Drug Development & Delivery

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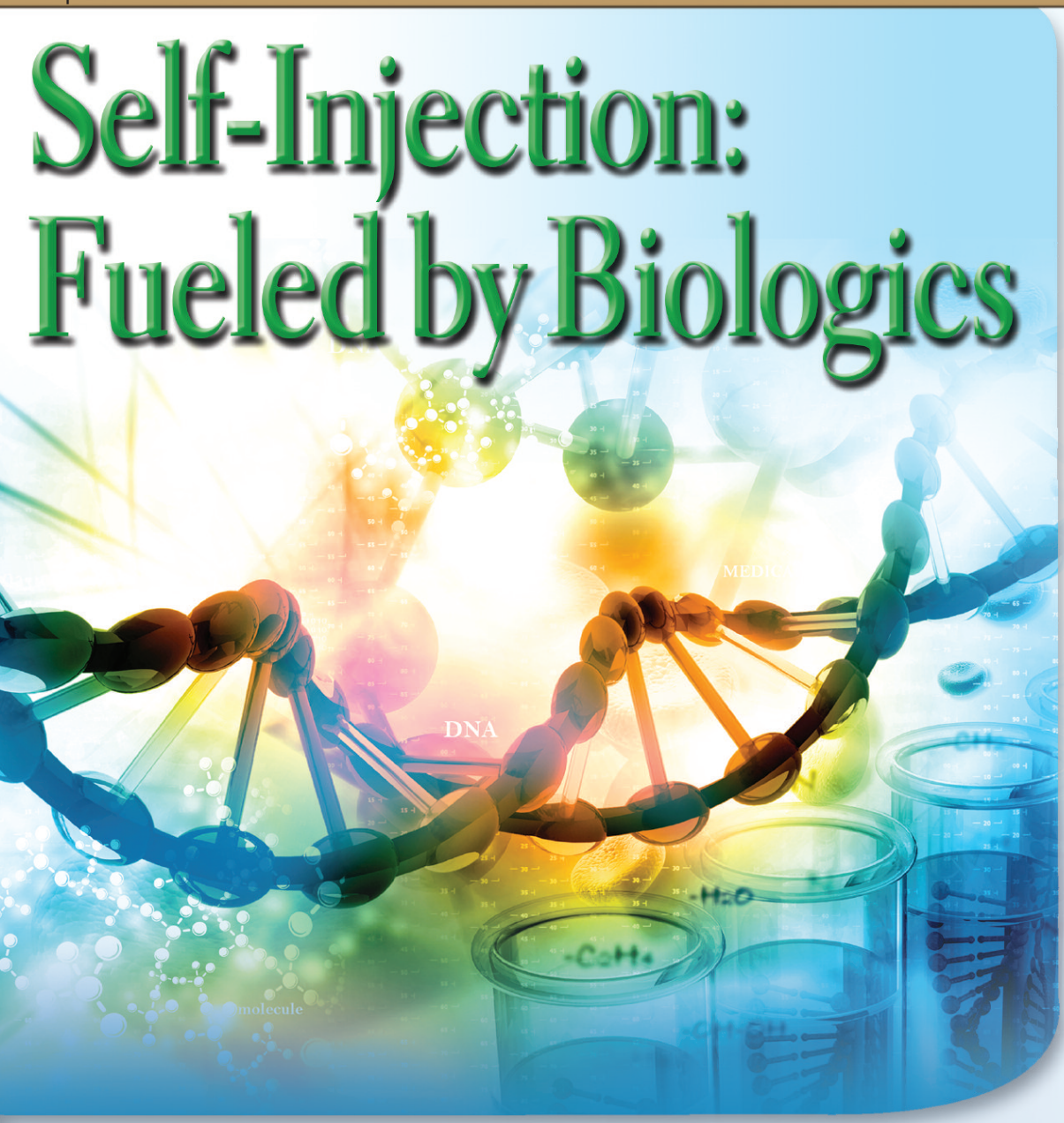
Self-Injection: Fueled by Biologics



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

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Cindy Dubin
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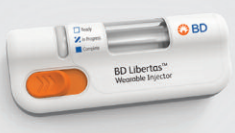
THE DIFFERENCE OF ONE DRUG DELIVERED

FOR BETTER TREATMENT OF CHRONIC DISEASES. Across the healthcare continuum, BD is the industry leader in parenteral delivery devices that help health systems treat chronic diseases. We not only continually advance clinically proven, prefillable drug delivery systems, we do so with a vision to help healthcare providers gain better understanding of how patients self-inject their chronic disease therapies outside the healthcare setting. This is why we partner with leading pharmaceutical and biotech companies worldwide to develop digitally-connected self-injection devices—including wearable injectors and autoinjectors—to capture valuable data that can be shared with caregivers. Discover how BD brings new ideas and solutions to customers, and new ways to help patients be healthy and safe. **Discover the new BD.**



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BD Libertas™ wearable injector, BD Libertas™ wearable injector with Smart option and BD Intevia™ autoinjector are products in development; some statements made are subject to a variety of risks and uncertainty.

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& Delivery

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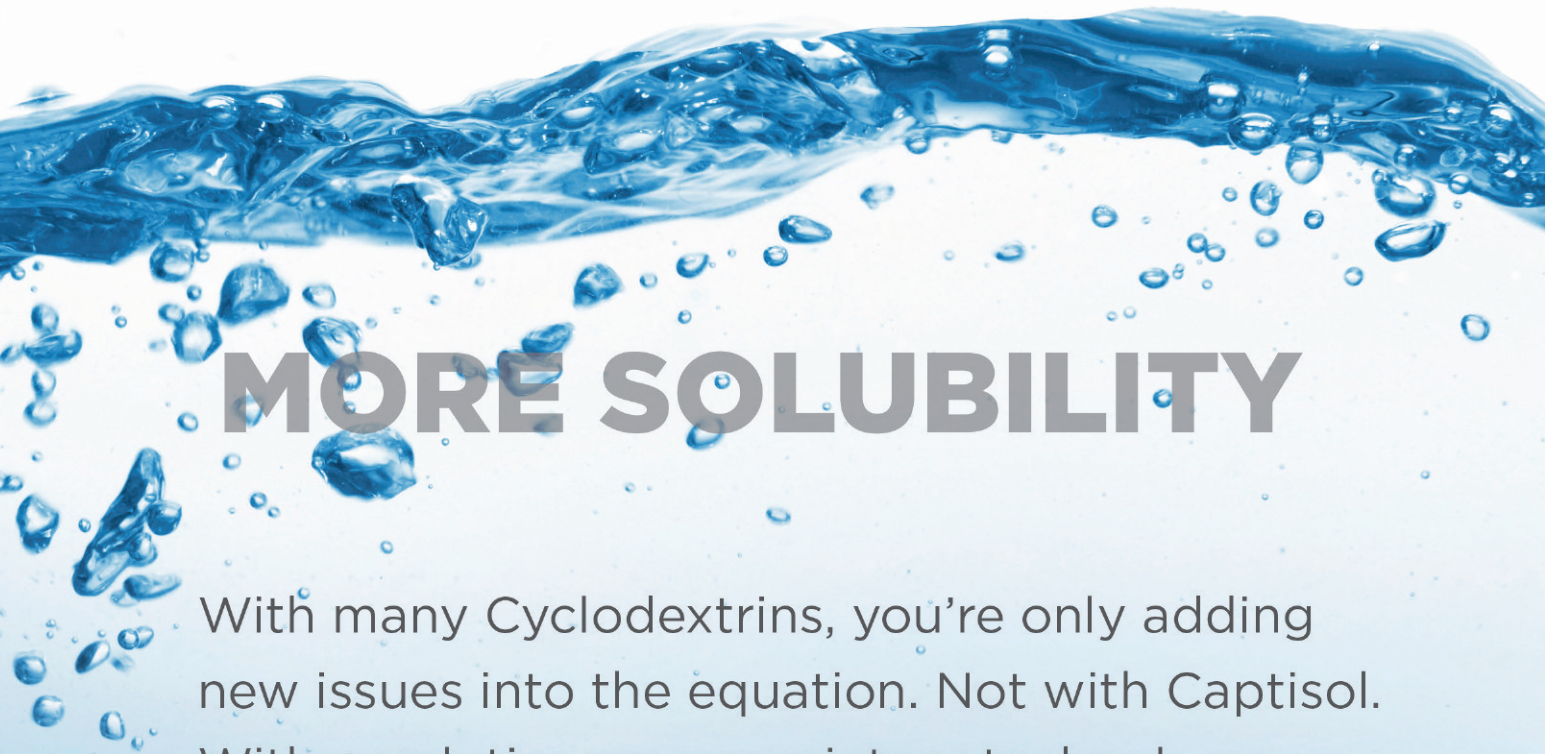

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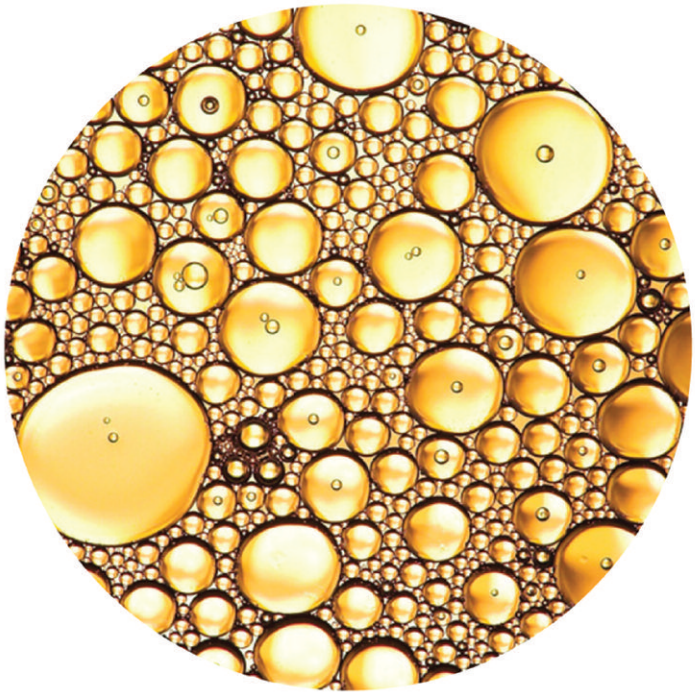
"SLN and NLC formulations maintain the enhanced solubility benefits of traditional liquid colloidal carrier drug delivery systems, but provide several additional benefits, such as increased chemical stability for API, potential for sustained release, targeted delivery, and lymphatic delivery, which allows for the avoidance of first-pass metabolism as well as lymphatic targeting."



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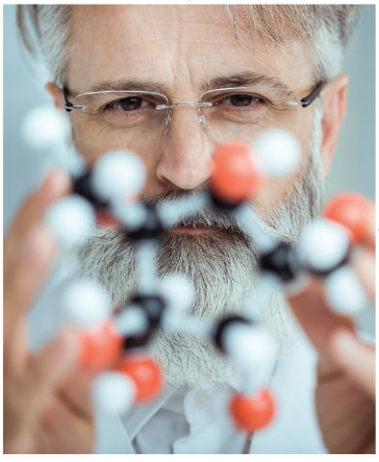

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Fueled by Biologics

"The global injectable drug delivery market is growing around 11.8% CAGR and will soon eclipse oral delivery as the primary route of administration of pharmaceuticals. The market was valued at $328 million in 2015 and is expected to reach $640 million by 2021. This growth is being fueled by biologics, which are expected to grow at a clip of 26.5% to over $250 billion by 2020."

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Avalon GloboCare Forms Strategic Partnership With Weill Cornell Medical College to Co-develop Technologies & Bio-production of CAR-T Therapy

Avalon GloboCare Corp. recently announced the company has formed a strategic partnership with Weill Cornell's cGMP Cellular Therapy Facility and Laboratory for Advanced Cellular Engineering headed by Dr. Yen-Michael Hsu. This strategic partnership aims to co-develop bio-production and standardization procedures in procurement, storage, processing, clinical study protocols, and bio-banking for Chimeric Antigen Receptor (CAR)-T therapy, in accordance with the Foundation of Accreditation for Cellular Therapy (FACT) and American Association of Blood Banks (AABB) standards. This strategic partnership will enable Avalon GloboCare to implement the resulting laboratory infrastructure and clinical plans in China and the US.

