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Drug Development & Delivery

September 2015 Vol 15 No 7 www.drug-dev.com

21st Century Injection Technologies

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William Hearl, PhD
A Vaccine Breakthrough That Could Change Lives & Enable Vaccine Development Programs

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JUICHI "JIM" TAKEUCHI

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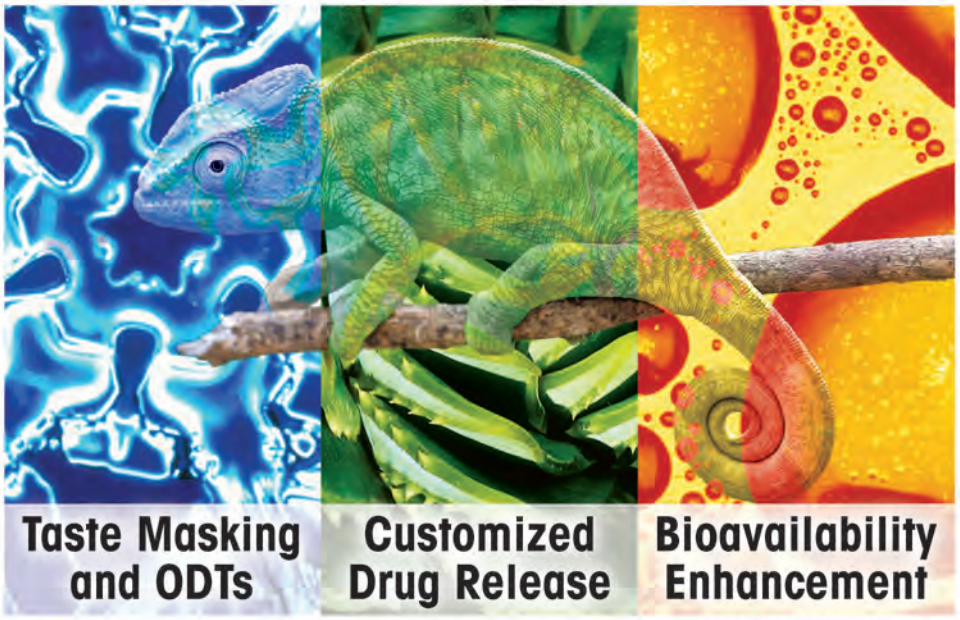

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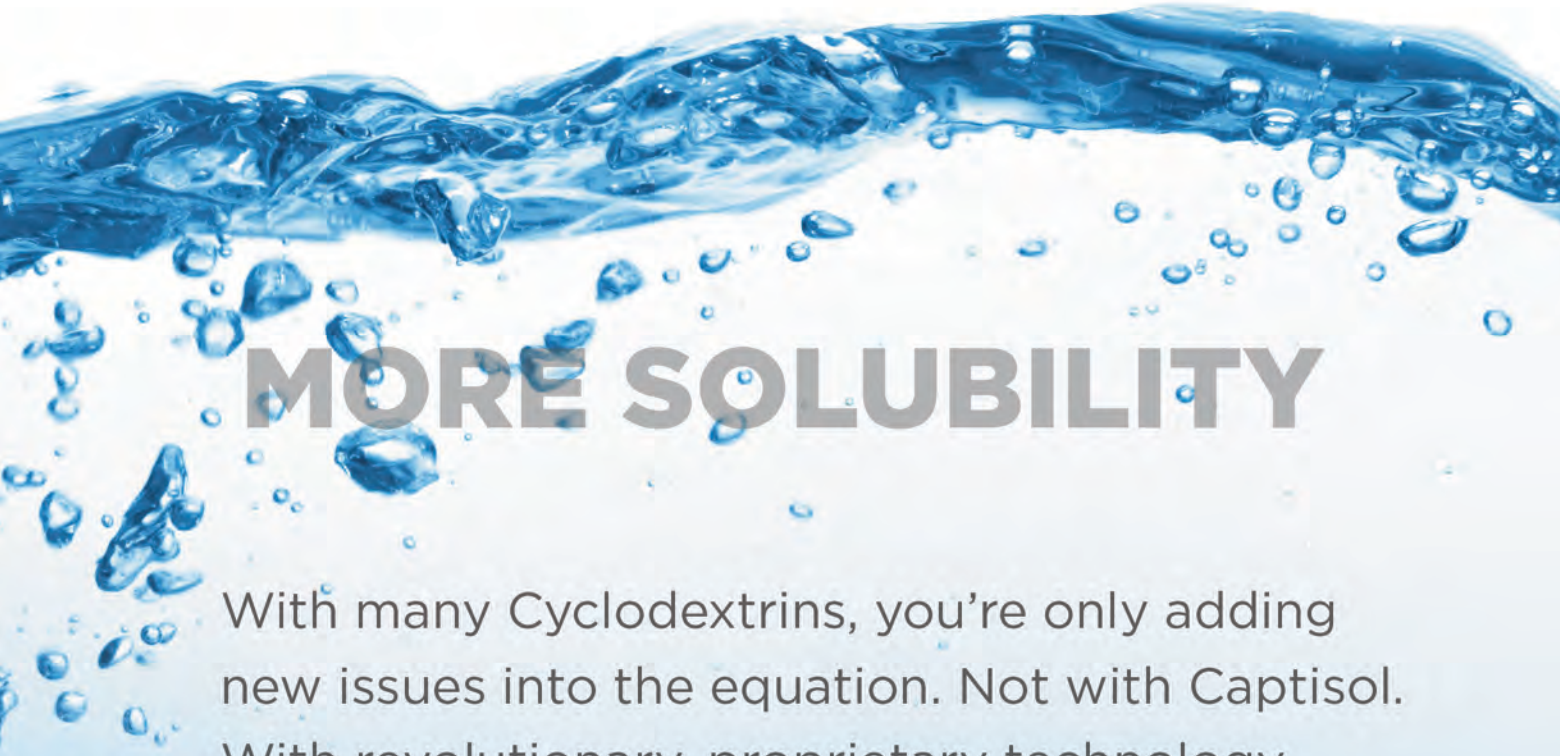

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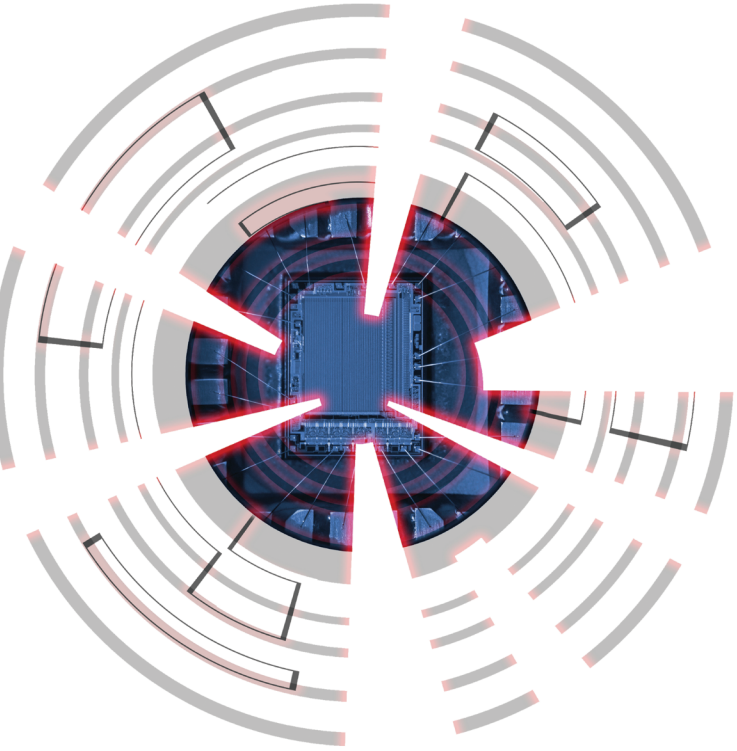

"The integration of Bluetooth LE within injectable drug delivery systems, such as insulin pumps, wearable injectors, and autoinjectors, represents a paradigm shift in medication delivery. For the first time, biopharma companies will be able to work with payers and prescribers to leverage the power of data informatics to improve rates of patient compliance and demonstrate the clear value-based healthcare outcomes associated with their brand of therapy."

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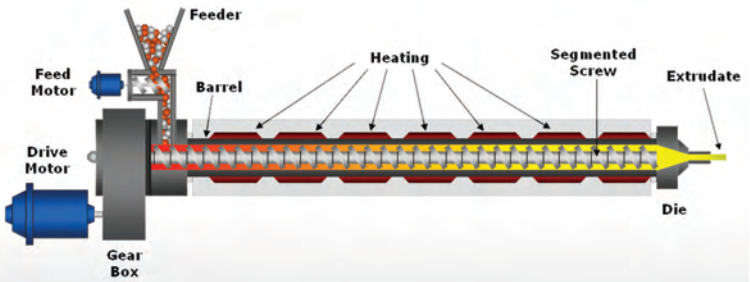

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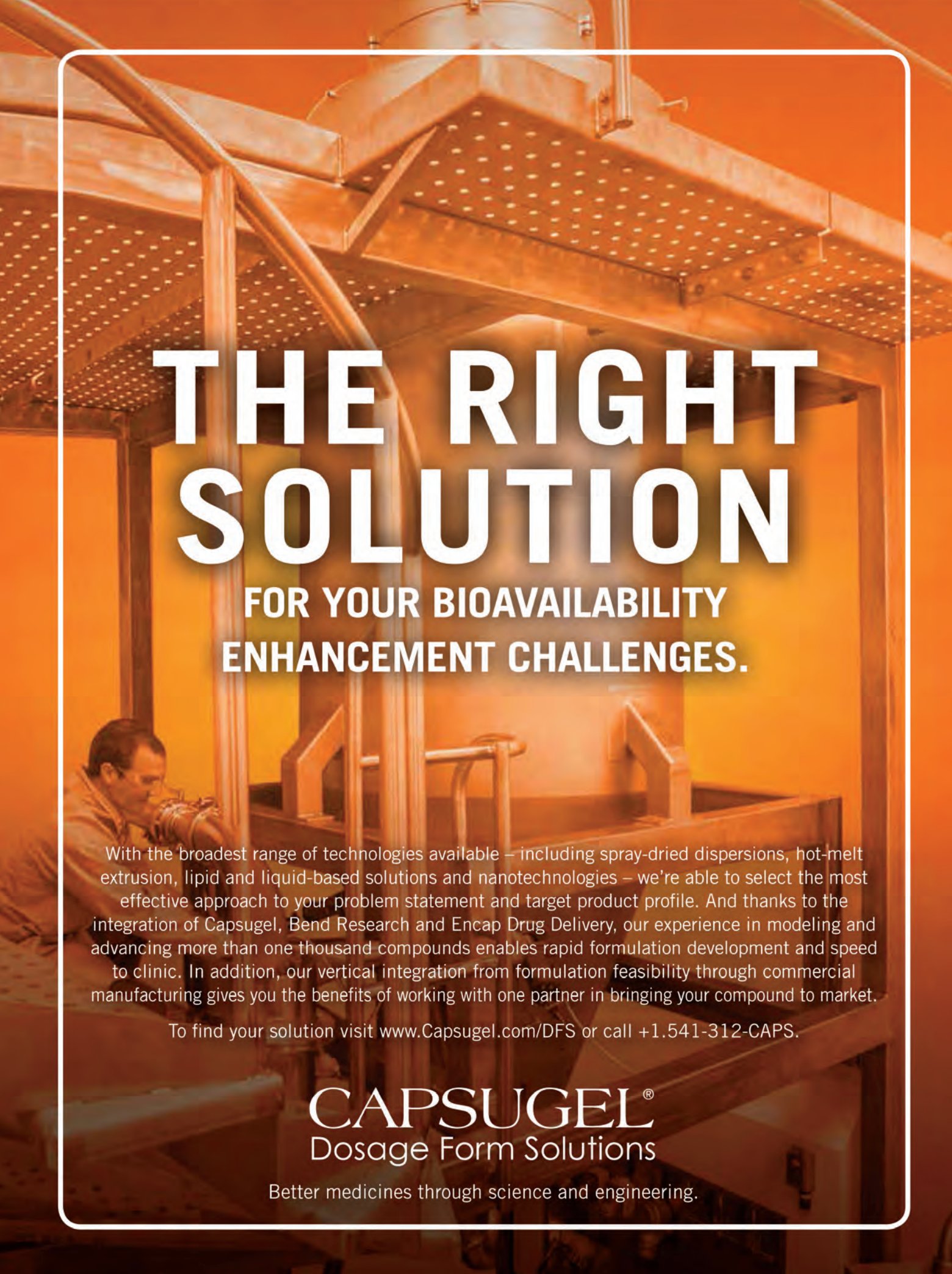
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Charleston Laboratories Announces Completion of Second Phase III Trial

Charleston Laboratories, Inc. recently announced completion of their second Phase III clinical study on CL-108, a novel bi-layered tablet containing 7.5 mg of hydrocodone and 325 mg of acetaminophen with 12.5 mg of immediate-release promethazine.

In this recently completed study, physicians in multiple clinical settings in the US diagnosed patients with flares of osteoarthritis of the knee or hip and monitored their course when they used CL-108.

"Charleston Laboratories, Inc. is announcing the completion of this Phase III open-label safety study because it represents real-life results with clinical relevance for practitioners who care for patients suffering flares of osteoarthritis," said Mr. Paul Bosse, Charleston Laboratories' President and Chief Executive Officer. "Charleston Laboratories takes pride in developing medicines like CL-108 that can have a real impact for patients."

Charleston Laboratories also announced that Dr. Raymond Dionne, Research Professor at the East Carolina University Brody School of Medicine, has been appointed to its Scientific Advisory Board. Prior to his current professorship, Dr. Dionne was a career Scientist at the National Institutes of Health (NIH), one of the premier research institutions in the world.

"It is an honor to have Dr. Dionne on our Scientific Advisory Board," said Dr. Bernard Schachtel, Chief Scientific Officer at Charleston Laboratories. "He is one of the true scientists in the study of pain and its treatment. He brings a wealth of experience and insight to Charleston Laboratories' different analgesic research programs."

"As presented at the Annual Meetings of the American Pain Society," Dr. Dionne said "the results of Charleston's first Phase III trial on CL-108 were impressive, demonstrating significant pain relief and reduction of opioid-induced nausea and vomiting. I look forward to working with Dr. Schachtel and the research staff at Charleston Laboratories on CL-108 and the other analgesic products they are developing."

Charleston Laboratories, Inc. is a privately held, specialty pharmaceutical company focused on the research and development of novel pain products to significantly reduce the burdensome side effects related to opioid analgesics and other products. The company has a strategic collaboration for the development and US commercialization of its novel hydrocodone combination products, including CL-108, which is being studied for the treatment of moderate to severe pain and prevention of Opioid-Induced Nausea and Vomiting (OINV). For more information, visit www.charlestonlabs.com.

Edge Therapeutics Reports Positive Top-Line Phase I/II NEWTON Trial Results

Edge Therapeutics, Inc. recently announced that its recently completed North American Phase I/II NEWTON (Nimodipine microparticles to Enhance recovery While reducing TOxicity after subarachNoid hemorrhage) trial has met its primary and secondary endpoints of safety, tolerability, maximum tolerated dose (MTD), and pharmacokinetics of a single intraventricular injection of EG-1962. EG-1962, the company's lead product candidate, is in development to treat patients who have suffered an aneurysmal subarachnoid hemorrhage (aSAH) resulting from a ruptured brain aneurysm.

The NEWTON trial evaluated six dose-cohorts (100, 200, 400, 600, 800, and 1200 mg). The primary endpoint was to establish the maximum tolerated dose, which has been determined to be 800 mg. Safety and tolerability data are available for all six cohorts, while EG-1962 efficacy results are reported for only five cohorts, as the sixth cohort (1200 mg) was not a tolerable dose. Safety results show that no patients (0 of 54) experienced EG-1962-related hypotension, while 17% of patients (3 of 18) treated with oral nimodipine, the current standard of care, experienced drug-related hypotension.

The secondary endpoint of characterizing the pharmacokinetics of EG-1962 was also met. The steady-state plasma concentration measured in patients treated with EG-1962 in the NEWTON trial were below 30 ng/ml, the level of plasma concentrations observed to cause systemic hypotension.

Exploratory endpoints measuring outcome results from the 90-day follow-up available demonstrated that 60% (27 of 45) of patients treated with EG-1962 experienced a favorable outcome (a score of 6-8) as measured by the extended Glasgow Outcomes Scale (GOSE). By contrast, the 90-day favorable outcome rate for patients treated with the current standard of care, oral nimodipine, was only 28% (5 of 18). (The GOSE is a clinically validated 8-point scale (1 = death, 8 = good recovery) used to assess recovery for patients who have suffered a ruptured aneurysm. A favorable outcome in the NEWTON trial protocol is defined as a GOSE score of 6 or greater as measured 90 days after aSAH.) In addition, improved efficacy was supported by a reduction in vasospasm, delayed cerebral ischemia and use of rescue therapies.

EG-1962 is a novel polymeric nimodipine microparticle containing nimodipine suspended in a diluent of hyaluronic acid that utilizes the Company's proprietary PrecisaTM development platform designed to improve patient outcomes following aSAH. EG-1962 has been granted orphan drug designation by the U.S. Food and Drug Administration (FDA) for the treatment of patients with aSAH.

The NEWTON trial is a multicenter, randomized, controlled, open-label Phase I/II trial evaluating the safety, tolerability and pharmacokinetics of escalating doses of EG-1962 compared to the current standard of care, oral nimodipine, in subjects with aSAH. Of the total of 72 patients enrolled, 54 patients were randomized to receive EG-1962 and 18 patients were randomized to receive oral nimodipine.

EG-1962 and EG-1964 both utilize the company's proprietary, programmable, biodegradable polymer-based development platform, known as Precisa. The Precisa platform allows the company to create therapeutics capable of delivering medicines directly to the site of injury, providing a novel delivery mechanism that enables targeted and sustained drug exposure while potentially avoiding the systemic, dose-limiting side effects often associated with current standards of care.

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Enteris Biopharma's Formulation Technology Enables Oral Delivery of Cara Therapeutics' Peptide

Enteris BioPharma, Inc. congratulates Cara Therapeutics on the dosing of the first patients in a Phase II trial of an oral tablet formulation of its peripherally selective kappa opioid agonist, CR845, for the treatment of osteoarthritis (OA). Cara's tablet formulation of CR845 utilizes Enteris' proprietary oral delivery technology.

The Phase II trial is a single blind, randomized, multiple ascending dose trial designed to evaluate the safety, pharmacokinetics, and effectiveness of oral CR845 tablets dosed over a 2-week treatment period in OA patients experiencing moderate-to-severe pain.

"We congratulate Cara Therapeutics on the dosing of the first patients in its Phase II study of oral CR845," said Brian Zietsman, President and CFO of Enteris BioPharma. "As Cara Therapeutics seeks to expand the clinical development of CR845 beyond the treatment of acute pain in an institutional setting, oral delivery of CR845 will be the key to unlock this opportunity."

"In our estimation, oral CR845 has the potential to address a significant market opportunity in the treatment of acute and chronic pain for which there continues to be a very large unmet need for safer, alternatives to narcotic opioids," added Derek Chalmers, PhD, DSc, President and Chief Executive Officer of Cara Therapeutics.

Cara Therapeutics is a clinical-stage biopharmaceutical company focused on developing and commercializing new chemical entities designed to alleviate pain and pruritus by selectively targeting kappa opioid receptors. Cara is developing a novel and proprietary class of product candidates that target the body's peripheral nervous system and have demonstrated efficacy in patients with moderate-to-severe pain without inducing many of the undesirable side effects typically associated with currently available pain therapeutics. For more information, visit www.caratherapeutics.com.

Enteris BioPharma, Inc. is a privately held, New Jersey-based biotechnology company offering innovative formulation solutions built around its proprietary drug delivery technologies. Enteris' proprietary oral delivery technology has been the subject of numerous feasibility studies and active development programs, several of which are in late-stage clinical development. For more information, visit www.enterisbiopharma.com.

Presage Biosciences Receives Strategic Investment from Takeda

Presage Biosciences, an oncology company pioneering a radical new drug development approach that incorporates human efficacy data much earlier in development and clinical trials, recently announced it has secured a strategic investment from Takeda Pharmaceutical Company Limited, through its venture capital arm, Takeda Ventures, Inc. Terms are not disclosed.

"Takeda and Presage have had an extraordinarily collaborative and productive research alliance over the past 3 years," said Nathan Caffo, President of Presage. "We continue to focus together on applying Presage's CIVO technology across the development pipeline at Takeda, from identifying novel drug combinations to translating that work to the clinic."

"Takeda Ventures is committed to investing in truly innovative technological approaches to make new treatments available for patients with cancer," added Graeme Martin, PhD, Chief Executive Officer of Takeda Ventures. "Presage's CIVO technology holds promise to better translate preclinical discoveries to patients, particularly in the field of novel cancer drug combinations."

Presage technology can be used to evaluate up to eight combinations of drugs or individual compounds, both investigational and approved, all without exposing patients to the toxicity of systemic dosing. Presage is validating its CIVO platform in the veterinary oncology setting in canine patients and expects to commence its second clinical study of the platform with the Seattle Cancer Care Alliance (SCCA) and the Fred Hutchinson Cancer Research Center in Q1 of 2016 in patients with soft tissue sarcomas. CIVO also is being employed in preclinical models to discover and evaluate novel combinations of cancer drugs.

Presage Biosciences is an oncology company pioneering the incorporation of human efficacy data much earlier in the drug development and clinical trial processes with its patented CIVO arrayed microinjection platform. The CIVO platform allows for simultaneous assessment of multiple drugs or drug combinations directly in a single solid tumor while still in a patient's body to assess efficacy, resistance, and drug synergies in the tumor's native microenvironment. Presage partners with oncology-focused pharmaceutical companies through strategic alliances to provide in vivo data to validate novel targets, promote drug candidates to the right indications, and discover effective drug combinations. Presage also is actively in-licensing cancer compounds and using CIVO to develop a portfolio of promising oncology therapies to advance to the clinic. Presage is privately held and based in Seattle. For more information, visit www.presagebio.com.

Proteon Therapeutics Initiates Second Phase III Clinical Study

Proteon Therapeutics Inc. recently announced that the first patient has been treated in a second Phase III clinical study of investigational vonapanitase (formerly PRT-201), the company's lead product candidate.

The second Phase III study complements the first Phase III study, which was initiated in July 2014 and is expected to complete enrollment by the end of 2015. Both Phase III studies are evaluating the safety and efficacy of a single treatment of vonapanitase in patients with chronic kidney disease (CKD) undergoing surgical creation of a radiocephalic arteriovenous fistula (AVF) for hemodialysis. Vonapanitase, a locally acting recombinant human elastase, is an investigational drug that may prolong the patency and reduce the failure of hemodialysis vascular access in patients with CKD.

The first patient in the second Phase III study was enrolled at Saint Luke's Hospital of Kansas City, by Christie Wynette Gooden, MD, Clinical Assistant Professor, Department of Surgery at the University of Missouri-Kansas City School of Medicine.

The second randomized, double-blind, placebo-controlled Phase III clinical trial will enroll 300 patients at approximately 40 centers in the US and Canada. Immediately after surgical creation of a radiocephalic AVF, each patient will receive either 30 micrograms of vonapanitase or placebo, delivered in a single, local administration to the external surface of the AVF. The primary efficacy endpoint, measured over 12 months, is primary patency, the time from AVF creation until a thrombosis or a procedure to restore or maintain patency. The secondary efficacy endpoint, also measured over 12 months, is secondary patency, defined as the time from AVF creation until AVF abandonment. Proteon is also conducting an ongoing Phase 1 clinical study of vonapanitase in patients with symptomatic peripheral artery disease (PAD).

In the most severe stage of CKD, also known as kidney failure, the kidneys can no longer function to sustain life. The majority of patients with kidney failure require hemodialysis and need a high-flow vascular access to repeatedly connect the patient's bloodstream to a hemodialysis machine for this life-saving, chronic treatment: Three times per week for 3 to 4 hours each session, blood is pumped from the body and passed through a dialysis machine that removes waste and excess water normally excreted by the kidneys. The preferred form of vascular access, used by two-thirds of hemodialysis patients in the US, is an arteriovenous fistula (AVF). An AVF is created when a surgeon connects a vein to an artery, typically at the wrist or elbow, resulting in a substantial increase in blood flow and vein dilation. A radiocephalic AVF is created between the radial artery and cephalic vein at the wrist.

HERMES PHARMA Brings Easy-to-Swallow Medicines to US Market

HERMES PHARMA, Europe's largest developer and manufacturer of user-friendly solid oral dosage forms, recently announced plans to ramp up its expansion into the US market. The company combines technical expertise and over 40 years of experience in making medicines easier to take. From the development of new products through to regulatory support and manufacturing, HERMES PHARMA provides customized solutions all along the pharmaceutical value chain. US healthcare companies will now be able to expand their product lines and grow their brands easier than ever before. A newly formed team will be specifically serving the US market and sharing the company's expertise in effervescent and chewable tablets, instant drinks, lozenges, and orally disintegrating granules (ODGs).

HERMES PHARMA's expansion into the US market comes at a pertinent time, given the FDA guidance released in June on improving the size and shape of tablets and capsules, as well as a recent survey conducted by the impartial market research firm SPIEGEL INSTITUT Mannheim. The latter (supported by funds from HERMES PHARMA) showed that half of the people in the US have difficulties swallowing tablets or capsules. They are often too big, become stuck in the throat, and have an unpleasant taste/odor. This causes people to chew, break up, or crush and dissolve tablets before swallowing them. Worryingly, some people even stop taking their medication altogether, highlighting the impact of swallowing difficulties on compliance.

User-friendly dosage forms solve this problem, as they are easy to swallow and have a pleasant taste. They come in a choice of flavors, convenient packaging, and can be easily integrated into the busy lives of modern consumers – much easier than the large and bulky multipacks of tablets or capsules prevalent in the US.

