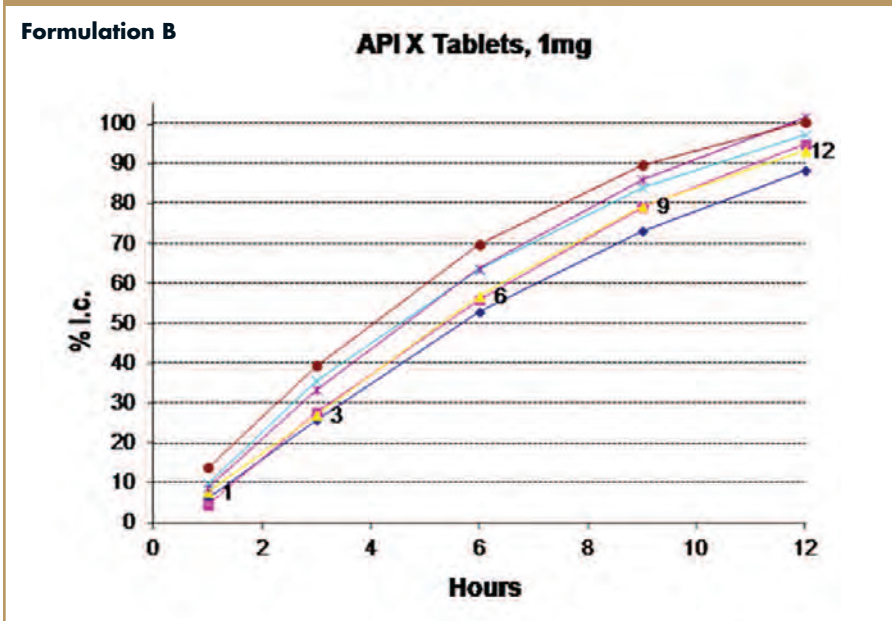
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FIGURE 3



vehicle have come from institutions such as ALZA Corp. ALZA has successfully produced several osmotic pump delivery systems, in addition to their more well-known OROS® technology. Shire Laboratories' EnSoTrol® platform utilizes several strong solubilizing and wicking agents in conjunction with semipermeable coating membranes to produce a pressure gradient across the

coating layer. Andrx developed the CPOP/Portab system, which relies on a drilled orifice as the location of drug release. Water transport across the semipermeable membrane builds osmotic pressure within the tablet, and the API is leached out at a constant rate through the orifice.

METHODS & MATERIALS

Both formulations consisted of no more than five excipients in the tablet core followed by the application of a thin film coating.

The release rate was designed to offer the drug out to 12 hours; however, it also can be extended well out to 20+ hours. In addition to being very easy to make/formulate, these tablets employ traditional tableting methods and require no specialized technology. As the trend toward once-daily dosing continues, the need for controlled-release tablets grows. This helps ensure patient compliance with taking medications as well as quality-of-life benefits, and ultimately aids consumer market acceptance.

Ingredients

- Active Pharmaceutical Ingredient (API)
- Emcompress (dibasic calcium phosphate dihydrate, USP), supplied by JRS Pharma Inc.
- Polyox® (polyethylene oxide), (PEO) varied molecular weights
- Kollidon® SR (polyvinylacetate/povidone)
- Pruv® (sodium stearyl fumarate, NF), supplied by JRS Pharma Inc.
- Surelease® Clear, supplied by Colorcon Inc.
- Analytical reagents and chemicals, all reagent grade

Equipment

- Key KG-5 Vertical Shaft High Shear Granulator/Mixer

FIGURE 4

Extended-release 10-mg tablets, from left to right: uncoated core, 3% coated, and 5% coated.



“Sustained-release tablets typically offer dissolution profiles that resemble first-order release kinetics. However, there is a growing need for the development of dosage forms that offer release rates that are zero-order (linear over time) or near zero-order. Tablets with this release rate are desirable for their ability to maintain blood levels throughout a greater time span in an in vivo environment.”

- V-shell Blender
- Manesty Beta-Press
- 5.6-mm standard round concave tooling, 8.6-mm standard round concave tooling
- O'Hara Lab Coater II equipped with 15" perforated pan insert

Preparation of the Core Tablets

Core tablets were prepared from a matrix of API (X), polyethylene oxide (PEO) of varying molecular weight ranges, Kollidon SR, dicalcium phosphate, and sodium stearyl fumarate. The API was pre-blended with dibasic calcium phosphate in a high-speed vertical shaft mixer. The pre-blend was combined and blended with the remaining excipients in a V-shell blender. The final blend was then compressed into tablets at a hardness of ~4-5 kp.

The tablets were coated in a perforated pan coater with a 15-inch pan insert, using an aqueous ethylcellulose dispersion, to a minimal weight gain of 3% to 5%. Dissolution testing was performed on both core tablets and coated tablets using USP Apparatus I (baskets) with standard pH 6.8 phosphate buffer as the dissolution media. Samples were removed at 1-, 3-, 6-, 9- and 12-hour time points after the introduction of the tablets to the media, and were analyzed using reverse-phase HPLC for the concentration of API released.

Tablet Description

Each 1-mg film-coated tablet was 5.6-mm round standard concave in shape, white to off-white in color with a total tablet weight of 78 mg. Shown in Figure 1 are the uncoated core, 3% coated, and 5% coated tablets, respectively.

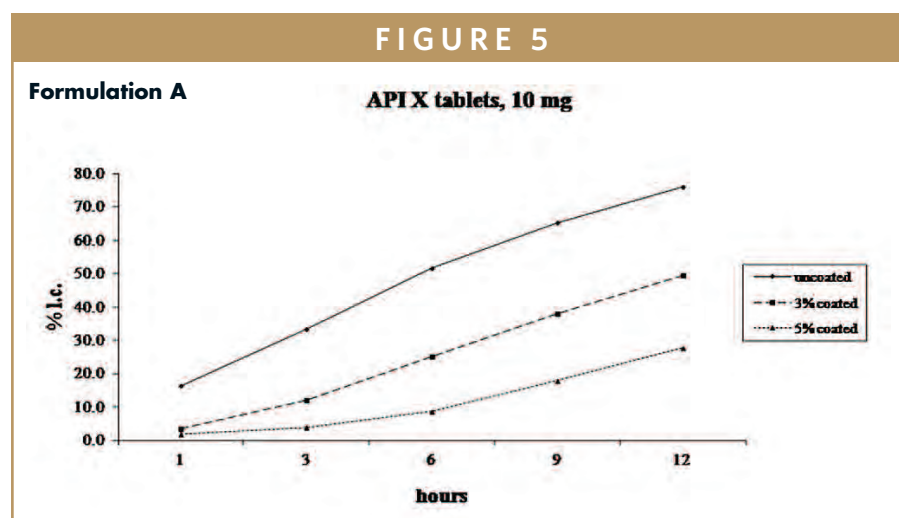
RESULTS

Two formulations were developed that demonstrate zero-order/near zero-order in vitro dissolution release profiles. Figure 2 depicts the in vitro release profile of Formulation A, while Figure 3 shows the in vitro release profile of Formulation B.

Further, proof of the zero-order release profile principle was demonstrated in a higher dosage strength tablet. Figure 5 illustrates the release profile of API X at 10-mg

strength. Each 10-mg film-coated tablet was 8.6-mm round standard concave in shape, white to off-white in color with a total tablet weight of 300 mg (Figure 4). Additionally, it should be noted that at higher tablet weight and strength, the effect of the polymers on the dissolution profile was greater. For example, with the smaller overall tablet, more coating was needed in order to achieve the zero-/near zero-order release profile as well as extended dissolution times. Figure 5 illustrates the release profile of API X at 10-mg strength at three different Surelease coating levels.

It should be noted that zero-order dissolution was not achieved with either formulation without the use of the ethylcellulose coating. Specifically, a core tablet formulation of either PEO or PEO/Kollidon SR sans coating was not able to provide a zero-order dissolution rate of drug.