This partnership also includes a CAR-T education program to support and foster collaborative research and training programs for scientists and clinicians between Weill Cornell and Hebei Yanda LuDaopei Hospital, which is Avalon GloboCare's main affiliated clinical facility as well as the world's single largest medical institution in CAR-T therapy.

"This strategic partnership will synergize Weill Cornell's world-class cGMP cellular therapy facility and our immense clinical resources at the LuDaopei hospital network to accelerate innovative CAR-T technology development, standardization in bio-manufacturing process, as well as knowledge exchange in CAR-T and other cellular therapies. Recently, we announced that Avalon formed a new wholly owned US subsidiary, Avactis Biosciences, Inc., which will be focused on accelerating commercial activities related to our proprietary CAR-T technologies. This new subsidiary is designed to integrate and optimize our global scientific and clinical resources, which will be instrumental as we advance this partnership with Weill Cornell," said Dr. David Jin, CEO and President of Avalon GloboCare Corp. and the recently established CAR-T focused subsidiary Avactis Biosciences, Inc. "We are very proud to initiate this endeavor with an overarching goal of integrating premium research and clinical resources worldwide to provide standardized, safer, and more effective CAR-T therapy," added Dr. Jin.

Avalon GloboCare Corp. is a global intelligent biotech developer and healthcare service provider dedicated to promoting and empowering high impact, transformative cell-based technologies and their clinical applications, as well as healthcare facility management through its core platforms, namely Avalon Cell and Avalon Rehab. In addition, Avalon provides strategic advisory and outsourcing services to facilitate and enhance their clients' growth, development, as well as competitiveness in both domestic and global healthcare markets. Avalon also engages in the management of stem cell banks and specialty clinical laboratories. Through its US subsidiaries, namely GenExosome Technologies Inc. and Avactis Biosciences Inc., Avalon will further establish its leading roles in the fields of CAR-T therapy, liquid biopsy, precision medicine, and regenerative medicine. For more information, visit http://www.avalon-globocare.com/index.html.

Nevakar & Endo Enter Exclusive Licensing Agreement for Multiple 505(b)(2) Injectable Products

Nevakar Inc. recently announced it entered into an exclusive licensing agreement with Endo International plc's subsidiary, Endo Ventures Limited, for the development of five differentiated, sterile injectable products in the US and Canada. Pursuant to the agreement, Nevakar will develop and seek US FDA approval for these products, and Endo's Par Pharmaceutical Sterile Products division will launch and distribute the products upon approval.

"We are pleased to establish this partnership with Endo, a respected pharmaceutical company with a significant and growing presence in sterile and critical care products. This agreement validates Nevakar's strong pipeline and business model and furthers our mission to develop innovative pharmaceutical products that improve patient care and quality of life," said Navneet Puri, PhD, Founder, President and Chief Executive Officer of Nevakar.

"This important strategic initiative provides us with products that align well with our goal of expanding our sterile injectables business and adding more complex 505(b)(2) products into our pipeline. If approved, these drugs will benefit patients by providing new treatment options in the hospital and critical care environment," added Paul Campanelli, President and CEO of Endo. "We look forward to once again working with Dr. Navneet Puri and the Nevakar team to bring these products to market."

Par Pharmaceutical currently markets several products that were developed by InnoPharma, a company which was also founded by Dr. Navneet Puri and subsequently sold to Pfizer in 2014.

Nevakar Inc. is growing as a fully integrated specialty pharmaceutical company with an extensive portfolio of products in the ophthalmic and injectable areas. Founded in 2015, and headquartered in Bridgewater NJ, the company is focused on developing and commercializing innovative products to address unmet medical needs, thereby improving patient care and quality of life. Nevakar utilizes the 505(b)(2) regulatory pathway, along with its proven expertise in the development of novel and proprietary sterile pharmaceutical products to identify, develop, and obtain regulatory approval for its products. Additional information is available at www.nevakar.com.

Endo International plc (NASDAQ: ENDP) is a highly focused generics and specialty branded pharmaceutical company delivering quality medicines to patients in need through excellence in development, manufacturing and commercialization. Endo has global headquarters in Dublin, Ireland, and U.S. headquarters in Malvern, PA. Learn more at www.endo.com.

Par Pharmaceutical, headquartered in Chestnut Ridge, NY, develops, manufactures and markets safe, innovative and cost-effective generic pharmaceutical products that help improve patient quality of life. Par, among the top leaders in the U.S. generics industry, possesses a portfolio that includes sterile injectables, alternative dosage forms and many other differentiated products. Par is advancing a research and development (R&D) pipeline of approximately 200 potential new products. Par is an operating company of Endo International plc. Learn more at www.parpharm.com.

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BioPharmX Receives IRB Approval to Initiate Phase 2 Trial

BioPharmX Corporation recently announced it has received Institutional Review Board approval for its Phase 2 study of BPX-04 for the treatment of papulopustular rosacea.

The company also announced that, based on data from its open-label feasibility study that assessed tolerability in subjects with papulopustular rosacea, it has selected the 1% minocycline concentration for use in the PRISM Phase 2 trial to evaluate the safety and efficacy of BPX-04, continuing in its patient-centric commitment to antibiotic stewardship by utilizing a lower dose of antibiotics for patients.

The 12-week, open-label feasibility study assessed the tolerability of BPX-04 topical minocycline gel in 30 subjects with moderate-to-severe papulopustular rosacea. Once-daily administration of either 1%, 2%, or vehicle was applied to the face. All treatment arms were well tolerated and there were no serious adverse events, further demonstrating the patient-centric benefits of the BioPharmX HyantX delivery system underpinning BPX-04.

"Optimizing delivery to the source of the disease, while minimizing the risks of oral antibiotics in patients with rosacea, has the potential to influence better prescribing options for dermatologists," said Dr. Neal Bhatia, a board-certified dermatologist at Therapeutics Clinical Research in San Diego and the study's principal investigator. "Dermatologists have long desired a new topical antibiotic option that minimizes the risks of systemic side effects while not contributing to the bigger issue of systemic antibiotic resistance."

Dr. Bhatia highlighted BPX-04 data at the recent American Academy of Dermatology Summer Meeting in a presentation titled Therapeutic Update in Chicago. Long-term safety and efficacy, as well as treatment strategies with these new regimens were also discussed.

The National Rosacea Society describes rosacea as a common, but poorly understood disorder of the facial skin that affects an estimated 16 million Americans, many of whom do not even know they have the condition. Rosacea is characterized by facial redness, pimples, bumpy breakouts, and thickening of the skin.

BPX-04 is the company's second candidate utilizing the novel, patented HyantX delivery system, which is designed to stabilize and solubilize hydrophilic molecules in an anhydrous gel environment. This delivery system is being developed to carry a variety of active ingredients – and even combinations of actives – into the skin. Research has shown the delivery system may allow for maximum solubility for multiple actives, which is intended to lead to enhanced skin penetration and increased efficacy and tolerability, has antibacterial properties, and hydrates the skin, making the delivery system a valuable asset in pipeline development and strategic partnering.

BioPharmX Corporation is a Silicon Valley-based specialty pharmaceutical company that seeks to provide products through proprietary platform technologies for prescription, over-the-counter, and supplement applications in the health and wellness markets, including dermatology and women's health. For more information, visit www.BioPharmX.com.

Aegis Awarded US Patent for Formulation & Non-invasive Delivery of Peptide Drugs

Aegis Therapeutics LLC recently announced it has been awarded US Patent No. 10,046,025, providing non-invasive delivery of cyclic peptide drugs. Cyclic-peptide drugs are an increasingly important chemical class of drugs that combine several favorable properties, such as good binding affinity, target selectivity, and low toxicity that make them an attractive modality for the development of therapeutics. More than 40 cyclic peptide drugs are currently in clinical use, including antimicrobials, human hormones, and drugs used to treat cancer, pain, and metabolic diseases. New powerful techniques based on rational design and in vitro evolution have enabled the de novo development of cyclic peptide ligands to targets for which nature does not offer immediate solutions.

Peptide drugs are not orally active and thus are nearly universally administered by injection. The advent of Aegis' Intravail-based non-invasive metered nasal spray formulations provides a highly effective non-injectable alternative for greater patient convenience and acceptance.

The enabling Aegis Intravail formulation technology is broadly applicable to a wide range of peptide and non-peptide drugs to increase noninvasive bioavailability by the oral, nasal, buccal, and sublingual routes and to speed attainment of therapeutic drug levels in cases where speed is important to the patient, for example in the treatment of pain, nausea, emesis, convulsive disorders, spasticity, and the like. Aegis ProTek excipients stabilize, prevent aggregation, and reduce polysorbate-surfactant induced immunogenicity and anaphylaxis of monoclonal antibody and peptide therapeutic formulations,

At present, more than a dozen different drugs employing Aegis Intravail and ProTek technologies have been reformulated for significantly improved performance by Aegis' licensees. Our licensees include seven of the top 10 largest pharmaceutical companies and two of the top 10 largest multinational generics companies, along with many public and private biotech companies. Aegis growing patent portfolio currently has more than seventy-five issued and pending drug formulation patents covering noninvasive delivery and stabilization of biotherapeutics, biosimilars, and small-molecule drugs.

Aegis Therapeutics LLC is a drug delivery technology company commercializing its patented drug delivery and drug formulation technologies through product-specific licenses. Its Intravail drug delivery technology enables the non-invasive delivery of a broad range of protein, peptide, and non-peptide drugs that can currently only be administered by injection, via the oral, buccal, and intranasal administration routes, and with high bioavailability. Our ProTek excipients stabilize, prevent aggregation, and reduce unwanted immunogenicity and anaphylaxis of protein and peptide therapeutics while avoiding the oxidative damage caused by polysorbate surfactants. For more information, visit http://www.aegisthera.com.

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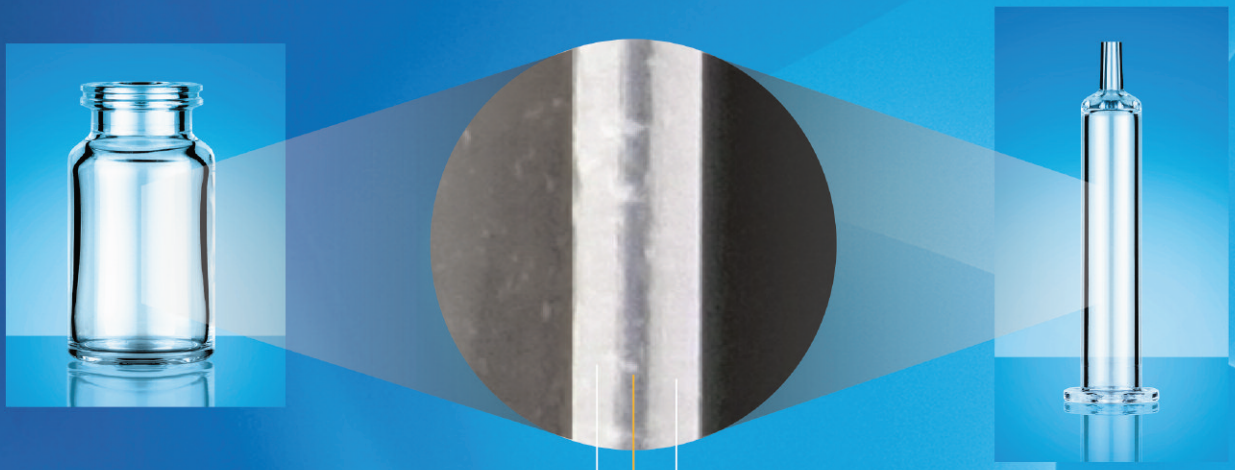

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- ✓ Suitable for Biologics

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https://www.mgc.co.jp/eng/products/abd/oxycapt.html

Baxter Announces Health Canada Approval of Spectrum IQ Infusion System

Baxter Canada recently announced Health Canada approval for the Spectrum IQ Infusion System with Dose IQ Safety Software. The Spectrum IQ system features new bi-directional electronic medical records (EMR) integration to help ensure the correct medications and fluids are delivered to the patient.