From a healthcare perspective, offering patients a medication that is a pleasurable rather than stressful experience has a positive impact on compliance. It reduces healthcare costs and thus minimizes the need for repeat visits to a doctor or healthcare professional.

Lastly, pharmaceutical companies looking to innovate can do so by introducing user-friendly alternatives of current and new drugs. This is an effective way of expanding existing product lines and extending product lifecycles, as well as better meeting the needs of specific market segments (eg, children, busy consumers, the elderly, etc). Such an approach can breed product and brand loyalty and help to better differentiate products in the marketplace.

Corbion & MedinCell Form Strategic Joint Venture

The joint venture, CM Biomaterials, will sell the PEG / PLA co-polymers to MedinCell partners who license the MedinCell technology (BEPO). Manufacturing of the polymers will take place in Corbion's medical biomaterials plants in the US and the Netherlands, while development and licensing of the technology remain the exclusive responsibility of MedinCell. CM Biomaterials will be established in the Netherands.

"Corbion and MedinCell have been in a joint development program since 2010, to optimize the manufacturing of PEG/PLA polymers for drug delivery," said Marco Bootz, SVP Biochemicals, Corbion. "This cooperation has now successfully developed into a joint venture for the supply of PEG/PLA polymers. In this joint venture, Corbion will be responsible for manufacturing the polymers, and with our complementary expertise in the field of polymers, we will together develop the optimal polymers for MedinCell's applications. Corbion is the global leader in the field of resorbable polymers for drug delivery and medical devices. This new technology will further enhance our position in medical biomaterials".

"The creation of CM Biomaterials validates our balanced network company model that aims to gather leaders in many fields to create best-in-class medicines for Global Health," added Christophe Douat, CEO of MedinCell. "Based on a complementary partnership, CM Biomaterials will best serve BEPO partners and secure the quality of the polymers used for all BEPO applications."

Based on a combination of co-polymers, solvent, and API, the BEPO technology can provide a controlled release of drug for days, weeks, or months from a fully biodegradable depot that forms after subcutaneous injection or local delivery of the formulated API. As a game-changing technology, BEPO combines many advantages compared to alternative drug delivery technologies, including improved patient compliance, efficacy, and tolerability, as well as versatility, development speed, and lower manufacturing costs.

Corbion is the global market leader in lactic acid, lactic acid derivatives, and lactides, and a leading company in functional blends containing enzymes, emulsifiers, minerals, and vitamins. The company delivers high-performance bio-based products made from renewable resources and applied in global markets such as bakery, meat, pharmaceuticals and medical devices, home and personal care, packaging, automotive, coatings, and adhesives. Its products have a differentiating functionality in all kinds of consumer products worldwide. For more information, visit www.corbion.com.

Every day, the MedinCell team acts for Global Health by developing innovative technologies that improve worldwide access to medicine and enable better treatment quality for all. MedinCell and its network of partners is developing the next generation of best-in-class medicines that combine low manufacturing cost with efficiency and compliance-related benefits. MedinCell is a self-funded and employee-owned entity running both commercial and non-profit activities. For more information, visit www.medincell.com.

Pluristem in Key Discussions With Europe's Adaptive Pathways Group on Phase II Protocol

Pluristem Therapeutics Inc., a leading developer of placenta-based cell therapy products, recently announced it has conducted detailed discussions with the European Adaptive Pathways Discussion Group regarding the clinical development plan for PLX cells in Critical Limb Ischemia (CLI) patients, and received guidance on the planned design of the initial Phase II trial of PLX cells in a subgroup of patients with severe CLI. Positive results from this trial could be sufficient for conditional approval to market PLX cells in this indication. Pluristem is receiving this in-depth guidance from European regulatory officials following the selection of this clinical program for the European Medicine Agency's Adaptive Pathways project in May 2015.

In the discussions Pluristem also presented other indications for potential development through the Adaptive Pathways project; these were ischemic stroke, muscle wasting, hip fracture, and additional subgroups of CLI.

The Adaptive Pathways project is part of the European Medicine Agency's (EMA) efforts to improve timely access for patients to new therapies. It targets treatments with the potential to heal serious conditions with an unmet medical need, and may reduce the time to a medicine's approval or to its reimbursement for targeted patient groups.

The purpose of Europe's Adaptive Pathways is to shorten the time it takes for innovative medicines to reach patients with serious conditions that lack adequate treatment options. The pathway is open to clinical programs in early stages of development only. After a therapy is selected for the program, the Adaptive Pathways Discussion Group provides detailed guidance to the applicant regarding the formal regulatory processes that precede a trial targeting early approval and further expansion of the indications.

Pluristem Therapeutics Inc. is a leading developer of placenta-based cell therapy products. The company has reported robust clinical trial data in multiple indications for its patented PLX (PLacental eXpanded) cells. The cells release a cocktail of therapeutic proteins in response to inflammation, ischemia, hematological disorders, and radiation damage. PLX cell products are grown using the company's proprietary three-dimensional expansion technology. They are off-the-shelf, requiring no tissue matching prior to administration.

BioClin Therapeutics Initiates Phase II Clinical Trial for Urothelial Cell Carcinoma

BioClin Therapeutics, Inc. recently announced it has initiated a Phase II clinical study of B-701, an anti-FGFR3 antibody being investigated for the treatment of locally advanced or metastatic urothelial cell carcinoma, also known as bladder cancer.

The study is a Phase II, randomized, double-blinded, placebo-controlled, multicenter, parallel-group, efficacy and safety study of B-701 in combination with docetaxel versus docetaxel alone for the treatment of patients with Stage IV, locally advanced or metastatic urothelial cell carcinoma who have relapsed after, or are refractory to, one or two prior lines of chemotherapy that have not included a taxane. This study is divided into two phases: an open-label lead-in phase, which will assess the safety and potential early signal of efficacy of B-701 plus docetaxel, and the randomized phase, which will compare B-701 in combination with docetaxel versus docetaxel alone. This announcement signals the start of the lead-in phase.

Separately, an investigator-sponsored study assessing B-701 in combination with a clinical-stage immune checkpoint inhibitor in patients with advanced/metastatic urothelial cell carcinoma is planned for later this year.

B-701 is a novel human monoclonal antibody specific for fibroblast growth factor receptor 3 (FGFR3) that is being developed to target FGFR3-positive tumors. Studies have shown that many patients with urothelial cell carcinoma overexpress FGFR3 on the tumor cell surface.

Preclinical studies have also shown that B-701 suppresses FGFR3-mediated cell proliferation and exerts strong anti-tumor activity in mouse xenograft models of bladder cancer, including in combination with gemcitabine, carboplatin, or paclitaxel, all standard-of-care therapies for urothelial cell carcinoma. B-701 monotherapy was tested in two Phase I studies, one of which included patients with locally advanced or metastatic urothelial cell carcinoma.

Bladder cancer is the sixth most commonly diagnosed cancer in the US.

Over 90% of bladder cancer is urothelial cell carcinoma; other less frequent variants include squamous cell and adenocarcinoma. It is estimated that 74,000 new cases and 16,000 deaths from bladder cancer will occur in 2015 in the US alone. There are an estimated 151,100 new cases and 52,400 deaths annually in Europe. Seventy to 80% of bladder cancer is superficial, while 20% to 30% is invasive. In approximately 15% of the cases, the tumor extends beyond the wall of the bladder (stage T4). Prognosis of the metastatic T4 tumor type is poor despite surgery and systemic chemotherapy.

Therapeutic options for metastatic bladder cancer include chemotherapy, generally gemcitabine in combination with cisplatin for first-line treatment. There are no approved therapies available for second-line therapy in which a patient has an average survival of 6 to 9 months.

NanoViricides Reports Dramatic Effects of Topical Anti-Herpes Treatment Were Reproduced Once Again

NanoViricides, Inc. recently reported that the dramatic improvements in clinical symptoms associated with herpes simplex virus infection were reproduced in an animal model in a different laboratory. These studies were performed by TransPharm Preclinical Solutions, a preclinical services company in Jackson, MI.

All of the nanoviricides tested improved clinical scores dramatically, with clinical presentation being arrested at redness or simply raised local lesions, and a complete absence of zosteriform spreading. All of the nanoviricides-treated animals survived the lethal HSV-1 infection challenge for the duration of the study while untreated animals died toward the end of the study. These nanoviricides are designed as topical treatment for the breakout of herpes sores.

Some of the nanoviricides found effective in the previous study were tested in this study for the confirmation of efficacy in a dermal animal model in Balb-c mice using the same highly aggressive and neurotropic HSV-1 strain H129c, which was used previously.

The earlier studies were performed in the laboratory of Dr. Ken S. Rosenthal at Northeast Ohio Medical University, where Dr. Rosenthal continued as a Professor Emeritus. He is a leading researcher in herpes virus anti-viral agents and vaccines.

In the previous study, two of the anti-Herpes nanoviricides reduced the extent of disease (morbidity) and mortality of the HSV-1-infected animals that were treated. These nanoviricides also reduced virus production in cell culture. Importantly, topical dermal treatment with these nanoviricides led to almost complete (>85%) survival of the infected mice in this animal model, whereas all untreated animals died of the disease. Further, these nanoviricides were superior to topical treatment with an acyclovir formulation employed as a positive control. The company reported on these studies in April, 2015. Professor Rosenthal consulted with NanoViricides and TransPharm for the establishment of the animal model for dermal HSV-1 infection using the HSV-1 strain H129c at the TransPharm laboratories.

Existing therapies against HSV include acyclovir and drugs chemically related to it. These drugs must be taken orally or by injection and are not very effective as topical agents. Other drugs are largely ineffective. Currently, there is no cure for any of the herpesvirus infections.

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MARKET SURVEY

Dosage Forms: It's Time to Listen to Consumers

By: Thomas Hein, PhD

INTRODUCTION

Millions of people use solid tablets and capsules every day to treat any number of ailments or to supplement their dietary or health requirements. Regarded as the most practical and cost-efficient method of drug delivery, it's no surprise they have become so widespread. However, a recent survey of people across the US and Germany has revealed that half of the population has difficulty in swallowing tablets and capsules.

Of the 1000 US participants, swallowing problems were attributed primarily to the size of the tablets and capsules - either being too big to swallow or that they became stuck in the throat.

Worryingly, many participants interfered with the tablets or capsules: 23% reported breaking tablets before swallowing, while another 14% crushed and dissolved them in water in order to swallow them. A full 10% stopped taking their medication entirely, while 9% looked to a different dosage form altogether. A lack of compliance on this scale not only has potentially serious consequences for the quality of a person's health, but it also comes with a substantial financial impact on healthcare systems.

The survey also delved further into people's experiences with a wide range of dosage forms in an effort to understand which properties they value or would like to see implemented. This included asking participants to score different dosage forms, such as solid tablets or capsules, effervescent and chewable tablets, lozenges, orally disintegrating granules (ODGs), and instant drinks, for factors such as convenience, ease of swallowing, taste, etc. The results raised several important issues, all of which represent valuable opportunities for healthcare companies to adjust their product development strategies to meet the expectations and preferences of modern consumers.

CHALLENGES & SOLUTIONS

Difficulties swallowing tablets or capsules are an issue experienced by a wide range of people regardless of age or gender. The natural tendency is to assume that swallowing difficulties are much more common in the elderly, and indeed 40% of elderly participants aged 65 or older reported some form of difficulty swallowing tablets and capsules. However, 66% of people aged 16 to 24 also indicated having the same problem. While 25% of both age groups complained that the tablets or capsules were too large to swallow, the most common issue reported by 35% of the younger participants was actually that the tablets or capsules had an unpleasant taste or smell. In contrast, only 8% of the elderly group had this issue with taste and smell. These results highlight that swallowing difficulties are a common problem affecting both old and young, but for different reasons.

In an effort to understand this, the survey asked respondents to rate which non-medicinal characteristics they value in a medication or food/dietary supplement. Well over half of the US participants (66%) reported that it should be easy and comfortable to swallow, 38% said that a pleasant taste or odor was important, and 34% wanted a product that integrates easily into their lives. The interaction with the product itself can also affect people's experience, with 36% of people indicating they would prefer packaging that was easy to open. This final point provides an excellent opportunity often

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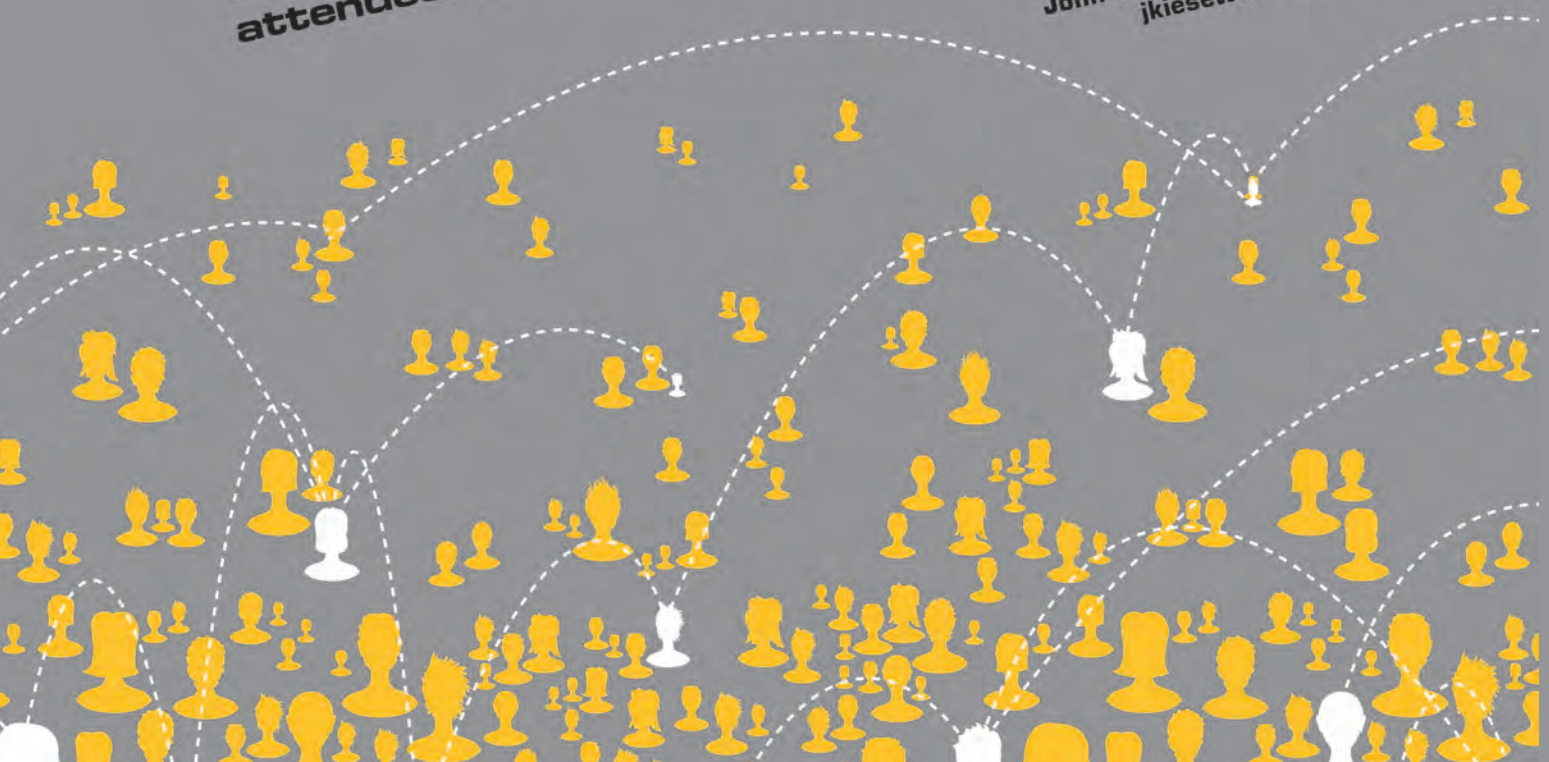


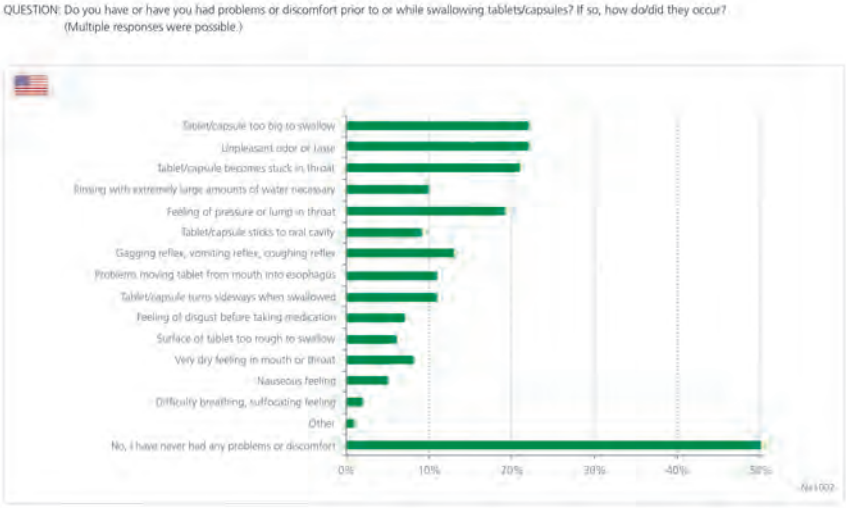
overlooked by pharmaceutical companies, but that is widely known in the fast moving consumer goods (FMCG) industry; if done well, packaging can be a powerful tool to help communicate the quality of a product to consumer.

An emerging trend is that people want convenient products that have a pleasing taste and smell, are easy to swallow, and can integrate easily in their busy daily lives. Put simply, conventional solid dosage forms do not offer the desired positive experience in many cases. Pharmaceutical companies that are willing to respond to these needs and offer people a wider range of choices have the chance to open up new market segments, capture market share, and breed brand loyalty, all the while successfully differentiating their own products from the competition.

User-friendly dosage forms already have a sizable base of awareness in the US, led by chewable tablets, which are already known to almost 90% of Americans. Other dosage forms are also well known: effervescent tablets or lozenges are known to 85% of people, instant drinks to 80%, and 48% of people know of ODGs.

It's not just a case of awareness - people are also now beginning to try and routinely use these forms of medication. For example, the survey results indicate that more than 60% of US participants had already taken chewable tablets and lozenges. When asked to compare tablets or capsules with user-friendly dosage forms, people consistently scored conventional tablets or capsules far less favorably across a number of characteristics, including ease of swallowing, sensation in the mouth, package opening, and ease of intake.

FIGURE 1



These data suggest that not only is awareness of user-friendly dosage forms relatively widespread, people also prefer taking them rather than traditional tablets and capsules.

TURNING A PROBLEM INTO AN OPPORTUNITY

It will come as no surprise that the pharmaceutical industry has been facing a number of challenges over the past few years. The ever-present patent cliff continues to claim millions of dollars in revenue as the patents on blockbuster medicines expire. R&D costs involved in creating new medicines are increasing - the number of medicines approved per billion US dollars spent on R&D has halved roughly every 9 years since 1950, falling by around 80-fold in inflation-adjusted terms.[1] Overall, the success rate for discovering new medicines remains notoriously low, and progressively fewer medicines are moving along the pipeline from the development stages through to market.

Some companies are responding by tackling these difficulties from new angles in the pursuit of innovative solutions.[2] Outsourcing or acquiring small companies involved in API discovery, for example, is allowing Pharma to tap into external sources of innovation. This allows them to avoid the risks of developing new active compounds from scratch. In other cases, rather than working to discover and optimize completely new APIs that they can patent, some companies are instead reformulating current medicines. Reformulation is appealing because medicines can be not only improved but also made more difficult to copy. It can also revitalize ageing brands and stimulate consumer interest.

For all of these solutions, a core strategy points to putting consumers directly at the center of the business. By developing user-friendly dosage forms, medicines, or supplements deliver additional value to consumers, and by extension, to healthcare providers and reimbursers. With clear messages on preferences being voiced through data, such as those from this survey, there is a clear opportunity to meet those preferences and win customers.

This approach could prove especially effective if the industry

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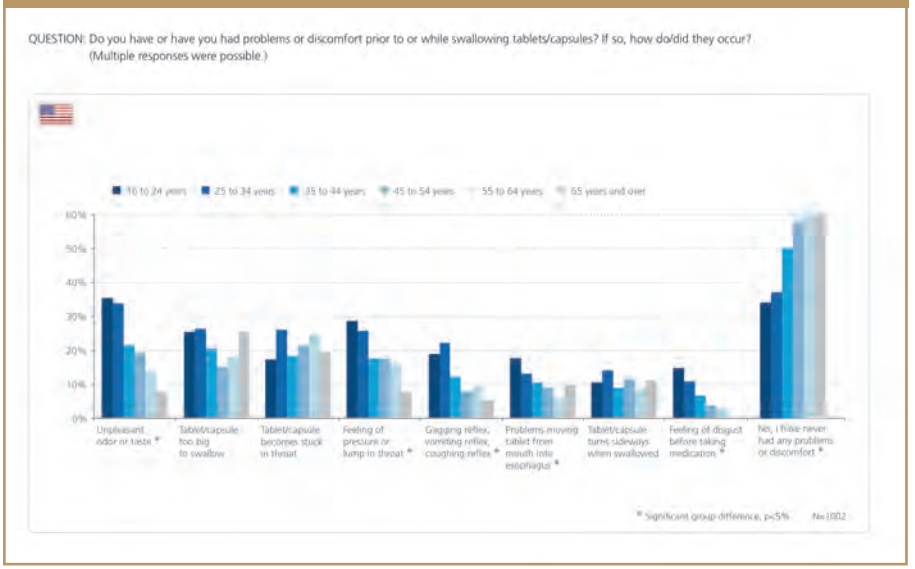
FIGURE 2



considers the over-the-counter (OTC) market as an opportunity to promote self-administration and reduce the need for doctor visits (therefore reducing healthcare costs). With OTC products, consumers have a direct influence on their medication. With increased knowledge of these medicines and how they work, OTCs effectively provide people with around-the-clock access to treatment. Currently the average US household spends about $340 per year on OTC products.[3] Without OTCs, an estimate 60 million Americans would not seek treatment for their illness.[4]

Considering the increased costs of healthcare and the pressures on reimbursement and pricing, a shift away from a reliance on prescriptions toward OTC medicines can help alleviate healthcare costs by reducing the need for doctor visits. In fact, the use of OTCs has been estimated to save the US healthcare over $100 billion annually, relative to alternatives.[3]

Paying attention to what consumers specifically want while taking advantage of OTCs in what is a growing market, could provide the industry with a very effective solution to many of its challenges. By creating medicines that people will want to take, rather than have to take, pharmaceutical companies have an opportunity to increase market share, even under the current challenging conditions facing the industry.

USER-FRIENDLY DOSAGE FORMS OFFER MULTIPLE BENEFITS

In addition to ease-of-swallowing, two other important factors affecting how people respond to medicines are taste and mouthfeel. As many APIs tend to be bitter, taste-masking is essential to making the final product more palatable – something we know from the survey to be an important criteria. While this is essentially true for all dosage forms, it is especially relevant when developing user-friendly dosage forms, as they tend to spend more time in the mouth and are tasted more thoroughly than conventional tablets and capsules.

Taste-masking is achieved via coating the API using specialist methods. Traditionally, this has been relatively time consuming and expensive, often including comparatively high-risk solvents in the process. Hot melt coating (HMC), on the other hand, is an advanced, alternative coating method that effectively masks the bitter taste of APIs. HMC does not require potentially toxic, flammable, and expensive solvents and is faster than solvent-based methods, making it ideal for dosage forms like ODGs.

Other cutting-edge technology, such as TOPO vacuum granulation technology for effervescent forms, results in a final product that has a high degree of stability in the presence of acids or bases. Effervescent dosage forms manufactured with TOPO technology have a high resistance to moisture and long shelf-life even under extremely humid conditions, making them suitable for even tropical regions. At the same time, they show characteristic short disintegration times on contact with water in a glass, even after prolonged storage. Effervescent tablets have further benefits in the form of enhanced bioavailability due to the release of carbon dioxide as they dissolve, improved permeability in the GI tract and enhanced API transport into cells.[5]

From a pharmaceutical industry perspective, reformulation of established medicines into new dosage forms can be particularly useful for extending patent protection. This safeguards the investments of companies by providing stronger IP protection. Such line extensions can also lead to a more differentiated product range that specifically addresses individual customer preferences. The end result is greater brand value and better differentiation from competitors – factors that increase revenue and market share irrespective of patent status.

