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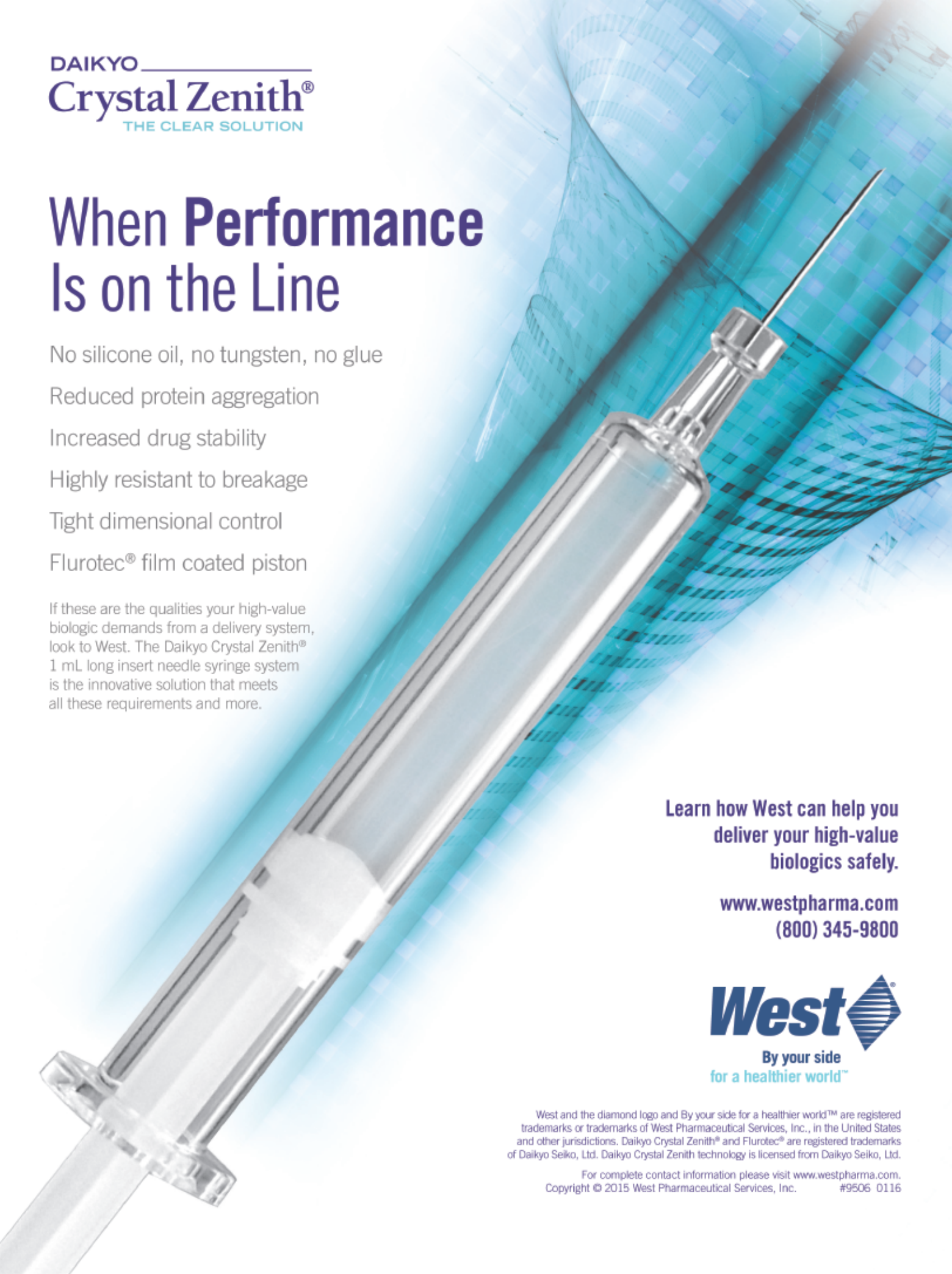

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Platform Technologies: Not Just for Big Pharma

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

Bill Welch
Device Development for Pharmaceutical & Biologic Combination Products

Michael Hooven, MSME
Sophisticated Connected Wearables: Boosting Biologics' Compliance, Value & Patient Satisfaction

Wetteny Joseph
Increasing Efficiency & Flexibility for the Clinical Supply Chain

IN THIS ISSUE

INTERVIEW WITH **PYRAMID LABORATORIES'** PRESIDENT & CEO MEDHAT GORGY

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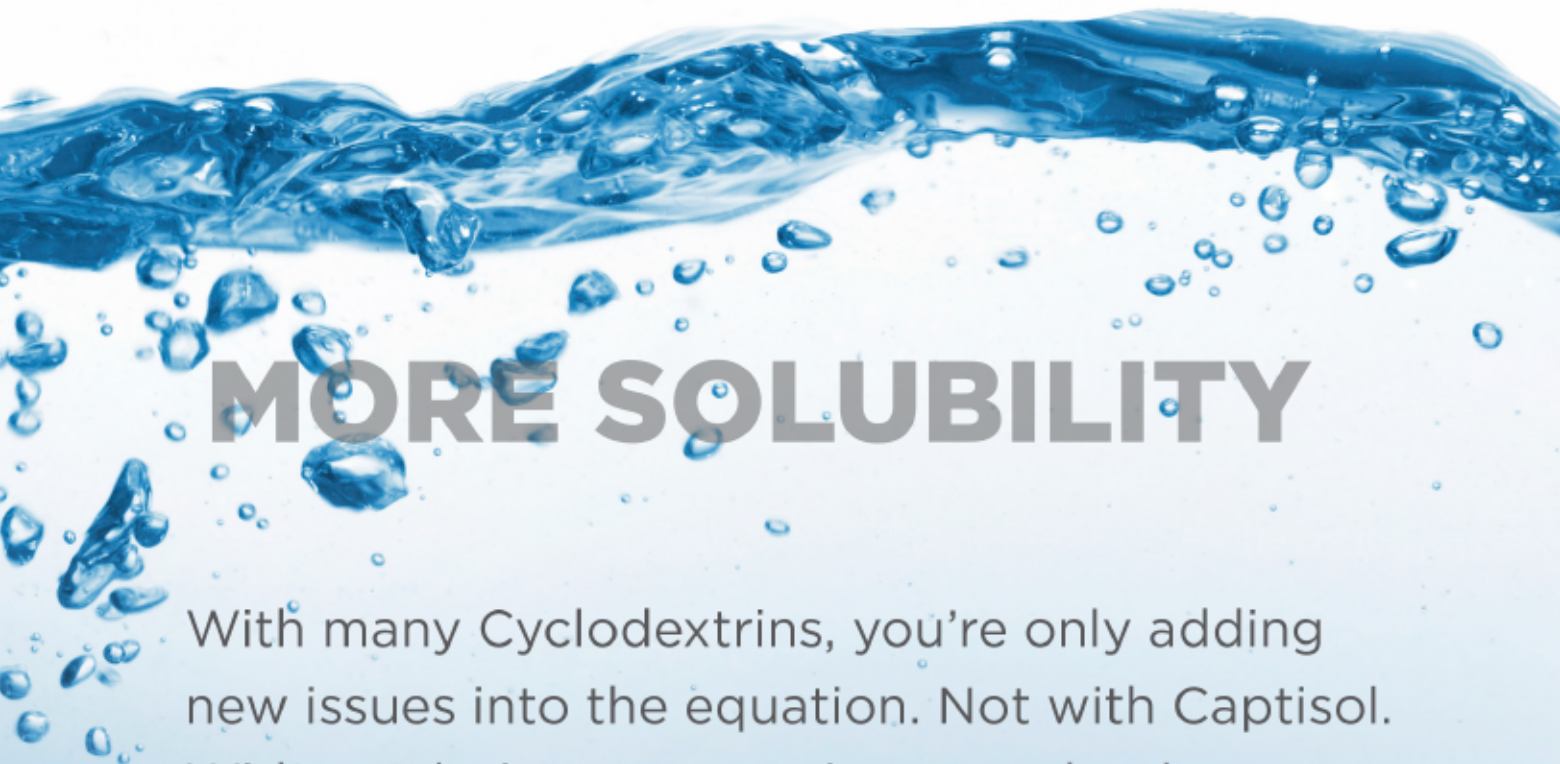

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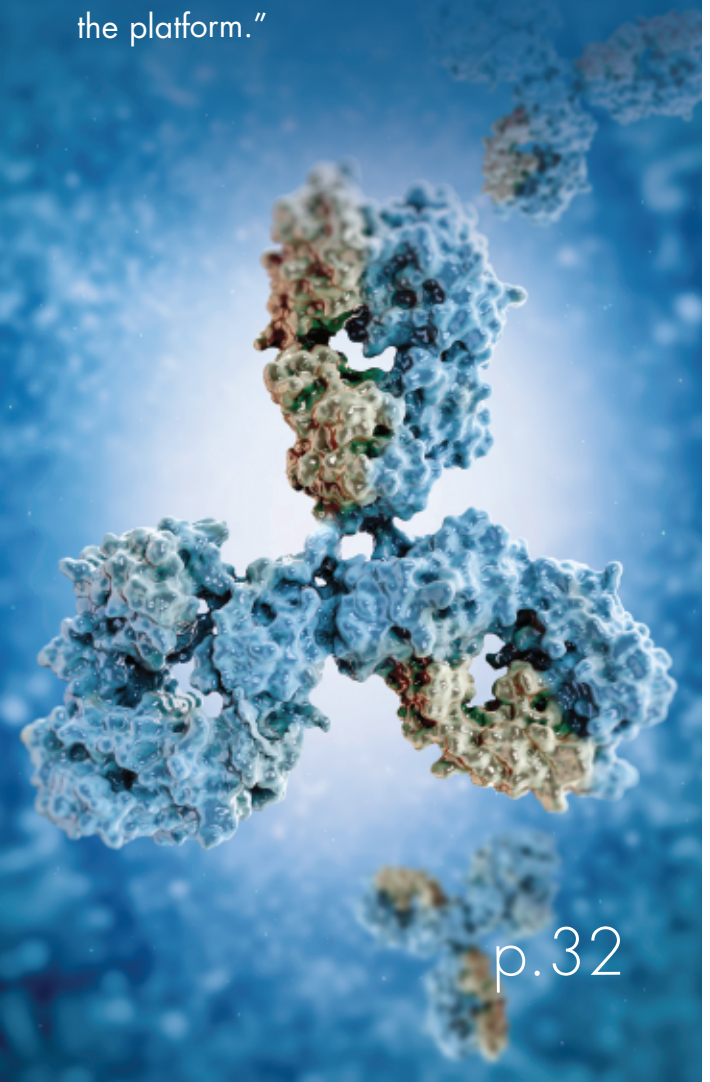

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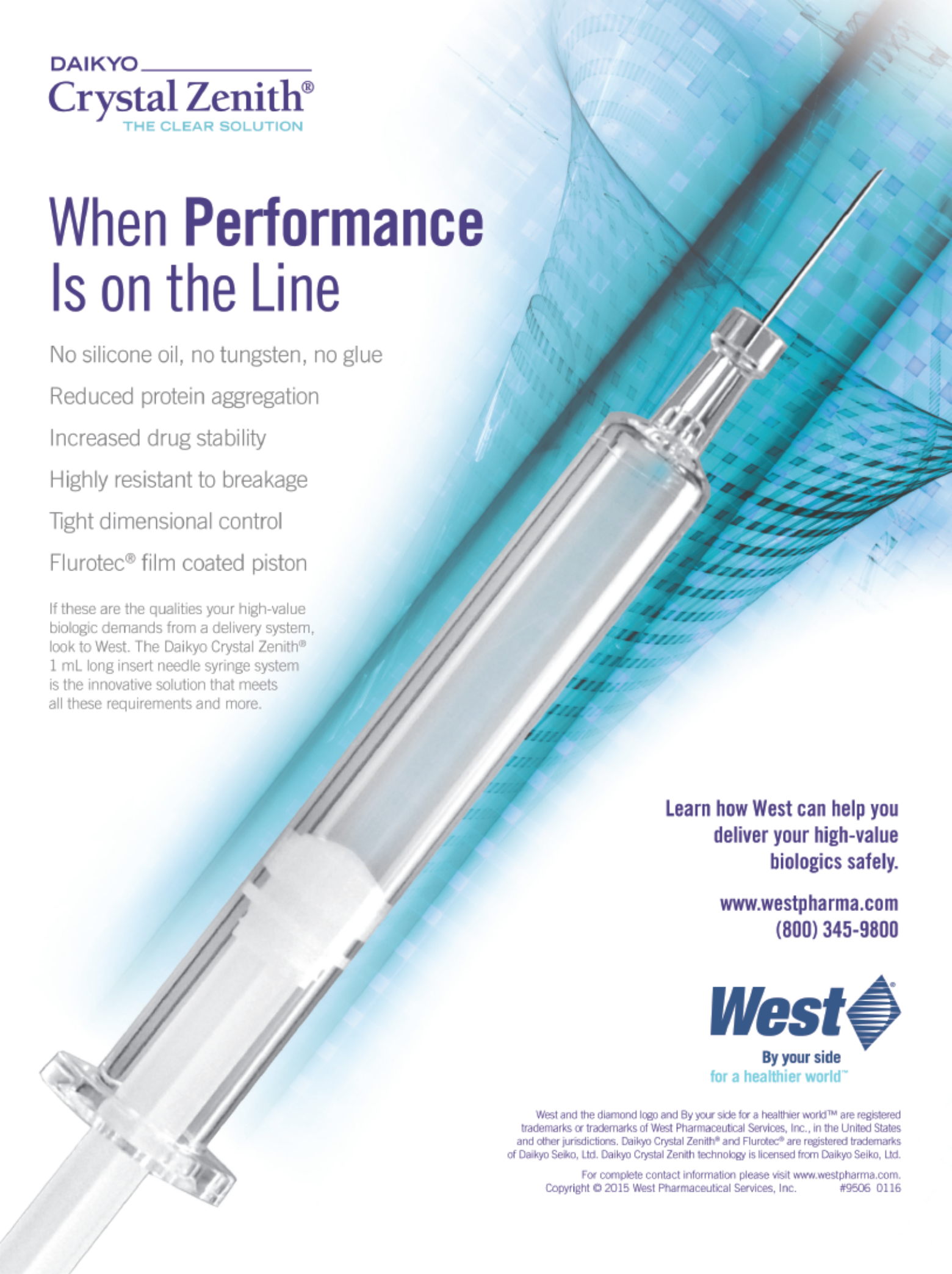

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Caladrius Subsidiary, PCT, Announces 5-Year Strategic Manufacturing Services Agreement

Caladrius Biosciences, Inc., a cell therapy company combining an industry-leading development and manufacturing services provider (PCT, LLC, A Caladrius Company) with a select therapeutic development pipeline, recently announced a new 5-year strategic manufacturing services agreement under which PCT will produce SPEAR T-cell therapies for Adaptimmune Therapeutics plc. PCT, through dedicated, specialized staff and facilities, will produce the SPEAR T-cell products at its Allendale, NJ, facility in a manner compliant with both US FDA and European Medicines Agency (EMA) regulations.

PCT's relationship with Adaptimmune is intended to provide Adaptimmune with operational flexibility for the manufacture of its SPEAR T-cell products from development through clinical manufacturing and, ultimately, subject to marketing authorizations, into commercialization.

"PCT is an elite contract manufacturing organization in the field of patient-specific cell therapies, and we are very pleased to strengthen and develop our existing relationship," said Dr. Gwendolyn Binder-Scholl, Adaptimmune's Chief Technology Officer. "We have worked with PCT over the past 3 years and their commitment to high-quality manufacturing, allied to timely delivery, makes them an ideal manufacturing partner for Adaptimmune. This arrangement will complement well our new manufacturing plant currently under construction in Philadelphia."

"We are delighted to expand our relationship with Adaptimmune. This extension is a perfect example of our ability to service our clients' needs from earlier-phase clinical trials through development toward commercialization," said Robert A. Preti, PhD, President of PCT and Senior Vice President, Manufacturing and Technical Operations of Caladrius Biosciences. "We appreciate Adaptimmune's continued confidence in PCT's ability to support their groundbreaking technologies in the US and Europe."

Adaptimmune is a clinical-stage biopharmaceutical company focused on novel cancer immunotherapy products based on its SPEAR (Specific Peptide Enhanced Affinity Receptor) T-cell platform. Established in 2008, the company aims to utilize the body's own machinery - the T-cell - to target and destroy cancer cells by using engineered, increased affinity TCRs as a means of strengthening natural patient T-cell responses.

Caladrius Biosciences, Inc. is advancing a proprietary platform technology for immunomodulation by pioneering the use of T regulatory cells as an innovative therapy for recent onset type 1 diabetes. The product candidate, CLBS03, is the subject of an ongoing Phase II clinical trial (The Sanford Project: T-Rex study) in collaboration with Sanford Research, and has been granted Orphan Drug and Fast Track designation by the US FDA and Advanced Therapeutic Medicinal Product classification by the European Medicines Agency. The company's PCT subsidiary is a leading development and manufacturing partner to the cell therapy industry. PCT works with its clients to overcome the fundamental challenges of cell therapy manufacturing by providing a wide range of innovative services, including product and process development, GMP manufacturing, engineering, and automation, cell and tissue processing, logistics, storage, and distribution, as well as expert consulting and regulatory support.

Catalent to Acquire Pharmatek, Adding Expanded Drug Development Services & Spray Drying Technology

Catalent, Inc. recently announced an agreement for Catalent, through its wholly owned subsidiary, Catalent Pharma Solutions, Inc., to acquire Pharmatek Laboratories, Inc., a West Coast, US-based specialist in drug development and clinical manufacturing. The acquisition will add extensive early phase drug development capabilities from discovery to clinic, bring spray drying into Catalent's portfolio of drug formulation and delivery technologies, and expand Catalent's capability for handling highly potent compounds. The addition of spray drying will also provide Catalent customers with a comprehensive suite of bioavailability enhancement solutions, while complementing and expanding Catalent's OptiForm Solution Suite platform, a science-driven parallel screening approach to identify the optimal formulation pathway for poorly soluble compounds. No financial details have been disclosed.

Founded in 1999, Pharmatek provides dosage form development and clinical-scale cGMP manufacturing of oral, injectable, and topical products for more than 100 customers globally. At its San Diego facility, Pharmatek offers a fully integrated drug development platform, with discovery formulation screening for lead selection and optimization, comprehensive formulation development and analytical services, and finished dose form manufacturing for clinical supply. Additional services include first-in-man strategies, solutions for poorly soluble compounds, controlled release formulations, and specialized facilities and controls for potent compound handling.

"Catalent continues to expand its industry-leading drug development and delivery technologies to help its pharmaceutical partners to fully unlock the potential of their molecules and provide better treatments for patients," said Barry Littlejohns, President of Catalent's Drug Delivery Solutions business. He added, "Combined with Catalent's existing technologies and network, the addition of Pharmatek's well-established scientific expertise and spray dry capabilities will create an unparalleled drug development platform, while the San Diego facility will expand our West Coast presence and provides additional access to the Asia-Pacific markets."

Pharmatek's site in San Diego is a cGMP facility that employs nearly 200 people, whose experience and expertise will complement Catalent's existing development and analytical services teams, based at multiple locations globally. Pharmatek provides development and analytical services for more than 120 molecules annually, and its facility comprises 68,000 square feet of laboratory, manufacturing and support space, with two analytical labs, two formulation labs, four engineering rooms and nine Certified ISO Class 8 manufacturing suites. The site also features 18,000 square feet of laboratory, manufacturing, and support space dedicated to development and manufacturing of highly potent compounds.

The transaction is subject to customary closing conditions and is expected to close in the next few weeks. Catalent intends to pay for this all-cash acquisition through a combination of existing cash and borrowings under Catalent's existing revolving credit facility. The acquisition will not change Catalent's fiscal 2017 financial guidance. The purchase price will not be disclosed as it is not material to Catalent's financial results.