DISCUSSION & SUMMARY

Two formulations were developed that demonstrate zero-order/near zero-order in vitro dissolution release profile. Both formulations consist of no more than five excipients in the tablet core followed by the application of a thin film coating of no more than 5% weight gain. Each formulation contains the highly soluble API at a concentration less than 2%, a tablet lubricant at concentration of 1%, and the bulk tablet filler at a concentration of less than 58%.

Formulation A was a combination of two molecular weights of PEO, formulated in a specific ratio determined to be most beneficial for the release of API. Formulation B was a combination of one grade of PEO and Kollidon SR. When in contact with water, PEO hydrates rapidly and forms a gelatinous barrier layer around the wetted tablet. Drug release occurs by diffusion of the API through the gel layer and/or by gradual erosion of the gel, exposing fresh surfaces containing drug to the dissolution medium. Diffusion is the dominant mechanism controlling the release of water-soluble actives, and erosion of the matrix is the dominant mechanism controlling the release of water-insoluble actives. Typically, however, drug release occurs by a combination of these two mechanisms. Kollidon SR is primarily hydrophobic and exhibits diffusional-based drug release when used with the PEO system. The coating layer is pH independent, thus eliminating the need for specialized coating development. The release rate was designed to offer API X out to 12 hours; however, it also can be extended well out to 20+ hours. These tablets are very easy to manufacture and formulate,

employ traditional tableting methods, and require no specialized technology.

Sustained-release tablets typically offer dissolution profiles that resemble first-order release kinetics. However, there is a growing need for the development of dosage forms that offer release rates that are zero-order (linear over time) or near zero-order. Tablets with this release rate are desirable for their ability to maintain blood levels throughout a greater time span in an in vivo environment.

Currently, there are several marketed products that offer zero-order release rates. These products are available in the form of patented devices or a result of bilayer coated tablets or use physical means of controlling the release rate, such as osmosis or laser-drilled holes. This new technology offers development partners an option that is much less expensive and easier to work with than current technologies.

As the trend toward once-daily dosing continues, the need for controlled-release tablets grows. Smaller dosage units combined with simpler dosing regimens help ensure patient compliance of taking medications and, ultimately, consumer market acceptance. ♦

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BIOGRAPHY



Dr. Thomas B. "Brad" Gold serves as Vice President of Pharmaceutical Development at Metrics Contract Services, where he is responsible for fast-track development, clinical batch manufacture, scale-up, and commercial validation of solid oral dosage forms. A contract pharmaceutical industry veteran of 20 years, Dr. Gold recently was awarded a US patent for a zero-order release kinetics coated tablet, which provides osmotic-like delivery benefits without the accompanying manufacturing challenges. Prior to joining Metrics, he held scientific roles at DSM as a group leader and Banner Life Sciences as scientist and pilot plant manager. At the latter organization, he led the start up of a business unit focused on early phase development and clinical supplies manufacture of soft elastic gelatin capsules. Dr. Gold earned his PhD in Pharmaceutics from the University of Kentucky, from which he also earned his MSc in Chemistry. One area of his expertise is the prediction of crosslinking and drug dissolution rates using near-infrared spectrophotometry.



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ORODISPERISBLE TABLETS

Advanced Drug Delivery for Repositioning Promethazine for Improved Application & Patient Outcomes

By: Srinivas Tipparaju, PhD, Anastasia Groshev, Danielle Dantuma, Brian McMillan, MS, Todd Daviau, PhD, Matthew MacPherson, Yashwant V. Pathak, PhD, and Vijaykumar B. Sutariya, PhD

INTRODUCTION

Promethazine is a derivative of phenothiazine that blocks histamine H1 receptors.¹ It is commonly used to treat a variety of allergies and allergic reactions.² This medicine is also used to control dizziness, motion sickness, nausea, and vomiting.³⁻⁵ The dosage of promethazine comes in three forms: syrup, tablet, or elixir. Usually, 25 mg of promethazine is taken orally every 4 to 6 hours when used to treat nausea and vomiting.² The delivery of promethazine via digestion can be problematic for someone who has undergone chemotherapy, anesthesia, or surgery due to nausea and emesis. Therefore, it is common for nauseated patients to take promethazine via direct intravenous injection or suppository. These inconvenient delivery methods can be avoided by the production of quick-release, orodispersible promethazine tablets.

Drug delivery by absorption through oral mucosa offers advantages such as direct absorption into the systemic circulation, thus avoiding presystemic elimination via the gastrointestinal tract.⁶ The sublingual mucosa is relatively permeable due to its thin membrane and large veins, allowing quick absorption and bioavailability of drugs due to high blood flow. However, sublingual delivery is not appropriate for sustained delivery formulations.⁷ When delivering orodispersible promethazine tablets, the sublingual mucosa is a

well-suited area for fast release, bringing rapid bioavailability of the drug.⁸⁻¹¹

To overcome the aforementioned delivery challenges, a formulation of orodispersible tablets (ODT) at three different compression settings (low, medium, and high) have been designed and characterized for friability, hardness, wetting time, disintegration, and in vitro dissolution. In order to determine the effective formulation and compression setting for manufacturing of rapid release of ODT promethazine tablets, these parameters were statistically analysed.

MATERIALS

Promethazine and crossprovidone were obtained from Spectrum Chemical Manufacturing Corporation, USA, and ISP Technologies, USA, respectively. Lactose monohydrate (316 Fast Flo) was provided by Foremost Farms, USA. Mannitol (Pearlitol) 300DC was provided by Roquette Corporate, USA. Camphor was obtained from Acros Organics, USA. Sodium Stearyl Fumarate, was purchased from JRS Pharma, Germany.

METHODS

Formulation Study Design

A simplex lattice design was used in order to develop response surface and contour plots.¹² The amount of lactose (A), camphor (B), and mannitol (C) were selected as the independent variables. The three variables were tested at three different levels - low, medium, and high compression settings. Disintegration time (Y1), percent release at 30 seconds (Y2), and percent release at 1 minute (Y3) were all used as dependent variables.

Preparation of Tablets

Tablets were made using a direct blend and compression method with ¼-inch standard concave tooling. For each formulation, the tablets were made using three different compression forces - low, medium, and high of ~5 kN, ~10 kN, and ~20 kN, respectively. The batches were then characterized, according to USP standards for variability of the tablet dimensions and weight, friability, hardness, disintegration, and dissolution times.^{13,14}