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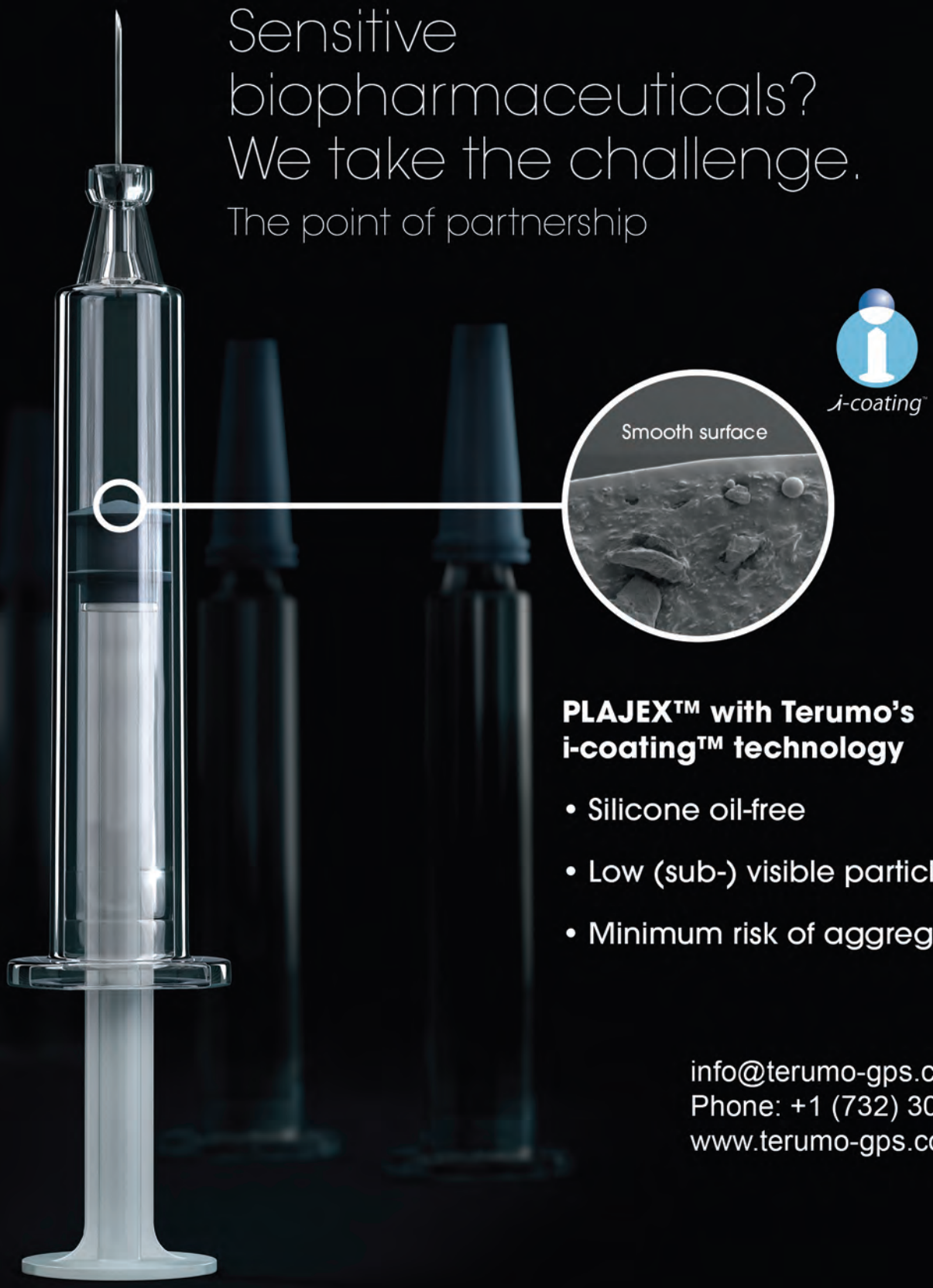

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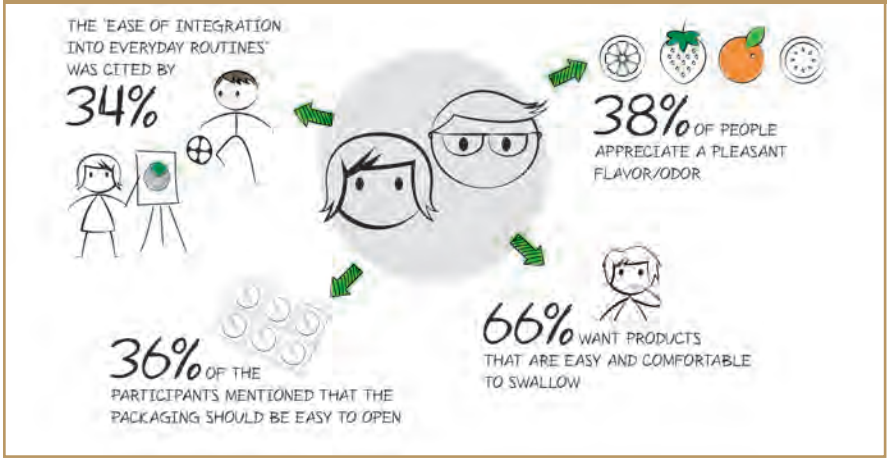
FIGURE 3



ADDRESSING NEEDS FOR THE GOOD OF MANY

In light of their huge success and widespread use, it is easy to assume that tablets and capsules are generally accepted by consumers and the industry. However, when robust data are available, showing that a large proportion of people are in fact less than satisfied for a variety of reasons, Pharma needs to sit up and listen. People are no longer content to passively take a prescribed or purchased dosage form if it does not meet their expectations or conform to their preferences. Failing to consider this can effect compliance, which has repercussions for individual well-being and places potentially serious financial burdens on a healthcare system already under pressure.

The technologies to develop the variety of user-friendly dosage forms described here are already available, and specialist companies have been manufacturing them with great success for a number of years. It's now time the rest of the medicine and supplement industries start to listen to what consumers clearly want in a dosage form. Addressing existing problems, such as swallowing difficulties, and accommodating preferences, such as enhancing flavor and odor, not only improves a consumer's experience, but also opens up valuable market opportunity for manufacturers.◆

For further details on the survey, which was conducted by the impartial market research firm SPIEGEL INSTITUT Mannheim, visit www.swallowingtablets.com or scan the QR code. The survey targeted 2000 people (1000 in Germany and 1000 in the United States) and was tailored to reflect overall population demographics in terms of age, gender and ethnicity in order to generate statistically reliable data.

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BIOGRAPHY

Dr. Thomas Hein is Senior Vice President Commercial and Regulatory Affairs at HERMES PHARMA, the third-party business division of Hermes Arzneimittel, a leading German OTC pharmaceutical company. Having earned his PhD in Pharmaceutical Technology at the University of Regensburg, Germany, Dr. Hein has made a significant entrepreneurial contribution to HERMES PHARMA from its inception. Since 2001, he has been responsible for the division's commercial operations, worldwide portfolio management, and marketing. He also takes an active part in strategy development and public relations. Dr. Hein initially joined Hermes Arzneimittel in 1992 as a Coordinator of Product Development and clinical projects, after obtaining his pharmacy approbation and completing scientific work with his alma mater. Head of Product Development from 1996 to 2001, he was instrumental in driving many in- and out-licensing projects prior to assuming his current position. He can be reached at info@hermes-pharma.com.

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DNA VACCINE TECHNOLOGY

A Vaccine Breakthrough That Could Change Lives & Enable Vaccine Development Programs

By: William Hearl, PhD

INTRODUCTION

What if there was the potential for a better and safer treatment for allergies, a less-toxic cancer therapy, or a breakthrough treatment to improve the health of a pet or valuable livestock? What if you could employ a new, patented technology that may make these treatments possible? LAMP-Vax™ technology is working toward this goal.

LAMP, which stands for Lysosomal Associated Membrane Protein, is the nucleic acid coding sequence added to DNA - and RNA - vaccines to direct the immune system to effectively respond to vaccination. LAMP diverts the synthesized protein products of DNA- and RNA-based vaccines directly to the lysosome in the dendritic cells, making them readily available to form antigen-MHC-II complexes. These MHC-II complexes, after transport to the cell surface, directly interact with helper T-cells and lead to the production of antibodies and Th1 cytokines, while maintaining enhanced CD8+ cytotoxic T-cell activation. Nucleic acid vaccines with LAMP are being developed to have many of the following advantages:

- Proprietary, intelligent antigen and vaccine design
- Fast, efficient vaccine design and validation (3-5 months)
- Enhanced safety for treatment of allergic diseases
- Excellent stability with long shelf-life
- High manufacturing yields
- Multivalent and multiplex capability

LAMP is potentially the "missing link" to effective DNA and RNA vaccinations because it:

- Is easily added to existing DNA or RNA nucleic acid formulations
- Can be applied to resuscitate failed vaccine programs through improving immunogenicity
- Quickly establishes immunological memory
- Can be used to enhance efficacy of existing peptide or protein vaccines
- Can provide for reformulation of a protein vaccine as a nucleic acid vaccine

IMMUNOMIC THERAPEUTICS & LAMP-VAX

Immunomic Therapeutics, Inc. (ITI), a clinical-stage biotech company, is developing next-generation DNA vaccines based on LAMP technology. The LAMP-Vax platform, initially developed in the laboratory of Dr. J. Thomas August at the Johns Hopkins University School of Medicine, aims to modulate and thereby improve the immune response to nucleic acid vaccines while taking advantage of other key features of nucleic acid vaccines, including simpler overall vaccine design and delivery, safer formulations and low-cost, high-yield manufacturing.

ITI is developing the next generation of DNA vaccines: LAMP-Vax vaccines for allergy, with other applications by

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collaborators in cancer and infectious disease. Some vaccines will be preventive and others therapeutic, some for human use and some for animal use.

Because of the unique design features of the LAMP platform, these vaccines are designed to activate both the acquired or adaptive immunity mediated by CD4+ T-cells and the cellular immunity mediated by CD8+ T-cells – both arms of the immune system. LAMP provides an elegantly designed solution to direct and enhance antigen processing and presentation, which in turn, aims to increase the immunogenicity of DNA vaccines. ITI's LAMP vaccines can complement and incorporate other advances and developments in next-generation DNA vaccine design, manufacturing, and delivery, as outlined further.

INCORPORATING LAMP TECHNOLOGY

Vaccine technologies have been in development since the initial use of killed viral and killed bacterial vaccines, including the first generation of live attenuated viral vaccines (eg, measles, mumps and rubella, and yellow fever); and the second generation of subunit vaccines (defined protein antigens [eg, tetanus toxoid] or recombinant protein vaccines [eg, hepatitis B vaccine]).

The newer third generation of vaccines, such as viral vector vaccines (eg, adenoviruses) and nucleic acid (DNA and RNA) vaccines, are still in development as protective and therapeutic vaccines for humans. For animals, next-generation vaccines have been licensed that are protective against West Nile virus in horses and infectious hematopoietic necrosis virus in salmon. There are also therapeutic vaccines for melanoma in dogs and for growth augmentation in swine.[1,2] Table 1 compares the various features of different generations of vaccine technologies.

TABLE 1

COMPARISON OF VACCINE TECHNOLOGIES
(adapted for Liu, 2003, p. 403.)

Live Attenuated Viruses
- Highly effective
- Potential risk for certain ones
- Manufacturing challenge

Recombinant Proteins
- Potent antibody response
- Effective
- Nin-native forms at times
- Nin-inducible of cytotoxic T lymphocytes (CTL)

Viral Vectors
- Potential risk
- Resistance/pre-existing antibody
- Inflammation

DNA Vaccines
- Need for increased potency
- Designer immune responses (e.g., type of helper T cell)
- Specificity: avoidance of deleterious or diversional antigens
- Relative stability
- Safety
- Generic manufacturing
- Cost advantage

Comparison of Vaccine Technologies

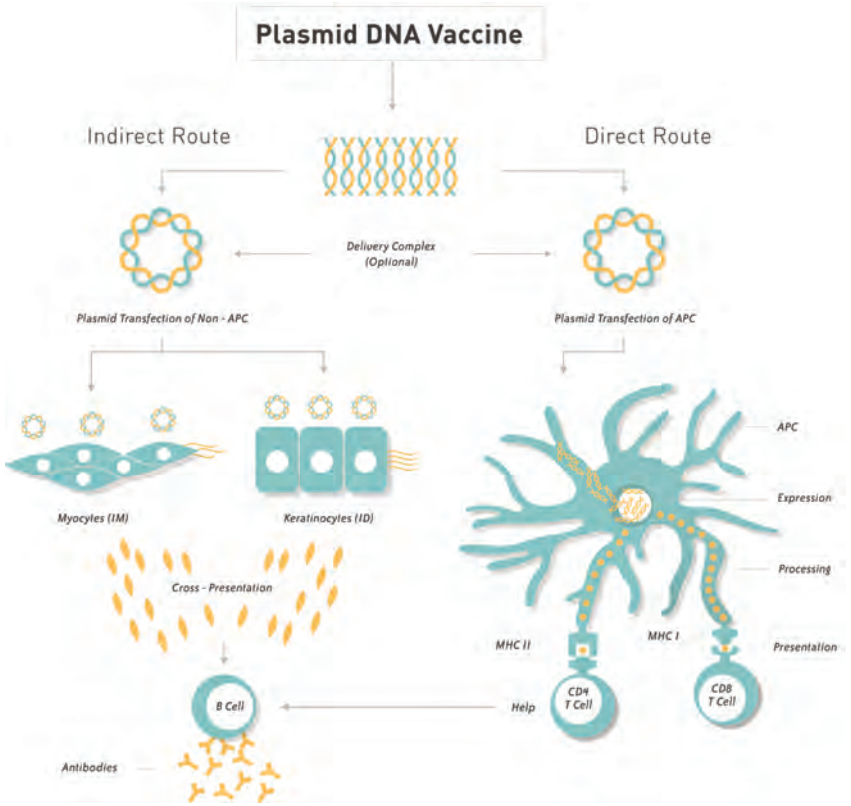
Next-generation nucleic acid vaccines deliver a non-viral plasmid DNA or mRNA sequence into target tissue, where the encoded protein is synthesized within transfected cells, producing significant quantities of the antigenic protein (identified from viral, bacterial, or parasitic genomes or from tumors) that ideally offers protective or therapeutic immunity.[3]

Upon vaccination, the DNA plasmid is taken up by target cells, and the plasmid vector gains entry to the cell nucleus, where the encoded DNA sequences are transcribed and then translated into the antigenic protein. By delivering into an Antigen Presenting Cell (APC)-rich area of the body, such as the skin, the vector may transfect an APC, allowing the expressed antigen to be directly presented to both CD8+ cytotoxic and CD4+ helper T-cells by MHC class I or II presentation.

If the vector transfects a non-APC, antigen presentation may occur through cross presentation (indirect route).[4] Upon delivery of the plasmid to a target organism, the plasmid transfects either non-APCs (indirect route) or APCs (direct route). After the plasmid gains access to the transfected cell's nucleus, the encoded antigen is expressed as mRNA, exported from the nucleus and translated into an antigenic protein. By encoding the antigen with LAMP-Vax, the antigen-LAMP fusion protein is routed for endosomal processing for efficient access to MHC-II-containing intracellular vesicles. The antigen can then be presented by MHC I or MHC II either directly in the case of APC cell transfection or indirectly by cross presentation to proximal APCs after the APC captures secreted antigen. Figure 1 depicts the process of DNA vaccination and the direct versus indirect routes of antigen presentation.

Recently, new ancillary technologies have come into play that may enable DNA vaccines to achieve enhanced

FIGURE 1



Plasmid DNA Vaccination: Indirect & Direct RoutesBrains

efficacy. For example, delivery devices are being co-developed with DNA vaccines to increase the efficiency of gene transfer. Techniques such as electroporation aim to deliver more DNA into the cells and thereby achieve higher antigen expression, which is believed by some researchers to correlate with improved humoral and cellular immunity. Innovations in plasmid backbone and antigen design have also greatly improved DNA vaccine performance. By building on these improved plasmid backbones, next-generation DNA vaccines can realize substantially increased antigen expression level and duration, improve manufacturing yield and quality, and address regulatory concerns by eliminating antibiotic selection markers through use of non-coding RNA selection markers.

IMMUNOMODULATORY MECHANISM OF LAMP

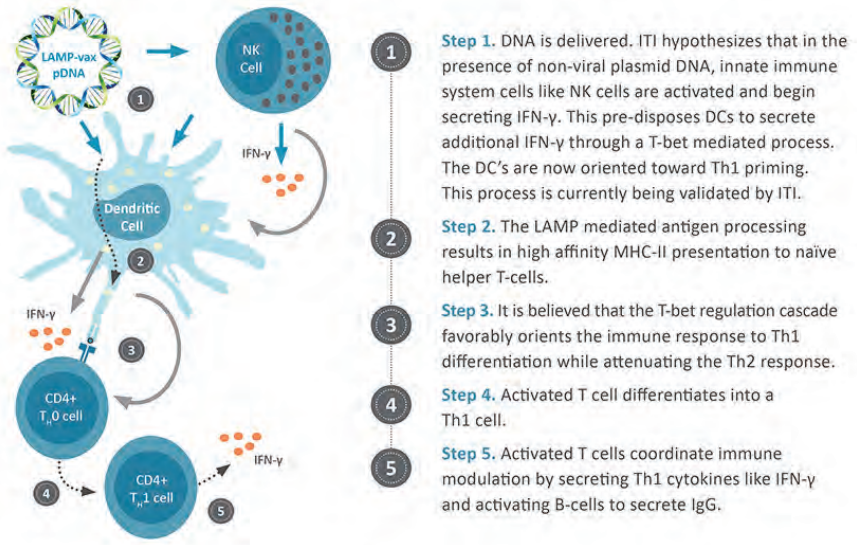
LAMP Technology advances the development of nucleic acid vaccines by using the cell's own mechanism to navigate antigens through the cell, enabling the delivery of the antigen directly to the intracellular organelle essential for effective immune system presentation. In this way, LAMP-mediated vaccines direct the immune system to effectively respond to vaccination by diverting the synthesized protein products of DNA- and RNA-based vaccines into the MHC-II/lysosomal compartment of APCs. The benefit of MHC-II trafficking is the efficient formation of antigen/epitope-MHC-II complexes, which after transport to the cell surface, activate helper T-cells. This begins a cascade of events that lead the adaptive arm of the immune system to produce antibodies, create Th1-biased memory T-cells, and maintain enhanced CD8+ cytotoxic T-cell activation.

In a simplified model of typical vaccination, exogenous antigens from infectious agents are delivered and then taken up through pinocytosis by APCs, which process the antigen for presentation to CD4+ T-cells through MHC-II-antigen complexes, leading to B cell activation and production of antibodies. Concurrently, APCs process antigens for presentation with MHC-I to activate CD8+ cytotoxic T-cells (CTLs), which are then permitted to destroy infected and diseased cells.[3]

DNA vaccines are often administered to somatic cells, such as muscle, which do not express MHC-II. Thus, when the encoded protein is synthesized, it is processed for presentation with MHC-I complexes to stimulate CTLs. Antibody production without antigen presentation through MHC-II can be weak. To address this, Dr. August and colleagues used the natural trafficking pattern of LAMP to divert the internally synthesized protein antigens to MHC-II-containing lysosomal vesicles. The process of LAMP activation of APCs and presentation on MHC-II to CD4+ T cells is outlined in Figure 2.

Because the diversion of internally synthesized antigens with LAMP-Vax is not total, two arms of the adaptive immune system are promoted by LAMP: the "outside-in" of MHC-I, resulting primarily in CD8+T cell activation, and the "inside-out" presentation through MHC-II, resulting in CD4+ T cell activation.

FIGURE 2



Step 1. DNA is delivered. ITI hypothesizes that in the presence of non-viral plasmid DNA, innate immune system cells like NK cells are activated and begin secreting IFN-γ. This pre-disposes DCs to secrete additional IFN-γ through a T-bet mediated process. The DC's are now oriented toward Th1 priming. This process is currently being validated by ITI.

Step 2. The LAMP mediated antigen processing results in high affinity MHC-II presentation to naïve helper T-cells.

Step 3. It is believed that the T-bet regulation cascade favorably orients the immune response to Th1 differentiation while attenuating the Th2 response.

Step 4. Activated T cell differentiates into a Th1 cell.

Step 5. Activated T cells coordinate immune modulation by secreting Th1 cytokines like IFN-γ and activating B-cells to secrete IgG.

Step-by-Step Process of LAMP-Vax™ Vaccination

PREVIOUS APPLICATIONS OF LAMP & CLINICAL SUCCESS

LAMP technology has been incorporated into the design of several DNA and RNA vaccines that have been tested in clinical trials with hundreds of patients and have been shown to enhance the human immune response.

Allergy

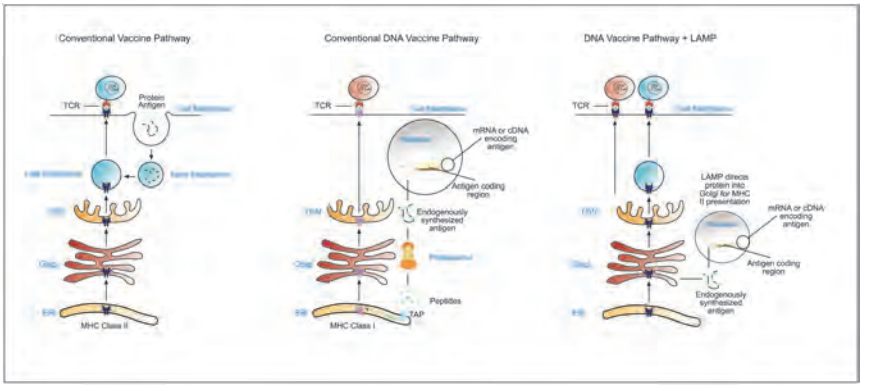
Immunotherapy for the treatment of allergies has the potential to significantly reduce the dependence on drugs, such as Benadryl, Claritin, and other drugs that treat symptoms only. Immunotherapy can be accomplished by reversing the "net allergic charge" in the immune system, moving from an IgE/Th2 allergenic response to an IgG/Th1 response. Standard immunotherapy involves subcutaneous delivery of small amounts of allergen over many months or years of continuous therapy. It often involves 100 or more shots. More recently, allergens have been formulated as sublingual drops that are taken daily or weekly for up to several years. With this formulation, the risk of severe adverse events, including anaphylaxis, remains because conventional immunotherapy utilizes allergen or allergenic proteins.

In contrast, LAMP-Vax allergy vaccine immunotherapy aims to offer a novel approach that requires few shots (four have been used in ITI's Phase IA,IB, and IC studies with JRC-LAMP-Vax, at times with a fifth "booster" shot). Further, it is believed that LAMP-Vax does not expose the patient to free allergen, potentially increasing the safety of the therapy.

ITI is currently developing several allergy vaccines, including ASP-4070 to treat Japanese red cedar allergy, and ARA-LAMP-Vax to treat peanut allergy. LAMP-Vax has been safely applied in several human clinical trials with favorable results and potential immune response using a well-established biomarker, and further in model animal systems for flea allergen, red cedar allergens, and peanut allergens, ITI has observed a strong Th1 response to these potent allergens following LAMP-Vax immunotherapy.

The company completed Phase IA and 1B trials for the first-generation Japanese Red Cedar (JRC) allergy vaccine, ASP4070 (formerly known as JRC-LAMP-Vax), in Q2 2013 and Q4 2013, respectively, and completed its Phase IC trial in 2015. In ITI's first human study for Japanese red cedar allergy (or JRC) it was observed that the LAMP-Vax therapy reversed the allergen-specific skin test reaction of all the allergic subjects. Further, the allergy vaccine therapy induced conversion of non-related allergens, suggesting a potential systemic response. Summary results of the Phase IA and IB studies are included in Table 2.

FIGURE 3



Immune System Activation with Conventional DNA Versus LAMP-Vax DNA Vaccines

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TABLE 2

CLINICAL STUDIES OF JRC-LAMP-VAX
SUMMARY OF PH. I RESULTS IN 24 SUBJECTS

Primary & Secondary Endpoints	Phase 1A	Phase 1B
SAFETY:		
No anaphylactic / allergic responses	Achieved	Achieved
No anti LAMP antibody generation	Achieved	Achieved
No severe adverse reactions	Achieved	Achieved
Skin test negative patients remain negative	8 of 8 subjects	Achieved
IgE levels stable or decreasing	Achieved	Maintained
IMMUNOLOGICAL ACTIVITY:		
Elimination of JRC/Mtn C/CryJ2 skin test reactivity	14 of 16 subjects	100% conversion
Conversion skin test from positive to negative	15 of 16 subjects	100% conversion

Clinical Studies of JRC2-LAMP-Vax: Summary of Phase I Results in 24 Subjects

ITI has already received a validation of the potential of its technology platform through a recent significant license of ASP4070, the full Japanese red cedar allergy vaccine formulation that targets the two main JRC allergens. Astellas Pharmaceutical, Inc. has entered into an exclusive license agreement for Japan to develop and commercialize ASP4070. Astellas recently initiated a Phase I trial of ASP4070 in Japan in Q3 of this year.

Under the agreement, Astellas is responsible for developing and commercializing ASP4070 in Japan, where Japanese red cedar pollinosis is endemic. Astellas will lead and fund clinical trial development costs and supporting development expenses for Japan. Immunomic Therapeutics also granted Astellas an exclusive option to negotiate a license for additional LAMP-Vax DNA vaccines to treat allergy indications other than Japanese red cedar pollinosis in Japan.

Meanwhile, ARA-LAMP-Vax, to address peanut allergy and anaphylaxis, is moving forward in preclinical development in the United States.The innovative LAMP platform and the promise it holds enabled the company to garner the interest of members the community working in food allergy research. ARA-LAMP-Vax was successfully tested in Dr. Hugh Sampson's lab using an animal model of food allergy. A second study is underway to expand on the immunological profiling of the vaccine, while the company prepares the vaccine for entering clinical development in either late 2015 or early 2016.

ITI's vision is to exploit the response to dominant allergens to create universal/multivalent allergy vaccines that would address entire classes of allergens, and enable ITI to eventually treat most allergens with just a few doses and potentially annual maintenance boosters.

Figure 4 summarizes the approach to creating allergy therapy classes with the LAMP vaccine platform, and how LAMP multivalent formulations could potentially simplify the current paradigm of allergy immunotherapy using the 900+ extracts on the market.

Oncology

Cancer immunotherapies, including vaccines, are novel investigational cancer therapies. As with traditional vaccination, the goal of cancer immunotherapy is to stimulate the body's immune system and overcome cancer's natural resistance to immune system-mediated cell death. Some current treatment modalities involve combining cancer vaccines with checkpoint inhibitors, using, for example, antibody therapy against CTLA-3 and PD-1/PDL-1, as well as other active immunotherapies.

Cancer vaccines are designed to generate a robust effector and a memory CTL response against antigens that are unique to a particular type of tumor, which results in destroying antigen-expressing tumor cells and establishing long-lasting immune-surveillance. Because

FIGURE 4

LAMP Platform

Allergy Classes:

- **Foods:** Peanut, Tree Nuts, Milk, Egg, Shellfish
- **Indoor allergens:** Dust Mite, Animal Dander, Cockroach, Molds
- **Pollens:** Trees & Grasses

LAMP-Vax Platform Applicable to Multivalent Formulations for Various Classes of Allergies

of the requirement for CD4+ Th cells for effective T-cell memory (TCM) generation and the absence of CD4+ activation in most DNA/mRNA vaccination strategies, LAMP-Vax has promising potential and is being explored by ITI in multiple cancer types as a broadly applicable immunotherapy platform to induce antigen-specific CD4+ and CD8+ effector and memory cells.