Abeona Therapeutics Announces Licensing of the AIM Next-Generation AAV Gene Therapy Vector Platform

Abeona Therapeutics Inc. recently announced the exclusive worldwide license of a next-generation gene therapy AAV capsid portfolio from University of North Carolina at Chapel Hill. The AIM vector system is a next-generation platform of AAV capsids capable of widespread central nervous system gene transfer and can be used to confer high transduction efficiency for various therapeutic indications. Studies indicate that AIM vectors can efficiently and broadly target CNS tissue, and may provide a treatment for patients that have inhibitory antibodies to natural AAV serotypes. Importantly, the AIM vector system may provide second-generation treatment approaches for patients that have received a previous AAV injection.

"As we continue to build out our orphan and rare disease drug portfolio and move additional programs into the clinic, this agreement with UNC continues the execution of our strategy to combine our expertise in advancing gene therapy programs with the development of a next-generation proprietary AAV vector platform," stated Steven H. Rouhandeh, Executive Chairman. "We look forward to harnessing the clinical utility and therapeutic potential of the AIM vector system technology platform to address a broad range of rare genetic diseases."

In addition to the AAV capsid library, the license also adds ABO-202, an AAV-based CLN1 program, to Abeona's Batten pipeline. ABO-202, developed at UNC by Steven Gray, PhD, with the support of The Saoirse Foundation, Taylor's Tale, Hayden's Batten Disease Foundation, and the Batten Disease Support and Research Association, is anticipated to enter clinical trials in 2017 for patients with infantile neuronal ceroid lipofuscinosis (INCL, infantile Batten disease), an inherited fatal genetic disease that primarily affects the nervous system.

"ABO-202 has shown promising preclinical efficacy in INCL mice after delivery of a functioning copy of the CLN1 gene to cells of the central nervous system, by extending survival and preserving strength when administered early in the disease course," noted Steven J. Gray, PhD, Assistant Professor, Department of Ophthalmology, Gene Therapy Center, University of North Carolina at Chapel Hill. "Our work in developing these novel, next-generation AAV gene therapy vectors have the potential to further advance the field of AAV-based technologies by efficiently and specifically targeting the CNS, with a likelihood of avoiding antibodies endogenously generated by natural AAV serotypes."

"The AIM vector system is a next-generation AAV-based gene therapy technology platform that represents a transformational opportunity for Abeona. The AIM platform will allow us to leverage our current pipeline into second- generation products for CNS and other tissue-specific delivery, and help provide an answer for patients that have existing inhibitory antibodies," added Timothy J. Miller, PhD, President & CEO. "In addition, we add another AAV-based product ABO-202 (AAV-CLN1) for treatment of patients with infantile neuronal ceroid lipofuscinosis (INCL), which builds on our expertise in developing treatments for patients with forms of Batten disease."

Abeona Therapeutics, Inc. is a clinical-stage company developing gene and plasma-based therapies for life-threatening rare genetic diseases.

Voyager Therapeutics & CHDI Foundation Collaborate to Develop Novel Gene Therapy for Huntington's Disease

Voyager Therapeutics, Inc. recently announced a research collaboration with CHDI Foundation, Inc. (CHDI) to advance Voyager's VY-HTT01 program, an adeno-associated virus (AAV)-mediated gene-silencing therapy for Huntington's disease. The collaboration builds upon a previous collaboration between CHDI and Sanofi Genzyme and includes funding from CHDI to help support preparation for and filing of an investigational new drug application, as well as completion of a Phase I clinical trial. CHDI will be reimbursed for its support of Voyager's program upon VY-HTT01 achieving certain commercial milestones.

"Voyager is pleased to collaborate with CHDI to help advance our gene therapy program for Huntington's disease," said Steven Paul, MD, President and Chief Executive Officer of Voyager Therapeutics. "The effort and expertise that Voyager and Sanofi Genzyme continue to commit to the VY-HTT01 program, now further strengthened with CHDI's extensive experience in Huntington's disease research, puts us in a strong position to advance the clinical development of a potential disease-modifying medicine for patients suffering from Huntington's disease."

"CHDI is committed to identifying and facilitating the development of a diverse pipeline of therapeutic strategies for Huntington's disease," said Robi Blumenstein, President of CHDI Management, Inc. "Voyager is a leader in gene therapy, particularly for central nervous system diseases, and we are confident that their expertise will allow us to further extend the important progress that Sanofi Genzyme has already made in our collaboration."

Huntington's disease is an inherited neurodegenerative disorder caused by a mutation in the huntingtin gene. The defect causes a DNA sequence called a CAG repeat to occur many more times than normal. Each child of a parent with a mutation in the huntingtin gene has a 50% chance of inheriting the mutation. As a result of carrying the mutation, an individual's brain cells degenerate leading to behavioral, cognitive, and motor impairments that, over the course of the disease, significantly reduce the individual's quality of life and ultimately cause death within 15 to 25 years of overt clinical onset. It is estimated that around one person in 10,000 carries the mutated huntingtin gene. There are currently no therapeutics approved that slow the progression of Huntington's disease.

CHDI Foundation, Inc. is a privately funded nonprofit biomedical research organization that is exclusively dedicated to rapidly developing therapies that slow the progression of Huntington's disease.

Voyager Therapeutics is a clinical-stage gene therapy company developing life-changing treatments for severe diseases of the CNS. Voyager is committed to advancing the field of AAV (adeno-associated virus) gene therapy through innovation and investment in vector engineering and optimization, manufacturing, and dosing and delivery techniques. The company's pipeline is focused on severe CNS diseases in need of effective new therapies, including advanced Parkinson's disease, a monogenic form of amyotrophic lateral sclerosis (ALS), Friedreich's ataxia, Huntington's disease, spinal muscular atrophy (SMA), frontotemporal dementia, Alzheimer's disease, and severe, chronic pain.

Lonza to Offer Novel Anc-AAV Gene Therapy Technology Through Exclusive Licensing Agreement

Lonza Houston, Inc. and Massachusetts Eye and Ear have entered into a strategic agreement that provides customers the ability to in-license Anc80 and other Anc-AAVs for the clinical development and commercialization of novel gene therapies. The agreement is designed to accelerate gene therapy drug development across the field in order to address diseases in need of treatments and thereby ultimately reach more patients.

Anc-AAVs are in silico designed synthetic adeno-associated viral vectors (AAVs), developed first in the laboratory of Dr. Luk H. Vandenberghe, Assistant Professor at Harvard Medical School, and Director of the Grousbeck Gene Therapy Center at Massachusetts Eye and Ear. As part of the agreement, an innovative platform development effort will be initiated with a focus on discovering additional next generation Anc-AAVs.

"In this era of personalized medicine, the partnership with Lonza is unique, and potentially very effective," Dr. Vandenberghe said, "as it brings a highly potent vector technology under one roof with a leading manufacturer of biologics. We believe this concept will bring innovative gene therapies to patients in a more efficient and expedient way, and that it will increase access to enabling gene therapy technology to unlock treatment for diseases of unmet need, including those affecting vision and hearing."

By applying its AAV manufacturing technology innovation, Lonza agrees to work toward the establishment of modern best-in-class large-scale manufacturing platforms for Anc80 and any future vectors generated out of Dr. Vandenberghe's lab. The agreement comes only months after Lonza broke ground in April 2016 to construct a state-of-the-art viral gene and cell therapy manufacturing facility in Pearland, TX (USA). The new facility, expected to come online at the end of 2017, is anticipated to be one of the largest facilities in the world for the supply of clinical and commercial grade viral-based gene therapies.

Under the agreement Lonza will fund research at the Grousbeck Gene Therapy Center at Massachusetts Eye and Ear to discover, characterize, and develop next-generation gene transfer reagents in order to improve upon important limitations of current AAVs, including pre-existing immunity, manufacturing yields, immunogenicity, tissue tropism, and specificity.

"This strategic licensing deal with Massachusetts Eye and Ear emphasizes Lonza's strong commitment to the field of gene therapy and our continuous quest for improving patients' lives," stated Marc Funk, COO, Lonza's Pharma & Biotech segment. "Drawing on our licensing expertise, we will be able to leverage our experience as the leading global AAV manufacturer in our broad range of service offerings."

As part of the agreement, Massachusetts Eye and Ear grants Lonza the exclusive position to commercially license Anc-AAV while it retains certain commercial and academic rights, including the ability to commercialize self-directed gene therapy programs and all rights in the challenging space of ultra-rare diseases.

Madrigal Pharmaceuticals & Tarveda Therapeutics Announce Exclusive License Agreement

Madrigal Pharmaceuticals, Inc. and Tarveda Therapeutics, Inc. recently announced an exclusive worldwide license agreement providing for the discovery, development, and commercialization by Tarveda of products based on Madrigal's HSP90 Drug Conjugate program, including the lead clinical candidate, PEN-866. Madrigal is a clinical-stage biopharmaceutical company focused on the development and commercialization of innovative therapeutic candidates for the treatment of cardiovascular, metabolic, and liver diseases, and Tarveda Therapeutics, Inc., is a biopharmaceutical company discovering and developing Pentarins as a new class of targeted anti-cancer medicines to advance the treatment of patients with solid tumors.

HSP90 drug conjugates are designed to increase cancer cell killing while reducing collateral damage to normal cells and overcome the challenges of current chemotherapies and other payloads, which are commonly limited by insufficient drug exposure in the tumor and/or systemic toxicities. HSP90 drug conjugates are small-molecule conjugates consisting of an HSP90 targeting molecule joined to an anti-cancer payload via a linker that is optimized for controlled release of the payload inside cancer cells. The conjugate's sustained anti-tumor effect comes from selectively accumulating and retaining the conjugate and, importantly, its potent payload in tumors. HSP90 drug conjugates contrast with previous HSP90 inhibitors that were designed to only inhibit HSP90. Madrigal acquired the drug conjugate platform via its recent merger with Synta Pharmaceuticals, Inc.

The lead HSP90 drug conjugate, PEN-866, is a small molecule drug conjugate that comprises an HSP90 ligand conjugated to SN-38, the highly-potent, active metabolite of the chemotherapeutic agent irinotecan. PEN-866 binds with high affinity to the intracellular HSP90 target. Once bound to its target, PEN-866 delivers the tumor-killing SN-38 payload. PEN-866 has shown an impressive degree of efficacy and durability of response in multiple preclinical tumor models, including patient-derived xenograft models. Studies demonstrate that SN-38 released from PEN-866 accumulated at high levels within the tumors and was associated with increased and widespread cancer cell death when compared with irinotecan alone.

Madrigal will receive an upfront payment and is eligible to receive up to an aggregate of $163 million of contingent payments based upon the achievement of specified development, regulatory, and sales milestones related to the first HSP90 drug conjugate product developed under the agreement. Madrigal is also eligible to receive a tiered, single-digit royalty based on future worldwide sales of HSP90 drug conjugate products. Potential development, regulatory, and sales milestone payments related to a second HSP90 drug conjugate product would be lower. Tarveda will be responsible for all of the development costs for the HSP90 drug conjugate program.

The Tarveda team is composed of seasoned oncology leaders, scientists, and drug developers who are taking a novel approach to cancer treatment by creating Pentarins, which are miniaturized drug conjugates uniquely designed to target, penetrate, and eradicate solid tumors. Creating Pentarin drug conjugates that drive efficacy in solid tumors is the core expertise and focus of the team at Tarveda.

Capsugel Investing in Enhanced Micronization Capacity & Capabilities

Capsugel, a global leader in delivering high-quality, innovative dosage forms and solutions, recently announced an expansion of its facility in Quakertown, PA, to meet increasing customer demand for its micronization services for both clinical and commercial manufacturing. The company will double the size of its current pilot-scale capacity for clinical trial quantities and increase the number of suites dedicated to commercial manufacturing.

Micronization of active pharmaceutical ingredients (APIs) is accomplished using proprietary jet milling equipment. The Quakertown facility, which Capsugel acquired as part of its purchase of Xcelience and Powdersize in January 2016, operates as a full-service provider of particle-size reduction and particle-size control/classification technologies for pharmaceutical customers. The acquisition expanded the company's suite of bioavailability enhancement tools aimed at improving the bioavailability of APIs with either dissolution or solubility challenges – an issue faced by more than 70% of new chemical entities. The expansion enables the company to add capacity for commercial manufacturing and is expected to further improve product lead times by up to 75%.

"Our customers are increasingly seeking specialized partners in early stage compound assessments and product design, with poor dissolution and/or solubility often being at the forefront of their challenges," said Amit Patel, Sr. Vice President, Capsugel. "Micronization and nano-milling technology is a significant component of Capsugel's overall service offering, and this investment further strengthens our ability to rapidly advance challenging compounds to clinic and ultimately commercialization."

In addition to enabling increased capacity, the added suites will feature new state-of-the-art, single-use containment technologies to accommodate continued growth in potent and highly potent compounds. The new equipment and suites are scheduled to be operational by January 2017.

"One of the many reasons we were eager to join Capsugel was the opportunity to become a part of its unique design, development, and manufacturing offering," said Wayne Sigler, President, Powdersize, a division of Capsugel. "This investment further supports the role of micronization and sub-micronization in compound assessments and product design through commercialization, bringing more benefits to our customers. It also enables us to stay ahead of rising customer demand, so we can help our customers meet aggressive development and clinical timelines."

Capsugel designs, develops, and manufactures a wide range of innovative dosage forms for the biopharmaceutical and consumer health and nutrition industries. Its unique combination of science, engineering, formulation, and capsule expertise enables customers to optimize the bioavailability, targeted delivery, and overall performance of their products. The company partners with more than 4,000 customers in over 100 countries to create novel, high-quality and customized solutions that align with customers' evolving needs and benefit patients and consumers. For more information, visit www.capsugel.com.

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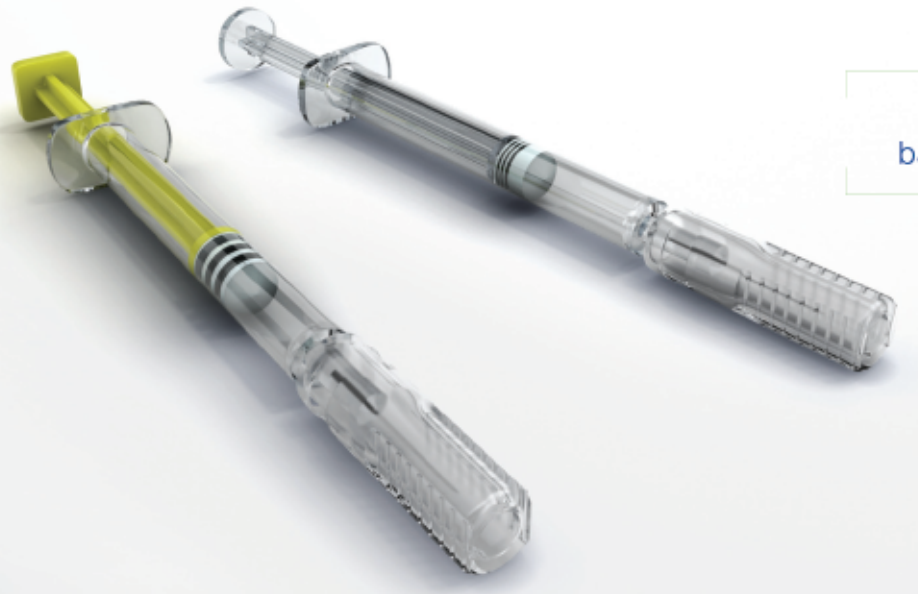

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COMBINATION PRODUCTS

Device Development for Pharmaceutical & Biologic Combination Products

By: Bill Welch

INTRODUCTION

Combination products are defined as therapeutics combining two or more products (drug/device, biologics/device, biologics/drugs, or drug/device/biologics) regulated and sold as a single unit. As these pharmaceutical and biological therapies and treatments have evolved, so has the need to develop appropriate delivery mechanisms for these applications. When developing a combination product, there are many things to be considered – relationships between device development and the pharmaceutical or biologic, early establishment of regulatory and clinical strategies, understanding user needs, determining product requirements, as well as device manufacturing variation.

DEVELOPMENT STRATEGY & SCALING

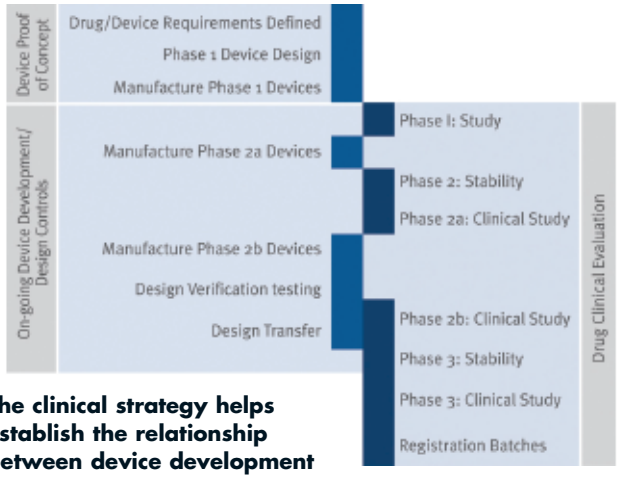
An efficient combination product development process begins with understanding regulatory/clinical strategies. Creating strategies early on will help ensure the device development is aligned with the pharmaceutical (drug) or biologic development and applicable regulatory requirements, in turn, reducing time to market.

An integrated regulatory/clinical strategy significantly de-risks the product in early development, as well as reduces the number of questions from the reviewing agency.

Regulatory Strategy

Combination product regulatory submissions involve fulfilling drug/biologic requirements and a scaled version of the device-design history file. The amount of device development documentation can vary based on the lead regulatory agency, based on the product's primary mode of action (PMOA), reviewing the documentation (device – CDRH, drug – CDER, or biologic – CBER). Designating the PMOA with the simplest form of intended use is the key to submission expediency. Accordingly, there are two questions to consider.

FIGURE 1



The clinical strategy helps establish the relationship between device development and clinical milestones.

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What is the Combination Product's PMOA?

The PMOA is the main therapeutic component that zeroes in on the combination product's intended use. For example, in a drug-eluting stent for opening diseased arteries, the PMOA is the device's ability to open the artery. The drug provides a secondary PMOA as an "aid." In this example, the product will likely be submitted through the FDA's Center for Devices and Radiological Health (CDRH), which approves and clears medical devices. If the PMOA is linked to a drug/device product's drug component, the Center for Drug Evaluation and Research (CDER) would be the lead FDA center. The assigned reviewing agency may/may not be involved in cGMP/PAI inspections for the registered facilities. However, the lead agency usually outsources review of the other constituent part to its counterpart(s).

Lastly, the sponsor needs to define the PMOA. Companies struggling to determine the PMOA may submit a request for designation (RFD), enabling the FDA to give a binding ruling. If not clear, the agency will use an algorithm to categorize the device's PMOA.

What Marketing Submissions & Applications Will be Required?

Depending on the PMOA and lead FDA center, a manufacturer may be required to undergo clinical trials using one or more of the following – investigational device exemption (IDE) for a device, and investigational new drug (IND) or new drug application (NDA) for a drug. Determining the submission pathway is essential to understanding the clinical trial strategy. Consequently, that knowledge helps identify the device development schedule and level of product robustness necessary before submission can occur.

Clinical Strategy

The clinical strategy establishes critical milestones for device development, such as when feasibility prototypes or breadboard-level electronics and software development are needed. Those milestones continue through the process to when design verification testing should be completed and commercial-equivalent product needs to be available. Early clinical studies may be conducted with prototype devices that produce the essential core device technology, but don't require the device in its final commercial configuration. There is, however, a point the device needs to be "production-like" and manufactured under full cGMPs, verified against the design input requirements and validated to show it meets its intended use and needs. That's when it is valuable to have an integrated regulatory/clinical strategy between the client and CMO/supplier.

It is imperative the device development team understands the critical drug development milestones so adequate resources are applied and it can be determined if the device will achieve the performance and repeatability levels needed to conduct effective drug development. Understanding the clinical schedule early on helps ensure the most efficient approach is considered by scaling the development strategy appropriately.