The Spectrum IQ system also features unique capabilities to help make auto-programming, protection for high-risk infusions and drug library compliance more consistently achievable for health systems and is the first-of-its-kind to offer the option to display information in both English and French languages.

"The Spectrum IQ system is intelligently designed with exclusive new features to simplify EMR integration for health systems while raising the bar for patient safety and clinician efficiency," said Stephen Thompson, General Manager and President, Baxter Canada. "We look forward to bringing this leading technology to more patients and healthcare providers across Canada, including being able to offer our Spectrum platform with French language capabilities for the first time."

The Spectrum IQ system features the broadest range of auto-programming workflows and feature sets and embedded on-screen barcode technology that helps eliminate the need for a sticker barcode and provides clinicians with scan prompts to help maintain or increase auto-programming compliance and automatically document infusion data into the EMR.

The Spectrum IQ pump is also the only infusion pump to feature Line Check Notification technology that supports line management by providing a visual notification matching the infusion pump and medication being infused.

Baxter has also partnered with First Databank (FDB) to incorporate an evidence-based library of IV medications called FDB Infusion Knowledge into Dose IQ safety software to help make infusion delivery safer. Dose IQ software powered by FDB Infusion Knowledge provides a knowledge base of suggested infusion parameters for the Spectrum IQ system such as dose limits, concentrations and durations. FDB is a leading provider of drug and medical device knowledge and supports healthcare professionals in making informed decisions at the point of care, intended to improve the quality of patient care.

The Spectrum IQ pump includes leading features designed to help drive the highest levels of drug library compliance in the industry, such as wireless drug library updates without interrupting clinical workflow and automatically defaulting to the installed drug library without requiring clinicians to take extra steps to use the safety features. Baxter's Spectrum systems — including the Spectrum IQ system — are the only infusion pumps with a built-in Dose/Rate Change Error Prevention Feature, which helps clinicians protect high-risk infusions during titrations, and helps allow pharmacists to customize dose change limits for individual drugs.

Other key features designed to facilitate increased hospital efficiency include: Built-in DeviceVue Asset Tracking Application, which displays pump status and location data on a PC, tablet or smartphone without the need to interface with third-party real-time location systems; Alarm and alert routing designed to help reduce "alert fatigue" among nursing staff by sending alarm start and stop messages directly from the pump bedside to secondary Alarms Management Systems, including smartphones or work stations; Enhanced data analytics and near real-time infusion data accessible from a single, centralized screen; and Standard set technology that can help yield up to 53% cost savings in IV tubing sets and up to 30% reduction in IV tubing usage.

Every day, millions of patients and caregivers rely on Baxter's leading portfolio of critical care, nutrition, renal, hospital and surgical products. In Canada, we've been operating at the critical intersection where innovations that save and sustain lives meet the healthcare providers that make it happen for 80 years. With products, technologies and therapies available in more than 100 countries, Baxter's employees worldwide are now building upon the company's rich heritage of medical breakthroughs to advance the next generation of transformative healthcare innovations.

MeiraGTx Announces AAV-CNGA3 Has Received Orphan Drug Designation

MeiraGTx Holdings Plc recently announced that the US FDA has granted orphan drug designation (ODD) for its AAV-CNGA3 gene therapy product candidate for the treatment of achromatopsia (ACHM) caused by mutations in the CNGA3 gene.

ACHM is an inherited retinal disease that severely limits a person's sight by preventing cone photoreceptors in the eye from functioning. Individuals with ACHM are often legally blind from birth, have extreme sensitivity to light, and experience involuntary eye movements. AAV-CNGA3 is an investigational gene therapy treatment designed to restore cone function, delivered to the cone receptors at the back of the eye via subretinal injection.

In June 2018, the European Medicines Agency's (EMA) Committee for Orphan Medicinal Products issued a positive opinion recommending orphan medicinal product (orphan drug) designation for AAV-CNGA3 for the treatment of ACHM. In addition to AAV-CNGA3, MeiraGTx also has orphan designation in both the U.S. and EU for three other inherited retinal disease gene therapy product candidates, AAV-CNGB3, AAV-RPGR and AAV-RPE65, all of which are in clinical development.

Orphan drug designation is intended to facilitate and expedite drug development for rare diseases or conditions for which there are no current treatments available. It also provides substantial benefits to the sponsor, including the potential for tax credits for clinical development costs and study-design assistance. If a product receives the first FDA approval for the indication for which it has orphan drug designation, the product is entitled to seven years of market exclusivity, except in limited circumstances.

Achromatopsia is an inherited retinal disorder that specifically prevents cone photoreceptors from functioning. ACHM is characterized by severely reduced visual acuity of 20/200 or worse, disabling light sensitivity (photoaversion) and involuntary back and forth eye movements (nystagmus). ACHM occurs in approximately one in 30,000 people in the United States, with 92 percent of cases caused by mutations in CNGB3 and CNGA3 genes. Currently, there are no effective treatments for this disease.

MeiraGTx is a vertically integrated, clinical stage gene therapy company with four ongoing clinical programs and a broad pipeline of preclinical and research programs. MeiraGTx has core capabilities in viral vector design and optimization and gene therapy manufacturing, as well as a potentially transformative gene regulation technology. Led by an experienced management team, MeiraGTx has taken a portfolio approach by licensing, acquiring and developing technologies that give depth across both product candidates and indications. MeiraGTx's initial focus is on three distinct areas of unmet medical need: inherited retinal diseases, severe forms of xerostomia and neurodegenerative diseases. Though initially focusing on the eye, salivary gland and central nervous system, MeiraGTx intends to expand its focus in the future to develop additional gene therapy treatments for patients suffering from a range of serious diseases. For more information, visit www.meiragtx.com.

Stemline Therapeutics Announces FDA Accepts ELZONRIS BLA & Grants Priority Review

Stemline Therapeutics, Inc. recently announced US FDA has accepted for filing the company's Biologics License Application (BLA) for ELZONRIS (tagraxofusp; SL-401) for the treatment of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN). The FDA also granted Priority Review for the BLA and has set a target action date of February 21, 2019, under the Prescription Drug User Fee Act (PDUFA).

The FDA grants Priority Review to product applications that, if approved, would provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications. ELZONRIS has also been granted Breakthrough Therapy Designation (BTD) and Orphan Drug Designation (ODD) by the FDA.

Ivan Bergstein, MD, Stemline's CEO, said "The acceptance of our BLA for filing and grant of Priority Review represent tremendous milestones for Stemline and the BPDCN patient community. We would like to thank the patients and their families who participated in our clinical trials, as well as recognize the tireless work of our investigators and entire Stemline team. Given both Priority and Breakthrough status, our commercial organization is positioning itself to rapidly launch ELZONRIS, if approved, to ensure this important new treatment reaches patients as quickly as possible."

ELZONRIS (tagraxofusp; SL-401) is a novel targeted investigational therapy directed to CD123, a cell surface receptor expressed on a range of malignancies. ELZONRIS successfully completed a pivotal trial in patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN), and a Biologics License Application (BLA) in this indication has been accepted for filing and been granted Priority Review by the US FDA. ELZONRIS has also been granted Breakthrough Therapy Designation (BTD) and Orphan Drug Designation by the FDA. ELZONRIS is also being evaluated in clinical trials in additional indications, including chronic myelomonocytic leukemia (CMML), myelofibrosis (MF), and others.

Stemline Therapeutics, Inc. is a clinical-stage biopharmaceutical company developing novel oncology therapeutics. Stemline is developing three clinical stage product candidates, ELZONRIS (tagraxofusp; SL-401), SL-801, and SL-701. ELZONRIS is a targeted therapy directed to the interleukin-3 receptor (CD123) present on a range of malignancies. ELZONRIS has completed a pivotal trial in blastic plasmacytoid dendritic cell neoplasm (BPDCN), for which it was granted breakthrough therapy designation (BTD). The pivotal trial met its primary endpoint, and a Biologics License Application (BLA) has been accepted for filing and granted Priority Review by the FDA. ELZONRIS is also being evaluated in clinical trials in additional indications including chronic myelomonocytic leukemia (CMML), myelofibrosis (MF), and others. SL-801 is a novel oral small molecule reversible inhibitor of XPO1 that is currently in a Phase 1 trial of patients with advanced solid tumors; dose escalation is ongoing. SL-701, an immunotherapeutic, has completed a Phase 2 trial in patients with second-line glioblastoma; data and next steps for the program are being evaluated.

Orchard Therapeutics Announces $150-Million Financing to Advance Pipeline

Orchard Therapeutics recently announced the completion of an oversubscribed $150 million Series C financing. Deerfield Management led the financing with significant new investments from RA Capital Management, Venrock, Foresite Capital, Perceptive Advisors, Cormorant Asset Management LP, ArrowMark Partners, Sphera Global Healthcare, Medison Ventures, Driehaus Capital Management and Ghost Tree Capital Group, LP, as well as additional US-based healthcare-focused funds. Existing investors also participated including Temasek, Baillie Gifford, RTW Investments, LP, Cowen Healthcare Investments and Agent Capital.

Proceeds from the Series C financing will be used to progress Orchard's three most advanced clinical programs: OTL-101 for adenosine deaminase severe combined immunodeficiency (ADA-SCID), OTL-200 for metachromatic leukodystrophy (MLD) and OTL-103 for Wiskott–Aldrich syndrome (WAS) toward registration and commercialization. The funding will also support the clinical and preclinical development of the company's rare disease gene therapy pipeline.

"We are thrilled to have such strong support from both new and existing investors in this financing round," said Mark Rothera, President and CEO of Orchard. "The quality of this investor syndicate is a testament to the confidence we have built among our stakeholders, based on the substantial progress of Orchard's clinical and preclinical programs since our Series B round last year."

Frank Thomas, CFO and Chief Business Officer of Orchard, said "This financing provides Orchard with additional capital to rapidly progress our most advanced clinical programs to commercialization. We are advancing our pipeline of potentially transformative gene therapies in primary immune deficiencies and neurometabolic disorders to reach patients as quickly as possible."

Elise Wang, Principal at Deerfield Management, added "Orchard has made an impressive transition from a start-up company to an emerging leader in gene therapy for rare diseases by building a comprehensive, industry-leading portfolio of ex vivo gene therapies and assembling a highly experienced team. We are pleased to have led this round of financing. We believe the company has generated compelling clinical data on products which have the potential to become breakthrough treatments for patients."

Orchard Therapeutics is a fully integrated commercial-stage biotechnology company dedicated to transforming the lives of patients with serious and life-threatening rare diseases through innovative gene therapies.

Orchard's portfolio of autologous ex vivo gene therapies includes Strimvelis, the first autologous ex vivo gene therapy approved by the EMA for adenosine deaminase severe combined immunodeficiency (ADA-SCID). Additional programs for primary immune deficiencies, neurometabolic disorders and hemoglobinopathies include three advanced registrational studies for ADA-SCID, metachromatic leukodystrophy (MLD) and Wiskott-Aldrich syndrome (WAS), clinical programs for X-linked chronic granulomatous disease (X-CGD) and transfusion dependent beta-thalassemia (TDBT), as well as an extensive preclinical pipeline. Orchard currently has offices in the U.K. and the U.S., including London, San Francisco and Boston. For more information, visit www.orchard-tx.com.

Innovest Global Signs Worldwide Agreement With Cedars-Sinai Medical Center to Commercialize Vaccine

StemVax Therapeutics, an Innovest Global Inc. holding, has been awarded an exclusive worldwide license agreement from Cedars-Sinai Medical Center in Los Angeles, CA, for all of the intellectual property needed to commercialize the StemVax Glioblast brain tumor vaccine.