ITI is exploring mechanisms to expand into the therapeutic oncology arena. LAMP-Vax has been advanced into multiple Phase I/II clinical trials with academic and corporate partners for use in patients diagnosed with Glioblastoma (GBM), Acute Myeloid Leukemia (AML), and melanoma. Most recently, it was announced that the LAMP+telomerase-based therapy that previously showed excellent results in prostate cancer and AML human trials is now moving forward in clinical development for AML as well as being applied to lung cancer, using a universal dendritic cell (DC) line, which greatly improves logistical and commercial considerations beyond current FDA-approved DC therapies such as Provenge™. The therapeutic mRNA used to load the universal DC vaccine includes the LAMP element to stimulate antigen-specific CD4+ and CD8+ T-cell responses against the promising cancer antigen hTERT. ITI previously granted a license to Geron to study LAMP+telomerase formulations in oncology. Subsequently, Geron granted a sublicense to Asterias Biotherapeutics Inc., who is now moving it forward in clinical development in collaboration with Cancer Research Technology (CRT).[5,6]

Animal Health

As of 2011, five DNA vaccines had been approved for sale in animal health indications. ITI, recognizing the significant opportunity to leverage the preclinical work done with LAMP technology in a variety of animal diseases, chose to join the surge of applications to veterinary vaccines. The company is currently focused on allergies for companion animals. In paralell, the pipeline below shows several other LAMP-DNA formulations in development for oncology and infectious disease for companion and herd animals.

Phase IA/IB Study in Allergy by ITI – Now Partnered With Astellas Pharma, Inc.

-24 subjects treated with JRC-LAMP-Vax (no SAEs observed)
-100% reversal of skin test results observed
-IgE levels decreased following treatment, while IgG levels increased

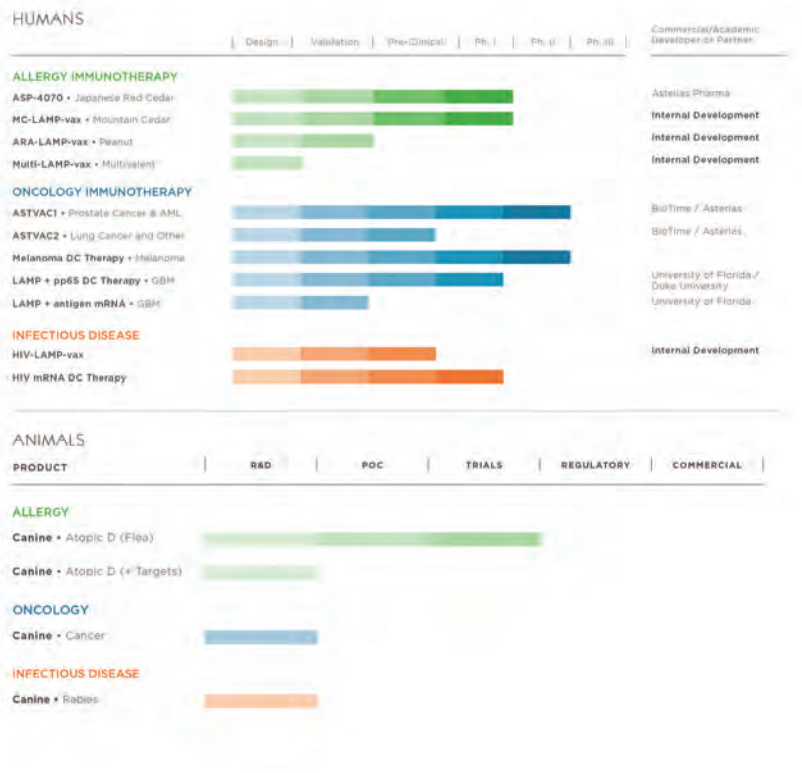
Phase II In Leukemia (AML) With Licensing Partner Asterias

-21 subjects treated with clinical effect on survival (no SAEs reported)

Phase I/II Melanoma With Academic Collaborator

-Over 90 subjects treated with strong CD4+ response (no SAEs reported)

TABLE 3



Immunomic Therapeutics Pipeline: Human & Animal Health

Various Phase I Studies in Glioblastoma by Academic Researchers

-Phase I studies conducted at Duke University w/LAMP in a LAMP-pp65-mRNA transfected DC therapy in Glioblastoma with clinically improved outcomes

SUMMARY

ITI has a robust pipeline with several clinical and preclinical vaccines in internal development and access to options from worldwide research laboratories. LAMP immunotherapies have been successfully used in Phase I and II clinical studies, and trial results show it is safe and effective for patients with prostate cancer, AML, melanoma, and pollen allergy. The company has already established commercial licenses with Geron/Asterias/BioTime for oncology and Astellas for JRC-LAMP-Vax and potentially other allergy vaccines. The pipeline (Table 3) shows the various products that are in development with LAMP. ITI has already established commercial licenses with Geron/Asterias/BioTime for oncology and, most recently, Astellas for JRC-LAMP-Vax and potentially other allergy vaccines. Several other products are currently available for collaboration and/or out license. ◆

To view this issue and all back issues online, please visit www.drug-dev.com.

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BIOGRAPHY

Dr. William Hearl is the Founder, President and Chief Executive Officer of Immunomic Therapeutics, Inc., a privately held clinical stage biotechnology company based in Hershey, PA with lab facilities in Rockville, MD. Dr. Hearl's experience in intellectual property management and business development led to the speedy sub-license of the LAMP Technology platform to the Geron Corporation shortly after formally beginning operations at ITI in 2006. His vision for the technology platform later led to the successful clinical development of JRC-LAMP-vax and ultimately to the license of this product to Astellas Pharma in 2015 in a $70+ million deal. Prior to founding ITI, Dr. Hearl also founded Capital Genomix, Inc., a genomic tools company that utilized two novel technologies for the identification and then characterization of genes associated with disease. He was also the VP of Research & Development at Kirkegaard & Perry Labs and a Section Leader at Life Technologies. He earned his PhD in Biochemistry from the University of Tennessee (Oak Ridge, Knoxville) and holds multiple patents and patents pending in the field of genetic immunization.

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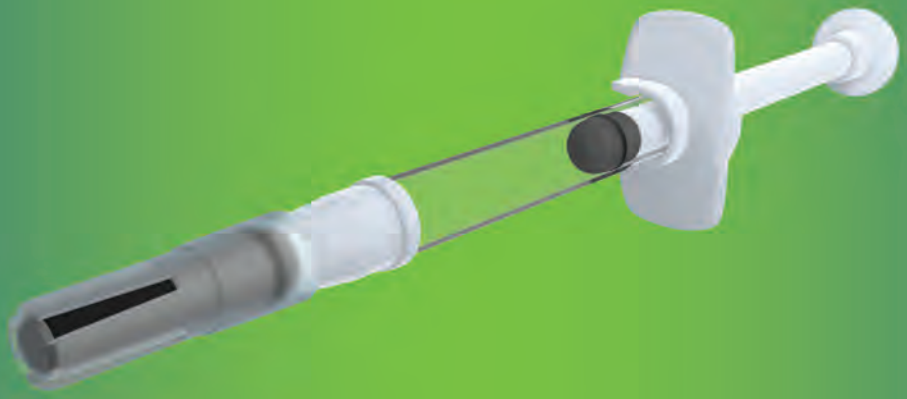

See the Companion at PODD and Universe of PFS

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- Existing primary package components
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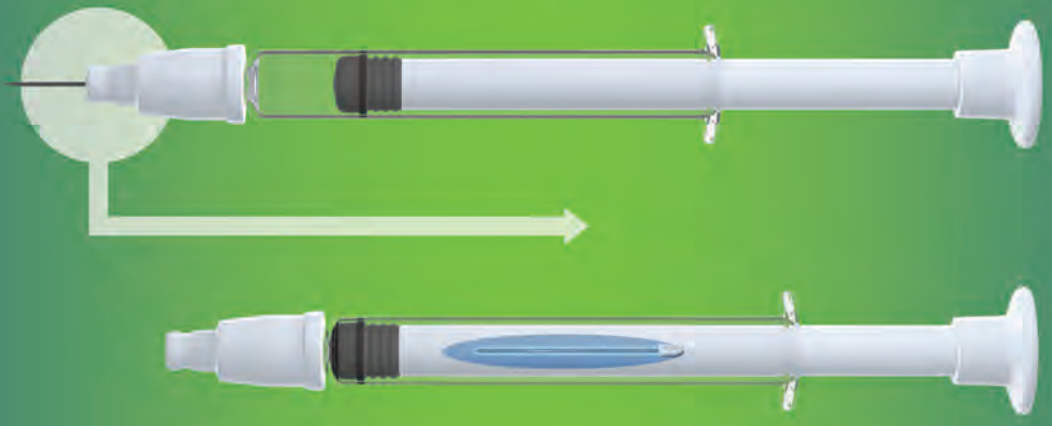
- Optional finger flange



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This product has not yet been evaluated by FDA

CREDENCE MEDSYSTEMS

Special Feature

Injection Devices: Manufacturers Focus on 21st Century Technology While Still Tackling Traditional Challenges

By: Cindy H. Dubin, Contributor

The global injectable drug delivery technologies market was valued at $22.5 billion in 2012 and is expected to reach $43.3 billion by 2017.[1] The market is broadly categorized into two major segments: device technologies and formulation technologies. Hormonal disorders commanded the largest share – 50% – of the global injectable drug delivery technologies market in 2012 and are expected to reach $21.6 billion by 2017. However, auto-immune diseases are the fastest growing segment of this market due to the advent of biologics, tumor necrosis factor (TNF) and Interleukin 1 (IL-1), and improving patient compliance by the development of self-injection devices.

Drug injection device designs are increasingly being based on the results of Human Factors

Sensile is building a bridge from drug to patient.

Engineering (HFE).[2] HFE is about more than just scheduling a study to make sure that a device can be safely and reliably used by the target patient population. "It requires constant engagement with the target patient population and other applicable stakeholders throughout the design and commercialization process," says Stephen Allan, Senior Vice President, Strategic Planning, Unilife.

The goal, he says, should be to maximize the safe, simple, and convenient use of the device by the target patient population. Key factors can include minimizing the number of steps for use and having a fully integrated device that is portable to carry and ergonomic to hold. "Intuitive devices with fully integrated features and minimal steps of use can make a big difference in maximizing rates of acceptability and preference for a therapy amongst your target patient population."

This annual *Drug Development & Delivery* report highlights some of the key players in the injectable delivery market. They will describe their focus on advanced technology, such as wearable smart devices and design issues related to HFE, as well as more traditional challenges related to breakage, leaching, and needlestick prevention.

Aptar Stelmi's PremiumCoat™ is an alternative coated stopper for sensitive drugs. The surface of the elastomer is coated with a thin fluoropolymer film that acts as an effective barrier to many of the extractables and leachables that can be released from the elastomer and contaminate the drug (Courtesy of Aptar Stelmi).

Aptar Stelmi—Maximizing the Integrity of the Container Closure

Maximizing the integrity of the container closure system while minimizing interaction between the closure system and the drug formulation is a vital concern for all pharmaceutical and biopharmaceutical companies. "Elastomeric closures remain the gold-standard solution to preserve the integrity of a container closure system composed of a primary container made either of glass or polymer," says Joel Cotten, Business Development Director for Aptar Stelmi.

Among several families of elastomers used to manufacture these closures, the synthetic halobutyls (Chloro- or Bromo-butyls) present the four main functions that are described by the standards, essential to pharmaceutical and biopharmaceutical industries, and required by the regulatory authorities:

- Compatibility with the drug formulation to prevent its modification and/or degradation over time;
- Physical functionality, i.e., self-sealing after multiple punctures (for a vial stopper) or gliding capability (for a syringe plunger);
- Leakproofness to minimize any exchange with the external environment; and
- Safety of use for the patient and end user.

"Over the past decades, we have witnessed a trend in reducing the number of ingredients in the elastomeric formulations to make them cleaner," says Mr. Cotten.

More recently, the development of coated technologies have proven to be successful for sensitive drug formulations. These coatings are usually applied onto the surface of the elastomeric components to reduce

leaching from the elastomeric closure into the drug formulation. Several coatings exist on the market: ETFE, PTFE films, and spray coatings.

Silicone is traditionally used to lubricate elastomeric closures, but may also interact with the drug formulations. Therefore, reducing and controlling its use remains an objective. Coating technologies and the reduction of silicone oil levels are sometimes combined to address both drug product protection and the fill/finish process.

"In addition to these solutions, which contribute to the reduction of potential leaching between the elastomeric closures and the drug formulation, Aptar has observed growth in fill-and-finish facilities equipped with isolators and Rapid Access Barrier Systems (RABS) to optimize the filling conditions," he says.

Isolators provide a highly controlled area for drug filling into primary containers. This technology ensures a lower level of contamination. As a result, elastomeric closures are supplied sterile and ready-to-use in packages that connect to isolators and RABS. In addition, the latest automated optical control machines used on the manufacturing line contribute to lowering the overall level of particulate contamination of the elastomeric components.

"Pharmaceutical and biopharmaceutical companies continue to develop novel, ready-to-use injectable drug delivery devices," says Mr. Cotten. "With these devices, there is a shift from traditional primary drug containers such as ampoules and vials to safer and more convenient integrated devices such as pefilled syringes and cartridge or bag systems. As a result, the functionality of the elastomeric closures is a key factor.

The Syrina™ range of self-injection devices from Bespak includes assisted syringes with needle safety features as well as three variations of autoinjector. All of these systems utilize the same VapourSoft™ powerpack system.

Bespak—Overcoming the Challenge of Delivering High-Viscous/High-Volume Injectables

Biopharma companies face fierce competition in most key therapeutic areas. One way to differentiate is with a device. Autoinjectors and bolus pump-based systems are being looked at to determine which device is best suited to patient needs, can safely and effectively deliver the drug, and has the highest likelihood of contributing to compliance. However, at the same time, some of the devices currently offered or already on the market, are not well positioned to address the needs of the next wave of biologics and injectables, which tend to be high-viscous/high-volume injectables.

In response, Bespak offers a technology called VapourSoft™ and its related Syrina™ autoinjector platform. The key to VapourSoft is its power source, which helps overcome issues related to spring-based autoinjectors. A small novel container of liquefied gas was developed as the basis for a next-generation powerpack. The propellant, when released, provides sufficient energy in the form of a pressurized vapor to power drug delivery and other functions.

The dampened nature of the delivery mechanism prevents unnecessary impact on the primary container, which is ideal for either glass PFS or cartridge, helping to further minimize any chance of glass breakage. This system is also flexible in that it can offer a complete spectrum of variation to adapt to the needs of the drug, therapeutic area, or the patient. For example, by simply altering the propellant within a single container format, injection time could be customized for even the most

Looking for a syringe system for your sensitive compound?

Today's complex compounds developed by pharma and biotech companies require new, innovative syringe concepts. Vetter-Ject® offers a syringe closure system specially designed for sensitive compounds. By combining a baked-in siliconization process with a staked needle, Vetter-Ject® provides a number of significant advantages:

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- **High product security**
  Baked-in siliconization process reduces product-silicone interaction

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viscous injectables.

"For the first time, changes in delivery volume and viscosity are able to be accepted with minimal physical changes to the device without having a significant impact on device development program timelines," explains Steven R. Kaufman, Global Business Development Lead, Bespak. "High viscosities and high delivery volumes can be handled with relative ease. For example, 2ml of a 200 cPs formulation can be delivered within about 10 seconds."

A variety of primary containers can be used with the VapourSoft powerpack. Containers with a wider diameter offer no additional challenges, and as such, 1ml standard, 1ml long, and 2.25ml syringes can be used without any significant impact on performance, says Mr. Kaufman. Furthermore, the nature of the drive mechanism ensures that the primary container is completely emptied once the device has been activated.

"Being able to offer consistent delivery performance across the Syrina range gives researchers and biopharmaceutical companies the ability to use Syrina with VapourSoft at a very early stage of development," says Mr. Kaufman. Several variations of the devices are available for clinical trials and a range of industrial designs are being considered for the body of the autoinjectors to best suit patient needs.

Credence MedSystems—*Innovation Without Change* Thrives With the Companion Safety Syringe System

As the Credence Companion Safety Syringe System product family has evolved and expanded, the innovation in the delivery systems has accelerated while the change required for drug manufacturers to implement this innovation has diminished even further. The Companion family has grown to include staked needle, luer lock needle, and dual-chamber reconstitution safety devices, all providing passive needlestick safety. Upon completion of the injection, audible, visual, and tactile cues signal that the injection is complete as the needle automatically retracts into the barrel of the syringe, rendering the syringe needle-free and permanently disabled.

Drug manufacturers can select from existing syringe, stopper, and tip cap/needle shield primary package components from the vendors they choose. They then simply incorporate the Companion needle (either kitted with the luer version or pre-attached with the staked version) and plunger rod. "The Companion's ability to utilize existing drug container components simplifies the development and regulatory path, since changing a drug's primary package can require several million dollars and years of development," explains John A. Merhige, Chief Commercial Officer, Credence MedSystems, Inc.

Supply chain risk is also vastly reduced, as drug companies can execute a dual sourcing strategy on critical primary package components. Additionally, the Companion is completely glue-free, eliminating any risk of interaction between glue and the drug product. The glue-free closure also allows alternate lubrication techniques such as baked-in siliconization, thereby enabling compatibility with drug products that are highly sensitive to silicone oil.

Equally important is the requirement to avoid disruption to the fill/finish and secondary manufacturing processes. Syringe filling is unchanged when using the Companion; the syringe barrels are supplied in standard tubs and filled in the conventional manner. Additionally, the Companion's design has simplified secondary packaging requirements. Because the finger flange is entirely optional, the only secondary process that is required for the Companion is the addition of the plunger rod, which is performed in the conventional manner.

For the end user, the Companion offers critical safety technology, with its passive needle retraction and automatic syringe disabling features. The Companion's usability features have been guided by multiple HFE studies. Mr. Merhige says that HFE is critical, and has resulted in the following features: The ability to clearly view the syringe barrel and its contents; the passive/automatic needle retraction; the end-of-dose cues; the capability to perform standard syringe operations like air bubble removal and aspiration; the feel in the user's hands; and the compact footprint for storage and environmentally sound disposal.

"*Innovation Without Change* combines these end-user benefits with a novel design approach that allows drug manufacturers a simplified path to best-in-class drug delivery," says Mr. Merhige.

The Enable Reconstitution System is a fully automated mixing and transfer system that is capable of mixing up to 2 x 10ml vials of liquid or liquid/powder.

Enable Injections—The Wearable Injector: Enabling the Biologic Drug Market

Analysts predict the market for biologic drugs will reach $215 billion in the next five years. More than 900 injectable biologic drugs are currently in development or on the market. However, injectable biologics will only fulfill their promise if the formulations that are developed can use drug delivery devices that are patient friendly, allowing patients greater mobility and convenience.

Larger dose, often viscous biologics are delivered intravenously in the hospital setting. Moving treatment from hospital to the home can reduce healthcare costs and improve patient quality of life. The wearable injector has the potential to meet these trending needs.

When a major pharmaceutical company sought to improve the comfort, convenience, and treatment compliance for patients, it carefully examined the drug delivery alternatives. Based on strong preference from its patient panels, it turned to Enable Injections to design a wearable injector that could deliver

a highly viscous biological product subcutaneously in high volume (2-20ml) as an alternative to the current infusion pumps. The device is expected to increase patient independence, mobility, convenience, and compliance, explains Michael D. Hooven, President and CEO of Enable Injections.

Enable Injections has developed wearable injectors capable of consistently delivering higher volume (1-10ml and 1-20ml) drug products designed to maximize tolerability and reduce pain. The injectors are customized to the specific drug product characteristics. Also, there are different transfer platforms, each compatible with a different, established primary container (syringe and vial), providing advantages to the product manufacturer, which include cost savings and shorter time to market.

"The evolution to smart injectors is of great interest to Enable Injections. Providing the means for users and healthcare professionals to track and record compliance to therapy can potentially provide information to help ensure better health outcomes. For product manufacturers, improving compliance and keeping a patient on therapy can be more profitable than recruiting new patients," says Mr. Hooven.

Enable Injections has focused on human factors to play a key role in the design and development of devices to make self-injection safe, easy, comfortable, and convenient for patients, yet cost-effective for the pharmaceutical industry and payers.

More sophisticated drug delivery devices are being differentiated from legacy injection systems by:

- Utilizing standard vials or syringes to eliminate new container closure development.
- Automatically warming the drug as the injector fills, thereby removing the typical wait time to use the device for a refrigerated medication.
- Automating mixing for lyophilized drugs.
- Using the smallest needle size possible to improve patient comfort.
- Designing small systems with a low profile that can be discreetly worn on the body, allowing greater freedom and mobility.
- Making the entire system environmentally friendly so that there are no electronics or batteries to remove or recycle.

Haselmeier—Technologies That Meet Patient-Centered Systems

Haselmeier has been providing customized devices for its pharmaceutical partners for more than 40 years. Many of these devices are created using current platform technologies and IP, then customized for specific drug and patient usability requirements. "We conduct ongoing research to understand both current and nascent device requirements and develop new systems to meet these needs," says Terry O'Hagan, Director Business Developement, Haselmeier. "New features such as dynamic speed control, variable dose prefilled syringes, distinct dosing, active safety systems, and electronics integration for improved patient compliance are all examples of current features and technologies we have developed to meet the growing need for patient-centered systems."

Use of unique forms and materials for improved styling and physical interaction all contribute to devices with improved patient

Haselmeier Axis-D® Disposable Pen System with larger ringed dose window.

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OmniPod Delivery Management System from Insulet Delivery Systems Group

acceptance and effective drug delivery. For example, Haselmeir integrated a new dose setting system in its Axis D disposable pen injector, which allows for a larger ringed dose window that better draws a patient's eye to the number while eliminating all other printing typical with standard pen designs, explains Mr. O'Hagan. "Research has shown this improves the patient experience with the device and removes dosing errors."

Mr. O'Hagan adds that the injection device market has seen a significant shift from pharmaceutical companies looking to use standardized devices to looking for more customized patient-centered systems. "This dynamic can be attributed to the particular requirements of a new range of biologics as well an interest to develop devices for specific patient populations," he says. "Current FDA guidance has led many companies to either design new devices or modify existing devices to meet increased regulatory requirements to create devices that are easier to use, safer, and more accurate. In addition, new technologies are providing a wider range of delivery methods to address new drug and patient needs."

As more drugs are approved for self-administration, the FDA has issued additional usability guidelines and more in-depth Human Factors Engineering requirements to ensure that devices are more intuitive and easy to use, safer, and more accurate to ensure that patients are getting an effective treatment. "Pharmaceutical companies must demonstrate, through extensive Human Factors Studies, that devices can be used safely and effectively by the specific patient population for that targeted indication."

As could be expected, the targeted patient population for a device can have a significant impact on the overall design and feature set of self-injection systems. Devices need to meet age-related needs such as pediatrics (often administered by a parent or care giver), young adults, adults, and seniors. In addition, some patients may have physical limitations with vision, dexterity, and strength that can have a large impact on the overall device design and feature set.

"New technology development is creating additional modes of delivery and supporting efforts to improve patient compliance with new drug regimens," says Mr. O'Hagan.

Insulet Corp.—The OmniPod Drug Delivery Management System

With an increase in complex drugs and biologics coming to market, drug developers continue to look for innovative technology that can simplify their delivery needs. Conventional methods of injection, such as syringes and pens, address simple injectable delivery routines. Advances in smart, wearable delivery, like the OmniPod Drug Delivery Management System from Insulet, address the problems of complex dosing regimens, without restrictions to patient lifestyle while emphasizing competitive differentiation, says Michael Graffeo, Vice President of Business Development for Insulet.

Since the launch of OmniPod 10 years ago, Insulet has expanded its wearable pump technology to include multiple drug delivery applications. OmniPod's intelligent, easy-to-use design delivers the exact dose of medication at the precise time, repeatedly and reliably. Its automatic and virtually pain-free insertion helps to eliminate the difficulties of self-

administration and provides valuable information to clinicians and biopharmaceutical companies. "Unlike other methods, OmniPod's platform can be customized to achieve drug delivery that was once impossible to imagine," he says.

OmniPod is being used with a treatment to help women ovulate, which requires an injected dose every 90 minutes throughout the treatment's timeframe. Additionally, the clinician may need to modify the dosage amount during the time of treatment. Prior to OmniPod, patients wore an inconvenient syringe pump, explains Mr. Graffeo. With OmniPod's smart, wearable technology, the clinician manages the dosing adjustments through the Drug Delivery Manager (DDM) while the patient receives regular dosing without needle fatigue.

"With OmniPod's intelligent delivery technology, patients no longer face the inconveniences previously found in complicated therapeutic dosing. OmniPod provides opportunities to create competitive differentiation and address problems pharmaceutical companies face in complex dosing regimens, efficiency, and efficacy."

Nemera—Passive Platform Addresses Human Factors & Needlestick Safety

In the parenteral industry, needlestick injuries are a global concern with more than three million exposures to blood occurring every year, according to the World Health Organization (WHO). In an environment where home care and self-administration of parenteral drugs are becoming more common, focusing on the safety profile of the drug and its outcomes are not enough, says Adrien Tisserand, Junior Category Manager-Parenteral, Nemera. Consideration of the hazards linked to the drug, its usage, and the user are critical to ensure the product is safe to use. As a result, the FDA has mandated the consideration of HFE and ergonomics in the design of medical devices.

Nemera has developed Safe'n'Sound®, a platform of passive safety devices for prefilled syringes to aid in the protection from accidental needlesticks.