Where the studies will take place is also important; it tends to be easier to enroll patients and less expensive to conduct studies outside of the US. However, the FDA may be less apt to accept the clinical data due to confidence with the sponsor's clinical data study plan and data integrity itself. With the 2015 guidance on this topic, firms have clearer guidelines and a better path to acceptance.

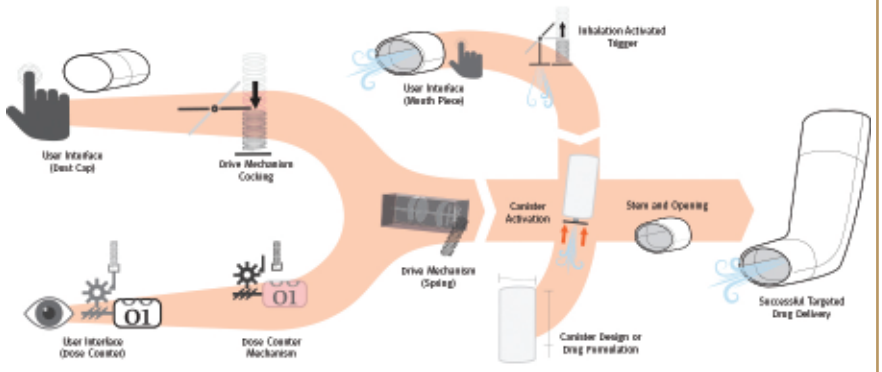
UNDERSTANDING PRODUCT NEEDS

Defining the needs of the user, business, or stakeholder is fundamental to developing a product that will be successful. To satisfy these needs, the product must be:

- Useful – meet a specific need
- Usable – easy to understand and manipulate
- Desirable – appealing to the intended user so it will be adopted into their daily use
- Manufacturable – the process output is true to the actual value or target desired and repeatable

An integrated product development process, combining human-centered design principles with a solid design for manufacturing philosophy, improves the probability of success and speed-to-market. Also, appropriate levels of design research are needed to fully understand user needs.

FIGURE 2



To ensure a combination product will perform as intended, the multiple subsystems need to be well defined and understood.

PRODUCT REQUIREMENTS

The user and stakeholder needs identified during device development are then translated into design input requirements (product requirements) – with engineering level of detail – and ultimately, into manufacturing specifications. Combination products consist of multiple subsystems that need to be well defined and understood to ensure the product will perform as intended. When software and electronics are an integral part of the drug delivery device, additional development complexity exists. While some requirements can be looked at independently, a set of requirements needs to be developed for the integration of the drug and device together – with emphasis on the way each constituent part may adversely affect the other.

Once the Target Product Profile (TPP) of the drug substance is established, relating this to the materials science aspects of device development is key for things such as stability, toxicity, and ADME studies. One way of more clearly defining this relationship is in early development, with use of Quality-by-Design (QbD). QbD (drug standpoint) and proof-of-concept (device) are not mutually exclusive. Through development of a design space, QbD helps establish the target product profile (TPP) of the drug substance. However, the design space for the TPP could be impacted by the properties of materials (drug delivery device) where product contact is made. This potential interaction over time (stability) can possibly alter the efficacy of the drug, sterility, etc, which in turn lowers the efficaciousness and effectiveness of the drug product for therapeutic effect.

Drug Performance

Requirements that focus on the drug alone typically describe how the molecule and formulation need to be configured such that the drug will have its desired effect once it is interacting with the patient. Those requirements often include pharmokinetics, pharmodynamics, and other pharmacological performance definitions.

Device Performance

Device-specific requirements typically describe how the device will interact with the user and how the drug will be readied for delivery. Human factors engineering, design research, and industrial design (collectively known as human-centered design) all have a significant role in establishing these device requirements. How the device is used is critical to ensuring the drug is delivered as intended. Combination products should be easy to use, and during the development process, appropriate levels of user risk should be assessed. Formal usability studies, early in the development process, inform the device design and technical performance studies.

Drug & Device Integration

Developing the requirements for where the device impacts drug performance is the most challenging part of this process. A partnership between the drug and device development teams is essential to success, along with an understanding of each group's needs (bilateral education). Device development companies need to understand the mechanics of drug dispersion (eg, aerosol, transdermal, subcutaneous) to identify device features that may impact drug delivery. Similarly, drug development companies need to understand device manufacturing and variation while paying attention to material selection – it could impact drug delivery and performance.

Both groups also need to understand the nature of device development and clinical nature of drug development, so these critical interfaces can be identified, quantified, and stabilized early and generate robust clinical data. The following are examples of drug/device interfaces and how both groups may generate requirements.

Container Closure System

Devices are often considered a part of or the entirety of a container closure system (CCS). Per FDA Guidance for Industry-Container Closure Systems for Packaging Human Drugs and Biologics, "A container closure system refers to the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product." This critical distinction is important as the vials, ampules, bottles, or molded components a company uses to house a drug must be tested with the drug and be considered a "whole" throughout the product development process.

Drug product integrity and effectiveness are additional aspects for why CCSs need to be thoroughly tested against edge-of-failure conditions. Any potential breach of a CCS for a sterile product, parenteral, or injectable could introduce byproducts, toxins, impurities, or other foreign materials that could impact the drug product stability profile; the drug product could be less effective for the targeted disease state, adverse reactions could manifest due to the foreign materials or degraded product, or a combination of these two could happen. The CCS must allow for the product's integrity throughout the supply chain until the end of expiration.

Formulation

The drug formulation may impact how the drug moves, interacts with, and is delivered through the device. Some formulations may be sensitive to molecular shearing and require slow, laminar delivery through the device, while other formulations (especially inhalers) may have high static charges that attract to plastic, requiring device materials that dissipate static electricity. Additionally, some formulations need to be developed with the intent of the device and sterilization method in mind. Some substances, especially peptides, are extremely heat labile, where protein molecules can break apart, degrade, or get altered into a new form with high impurity profiles that can become toxic if administered.

Device

The device can have a significant impact on product performance. First, the device is the primary user interface, controlling the user portion of how the drug is delivered. Human factors engineering and industrial design should influence this portion of device development. The device is the means by which the drug is pressed, extruded, inhaled, or otherwise "delivered" to the patient. Requirements that establish the position of the drug – prior to delivery, the delivery path, the method of delivery activation – all impact how much (volume) and at what rate (time) the drug enters the patient.

DEVICE MANUFACTURING VARIATION

It is common knowledge device A is not the same as device B when viewed on a micro-scale. This is where specifications come into play. A device will be manufactured to specifications that most commonly control the size of a feature and/or its position relative to another feature. This is very important to understand, especially for those with pharmaceutical or biological backgrounds. A device consists of multiple components, each with multiple features and every feature requiring some level of manufacturing tolerance, creating a lot of room for device performance variation.

Specifications are derived from requirements; however, specifications are not requirements themselves. If the requirement of a spring-loaded syringe is to deliver the drug within 1-2 seconds of actuation, the device team must create manufacturing specifications and tolerances to generate this result.

In the following example, the drug viscosity needs a specification in order for this system to meet the requirement. Similarly, different features of this simple spring-loaded syringe have specifications and tolerances applied to them to meet this requirement.

- Syringe inner diameter: 1.00 mm +/- 0.05 mm
- Plunger outer diameter: 1.10 mm +/- 0.05 mm
- Needle inner diameter: 0.3 mm +/- 0.01 mm
- Drug viscosity: XXXX +/- XXXX
- Spring rate: XXXX +/- XXXX

The syringe manufacturer is responsible for ensuring the syringes meet the specification of 1.00 mm +/-0.05 mm. The plunger manufacturer is responsible for ensuring the plungers meet the 1.10 mm +/- 0.05 mm specification, and so on.

Similarly, when software and electronics are involved, complex

algorithms may be developed early on to perform a function using one, two, or three prototype devices. During development, the software and electronics teams need to understand the manufacturer's tolerances for sensors, processors, and the like, as well as molded or fabricated components. Software development may require ongoing development as additional units are produced and component variation begins.

Regulatory expectations regarding configuration management for medical devices with software platforms shouldn't be overlooked. Configuration management ensures as-built configurations conform to their documented requirements and are built to the correct versions of those documents. A configuration management capability model should be established from early stages of device development through end of life.

The Right Tolerances for Different Features

Partnering with the manufacturer during the design process, or working with a device development company that truly understands manufacturing, ensures early concepts aren't reliant on component features that can't be produced in higher volumes. When making a single, or a low volume of components, smaller tolerances can often be achieved. However, in higher volumes, more variation is inserted into the manufacturing process.

Characterization Testing

Once the initial specifications and tolerances are established (with manufacturing input), parts can be prototyped at their specification limits to determine if the tolerances are appropriate. When performance is characterized against a range of feature sizes, it is often referred to as characterization testing. This provides confidence the manufacturing specifications and tolerances will result in a product that will meet requirements when manufactured at commercial volumes. Prototyping features, at their size limits, allow for refinement of software and complex algorithms that may interface with the user or be responsible for controlling some aspect of drug delivery.

Characterization testing, integrated into the development process, is key to understanding how drug and device interactions will be observed in full-scale manufacturing. This activity can be planned for and executed as part of the strategy rather than troubleshooting errors/defects once component variation enters the process.

SUMMARY

There are many things to consider when developing a combination product and a greater opportunity for success with early design involvement and careful consideration of everyone's knowledge needs. Before you begin development of your combination product, consider the following:

- Early establishment of the regulatory and clinical strategy will help ensure appropriately scaled device development meets regulatory requirements and is in-line with the clinical milestones.
- User and stakeholder needs are the foundation of product development and help ensure the right product is developed.
- Product requirements ensure the product was built right and need to be determined for:
  - Drug performance
  - Device performance
  - Drug/device integration performance
- Device manufacturing variation needs to be understood and designed for. Characterization testing should be conducted to understand the impact of manufacturing specifications and tolerances on product performance. ◆

BIOGRAPHY

Bill Welch is the CTO of Phillips-Medisize and manages all product development, manufacturing, and engineering responsibilities for their drug delivery device business. He can be reached at bill.welch@phillipsmedisize.com.

Advanced Delivery Devices

Sophisticated Connected Wearables: Boosting Biologics' Compliance, Value & Patient Satisfaction

By: Michael D. Hooven, MSME

In 2015, sales of AbbVie's biologic treatment for rheumatoid arthritis and related autoimmune diseases, Humira, topped $14 billion. Another 39 biologics also reached blockbuster status, exceeding $1 billion in sales according to Morningstar. Nine of these biologics brought in $5 billion in global sales.

Given the potential — both therapeutic and financial — it comes as no surprise that some 900+ biologics are currently progressing through pharmaceutical companies' R&D pipelines. This year, these large molecule, protein-based therapeutics continue to be the main drivers of industry growth and are predicted to reach $445 billion in sales by 2019, up from $289 billion from 2014.[1]

However, biologic drugs consist of mega-molecules that are hundreds of times the size of conventional small molecule drugs. They are frequently composed of a heterogeneous mixture of more than 1,300 weighty amino acids. That creates three main challenges for pharmaceutical companies seeking to develop the next blockbuster biologic:

1. They are hard to make[2]
2. They are hard to take
3. They can be expensive

Despite these difficulties, targeted as they are to particular genes or proteins, biologics are compelling for treating diseases due to their higher specificity and fewer side effects.[3,4]

Biologics on the market and in development are also broad ranging, suitable for treating a large number of disparate diseases. Currently, cancers and related conditions are the most researched area for biologics, according to analysts. Other prominent target diseases are autoimmune diseases, blood disorders, and genetic disorders. The list includes, but is not limited to:

Wearable high-volume injector can be worn discretely under clothing.

- Numerous cancers
- Rheumatoid arthritis
- Multiple sclerosis
- Hemophilia
- Myasthenia gravis
- Lupus
- Vasculitis
- Sickle cell anemia
- Crohn's disease, ulcerative colitis, and other digestive disorders

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- Neurologic disorders

Clearly, opportunity abounds. To take advantage of it, the most proactive biopharma companies are turning to new drug delivery technology that may help dissipate top challenges and at the same time, create demand for their products and improve compliance. Yes, new drug delivery technology can help tackle development, delivery, and cost challenges.

WHY PHARMAS ARE EXPLORING THE NEW DELIVERY OPTION

Why change the way pharmas create and administer drugs now? Because pressures have increased and because ultimately it's likely to pay off. Despite optimism that molecules in R&D could potentially turn to biologics gold, pharmaceutical executives are under tremendous pressure. They must reduce costs. They need to increase efficiency. Margins are eroding, and now they also have to prove the value of their expensive biologic drugs as the healthcare system moves inexorably toward value-based care.

These rapid changes are testing long-held industry beliefs. As a result, forward-thinking pharmaceutical companies are responding by employing entirely new operational models and adopting new tools that can better position them to succeed in the rapidly emerging outcomes-based environment.

These changes in the way pharmas do business are imperative - but promising. Data show that the most innovative pharma companies prosper most. Top innovators saw 25% of revenues coming from new products or services versus 14% for less-innovative pharmas. And the majority of pharma executives surveyed said innovation is a competitive necessity.[5]

So in addition to various IT infrastructure and R&D informatics upgrades, pharmaceutical companies are turning to patient-focused technology. For example, they are exploring combining their biologic drugs with the newly available, more advanced wearable high-volume drug delivery devices. In conjunction with creating new treatments, they are simultaneously reaching out to similarly innovative drug delivery partners to assure that once the new drugs reach the market, their value proposition is realized and patients take them, a requisite for improved outcomes.

As a result, partnerships with companies developing new connected wearable large-volume injectors are rapidly proliferating, and more biologic-device combos are expected to gain regulatory approval soon.

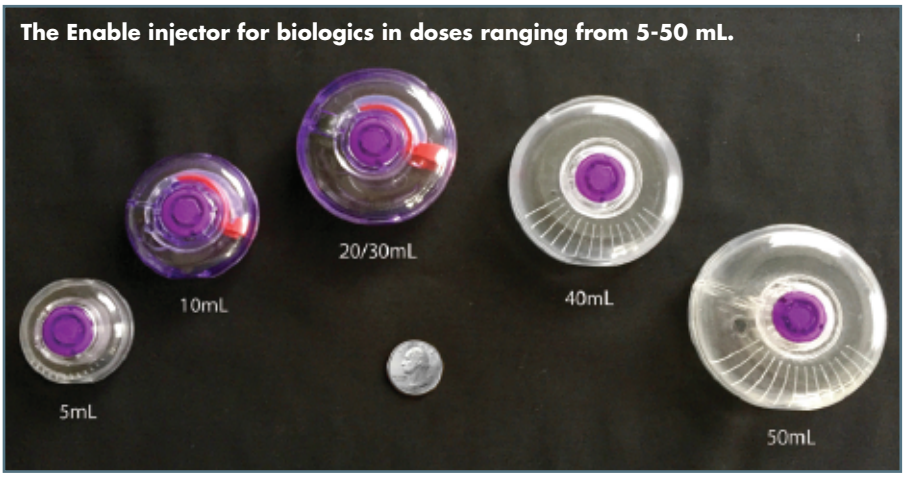
Companies with biologics already on the market are also looking at new drug delivery technology as they plan their patent extension strategies. Eleven established biologic products – representing 48% of total biologic sales – are slated to lose patent protection by 2022.[1]

WEARABLE LARGE-VOLUME INJECTORS REDUCE FORMULATION TIME & EFFORT

Scientists developing biotherapeutics spend enormous time and effort on formulation – sometimes years. This amount of time and effort can be significantly reduced with use of the newest biologics delivery technology, the on-body delivery systems now available for clinical studies and commercial use.

These wearable large-volume injectors bring to market a novel product development aid that reduces formulation time and effort by enabling a simpler method of product preparation.

The Enable injector for biologics in doses ranging from 5-50 mL.



Patients need only insert any standard vial, cartridge, or syringe, adhere the auto-filled injector to their body, and push one button. The Enable Injector automatically warms as it fills - no waiting time.

Formulation teams can take advantage of the innovative delivery technology to speed development of stable, bioavailable, clinically relevant formulations.

Formulation teams can also facilitate patient self-injection of biologics by adopting drug delivery technology that aids in:

- Delivering more volume of product
- Delivering much higher viscosities caused by higher concentration of proteins
- Resolving biologics' greater propensity to precipitate out of solution

The time and effort savings are accomplished with automated lyophilization, which accelerates or eliminate tedious, time-consuming formulation functions for more rapid - and less costly - product development. In addition, the requirement for formulation teams to concentrate the product in the smallest possible dose for delivery by an auto-injector (typically < 1 ml) may no longer be relevant. The latest generation of injectors has the ability to provide a comfortable injection experience for higher volume product delivery. Patient acceptance of new higher volume on-body delivery systems should be high because the devices support mobility, are easy to use, and minimize any injection discomfort.

PATIENT-FOCUSED TECHNOLOGY: REMOVING COMPLEXITY

The medical literature leaves little doubt that taking medication as prescribed and for the recommended time period is problematic for many patients and can significantly impact healthcare outcomes and cost of care. A World Health Organization (WHO) report cites non-adherence as a leading cause of preventable morbidity, mortality, and cost.[6] Yet, compliance among chronic disease patients averages just 50%. The WHO report cites complexity among the major causes of failure to comply with prescribed medication.

Reducing this complexity and its associated cost is another major challenge facing the pharmaceutical and biotech companies developing the biologics, monoclonal antibodies, and immunoglobulins that are revolutionizing treatment of cancers and chronic diseases.

The most advanced wearable large-volume injectors, such as the Enable Injector, are designed to eliminate complexity entirely so that the promise of new and existing products is realized, potentially helping create tomorrow's blockbusters. Patient confusion and errors are minimized by requiring only a few simple steps:

- INSERT a standard drug vial/syringe/cartridge into the transfer system, which automatically warms any refrigerated product in the 30-40 seconds it takes to fill the on-body delivery system
- PLACE the injector on skin
- PULL the safety tab
- PRESS one button

A large pharmaceutical company's patient panels testing a range of injectors strongly favored the Enable Injector, citing its small size, ease of use, convenience, and "cool" shape among the reasons for their choice. The findings are replicated in a small clinical trial with a different cohort.

"Why change the way pharmas create and administer drugs now? Because pressures have increased and because ultimately it's likely to pay off. Despite optimism that molecules in R&D could potentially turn to biologics gold, pharmaceutical executives are under tremendous pressure. They must reduce costs. They need to increase efficiency. Margins are eroding, and now they also have to prove the value of their expensive biologic drugs as the healthcare system moves inexorably toward value-based care."

FOR PATIENTS, BIOLOGICS ARE NOW EASY TO TAKE

On-body delivery systems will also change the way patients think about injections. Subcutaneous injection remains the preferred method of delivering injectable drugs, including biologics. Yet, historically injectable drug administration has been particularly problematic, in large part because most patients dislike injections, especially those that are self-administered. Injecting biologics would be even more difficult for patients due to the large biologics doses required and their viscosity. Legacy systems, such as syringes and earlier large-volume injectors, could not handle anywhere near the large doses of up to 50 mL or their viscous formulations.

But now, such large doses are possible for patients to self-inject easily and comfortably. Today's wearable high-volume injectors offer safety, ease of use, and injection comfort - vital attributes if uncomplicated self-injection of biologics is to gain traction. And now the injector technology is connected and can monitor compliance, potentially a major step in improving treatment outcomes.