"The StemVax business model is a low-cost, high-output strategy of partnering with a major health organization to get the technology to market and start helping people," said Dr. Dwain Morris-Irvin, President of Innovest's Biotech Division, the StemVax Chief Science Officer, and co-author of the intellectual property. "This agreement, which was negotiated over a 9-month period, is critical because we now has everything we need, and we have it all in house."

Innovest announced the approved patent of the primary technology on July 25, 2018. Now, Cedars-Sinai Medical Center, the organization that filed for that patent, has provided StemVax the exclusive, worldwide right to it and three other related Intellectual Properties subsequently filed for patent protection.

"This illustrates Dr. Irvin's status as a scientist, and is exactly the type of progress Innovest shareholders are thrilled to see. It's progress, but it's also just a little better than you might have thought possible," said Dan Martin, CEO of Innovest Global. "When an organization like Cedars grants these types of rights, and Dr. Irvin's peers and co-authors sign-off on the arrangement – these are monumental endorsements of him and StemVax. I'm honored to be a part of it, and excited that Innovest continues to engage with people and organizations that are world class."

Cedars-Sinai Medical Center is a non-profit hospital and academic health science center located in Los Angeles, CA. They employ over 2,000 physicians and are considered one of the top hospitals and research organizations in the world. Dr. Irvin previously was one of their key contributors in the areas of research that he founded StemVax to pursue.

StemVax Therapeutics is a Translational biotechnology company that develops novel therapies for brain tumor patients. We focus our efforts on developing immunotherapeutic approaches to treating patients with Glioblastoma Multiforme (GBM), a devastating brain cancer. We also focus our research efforts on novel drug development to target Cancer Stem cells and other multi-resistant cancer cells. We seek to make a difference in patient's lives. Bringing new beginnings to the market by developing novel therapeutics.

Innovest Global, Inc. is in the Conglomerates industry, a diversified holding company with operations in commercial and industrial products and services, energy, biotechnology, and health services. Innovest Global utilizes novel technology and marketing to efficiently acquire customers. Our primary growth strategy is to acquire existing companies in a select few industries, and attract new customers in cost effective ways. Currently, we have a Commercial & Industrial Division, and a Biotechnology & Health Services Division. For more information, visit: http://www.innovestglobal.com.

International Stem Cell Corporation Developed 3D Liver Structures

International Stem Cell Corporation recently announced that ISCO's Research and Development team has developed novel methods that efficiently generate human 3D liver-like tissue.

According to the American Liver Foundation, approximately 17,000 patients are on the US liver transplant waiting list with only 6,000 liver transplants performed each year. While liver transplantation is a practical treatment option for these candidates, increasing waiting times for organ transplantation has led to the deaths of nearly 17% of those who were on the waiting list. But, ISCO is working to provide a viable 3D printable treatment option, which has the potential to significantly reduce wait times for many of these patients.

The 3D liver structures themselves are produced from human pluripotent stem cell derived-liver progenitor cells (hpLPC). As these cells differentiate in 3D culture, they form liver-like tissue that consists of hepatocytes, choangiocytes, and hepatic stellate cells. The 3D liver tissue can be maintained in culture for more than 1 month, with stable albumin, transthyretin, alpha-1 antitrypsin, and metabolic P450 (CYP3A4, CYP1A2) enzyme protein expression levels that are typically found in mature human liver tissue.

The hpLPC can be derived from any kind of pluripotent stem cells, including human embryonic, induced pluripotent, or parthenogenetic stem cells, via ISCO's proprietary highly efficient and scalable differentiation method. This opens wide opportunities for licensing the technology for use in drug development and potentially as therapeutic tissue for the treatment of liver disease.

"Such realistic 3D representations like the one we've developed will be invaluable for the future study of the abnormalities in liver diseases, as well as testing the efficacy of certain drug therapies," said Russell Kern, PhD, Executive Vice President and Chief Scientific Officer of ISCO. "For us, the next phase will involve testing the structures in rodents to see whether or not they will engraft and start functioning like a real liver."

The liver works to actively remove toxins and other impurities from the blood through a unique filtering system. The liver is also an important site for converting food to energy and storing fat-soluble vitamins like D and E. Liver disease typically develops when the liver's ability to perform these metabolic functions is compromised.

Currently, there are no alternatives available for patients in need of a liver transplant other than to join the waiting list. Cirrhosis is the end stage in patients who have chronic progressive liver disease. According to Allied Market Research, the liver disease treatment market will be over $19 billion in 2022.

International Stem Cell Corporation (ISCO) is focused on the therapeutic applications of human parthenogenetic stem cells (hpSCs) and the development and commercialization of cell-based research and cosmetic products. ISCO's core technology, parthenogenesis, results in the creation of pluripotent human stem cells from unfertilized oocytes (eggs).

Evotec & Novo Nordisk Form Strategic Research Alliance in Diabetes & Obesity

Evotec AG recently announced a strategic alliance with Novo Nordisk to discover and develop novel small molecule therapies to treat patients suffering from diabetes and obesity as well as co morbidities such as nonalcoholic steatohepatitis (NASH), cardiovascular diseases, and diabetic kidney disease.

Evotec will apply its drug discovery platform, especially in ligand-based design, to seek to design novel, safe and efficacious products to address diabetes and associated morbidities. Once suitable pre-clinical candidates are selected, Novo Nordisk will use Evotec's INDiGO platform to move through pre-clinical studies to enter IND registration.

Dr. Mario Polywka, Chief Operating Officer of Evotec, said "Novo Nordisk is one of the largest, most successful Pharma companies in the world with a proven leadership position in diabetes and obesity. The integration of our industry-leading discovery and development platform with Novo Nordisk's deep disease expertise will create a powerful combination that we hope will create a difference for patients with diabetes or obesity. We very much look forward to working with such an innovative partner."

Dr. Marcus Schindler, Senior Vice President, Global Drug Discovery, Novo Nordisk, added "Evotec is a highly esteemed company in the field of small molecules and we are very excited about the collaboration. Novo Nordisk is confident that this will open up new possibilities in small molecule drug discovery and development targeting diabetes and obesity with the potential to make a difference for people living with these serious diseases."

Evotec is a drug discovery alliance and development partnership company focused on rapidly progressing innovative product approaches with leading pharmaceutical and biotechnology companies, academics, patient advocacy groups and venture capitalists. Drug discovery solutions are provided in form of fee-for-service work, integrated drug discovery alliances, development partnerships, licensing of innovative drug candidates and consulting arrangements. The Company operates worldwide and has leading scientific experts, state-of-the-art technologies as well as key therapeutic expertise in the areas of neuroscience, diabetes and complications of diabetes, pain and inflammation, oncology, infectious diseases, respiratory diseases and fibrosis. By leveraging this expertise, Evotec intends to develop best-in-class and first-in-class differentiated therapeutics on its systematic, unbiased and comprehensive infrastructure. The Company's headquarters are located in Hamburg, Germany. Additional operating sites exist in Abingdon and Manchester, UK, Goettingen and Munich, Germany, Verona, Italy, Branford, Princeton and Watertown, USA, Basel, CH as well as Lyon and Toulouse, France.

Novo Nordisk is a global healthcare company with 95 years of innovation and leadership in diabetes care. This heritage has given us experience and capabilities that also enable us to help people defeat obesity, haemophilia, growth disorders and other serious chronic diseases. Headquartered in Denmark, Novo Nordisk employs approximately 43,100 people in 79 countries and markets its products in more than 170 countries.

CONTROLLED RELEASE

Informed Selection of Modified-Release Technologies Provides Simpler Oral Dose Regimens

By: Ronak Savla, PhD

INTRODUCTION

Controlled drug delivery (CDD) formulations are one of the favored tools for the lifecycle management of pharmaceutical products. Typically, a drug that is initially launched as multiple daily doses of an immediate-release (IR) product is reformulated into a once-daily modified-release product, simplifying dosing regimens while retaining efficacy and potentially improving its safety profile.

CDD formulations have many benefits, including extending the duration of effect, reducing toxicity that results from a high peak in plasma concentration, minimizing fluctuations in plasma concentration, and targeting drug release at a specific site within the gastrointestinal (GI) tract. Drugs with rapid clearance and short half-lives may require multiple daily doses and present adherence issues. Reducing frequency to once or twice daily dosing can lead to better patient adherence and acceptance.[1]

Delayed-release formulations are commonly used to release drugs in the correct part of the GI tract, notably drugs to treat colitis and Crohn's disease, such as mesalazine.[2] This approach can also protect an active pharmaceutical ingredient (API) that is sensitive to digestive acids or enzymes, or those that can cause gastric irritation.

Several drugs have a combination of immediate release with a controlled- release profile. This ensures rapid onset and sustained effect. The extended release (ER) formulation of the sedative-hypnotic, zolpidem, gives a biphasic absorption profile, with an IR component, inducing rapid onset of sleep; and then an ER maintenance dose gives a longer duration of action. As the API's elimination half-life is less than 3 hours, it does not accumulate to cause daytime sleepiness.[3] Similarly, the ER formulation of the attention-deficit/hyperactivity disorder (ADHD) drug, methylphenidate, has an IR coating over an osmotically active CR core to give rapid onset plus a 12-hour duration of action.

Before investing time and resources to develop a CDD formulation, thorough drug characterization should be performed, and the data should be used for feasibility assessment. There are many important factors to determine if a CDD system is feasible and to help guide development. The following reviews some of the physicochemical and biopharmaceutical characteristics of drugs and how they influence creation of a CDD formulation.

ASSESSING FEASIBILITY & RISKS

Careful preparation and thorough understanding of drug properties underpin successful formulation and dosage form development and minimizes costs, risks, and time. Many factors contribute to the success or failure of CDD systems, as listed in Table 1.[4,5] To achieve success, the fundamental physical and chemical characteristics of the API should be studied and applied, both on its own and in combination with proposed excipients to assess the feasibility of a CDD system. Physicochemical characterization should focus on the expected dosage forms and be designed to predict processing problems. For speed, minimal quantities of API should be consumed, and readily available analytical instruments are preferable.[6]

DOSE

Ideally, the dose will be in the range of 10 to 250 mg, which is large enough for uniformity not to be an issue, yet small enough to make a single, swallowable dosage form. If large amounts of excipients are necessary, this may require manufacturing of large tablets and capsules and present swallowability challenges.[7] To avoid large dosage units, patients may need to take multiple tablets or capsules.

SOLUBILITY & DISSOLUTION RATE

Perhaps the most important parameter for CDD development is adequate solubility across the physiological pH range, particularly in relation to the dose. The drug should remain solubilized throughout the GI tract and not precipitate out. Table 1 shows that if the entire dose is soluble in 1 to 100 ml of GI fluid, the drug should present an average level of difficulty to formulate as a CDD. In contrast to IR formulations, which are predominantly absorbed in the upper GI tract, CDD products are more likely to also be absorbed in the distal small intestine and colon, and time to reach maximum plasma concentration may not be reached for at least 18 hours after dosing. If once-daily dosing is to be achieved, the drug will need to be soluble in the higher pH of the colon and also absorbed in the colon (see section on permeability).

Whatever the format of the CDD system (matrix, osmotic pump, layered tablet, coated systems), the system must also retain an appropriate dissolution rate throughout the physiological pH range. If a drug dissolves very rapidly, a CDD format is unlikely to be successful; one that dissolves very slowly may not need CDD. Historical applications of CDD focused on decreasing the dissolution rate of very soluble APIs to achieve constant plasma levels, perhaps by using a salt form with lower solubility. Granulation with lipophilic excipients, such as stearic acid, high-molecular weight polyethylene glycol (PEG), or white wax, have been used to slow down the dissolution rate. Drug release from these matrices is partially dependent on the excipient digestion. Because of differences in digestion processes between individuals, this approach can introduce inter-patient variability. New molecular entities (NMEs) in the current pharmaceutical pipeline tend to be more lipophilic and lower solubility. For these molecules, solubility enhancement must be combined with CDD or targeted delivery to attain adequate bioavailability and pharmacokinetics (PK) for CDD applications.