Medical devices should ensure four aspects: safety, effectiveness, usability, and satisfaction. Therefore, a medical device must be designed first to be safe, then functional and usable, before being designed to generate pleasure. To achieve those four aspects, it is mandatory to consider the device failure hazards and use-related hazards. Investigating those hazards requires a complete understanding of the device, its environment, and its users. This includes analyzing the marketed devices and unmet needs to determine room for improvement, to perform user studies, to identify hazards and problems, usability, and simulated clinical studies for verification and validation.

In response to needs for improved user safety and injection conditions, Nemera has developed Safe'n'Sound®, a platform of passive safety devices for prefilled syringes to aid in the protection from accidental needlesticks. Safe'n'Sound is a single-use device and is an adaptable platform to give flexibility to pharmaceuticals and users. Safe'n'Sound is compatible with syringes of different filling volume (1ml & 2.25ml) and flange types from different suppliers.

The safety feature activates

automatically at the end of the injection, easing the use. User interface features have been integrated: a large thumb pad surface to smooth the injection; large built-in finger flange to facilitate handling; a round shape for easy and comfortable handling; and a spring located at the syringe flange position to provide good visibility of the tip of syringe and inspection of the drug.

Sensile Medical—Wearable Injector is Reusable & Cost Reducing

As time-to-market is essential, Sensile Medical offers a platform device usable as a large-volume injector, yet flexible enough to meet the customized needs of drugs and patients. The SenseCore wearable injector pumps drug into the body over an extended period of time.

"SenseCore administration does not require special skills and is less invasive from a patient perspective than IV administration," says Sandra de Haan, Head of Business Development, Sensile Medical. "Instead of requiring patients to visit the hospital the day after chemotherapy for an injection, for example, patients can now use a wearable device that automates delivery and alerts the patient when the injector is active and once the delivery is completed. This approach is much more convenient for the patient and can dramatically reduce the costs for administration compared to a hospital infusion center or treatment at a doctor's office."

The device comes with a randomly fillable internal reservoir for a volume up to 20ml, offering the possibility to use standard vials as the primary package. The option of using a standard primary container, combined with the auto-fill feature, eliminates the need for development and testing of a new or novel primary container and a separate fill facility for the container, explains Ms. de Haan. This can reduce time to clinical use or market by several years, as new primary packaging alone may take 4-5 years, she adds.

SenseCore is a reciprocating-type positive displacement pump. Specifically, it is a piston pump with a ring-shaped piston area. The rotating piston, together with an injection-molded valve structure, mechanically drives intake and outlet valves and additionally generates the correct pumping stroke derived from the primary rotation.

The nominal delivery volume can be designed to the required optimum delivery volume per stroke, typically ranging from less than 1µl to 25µl per cycle.

SenseCore handles highly viscous liquids as well as gases and liquid/gas mixtures. It can also be used to reconstitute lyophilized products with diluents, mixing both products in a defined reconstitution process, transferring the reconstituted liquid into a primary container or administering it directly. Dose accuracy from the first until the last partial dose is highly accurate, around +/- 5%.

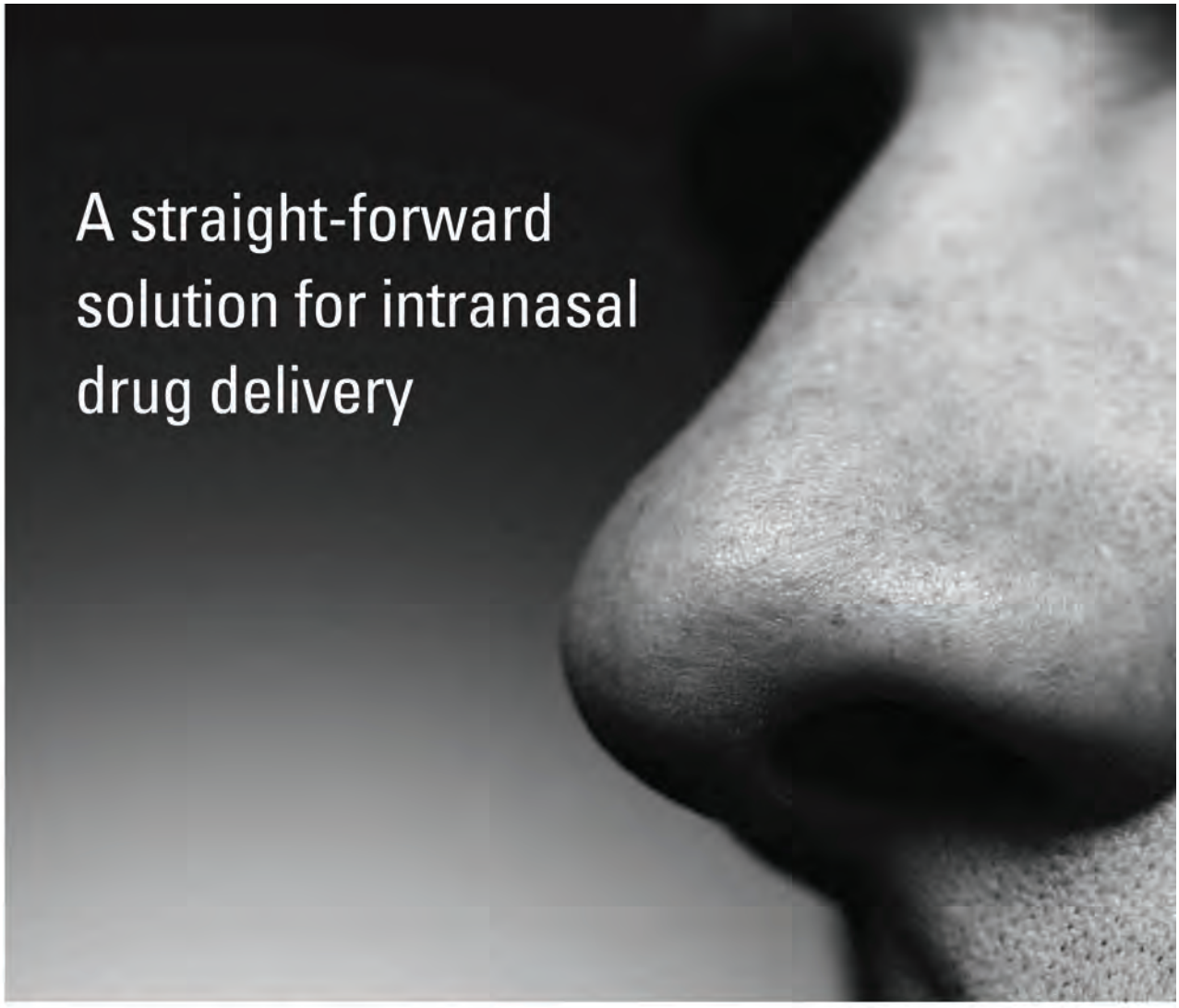
With Sensile's Disposable/Reusable concept, there is no need to discard the entire device after use, as the mechanism that provides the force and energy is part of the reusable unit that can be reused over a defined period.

SiO_2 Medical Products, Inc.—A Company Built Around Plastic

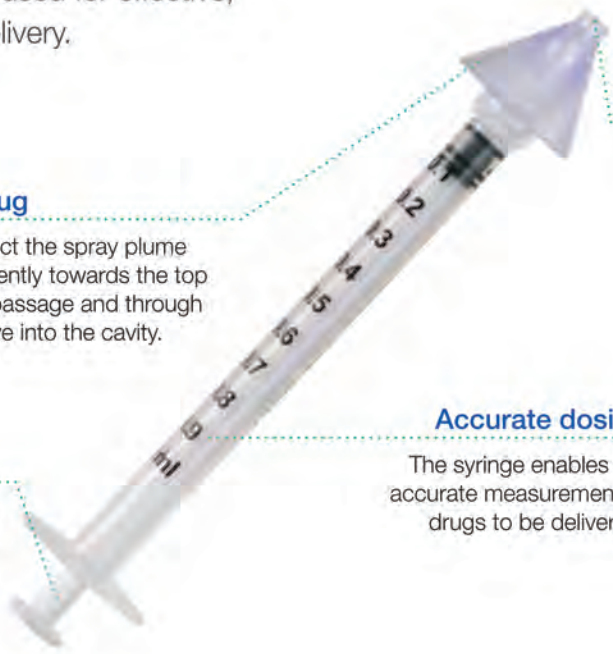
While glass has been used as a container for decades, it has a number of issues (pits, cracks, breakage, delamination, particles, incompatibility with some methods of sterilization, variable optical quality, workplace safety risks, difficulty of disposal at hospitals, and leachables depending on the drug product). These issues are eliminated entirely through the use of SiO_2's plastic/glass lined primary containers. SiO_2 Medical Products, Inc.'s SiOPlas™ line of containers address all of the issues of glass containers and are tungsten free, resist breakage, and are comparable to glass as a gas barrier.

Autoinjectors and pens are precision-molded products that can put incredible stress on a primary container. Having tight control over lubrication (non-silicone) and tolerances can ensure a better designed, functioning product overall. During the design process for some autoinjectors and pens, more than 50% of the stack-up tolerances can be due to dimensional variability just in the glass container. Reducing the

A straight-forward solution for intranasal drug delivery



The Teleflex VaxINator™ is used for effective, easy-to-use nasal drug delivery.



Atomization spray

The spray atomizes drugs into a fine mist of particles 30-100 microns in size.

Conical plug

An aid to direct the spray plume more consistently towards the top of the nasal passage and through the nasal valve into the cavity.

Accurate dosing

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Patent pending.

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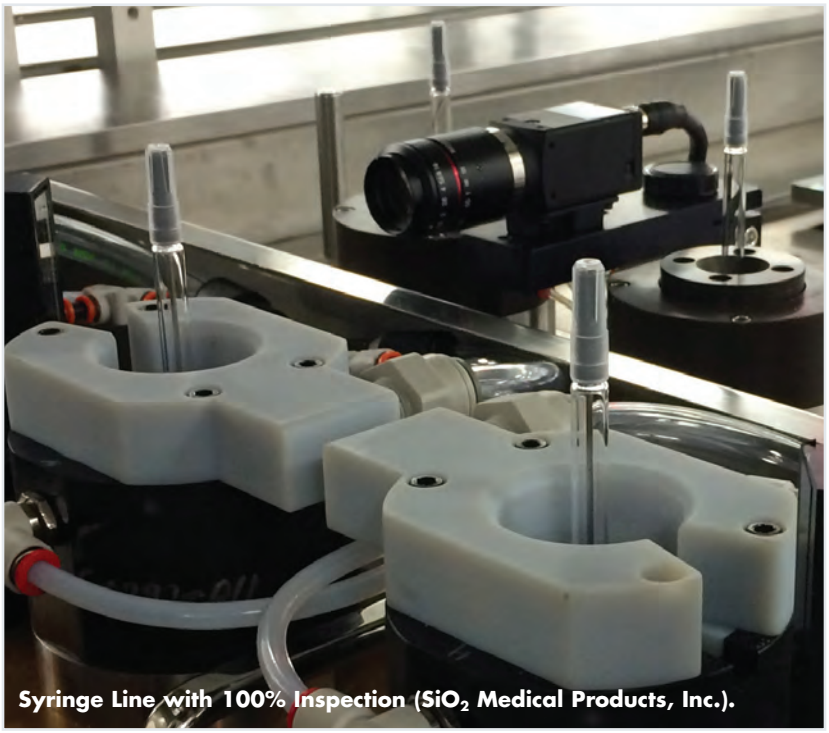
variability through a plastic container allows the injector to function more precisely, with less variability and a reduced chance of failure.

SiO_2 Medical Products, Inc. is a company that has been built around plastic. Designed specifically for the parenteral market, SiO_2 offers a line of primary containers that provide improved performance and consistency over existing glass containers. "Our syringes, vials, cartridges, and custom containers have a thin, transparent, silicon-oxide barrier coating deposited on the interior surfaces," says Christopher Weikart, PhD, Director of R&D. "Our barrier system effectively addresses current issues being experienced by the parenteral drug industry and our containers are ideally suited for sensitive biologics."

The company's proprietary barrier coating system eliminates the need for silicone. In addition, Peter Sagona, Senior Vice President, says that SiO_2 has much greater dimensional control than glass, allowing tighter tolerances in the design of autoinjectors and pens. "Similar to other products, we use state-of-the-art injection molding. In addition, when your containers leave our factory ready to be filled (clean, sterile, and packaged), we have conducted 100% inspection, not just a sampling, to ensure quality. We also offer individual serialization of every unit that comes off our line, providing complete track and trace of every container used."

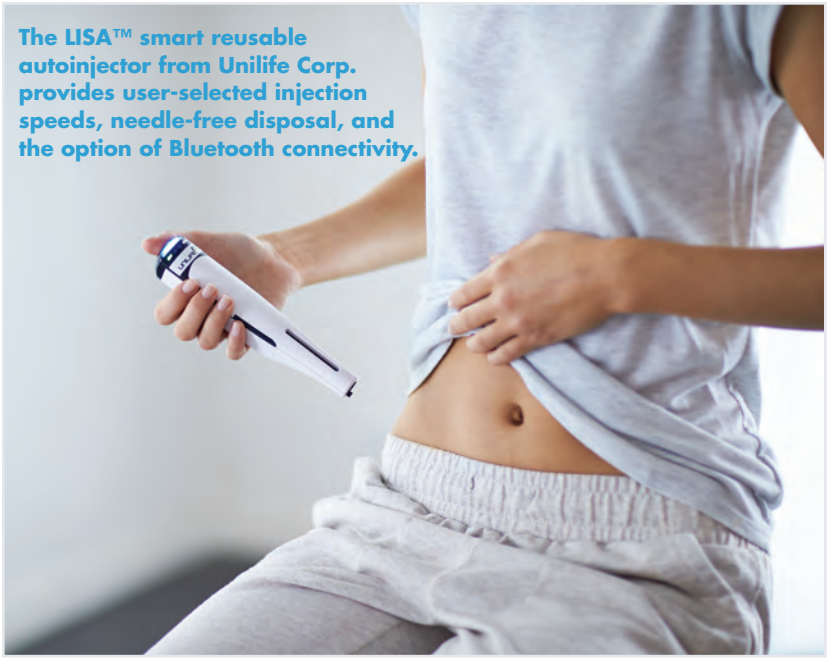


Syringe Line with 100% Inspection (SiO_2 Medical Products, Inc.).

Unilife Corp.—Customizable Devices that Address a Range of Injectables

The integration of Bluetooth LE within injectable drug delivery systems such as insulin pumps, wearable injectors, and autoinjectors represents a paradigm shift in medication delivery. For the first time, biopharma companies will be able to work with payers and prescribers to leverage the power of data informatics to improve rates of patient compliance and demonstrate the clear value-based healthcare outcomes associated with their brand of therapy. For patients, it means timely reminders and injection status updates via their smart phones to help improve health and overall quality of life. For prescribers and payers, it means access to real-time or historic data on how patients are complying with their therapy regimes within a particular disease area. Unilife is working with customers seeking access to devices with Bluetooth capabilities across several segments including wearable injectors, insulin patch pumps, and smart reusable autoinjectors.

To minimize risk and maximize flexibility, biopharma companies are increasingly seeking to select one preferred platform-based technology that can be used across a family of biologics. Platform-based devices allow pharmaceutical companies to efficiently customize each product to the specific drug, patient, and commercial requirements of each target indication. "Unilife provides customers with a range of customization options that can be easily leveraged to optimize the containment, delivery, and commercial success of their drug-device combination products," says



The LISA™ smart reusable autoinjector from Unilife Corp. provides user-selected injection speeds, needle-free disposal, and the option of Bluetooth connectivity.

Stephen Allan, Senior Vice President, Strategic Planning, Unilife.

Unilife has created a broad portfolio of highly differentiated, fully customizable devices that can accommodate the needs of virtually any injectable biologic, drug or vaccine, adds Mr. Allan. Its portfolio includes wearable injectors, instant insulin patch pumps, smart reusable autoinjectors, single- and dual-chamber prefilled syringes, ocular delivery systems, and novel delivery systems. This portfolio can be leveraged by customers with liquid, lyophilized or combination therapies for drugs measured in microliters to large dose volume therapies of 10ml or more.

West Pharmaceutical Services, Inc.—Focused on Next-Generation Care

West provides a variety of self-injection technologies focused on improved patient experience and compliance. Offerings include the SmartDose® electronic wearable injector, an integrated drug delivery solution designed to ease self-injection and mitigate the risk of accidental needlestick injuries through an integrated safety system. This single-use injector adheres to the patient's body, usually on the abdomen, and is pre-programmed to deliver high volumes of viscous or sensitive drug products. Intuitive and easy-to-use, the SmartDose injector incorporates a polymer-based drug container (made from DaikyCrystal Zenith® resin) with a drug delivery system that controls the delivery of large doses over time, making it easier for patients to self-administer medication outside of the clinical setting. Additionally, the ConfiDose® autoinjector provides an easy-to-use solution for a wide range of pharmaceutical therapies and is an ideal option for self-injection of a fixed-needle prefilled syringe.

"West offers a full range of custom development and manufacturing capabilities to help bring our customers' devices and delivery systems to market," says Graham Reynolds, Vice President, Marketing and Communications, Delivery Systems, West Pharmaceutical Services, Inc.

"Increasingly there is not a "one-size-fits-all" option, and West's ability to offer a range of developed solutions, as well as customizable or customer-specific delivery systems, enables us to meet the needs of our customers."

Each element of these drug delivery models – the Daikyo Crystal Zenith polymers, the SmartDose electronic wearable injector system, and the connected health applications from West's partnership with HealthPrize – are next-generation tools. "Together, they help pharmaceutical companies create cutting-edge systems that not only benefit patients by helping them to avoid the consequences of non-adherence to medications but help the drug manufacturer ensure that a product delivered to market is used to its full potential. The combination of these three drug delivery components also can yield data points previously unavailable to drug companies for analysis. By performing data analytics on usage patterns, more can

West SmartDose® electronic wearable injector.

be learned about these medications and the way they are used by patients in their homes, which can ultimately lead to the development of improved therapies and better quality of life for patients living with chronic diseases," he says.

The shift to self-care in the home setting and increased use of biologics in the management of chronic diseases has driven demand for novel approaches to drug delivery. Many injectable drugs currently on the market, and many in development, require repeated dosing and are intended for self-administration. To help patients who must self-dose, West is designing systems such as the SmartDose injector that are easy to use and that encourage patients to comply with a dosing regimen by making it simple for patients to self-administer medication outside of the clinical setting.

As a company invested in next-generation care, with the help of HealthPrize Technologies, West is exploring opportunities to connect injectable drug delivery systems with connected health tools that can improve the user experience and drive adherence. "Specifically, we are working to realize the potential of using consumer technology and electronic devices to further engage patients in their care and address the issue of non-compliance," says Mr. Graham. "In our first offering with HealthPrize, patients will manually scan barcodes or otherwise enter data about their medication compliance into the smartphone/tablet app or on an Internet browser from a computer if they don't have a wireless device. In the near future, we would like to make app use even more automated, streamlined, and interactive. This is our way of getting involved with the connected health movement to encourage patient engagement and offer our pharma partners a range of choices."

Ypsomed—Comprehensive Range of Platforms for Customized Self-Injection Devices

Biopharmaceutical companies increasingly focus on self-injection devices as a mechanism for differentiating the drug product. As a result, manufacturers of innovative drug delivery systems have become key partners in the successful development and commercialization of the final combination product. Increased pressure on healthcare product prices, increased complexity in drug formulation, and stringent regulatory scrutiny require manufacturers of injection systems to flexibly supply biopharmaceutical companies with novel injection pens and autoinjectors customized to their individual needs.

Responding to these emerging requirements, Ypsomed has built up comprehensive platform products that each meet key customer needs, yet are specifically designed to be modified into customer-specific products. Platform products enable flexible customization while minimizing project risks and shortening time to market. "Ypsomed decouples the development of new platform products from the customer project and thereby moves risk in-house to cover platform development and installation of manufacturing infrastructure," says Ian Thompson, Vice President Business Development, Ypsomed. "Each customer project stems from an existing platform based on an established patent position and

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UnoPen Disposable Pen, YpsoMate Disposable Autoinjector, LyoTwist Devices for GlaxoSmithKline and AstraZeneca (Ypsomed).

proven technology."

Driven by patient needs, market intelligence, and new technology, the development of novel platform products also requires significant investments in manufacturing capacity. Ypsomed supports its partners by customizing the injection systems to market demands, dosing needs, and to the primary container, but also by incrementally expanding its installed manufacturing infrastructure to match customer capacity requirements, says Mr. Thompson.

Consider the UnoPen, Ypsomed's variable and multi-dose disposable pen platform that offers key features such as intuitive dial-and-dose handling, audible feedback during dosing and delivery, or the last-dose stop functionality to ensure that the dialed dose cannot exceed the remaining volume in the cartridge. Customization to individual design, dosing, and cartridge requirements makes the UnoPen platform suited to a range of hormone-based therapies, including insulin, glucagon-like peptide-1 (GLP-1), human growth hormone (hGH), follicle stimulating hormone (FSH), or parathyroid hormone (PTH).

Ypsomed's platform products also include the autoinjector segment for pefilled syringes. The YpsoMate disposable autoinjector provides patients with an easy and convenient two-step automatic injection. The patient triggers the injection by pushing the autoinjector onto the skin. The device then signals completion of the injection through a clearly audible end-of-injection click and visual feedback in the large viewing window. The needle remains hidden during injection and is shielded after use.

Ypsomed's LyoTwist dual-chamber devices are for single-dose injections. The LyoTwist "monodose" device family is based on Ypsomed's twisting method for reconstitution and priming. The devices provide visualization of reconstitution, priming, and injection. LyoTwist devices can be used with standard Ypsomed Clickfine pen needles or in combination with Clickfine AutoProtect safety pen needles that provide built-in needle safety. Ypsomed can customize LyoTwist according to an individual drug and therapy needs.

The simplest member of the LyoTwist family known as LyoTwist Trio was successfully launched in 2014 for two versions of long-acting glucagon-like peptide-1 (GLP-1), a drug that is becoming increasingly important in the treatment of Type 2 diabetes. GlaxoSmithKline markets its Eperzan®/Tanzeum™ and AstraZeneca, its Bydureon® GLP-1, both for subcutaneous administration, based on LyoTwist devices.

"User-friendliness and a simple, robust design were key requirements for both injection systems, which were convincingly implemented by Ypsomed," says Mr. Thompson. ◆

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SYRINGE STUDY

Gerresheimer - Scrutinizing 20,000 Syringes, A Long-Term Study (2011-2015)

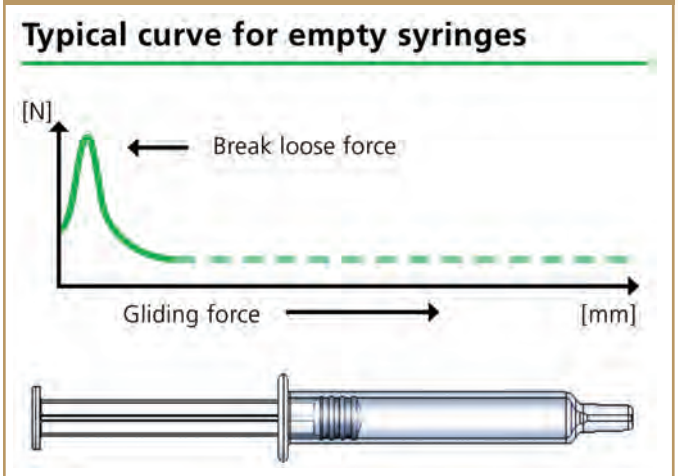
By: Bernd Zeiss, Manager Technical Support Medical Systems Business Development, Gerresheimer Medical Systems

INTRODUCTION

All kinds of factors can affect syringe system performance. This Gerresheimer study focused on the parameters that affect break loose and gliding forces. The study investigated the influence of syringe diameter (1ml short and 1ml long (inside diameter 6.35mm or 8.65mm), the siliconization process (RTF® spray-on siliconization with pure silicone oil and RTF® baked-on siliconization with silicone oil emulsion), the content (empty syringes and syringes filled with water for injection), plunger stopper placement (vacuum or vented placement), the plunger stopper itself (established plunger stoppers and plunger stoppers being developed by various manufacturers, in various dimensions/designs, with different rubber formula, uncoated and surface treated/coated, various siliconization levels).

The comparison also extended to different storage periods. Measurements were taken immediately after plunger placement, as well as after 3, 6, 12, 24 and 36 months of storage at room temperature. Further measurements were taken in an accelerated aging environment (40°C, 75% humidity) after 3 and 6 months. In order to verify the statistics of the results, 20 parallel samples of all the aforementioned syringe systems were studied to create a database of more than 20,000 individual data records. The study determined the minimum, maximum, and mean values, as well the standard deviation of break loose and gliding forces. When the content of a syringe is discharged, there are two phases with different force profiles. First, it is necessary to overcome the resistance between the syringe barrel and plunger stopper to move the plunger head. This is called break loose force. Then, as the plunger stopper moves down the syringe barrel, it encounters friction resistance until the syringe barrel is emptied. That's gliding force. Ideally, the gliding force curve is horizontal. The study identified a range of critical parameters that can cause problems in syringe usage. These are initially too high break loose forces, especially in connection with a sharp decline at the transition from break loose to gliding force. Both can cause distinct problems for the syringe user. Significant deviations between the same syringe combinations (parallel samples) are also critical because they make their use in autoinjectors problematic. Auto-injectors depend on a "reliable" syringe and constant forces. When syringes are used manually, such deviations mean that the user will experience some syringes with plungers that are easy to depress and some with plungers

FIGURE 1



Typical gliding force curve for empty syringes.