Fulfilling the vision of self-injection that is safe, easy, comfortable, and convenient for patients, yet cost effective for the pharmaceutical industry and payers, today's most sophisticated drug delivery devices are distinguished by the following:

- Use standard vials, syringes, or cartridges so no change to the primary container is required. This eliminates additional time-consuming and expensive stability studies.
- Automatically warm the drug as the injector fills, reducing the typical 30-minute or longer wait time to use a refrigerated drug to seconds.
- For lyophilized drugs, completely automate mixing and reconstitution, removing any patient variability from the mixing process.
- Use only standard intravenous-set materials in the drug delivery path, minimizing short-term material-drug compatibility issues.
- Use a small needle size to optimize injection comfort.
- Very small in size with a low profile that can discretely be worn on the body, eliminating the problems and inconvenience associated with carrying larger, heavier devices while ambulating.
- Environmentally friendly – no electronics or batteries to remove or recycle.
- Total volume of materials and packing less than that for a standard IV set.
- Enable subcutaneous injection up to 50 mL.
- Customizable drug delivery rate,

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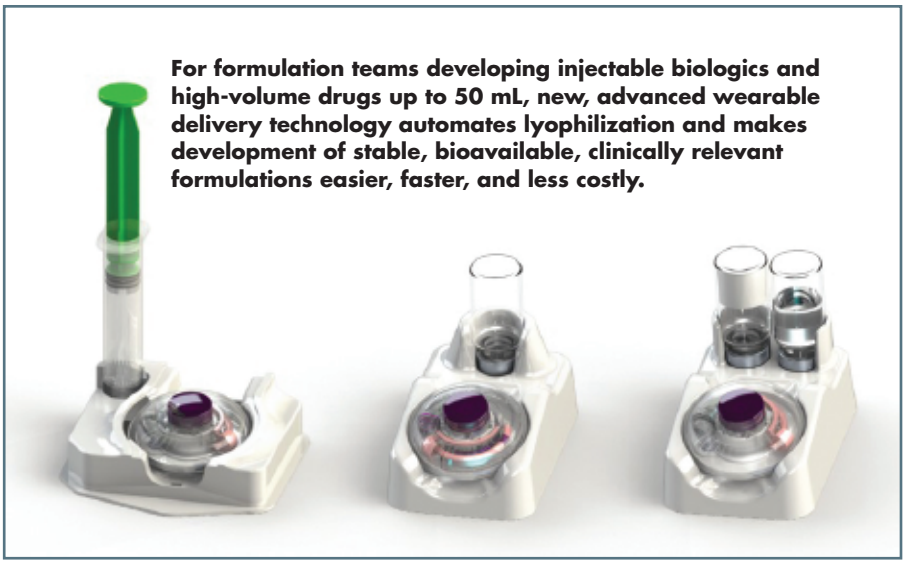

For formulation teams developing injectable biologics and high-volume drugs up to 50 mL, new, advanced wearable delivery technology automates lyophilization and makes development of stable, bioavailable, clinically relevant formulations easier, faster, and less costly.

duration, volume, and needle size for creation of a much improved patient injection experience.

- Apps-based connectivity

Will these factors boost compliance? Overall drug regimen compliance has historically been low, and any improvement would benefit both patients and drug makers. It remains to be seen whether using new injectors, patients with chronic conditions prescribed injectable biologics are more likely to keep taking their medications for potentially improved outcomes and far less drug wastage. Connectivity can be helpful in that assessment.

It looks promising. Among the key attractions of the newest on-body delivery systems: with never a needle in sight, patients like using them, removing the many barriers to compliance that have vexed the industry for decades.

WEARABLE LARGE-VOLUME INJECTORS CAN REDUCE COSTS SIGNIFICANTLY

For payers, patients, and prescribers, one problem with biologics is their cost, especially as they are often used to treat chronic conditions, such as rheumatoid arthritis. Whereas a small molecule drug costs on average $1.00 per day, with a generic drug costing just cents, a biologic drug costs on average $22 per day.[7]

In addition to the cost of the drugs themselves, delivery location can add substantially to the price tag. Almost all biologics currently require delivery via infusion or injection, traditionally in a hospital setting, administered by a healthcare provider. The added costs of drug delivery in a health facility can be astronomical. A *New York Times* article, Even Small Medical Advances Can Mean Big Jumps in Bills, cited a $133,000 charge for a single infusion for psoriatic arthritis at a hospital outpatient clinic – of which the insurer paid $99,593.

The new technology offers a new, lower cost delivery option: uncomplicated, comfortable self-administration of biologics by patients in the comfort of their home, office, or in transit with the added bonus of giving patients the ability to move freely during treatment. It also could eliminate the inconvenience and costs incurred by patients. For example, a breast cancer patient prescribed Herceptin has to travel to a health facility for a 30- to 90-minute IV infusion. Using a wearable large-volume injector, the same dose can easily and comfortably be self-administered by the patient at home, work, or on the go in just a few minutes.

As a result, wearable high-volume injectors have the ability to move drug delivery from healthcare facilities into the home or workplace and from health provider-mediated injection to patient self-administration. This could significantly reduce overall health system costs and for patients or caregivers, the benefit of no longer needing to travel for treatment, even if only as an option for inclement weather or other inability to travel, is enormous in promoting compliance.

SUMMARY

The new, most advanced wearable large-volume injectors available now for clinical trials and commercial application are designed to address the challenges of formulating biologics, delivery complexity, patient compliance, and cost.

For patients, they promise a more convenient, comfortable, and less stressful way of delivering large-volume medications that treat serious medical conditions and rare diseases.

It is widely anticipated that the most sophisticated new wearable injectors, those designed on the basis of multiple human factors studies and preferred by patient panels, will perform these functions:

- Ease injectable drug administration significantly
- Deliver high-volume and/or viscous drugs subcutaneously
- Lower cost of drug development by reducing development times
- Increase patient compliance
- Monitor compliance
- Enable patients to inject easily at home, at work, or on the go
- Replace some infusions (particularly those administered in a hospital setting), significantly reducing the high costs of provider-mediated drug delivery
- Reduce or eliminate needlestick injuries by removing needles from sight
- As with fitness wearables, employ connectivity to provide data

One of the greatest promises of on-body delivery systems uptake, and the reason they will be rapidly and widely adopted, is that by creating value on several fronts, they have the potential to help lower healthcare costs substantially as patients no longer need to visit a healthcare facility for large-volume drug administration. ◆

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BIOGRAPHY

Michael D. Hooven is President and CEO, Enable Injections, LLC. He has over 30 years of experience in the medical device industry in a broad variety of business, technical, and clinical areas. He is the Founder of five medical device companies and holds over 100 issued and pending US patents. Mr. Hooven is the Founder and a Director of AtriCure, Inc. (NASDAQ:ATRC), where he previously held positions as the Chairman and CEO. He is also Founder and Chairman of Enable Medical, a surgical device manufacturer that was acquired by AtriCure in August of 2005. Prior to Enable Medical, he was Director of Product Development at Ethicon Endo-Surgery from 1988 to 1994, where he had responsibility for all in-house product development and supervised a staff of 200 engineers. He held Engineering positions in pacemaker and lead development at Siemens/Pacesetter from 1986 to 1988 and at Cordis Corporation in neurosurgical products from 1981 to 1986. In addition, he is Director and past Chairman of BioOhio, a state-funded organization to accelerate life-science startups in Ohio. He earned his BSc in Physics and a MSME in Mechanical Engineering from the University of Michigan.

Special Feature

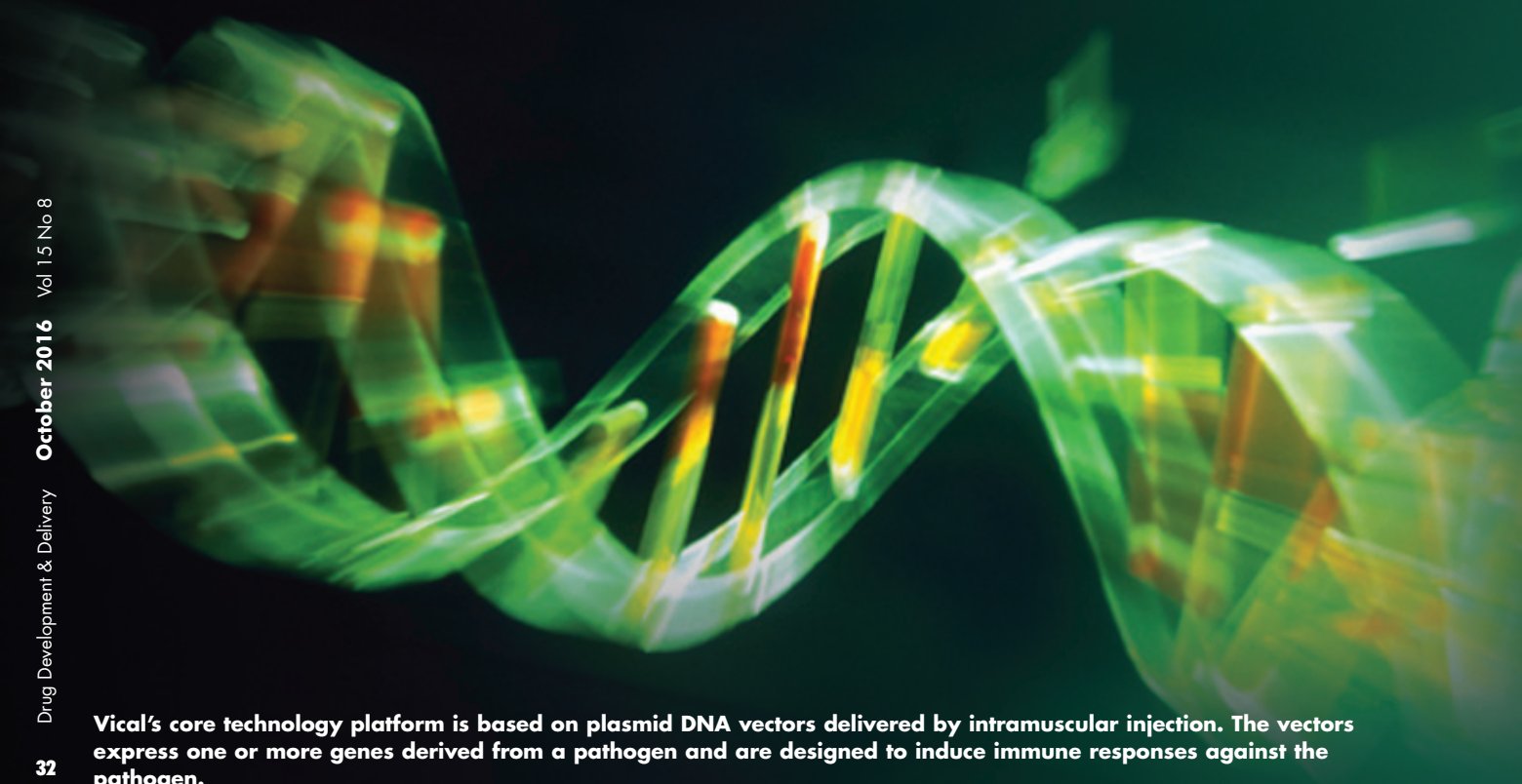
Platform Technologies: Not Just for Big Pharma

By: Cindy H. Dubin, Contributor

Platform technologies are considered a valuable tool to improve efficiency and quality in drug product development. The basic idea is that a platform, in combination with a risk-based approach, is the most systematic method to leverage prior knowledge for a given new molecule. Furthermore, such a platform enables a continuous improvement by adding data for every new molecule developed by this approach, increasing the robustness of the platform.[1]

But it has often been said that access to the latest technological platforms to aid efficient drug discovery and development is limited to Big Pharma, which can more easily justify the costs of creating and operating these platforms.[2]

Drug Development & Delivery recently spoke with several companies that are debunking that theory and developing innovative platform technologies for a range of therapeutics.



Vical's core technology platform is based on plasmid DNA vectors delivered by intramuscular injection. The vectors express one or more genes derived from a pathogen and are designed to induce immune responses against the pathogen.

Argos Therapeutics: Immunotherapy Platform for Treating a Range of Cancers

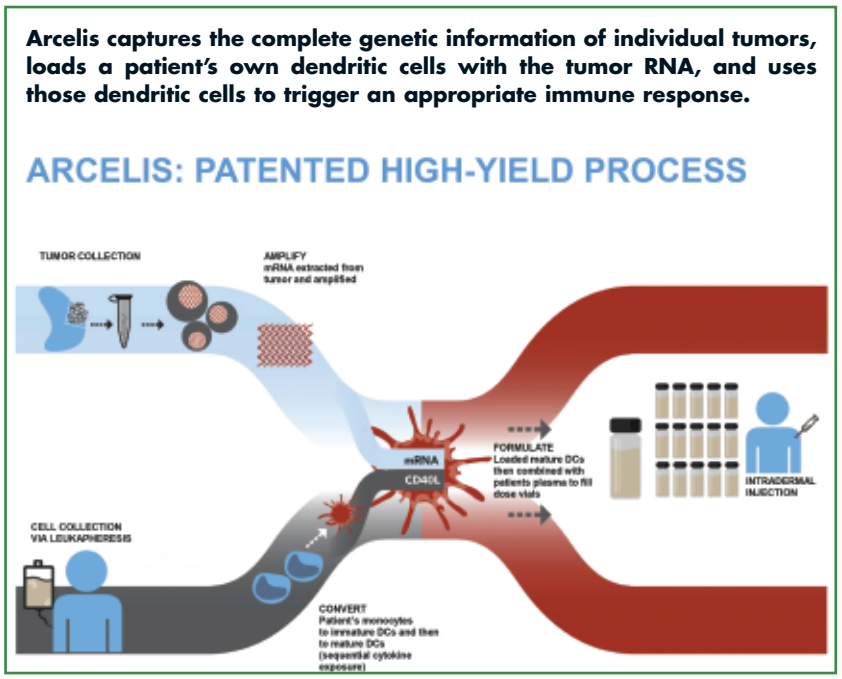
Argos Therapeutics is an immuno-oncology company developing individualized immunotherapies for the treatment of cancer using its Arcelis® technology platform to capture mutated and variant antigens that are specific to each patient's disease.

Every patient's tumor contains a unique repertoire of antigens because the genetic mutations and chromosomal abnormalities that lead to the development of cancer are often random events. "Arcelis captures the complete genetic information of individual tumors, loads a patient's own dendritic cells with the tumor RNA, and uses those dendritic cells to trigger an appropriate immune response," explains Dr. Charles Nicolette, Chief Scientific Officer and Vice President of Research and Development at Argos. "This approach is designed to overcome immunosuppression by producing a durable memory T-cell response without adjuvants that may be associated with toxicity."

This precision immunotherapy technology is potentially applicable to a range of different cancers and is designed to overcome many of the manufacturing and commercialization challenges that have impeded other personalized, cell-based immunotherapies, says Dr. Nicolette.

The Arcelis process uses only a small tumor or blood sample and the patient's own dendritic cells, which are optimized from cells collected by a leukapheresis procedure. The activated, antigen-loaded dendritic cells are formulated with the patient's plasma and administered via intradermal injection. A single production run makes enough product to continuously treat the patient for several years, and Argos has developed an automated manufacturing process to support post-launch commercial demand.

Arcelis captures the complete genetic information of individual tumors, loads a patient's own dendritic cells with the tumor RNA, and uses those dendritic cells to trigger an appropriate immune response.



Argos' most advanced Arcelis-based product candidate, AGS-003, is being evaluated in a pivotal Phase III ADAPT clinical trial for the treatment of metastatic renal cell carcinoma (mRCC), and in ongoing investigator-initiated Phase II trials in neoadjuvant renal cell carcinoma and adjuvant non-small cell lung cancer.

Argos believes its Arcelis technology platform can also be used to create immunotherapies for other chronic infectious diseases that don't respond to current treatments. The company has been awarded a National Institutes of Health (NIH) contract to develop AGS-004, an Arcelis-based product candidate currently being evaluated in an investigator-initiated Phase II clinical trial aimed at HIV eradication in adult patients.

Assembly Biosciences: Targeted, Dual-Release Delivery to the GI Tract

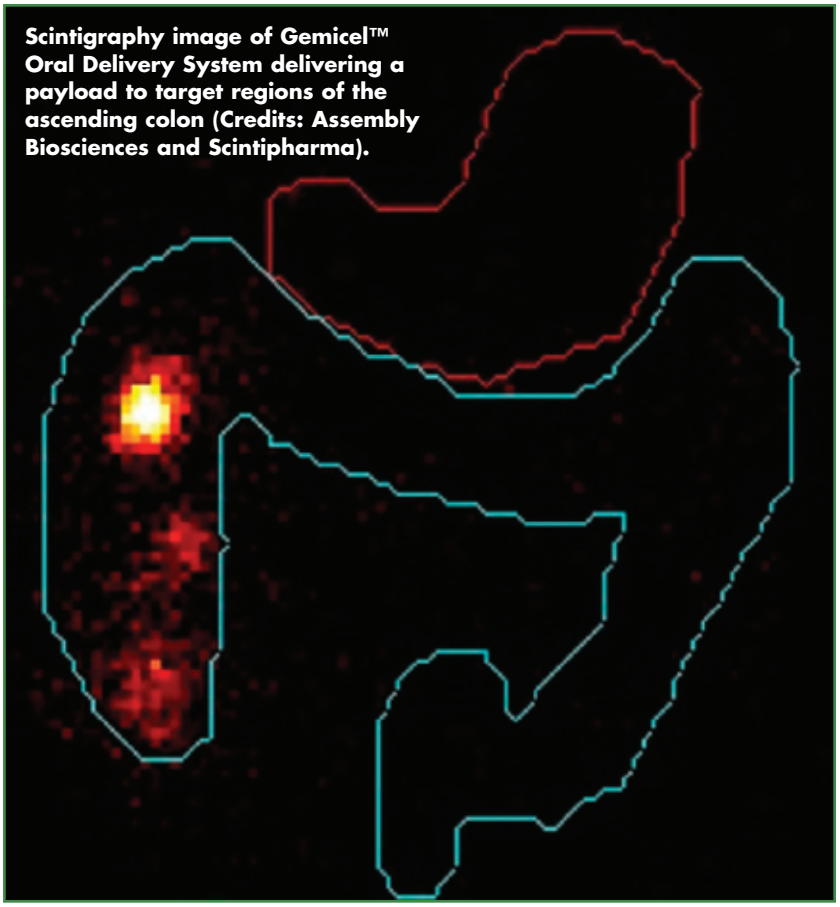
Targeted drug delivery to the lower gastrointestinal (GI) tract is difficult to achieve. Assembly Biosciences' Gemicel™ is a patent-pending platform technology that allows for targeted delivery of a range of agents in an oral capsule to the GI tract, including the colon. Gemicel's novel formulations, coating and encapsulation technology, and dual-release system are designed to enable

oral targeted delivery of live biotherapeutics, such as vegetative bacteria and bacterial spores, vaccines, complex macromolecules, and genetic materials, as well as small molecules and other agents.

Recent human clinical scintigraphy studies performed by Assembly have confirmed that Gemicel can successfully deliver bolus doses to specific regions of the lower GI tract. Assembly believes scale-up and manufacture of the Gemicel delivery technology to be straightforward, efficient, and cost-effective. Gemicel capsules do not require refrigeration or special handling.

"Some therapies, such as microbiome-modifying beneficial bacteria and certain vaccines, will achieve better efficacy if they can be reliably delivered to the lower portion of the GI tract — the ileum and colon," says Thomas Rollins, Chief Development Officer and Head of Microbiome Programs at Assembly. "But effective delivery to the lower GI tract is challenging, especially for large and complex molecules, such as therapeutic microbes and other biologics. The Gemicel technology is designed to overcome these barriers and ensure that the capsule is intact when it reaches the lower GI tract."

Gemicel achieves its targeting effects by leveraging parameters that vary in different parts of the GI tract, especially changes in pH. The Gemicel capsule is formulated to release its therapeutic payload in targeted sections of the GI tract based on their characteristic pH levels.



Scintigraphy image of Gemicel™ Oral Delivery System delivering a payload to target regions of the ascending colon (Credits: Assembly Biosciences and Scintipharma).

In addition, Gemicel capsules have inner and outer compartments that can be designed to dissolve at different pH levels, making it possible to deliver two doses of drug in two locations, or to deliver two different therapies to different parts of the GI tract using a single capsule.

Assembly conducted a proof-of-principle Gemicel clinical study in healthy volunteers. The study used radioisotope-based scintigraphy to precisely image the drug delivery properties of Gemicel.