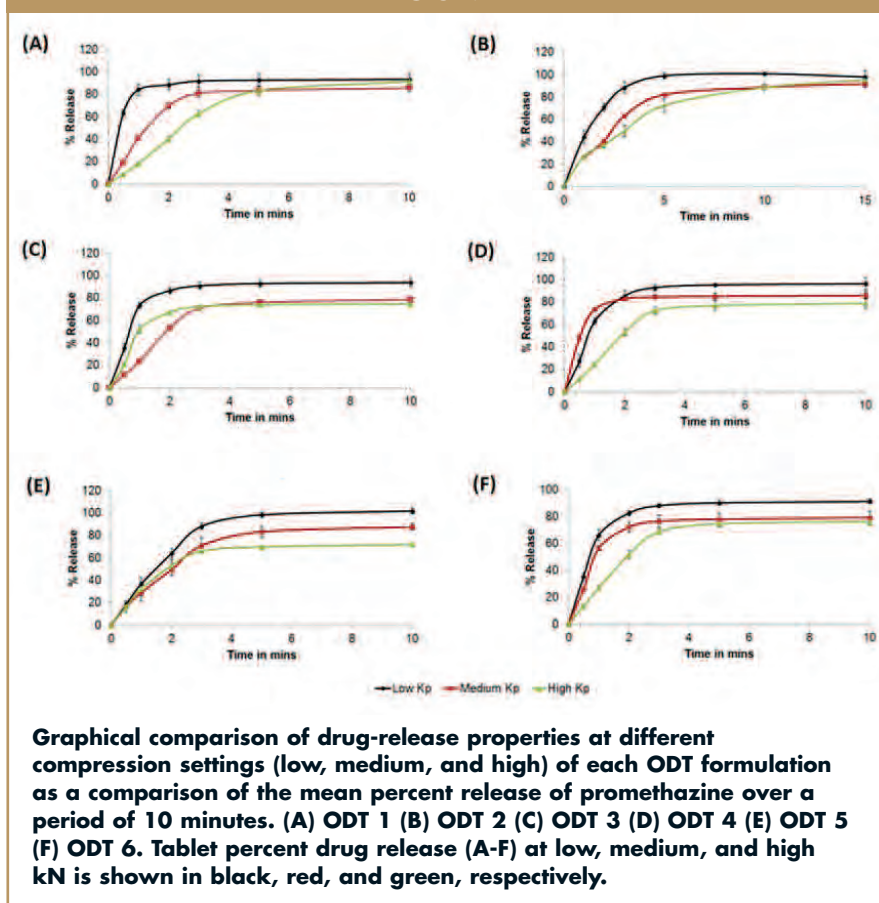
Friability

Friability was tested by weighing each tablet, then setting the Friability Tester Model FTV-2 (Dr. Schleuniger Pharmatron, Switzerland) at 50 revolutions per minute for 1 minute. The largest piece of the remaining tablet was weighed to determine percent loss.

Hardness

Each tablet was aligned in the center of the VK 200 Tablet Hardness Tester (Varian, USA), and the hardness was recorded in kiloponds (kp).

FIGURE 1



Wetting Time

Wetting time was studied using a published method.¹⁵ In brief, a crude filter paper of 10-cm diameter was placed on the bottom of a 10-cm diameter Petri dish, and 10 mL of water containing methylene blue was added. Each tablet was carefully placed in the petri dish, and the wetting time was recorded when the water had reached the upper surface of the tablet.

Disintegration

Disintegration time was measured in sink conditions using de-ionized water in DT2-IS Disintegration Tester (Dr. Schleuniger Pharmatron, Switzerland). When all the granules passed through the basket, the disintegration time (seconds) was recorded.

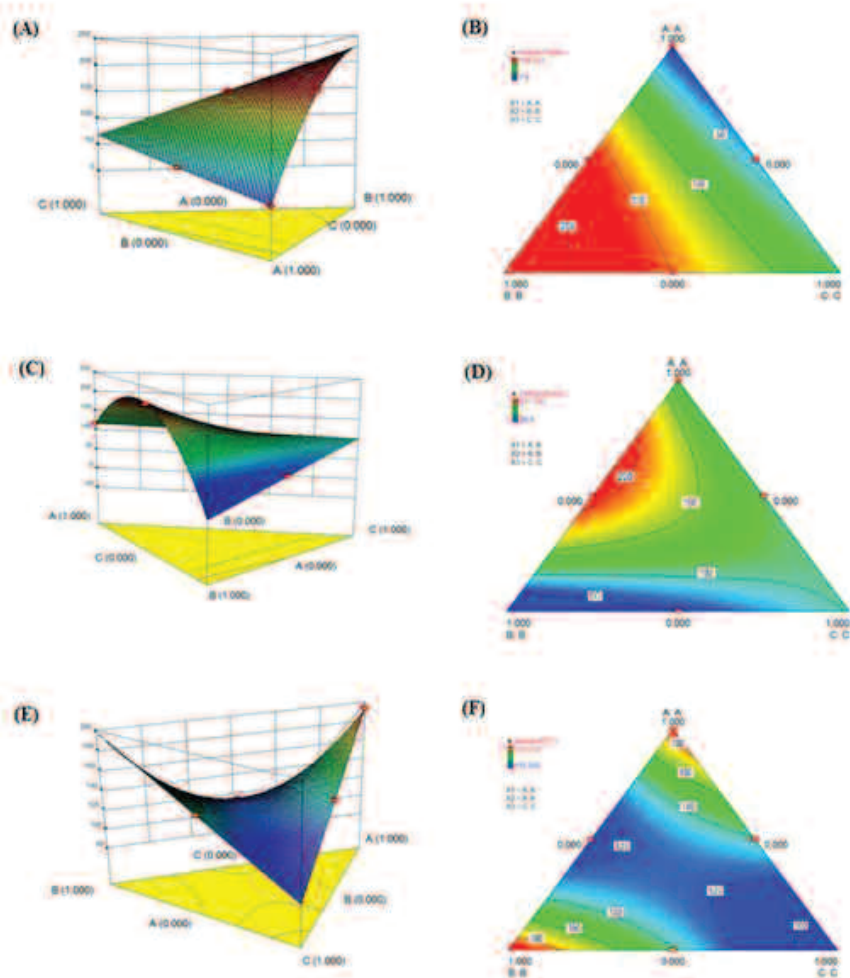
Dissolution

Release of the drug was studied for each batch using Vision Classic 6 (Hanson, USA) USP Dissolution Apparatus II in 900 mL of phosphate buffer release medium pH 6.8 at $37 \pm 0.5^\circ\text{C}$ with paddle speed at 100 rpm.¹⁶ 3-mL samples were collected at predetermined time points (0, 0.5, 1.0, 2.0, 3.0, 5.0, and 10.0 mins) and replaced with 3 mL of medium. The sample was filtered using a coarse filter paper to remove any particulates, cooled at room temperature, and promethazine content determined by absorbance at 253 nm.

Statistical Analysis

Simplex lattice matrix was utilized for analysis of three formulation variables at three levels and their effect on

FIGURE 2



Response surface plots (A, C, E) and contour plots (B, D, F) for disintegration time (secs) of low kN (A, B), medium kN (C, D), and high kN (E, F) are shown, where the increasing data values are represented as: blue, light blue, green, yellow, orange, then red (as the highest value).

RESULTS

dependant variables. All data was obtained as a mean of at least three experiments \pm standard error. The differences in effect on dependant variables of the formulations were studied by two-way ANOVA using DesignExpert 8.0 software to obtain regression fit and surface response graph. 5% significance level (p value ≤ 0.05) was utilized for all statistical analyses.

In order to understand the effect of excipients on the properties of the tablets, six various formulations were designed for testing tablets containing various amounts of lactose, camphor, and mannitol. The effect of the formulation composition has been studied by assessment of physical parameters of the tablets - friability, hardness, wetting time, and disintegration time.

All tablets demonstrated friability of less than 1% loss and are in accordance with USP regulations of ODT tablets, and

therefore, can endure shipping and handling without breaking.¹⁷

The hardness of the formulations at low, medium, and high compression settings were in the range of 3.03 ± 0.19 to 4.17 ± 0.03 (kP), 4.03 ± 0.17 to 6.27 ± 0.13 (kP), and 4.73 ± 0.23 to 8.10 ± 0.5 (kP), respectively. The hardness for each ODT formulation increased with increasing compression setting. However, ODT 2 showed only a slight difference between medium (5.53 ± 0.15 kP) and high (5.53 ± 0.27 kP) compression tablets. The steepest increase in hardness was displayed with ODT 1, and the most gradual increase was seen with ODT 4.

Tablets at low, medium, and high compression were tested and found to have wetting times in the range of 9.53 ± 0.99 to 49.30 ± 24.05 (secs), 9.93 ± 2.02 to 49.40 ± 6.78 (secs), and 26.30 ± 3.01 to 41.40 ± 9.75 (secs), respectively; disintegration times in the range of 8 ± 0 to 163.67 ± 16.13 (secs), 18.67 ± 3.67 to 198.33 ± 13.64 (secs), and 95.33 ± 2.91 to 303.33 ± 29.67 (secs), respectively. Dissolution times varied with compression setting and formulation (Figure 1), but ODT1 demonstrated the fastest release at the low compression setting. Overall, all tablets resulted in rapid disintegration, making them suitable for consideration for orodispersible delivery.