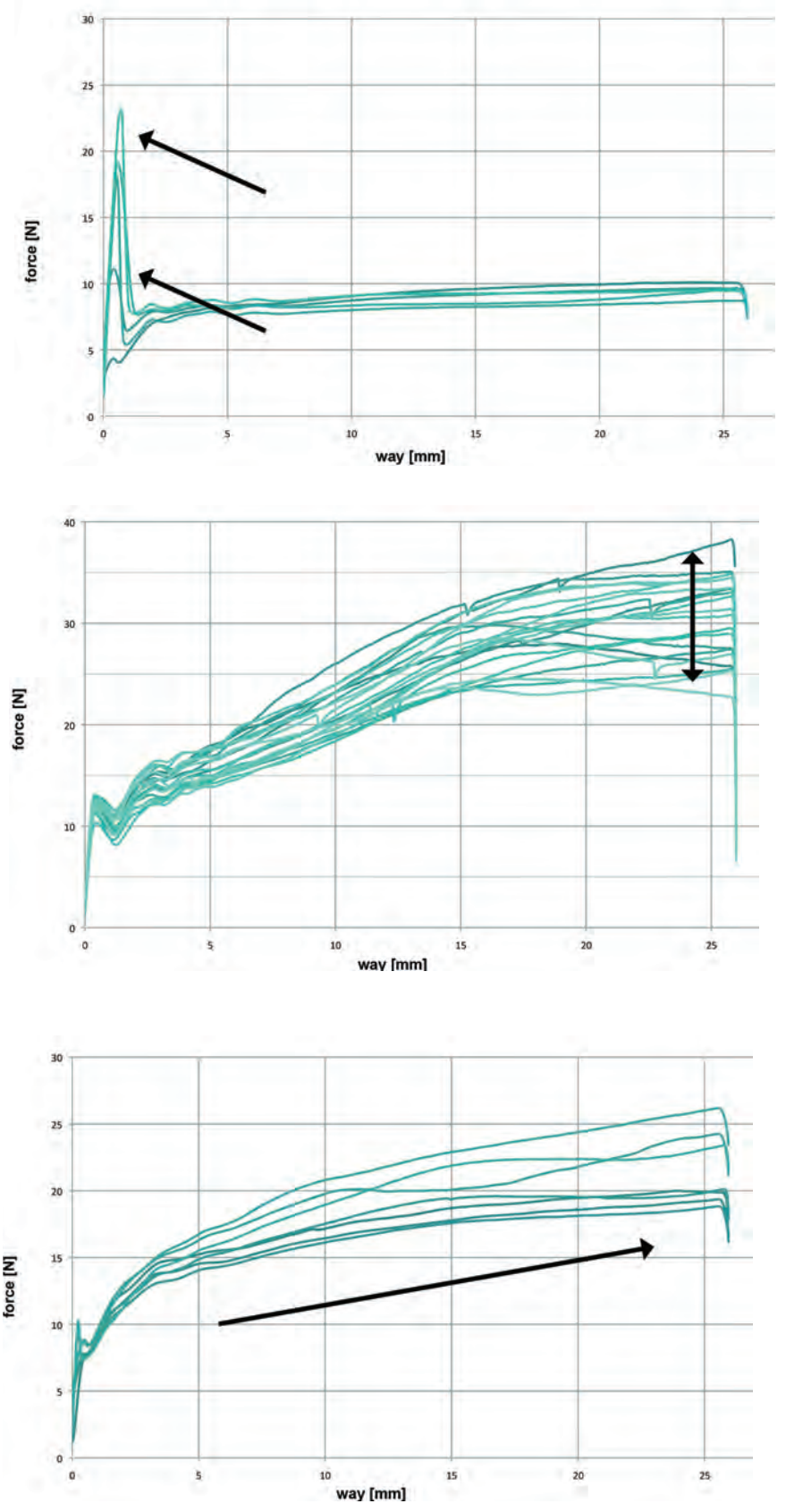
that are hard to depress. Syringe systems with gliding forces that increase from the start to the end of the injection were also problematic. Changes occurring over storage time, e.g. higher gliding forces after several months of storage, are also critical.

SILICONIZATION: THE CORRECT QUANTITY MAKES THE DIFFERENCE

Gerresheimer believes that the syringe's siliconization is a decisive factor that can be influenced in the production process. The mechanical function of a syringe depends on the precise dimensioning of all parts and, more importantly, the optimum interaction of the syringe barrel and plunger stopper. Other criteria include simple and safe handling, the complete discharge of all content, especially when the syringe is incorporated in a spring-driven autoinjector that always builds up exact pressure. The syringe's siliconization has decisive influence on all these factors. It reduces the break loose and gliding forces during use, creates a tight connection between the plunger stopper and the glass, and provides a hydrophobic surface that facilitates the more effective discharge of syringe content.

The adsorption of pharmaceutical drugs by the glass surface can also be reduced with some formulations. Medical silicone oils are long established because they are harmless to health, more or less inert, viscoelastic, and hydrophobic. They are also included in the relevant pharmacopeia (Ph. EUR and USP). When using silicone oil as an anti-friction coating in ready-to-fill syringes, it

FIGURES 2A,B & C



Critical parameters of break loose forces, force variation and increasing gliding forces.

The mechanical function of a syringe depends on the precise dimensioning of all parts and, more importantly, the optimum interaction of the syringe barrel and plunger stopper. Other criteria include simple and safe handling, the complete discharge of all content, especially when the syringe is incorporated in a spring-driven autoinjector that always builds up exact pressure.

is necessary to take several decisive factors into consideration to guarantee syringe function. A silicone coating that is too thin or uneven can impair the syringe's mechanical function. Too much silicone oil can, in some circumstances, result in the formation of free silicone oil droplets. Visible droplets are a cosmetic defect that is categorized as critical, particularly when the syringes contain ophthalmological medications.

Droplets in biotech drugs can also cause sub-visual problems because the active ingredient binds with them, thereby reducing the quantity of available active ingredient. In many cases, therefore, the objective when developing prefillable syringes is to reduce the quantity of silicone oil to the minimum level possible without impairing the syringe's mechanical function. In particularly critical fields of application, the silicone oil can be thermally bonded to the glass surface. In this case, the silicone oil is applied as an emulsion and then burnt on at temperatures more than 300°C. This creates stable covalent bonds between the glass surface molecules and the silicone oil to form a permanent hydrophobic anti-friction coating. The quantity of free droplets is less than 10% of those associated with traditional spray-on siliconization.

FIGURE 3

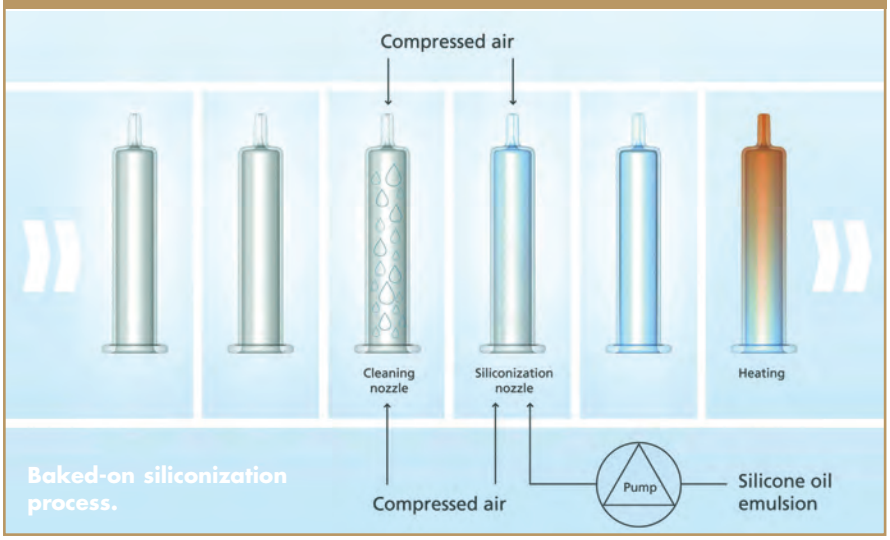
Prefilled syringes simplify the administration of injectable pharmaceutical drugs.

THE RESULTS

The results of the study contribute to a clearer picture of the factors of influence that are crucial to syringe function. Several common hypotheses were verified, while others were refuted. For example, the study design confirmed that accelerated aging is a reliable way of achieving faster and more informative results. This can considerably reduce the time required to perform future studies. The comparison of baked-on and spray-on siliconization revealed higher gliding forces in the case of baked-on siliconization, which is due to the lower quantities of silicone oil used. On the other hand, the number of free silicone particles was significantly lower in the case of baked-on siliconization. The widespread assumption was not confirmed that break loose forces in syringes with spray-on siliconization increase at a faster rate over the storage period than in syringes with baked-on siliconization. Generally, the effect of long-term storage tends to be moderate.

However, the type of plunger stopper used is of decisive significance. The choice of plunger stopper design, the rubber formula, the coating, and the siliconization have considerable

FIGURE 4



influence on syringe function. Whether the plunger stopper is inserted by vacuum or vented placement only affects break loose and gliding forces in some plunger stopper types. The complex interrelationship between the components and the siliconization makes it clear that there is no universal solution for syringe function. Rather, a syringe system has to be individually tailored to the pharmaceutical drug, user and, in some cases, to requirements for integration in auto-injectors. The comprehensive data obtained in our long-term study enables us to provide customers with detailed advice on the choice of the right syringe system and to offer customized solutions that are optimized for all the parameters of their specific application.

REVIEWING QUALITY MANAGEMENT: RECERTIFICATION AT THE BÜNDE PLANT

Bünde underwent a recertification audit for its quality management system in 2015. Over the 7.5-day audit, the plant's quality management system was reviewed to assess its compliance with the ISO 9001, DIN EN ISO 13485, and DIN EN ISO 15378 standards. The audit had a very positive outcome. Only one minor non-compliance was ascertained and immediately remedied, which meant that all the certificates could be reissued without a problem. This is a very positive result considering that the framework was extremely challenging. First, the audit was implemented with only one team, which shows that our quality management system is very well established and stable. Second, the recertification audit was a witness audit, so the auditors themselves were also being assessed. It was performed by the DQS auditors, who were assessed by auditors from the German Accreditation Body (DAkkS) in order to retain their accreditation. A witness audit doesn't change the recertification process, but it does mean that the audit is generally very stringent and in strict conformity with the rules. ◆

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BIOGRAPHY

Bernd Zeiss studied Biology, Microbiology and Chemistry at the University of Göttingen, Germany. After several years working in the fields of contract research, clinical sales management and automated laboratory equipment, he today is a member of the Gerresheimer Buende business development team. He works in the Gerresheimer Centre of Excellence for prefillable syringes as Manager Technical Support Medical Systems Business Development. His main areas of work are customer support, investigating possible interactions between syringe components and drug substance and the evaluation of innovations like COP syringes in comparison to glass. Bernd Zeiss also carries out inhouse prefillable syringe studies and prepares technical documentations for customers called "Technical Bulletins."

HOT MELT EXTRUSION

OptiMelt™ Hot Melt Extrusion Technology to Improve Bioavailability of Poorly Soluble Drugs

By: Sampada Upadhye, PhD

INTRODUCTION

One of the biggest challenges faced today by the pharmaceutical industry lies in enabling the delivery of difficult-to-solubilize molecules. Solubility is an essential physico-chemical characteristic of active pharmaceutical ingredients (APIs), as it directly relates to bioavailability of the molecule internally in the body. Poorly soluble APIs dissolve/disperse sparingly in the gut and have generally low bioavailability. Approximately 40% of currently marketed drugs are classified as poorly soluble (BCS Class II/IV), and more than 70% of drugs in development are also poorly soluble, representing an increasing industry challenge, especially so given that it can be quite resource intensive to develop formulations for poorly soluble drugs. The problem is most severe when the molecule has both low solubility and a high dose.

To accelerate the development of molecules through the clinical programs, technologies for mitigating the effects of the poor solubility and in turn poor bioavailability are becoming essential for the success of new drug molecules.

Hot melt extrusion (HME) is a technology that is gaining interest in the pharmaceutical industry as a novel technique to generate physically stable and processable amorphous forms of APIs. Relative to crystalline APIs, amorphous solid dispersions improve bioavailability in more than 80% of cases, thus enhancing R&D productivity and enabling effective drug development. The mechanism of HME is to disperse APIs in the polymer matrix at the molecular level to form solid dispersions or solid solutions. The main driver of increased use of HME technology in the pharmaceutical industry is its capability of continuous manufacturing with solvent-less processing and the versatility of the downstream processing of extrudates into final dosage forms (tablets, capsules, controlled release forms, stick packs etc).

QUALITY-BY-DESIGN

HME enables product development driven by Quality-by-Design (QbD). Thus, parameters including degree of dispersion, level of impurities, extent of dissolution, stability, and morphology are optimized through the application of an extrusion process, in which characteristics such as residence, time, and shear stress, are controlled via a number of input variables. These include feed rate, temperature, screw design, screw speed, and the physical properties of the materials.

Selection criteria for the polymeric carrier to be used include its interaction with the drug; the potential for

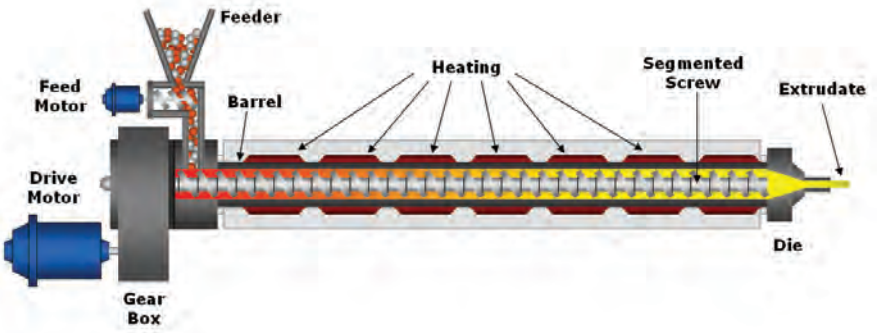
FIGURE 1

supersaturation; and the solid-state solubility of the drug in the carrier. Important polymer characteristics include the design of the manufacturing process, the solubility of the polymer in water and organic solvents, its molecular weight, and its glass transition temperature (Tg). Ideally, the polymer matrix acts as a solid solvent, and the drug is molecularly dissolved. To achieve this, the polymer should have good thermoplastic behavior (deformability is essential); thermal stability (Tg from 50°C to 180°C); low hygroscopicity to prevent crystallization; no toxicity, so that it may be used in large amounts; and either high or no solubility to ensure thermodynamic stability.

To develop suitable formulations, it is desirable to keep the extrusion formulation and process as simple as possible through the choice of a suitable polymer; the use of a plasticizer for improved solubility only if necessary; and the use of a solubilizer for improved drug content and prevention of crystallization in gastric and intestinal fluid.

The quality of the extrudate is determined through the application of a number of analytical techniques, including optical microscopy to determine sample surface morphology and the presence of crystalline particles; scanning electron microscopy (SEM) higher-resolution imaging; and atomic force microscopy (AFM) to provide three-dimensional images. Other analytical techniques commonly used to determine the quality of the API/polymer extrudate include differential scanning calorimetry (DSC), X-ray diffraction crystallography (XRD); solid-state nuclear magnetic resonance (ss-NMR); and infra-red and Raman spectroscopy.

FIGURE 2



INTEGRATED APPROACH TO ENHANCING BIOAVAILABILITY

Catalent and BASF have formed an open alliance in which scientists from the two companies are working together to deliver optimal solubility solutions, thus saving customers time, money, and resources. API and preformulation studies combine Catalent's Optiform® salt screening API optimization technology with solubilizers and refinements proposed by BASF. Drug formulations are designed through combining Catalent's expertise in polymer screening for HME processing with BASF's Solu-HTS high throughput solubilizer screening and polymer selection expertise; HME lab-scale processing is accomplished through combining Catalent's lab-scale HME (OptiMelt™) and RP Scherer Softgel/OptiShell™ screening technologies with BASF's experience in polymer and formulation optimization. Scale-up and downstream processing, including HME scale-up, tableting, coating, and encapsulation, is performed by Catalent using binders, disintegrants, and coatings supplied by BASF and by applying its own expertise in formulation optimization.

ENABLING HOLISTIC BIOAVAILABILITY ENHANCEMENT

An integrated end-to-end HME process provides the capability to formulate, develop, and commercialize differentiated final dosage forms. It enables holistic bioavailability enhancement by broadly addressing multiple bioavailability factors, including optimization of product efficacy, safety, and release properties. Beginning with initial API and preformulation studies, the required formulations can be developed through the application of a range of formulation screening technologies and analyses.

To maximize the efficiency of HME extrusion processes, predevelopment laboratory studies are necessary. These include API thermostability, including DSC of binary mixtures to identify the Tg of the API; hot-stage microscopy to observe phase melting/dissolution at different temperatures; miscibility studies using predictive or small-scale experimental techniques (film casting and hot plate); and film casting of binary mixtures from a common solvent and visual examination for crystal formation process simulation. The properties of an API determined in such studies, including Tg if available or otherwise estimated

"Catalent and BASF have formed an open alliance in which scientists from the two companies are working together to deliver optimal solubility solutions, thus saving customers time, money, and resources. API and preformulation studies combine Catalent's Optiform® salt screening API optimization technology with solubilizers and refinements proposed by BASF."

(Tg/Tm [Kelvin] ratio ~0.7 based on fragility theory), API chemical stability at increased temperature, and API availability for hydrogen-bonding, direct formulation strategy and the subsequent establishment of a development plan.

HME high-throughput processing gives rapid proof of concepts and is energy-efficient; continuous processing gives rapid scalability to commercial supply and reduces waste; and solvent-free processing eliminates solvent-API interactions, residual solvent risk and solvent handling.

Final dosage form development comprises the HME process followed by pelletizing or milling. The extrudate of API solid dispersion is prepared in a polymer/excipient matrix, the process being typically co-located with downstream processing and solid dose form manufacture. Process development and optimization is performed on various sizes of extruder, and includes Design of Experiments (DoE) trials, production of prototype batches, formulation transfer and scale-up, before progressing to full-scale GMP production. Auxiliary equipment within a manufacturing facility would usually include a gravimetric feeder, cooling conveyor, milling facilities, a multi-cut strand pellitizer, and a mini-calender. However, the exact nature and specifications of these would vary depending on customer specifications for final dose forms.

HME allows great flexibility and variation in the final dose form. Tablets, either uncoated or coated, with the option of multi-layered formulations, are possible, as is the option of formulating products with controlled-release properties. Powders, beads, or granules can be manufactured to be formulated into capsules or packaged as "stick pack" sachets with free-flowing contents.

IMPROVED THERAPEUTIC PROFILES

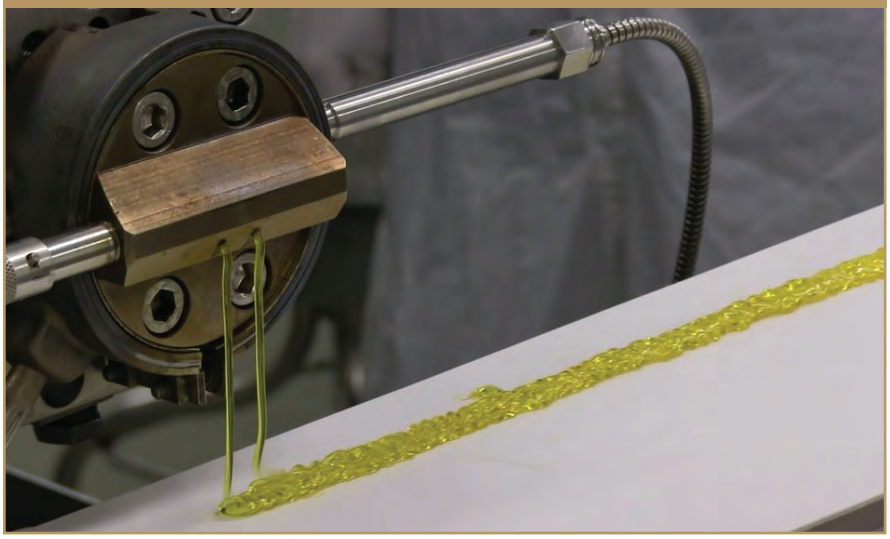
HME technology improves therapeutic profiles of new drugs in a number of ways and enables treatment optimization, the wide range of solubilities and dispersion concentrations possible giving the flexibility to achieve desired efficacy and dosing. The very high drug loading possible (up to 90%) gives a reduced daily pill burden and enhances patient compliance, while patient abuse-deterrence formulations also enhance patient safety and compliance. In addition, the greater consistency for APIs with high food effect absorption gives enhanced efficacy and reduces patient variability, and the taste-masking capability achievable with an HME formulation also contributes to product differentiation while enhancing patient compliance.

CASE STUDY 1: INCREASED BIOAVAILABILITY OF A CHRONIC INFLAMMATORY DISEASE DRUG

The following case study demonstrates how OptiMelt technology increases bioavailability and shortens time to market. The challenge was that a poorly bioavailable product for treating chronic inflammatory disease required effective formulation for Phase II development. Formulation, process development, and downstream tableting were all required. Using OptiMelt technology, Catalent developed and optimized an effective tablet formulation through the application of:

- HME polymer screening and selection
- Drug/polymer formulation development
- Determination of HME processing parameters
- Scale-up from feasibility to development using a 10-mm extruder (50 g) to 18-mm extruder (4 kg)
- Downstream tableting, including extrudate/tablet formulation and tableting operating parameters selection

FIGURE 3



OptiMelt enabled effective Phase II development of the customer's candidate

- Scale-up and commercial manufacturing

The result was a successful product launch with a unique formulation, complementing the leading analgesic OTC brand.

CASE STUDY 2: ENHANCING BRAND PERFORMANCE OF AN OTC ASPIRIN PRODUCT

In another example, Catalent applied OptiMelt technology to enhance the product and brand performance of an OTC aspirin product. The challenge was that a large company wanted to develop and launch an effervescent aspirin OTC product as a line extension to a very well-recognized brand. Catalent partnered with the company for product formulation, scale-up, and commercial manufacturing to provide:

- An innovative effervescent aspirin formulation
- HME process development
- Downstream processing in which the product was milled, mixed, and filled into a unique and distinct single-dose packaging solution stick packs

SUMMARY

Bioavailability enhancement with formulation and dose form flexibility can be achieved through the application of HME technology to produce stable drug formulations and increased development success rates. The wide range of dose functionality achievable allows immediate- and controlled-release formulations to deliver more active drug, when and where it is needed in the body. The multiple possibilities of dose forms available with the technology, including tablets, capsules, and free-flowing granules, results in a preferred patient dose form, thus enhancing patient compliance and providing product differentiation. ◆

To view this issue and all back issues online, please visit www.drug-dev.com.

BIOGRAPHY

Dr. Sampada Upadhye is Technology Platform Leader for Bioavailability Enhancement and OptiMelt™ at Catalent Pharma Solutions. She earned her PhD at The University of Mississippi under the supervision of Dr. Michael A. Repka, where her graduate research focused on hot melt extrusion of highly degradable new chemical entities. Before joining Catalent, she worked for Colorcon, Inc. and Pfizer, where she gained extensive experience in the area of solubilization of preclinical NCEs and formulation design of amorphous solid dispersions using hot melt extrusion and spray drying technologies. Her ongoing research interests include formulation design and process development of extruded formulations with twin screw technology. Dr. Upadhye is the author of a number of publications and has contributed chapters to the following books: *Hot Melt Extrusion: Materials, Technology and Drug Product Design* (Edited by MA Repka, et al) and *Contemporary Research Topics in Pharmaceutical Excipients* (Edited by Ajit Narang, *et al*).

Drug Development
EXECUTIVE

Juichi "Jim" Takeuchi
Executive Officer & President, Global Pharmaceutical Solutions
Terumo Corporation

Terumo: Innovating at the Speed of Life for Cutting-Edge Solutions in Medical Devices & Services

PLAJEX™ provides 1 ml staked needle in a cyclo olefin polymer (COP). PLAJEX™ is silicone oil free, tungsten free, epoxy/adhesive free, has very low subvisible particles, and it has higher resistance to breakage. It has i-coating™ on the surface of stopper, which is bounded to the surface of rubber. PLAJEX™ does not have inherent defects (pits, stones, air lines, cracks) or fragility of glass. It can be sterilized by autoclave for a ready-to-fill nested format. The development and adoption of PLAJEX™ with i-coating™ technology by Terumo® ensures that important biopharmaceutical therapies can be safely administered minimizing medical errors and contributing effectively to the needs of patients, healthcare workers, and the global pharmaceutical industry. *Drug Development & Delivery* recently interviewed Mr. Juichi "Jim" Takeuchi, Terumo® Corporation's Executive Officer and President of Global Pharmaceutical Solutions, to discuss its innovative approach to parenteral drug delivery using integrated science and technology.

Q: Can you introduce us to the Terumo® Corporation and its history?

A: Terumo® was founded in 1921 by a group of physicians, led by Dr. Shibasaburo Kitasato. Their focus at this time was to manufacture superior clinical thermometers in Japan. Dr. Kitasato's most significant contribution was his extensive knowledge about tetanus and diphtheria. He identified a toxin that was secreted by the tetanus bacteria that could be used to produce immunity to tetanus.

Today in Terumo®, Dr. Kitasato's spirit of innovation and patient centricity is still our driving force. We strive to bring outstanding innovation to medicine, which facilitates the best possible care for patients all over the world. This passion for advancement and the determination to be

Dr. Shibasaburo Kitasato (Picture Courtesy: The Kitasato Institute)

able to contribute to society through better healthcare motivates our valued Terumo® employees worldwide.

Our corporate mission and new vision is "Innovating at the Speed of Life." This reflects our proactive approach to provide high-quality medical devices and services for the benefit of patients and medical environments in more than 160 countries.

Terumo® is a globally operating medical technology company with sales revenues of 489.5 billion yen and is active in three business segments: Cardiac & Vascular Group, Blood Management Group, and General Hospital Group. Terumo® Global Pharmaceutical Solutions is the dedicated group servicing pharmaceutical customers. We have established long-lasting business relationships with top-tier pharmaceutical and biotech companies in the global market. Our business relationships are based on providing medical devices and services globally, including our technology used in prefilled syringes and CMO fill & finish activities.

Q: What does the Terumo® global presence look like?