"The scintigraphy study confirmed that Gemicel can effectively deliver a bolus payload to specific locations in the lower GI tract, and suggested that Gemicel can yield higher and more reproducible doses compared to conventional approaches, and that its capsule formulation process is scalable and affordable to produce," says Assembly's Mohan Kabadi, PhD, Vice President, Pharmaceutical Development.

Assembly intends to use the Gemicel technology to deliver its investigational microbiome therapy to treat recurrent C. difficile infections, which is expected to enter clinical trials later this year. The company is also using its microbiome platform to develop additional product candidates for use with Gemicel. "We are also interested in partnering with other companies to develop therapies that might benefit from Gemicel's attributes," says Micah Mackison, Vice President, Corporate Development & Strategy at Assembly.

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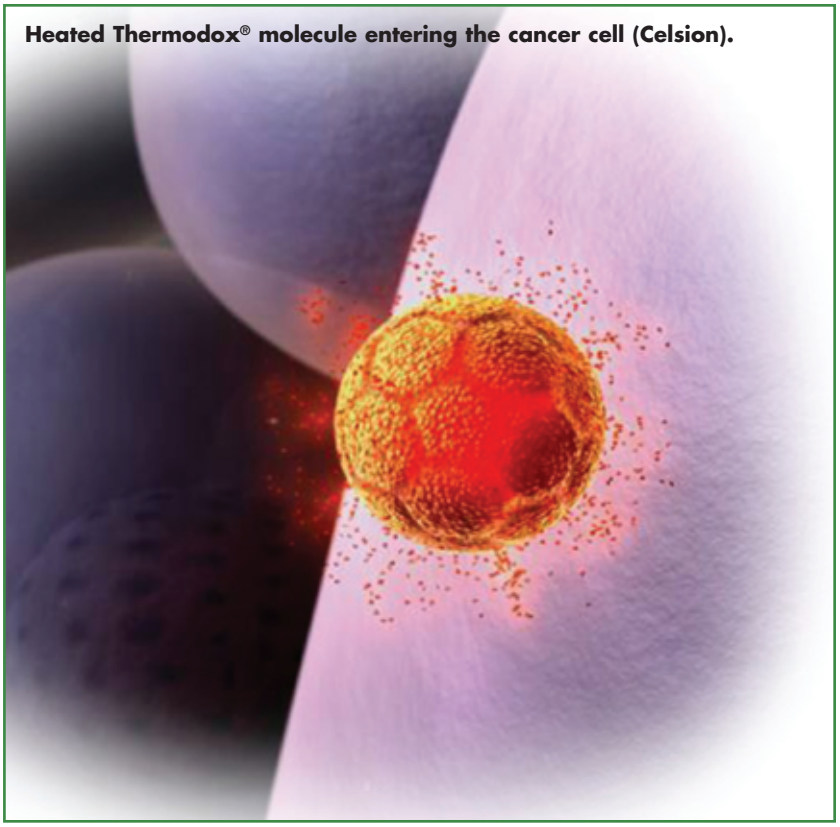
Celsion: Tumor-Targeting Technology Employs Heat-Sensitive Liposome

Celsion is an oncology company dedicated to the development and commercialization of cancer drugs based on two clinical-stage technology platforms. The most advanced program is a heat-mediated, tumor-targeting drug delivery technology that employs a novel heat-sensitive liposome. The technology is engineered to address a range of difficult-to-treat cancers.

The first application of this platform is ThermoDox®, a lyso-thermosensitive liposomal doxorubicin (LTLD), whose novel mechanism of action delivers high concentrations of doxorubicin to a region targeted with the application of localized heat above 40°C, just above body temperature. In one of its most advanced applications, LTLD, when combined with radio frequency thermal ablation (RFA), has the potential to address a range of cancers. For example, RFA in combination with ThermoDox has been shown to expand the "treatment zone" with a margin of highly concentrated chemotherapy when treating individual primary liver cancer lesions, explains Michael Tardugno, Celsion's Chairman and CEO. The goal of this application is to significantly improve efficacy.

"Celsion's LTLD technology leverages two mechanisms of tumor biology to deliver higher concentrations of drug directly to the tumor site," says



Heated Thermodox® molecule entering the cancer cell (Celsion).

Dr. Nicholas Borys, Chief Medical Officer, Celsion. "Rapidly growing tumors have leaky vasculature, which is permeable to liposomes and enables their accumulation within tumors. Leaky vasculature influences a number of factors within the tumor, including the access of therapeutic agents to tumor cells. Building on this finding, researchers have shown that blood vessels in tumors become even more permeable when heated."

Administered intravenously, LTLD is engineered with a half-life to allow significant accumulation of liposomes at the tumor site as these liposomes recirculate in the bloodstream. Drug concentration increases as a function of the accumulation of liposomes at the tumor site when activated by heat above 40°C. Once heated, the liposomes rapidly change structure when the liposomal membrane selectively dissolves, creating openings that quickly release a chemotherapeutic agent (doxorubicin) directly into the tumor and into the surrounding vasculature. This occurs only where the heat is present, supporting precise drug targeting.

"Our first drug utlilizing the platform, ThermoDox, is agnostic to the heating device and is designed to be used with a range of hyperthermic treatments, such as RFA, microwave hyperthermia, and high-intensity focused ultrasound (HIFU)," says Dr. Borys.

ThermoDox is currently in a Phase III clinical trial for the treatment of primary liver cancer, The OPTIMA Study; and a Phase II clinical trial for the treatment of recurrent chest wall (RCW) breast cancer, The DIGNITY

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Study. Results from Celsion's recently completed Phase I/II US Dignity study of ThermoDox, in combination with mild hyperthermia in patients with RCW breast cancer, showed patients treated with ThermoDox demonstrated a combined local response rate of 61.9%. The latest overall survival (OS) analysis for primary liver cancer demonstrated that in a large, well bounded, subgroup of patients, treatment with a combination of ThermoDox and optimized RFA provided an average 58% improvement in OS compared to optimized RFA alone. Median OS for the ThermoDox plus otpmized RFA translated into a 25.4-month survival benefit over optimized alone.

"ThermoDox holds promise in a variety of tumor types for which doxorubicin is already widely used, including pancreatic cancer and glioblastoma, a type of brain cancer," says Mr. Tardugno. "The LTLD platform has the potential to support development of other drug products."

In addition to ThermoDox, Celsion is applying LTLD technology to develop liposomal formulations of docetaxel and carboplatin. Celsion also continues to invest in liposomal technology, developing proprietary formulations of other marketed chemotherapeutics.

Nexvet: Veterinary Therapeutic Developer Converts mAbs for Species-Specific Treatments

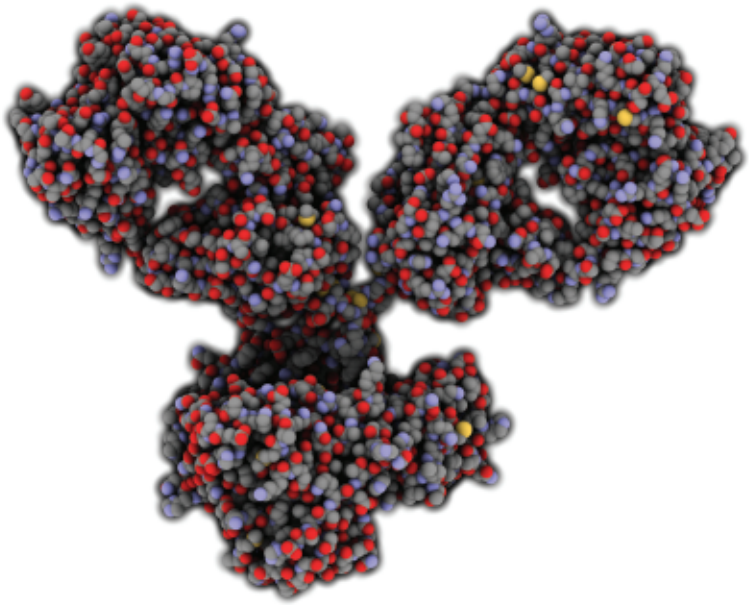
PETization is the proprietary platform technology of veterinary therapeutic biologics company Nexvet. It rapidly converts monoclonal antibodies (mAbs) among species, with the end products being 100% species-specific. Nexvet has clinically validated PETization in dogs, cats, and horses with its portfolio of anti-nerve growth factor (NGF) mAbs.

PETization is an *in silico* process: proprietary algorithms act to determine the minimal number of amino acid changes required to convert donor mAb heavy and light chain sequences into mAb sequences containing only amino acids identified within the target species, at each position on the sequence. Proprietary cDNA libraries are harnessed to provide the species comparison data. "The resulting 100% species-specific mAb sequences carry a lower risk of rejection due to immunogenicity, while preserving the donor mAb's affinity," says Dr. Mark Heffernan, CEO of Nexvet. "This maintains the function of the parent antibody in the new species."

PETization also has applications beyond pet biopharmaceuticals. The rapidity of the process (which does not use traditional time-consuming mAb design processes like CDR grafting or iterative affinity maturation) means that PETized mAbs can be created (and *in vivo* proof-of-concept studies entered) very quickly, explains Dr. Heffernan.

Nexvet is also interested in investigating how veterinary medicine can be used to inform (and benefit from) the development path of new and existing treatments in human health. Dogs, in particular, are susceptible to many of the same diseases and pathologies that afflict humans, such as diabetes, cancer, and inflammatory disease. Clinical studies

PETizing an mAb lowers risk of immune rejection in a target species.



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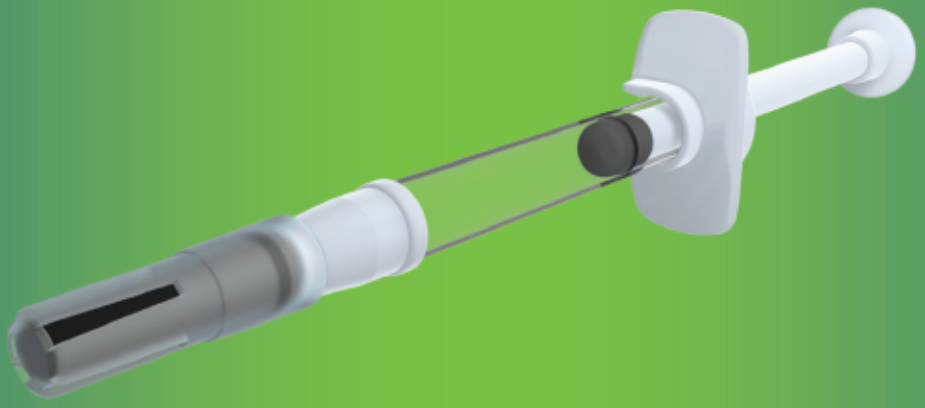

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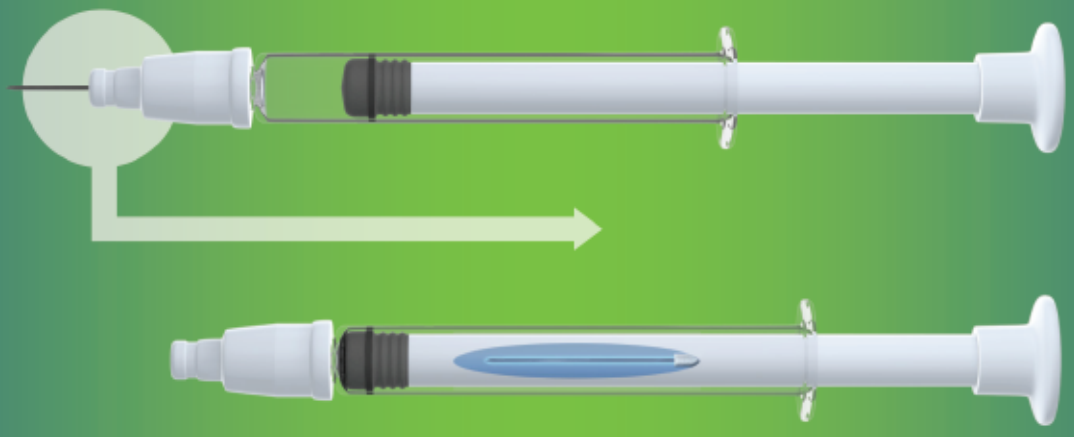

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in animals with disease, therefore, can be a useful intermediary between traditional preclinical models and human clinical trials. These proofs-of-concept are usually performed with mouse mAbs in engineered mouse models of disease with sometimes questionable validity for human disease, says Dr. Heffernan.

"PETization enables rapid production of fully caninized mAbs, with high affinity and low immunogenic potential, suitable for testing in dogs with spontaneous/natural disease."

Thus, Nexvet is exploring research collaborations whereby human pharma partners can benefit from rapid entry to better proof-of-concept studies, and Nexvet can benefit by developing new mAbs for PETizing and clinical assessment, in the pursuit of new veterinary therapies.

In addition to its pivotal-phase portfolio of anti-NGF mAbs ranevetmab (NV-01) and frunevetmab (NV-02) for the treatment of chronic pain in dogs and cats, respectively, Nexvet is advancing PETized anti-PD-1 mAbs in collaboration with Japan-based Zenoaq, for the treatment of canine cancers. PD-1 is an immuno-oncology target, which in human development, has led to the approved human drugs nivolumab (Opdivo®) and pembrolizumab (Keytruda®). Nexvet is also advancing PETized dog and cat mAbs against tumor necrosis factor alpha (TNF), the target of the approved human anti-inflammatory drugs infliximab (Remicade®) and adlimumab (Humira®), and is investigating mAbs for allergic conditions against undisclosed targets.

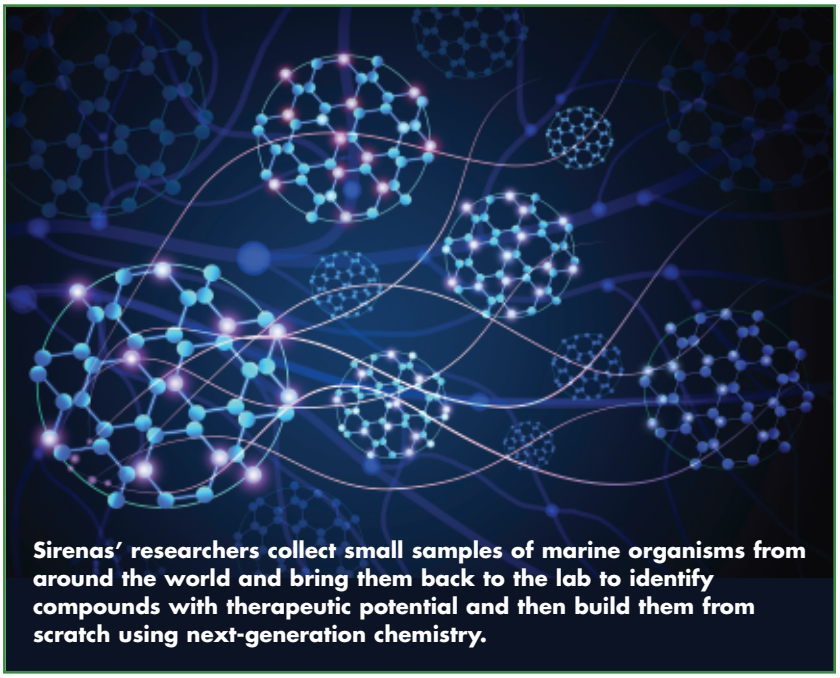
Sirenas: Speeding Discovery & Development of Marine-Inspired Therapeutics

Marine organisms present potent compounds with potential to be the next blockbuster cancer drug, the newest weapon in humanity's fight against antibiotic resistance or a novel non-opioid pain medicine. But identifying these unique compounds and understanding how they might work as a drug is a complex task requiring specialized training and equipment. After obtaining biological samples from remote marine environments, scientists must isolate and understand the chemistry of novel marine-derived compounds. Marine compounds tend to be more chemically unique and less amenable to lab synthesis or fermentation.

To significantly accelerate the process of marine-inspired drug development, biotechnology company Sirenas has developed the Atlantis™ platform, a data-driven approach to documenting, analyzing, and synthesizing compounds that show promise as a medicine. In the case of Sirenas' lead antibody drug conjugate payload, SMD-5033, the company spent less than 9 months to isolate and characterize the marine-derived compound, analog it to see how it may be applied in a therapeutic setting, synthesize it, conjugate it with several antibodies, and then prepare it for *in vivo* trials.

"Sirenas works with research institutions to collect samples of specific organisms — usually sponges, cyanobacteria, and algae," explains Eduardo Esquenazi, PhD, Founder and CEO of Sirenas. "These organisms, which typically lack immune systems, have evolved in complex relationships with bacteria and other microorganisms for millions of years, creating rich small-molecule arsenals that can be leveraged for drug discovery."

At the heart of the Atlantis platform is an ultra-efficient database and software platform. Sirenas isolates



Sirenas' researchers collect small samples of marine organisms from around the world and bring them back to the lab to identify compounds with therapeutic potential and then build them from scratch using next-generation chemistry.

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and chemically analyzes compounds and tests the samples in a range of biological disease assays. The data is uploaded into the platform, which contains the digital fingerprint of Sirenas' entire chemical library of more than 25,000 drug-like fractions of compounds.

Because the analytics software can combine the rich chemical data with High Throughput Screening (HTS) results and other biological and biomedical profiles, modern statistical, machine-learning, and metabolomics algorithms can be deployed to rapidly identify promising starting matter for nearly any disease system or biological assay.

Once a lead compound is identified, the marine-derived compounds are synthesized in the lab. Sirenas' team replicate, iterate, and fine-tune the complex chemical structures of the molecules, creating new compounds to advance to the clinic.

In addition to developing its own drug candidates, Sirenas partners with pharmaceutical and biotechnology companies who wish to leverage the Atlantis platform. Current partnerships include programs for discovering new ADC payloads, and discovering and developing novel small molecules for immune-oncology and infectious disease. Sirenas is actively seeking new partnerships.

Vical Inc: DNA-Based Vaccines for Infectious Diseases

Vical Incorporated develops biopharmaceutical products for the prevention and treatment of chronic and life-threatening infectious diseases. The company's core technology platform is based on plasmid DNA vectors designed to express various proteins of interest after injection into muscle tissue. The plasmid DNA contains gene expression elements to regulate high-level expression of any gene sequence that is genetically engineered into the vector. Vical's major focus has been in developing therapeutic and prophylactic vaccines for the treatment of infectious diseases.

There are key advantages to using plasmid DNA-based vaccines, says Larry R. Smith, PhD, Vical's Vice President of Vaccine Research. First, plasmid DNA is manufactured by a relatively simple fermentation process in *E. coli* and doesn't require handling any pathogen. A powerful manufacturing attribute is that only a single manufacturing process is required regardless of which gene sequence is encoded by a plasmid DNA.

Second, vaccine stability (a limitation with some live-attenuated vaccines) is not an issue with plasmid DNA vaccines as they can be stored frozen for long periods with minimal loss of potency.

Finally, plasmid DNA vaccines can elicit both arms of the adaptive immune response (T-cell- and antibody-mediated responses) in contrast to inactivated and protein subunit-based vaccines that generally elicit high levels of antibody responses.

To create a plasmid DNA encoding the gene of interest, standard genetic engineering/cloning techniques are used with a plasmid vector backbone that has been optimized by Vical scientists; the gene sequence is synthesized to create a codon-optimized version that is designed for maximum expression. The plasmid DNA is combined with specific excipients to create the final drug product for a given indication.

Dr. Smith states that two plasmid DNA products using this platform technology are undergoing advanced clinical testing. The lead program is a Cytomegalovirus (CMV) vaccine, ASP0113, being developed in partnership with Astellas Pharma. ASP0113 is being tested in a global Phase III trial in approximately 500 hematopoietic stem cell transplant recipients who are at high risk of developing CMV-associated disease and complications. Phase II trial results found the vaccine significantly reduced CMV viremia. ASP0113 is also being tested in a global Phase II trial in 150 high-risk subjects undergoing kidney transplantation.