In order to systematically analyze the

“In order to understand the effect of excipients on the properties of the tablets, six various formulations were designed for testing tablets containing various amounts of lactose, camphor, and mannitol. The effect of the formulation composition has been studied by assessment of physical parameters of the tablets - friability, hardness, wetting time, and disintegration time.”

effect of independent variables (lactose, camphor, and mannitol) on tablet properties, a simplex lattice matrix was used. The coded values (A, B, and C represent lactose, camphor, and mannitol, respectively) were used in each design. Each design was separately imputed into the SAS to analyze the effect of lactose, camphor, and mannitol on disintegration time (Figure 2), drug release at 30 seconds (Figure 3), and drug release at 1 minute.

To ensure drug is successfully delivered via orodispersible tablet, rapid disintegration is essential. Equations 1-3 demonstrate the importance of camphor (B) in rapid dissolution that can be described by a negative coefficient effectively decreasing the time for the tablet to disintegrate (-33854.56, -11324.53, +11267.94 for low, medium, and high kN, respectively). The effect of camphor decreases with compression as evidenced by a more positive coefficient for disintegration time equations for low, medium, and high kN (Equations 1-3).

Lactose (A) increased disintegration time of the tablets, and this effect is more pronounced with increased compression setting as the coefficients were +7.50, +118.83, and +193.33 for low, medium, and high kN, respectively. Mannitol had a negative effect on disintegration time at low kN, resulting in an increase of disintegration time. However, at high kN, mannitol had a positive effect on disintegration with +34153.56, +11425.53, and -10985.27 constants at low, medium, and high kN, respectively.

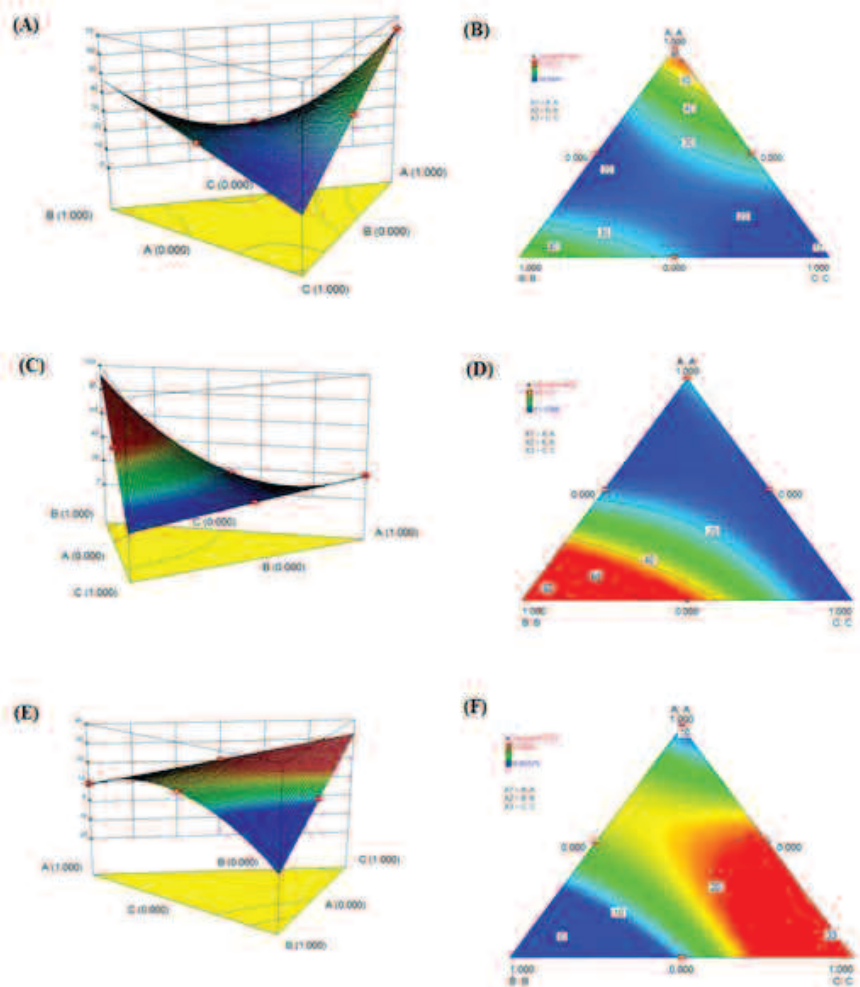
Equations 1-3: Disintegration Time

1. Low kN: $Y1 = + 7.50A - 33854.56B + 34153.56C + 68367.45AB - 68170.78AC$
2. Medium kN: $Y1 = + 118.83A - 11324.53B + 11425.53C + 23256.74AB - 22647.40AC$

3. High kN: $Y1 = + 193.33A - 11267.94B + 10985.27C - 22461AB + 22139.21AC$

The effect of the independent variables A, B, C (lactose, camphor, mannitol) on drug release were in line with disintegration time. In this study, percent release of promethazine at 30-seconds and 60-seconds time points were considered (Equations 4-9). Lactose had a positive effect on drug release regardless of the compression setting (low, med, and high kN) with coefficients +63.43, +19.47, +8.96 (30 secs, Equations 4-6) and +84.21, +41.17, +18.41 (60 secs, Equations 7-9). This effect appears to decrease with increase in compression. Camphor (independent variable B) positively affected the release with increasingly negative impact with increase in compression - coefficients of +7418.57, +3173.61, -2825.64 (30 secs), and +7706.38, +12953, -8542.79 (60 secs) for low, medium, and high kN, respectively (Equation 4-9).

FIGURE 3



Response surface plots (A, C, E) and contour plots (B, D, F) for percent release at 30 seconds of low kN (A, B), medium kN (C, D), and high kN (E, F) are shown, where the increasing data values are represented as: blue, light blue, green, yellow, orange, then red (as the highest value).

Mannitol (independent variable C) had a negative effect on drug release, which became less pronounced, and even positive at higher compression with coefficients of -7363.42, -3077.26, +2848.08 (30 secs) and -7580.50, -12806.50, +8591.98 (60 secs) for low, medium, and high kN. In other words, mannitol demonstrates more of a binding property with lower compression and is more contributive to disintegration at higher kN.

Equations 4-6: Percent Release at 30 Seconds

4. Low kN: $Y_2 = +63.43A + 7418.57B - 7363.42C - 14889.68AB + 14742.14AC$
5. Medium kN: $Y_2 = +19.47A + 3173.61B - 3077.26C - 6320.46AB + 6161.74AC$
6. High kN: $Y_2 = +8.96A - 2825.64B + 2848.08C + 5699.20AB - 5630.53AC$

Equations 7-8: Percent Release at 60 Seconds

7. Low kN: $Y_3 = +84.21A + 7706.38B - 7580.50C - 15433.93AB + 15286.10AC$
8. Medium kN: $Y_3 = +41.17A + 12953.61B - 12806.50C - 25873.03AB + 25264.39AC$
9. High kN: $Y_3 = +18.41A - 8542.78B + 8591.98C + 17177.87AB - 17012$

The effect of combining all of the formulation components were computed, and the data for ODT 1 shows highest rapid disintegration with highest percentage of drug release at 30sec and 60sec. Interestingly, compression of the tablet also plays role, where ODT4 showed the shortest disintegration time with highest percentage of drug release as compared to other formulations at medium compression setting. At the highest compression settings, ODT 5 had the most rapid disintegration time and ODT 3 showed the most rapid release. This may be due to increased formation of tight granules in the tablet at high compression, resulting in prolonged and more variable release.

DISCUSSION

The optimal characteristics of fast-release, orodispersible promethazine tablets in this study are described as: weight, diameter, and thickness and were within USP range below 5% RSD with appropriate tablet friability of less than

1% loss for all of the formulations. With hardness ranging from 4 to 5 kP, the tablets are expected to withstand the normal forces experienced during handling and transport. Short wetting and disintegration times, and at least 90% drug release within 5 minutes to allow fast disintegration in the mouth, promote adequate release of promethazine and time for absorption through the buccal mucosa. Disintegration time for the medium kN tablets was 4 to 18 seconds and higher for batches with higher punching pressure ranging between 1 to 4 minutes. The wetting time of the low and medium compression tablets show a trend in which the concentration of camphor has a positive impact, decreasing wetting time, whereas the concentration of mannitol has a negative impact on wetting time.