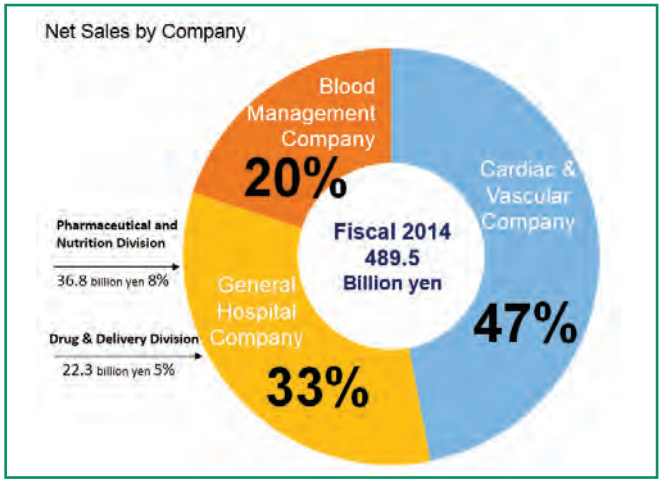
A: Terumo® actively acquires companies and technologies and establishes subsidiaries on a worldwide basis. Our objectives are to explore new technologies, strengthen and build on our product lines, and to capture the market share.

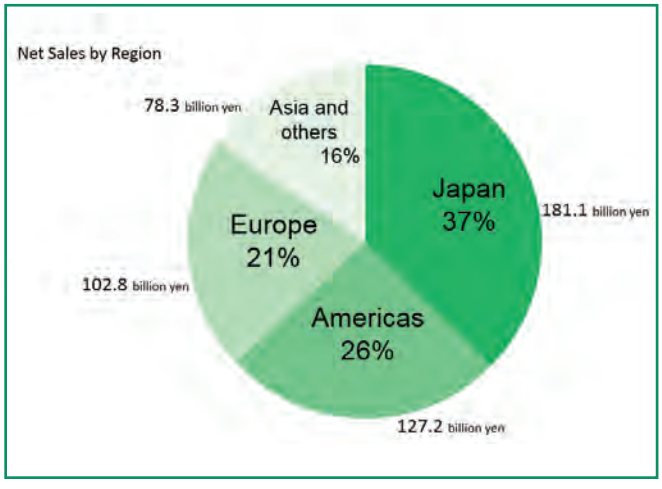
A key interest for us is the creation of synergies by combining fundamental technologies, our significant strength with those of other companies, which brings new value through this technological innovation. This blend of active cooperation with other companies with our own development activities enables us to expand the markets we serve beyond our existing fields of business. Hence, the proportion of international sales has increased over the past years, reaching more than 60% of our consolidated revenues.

Q: In terms of innovation, what makes Terumo® unique?

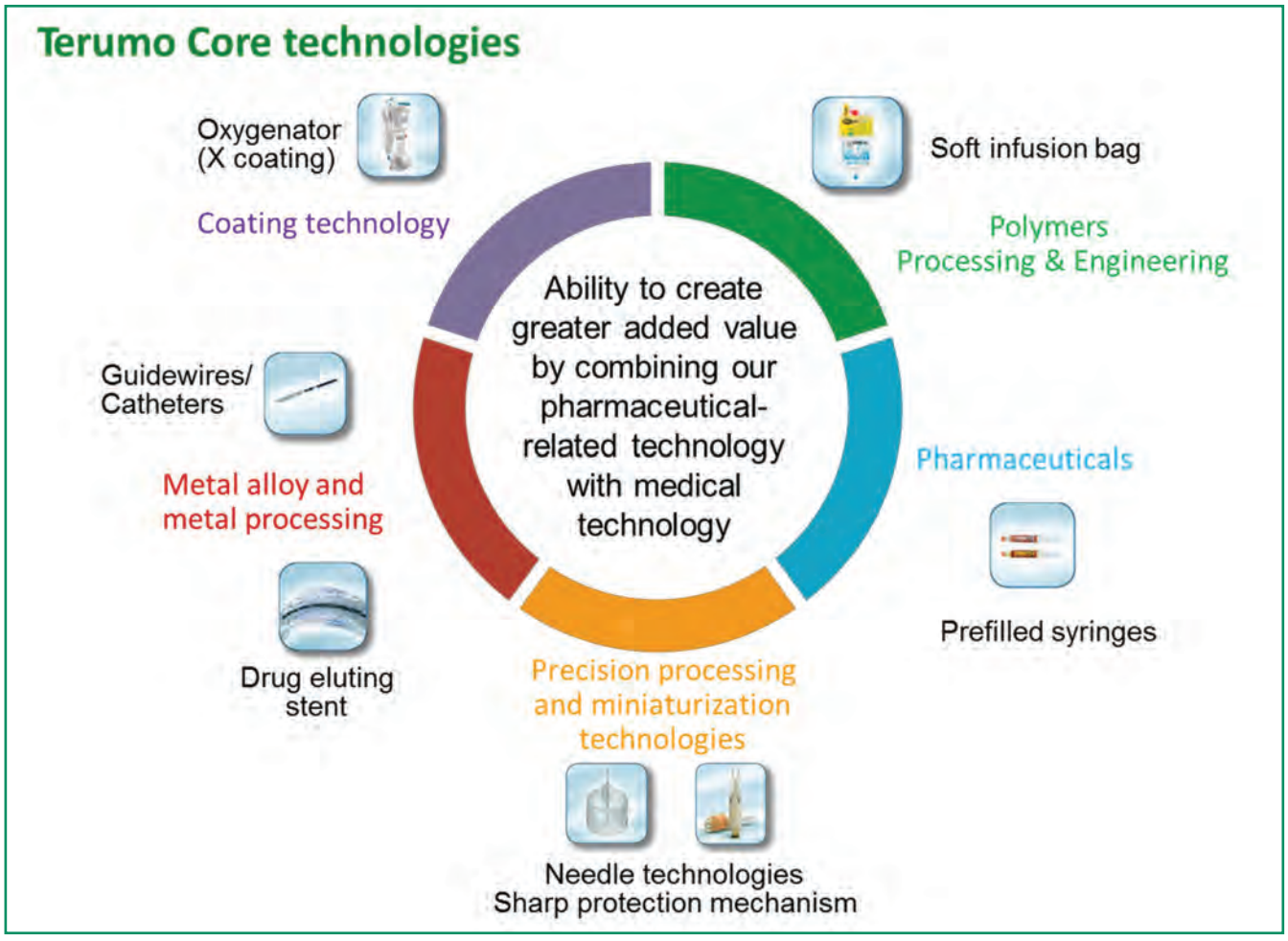
A: We are "Innovating at the Speed of Life," and we are actively working together with our partners to improve the life of patients. We really do want to make a difference to society and the healthcare service. This is made possible by our motivation to find new possibilities in technology and to make life better through our innovations.

We are very proud of our roots in scientific and technological advancements, where high-quality, unique, and innovative products in many areas and applications have grown from. When designing medical devices, there is a host of scientific disciplines to consider, such as physiology, biochemistry, pharmacology, cell technology, polymer technology, metal processing technology, and electronics. All these disciplines are integrated and used in our technology innovations alongside our business processes, which enables us to move forward in an efficient and effective manner.





"Speed articulates the pace of change and the never-ending cycle of our global business environment. Speed for us means leading the change, not reacting or responding to it. By staying ahead of the ever-changing environment, we can drive scientific advancements in the marketplace."



Speed articulates the pace of change and the never-ending cycle of our global business environment. Speed for us means leading the change, not reacting or responding to it. By staying ahead of the ever-changing environment, we can drive scientific advancements in the marketplace.

Life is about the patients we serve and the quality of life that our science and technology supports. We take great pride in doing the extraordinary in an ordinary market and understanding our customers and their customers – the patients – and pursuing better healthcare for all.

Q: How do you view the recent challenges in the pharma industry?

A: The pharma industry faces challenging times in bringing new medicines to the market. They are dealing with steep R&D costs, tighter regulations, and difficult market conditions. Soaring healthcare expenditures has resulted in tighter healthcare payer's policies and economic governance.

At the same time, there is an escalating demand for medicines to serve the rising global population and the need to

cope with diseases associated with an ageing population. An example of this is the diabetes pandemic. Prophylactic vaccines will remain important for the future, and a new generation of vaccines for non-infectious diseases are currently in development.

Together with vaccines, therapeutic proteins are leading players in pharmaceutical development. The use of prefilled syringes in the development of liquid formulations of these biotech products is experiencing a significant growth. This is due to the fact that prefilled syringes provide enhanced safety in use, improved user convenience, and ease of administration. Another important trend is the shift from hospital treatment to homecare and self-injection for chronic diseases and specific therapeutic areas.

Biotherapeutics have specific challenges and requirements, and typically, these therapeutic proteins are both physically and chemically sensitive. Being large and complex molecules, such drug products are also creating explicit challenges for injectability. This will lead to the need for tailor-made drug delivery devices that ensure drugs can be administered safely and reliably, avoiding errors in medical practice while minimizing patient discomfort.

Q: What kind of value does Terumo® bring into this industry?

A: Our Vision is to be the preferred partner to the pharmaceutical industry by offering patients high-quality, innovative medical devices and insightful solutions. Terumo® believes that to produce medication without giving due consideration to the final drug delivery device is to miss the point of pharmaceutical development.

In fact, it was this belief that led us to apply our vast experience in medical technology for pharmaceutical purposes. Today, various social conditions are causing a diversification of needs in healthcare. Terumo® is responding to these changes by developing and providing devices and systems that enhance safety and efficiency while also improving patient comfort.

Q: What is the future direction for Terumo® in this area?

A: Terumo® Global Pharmaceutical Solutions is committed to advancing its research and development activities. We are developing a portfolio of parenteral drug delivery devices focused particularly on the pharmaceutical development of biologics, vaccines, and sensitive therapeutic proteins. Since 1999, we have led the way in producing polymer-based prefilled syringes through a fully integrated production model. Process capabilities include terminal sterilization as well as aseptic filling for biotherapeutics. The addition of pharmaceutical capabilities in fill & finish services allows us to optimize our know-how in polymer-based primary containers. Our PLAJEX™ ready-to-fill syringe system came from Terumo®'s profound knowledge of life sciences, pharmaceutical operations, and prefilled syringe manufacturing. These polymer-based prefilled syringes have specific features that address several current challenges in applications with protein/peptide biopharmaceuticals, such as silicone oil interaction, aggregation, (sub-) visible particles, and immunogenicity. With the launch of Nanopass® pen-needles in the European and Asian markets, Terumo® introduced a proprietary platform for the production of tapered needles. This technology can be applied in various therapeutic areas. Terumo®'s innovative tapered needle technology makes it possible to minimize needle size for patient comfort. This also reduces viscous resistance within the needle and thus improves flow and enhances injectability. These qualities are paramount in needle-based injectors for self-injection.

By combining our proprietary technologies, our know-how, and our experience, the market can certainly expect us to bring new and innovative drug delivery devices and integrated systems to the business. Our aim is to ensure drugs are administered safely, reliably, and uncontaminated. We strive to avoid errors in medical practice and minimize patient trauma and discomfort.◆

To view this issue and all back issues online, please visit www.drug-dev.com.

Overcoming Formulation Challenges

For decades, **Adare Pharmaceuticals** has successfully overcome complex formulation challenges, delivering medicines that benefit more patients. With a broad range of proprietary technologies—including taste masking and ODTs, customized drug release, and bioavailability enhancement—we have the ability to transform drug formulations, developing novel Rx and OTC products. For example, we recently partnered with Sanofi K.K. to launch Allegra® (fexofenadine HCl) Dry Syrup 5% in Japan. By using Microcaps® Taste Masking Technology, we successfully taste masked the API and delivered an oral powder formulation that can be sprinkled on easy-to-swallow foods to improve convenience of administration. To learn more about our proprietary technologies or partnership opportunities, visit us at CPhI Worldwide 2015 and the 2015 AAPS Annual Meeting & Exposition or visit **www.AdarePharma.com**.

Coated Elastomeric Stoppers

PremiumCoat™ is a novel range of elastomeric stoppers developed by **Aptar Stelmi**. The surface of the elastomer in contact with the drug is coated during manufacturing with a thin fluoropolymer film. This coating acts as an effective barrier to many of the extractables and leachables that can be released from the elastomer and contaminate the drug. As a result, compatibility of the drug and the closure is significantly superior with PremiumCoat stoppers. Part of the Pharma segment of AptarGroup, Inc., Aptar Stelmi is a trusted partner of leading pharmaceutical companies in the design and manufacturing of elastomeric closures for parenteral applications. AptarGroup, Inc. (NYSE: ATR) is headquartered in Crystal Lake, IL, with manufacturing facilities in North America, Europe, Asia, and Latin America. For more information, visit Aptar Stelmi at **www.aptarstelmi.com**.

Dosage Form Solutions

Capsugel's Dosage Form Solutions business unit, with the addition of Bend Research and Encap Drug Delivery, solves customers' most pressing product development challenges, including bioavailability enhancement, modified release, abuse deterrence, biotherapeutic processing, and inhalation formulation. We utilize an integrated product development approach ensuring that our clients can rely on one partner from design to commercial-scale production of innovative drug product intermediates and finished dosage forms. Capsugel Dosage Form Solutions accelerates and improves product development through an array of technologies, including lipids and liquids, spray-dried dispersions, hot-melt extrusion, and through specialized manufacturing, including FDA/MHRA-accredited finished dosage sites that can handle highly potent, controlled substance, hormonal, and oncology compounds. High-quality science and engineering is core to our offering at each stage of the product development cycle and has enabled the successful advancement of hundreds of compounds. For more information, contact Capsugel Dosage Form Solutions at (541) 382-4100, dfsinquiry@capsugel.com, or visit **www.capsugel.com/dfs**.

HPMC Capsules

Capsugel's Vcaps Plus HPMC (hypromellose) capsules are non-animal capsules with low-moisture content that also meet global pharmaceutical standards. A proprietary capsule-manufacturing process eliminates the need for gelling agents and delivers gelatin-like consistent disintegration and dissolution properties. The unique performance characteristics of Vcaps Plus HPMC capsules expand the range of applications for two-piece capsules. The proven properties of Vcaps Plus capsules make them an excellent alternative to gelatin or traditional HPMC capsules for optimizing delivery, performance, and stability of over-the-counter, New Chemical Entities, and off-patent products, as well as reduce development timelines. For more information, contact Capsugel at (888) 783-6361 or visit **www.capsugel.com**.

Platform Technology

Captisol is a patent-protected, chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. Captisol was invented and initially developed by scientists in the laboratories of Dr. Valentino Stella at the University of Kansas' Higuchi Biosciences Center for specific use in drug development and formulation. This unique technology has enabled 7 FDA-approved products, including Onyx Pharmaceuticals' Kyprolis®, Baxter International's Nexterone®, and Merck's NOXAFIL IV. There are more than 30 Captisol-enabled products currently in clinical development. For more information, visit Captisol at **www.captisol.com**.

Softgel Technologies

Catalent has over 80 years of softgel manufacturing experience, and continues to deliver innovation with technological enhancements, such as chewable softgels and coatings, and formulations to enable modified-release for Rx, OTC and consumer health products. OptiGel™ Bio softgel technology enables macromolecules to be delivered orally and overcome permeability and stability challenges in a more easily administered form than intravenous injection. Enteric coatings enable targeted delivery of drugs and can limit degradation of the API in the stomach. The OptiShell™ platform allows for high-temperature encapsulation of semi-solid fill material within a non-gelatin, plant-based shell. This technology is ideal for the encapsulation of higher melting-point fill formulations, and the production of soft capsules containing semi-solid matrices for modified-release of poorly soluble and/or poorly permeable drug compounds. For more information, visit Catalent at **www.catalent.com**.


2015
AAPS Annual Meeting
and Exposition
October 25–29, 2015
Orange County Convention Center
Orlando, Fla.
Mark Your Calendar for the Meeting that Extends Your Boundaries:
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• Explore Programming Covering Both Large and Small Pharma;
• Find the Latest Advances with over 2,500 Contributed Papers;
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Differentiated Injectable Delivery

Credence MedSystems is focused on delivering medications safely for the benefit of our patients, caregivers, and partners. The philosophy of Innovation Without Change resonates throughout the company and our products. It results from the team's fresh perspective and intense desire to understand the needs of the end-user and pharmaceutical manufacturer in the overriding goal of improving patient care. The Credence Companion Safety Syringe System offers best-in-class drug delivery with a vastly simplified path to market for our biopharmaceutical partners. The Companion uses any prefilled syringe and primary package components as a foundation to build an advanced passive needle-retraction device with automatically disabling technology. Because the primary package, vendor, and filling are unaffected, the development and regulatory requirements as well as the sourcing impact are minimized for our pharmaceutical partners. For more information, contact Credence MedSystems at 1-844-CMEDSYS or visit **www.CredenceMed.com**.

Pen Injectors

HASELMEIER

Haselmeier is a leading designer and manufacturer of pen injectors for use with injectable pharmaceuticals. Our devices are used by leading pharmaceutical and biotechnology companies around the world. Founded in 1920 in Stuttgart, Germany, Haselmeier is now one of the leading manufacturers of pen injection systems in the world with locations in Germany, Switzerland, United States, Czech Republic, and India. Our pen injection systems feature patented designs that focus on the highest quality and manufacturing efficiency. Device development programs target patient requirements and include risk management and analysis, FMEA reviews, Human Factor data, and Design History Files (DHF). For more information, visit Haselmeier at **www.haselmeier.com**.

Delivery Management System

Drug delivery has never been more convenient than with the OmniPod Drug Delivery Management System from **Insulet Delivery Systems Group**, an innovative medical device company. Since the launch of the revolutionary OmniPod 10 years ago, Insulet has expanded its wearable pump technology to multiple other drug delivery applications and is used to treat thousands of patients worldwide. This discreet wearable infusion pod offers an innovative, easy-to-use design with no tubing and an automatic and virtually pain-free insertion to promote improved patient adherence in multiple therapeutic areas. For more information, contact Insulet at (866) 941-4576 or email **drugdelivery@insulet.com**.

Marketing & Communications

LifeSciencePR
we'll get you there.

Get Noticed. Get Funded. Grow Faster. When you need to connect with investors, business partners, and regulatory agencies, **LifeSciencePR** can make that happen. Our integrated communication strategies and well-established industry contacts will help your life science company achieve its short- and long-term corporate objectives. We work seamlessly with your senior management team to develop the most effective communication initiatives to reach your prospective investors and partners. Our experienced staff knows what it takes to break through with your breakthroughs, powering your engine in your continued drive toward your success. LifeSciencePR will get you there smarter, faster, and easier than any other marketing and communications firm in the industry. For more information, contact LifeSciencePR at (800) 724-2372 or visit **www.LifeSciencePR.net**.

Expanded Analytical Lab Capabilities

metrics contract services

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**.

Components & Assemblies

Minnesota Rubber and Plastics produces high tolerance medical components and assemblies for the most demanding applications. Our experience in advanced material formulation enables us to be compliant with FDA, ISO 10993, and ISO 13485 to meet your unique product requirements. Our over 60-year history in the design and manufacture of complex devices makes us the preferred partner for industry leaders throughout the world. The next time your component or assembly project seems impossible, there's no one better to partner with than Minnesota Rubber and Plastics. We'll make your tough application a reality with advanced material technologies. For more information, contact Minnesota Rubber and Plastics at (952) 927-1400 or visit **www.mnrubber.com/medical1**.

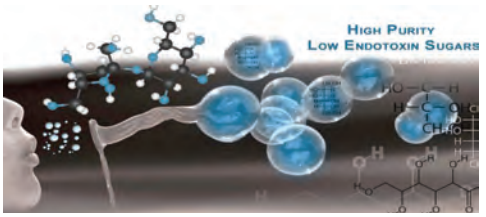
Drug Delivery Solutions

Nemera is one of the world leaders in the design, development, and manufacturing of drug delivery solutions for pharmaceutical, 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.**

Complete Development Solution

Patheon OneSource™ Reach Your Milestone Faster with the Simplicity of a Complete Development Solution. Only Patheon OneSource™ gives you the speed and simplicity of combining drug substance and drug product development and manufacturing into a single customized solution for either small or large molecule discoveries. Patheon® is a leading global provider of outsourced pharmaceutical development and manufacturing services. With approximately 8,700 employees worldwide, Patheon provides a comprehensive, integrated and highly customizable set of solutions to help customers of all sizes satisfy complex development and manufacturing needs at any stage of the pharmaceutical development cycle. The company is owned by JLL Partners and Royal DSM. For more information, visit Patheon at **www.patheon.com**.

Specialized Products & Services



Pfanstiehl is a leading cGMP manufacturer of parenteral grade excipients and highly potent APIs. Pfanstiehl develops and manufactures high-purity, low-endotoxin (HPLE) carbohydrates such as trehalose, sucrose, mannitol, galactose, and mannose utilized as injectable excipients for the stabilization of proteins, mAbs, and vaccines. These HPLEs are also used as supplements for industrial cell culture, cell therapy, and cryopreservation media. Pfanstiehl also works closely with some of world's largest multinational pharmaceutical and biopharmaceutical firms, as well as with virtual pharmaceutical companies, to synthesize proprietary and commercial compounds in quantities ranging from grams to MT quantities. Manufacturing and development occur at Pfanstiehl's a 13-building campus located near Chicago, IL. For more information, visit us at **www.pfanstiehl.com**.

Global Data & Analytics

PharmaCircle is a leading provider of global data and analysis on the pharmaceutical, biotechnology, and drug delivery industries. PharmaCircle's premier database delivers an integrated scientific, regulatory, and commercial landscape view with unprecedented access to hundreds of company, product, and technology attributes. PharmaCircle connects product and pipeline information for drugs and biologics with formulation and component details, and provides due diligence level data on nearly 6,000 drug delivery technologies and devices. Drug label comparison tools and full-text document search capabilities help to further streamline research. No other industry database matches PharmaCircle's breadth of content and multi-parameter search, filtering, and visualization capabilities. To learn more, email contact@pharmacircle.com, call (800) 439-5130, or visit **www.pharmacircle.com**.

Room-Temperature Sterilization

REVOX™ Sterilization Solutions by Cantel Medical

REVOX® Sterilization uses a patented, room-temperature peracetic acid (PAA) vaporized sterilant that achieves exceptionally low chemical residuals and unsurpassed materials compatibility. With superior compatibility across a wider range of materials, engineers have more options to create products more efficiently. Companies can now create the products that will demonstrate their true potential. The REVOX™ technology eliminates inefficiencies associated with pre-conditioning and lengthy post sterilization wait times. This allows REVOX Sterilization to offer manufacturers a quick-turn, off-site sterilization service or cost efficient on-site, in-line processing. In May 2014, a Class II implantable device was granted FDA clearance with the REVOX sterilization process. The REVOX innovation is backed by a company with over 35 years of infection prevention and control advancements structured under strict regulatory compliance standards. For more information, visit REVOX at **www.revoxsterilization.com**.

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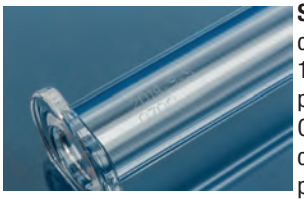

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SPRAY-DRIED DISPERSIONS

Developing Process Control Strategies for the Manufacture of Spray-Dried Dispersions

By: Devon DuBose, Dana Settell, Nathan Bennette, and Amber Broadbent, PhD

ABSTRACT

A significant share of current drug development pipelines include active pharmaceutical ingredients (APIs) that fall into BCS (biopharmaceutical classification system) 2 and 4 spaces. These compounds are typically characterized by their low-aqueous solubility and thus poor bioavailability, requiring advanced formulation approaches.[1] Various approaches have been developed to enable these types of compounds, including particle size reduction (eg, micronization), chemical modification (eg, salt forms and pro-drugs), complexing agents, solubilized liquid forms (eg, SEDDS), and solid amorphous dispersions.

In recent years, amorphous dispersions manufactured via spray drying have gained considerable traction with the commercialization of numerous products. Additionally, increased access to and familiarity with small-scale spray drying equipment has enabled formulation scientists to include spray-dried dispersions (SDDs) early in compound screening and drug development. With greater use of SDDs as an integral part of the formulation toolbox, and a considerable portfolio of SDDs progressing toward commercialization, adoption of a Quality-by-Design (QbD)-based development approach can help streamline scale-up and regulatory approval in bringing these compounds to market.

INTRODUCTION

This paper will broadly describe a model-based SDD product development methodology as well as a control strategy that is based upon fundamental understanding of the formulation and the process. The product development flow and general activities for SDD product development are presented in Figure 1. Key to this development strategy is the early identification of critical SDD attributes and process parameters, which contributes to the development program and facilitates identification of functional relationships between key material attributes and their controlling parameters. This understanding can later be translated into a robust control strategy for commercial manufacture.

IDENTIFYING THE IMPORTANT SDD ATTRIBUTES

SDD development begins with identifying the formulation goals, or Target Product Profile (TPP), of the compound and designing a formulation to achieve those goals. Formulation maps, which consider the API's physical and chemical properties, can be used in conjunction with the TPP to identify a formulation that is likely to produce a physically stable SDD with the desired performance early in development.[2] The TPP that is created during initial formulation screening can guide the entire development process and be refined with additional product and process information.

Early in a development program, predictive in vitro dissolution tests and physical stability maps can be combined with risk assessments to identify critical quality attributes (CQAs) for further study. Building a mechanistic understanding of the in vitro dissolution of an SDD guides thinking in the early stages of product development and ultimately allows prediction of the impact of SDD attributes on in vivo performance. Similarly, physical stability maps can be used to predict whether drug loading, humidity, residual solvent levels, or temperature exposure represent a risk to the stability of the SDD during manufacture or long-term storage.

Several common CQAs and their potential impact on the TPP are listed in Table 1. The formulation and process parameters that commonly define the SDD attributes are also shown in Table 1.