The second product is a therapeutic HSV-2 vaccine candidate that was tested in a first-in-human Phase I/II trial. The bivalent vaccine significantly reduced genital herpes lesion rates in this study, and a Phase II trial is planned for further evaluation.

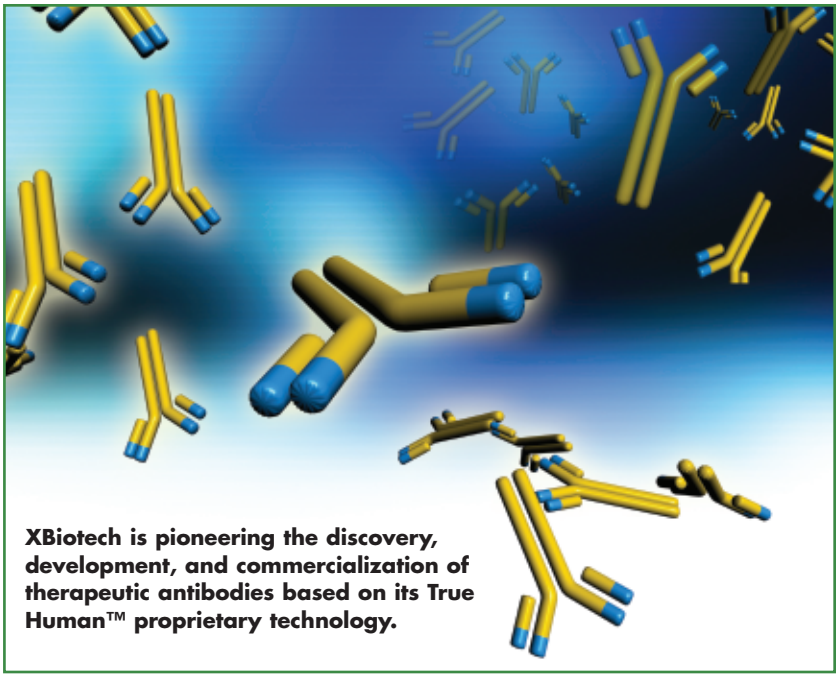
In addition to these programs, Vical is under contract with the Pox-Protein Public-Private Partnership for the development of an HIV vaccine. Vical will manufacture HIV plasmid DNA vaccine to be evaluated as a priming component of a prime/boost vaccine regimen in a planned Phase I trial.

XBiotech: Therapeutic Antibodies Harness the Body's Natural Immunity

XBiotech is a fully integrated global biosciences company dedicated to pioneering the discovery, development, and commercialization of therapeutic antibodies based on its True Human™ proprietary technology.

XBiotech was founded on the belief that cutting-edge medicines should work in a targeted way to make patients feel better, not worse. With this guiding principle, XBiotech has created a new class of antibody therapies called True Human, which are derived without modification from individuals with natural immunity to specific diseases. This approach differs from previous generations of antibody therapies, even those referred to as "fully human," which are created using gene sequence engineering technologies in the laboratory. According the company, because True Human antibodies are derived from naturally occurring antibodies, they have the potential to harness the body's natural immunity and have been developed to fight disease with increased safety, efficacy, and tolerability.

XBiotech's lead product, Xilonix™, which is in late-stage clinical development for the treatment of advanced colorectal cancer, has been fast tracked by the US Food and Drug Administration and is currently under accelerated review in Europe. Xilonix is a first-in-class True Human monoclonal (IgG1k) antibody that neutralizes the biological activity of interleukin-1alpha (IL-1α), a protein associated with the growth and spread of tumors as well as the metabolic changes that can cause muscle and weight loss, fatigue, and anxiety.



XBiotech is pioneering the discovery, development, and commercialization of therapeutic antibodies based on its True Human™ proprietary technology.

Debilitating symptoms, including wasting, pain, fatigue, and anorexia, are prognosticators for overall survival in patients with advanced colorectal cancer. A pivotal Phase III study in Europe was developed to assess recovery from these symptoms to rapidly evaluate the ability of Xilonix in improving the health of patients while treating their cancer.

"Xilonix represents an important advancement in the treatment of advanced colorectal cancer and may be a therapy that could be used in treating a broad range of other malignancies," says XBiotech Founder and Chief Executive Officer John Simard.

The company is also rapidly advancing a robust pipeline of True Human antibody therapies to redefine the standards of care in oncology, inflammatory conditions, and infectious diseases. Since its founding a decade ago, XBiotech has developed the capabilities to identify, isolate, and manufacture True Human antibodies, and currently has clinical trial programs underway in nine disease categories, including cancer, diabetes, restenosis, acne, psoriasis, and *Staphylococcus aureus* infections. "We continue to see that our ability to rapidly and cost-effectively transition from discovery to potential breakthrough therapies is unprecedented," says Mr. Simard. ◆

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Catalent: Increasing Efficiency & Flexibility for the Clinical Supply Chain

Clinical trial supply is traditionally rigid and inflexible, with high material overages and lengthy production lead times. These factors combined can result in a lack of stock in the correct location, which can jeopardize the execution of trials, put patients at risk, increase pressure on clinical site workload, and increase costs of studies at a time when the industry is looking to improve efficiency, minimize risks, and shorten trial duration. *Drug Development & Delivery* recently interviewed Wetteny Joseph, President of Clinical Supply Services at Catalent Pharma Solutions, to discuss the changing nature of clinical trials and the supply of materials for studies, and how Catalent is investing in new solutions, systems, and facilities to assist the biopharmaceutical industry in bringing potentially life-changing therapies to patients, faster and more efficiently.

Q: What is FastChain™ demand-led supply?

A: Clinical studies are becoming increasingly complex and creating a strategic imbalance between sponsors' evolving demands and the potential benefits of using a traditional clinical supply model. Traditional models that work on either a supply-led or a "just-in-time" additional labelling approach lack either the flexibility or efficiency to match the needs of trials that are becoming more fluid in nature, and where study sponsors are under increasing pressure to provide results faster, and in a more efficient manner.

As such, it is vital the right drug is in the right place, on time and on budget. Catalent has made significant investments over a period of nearly 2 years to develop an alternative to the traditional supply models available to the industry at large. FastChain demand-led supply takes a dynamic approach to inventory management through the combination of primary packaged bright stock and delayed secondary packaging processing, which is conducted regionally instead of

from a central location. This two-stage process sees the primary packaging of the drug product being undertaken at a central location, before being distributed to regional GMP secondary packaging facilities, which are strategically located geographically around the world. Secondary packaging (kit assembly) and the final, patient-specific labelling only then takes place within these regional packaging facilities once there is an actual patient or clinical site need.

Q: What are the advantages of a demand-led model over a centralized supply-led one?

A: No single model is a perfect fit for every study. Demand-led supply offers a number of strategic benefits that make it possible for study sponsors to deploy a more flexible supply chain that offers better alignment with individual trial requirements.

In the traditional supply-led model, long lead times require that discrete primary packaging and secondary packaging runs for each protocol are performed well in advance of the projected study start. Where a study is planned for a number of countries, booklet labels become necessary so that these pre-packaged patient kits can be distributed to any clinical site regardless of country or language. These booklet labels are costly to produce, have a significant lead time, and can be difficult to update if new countries are added to the study. Each clinical site receives a bulk shipment of uniquely numbered patient kits at the start of the study from the centralized inventory that may not align with the site's forecasted need versus its actual need based on patient recruitment activity. A buffer stock of 200% or more is commonly included in the supply forecast to help alleviate the potential impact of uneven demand even though much of this excess stock may go unused.

However, by using a demand-led supply model, such as our FastChain approach, the clinical site where the kit is needed is known, which makes applying country-specific labelling possible, eliminating the need for booklet labels and their superfluous information. The flexibility of having decentralized bright stock that is not committed until there is an actual clinical site or patient need can reduce clinical waste to less than 20%. Single language labels are also a significant benefit to the patient by allowing them to easily and clearly see their trial instructions.

Q: What are the differences between FastChain demand-led supply and "just-in-time" labelling?

A: Just-in-time (JIT) labelling is a model also based on a static stock-based approach that uses discrete primary and secondary packaging runs by protocol to produce partially finished, base-labelled patient kits. These kits are typically held in a central location to await final, usually fixed text label updates prior to release and distribution. The base-labelling on the partially finished kits contains basic regulatory compliance information, such as storage conditions and route of administration – booklet labels are used for multi-country studies. Once an order for kits is received, the partially finished kits needed to fulfil an individual order are pulled from inventory and have the final pre-printed label, with details such as protocol number, latest expiry date, and investigator name. The kits are then inspected, released, and shipped to the clinical site, although transit time may vary considerably depending upon where the order is going. JIT labelling is a customization of the traditional model that allows some flexibility at the point of dispatch. However, it can be a disruptive process that can add cost.

FastChain demand-led supply produces bright stock, which includes a batch-lot barcode (or other unique identifier) and undergoes all necessary analysis and quality release immediately following primary packaging. This information is fed into a centralized inventory tracking system, which enables the movement of each item of bright stock to be tracked throughout the supply chain. In some cases (depending upon established stability data), release testing may be completed on the bulk primary packaged product and remove the need to complete release testing of the finished patient kits later, which could slow down the release process.

Under the FastChain demand-led approach, bar code scanning during secondary packaging at regional GMP-certified facilities verifies that all elements have been assembled correctly in each kit, and the inventory system is automatically updated. Patient kits are distributed to the clinical sites based on actual site and patient need, finished kits receive a single-panel, country-specific label, and the lead time to the clinical site is as short as a few days because they are geographically closer to where they are needed. Again, the absence of a booklet label greatly reduces the lead time required for the secondary packaging process, and additional countries can be easily added with a country-specific label.

"FastChain demand-led supply takes a dynamic approach to inventory management through the combination of primary packaged bright stock and delayed secondary packaging processing, which is conducted regionally instead of from a central location. This two-stage process sees the primary packaging of the drug product being undertaken at a central location, before being distributed to regional GMP secondary packaging facilities, which are strategically located geographically around the world."

The decentralized secondary packaging and distribution is a patient-focused supply model that enables new patients in all regions to be rapidly enrolled, which promotes patient engagement.

Q: Are client demands changing for clinical supplies?

A: As with every area of the industry, clients are looking for shorter timelines, but they also want greater efficiency, flexibility, and reduced costs. FastChain demand-led supply caters to these needs and has drawn a lot of interest because of its flexibility and speed. Furthermore, because no one clinical supply model can address all study types, we are exploring ways in which our customers can benefit from a combination of models to really take advantage of Catalent's full suite of services and global capabilities – allowing us to apply the most suitable solution for the unique requirements of each study.

The inherent flexibility of demand-led supply enables the model to be a potential fit for a variety of study types and designs from highly targeted orphan disease studies to very large global trials. Sponsors for whom it is strategically important to achieve shorter study timelines, maximize the use of scarce or high-value stock, or reduce supply chain variability risk may be well served to consider implementing a demand-led approach.

Q: What geographical changes are you seeing in the clinical trials market?

A: Asia has become a thriving region for studies, especially within countries such as China and South Korea. Already established in Singapore, Catalent opened its second facility in the region in Shanghai in 2013 to better service this burgeoning market. That facility was the first in China from a global clinical supply provider standpoint to offer end-to-end clinical supply solutions from clinical supply management, comparator/reference product sourcing and primary packaging to clinical storage and distribution. In the 3 years it has been open, we have invested further, expanding the facility to ensure it grows and accommodates the increased market demand, most recently in its provision for a four-fold increase in cold-chain storage capacity to reflect the trend toward more trials involving biologics and temperature-sensitive drugs. Additionally, we have expanded our Singapore facility to offer secondary packaging and additional clinical storage capabilities, and in June, opened a new clinical packaging facility in Kakegawa, Japan, to better service that local market.

Q: What other investments is Catalent making to adapt to market demands?

A: Catalent's global clinical supply network has facilities in the US, UK, Germany, Singapore, China, Japan, and a network of over 50 audited depots. We have made strategic investments in our facilities around the globe, including those detailed, that reflect the growing importance of the Asia-Pacific region. Other recent examples include a 6,000-sq-ft separated and segregated potent handling suite that has been added to our Kansas City facility, and we can now offer pre-filled syringe finishing in Schorndorf, Germany, in addition to Philadelphia, while our Bathgate, Scotland, facility can now handle products that require cryogenic storage conditions just to name a few. ◆

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TRAINING DEVICES

Best Practices & Considerations in Developing Effective Training Devices for Injectable Healthcare Markets

By: Joe Reynolds, MS Pharm

INTRODUCTION

Over the years, many industry stakeholders and pharmaceutical manufacturers have come to realize the importance of training and the role it has on promoting healthy patient outcomes and effective disease management. Many studies suggest that without proper training during the onboarding process, or the first 30 to 90 days of treatment, patients are more likely to drop off from therapy or incorrectly use drug delivery devices, such as autoinjectors, prefilled syringes, and other forms of self-administration.

One of the most common drug delivery devices on the market currently is the autoinjector. Designed primarily for patient at-home use, autoinjectors were developed to improve the patient experience and address the limitations and administration barriers of legacy injection systems. Many of today's autoinjectors incorporate tactile and mechanical features that provide auditory and visual feedback during the injection process.[2] While these devices provide a number of benefits to patients, administration errors and device misuse can result in injuries and sub-optimal therapeutic outcomes for patients.

According to a study conducted by the University of Texas Medical Branch at Galveston (UTMB), 84% of patients failed to demonstrate correct use of an autoinjector, with more than half skipping up to four steps. Common errors included: failing to hold the device correctly, choosing an unsuitable injection site, and not applying enough force to actuate the drug delivery device. The study also found that, at 86%, "wet injections" were the most common patient error, which in practice would result in patients not receiving their full prescribed doses of medicine.[1]

Further research demonstrates that many patients do not read or fully understand the instructions for use (IFU) that accompany their drug delivery device. A study conducted by Noble and researchers from Auburn University surveyed more than 700 injection experienced patients and found that more half did not read their IFU document prior to beginning treatment.

In addition to traditional instructions and package inserts, healthcare providers are often leveraged as learned intermediaries to onboard patients and provide access to training and education. While these training strategies can be very effective, research suggests that there is often a great deal of variability and inconsistencies with these methods of trainings and patients' ability to retain this information and apply it to the successful use of their delivery system.

To address the common gaps in patient onboarding, training devices are often used to create consistent onboarding experiences for patients through the use of novel technologies and mechanisms that fully simulate the mechanical aspects of the injection experience. While these devices appear to be fairly simple at first glance, numerous design and engineering challenges must be addressed in order to successfully develop training devices and other onboarding solutions.

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INTERNAL DESIGN & TECHNOLOGY OF TRAINING DEVICES

Engineering training devices for manufacturability and repeatability is a delicate balance. Fully understanding device development and mechanical design is one of the first steps in engineering robust training device solutions. The exterior of the device should emulate the real autoinjector so that patients become familiar with key features and physical characteristics such as the look, feel, and weight of their commercial delivery devices. The interior design of training devices also need to be meticulously engineered in order to provide a proper training experience. To accomplish this, human factors are taken into consideration throughout the design process to ensure that training devices align with the physical, cognitive, and emotional needs of users. In addition to understanding user needs, Noble has analyzed a variety of on-market delivery systems to understand their handling requirements and critical functions. Though in some cases mechanisms similar to commercial devices are used, ground-up mechanical design is usually employed to integrate all necessary functions in a resettable and reusable training device. This means that the trainer will look the same on the outside; however, internally it will be vastly different.

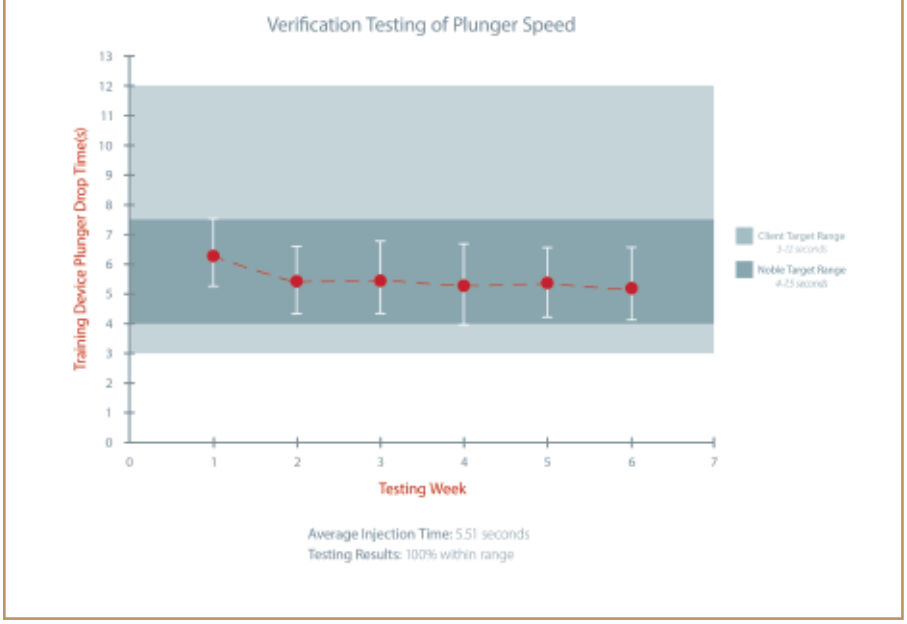
Because one of the most common autoinjector errors is the aforementioned "wet injection," accurately simulating plunger speed is a key component to designing an effective training device that can be used to properly onboard patients. This is done by setting target ranges based on the specifications of a commercial product to ensure that the training device replicates the plunger drop speed that is representative of patients' actual injections. Plunger simulation also takes into account the formulation characteristics of therapeutic entities, such as the viscosity and dosing volume, without containing an actual liquid. This is done so that patients can realistically learn how long it takes for the medication to deploy by tracking the progress through the end-of-dose indicator viewing window.

FIGURE 1

Many autoinjectors utilize a stored-energy feature, typically a compression spring, to energize the power-pack and deploy the plunger. Repeating this design within a trainer can be very challenging because the inherent viscous damping in the medicament delivery device does not exist in the trainer, as training devices do not contain needles or liquid. Therefore, to accurately represent plunger speeds, controllable friction and damping must be created with alternative methods. Significant research and development efforts have gone into this challenge, especially considering the trend of higher dosing volumes and increased injection times, some of which now target 15 or more seconds.

In addition to addressing speed control, all functions that require force application by the user must accurately represent the real device. These include cap removal force, safety shield deflection force, and activation force (for shield or button-activated). Force profiles can also play a significant role; some forces may ramp-up slowly while others have a fast on-set for activation. There are also other unique devices that require unlock steps, twisting, priming, shaking, and a variety of other features to replicate. Other considerations include representing the audible click levels that are present and integrating tactile feel elements, such as subtle internal mechanism vibrations. All these items included, along with the fact that it needs to be easily resettable versus just a single-use product, the trainer must also maintain a 1:1 size ratio (ie, it cannot get any larger than the real drug delivery device).

FIGURE 2



EXTERNAL DESIGN OF THE TRAINING DEVICE

As mentioned previously, external details are also crucial to the design and engineering process. Characteristics of the autoinjector such as the shape, barrel dimensions, viewing window, size, and shape of the actuation button, needle shield, and end cap are all accurately matched so that patients are able to familiarize themselves with the look and feel of the device. However, this is complex because the interior of a training device contains additional mechanisms that allow the device to be used multiple times.

One of the most seemingly simple design challenges is to make the device look like the real product externally. Upon further investigation though, this can present its own challenges. For example, if the trainer looks exactly like the real device, one may mistakenly use a trainer in an emergency or vice-versa. This is typically addressed with optimized packaging, labeling, and graphical training instructions. Trainers usually have large labels that read "Trainer, This Device Contains No Needles or Drug." Though in every other regard, the trainer appears exactly the same: size, shape, textures, and Pantone-matched color schemes (or complementary colors to denote that it is a trainer).