The response surface and contour plots for disintegration time and drug release demonstrate overall trends with respect to the independent variables. With a pronounced peak at independent variable B, camphor has a negative impact on the disintegration time of low, medium, and high kN tablets (Figure 2). The response surface plot for medium compression tablets (Figure 2C) has a saddle configuration in which mannitol has a positive impact on disintegration time as the concentration of camphor has the most positive impact on disintegration time, and the highest point is where the concentration of variable C (mannitol) is the lowest (Figure 2A & B). The response surface plot for high kN tablets shows a deep valley in which the lowest points are at the highest and at the lowest concentrations of mannitol, and the highest points are at the highest

concentrations of lactose and camphor. This shows that at a high compression setting, the concentration of lactose and camphor both have a negative impact on disintegration time (Figure 2).

Considering the percent drug release at 30 seconds, mannitol has a negative impact on percent release of low compression tablets. In addition, both variable A (lactose) and variable B (camphor) have a positive impact on percent release, allowing more of the active ingredient to be released at 30 seconds; however, lactose shows the most positive impact. This analysis can be seen in Figure 3A & B. At a medium compression setting, camphor has a substantial positive impact on percent release at 30 seconds, shown by a peak in the response surface plot (Figure 3C). Also, mannitol has a negative impact on percent release of medium kN tablets, seen as the lowest point in Figure 3C. At high compression setting, camphor becomes less important for rapid drug release due to impact drug release, whereas mannitol has a positive impact on percent release at 30 seconds. This is represented in Figure 3E & F. Drug release at 60 seconds shows identical trends at the distinct compression settings as the percent release at 30.

In this study, the formulations for delivery of promethazine have been successfully prepared and characterized. The importance of the punching pressure during the preparation process is considered as the contribution of the independent variables to the tablet properties may vary. Out of the six formulations considered in this study, ODT 4, made with a high punching pressure, is the most suitable candidate for orodispersible promethazine delivery

with hardness of 4.73 ± 0.23 and friability of $0.39 \pm 0.14\%$ - both parameters are compliant with USP regulations, and a wetting time of 20.37 ± 4.97 seconds, allowing quick disintegration in the mouth. Most importantly, in vitro dissolution testing demonstrated rapid and sustained drug release of 90% over a 3-minute timespan.

CONFLICT OF INTEREST

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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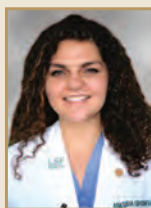
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BIOGRAPHIES



Dr. Srinivas M. Tipparaju is faculty at University of South Florida College of Pharmacy working as Assistant Professor in the area of cardiovascular diseases, drug development, and innovation. Currently, he is focused on understanding the mechanisms for diabetes, arrhythmias, and heart failure. He directs research efforts and established a research team and funding for projects including drug development and formulation design using innovative technologies.



Anastasia Groshev is currently a medical doctorate candidate at the University of South Florida Morsani College of Medicine. Her work in research focuses on development of drug delivery forms for penetration of blood barriers and sustained release for treatment of brain tumors, Alzheimer's disease, and glaucoma.



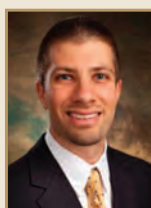
Danielle Dantuma is a Research Assistant at the University of South Florida College of Pharmacy. She is Operations Coordinator at the BRIDGE Pharmacy Clinic, Secretary of International Health Service Collaborative, and CIC Program Coordinator of the Student National Pharmaceutical Association chapter at USF.



Brian McMillan is the Vice President of Product Development and Co-founder of CoreRx, Inc. in Clearwater FL, and Adjunct Assistant Professor of Pharmacy at The University of South Florida.



Dr. Todd R. Daviau is the Founder, President, and CEO of CoreRx, Inc., bringing 27+ years of pharmaceutical experience and knowledge to the project. Prior to CoreRx, he served as VP of the Analytical and Pre-Formulation Laboratory for MDS Pharma Services and Strategic Analytical Team member with Guilford Pharmaceuticals, where he was involved in the development of Natrecor and Gliadel.



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ANALYTICAL SUPPORT SERVICES



ABC provides IND-enabling, registration, and post-commercialization support for the development, quality control, and lifecycle management of innovative therapies and generic medicines. Our personalized, results-based approach to development strategy is backed by

decades of experience delivering GLP- and CGMP-compliant analytical testing services across all types of APIs and formulations. Through development know-how, cross-disciplinary technical expertise, and applied experience with evolving global regulatory frameworks, we help efficiently advance and manage programs for large and small molecule drugs, medical devices, and combination products. Our mission is to become a trusted extension of our client's product development teams, helping them meet the global demand for safer, more effective products. Our approach to doing business promotes relationships beyond a simple transaction. This, in turn, improves decision-making, expedites development, and reduces risk. In other words, "better insight, better outcomes." For more information, visit ABC Laboratories at www.abclabs.com.

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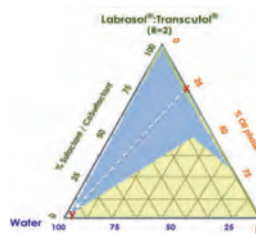
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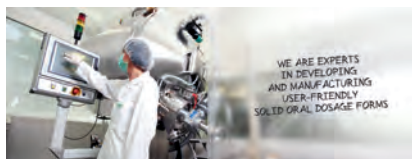
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Lauroglycol™ +75% mixture of Labrasol®: Transcutol® (2:1). Continuously adding water to formulation "X", we would be following the dilution path along the white arrow. In other words, the formulation "X" may be diluted with no risk of phase separation as it will remain a nano-dispersion even at a very diluted state. Designing SMEDDS and Microemulsions binary and ternary diagramming is a Gattefossé expertise. For more information, please contact jmusakhanian@gattefosssecorp.com

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The company's investment in leading liquid chromatography technologies will provide additional capability in services clients are seeking. This equipment acquisition is the latest in a series of investments Metrics has been making in its physical facilities and equipment. Metrics has long appreciated the importance of analytical support within the context of pharmaceutical development and manufacturing. Learn more about our new equipment at www.MetricsInc.com.

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biotechnology & generics industries. Nemera will exhibit its products at Booth No. 4C40 at CPhI, but also at the Innovation Gallery with 2 displays: (1) The preservative-free ophthalmic multidose Novelia® with bottelpack® BFS technology, and (2) Advancia®: A NEW response to demanding regulations for nasal sprays featuring SP270+: The cost-effective pump for pharmaceutical sprays, and CRC: NEW innovative concepts for nasal and dermal pumps. Nemera will also speak at the Exhibitor Showcase on October 13 (3 PM): Preservative-free ophthalmic multidose Novelia® with bottelpack® BFS technology and October 14 (11 AM): Safe'n'Sound®, the safety device solution for small molecules and biologics. For more information, visit Nemera at www.nemera.net.

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in Europe, with strong experience in the manufacture of products as stick-packs and effervescent tablets, as well as in pharmaceutical development. Created in 1993 with the purchase of a manufacturing plant from the Sanofi group, UNITHER developed in sterile unit dose manufacture. UNITHER acquired a second manufacturing site in 2002 for its traditional activity of sterile unit dose manufacture, and then diversified its activity by entering the areas of effervescent products and pharmaceutical development on taking over the Créapharm group in 2005. In 2009, UNITHER purchased the Colomiers site from Sanofi-Aventis, gaining a competitive platform for the production of liquid stick packs. For more information, visit Unither at www.unither-pharma.com.