TABLE 1

SDD Critical Quality Attributes	Potential TPP Impact	Important SDD Formulation Parameters	Important SDD Process Parameters
Physical State	Amorphous versus crystalline state can impact the product's *in vivo* performance and physical stability	API loading, stabilizing polymer chemistry and molecular weight (MW), spray solvent, spray solution solids concentration	Droplet size and drying rate
Particle Size	Can affect *in vivo* performance and/or downstream processing, which can impact final dosage form quality (eg, tablet hardness, content uniformity)	Stabilizing polymer chemistry and MW, spray solution solids loading	Droplet size
Bulk Density/Morphology	Can affect downstream processing, which can impact final dosage form quality (eg, tablet hardness, content uniformity)	Stabilizing polymer chemistry and MW, spray solution solids loading, glass transition temperature	Droplet size and drying rate
Residual Solvents	Can affect intermediate physical stability	Polymer and API interaction with the spray solvent, MW of the spray solvent	Droplet size and drying rate
Water Content	Can affect physical stability (shelf-life) and assay/potency	Polymer and API hygroscopicity	Secondary drying parameters and product exposure to room humidity
Assay, Related Substances & Potency	Can affect product safety, chemical stability, and efficacy	Product and/or API specific	Product and/or API specific

Summary of Common SDD Critical Quality Attributes & Potential Important Formulation & Process Parameters

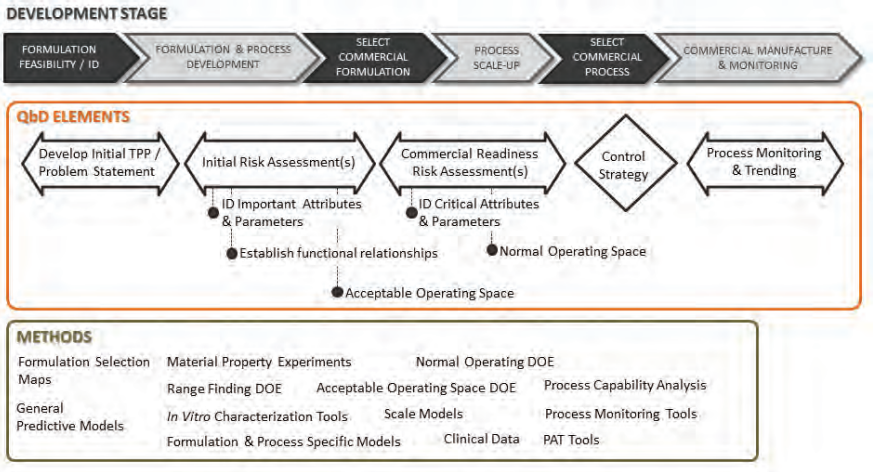
DETERMINING THE IMPORTANT SPRAY DRYING PARAMETERS

Spray drying is a well understood process that is ideally suited for the manufacture of amorphous dispersions. As shown in Figure 2, drug and polymer are dissolved in an organic solvent to form a solution that is atomized into droplets. The droplets are dried upon contact with a hot drying gas inside the spray drying chamber. Residual solvent remaining on the SDD after spray drying is removed in a secondary drying step. In this paper, we will focus on the spray drying unit operation and will not discuss solution preparation or secondary drying operations. As described in previous articles contributed by Bend Research, the process parameters required to produce target SDD attributes can be defined and controlled by understanding two key aspects of spray drying: droplet formation or atomization and droplet drying.[3] Droplet size and drying rate parameters can be correlated to SDD attributes.

UNDERSTANDING & ESTABLISHING FUNCTIONAL RELATIONSHIPS

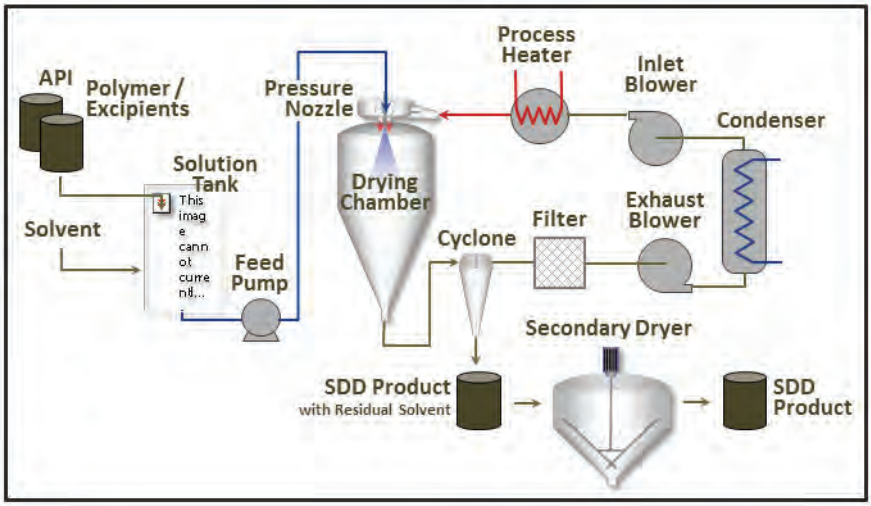
Dependence of the critical SDD attributes on formulation and process parameters can be understood through investigation of the formulation material attributes and the spray drying process.

FIGURE 1



SDD Product Development Flow & Key Activities

FIGURE 2



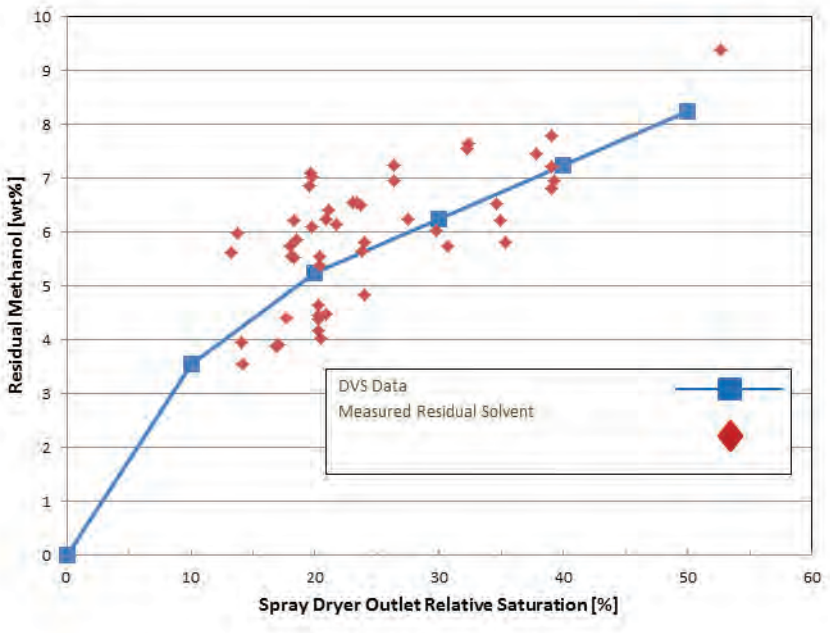
Spray Drying Process Overview

Material Attribute Evaluation – Solid State

For an amorphous dispersion, a fundamental understanding and study of the solid state during manufacture and upon storage is critical to controlling and maintaining physical stability. Physical stability of a spray dried amorphous dispersion is governed thermodynamically by the miscibility of the drug and polymer and kinetically by molecular mobility. Primary physical stability failure modes include phase separation and/or crystallization. The mobility of a SDD is dependent on the formulation through the glass transition temperatures (Tg) of the components, and on the degree of plasticization from residual solvents or water.[4,5] The impact of humidity can be assessed by equilibrating samples to a range of relative humidity (%RH) conditions and measuring the Tg of the humidified SDD sample. This data can be used to predict the long-term stability of an SDD at a given storage condition and to establish functional relationships between SDD attributes and storage parameters, including temperature, RH, time, and packaging configuration.

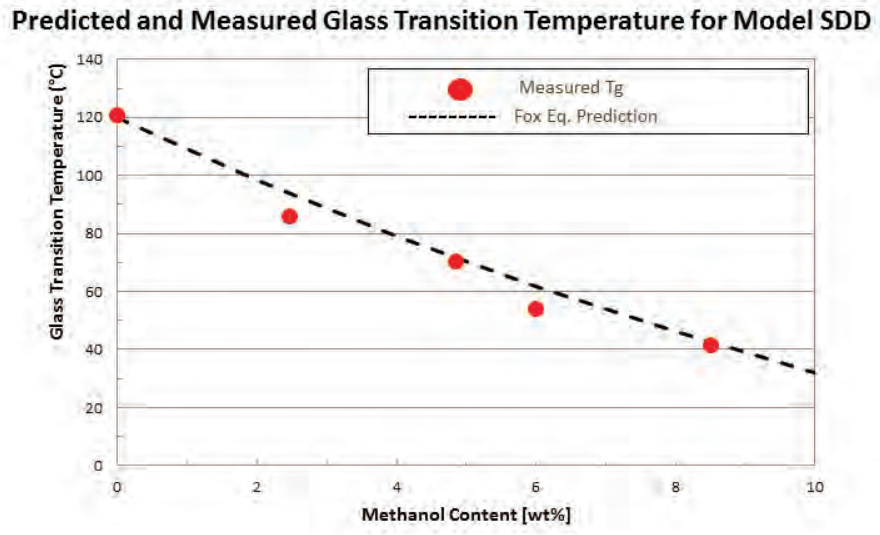
Analogous to the situation with water, residual spray solvent plasticizes a SDD and lowers the Tg, sometimes significantly.[6] Understanding the impact of residual solvent on the Tg is critical to ensure robust manufacturing and in-process stability. This effect can be estimated by the Fox equation and studied with solvent vapor sorption and calorimetry experiments, as seen in Figures 3 and 4. The spray drying process can be defined by the relative saturation (%RS) of solvent inside the dryer, which is a function of the key spray drying parameters. Common ranges of dryer outlet %RS may vary between 10% and 35% depending on the solvent and the spray drying parameters. The residual solvent remaining on the SDD after spray drying can be predicted by calculating the %RS from the spray drying parameters and conducting a vapor sorption study on the SDD, as shown in Figure 3. The Tg of the solvent wet SDD can be predicted, as shown in Figure 4. This data can be used to select spray drying parameters to yield spray dryer outlet target %RS and SDD solvent content. Quantifying the

FIGURE 3



Example Material Attribute Study of Initial SDD Residual Solvent Content Versus Spray Dryer Outlet Relative Saturation Compared With Equilibrium SDD Dynamic Vapor Sorption Data

FIGURE 4



Example Material Attribute Study of Plasticization of SDD by Residual Solvent & Impact to the Tg.

dependence of a formulation's physical stability and residual solvent on spray drying, secondary drying, and storage parameters is critical to selecting the appropriate operating space, storage conditions, and packaging controls.

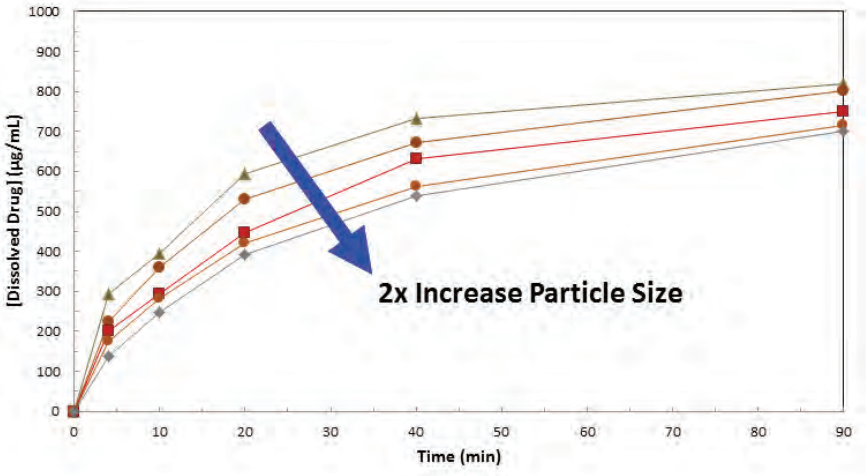
Material Attribute Evaluation – Dissolution

In addition to studying the physical state of the SDD, understanding the SDD performance mechanism by analyzing dissolution can help define attribute and parameter criticality and functionality. SDD dissolution mechanisms vary depending on the API physical and chemical properties and the specific formulation, but the mechanism for most SDDs can be described by two scenarios: erosion and spinodal decomposition.[7] Most SDD dissolution mechanisms are a combination of these scenarios, and fall on a spectrum between the two. In both mechanisms, water diffuses into the SDD particle, and the polymer hydrates. If the drug is largely soluble in the hydrated polymer, the particle erodes at the edges, and the drug dissolves and diffuses away from the particle at the boundary layer. In the second case, if the drug is largely insoluble in the hydrated polymer, drug-rich amorphous domains phase separate and are stabilized as nanoparticles through an added surfactant or amphiphilic and charged polymers, leading to disintegration of the primary SDD particle into drug/polymer nanoparticles.

By performing tests at non-sink conditions in biologically relevant dissolution media, it is possible to measure the dissolution rate and extent of supersaturation that SDDs provide relative to the crystalline API. Differential centrifugation, light scattering, UV-Vis spectroscopy, and other techniques help to identify and measure the formation of drug-related species important to absorption in vivo, and yield insight into the dissolution mechanism.

In a SDD formulation in which the dissolution mechanism more closely follows the erosion-based model, the dissolution rate is often inversely related to the particle size of the SDD powder. Maximizing the surface area of the powder by making smaller particles can improve the dissolution rate of the drug. As shown in Figure 5, the particle size has potential to significantly impact the dissolution performance of a SDD. Understanding the important material attributes with these in vitro dissolution tests can define target SDD particle size targets and spray drying parameters.

FIGURE 5



Example Material Attribute Study of Defined Target Particle Size for Optimized Dissolution Performance

"Drug pipelines increasingly feature new drug candidates that exhibit poor solubility and require well-established enabling technologies to address this critical issue. In addition to being an enabling technology for low-solubility compounds, spray drying has a track-record of success for robust processing and correspondingly strong commercializable control strategies."

Spray Drying Process Parameters – Atomization

The droplet size, coupled with the solid components and their solubility, ultimately define the SDD particle size. As previously described, particle size can be an SDD CQA if it impacts in vivo dissolution. The interdependent spray drying parameters that define droplet size are the nozzle geometry, spray solution properties (viscosity, density, and surface tension), solution flow rate, and nozzle pressure. Droplet size can be established both by direct measurement and/or by empirical correlations for a specific nozzle geometry. Droplet size can be correlated to particle size through range-finding experiments and formal Design of Experiments (DOEs). After identifying the target SDD particle size that meets dissolution requirements, the upper droplet size can be constrained and associated nozzle geometries and atomization conditions identified.

Spray Drying Process Parameters – Drying Rate

Upon fixing the target droplet size, the droplet drying rate is defined by the thermodynamics of the system, which can be predicted and characterized by a simple mass and energy balance on the spray dryer. The outlet temperature and calculated %RS characterize kinetic- and equilibrium-driving forces for evaporation of the solvent from the droplets and correlate with potentially critical SDD attributes such as bulk density, residual solvent and physical state. The material attribute studies described above can be used to select low-risk manufacturing conditions. These correlations of dryer outlet temperature (or %RS) to the SDD attributes are established through range finding and screening DOEs.

A wide droplet size and drying rate space can be evaluated to develop correlations and establish a wide acceptable SDD attribute space. This space needs to consider the downstream process space, as both bulk density and particle size may be critical inputs for the selected dosage form.[8] The correlations in conjunction with continued risk assessments can be used to define attribute and parameter criticality.

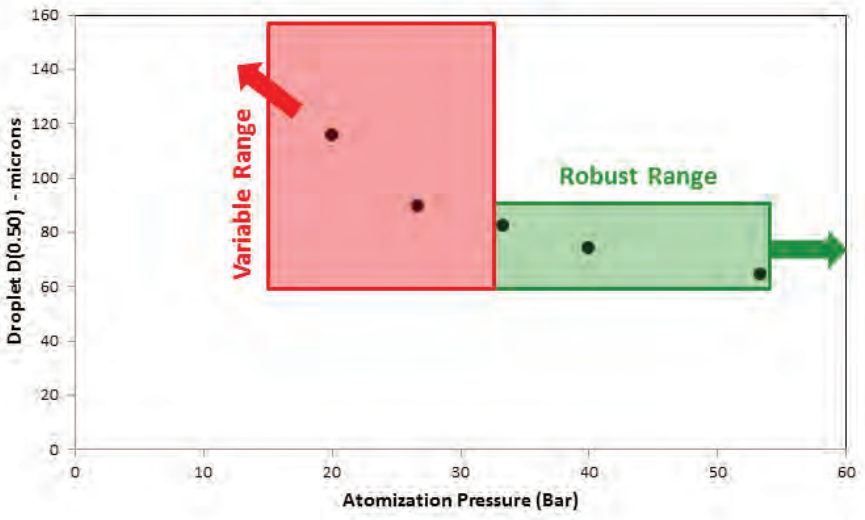
CONTROLLING THE CRITICAL PARAMETERS

Once SDD CQAs are identified, a robust control strategy for the critical process parameters (CPPs) can be implemented by maintaining target droplet size and drying rate.

To ensure robust control over droplet size and thus SDD particle sizes, the nozzle geometry and operating conditions are selected with inherent stability. Figure 6 shows a graph of droplet size verses nozzle pressure for a specific nozzle geometry. The target droplet size can be maintained over a wide range of nozzle pressures for this nozzle and formulation. Therefore, slight variations in nozzle pressure will produce the same target droplet size and SDD particle size. Under this control strategy, nozzle pressure becomes the critical control parameter for ensuring that the target droplet size is maintained, as shown in Figure 6.

Once droplet size is fixed, the spray dryer thermodynamics can be used to ensure robust control over drying rate and thus SDD bulk density, physical state, and residual solvent. The key

FIGURE 6



Example Nozzle Selection Curve Demonstrating Droplet Size Control Over a Wide Range of Nozzle Pressures

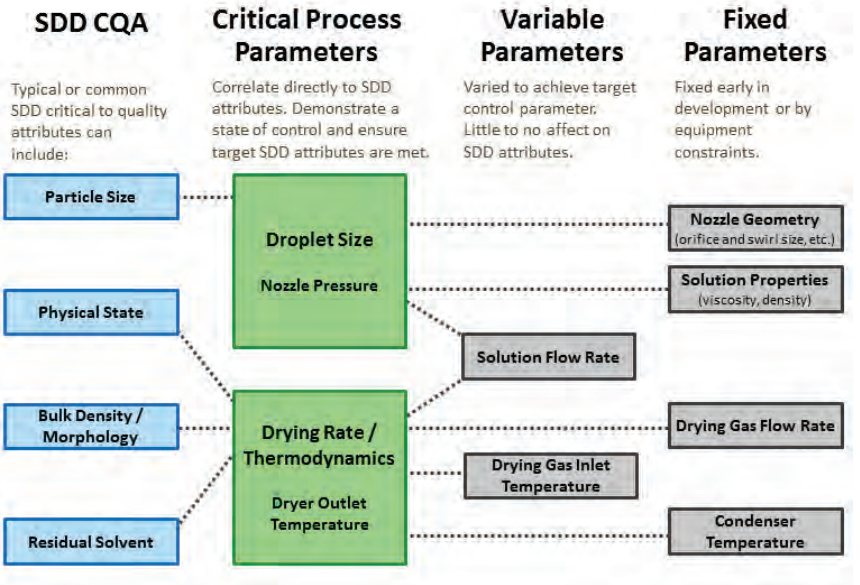
interdependent thermodynamic process parameters are dryer outlet temperature, solution flow rate, drying gas inlet temperature, drying gas flow rate, and condenser temperature, which dictates the amount of solvent vapor recycled into the inlet gas stream.[9] These parameters are all related through mass and energy balances. Maintaining dryer outlet temperature within the proven acceptable range ensures that the target SDD attributes are achieved. Drying gas is typically fixed over a narrow range for a given scale spray dryer. Condenser temperature is easily maintained within a narrow range and is limited by chilling equipment. Solution flow rate may vary slightly within a predetermined range to maintain atomization parameters and target droplet size.

Therefore, drying gas inlet temperature is varied within a predetermined and calculable range to maintain target outlet temperature and SDD attributes, as shown in Figure 7. In addition, the interdependence of the thermodynamic parameters through the mass and energy balance can be used to demonstrate a state of process control.

SUMMARY

Drug pipelines increasingly feature new drug candidates that exhibit poor solubility and require well-established enabling technologies to address this critical issue. In addition to being an enabling technology for low-solubility compounds, spray drying has a track-record of success for robust processing and correspondingly strong commercializable control strategies. In development, CQAs are rapidly identified to achieve the target product profile. Through fundamental, semi-empirical, and/or empirical modeling, CQAs are related to the CPPs that determine them. Knowledge of these relationships and mechanistic understanding of performance and physical stability lead to the selection of processing parameter ranges that maintain CQA target ranges. This is the foundation of both a strong regulatory submission and a control strategy to deliver successful commercial products.◆

FIGURE 7



Example SDD CQAs & Control Strategy for Spray Drying Process Parameters

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BIOGRAPHIES

Devon DuBose is a Director of Engineering at Bend Research, a division of Capsugel Dosage Form Solutions. His responsibilities include spray drying development and scale-up for preclinical and clinical projects, and transferring spray drying processes into a current Good Manufacturing Practice environment. He also has expertise with special spray drying projects for biologics and inhalation and has led numerous private client programs, ranging from preclinical feasibility through Phase III clinical manufacture. Mr. DuBose has been with Bend Research since 2007. He graduated with a BS in Chemical Engineering from Oregon State University and is a registered professional engineer in the State of Oregon. Mr. DuBose has four U.S. patents pending.

Dana Settell is Vice President at Bend Research, a division of Capsugel Dosage Form Solutions, where she oversees late-stage engineering and manufacturing programs. She has extensive experience with scaling up drug production from development through commercial manufacture. She was instrumental in the startup of a commercial plant plan to manufacture spray-dried dispersion technology at the metric ton scale. Ms. Settell earned a Bachelor's degree in Chemical Engineering from the University of Colorado. She holds two patents and is a member of the American Institute of Chemical Engineers.

Nathan Bennette is a Senior Research Chemist and Technical Lead at Bend Research, a division of Capsugel Dosage Form Solutions. In collaboration with engineering and manufacturing teams, he leads a team of scientists to develop high-energy solid-state formulations and solid dosage forms for oral delivery. His primary areas of expertise and responsibility include the development, characterization, and scale-up of solid amorphous dispersions and nano-crystalline formulations for bioavailability enhancement. He earned his MS in Inorganic/Organometallic Chemistry from the University of Washington and his BS in Chemistry from the University of Oregon.

Amber Broadbent, PhD is a Director of Engineering at Bend Research, a division of Capsugel Dosage Form Solutions. She leads interdisciplinary teams of scientists and engineers to develop and manufacture novel pharmaceutical formulations. Her primary areas of expertise include process development, scale-up, and commercialization of spray dried-dispersions (SDDs) and osmotic controlled-release tablets. Dr. Broadbent has been with Bend Research since 2011. She earned her PhD in Engineering, with a Chemical Engineering focus, from Montana State University.

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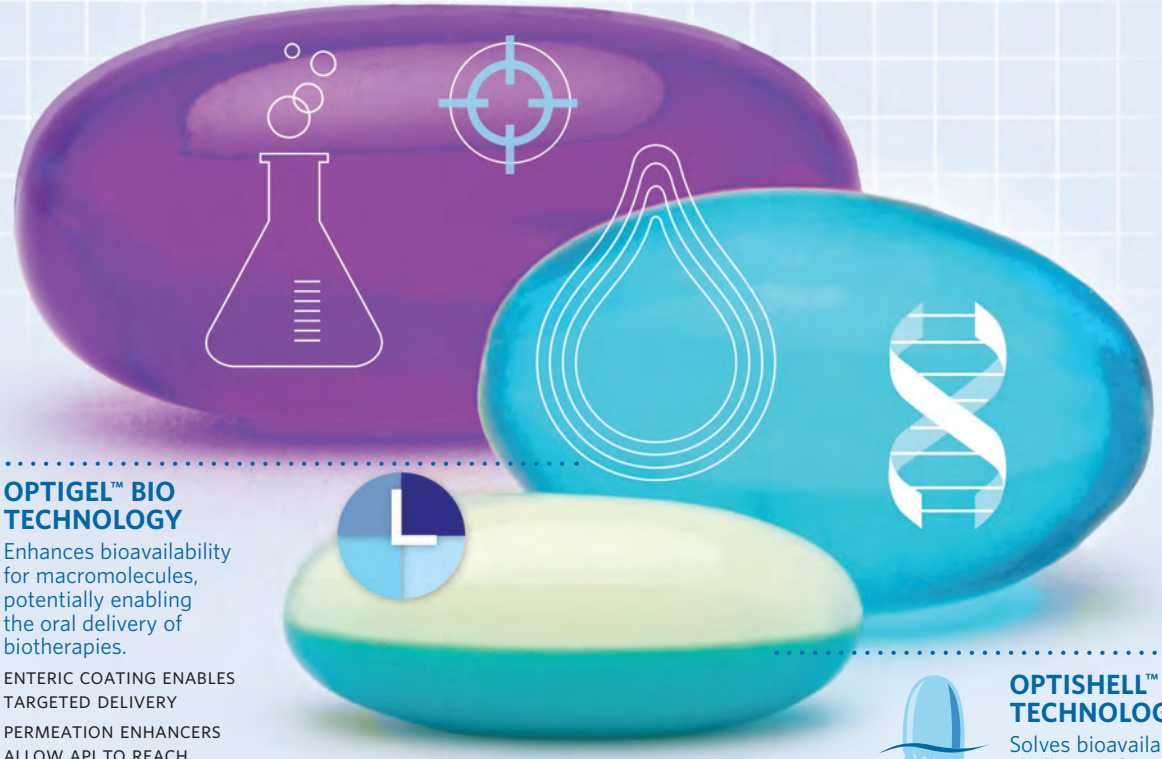

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