Other considerations that must be prioritized are ancillary training features like augmented auditory or video-based training instructions. Many of the trainers currently in development include some form of collateral training like talking packaging, sensor-based error-correction, smart device application, or a combination of these features.

QUALITY CONTROL PROCESS

Quality design standards are paramount when designing training devices in order to ensure that every patient has a consistent and accurate training experience. Noble conducts rigorous device testing, taking into consideration each brand's specified requirements. One of the keys to success is utilizing optimized Standard Operating Procedures (SOPs) and Standard Inspection Procedures (SIPs) in the assembly process at the factory. Many manual and semi-automated tests and inspections are integrated throughout the process to verify targets will be met on the final assembly stage, reducing scrap rate and ensuring a high-quality product.

Critical functions like shield and activation forces are tested at several points during assembly. Plunger speed, one of the most important characteristics, is measured at three different points in the line. The final step in assembly is a 100% inspection and test on all functions, a luxury that can be afforded with a reusable trainer versus a single-use drug delivery device. During pilot runs, many other tests are also performed to determine steady-state value results. Some of these include environmental, accelerated aging/life, shipping, drop-testing, and materials compliance. Though not a formally regulated device category, Noble treats the design and manufacturing of mechanical trainers much like a regulated product to ensure the highest final quality product.

To ensure the autoinjection times and other important functions of device trainers are consistent with those in the actual drug delivery devices, Noble also performs Acceptable Quality Limit (AQL) sampling. For example, Noble recently pulled a random sample of 35 units from the final production line, and each device was tested over a 6-week period. The target range for injection speed requested by the client was 3 to 12 seconds. Not only did the training devices all fall within this range, the devices averaged at

approximately 5.51 seconds per week throughout injection time testing, which was within Noble's more rigorous internal standard of 4 to 7.5 seconds.

CONCLUSION

As training technology becomes more prevalent in the pharmaceutical industry, the engineering and capabilities of these devices will continue to advance, creating a more complex and intricate engineering process. These advancements are necessary as they will allow patients to become more confident in their treatments, overcome treatment barriers, and ultimately lead healthier lives.

In order for training devices to work efficiently, it is necessary that the devices are tested with stringent standards. Patients need to become familiar with the device in order for them to learn and anticipate the steps necessary for proper drug administration. This requires training devices to accurately replicate the ergonomics, interaction, and injection time of the actual device.

In today's market, a growing number of patients are being prescribed self-administered injectable treatments. Pharmaceutical companies that prioritize the patient experience, using training technology to help these patients properly onboard to therapy, will continue to benefit through competitive advantages and the value they create within the industry. ◆

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BIOGRAPHY

Joe Reynolds is Research Manager at Noble, where he leverages his knowledge and experience to develop and implement strategies that improve the patient experience and maximize value for stakeholders. His experiences include commercial, managed care and product development initiatives with leading medical device, pharmaceutical and biopharmaceutical manufacturers. Mr. Reynolds earned his Bachelor of Science in Business Administration from the University of Central Florida, a Master of Science in Marketing from the University of South Florida, and a Master of Science in Pharmacy and Master Certificate in Drug Regulatory Affairs from the University of Florida.

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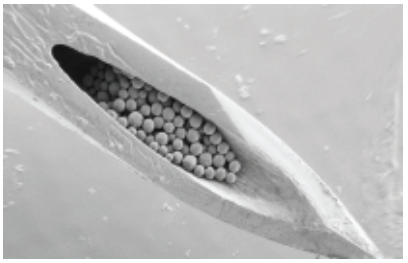

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PACKAGING SYSTEMS

Container Closure Integrity in Cryogenic Storage Environments

By: Eugene T. Polini, MBA

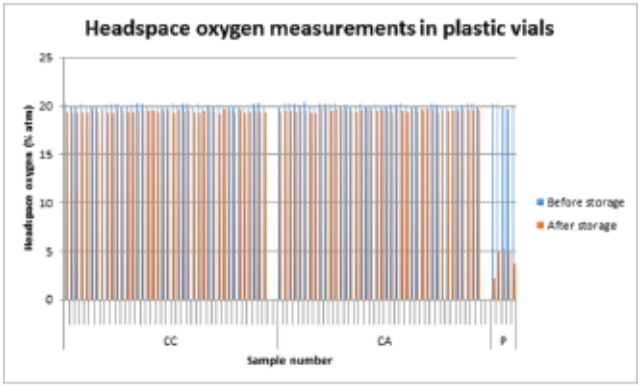
INTRODUCTION

Just a few decades ago, cryogenics – the study of the production and behavior of materials at very low temperatures – was often regarded as being in the realm of sci-fi. In recent years, however, cryogenics has become firmly enmeshed in a number of applications across industries, including fuel production, power transmission, and food transportation. Cryogenics has also proven to be especially useful in the pharmaceutical industry, where cryogenic storage is being utilized to ensure the efficacy of advanced therapeutics, such as biologics and stem cell therapies.

Injectable biologics and cell-based therapies often require low-temperature storage in order to maintain the stability and integrity of the drug product. This presents a significant challenge for drug packaging systems and components: many packaging containers are made of glass, which can't handle the challenges of cryogenic storage, nor can glass systems maintain seal integrity at such low temperatures. Issues like breaking and cracking when the vials are dropped or brought to room temperature can lead to cell death. In addition, many cryovials are not transparent, making visual inspection of the drug product contained within the vials difficult.

This is a good point to comment on some of the risks associated with the loss of container closure integrity (CCI) during cold and cryogenic shipment and storage. Clients initially reported pH change in their aqueous drug product caused by the ingress of carbon dioxide gas (CO2) during cold chain shipment. Loss of CCI while using cryopreservation techniques may lead to the possibility of microbial ingress due to cold gas rushing into the vial under septic conditions of storage. Cryopreservation techniques could also lead to an over-pressurization condition in the vial. Cold gas trapped in the vial when the elastomer regains its elasticity could become dangerously high after the vial returns to room temperature (remember the Ideal Gas Law? PV=nRT), which could lead to healthcare worker injury. Just picture the scenario whereby a nurse introduces a disposable syringe into a pressurized vial, and before he knows it, the plunger flies out, hitting his face due to the high pressure in the vial.

FIGURE 1



Headspace oxygen levels in the vial/stopper combinations CC and CA measured before and after storage at cryogenic temperatures. Five positive control vials are plotted on the far right of this graph indicated by the letter P. Reduced headspace oxygen levels are only observed for the positive control vials and not for the vial/stopper combinations CC and CA. The low headspace oxygen levels for the positive control vials indicate that the initial air headspace has been exchanged with nitrogen gas from the cryogenic environment.

STUDY OVERVIEW

Driven by advances in biotechnology, pharmaceutical products, such as stem cells and biologics, are now more frequently stored and shipped in rubber-stoppered vials at cryogenic conditions (eg, -165°C/vapor phase liquid nitrogen). Commonly used butyl stoppers lose their elastic properties and sealability below their glass transition temperature (Tg), raising concerns about CCI failure.

A study was performed to better understand how rubber-stoppered glass and plastic drug vials function in cryogenic storage conditions and to provide guidance on the use of packaging components and the testing regimen used to qualify cold and cryogenic storage as part of a cold-chain strategy.

The study compared the CCI of two types of parenteral vials (glass and plastic), as well as two elastomeric formulations for the closure. Changes in headspace pressure and oxygen content were used to determine whether the empty vial samples maintained CCI. Headspace pressure and oxygen content measurements were made using a Lighthouse non-destructive headspace oxygen analyzer. Vials were sealed with FluroTec®-laminated elastomeric closures under ambient conditions and tested for seal integrity to ensure the crimping process was successful prior to placement in a cryogenic storage chamber for 8 days.

METHODS

The study utilized sterilized Type 1A borosilicate glass and Daikyo Crystal Zenith® cyclic olefin polymer vials sealed and capped with stoppers containing two chlorobutyl elastomer formulations (West 4432/50 Gray and D21-7S with fluoropolymer lamination on the closures' plugs). A total of 170 sample vials and stoppers were used to determine CCI when stored at cryogenic temperatures. Four different vial/closure combinations were prepared using a Crimptronic CR-5000 USB device. All components were ready to use, and no further sterilization step was performed. Glass and elastomeric components were internally sourced, and vials were made to US GPI (Glass Producers Institute) standard. Materials used included the following:

TABLE 1

Vial type	Stopper type	Reference Code	# Vials
Crystal Zenith® – Plastic 2mL 13mm	West D21-7S	CA	40
Crystal Zenith® – Plastic 2mL 13mm	West 4432	CC	40
Crystal Zenith® – Plastic positive control	West D21-7S		5
Crystal Zenith® – Plastic positive control	West 4432		Not Tested
Afton Ready-To-Fill® sterilized vials – Glass 2mL 13mm	West D21-7S	GA	40
Afton Ready-To-Fill® sterilized vials – Glass 2mL 13mm	West 4432	GC	40
Afton Ready-To-Fill® sterilized vials – Glass positive control	West D21-7S		Not Tested
Afton Ready-To-Fill® sterilized vials – Glass positive control	West 4432		5

Overview of the sample set.

TABLE 2

Vial/ stopper combination	Average stopper compression (%)	Set crimping pressure (N)	Average actual pressure (N)	Average RSF (lbf)
GC	30.6	250	286	13.0
GA	35.9	300	346	11.4
CC	27.4	260	289	12.5
CA	36.2	280	343	10.7

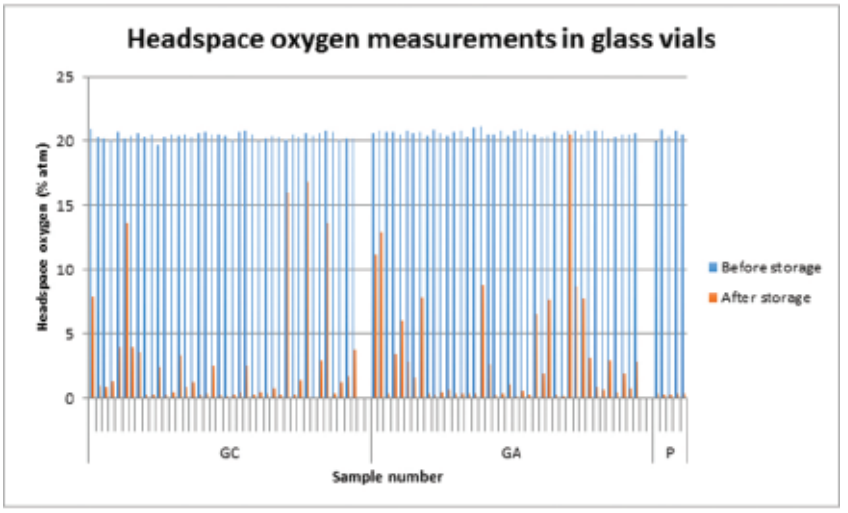
Overview of the stopper compression, crimping pressure, and residual seal force parameters per vial/stopper combination.

TABLE 3

Label	11 May 2015		20 May 2015	
	Mean (% atm)	St.dev. (% atm)	Mean (% atm)	St.dev. (% atm)
0% standard	0.14	0.09	0.20	0.08
1% standard	1.06	0.28	0.96	0.27
2% standard	1.92	0.06	2.00	0.13
4% standard	3.81	0.30	3.98	0.15
8% standard	8.00	0.17	7.76	0.11
20% standard	19.91	0.19	19.93	0.17
Glass sample	20.40	0.22	8.00	0.11
CZ sample	20.07	0.11	19.39	0.12

Measurements of known oxygen standards and two sample vials.

FIGURE 2



Headspace oxygen levels in the vial/stopper combinations GC and GA measured before and after storage at cryogenic temperatures. Five positive control vials are plotted on the far right of this graph indicated by the letter P. Reduced headspace oxygen levels are observed for all vials of vial/stopper combination GC. Only one vial from vial/stopper combination GA retained closure as indicated by atmospheric levels of headspace oxygen after storage. All positive control vials showed lowered headspace oxygen levels as well, indicating that the initial air headspace has been exchanged by nitrogen gas from the cryogenic environment.

- Daikyo Crystal Zenith vial 2 mL x 13 mm #19550057
- Afton Ready-to-Fill® sterile vial 2 mL x 13 mm # 68000367
- 13mm Flip-Off® seal #54131329
- 13-mm Serum NovaPure® RP S2-F451 4432/50 Gray #19700302
- S2-F451 D21-7S R B2-40 WESTAR® RS #19560253

All vials were empty with an initial air headspace. A total of 10 positive control vials of two container types were created by puncturing the stopper with a single 10-µm capillary tube. Two different vials and two different stoppers were used, resulting in four combinations. All containers were empty with an initial air headspace, and all vials were capped with Afton Ready-to-Fill sterilized seals 3767 (Table 1).

The packaging components were shipped to Lighthouse laboratory in Amsterdam and prepared at this location. Stopper compression and residual seal force (RSF) were optimized for the different vial/closure combinations (Table 2.)

After preparation, the samples were stored for 48 hours in a nitrogen-rich environment to confirm there was no loss in CCI of the samples before storage. If a leak was present, the nitrogen was exchanged with oxygen in the vial, causing oxygen levels to decrease.

All vials were measured with the Lighthouse FMS-Oxygen Headspace Analyzer, and passed this pre-leak test. In addition, RSF testing was performed to check the seal quality of all test containers. Packages with low RSF (< 6 lbf) were eliminated from the study. At this point, every group (CA, CC, GA, and GC) contained 40 samples.

Samples were stored for 8 days in a Linde Gas K24 storage container and were placed in the gas phase of the liquid nitrogen at a temperature of -165°C. Prior to final analysis all samples were allowed to return to room temperature.

RESULTS

Prior to analysis of the test samples, a set of known oxygen standards were measured to determine the performance of the oxygen analyzer. For each measurement time point, the standards of known oxygen levels were each measured five consecutive times. In addition, one sample of each vial type was measured 10 times to give more insight on the standard deviation of the sample vials. The mean measured headspace oxygen levels and the corresponding standard deviations are listed in Table 3.

The headspace oxygen levels of all package combinations were measured before and after storage at cryogenic conditions. Lower headspace oxygen levels would be indicative of a loss of CCI. These measurements are detailed in Figures 1 and 2.

All glass vials that showed loss of closure during the cold storage period were analyzed again for headspace oxygen 1 day after the vials were removed from the cryogenic environment. The measured headspace oxygen levels were similar to the first analysis after removal from the cold storage. This analysis was performed to confirm that the glass vials only leaked temporarily during the cold storage period and that the leak was re-sealed once the samples were brought back to room temperature.

CONCLUSION

The ability to rapidly and non-destructively measure headspace conditions in product samples enabled quantitative insight into the CCI of glass and plastic containers stored at cryogenic temperatures. In this study, headspace inspection of a total of 170 samples from four different vial/stopper configurations was performed following storage at cryogenic temperatures for 8 days. A loss of CCI would be indicated by decreased levels of headspace oxygen. It was found that none of the Crystal Zenith vials lost container closure integrity. However, the measurements performed on the glass vials showed strikingly different results.

Only one glass vial from vial/stopper combination GA did not lose container closure integrity during the cold storage period. All of the vials from the GC vial/stopper combination, as well as the positive controls vials, showed lowered headspace oxygen levels measured after the storage period. Clues to the remarkable difference in behavior between vials made of Crystal Zenith and ones made of glass may be found in observations made after the headspace measurements had been completed. When the glass vials were analyzed after the study, it was observed that the stoppers were easily removed and there was a popping sound due to the release of pressure from within the container.

This is likely because the rubber had been exposed to temperatures below its Tg and could no longer form a seal with the crown finish of the vial; the nitrogen gas was able to ingress into the vial, effectively displacing the oxygen. When the vial was returned to room temperature, the stopper went above the glass transition point enabling it to form a seal against the glass and effectively trapping the cold dense gas inside the vial.

When the Crystal Zenith vials were examined after the study, the stoppers were difficult to remove and appeared to be bound to the top of the Crystal Zenith vial. It is believed that this is an example of polymer entanglement, a phenomenon not unfamiliar to manufacturers of elastomeric components, in which polymers will cold flow into each other effectively gluing them together.

Because of this process, the rubber should remain sealed against the Crystal Zenith polymer even while the rubber has gone through its Tg twice. Consequently, nitrogen will not have an opportunity to ingress the Crystal Zenith vials during storage at cryogenic temperature, resulting in a maintenance of CCI.

As the demand for biologics and stem-based therapies expands, the need for innovative components that preserve the integrity of drugs in cryogenic environments will also continue to grow. By partnering with drug packaging and delivery systems providers that offer innovative component solutions for maintaining the efficacy and integrity of injectable drug products in cryogenic storage environments, pharmaceutical manufacturers can focus on manufacturing a safe, effective drug and meeting increased market demand. The end result is a strengthened relationship between both parties.◆

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BIOGRAPHY

Eugene Polini, formerly of West Pharmaceutical Services, has a background in analytical chemistry, biology, and international business. Mr. Polini earned his BSc in Biology from Villanova University and his MBA in Health Care Administration from St. Joseph's University.

DEVICE STUDY

The Intuitiveness, Ergonomics & Usability of the Credence Companion® Safety Syringe: A Formative Study

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

INTRODUCTION

From the first conceptualization of a disruptive drug delivery device that could meet the emerging needs of biopharma manufacturers, Credence MedSystems has focused on providing the best possible injection device with the least possible impact on the drug manufacturer's development, regulatory, and supply chain processes. This commitment to *Innovation Without Change* has resulted in the Credence Companion platform of injectable safety drug delivery devices. Credence incorporates the use of commercially available syringe barrels and closure components to result in a fully integrated syringe system with passive needle-retraction safety; upon completion of the injection, the user receives audible, visual, and tactile cues that the dose has been delivered, and then the needle automatically retracts through the stopper and into the barrel of the syringe, rendering the syringe needle-free and preventing reuse. See Figure 1, which depicts the single step mixing and passive needlestick safety features of the Companion Dual Chamber Reconstitution Syringe. The benefits of the Companion Platform have been discussed in prior *Drug Development & Delivery* articles, including Jan/Feb 2015 and Oct 2015, which can be viewed at www.drug-dev.com. These benefits, however, are only fully realized if the device can be utilized easily and correctly by the end-user. Credence has recently completed a formative human factors study to assess the intuitiveness, ergonomics, and usability of the Companion Staked Safety Syringe. A White Paper summarizing the results of that evaluation is presented herein.

FORMATIVE HUMAN FACTORS STUDY REPORT

2016 Formative Human Factors Study of the Credence Companion Staked Safety Syringe*

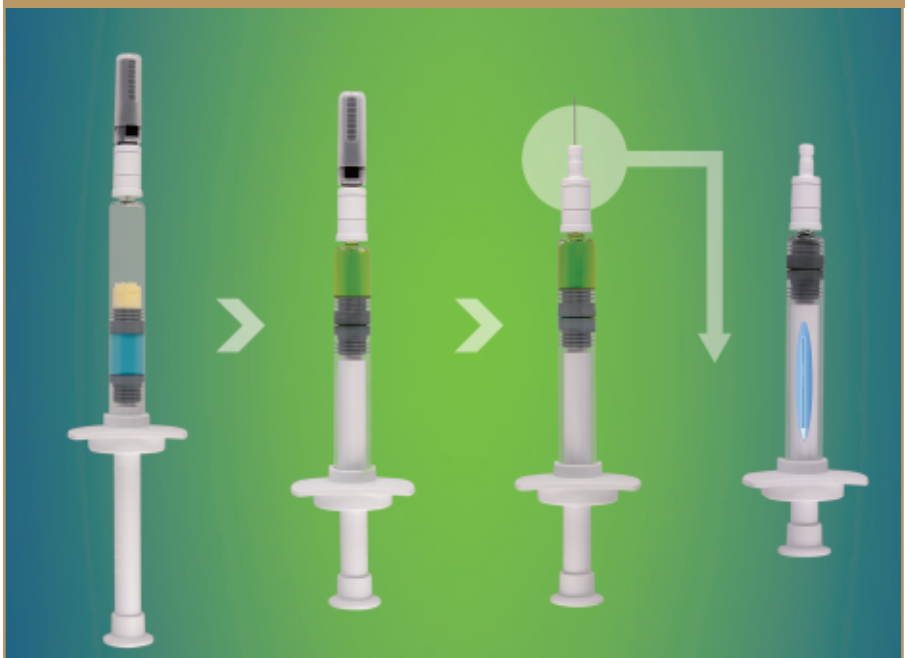
Purpose

The primary objective of this formative human factors study was to evaluate and assess the intuitiveness, ergonomics, and usability of the Credence Companion® Staked Safety Syringe.