TABLE 1

Factor	Values	Impact
Dose	< 1 mg	Greater development complexity (potential drug content uniformity issue)
	10-250 mg	Average degree of difficulty
	> 250-300 mg	Multiple dosage units may be needed
Dose/solubility ratio (highest dose ÷ lowest solubility in the pH range 1-7.5)	< 1 ml	Straightforward CDD development Multiple technology options exist May need a more lipophilic salt form if high solubility causes very fast dissolution
	1-100 ml	Average degree of difficulty
	100-1000 ml	CDD development is challenging but feasible
	> 1000 ml	Need solubilization – development will be difficult
	> 10000 ml	CDD development is not recommended
Stability	Generally stable as a solid or solution and with common CR excipients	Predict average degree of difficulty
	Compound shows or is predicted to have significant degradation	Predict higher degree of difficulty
Regional Colonic Permeability	Good absorption across entire GI tract Good solubility and permeability and stable	CDD development likely to be feasible
	Risk for poor colon absorption High permeability after efflux inhibition or intermediate solubility or rapid degradation	CDD development is challenging but feasible
	Poor colonic absorption Low permeability or low solubility	CDD development is not recommended
PK Half-Life	< 1-2 hours	Half-life too short
	2-10 hours	Acceptable half-life
	> 10 hours	Compound might not need CDD
Metabolism & Efflux	High gut or first pass metabolism	Relative bioavailability might be low
	Substrate of efflux pumps or metabolizing enzymes	CDD performance is difficult to predict
Food Effect	Positive or negative food effect	Introduction of pharmacokinetic variability especially for pH-responsive CDD systems

Factors influencing feasibility of CDD development. (modified from references 4 and 5)

POLYMORPHISM & SALT FORMS

Solid state properties, such as polymorphism and salt formation, influence solubility and dissolution rate. Polymorph screening is an important step in a preformulation campaign, as it is estimated half of all organic molecules with a molecular weight below 600 have true polymorphs, and if solvates are counted, then it may be as high as 87%.[8]

Solubility can be tailored by changing the salt form if the API is ionizable. For a CDD product, the aim is to control solubility and dissolution to ensure prolonged release. If a drug is highly soluble, a salt form that reduces solubility may be advis-

able. Conversely, a salt may be used to improve solubility for those where it is very poor. Solubility enhancement will almost certainly still be required as part of the CDD system, but possibly not as much as would be necessary for an IR product.

PARTICLE SIZE

Drug particle size can affect parameters, including dissolution rate, and provide challenges for content uniformity, stability, and processing. Micronization can reduce particle size and improve uniformity, but micronized particles tend to agglomerate, particularly if they have a high surface energy. This can be minimized by specifying minimum particle size or adding excipients, such as silicon dioxide. Co-micronization is a technique in which pure drug is blended with a small amount of surfactant and micronized. This approach may improve particle wettability, very modestly improve solubility, and overcome processability issues seen in micronization. Homogeneity of a final product is more difficult to achieve when mixing ingredients with very different particle sizes, so size distribution may need to be carefully controlled.

PERMEABILITY

Once dissolved in GI fluid, drugs must have high permeability to be absorbed in the bloodstream by paracellular or transcellular routes, or both. The former is the main route for hydrophilic molecules, while the latter can be passive or carrier-mediated. While CDD development is of average difficulty for passive routes, it is harder to predict where other mechanisms, such as metabolism in the gut, are in play, or if it is subject to efflux.

A CDD must remain permeable throughout the GI tract, including the colon, and colonic permeability must be part of a feasibility assessment. Caco-2 cell permeability studies are routinely carried out, and there is some correlation to human colonic permeability.[9] The higher levels of anaerobic bacteria in the colon makes it more difficult to correlate in vitro studies of colonic stability with in vivo behavior.

STABILITY & EXCIPIENT COMPATIBILITY

The stability of a drug decreases when combined with excipients, and continues to decline as drug concentration falls. There is no standard method for testing drug-excipient compatibility, and most methods are poor at predicting the final dosage form's stability. Poor sample uniformity, unrealistic ratios of drug and excipient, the exclusion of key excipients, and the compatibility of testing methods with mixtures of excipients, can all limit their accuracy.

The ICH Q1A guideline lays out the required stability data package for a new drug.[10] Its aim is to provide evidence of how environmental factors, such as temperature, humidity and light affect drug quality, shelf-life, and recommended storage conditions.

Studying stability both in solution and the solid state, and compatibility with excipients, is an important part of the Quality by Design (QbD) process, and forced degradation studies in both solution and solid state are very useful when determining optimal manufacturing and processing conditions. For example, if it degrades at high temperature, hot melt extrusion is not appropriate. Chromatography techniques are the most sensitive for determining stability; PXRD, infra-red and Raman spectroscopy, and nuclear magnetic resonance less so.

When selecting excipients for testing, the first step should be a literature search to identify any known incompatibilities between the drug's functional groups and the excipient. Then, the compatibility of a single excipient is assessed at ratios that simulate finished dosage form. These studies take time – typically the combinations are stored in open bottles at 40°C and 75% relative humidity for 14 to 28 days, with the drug alone as a control, and then high-performance liquid chromatography (HPLC) used to quantify potency and impurities. Any excipients showing any incompatibility can be eliminated. Water may also be added to samples as moisture can trigger degradation.

MODELING DRUG METABOLISM & PHARMACOKINETICS

CDD formulations essentially work by altering drug release from the formulation and therefore the pharmacokinetics. As CDD formulations will have extended-release properties, the drug will be absorbed more slowly, the time to maximum concentration will be longer, and peak plasma concentration will be lower. Yet the area under the curve (AUC) should be the same for both IR and CDD products. Time to reach maximum plasma concentration is important for a CDD dosage form, as if it is reached quickly, this will not provide a successful once- or twice-daily dosing regimen. Similarly, if maximum plasma con-

centration is high, it may indicate that the formulation is inadequate because the drug is being released too rapidly.

The nature of CDD products increases the likelihood of food interactions, making APIs with significant food effects more difficult to formulate. The food effect introduces PK unpredictability, and makes it more difficult to achieve the desired plasma profile. Also, a CDD product that relies on pH for drug release may not perform as planned when co-administered with food, as this increases stomach pH, followed by increased gastric secretion and gastric emptying, which lowers duodenal pH. A "take on an empty stomach" label may be required.

PK modelling tools can be applied to assess the likelihood of CDD being viable by conferring PK/PD advantages. A range of commercial modelling and simulation tools are available to predict plasma profiles based on in vitro dissolution data, dose, and clearance. They can also be used to deconvolute data from PK studies.

The power of PK modelling is greatly influenced by both the amount and quality of data available. Early in the development process for a NME, much of the useful data may not be available, or only exist in preclinical species. Estimates may need to be made, based on similar molecules. When a CDD product is a follow-on from an IR dosage form, these data are likely to be known already. Data important to create accurate PK models largely reflect those discussed earlier and include dose, solubility, permeability, half-life, site of absorption, therapeutic window, and pH sensitivity. Data on food effect, logP, pKa, solubility in fasting and fed state simulated intestinal fluids (FaSSIF and FeSSIF), unbound fraction in human plasma, ratio of blood to plasma, intrinsic clearance, and fraction absorbed are also useful.

CONCLUSION

Ultimately, the successful development of a CDD product relies on a comprehensive preformulation strategy to characterize the molecules. The information gleaned in these studies will inform feasibility assessments, and minimize the risks, costs, and time in developing the product, greatly improving the chances of success.◆

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BIOGRAPHY

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DRUG DEVELOPMENT

Cell & Gene Therapies Calling for Innovation in Drug Development

By: Lev Gerlovin and Pascale Diesel, PharmD

INTRODUCTION

Decades in the making, the promise of cell and gene therapy research is finally poised to deliver results. Products including Kymriah, Yescarta, and Luxturna are now on the market, and many others are in late-stage clinical development. There are now clinical-stage development programs in gene therapy targeting almost 50 different diseases, up from 10 only a few years ago.[1] While US and EU companies (53% and 32%, respectively) are sponsoring most of these programs, others are underway in China and South Korea.[2]

The prospect of a generation of new cell and gene therapies introduced in succession, many of them offering potentially curative efficacy, is obviously good news for many patients, but it also presents many significant considerations for the optimal strategies in drug development. Challenges can include the need for highly specialized expertise, limited production capabilities, small patient populations, and, in some cases, single-dose delivery to patients. Products might also have to be reviewed and approved based on data from small patient populations. Lack of robust and statistically significant data can raise concerns among clinicians, patients, and investors. As progress continues, the need to develop and implement the innovative business models that can address these issues is fast becoming a critical need for industry and for health systems, clinicians, payers, investors, and other stakeholders. The path forward may require untried strategies to help drug developers advance high-risk clinical programs to commercialization.

THE SEARCH FOR EXPERTISE & PRODUCTION CAPACITY

Many companies working to develop new cell and gene therapies face challenges in building teams with the specialized expertise they need and in accessing production capabilities to meet demand at every stage. Unlike development of small molecules, where the path from discovery to clinical development is fairly standardized, the development path and timelines for gene and cell therapies can vary widely. One critical issue is identification of the optimal drug delivery mechanisms. For many advanced therapies, the precise mode of drug delivery cannot be confirmed until late in the development process, making later-stage research much riskier. For gene therapies based on nucleic acids, for example, it is often difficult to determine how to stabilize these molecules long enough for them to take effect. It can also be difficult to confirm whether viral vectors used in cell and gene therapies present a risk of immune response or other unwanted side effects in patients.

New levels of complexity in drug development require highly specialized expertise and technology to support both research and manufacturing. For example, very few biotechnology companies have the in-house skilled professionals and technology to produce their own viral vectors. Among those that do, it is often unclear whether they can expand production to meet global demand for their products. Limited options for third-party production of viral vectors can also mean that many development programs will face significant delays and unpredictable manufacturing costs.




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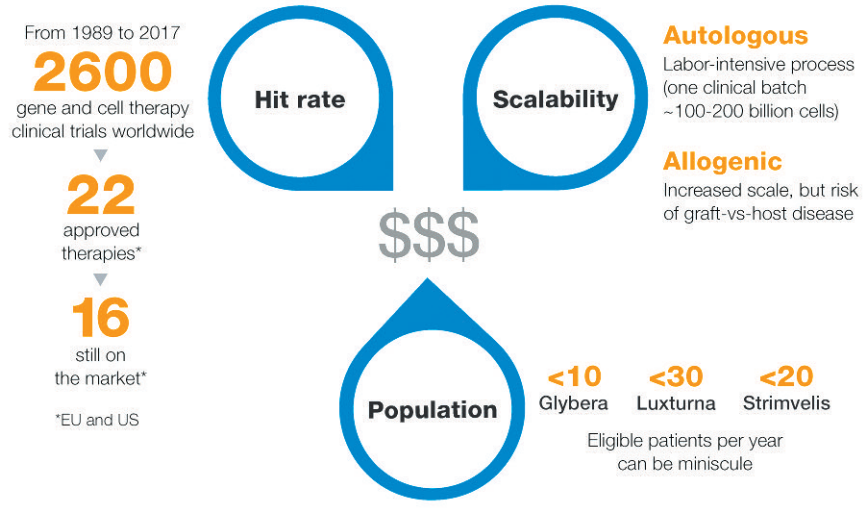
CHALLENGES OF PERSONALIZED MEDICINES

The fact that many cell and gene therapies are personalized medicines that are produced for each patient can also put pressure on costs compared to small molecule drugs. With most small molecules, the cost per unit will decrease as production levels rise, which can play an essential role in commercial planning. But these benefits are often not achievable with personalized medicines. For example, while the emerging generation of CAR T cell therapies shows significant promise in treating a range of cancers, these drugs are developed using a complex process to produce a drug for each patient while also often targeting very small patient populations. Costs associated with commercial production therefore typically cannot achieve significant economies of scale. Additionally, curative therapies administered in a single dose do not allow costs to be recovered based on multiple doses administered over months or years.