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Drug Development EXECUTIVE



J. David Enloe Jr.
President & CEO
Althea



ALTHEA: Giving Biopharmaceutical Companies the Power To Make

The biopharmaceutical industry has the power to make a difference, by creating new therapeutics that are improving the quality of life and inspiring a healthier world. To do this, these companies need a manufacturing partner who embraces their every challenge as its own, who shares the unwavering tenacity and dedication and can support them through the drug approval process. That's The Power To Make. Althea is a fully integrated contract development and manufacturing organization committed to the success of its clients and for process development, drug substance manufacturing, and drug product manufacturing. With the capacity to support early stage clinical requirements through commercial manufacturing, Althea is giving Biopharmaceutical companies The Power To Make. *Drug Development & Delivery* recently caught up with David Enloe, Althea's President and CEO, to discuss his company's business strategy, why companies choose Althea, trends in the CMO industry, and how the company is growing since the acquisition of Ajinomoto.

Q: Can you provide our readers some history of the company and an overview of your business today?

A: Althea was founded in 1998 with an initial focus on developing plasmid kits and gene quantification assays. In 2000, the company expanded into microbial biologics manufacturing and eventually began offering fill and finish manufacturing. As Althea added analytical development services, the company became a fully integrated CMO. In 2013, Althea was acquired by Ajinomoto, a large Japanese company with more than 100 years of providing critical ingredients to the food industry, but with a growing life sciences portfolio of companies.

To date, Althea has partnered with hundreds of clients ranging from small to large biopharmaceutical companies, government agencies, and universities on both a local and international scale. We have worked on projects varying from the production of recombinant proteins, plasmid DNAs, vaccines, antibody fragments, to the fill and finish of injectable peptides, monoclonal antibodies, oligonucleotides, and small molecules. The number of lots of finished cGMP product that have been filled in our facility is in the thousands. Critical to all of this success and growth has always been Althea's strong regulatory track record. We take great pride in the relationships we have established with multiple regulatory agencies, as well as in our numerous successful inspections which support advancing our clients' products.



Althea is a leading expert in executing drug formulation and aseptic fill finish, offering a broad range of sterile dosage forms, including prefilled syringes, liquid vials, and lyophilized vials. We have five Formulation Suites and five Independent Fill & Finish Suites with three automated aseptic filling lines. In addition, Althea offers a proprietary formulation technology platform, Crystalomics®, which offers a solution for large molecule products that must be delivered at high concentrations or as sustained-release formulations. We also have an innovative and proven recombinant protein expression technology called Corynex™, which can deliver simplified production with better results. In a single location, we have the capacity to support early stage clinical requirements through commercial manufacturing.

Q: What does Althea offer when it comes to contract manufacturing services?

A: Althea offers cGMP production of microbial-derived recombinant proteins and plasmid DNA. In conjunction with these manufacturing operations, we offer comprehensive development services, including upstream and downstream process development, analytical development, lyophilization cycle, complex formulation, product release, and ICH-compliant stability testing.

Q: Why do companies choose Althea?

A: Althea offers a broad range of development and manufacturing services for biotherapeutic drug development. We are often told that clients come to us because of our responsiveness, technical expertise, and our commitment to always understanding our clients' true needs. We completely align ourselves with our clients' clinical programs, understanding the time-sensitive nature of their drug programs. Taking the time to understand our clients' pain points and challenges shows the dedication and support we provide to

“To date, Althea has partnered with hundreds of clients ranging from small to large biopharmaceutical companies, government agencies, and universities on both a local and international scale. We have worked on projects varying from the production of recombinant proteins, plasmid DNAs, vaccines, antibody fragments, to the fill and finish of injectable peptides, monoclonal antibodies, oligonucleotides, and small molecules.”

them during their critical path through the clinic and into the marketplace.

We are also often told that we “get it,” we understand what our clients are going through, the pressures they are feeling, etc. At Althea, each client relationship is a partnership, and we are “in it together for the long haul.” From the time we embark with a client on their current phase of development and as they move through the drug approval process, we are right there with them every step of the way. The fact we are willing to get that detailed and that involved really lends itself to a different intensity with respect to our flexibility and our commitment, and I believe that is a real asset. We are often seen as an extension of our clients’ teams. This is one of the things about Althea that I am most proud of.

Q: What trends are you seeing in the CMO industry?

A: A trend that I’ve noticed for the past several years, and something I believe will continue in the future, is that biopharmaceutical companies, regardless of size, are identifying and understanding where their core expertise is and where they are lacking. Often, they are concluding that manufacturing is not within their core competencies, and certainly it is not an area that they wish to invest inside their organizations to expand.

There is great risk involved in carrying the entire amount of manufacturing infrastructure needed to introduce a new drug to the clinic that may not get all the way to a commercial

success. Avoiding the “sticks and bricks” and instead keeping clinical development and other less-costly items in-house, they are coming to companies like ours and relying on our expertise as an extension of their team. We are able to spread out the manufacturing infrastructure costs basis over multiple clients, therefore making it more cost effective to produce their drugs as they proceed through clinical trials toward commercial distribution.

Q: What are the future plans for Althea?

A: Althea’s acquisition by Ajinomoto has led to several meaningful investments in our business, facilities, and overall operations. Recently, Ajinomoto and Althea’s boards of directors have approved the commitment to enter one of the most promising new cancer therapeutic markets, the Antibody Drug Conjugate (ADC) sector. Althea will soon be what we believe to be the only contract manufacturer in the United States to offer antibody drug conjugation services in conjunction with the fill and finish services required to get the product into vials to be used in clinical trials and commercial distribution. This new division of Althea will give us the capabilities to service the emerging biotech and pharma companies and support their needs with developing ADCs for oncology therapeutic drug programs. ♦

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SYRINGE SYSTEM

The Credence Companion Syringe System Delivers on Safety & Usability Using Human Factors Studies

By: John A. Merhige, MEM, and Lisa Caparra, RN

INTRODUCTION

Credence MedSystems' core philosophy of *Innovation Without Change* has produced the Credence Companion lineup of injectable drug delivery products. As discussed in prior articles, *Innovation Without Change* has delivered a platform of high-impact products because it is guided by two voices, the end-user performing the injection and the drug manufacturer. This article focuses on how development of the Companion product line has been driven by these two constituents, the *innovation* driven by the end-users' needs and the *avoidance of change* driven by needs of the drug manufacturer. With Human Factors (HF) analysis driving the Companion's evolution, this article will also discuss the findings of two formative HF studies.

INNOVATION WITHOUT CHANGE & THE COMPANION PLATFORM

Innovation Without Change simplifies the commercialization path for drug manufacturers while introducing critical innovation in the end device. The modular approach gives drug manufacturers the freedom to select existing syringe barrel, stopper, and cap/shield primary package components from preferred vendors, mitigating much of the development, regulatory, and supply chain risk

FIGURE 1



The Companion provides integrated passive needlestick safety and prevents syringe reuse.

associated with combination product development. The Companion needle and plunger rod are incorporated with the syringe barrel, yielding an end device that features passive needlestick safety and syringe disabling technology. Upon completion of the injection, the user receives audible, visual, and tactile cues that the dose has been delivered, and then the needle automatically retracts into the barrel of the syringe, rendering the syringe needle-free and preventing reuse (Figure 1). This shifts the paradigm for conventional drug delivery device development, allowing drug manufacturers to provide their end-users the best safety and usability features that have traditionally been abandoned due to the time, cost, and risk conventionally associated with implementing innovation. Credence has expanded the *Innovation Without Change* concept to a platform of products that includes the Luer Companion, where the user attaches the needle, the Staked

FIGURE 2



Syringe filling is unchanged. The Companion can be delivered in standard pre-sterilized ready-to-fill tubs.

to offer any practical needle length or gauge as a luer or staked needle, while still providing passive needle-retraction safety.

THE INFLUENCE OF THE END-USER & HUMAN FACTORS STUDIES

An early formative HF study demonstrated user dissatisfaction with conventional active-safety devices. OSHA guidelines call for user-cues and passive needlestick safety, where the safety mechanism automatically activates without the need for specific user action.