Materials & Methods

The study was conducted by a leading human factors, usability, and ergonomics consulting firm with expertise in the research, design, evaluation, and testing of injectable drug delivery products in the use environment. The registry included 2 arms consisting of a first arm of 10 formal Health Care Providers (HCPs) and a second arm of 10 Self-Injecting Patients, each with varied experience with injections and safety syringes. All of the HCPs were Registered Nurses with years in service ranging from 5 to 36 years. Notably, 50% had experience injecting patients using commercially available safety syringes, while 50% had no prior experience with safety syringes. The Self-Injecting Patients were composed of 70% of participants with prior experience injecting themselves with prescribed medications and 30% with no prior experience with self-injections. Similar to the HCPs, 50% of the Self-Injecting Patients had injected themselves previously using a commercially available needlestick safety device, while 50% had no prior experience with safety devices.

FIGURE 1



The Companion Dual Chamber simplifies reconstitution and provides passive needlestick safety.

See Table 1 for the Participant Demographic Summary.

The test article was the Credence Companion Safety Syringe (see Figure 2). Additional supplies utilized included injection pads, a manikin for use by the HCPs, sharps container, gloves, and rating scales.

Each subject was first asked to perform a total of three injections into an injection pad using the Credence Companion Syringe. The first two injections were performed without any prior instructions or training guidance provided to the user. After the second injection, the user was asked to view a short (approximately 20 seconds) training video and then perform the third injection. Injection techniques differed between the two subject arms: Health Care Providers performed the injections into a manikin as if they were delivering medication to a patient, whereas the Self-Injecting Patients performed the injections as if they were administering the medication to themselves. The pad positions for both the Self-Injecting Patients and HCPs included injection sites on the thigh and the abdomen to allow for variations in hand position and injection technique. No guidance was provided on either hand position or technique.

After each use of the Companion syringe, the participant's subjective interaction and feedback were recorded. Thirty (30) injections were performed by each the HCP and Self-Injecting arms, resulting in a total of 60 injections with the Credence Companion.

Results

Participants using the Credence Companion delivered the full dose in 100% (60 out of 60) of the injections, despite having no product training. 100% of the participants (20/20) used the Credence Companion correctly with either no or minimal training, achieving needle retraction at the end of the dose. 90% (18/20) achieved needle retraction without any training. Two of 20 subjects (10%) required minimal training, after which both used the device properly on the subsequent attempt. The minimal training consisted of a 20- second training video with the guidance to "depress the plunger until you hear a click."

Following use of the Companion Safety Syringe, participants rated elements of their experience on a scale of 1 to 7, where 1 represented the least favorable score, and 7 represented the most favorable score. Overall Safety During Use was rated a mean of 6.8/7, indicating very high satisfaction with the Companion's passive needle retraction

FIGURE 2

Test Article, the Credence Companion Staked Syringe

mechanism. The Ability to Inspect Medication was rated extremely high (mean 7 out of 7) as were Smoothness of Injection (6.7/7), Force Required to Deliver Medication (6.5/7), and Force Required to Activate Safety Mechanism (6.4/7). Participants stated that the device was easy to handle in their hands, did not look visually intimidating or scary, and that they could inspect the syringe contents without any difficulty. The response was very positive for appearance, use, confidence, and overall safety of the device during use. In addition, many participants indicated that the "click" sound helped them know that the full dose was delivered, the needle was retracted, and the device was safe for disposal, which supports the mean rating of 6.6/7 for Sounds During Safety Activation. There were no notable dislikes verbalized toward the Companion syringe, and all of the criteria were scored ≥6.3 out of 7 (See Figure 3).

TABLE 1

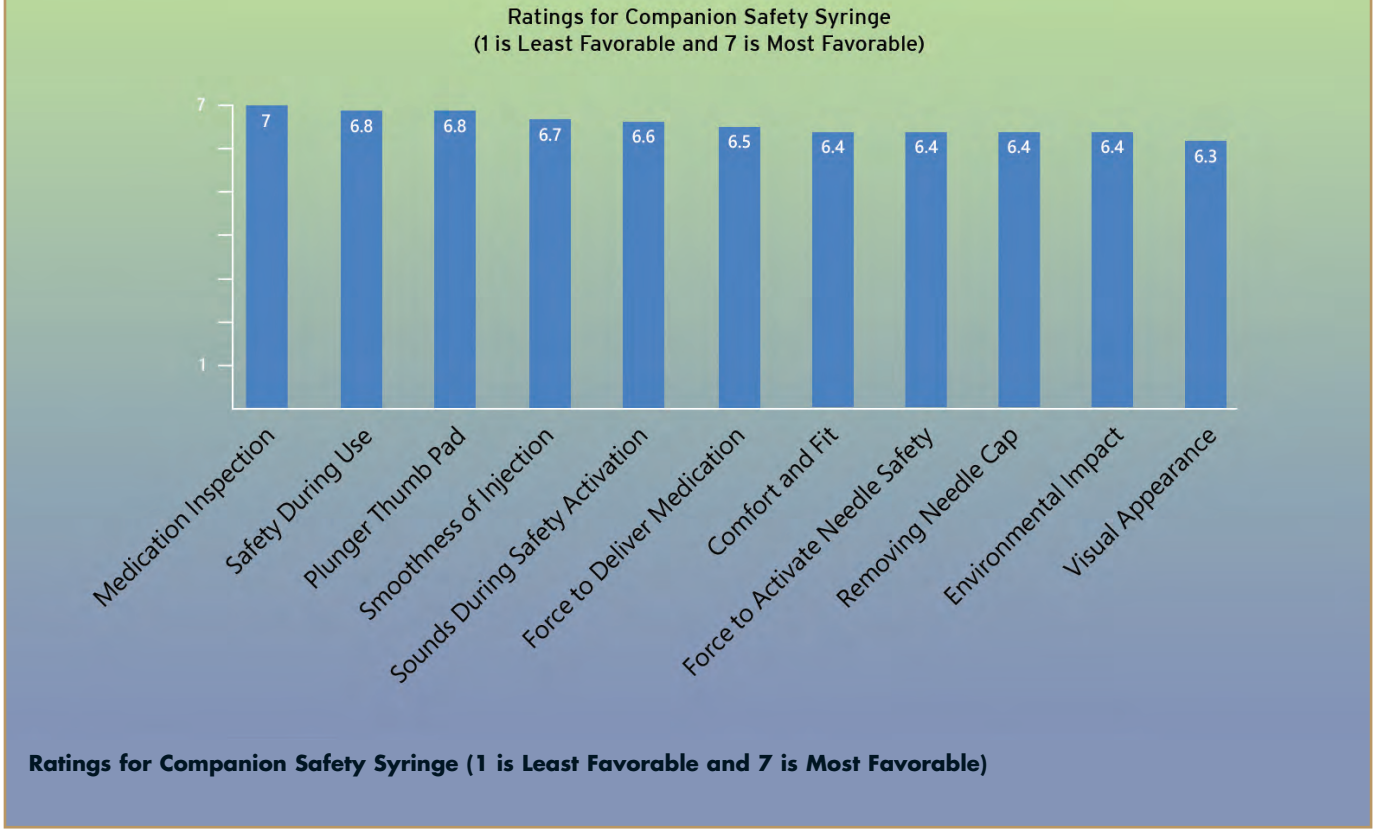
Health Care Providers N = 10		Self-Injecting Patients N = 10	
Registered Nurses	10/10	**Education**	High School: 30% Associate Degree: 30% Bachelor's Degree: 30% Master's Degree: 10%
Length of time as HCP (Range):	5-36 Years	**Self-injection Experience**	Yes 70% No 30%
Safety Syringe Experience:	50% Experienced 50% Naïve	**Safety Syringe Experience**	50% Experienced 50% Naïve
Age Range:	30-57 Years Old Mean: 39.4	**Age Range**	31-68 Years Old Mean: 50.2
Gender:	Female: 70% Male: 30%	**Gender**	Female: 50% Male: 50%

Additionally participants were able to utilize the syringe with a wide variety of hand postures and in a variety of injection sites, whether injecting themselves or a patient. Very little of the handling confusion or difficulties that commonly accompany use of a new device were observed while manipulating the syringe. There were no significant differences in preference between the HCP versus Self-Injecting Patient user groups or between the experienced versus naïve test subjects.

Study Conclusion

The results of this Formative Human Factors Study indicate that the Credence Companion Staked Safety Syringe is an intuitive device, able to be successfully utilized by experienced and naïve injectors with no or minimal training. 100% of participants delivered the full

FIGURE 3



Ratings for Companion Safety Syringe (1 is Least Favorable and 7 is Most Favorable)

dose, and 90% of injectors successfully activated the safety mechanism with no training. The remaining 10% required minimal training to activate the device. Participants especially liked the Companion for its: ease of medication inspection; non-intimidating familiar appearance, and lack of extraneous components; small size allowing easy grip and manipulation; and simple automatic safety retraction followed by a click, indicating completion of the dose and activation of the safety mechanism.

SUMMARY

Credence has been guided by feedback from both end-users and drug manufacturers in the development of the Companion Safety Syringe System. Listening to both voices has allowed the rapid development of a full platform of safety injection devices. Across the platform, these solutions offer end-users the safe and intuitive experience they deserve while simplifying implementation for the manufacturers. This lowers the hurdle to the implementation of a differentiated delivery system that helps gain market advantages while maximizing the ease-of-use and safety for their end users. For more information, please visit www.CredenceMed.com or email info@CredenceMed.com. ◆

This product has not yet been evaluated by FDA.

*Credence Safety Syringe Formative Comparative Human Factors Study Report, May 17, 2016.

BIOGRAPHIES

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

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

Drug Development
EXECUTIVE

Medhat Gorgy
President & CEO

PYRAMID
Laboratories, Inc.

PYRAMID: Prescription for Building Success Through Partnerships

Quality. Integrity. Performance. These words may best describe the foundation upon which PYRAMID was built when it was founded in 1988 as an analytical services and method development company. This foundation has grown ever stronger throughout the past 28 years as it has transitioned from a 600-sq-ft laboratory into a 70,000-sq-ft commercial manufacturing facility with the expertise and flexibility to provide analytical, development, and small- and large-scale aseptic manufacturing and filling services to small start-up biotechs, big pharmas, and everyone in between. Drug Development & Delivery recently spoke with Medhat Gorgy, President and CEO of PYRAMID Laboratories, Inc., to discuss his success in building futures with his clients and more importantly, the lessons he's learned along the way.

Q: What sets PYRAMD apart from other contract manufacturing organizations?

A: Since the beginning, I founded PYRAMID to be a quality organization and not profit driven. This is evident through the fact that PYRAMID remains a privately held company, which allows us to be flexible to our clients' needs and timelines, without having to answer to shareholders or a Board of Directors. Our project managers are involved in each project from the very first point of contact to the very last invoice. Our clients will never be approached by sales or business development people as we operate on word-of-mouth recommendations based on our reputation of quality, integrity, and performance. This approach has sustained our business for 28 years. Our team is highly technical with years of experience in designing drug development programs from the straightforward to the most challenging formulations or lyophilization cycles, and we back this up with a track record of incredible success.

PYRAMID builds relationships, and through these relationships, we develop partnerships. We are not just doing a job for our clients, we are building a future with them. PYRAMID understands the long-term benefits of successful development or the severe consequences of a failed project, not just to ourselves but to our clients and ultimately, to the patients. We participate in all aspects of each project, providing expertise when necessary, and we efficiently take projects through all phases of drug development without losing focus on quality.

Q: What do you believe should be considered when evaluating a potential CMO?

A: The primary point to consider is the type and complexity of the project and how it fits to the CMO's expertise and experience. Smaller companies that do not have in-house CMC experience should seriously consider engaging a CMC consultant to help evaluate CMOs, as a person with this type of background is able to ask the right questions and perform an on-site audit that is relevant to the project.

Also of importance is the team that is assembled for the first meeting. Are you speaking with sales or business development folks, or a team of highly trained, technical people who can interpret your needs and create a well-thought- out program? Is the project manager involved from the first engagement through to the end of the project, and is that person experienced enough to translate your passion and vision into a successful project?

Is the proposal of sufficient technical detail or simply a list of line items? The right CMO may not always be the least expensive, but working with a CMO who partners with you to deliver a quality product on schedule can save time, money, and headaches as you enter expensive clinical trials.

Q: We all have audit checklists, but what should clients be aware of during an audit that may not be written on a piece of paper?

A: Behavior during an audit can be very telling. How quickly is the Quality Assurance group able to pull requested documents? How knowledgeable are they about their own documents? Are they able to pinpoint information within a document quickly, or do they have to read through it to find requested information? There is a difference between a team that has prepared for an audit and a team that owns their systems, and during an audit, it's important to look for the subtle differences between the two. A quality team that shows ownership and knowledge of their systems is a team that is prepared for unannounced inspections by the FDA.

Q: What should clients learn from a CMO's regulatory history?

A: Regulatory inspection history is clearly important based strictly on inspection outcome, such as the number and types of 483s that may have been issued, the frequency of inspections, and how frequently 483s are issued. Sponsors should always consider the seriousness of the substance of the observations. How many are serious and substantive observations, and are they still open? Or, are the observations relatively simple oversights? You should be able to evaluate and judge the company through analysis of the observations. It's also important to understand how a CMO responds to inspections, both positive and negative. Are inspections considered an opportunity to

"PYRAMID builds relationships, and through these relationships, we develop partnerships. We are not just doing a job for our clients, we are building a future with them. PYRAMID understands the long-term benefits of successful development or the severe consequences of a failed project, not just to ourselves but to our clients and ultimately, to the patients. We participate in all aspects of each project, providing expertise when necessary, and we efficiently take projects through all phases of drug development without losing focus on quality."

learn and improve quality systems or are they a finite target that that the team works toward achieving, and when complete, all is forgotten until the next inspection? Who within the company is involved in the inspection? How engaged is upper management, and how frequently are functional area experts relied upon?

Q: Can you provide a detailed example of what can happen when choosing a partner for the wrong reasons?

A: Yes, of course, we have many examples. One that comes to mind is a company that PYRAMID worked with on a new project several years ago. This is a perfect example of what happens when selecting the wrong CMO. PYRAMID's technical team met with the company to discuss the project, and while the company was impressed with our knowledge and recommendations, they chose a different CMO based solely on cost. About 10 to 12 months later, the company returned to PYRAMID lamenting the delays and struggles with the CMO, who claimed to have the expertise and equipment to manufacture their lyophilized product, but clearly they did not. Now the project was behind schedule, and the budget was climbing. Once again, the sponsor chose to work with yet another less-expensive CMO in an effort to recuperate some of their costs. Again, a year later, they returned to us frustrated and demanding help on a fast track because the new CMO could not maintain consistent weight checks nor keep air bubbles out of their solution during the filling process, therefore no product was manufactured, and clinical trials were delayed.

PYRAMID agreed to assist with the issues and took over the project from this point. The formulated bulk was shipped to us for evaluation, and we were able to quickly identify the root cause for their problems. In fact, within minutes of receipt, and upon first glance, our technical team determined the cause of the problem was air bubbles mixed with the slightly viscous solution that lead to fluctuation of fill weight checks. As the client experienced negative performance from the previous two CMOs, they requested confirmation studies to alleviate uncertainties that were born from ill-suited guidance. While we were more than happy to conduct these studies, they further increased the cost and unnecessarily extended the duration of the program. Risk-based decisions are made by sponsors every day, but sometimes saving a few thousand dollars can ultimately cost a great deal more in the long run, including delays in initiating clinical trials and subsequently delays in the regulatory path to approval and finally, to the patients who desperately need the treatment.

There are more examples that can be discussed to show that partnering with a CMO based strictly on cost may not be the wisest approach to a successful relationship and program, but this story clearly demonstrates how selecting a CMO based on cost alone, especially when due diligence points to a different direction, can be extremely consequential.

PYRAMID's core values will not allow us to accept work that is outside of our areas of expertise and therefore, time and again, our clients speak only of successful projects. ◆

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FROST & SULLIVAN

What do you *really* know about end users of drug delivery technologies?

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For more information on how to find growth opportunities in the drug delivery market, please contact Mireya Espinoza at mireya.espinoza@frost.com or **210-247-3870**.

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John Kiesewetter – T: 541-338-0022 Email: jkiesewetter@drug-dev.com

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External Delivery

Social Responsibility

By: John A. Bermingham

John A. Bermingham is former Executive Vice President & COO of 1st Light Energy & Conservation Lighting, Inc. and former Co-President and COO of AgraTech, a biotech enterprise. He was also President & CEO of Cord Crafts, LLC; President & CEO of Alco Consumer Products, Inc., Lang Holdings, Inc., and President, Chairman, and CEO of Ampad, all of which he turned around and successfully sold. With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona, Corporation, and Rolodex Corporation as well as turning around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group, and President of the Magnetic Products Group, Sony Corporation of America.

This article is not a lesson in economics, although the way it starts out, you would believe that it is. Not so. The free enterprise system is one of the many great factors that drive our economy. A free enterprise system has five main principles: freedom of choice, the right to private property, making and retaining profits, competition in the market, and consumer sovereignty. Free, as in Free Enterprise, means simply that you are able to run your own enterprise (business) without any substantial restrictions from the government.

One very important factor in free enterprise is that products and services and their associated pricing are determined by the market. The government really has no say in what your company does or produces except for illegal activity and assets that are for national security.

All of that said, what's all the ruckus about with these two companies, Mylan, maker of the EpiPen, which raised the cost for a pair of EpiPens over $600, and Turing Pharmaceuticals, maker of toxoplasmosis treatment Daraprim, which raised its price by over 5,000%?

In the two paragraphs above this one, it is clearly stated that pricing for products and services is determined by the market. So if Mylan and Turing Pharmaceuticals can raise their prices to an exorbitant level, that's their decision right? I mean, if no one wants to pay their prices because they are too high, then so be it.

Yes, but suppose the two products in question are patented, are sole sourced by the two aforementioned companies, and are life-saving. People are alive today because of the usage of these two life-saving products throughout the years, but many can now no longer afford them. This is where social responsibility comes into play.

Companies are not tangible things that exist unto themselves. Companies are formed and run by people, thus the company is the people. So it's not really Mylan or Turing that set these exorbitant prices, it was the people in the companies who did this, and in particular, the CEOs.

Mylan has a code of Business Conduct and Ethics. It states in part: "We will continue to address patients' unmet needs and provide them with access to our products virtually anywhere in the world. Because of this unwavering commitment, we believe we can unlock additional value for patients, customers, shareholders, and our employees, without compromising the quality of our products or the integrity of our enterprise, and become the most efficient global generics and specialty pharmaceutical company in the industry."

Not if you're going to raise the price of a life-saving drug over $600, resulting in a significant amount of people having to forgo buying the drug.

Turing has a set of guiding principles and a Vision. The vision states in part: "Our mission is to identify and implement sound, flexible, and easy-to-use solutions that enable users information to make faster and more informed business decisions. We can do this by achieving the highest levels of passion, performance, and professionalism. The higher we set our sights and standards, the better we serve the people we care most about."

It looks as if the people they most care about are themselves. I mean they did raise the cost of their life-saving drug over 5,000%.

So in my opinion, the CEOs of these two companies failed in their social responsibility and thought only of their immense personal wealth that would be the result from these outrageous price increases. I guess they forgot to read their codes of conduct and vision statements. ◆

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