Many curative therapies could also face stringent regulatory requirements and substantial costs to monitor and validate efficacy and safety over the long-term. This can require collection and analysis of real-world data from patients during or after a course of treatment. While the FDA recently issued a plan to expedite the review of gene therapies for certain diseases to help support drug innovation, it also requires sponsors to observe subjects for potential treatment-related adverse events for at least 15 years, with a minimum of 5 years of annual examinations.[3,4]

FIGURE 1



Drivers of High-Development Cost

NEW LEVELS OF COMPLEXITY IN CLINICAL RESEARCH

For cell and gene therapies to treat rare diseases, it can be especially difficult to identify appropriate patients for clinical research and connect them with available treatment centers. Small patient populations can also impose limitations on clinical data that, while sufficient to support approval, may affect clinician and patient confidence. When a gene therapy for lipoprotein lipase deficiency was pulled from the market after treating only one patient, the treating physician cited concerns about the clinical data from research based on just 27 patients with no control group. Many other clinicians appeared to be hesitant to prescribe a drug based on results from a trial that was widely viewed to be underpowered.[5,6]

In late 2017, the FDA issued guidance to help address the lack of available patients for research in rare diseases by encouraging extrapolation of data across different populations, increased use of models and simulations, and use of a single control group as the basis for more than one investigational drug.[7] While these modifications could help a greater number of development-stage programs advance to the regulatory finish line, there is a concern that they could also create an over-reliance on computer simulations, potentially even in cases where more traditional or reliable data sources are available, or lead to safety and efficacy results that are less statistically sound than current industry standards.

THE NEED FOR NEW DEVELOPMENT MODELS

Many established and emerging challenges in development of cell and gene therapies are in place even as several therapies are positioned for commercial availability. As a result, many companies are working aggressively to identify the new approaches in clinical research that can effectively support these development programs. One example is the focus on platform diversification. In contrast to single-target small molecules or monoclonal antibodies, many gene and cell therapies

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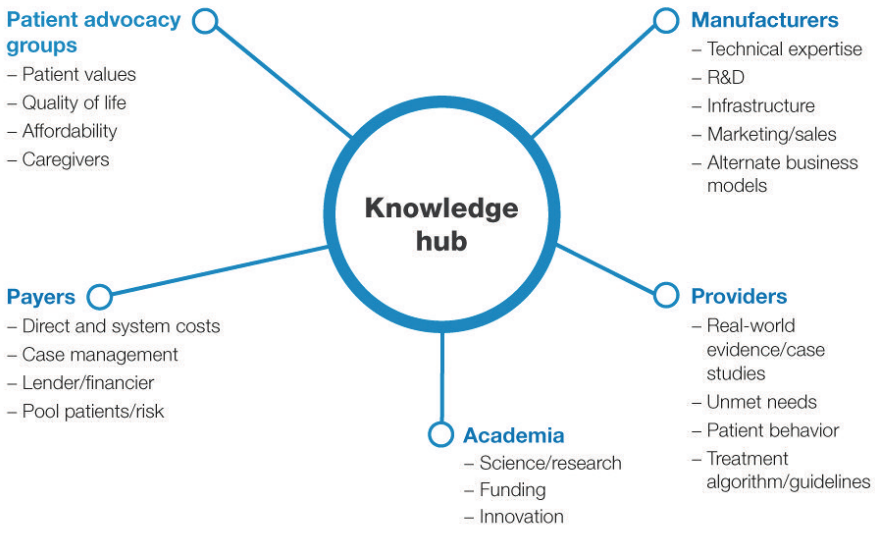
FIGURE 2



Stakeholder Collaboration

have the potential for a diversified development platform with a unifying focus. When Alnylam Pharmaceuticals discontinued its development program for revusiran for the treatment of hereditary ATTR amyloidosis with cardiomyopathy (hATTR-CM), the company was well positioned to adapt the platform to target other diseases, such as hereditary TTR-mediated amyloidosis and acute hepatic porphyria. The ability to pivot and apply one cell or gene therapy development program to different therapeutic areas could present new growth opportunities or mitigate risk for many companies.

To promote knowledge sharing and allow for more rapid technological advances in gene and cell therapy, industry leaders are also now considering new approaches in stakeholder engagement. Some examples include the models used in the Human Genome Project or the International Rare Diseases Research Consortium.[8] Structuring development programs to engage a range of healthcare stakeholders — potentially including manufacturers, academic research centers, payers, providers, charitable organizations, and patient advocacy groups — can help facilitate innovative solutions and help align diverse but similar gene and cell therapy research efforts. These collaborations can lead to new options in raising capital, build stronger awareness among patients and clinicians, facilitate broader sharing of data, accelerate translational research, and support development of essential manufacturing and processing technologies. The involvement of stakeholders spanning different geographies could also strengthen efforts in global access and help companies address post-marketing requirements in patient surveillance.

Broader access to government funding to support high-risk translational research and drug development programs is another potentially effective option. New models might include direct public funding to manufacturers as an avenue for development of gene and cell therapies, as opposed to the use of publicly funded discovery to feed private development of novel therapies. This approach might better reflect the potential global impact of many gene and cell therapies, especially those positioned to deliver curative benefit to patients and health systems.

Manufacturers might also consider expanding academic partnerships and leveraging financing from charitable foundations to pursue development of higher-risk gene and cell therapies. Examples of this strategy are already emerging. Orchard Therapeutics recently launched a transformative gene therapy development program in partnership with a range of research organizations, including UCLA, Boston Children's Hospital, University College London, Great Ormond Street Hospital for Children NHS Foundation Trust, and the University of Manchester. The program will exploit ex-vivo autologous stem cell therapy technology for the potential treatment of a range of primary immune deficiencies, metabolic diseases, and hematological disorders.[9]

As the rate of innovation continues and potentially increases in the years ahead, more established companies may also see benefit in partnering with and nurturing early stage gene and cell therapy assets. For example, a company with a robust portfolio of immunology assets might wish to engage with synergistic discovery-stage platforms to expand their model to include next-generation curative therapies. Celgene's acquisition of Juno Therapeutics and Gilead's acquisition of Kite Pharma are recent examples of larger companies that have expanded their pipelines in this way. In addition to new assets, these alignments can bring established companies different technology platforms that can further expand and accelerate future drug development efforts.

SUMMARY

There is significant evidence to indicate that we are entering a golden age of gene and cell therapy development. While industry works to advance these programs, the debate over new approaches in both structuring and financing clinical research is likely to continue. Solutions might involve strategic partnerships and collaborations among a broader range of stakeholders, but these complex alignments will, of necessity, require new levels of risk- and responsibility-sharing. Efforts to modify clinical and regulatory standards to address the unique factors associated with development of cell and gene therapies can also play an important role. If successful, it is possible that many of the promising development programs currently underway, and more to be initiated, will reach commercialization and bring advanced therapeutic options to thousands of patients who need them.

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BIOGRAPHY

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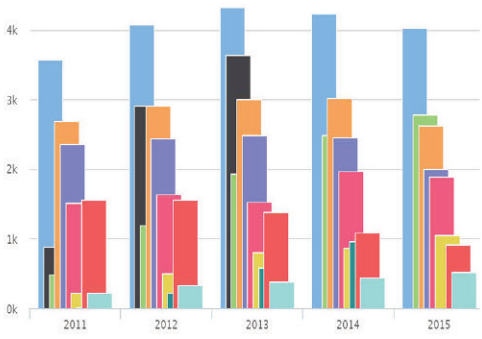

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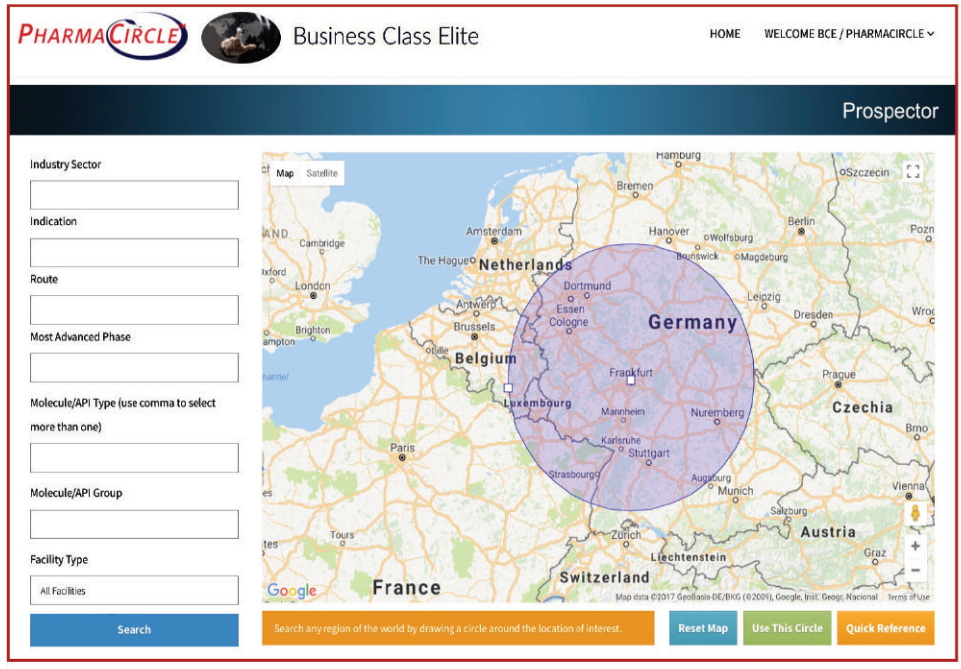

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LIPID-BASED DELIVERY

Advanced Lipid-Based Drug Delivery Systems: Solid Lipid Nanoparticles & Nanostructured Lipid Carriers

By: John K. Tillotson, RPh, PhD

INTRODUCTION

The utility of functional lipids in enhancing the dissolution and bioavailability of poorly water-soluble actives is well known. The use of lipid-based drug delivery systems in pharmaceutical product development is increasing due to the versatility of functional lipid excipients and the compatibility of these excipients with liquid, semi-solid, and solid pharmaceutical dosage forms.[1] In addition to solubility and bioavailability enhancement, functional lipids have been employed in a multitude of broad-based excipient applications, including matrix and encapsulated sustained release, tablet lubrication, tablet dry binding, and as pharmaceutical unit operation processing aids.[2-5] Although the applications of functional lipids as excipients and drug delivery systems for the pharmaceutical industry has been understood for quite some time, novel features of functional lipids continue to be discovered and employed in ever-emerging drug delivery systems. Two examples of innovative lipid-based nanoparticle drug delivery technologies are solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). SLN and NLC formulations maintain the enhanced solubility benefits of traditional liquid colloidal carrier drug delivery systems, but provide several additional benefits, such as increased chemical stability for the Active Pharmaceutical Ingredient (API), potential for sustained release, targeted delivery, and lymphatic delivery, which allows for the avoidance of first-pass metabolism as well as lymphatic targeting.[6]

SOLID LIPID NANOPARTICLES (SLNS)

SLNs are solid particles of functional lipids typically formulated with fatty acids, monoglycerides, diglycerides, and triglycerides as carrier materials. Additionally, surfactants, such as macrogolglycerides, polaxamers, polysorbates, or ethoxylated castor oils, can be employed as emulsifying agents in the formulations. SLNs are typically formulated with a single high-purity lipid as the primary carrier material. SLNs can be formulated by numerous technologies, including high-shear homogenization (including both hot and cold methodologies), ultrasonication, solvent emulsification/evaporation, micro-emulsion precipitation, supercritical fluid processing, spray-drying, and the double emulsion method.[7] There are numerous advantages to employing SLN drug delivery systems, including controlled release, targeted release, increased stability, increased carrier capacity, ability to carry both hydrophobic and hydrophilic actives, reduced systemic toxicity, non-solvent-based manufacturing methods, ease of manufacturability, lower cost formulation materials, and ease of regulatory approval.[8]

NANOSTRUCTURED LIPID CARRIERS (NLCS)

NLCs are a formulation extension of SLNs in which the NLC lipid particle carrier matrix is composed of multiple lipids. The most common type of NLC matrix is a mixture of a solid lipid with chemically different liquid lipids. The combination of a solid lipid