Companion, where the needle is provided to the user pre-attached, and most recently, the Dual Chamber Reconstitution Safety Syringe.

THE INFLUENCE OF THE DRUG MANUFACTURER

When Credence first introduced the Companion technology, the value of maintaining existing primary package components was immediately understood by our biopharm manufacturing partners, as changing a drug's primary package can require several million dollars and extend up to 3 years of development.¹ They quickly communicated the further importance of avoiding disruption to the fill/finish and secondary manufacturing processes. As a result, the Companion was developed to work seamlessly within existing tubs and to allow syringe filling to occur without modification. Even with the Staked Companion, drug manufacturers will be able to source syringes with pre-attached Companion needles using the supply chain within which they have traditionally operated (Figure 2).

In order to simplify the secondary assembly requirements, Credence advanced the Companion's design to make the finger flange optional. The only required secondary assembly step is the addition of the Companion plunger rod, which is performed using existing equipment and processes. This simplicity of design eliminates the additional equipment needed to mount a finger flange or the external spring-loaded devices common in the market, avoiding the capital expenditure as well as the assembly cost, labor, and time (Figure 3).

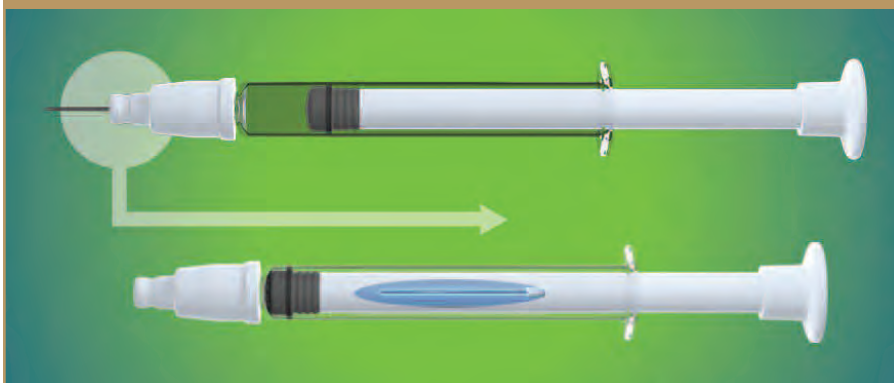
Drug manufacturers further communicated concerns about the interaction between their drug and foreign substances like silicone or adhesive conventionally used to mount staked needles. Both have been shown to cause protein aggregation with sensitive drugs.²⁻⁴ In response, Credence eliminated glue from the Companion lineup, removing any risk of interaction with the drug, and allowing alternate lubrication techniques, such as baked-in siliconization, even in a staked needle presentation. Further, the glue-free needle mount provides Credence the flexibility

FIGURE 3



Only the Companion plunger rod and needle are required, simplifying secondary assembly.

FIGURE 4



The needle automatically retracts into the syringe and plunger rod, allowing safe and compact disposal.

Further, World Health Organization has called for the broad application of “smart” syringes that prevent reuse.⁵ The Companion addresses these needs and more. Rather than simply providing cues of safety activation, the user also receives cues that the dose has been completely delivered, allowing the user to focus on the injection and/or the patient. After delivery of the dose, the needle retracts into the barrel of the syringe and the plunger rod, while the plunger rod stays in the depressed position; this allows for an additional boundary of safety as well as compact disposal (Figure 4).

HF studies delivered another important message: state-of-the-art safety features are critical, but are not enough to deliver on the promise of a best-in-class injection experience. Critical usability design criteria grew out of this feedback, including the ability to perform all syringe operations required for safe and effective drug delivery. The Companion allows unobstructed viewing and inspection of the drug product in the syringe, air bubble purging, aspiration, and reconstitution. These operations are often prevented with conventional safety devices due to premature safety activation caused by plunger rod

manipulation or because the syringe barrel is shielded. Further, the Companion offers an optional finger flange to facilitate comfortable use with multiple hand positions while always keeping hands behind the needle (Figure 5).

Each member of the Companion family has user-driven design features as well as the hallmark elements of providing passive needlestick retraction while employing existing primary package components. **The Staked Companion** offers the obvious advantage of a pre-attached needle, as well as the more subtle advantage of a reduction in the force required to remove

the needle shield. This addresses the

common “recoil effect” that leads to needlesticks when removing shields from conventional staked needles. **The Luer Companion** addresses the risk of poorly attached luer needles that can result in drug leakage, inaccurate dosing, wasted drug product, complaints, and needles left in patients. The Guide-On Needle Cover assures proper needle attachment before allowing the user to remove the cover and attempt the injection. Finally, **The Dual Chamber Reconstitution Safety Syringe** reduces the user steps needed for conventional reconstitution to one simple act of depressing the plunger, but further offers a pre-attached needle and passive needle retraction.

The end-users have guided the Companion’s evolution from the beginning. Seen below are reports on two of the Companion’s Formative Human Factors studies demonstrating what the users have communicated about their needs as well as how they have received the Companion.

FIGURE 5



The optional Flex Finger Flange can provide flexibility in hand positions.

2014 FORMATIVE HUMAN FACTORS STUDY OF THE CREDENCE COMPANION SAFETY SYRINGE

PURPOSE

The primary goal of this formative human factors study was to determine the satisfaction and acceptance level of the core features of the Credence Companion Safety Syringe technology and to assess intuitiveness and ease-of-use.

MATERIALS & METHODS

The registry included 10 nurses, with current experience in pediatrics, critical care, ER, med-surg, OB, and surgery. Participants provided demographic information, evaluated appearance, performed one or more injections, and rated performance of the Credence Companion device. Subjects were given only the instructions to attach the needle to the luer, remove the cap, purge air bubbles, and give the injection. Subjects rated items on a scale of 1 (strongly agree/extremely satisfied) to 5 (strongly disagree/extremely dissatisfied). A score of 1 or 2 was designated as "Acceptance."⁶

RESULTS

Almost half of subjects had experienced an accidental needlestick in their career, and 60% indicated the most undesirable feature of their current devices was the "manual activation" of the safety mechanism. The results of the evaluation showed high acceptance of the Companion's safety and usability features. All subjects determined this device would protect them from needlesticks (Table 1).

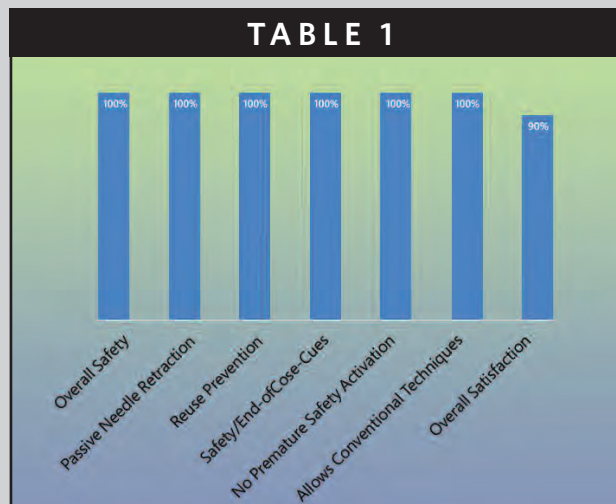
Usability of the Companion was rated very highly; 100% of subjects strongly agreed that the customized needle cover promotes proper needle attachment, there is good visibility of the drug in the syringe barrel, the needle can retract directly from the

patient's skin, and the device will work with any required needle sizes. 90% of test subjects judged that the Companion would not increase the time to perform an injection compared to non-safety devices. 80% were satisfied the Companion allows conventional syringe techniques, such as air bubble purging, aspiration, flexibility to approach the injection site from multiple angles, use of multiple hand grips, and disposal of a used syringe. Subjects also expressed high acceptance of the device's safety. 100% of subjects expressed high acceptance of the safety criteria presented to them, ie, the ease and one-handed activation of the safety mechanism, the ability to keep both hands behind the needle during use, and the clear indicator the safety feature is enabled. 100% of participants also determined the syringe could not be reused following the injection. The human factors tested (nurses working in varied areas with an average of 11.7 years of experience ranging from 1 to 32 years) resulted in 100% of participants stating that IFU device compliance would be achievable with minimal or no training, as device design suggests proper use and the activation of the safety mechanism is intuitive.