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with liquid lipid(s) results in areas of carrier matrix inconsistency, which provides for a series of advantages for NLCs over typical single matrix material SLNs.[9] NLCs provide for higher active loading than SLNs, due to the presence of liquid carrier materials, which have a higher solvent capacity in the finished NLC. This increased solvent capacity is due to additional active incorporation space created through the generation of crystal imperfections due to the presence of liquid lipid, in the highly ordered crystal structure of the solid lipid material.[10] NLCs provide for a biphasic drug-release pattern, which results from a rapid release of active from the liquid phase of the NLC, with a comparatively slower release of the API from the solid lipid portion of the NLC. This release pattern can be modulated by adjusting the proportions of the liquid and solid lipid carriers within the NLC.[11] NLCs also provide for long- term active stability during storage, as the presence of liquid lipid in the carrier particle reduces the amount of active crystallization that will occur.[12] NLC formulations require less surfactant than liquid emulsion systems, allowing for greater active loading.[13]

NANOLIPID MANUFACTURING & CHARACTERIZATION

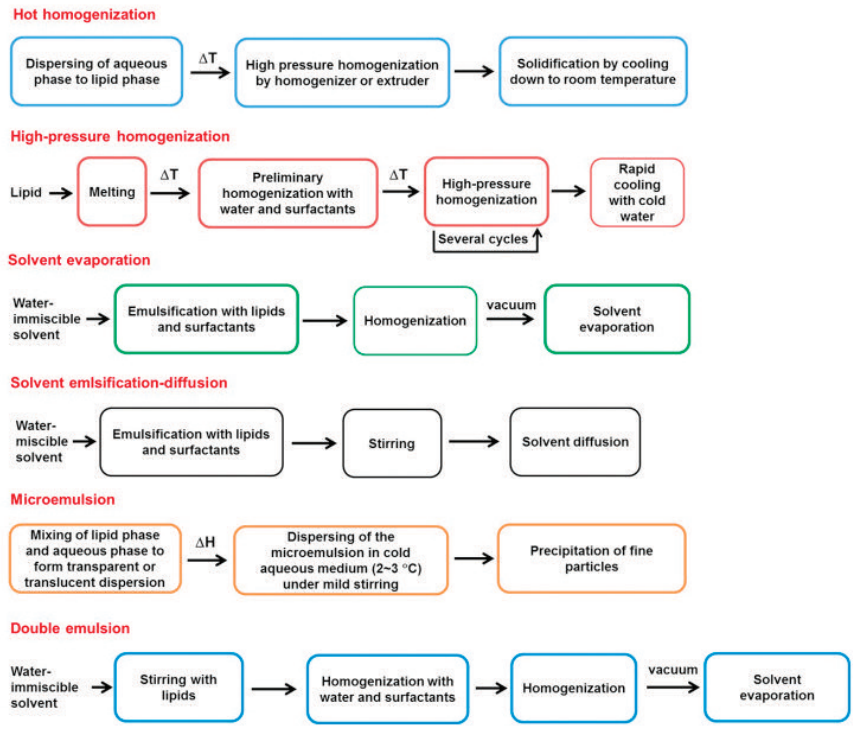
Hot Homogenization

Hot homogenization is a manufacturing technique carried out at temperatures above the melt point of the lipid(s). A pre-emulsion of the active- loaded lipid melt and an aqueous emulsifier is generated by high-shear mixing. Typically, more than one pass is required through the high-shear homogenizer. It should be noted that increasing homogenization leads to an increase in nanolipid particle size due to particle coalescence. Typically, lower nanolipid particle sizes are obtained at higher processing temperatures due to reduced viscosity of the lipid phase.[14]

Cold Homogenization

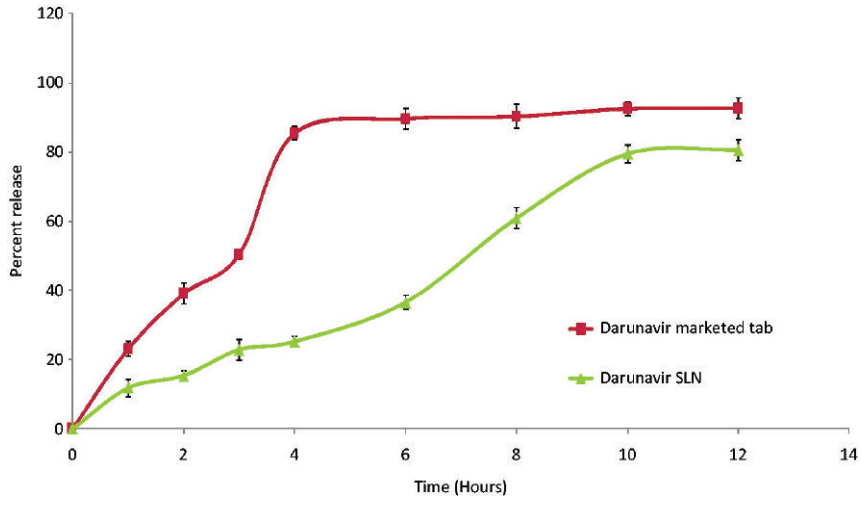
Cold homogenization is carried out on solid lipids. Adequate temperature control has to be in place during this process to ensure the lipid does not melt. Cold homogenization can solve issues faced dur-

FIGURE 1



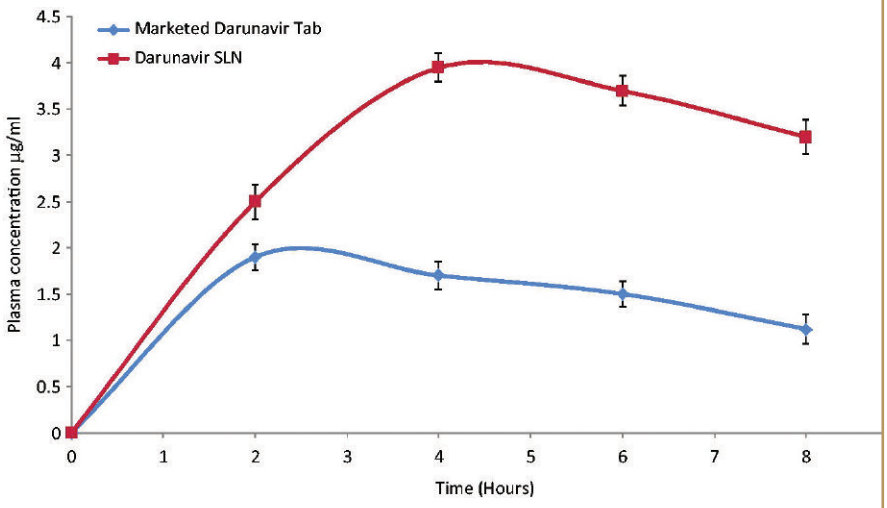
Some methods' unit operations for preparing lipid nanoparticles[7]

FIGURE 2



***In vitro* release profile of darunavir-SLN in simulated gastric condition (n=6, mean (+/-) SD)[30]**

FIGURE 3



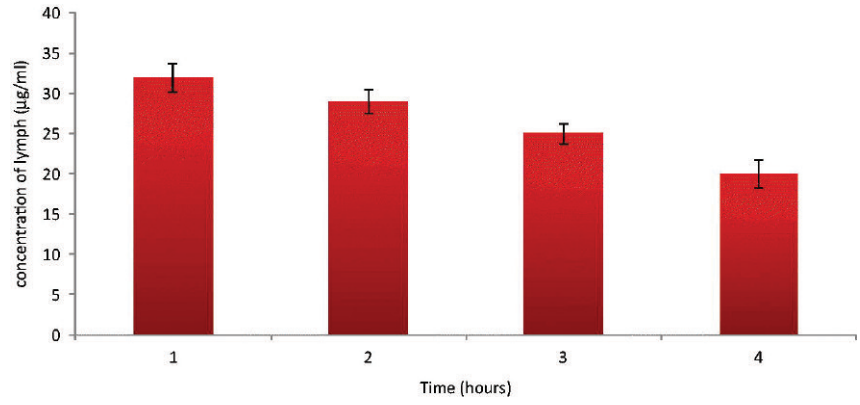
In vivo plasma concentrations profile of marketed tablet and darunavir-SLN in rats (n=6, (+/-) SD)[30]

ing hot homogenization, such as heat degradation of the active, partitioning and loss of the active to the aqueous phase, and unwanted polymorphic transitions. Active is dispersed in the lipid melt, which is cooled rapidly. The cooled melt is size reduced by employing a milling operation. Subsequently, the milled particles are dispersed in a chilled emulsifier solution. This dispersion is subjected to high-pressure homogenization at or below room temperature, to generate the nanoparticles. Cold homogenization typically results in larger particles and broader particle size distributions than hot homogenization.[15]

Ultrasonication/High-Shear Homegenization

In this method, lipid nanoparticles are generated by high-speed stirring or sonification. This is a method that can generate lipid nanoparticles on lab-scale equipment that is readily available. This dispersion technique does not require solvents or large amounts of surfactant. The melted drug and lipid mixture is added and dispersed in aqueous surfactant and placed under high-shear homogenization or ultrasonification. The emulsion is then cooled to room temperature to form the lipid nanoparticles.[16]

FIGURE 4



Concentration of darunavir in the lymphatic fluids of rats (n=6, (+/-) SD[30]

Solvent Emulsification/Evaporation

In this method, lipid nanoparticles are prepared by precipitating oil/water emulsions.[17] The lipophilic material is dissolved in a water-immiscible organic solvent that is emulsified in an aqueous phase. Upon evaporation of the solvent, a nanoparticle lipid dispersion is formed by precipitation of the lipid in the aqueous phase.

Micro-Emulsion Based on SLN Preparations

Manufacturing lipid nanoparticles by this method involves dispersing hot microemulsions in cold water under stirring. The emulsions typically consist of a low-melting fatty acid, an emulsifier, co-emulsifiers, and water. The droplet structure is generated by the emulsion globule size, and no additional energy needs to be added to the system to generate submicron particle sizes.[18]

Supercritical Fluid

In this method, solutions of supercritical CO2, active, and lipid are rapidly expanded into an aqueous phase containing surfactant and then sonicated and lyophilized to obtain the lipid nanoparticles.[19] A major advantage of this system is that no organic solvents are required.[20]

Spray Drying

Manufacturing lipid nanoparticles by spray drying is a one-step process that converts a liquid feed of organic solvent solution, in which the lipid-active mixture is dissolved, which is atomized by spraying. This spray atomization contacts a hot gas that results in the evaporation of the solvent, forming dried lipid particles. The dried particles are separated from the gas by a cyclone, an electrostatic precipitator, or bag filter.[21]

Double Emulsion

Lipid nanoparticles are obtained from water/oil/water multiple emulsions employing solvent-in-water emulsion-diffusion techniques. Typically, a hydrophilic active can be dissolved in the aqueous inner phase and consequently carried in the interior of the lipid nanoparticle. The lipid nanoparticle is generated by aqueous dilution of the water/oil/water emulsion.[22] This manufacturing technique can readily incorporate both hydrophilic and hydrophobic actives.