100% of subjects were satisfied with the overall safety of the Companion for passive/automatic needle retraction, automatic disabling of the syringe following injection, cues the safety feature is engaged, and confidence that safety activation would not happen prematurely.

CONCLUSION

This study demonstrated a high level of acceptance of the usability and safety features of the Credence Companion Safety Syringe within a cohort of registered nurses. The study additionally indicated that these nurses are not satisfied with their current choices in safety syringes.



Percentage of Subjects Rating a Score of 1 or 2.

CONCLUSION

2015 FORMATIVE HUMAN FACTORS STUDY OF THE CREDENCE COMPANION STAKED NEEDLE SAFETY SYRINGE

PURPOSE

This study evaluated the human factors affecting the ease-of-use and safety of the Credence Companion Staked Needle Syringe. The Credence Staked Companion was evaluated against a comparative device representative of those present in the market today.

MATERIALS & METHODS

This registry included 10 nurses with current experience across pediatrics, critical care, ER, med-surg, OB, surgery, dermatology, and NICU nursing. Each subject first evaluated the Credence Staked Companion independently and then compared it to the comparative device. Three subjects had previously participated in a formative study of the Companion. The comparative product has a plastic housing and spring mounted to the exterior of the syringe, allowing one-handed, passive needle guard activation. At the completion of the injection with the comparative device, the spring releases and extends an external sheath over the needle. A total of 20 injections were performed and evaluated for the Staked Companion and the comparative device. Subjects were given the instructions to remove the needle shield, purge air bubbles, and give the injection until a click is heard. Subjects rated items on a scale of 1 (strongly agree/extremely satisfied) to 5 (strongly disagree/extremely dissatisfied). A score of 1 or 2 was designated as "Acceptance."⁷

RESULTS

Nine out of 10 subjects had experienced one or more accidental needlesticks in their career, and 50% indicated they have a choice of safety syringes used at their hospital. The independent evaluation of the Staked Companion device demonstrated high acceptance by the subjects; 100% of subjects would be satisfied with the choice of the Companion by their employer and indicated the device protects against needlesticks. 90% of subjects also expressed high acceptance of the functionality of the Companion for injection force and one-handed activation of the safety feature, while 100% of subjects expressed high acceptance for automatic disabling of the syringe after injection and facilitation of safe and convenient disposal. The human factors tested (nurses working in different areas of expertise with an average of 21.5 years of experience ranging from 6 to 32 years) resulted in 90% of participants stating that IFU device compliance would be achievable with minimal or no training as the device design suggests proper use and the activation of the safety mechanism is intuitive. 90% of test subjects documented high acceptance for ease-of-use, simplicity of the product, and needle retraction speed/motion. 80% of participants stated the device ensures the entire dose is delivered, and 100% reported the

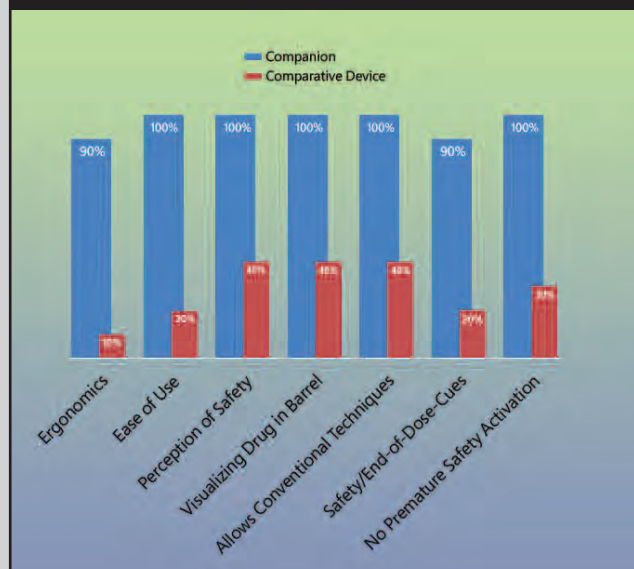
Companion prevents reuse after injection. Overall, the Companion device received high test subject acceptance in all of the tested criteria for appearance, usability, functionality, and safety.

When rated against the comparative device, participants found the Companion to be favorable in all areas of comparison (Table 2). Ease of use and perception of safety resulted in acceptance by 100% of subjects for the Companion in comparison to 40% for the comparative device. The ability to visualize the drug product in the barrel and to perform conventional syringe functions (ie, purging air, aspiration, use of multiple handgrips, etc.) showed the Companion was favorable to the comparative device with 100% to 40% acceptance. The subjects preferred the Companion syringe for the safety engagement cues it provides over the comparative device, 90% to 20%, and for the low risk of premature safety activation, 100% to 30%. The ergonomics of the Companion achieved 90% acceptance as opposed to 10% for the comparative device. Lastly, 90% of subjects rated the overall look of the Companion device acceptable, while only 30% did so for the comparative device.

CONCLUSION

The test subject's acceptance of the Credence Companion Staked Safety Syringe was high, and the Companion was accepted by a higher percentage of nurses than the comparative product in all areas, including ergonomics, safety, and functionality. This study further demonstrated this cohort of registered nurses believe that IFU device compliance with the Credence Companion would be achievable with minimal or no training.

TABLE 2



Device Comparison-Percentage of Subjects Rating a Score of 1 or 2.

BIOGRAPHIES

The Credence Companion Syringe System was born from *Innovation Without Change*, guided by drug manufacturers through collaboration and end-users through Human Factors feedback. Pleasing only the drug manufacturer or the end-user is inadequate; the former can result in a dissatisfied user placed at risk by an unsafe device, while the latter can result in an abandoned technology that never reaches the market. *Innovation Without Change* delivers for both constituents by enabling drug makers to provide their end-users with the safe, effective, and intuitive injection experience they need. Formative Human Factors studies indicate that the Credence Companion effectively fulfills this mission. ♦

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For more information, please visit www.CredenceMed.com or email info@credencemed.com.

This product has not yet been evaluated by FDA.



John A. Merhige, MEM, BE, AB, is Chief Commercial Officer at Credence MedSystems, leading the Company's business development, sales, and marketing strategies. Previously, he was Vice President, Market Development at Sanofi BioSurgery. He joined Sanofi upon its acquisition of Pluromed, which he joined in its early stages and was a member of the executive management team. Previously, he founded Prelude Devices to identify early stage medical device ventures and gained general management and commercial leadership experience at Ford and Avery Dennison. Mr. Merhige graduated from Dartmouth College with a Mechanical Engineering degree and returned to Dartmouth for a Masters in Engineering Management from the Thayer School of Engineering and the Tuck School of Business. He is a member of MassMEDIC, MassBio, PDA and has served on the board of directors of the MedDev Group (MDG).



Lisa Caparra, RN, BA, serves as Director of Regulatory, Clinical, and Quality Assurance at Credence MedSystems, contributing her registered nursing background and 19 years of Class II and III medical device experience to the regulatory compliance and approval of useful, quality-oriented medical devices. Prior to joining Credence MedSystems, she held management roles with multiple start-up medical device manufacturers of various devices, including drug-eluting coronary stents, heart pumps, breast tissue expanders, glaucoma stents, AAA stent grafts, and embolic protection devices. She is experienced in meeting FDA regulations for devices and combination products, as well as ISO standards, MDD, and CDR requirements. Ms. Caparra created and manages the company's effective quality/clinical/regulatory systems, establishing the organization as a compliant medical device manufacturer with regulatory bodies.

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