Common characteristics evaluated for lipid nanoparticles are particle size and particle size distribution by photon correlation spectroscopy and laser diffraction. Also: zeta potential by zetameter to predict particle agglomeration potential, electron microscopy to determine particle shape, nuclear magnetic resonance to determine particle size and qualitative structure of the particles, x-ray diffraction to determine the degree of crystallinity, and differential scanning calorimetry to determine the nature and speciation of crystallinity within lipid nanoparticles.[23,24]

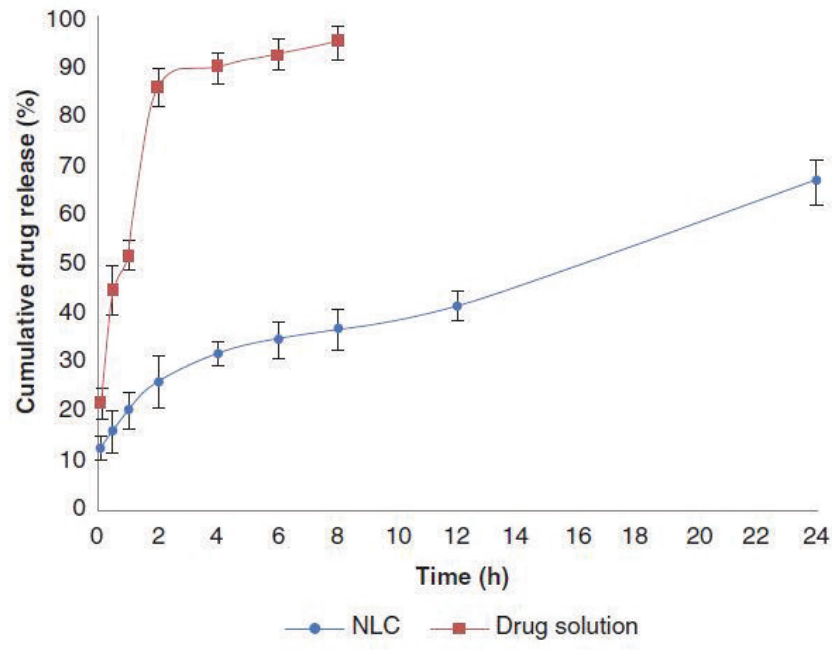
DRUG DELIVERY ADVANCEMENTS WITH NANOLIPIDS

Two major drug delivery advancements of SLNs and NLCs are the lymphatic uptake of these materials, as well as the ability of these materials to transport actives across the blood brain barrier (BBB).

The lymphatic system is part of the circulatory system, which is composed of an intricate network of conduits that carry lymph. The primary function of the system is to carry interstitial fluid accumulation back to the circulatory system and to transport immune cells to the lymph nodes.[25,26] Per-oral actives incorporated in SLNs and NLCs reach the systemic blood circulation through the intestinal lymphatic system, as opposed to entering the systemic blood circulation through the portal blood. This pathway allows for a reduction in first-pass metabolism and an increased overall bioavailability for the active.[27] In addition to intestinal lymphatic uptake, SLNs and NLCs can be delivered by means of other lymphatic pathways, including subcutaneous and pulmonary lymphatic uptake.

Advantages of subcutaneous lymphatic uptake of actives are active accumulation at the site of administration, low clearance, avoidance of first-pass metabolism, sustained release, and increased absorption. Advantages of the pulmonary lymphatic uptake include avoidance of first-pass metabolism, reduced systemic toxicity, reduction in the need for continuous dosing, increased local concentration of active, and direct delivery of the active into less-accessible parts of the lung.[28]

FIGURE 5

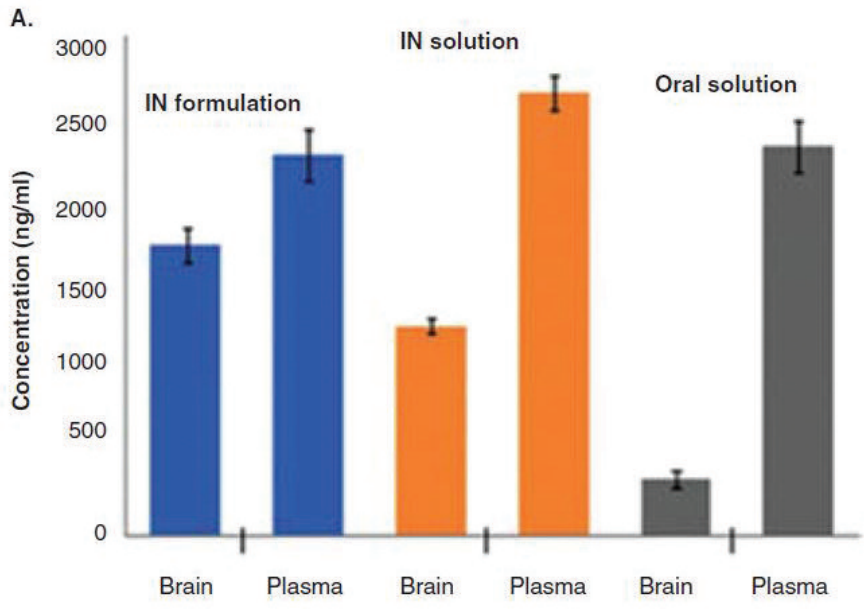


In vitro release of LMT from LMT-NLCs and LMT Solution[34]

Darunavir is effective against wild-type and PI-resistant HIV, and has a very low oral bioavailability of 37%. It is formulated with ritonavir to increase its bioavailability to 82%. This low bioavailability is common for oral anti-retrovirals, which typically have low-aqueous solubility, high CYP-mediated metabolism, and are often a substrate for P-glycoprotein efflux.[29]

In order to study the effect of lipid nanoparticle drug delivery on the bioavailability of darunavir, SLNs composed of darunavir, glyceryl monostearate, glyceryl caprylate, Span 80, and Tween 80 were prepared by high-pressure homogenization and subsequent lyophilization. The darunavir SLNs were evaluated for lymphatic uptake, dissolution, and bioavailability. The in vivo studies were conducted in male Wistar rats. It was observed that the in vitro dissolution of darunavir from SLN was slower and less extensive than the dissolution of darunavir from marketed tablets (Figure 1); in contrast, the bioavailability of darunavir from SLN was signifi-

FIGURE 6



Concentration of LMT in LMT-NLCs, LMT intranasal solution, and LMT oral solution[34]

cantly higher than the bioavailability from the marketed tablets (Figure 2). Additionally, lymphatic uptake evaluation indicated that the SLN exhibited significant lymphatic absorption of darunavir (Figure 3).[30]

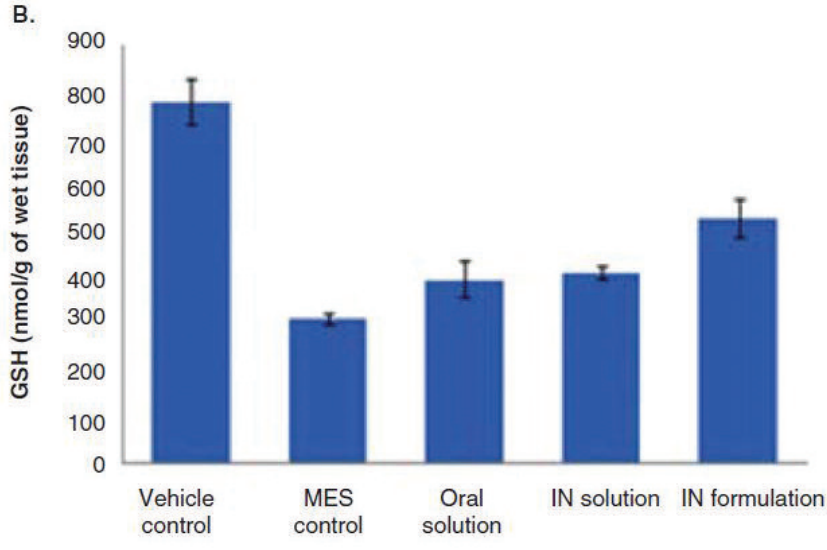
These results demonstrate the efficacy of darunavir SLNs with regard to both uptake by the lymphatic system and overall increase in bioavailability due to lymphatic absorption of the formulation (Figure 4). These points are further enforced given that the in vitro release of darunavir SLNs was slower and less extensive than marketed tablets, yet the bioavailability was much greater.

The BBB is a group of astrocytes, neurons, and endothelial cells that restrict passage of numerous biological or chemical entities to the brain tissue. It provides significant protection to the brain, but this protection inhibits the delivery of many actives to the brain, and therefore, the BBB represents a significant challenge to drug delivery.[31] The most formidable obstacles that impede drug delivery to the brain are the largely impermeable endothelial cells and tight junctions, P-glycoprotein efflux, and enzymatic activity. Both SLNs and NLCs exhibit bioacceptable and biocompatible characteristics compared with polymeric nanoparticles, and they are more readily able to traverse the BBB due to their lipidic nature.[32]

Lamotrigine (LMT) is a broad spectrum efficacy antiepileptic active. Over-expression of P-glycoprotein in the BBB reduces the passage of LMT across the BBB.33 Due to the limited passage of LMT into the brain, relatively high doses are required to reach therapeutic concentrations. These high doses lead to high plasma concentrations of LMT, which can lead to systemic side effects.

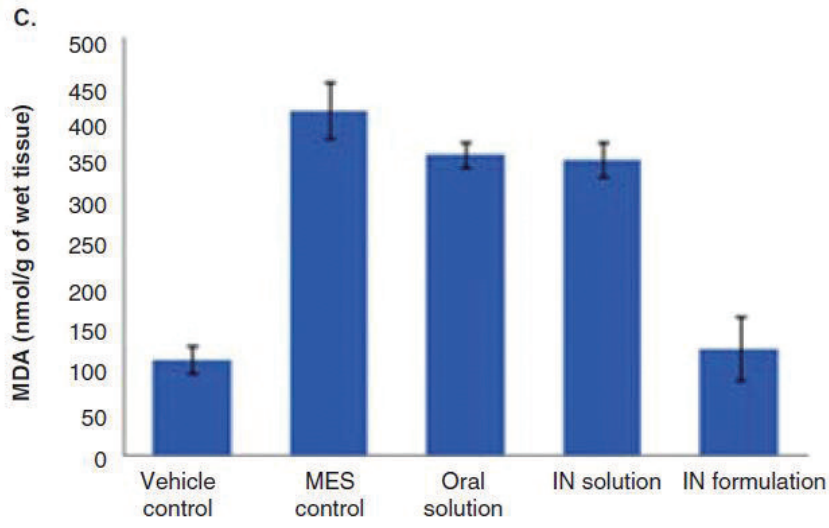
In order to evaluate the effect of NLC on the bioavailability of Lamotrigine, LMT containing NLCs were formulated by solvent evaporation method. The NLC was composed of glycerol monostearate (GMS) as a solid lipid and oleic acid (OA) as a liquid lipid. The GMS, OA, and LMT were dissolved in a mixture of ethanol and acetone (1:1). The solvents were evaporated off with subsequent centrifugation to obtain the final active carrying NLC. Intranasal LMT-NLCs, intranasal LMT solution, and oral LMT solution were evaluated for plasma and brain concentration of LMT. The LMT-NLC and LMT solution were evaluated for in vitro LMT release.[34] Additionally, malondialdehyde (MDA) levels and glutathione (GSH) levels were measured to gauge the maximal electric shock (MES)

FIGURE 7



GSH levels before and after MES induction[34]

FIGURE 8



MDA levels before and after MES induction[34]

seizure mitigation levels of LMT administered in each respective formulation, as typically MDA levels increase and glutathione levels decrease after MES induction.[35] It was observed that the in vitro release of LMT from NLCs was slower and less extensive than the release of LMT from solution (Figure 5). Plasma concentration for LMT-NLCs was lower than plasma concentration for intranasal solution of LMT and roughly equivalent to the plasma concentration of the oral solution of LMT; however, brain tissue concentration was significantly higher for LMT-NLCs than either intranasal solutions or oral solutions of LMT (Figure 6). GSH levels after MES induction were highest in the LMT-NLC formulation, while MDA levels after MES induction were the lowest in the LMT-NLC formulation (Figures 7 & 8).

These results demonstrate the efficacy of LMT-NLCs in enhancing the brain concentration of LMT as compared to intranasal and oral solutions of LMT. The results are more impressive in light of the reduced *in vitro* dissolution observed for LMT-NLCs, indicating that lipid-based nanoparticles can produce active bioavailability, which is not directly predictable by *in vitro* dissolution testing.

SUMMARY

Functional lipids have long been employed effectively in pharmaceutical formulations as excipients, solubility enhancers, and processing aids. More recent applications employing functional lipids are focused on targeted drug delivery and overcoming complicated absorption issues to increase bioavailability of actives as well as target actives to specific tissue locations. SLNs and NLCs are effective, easily manufactured drug delivery technologies that allow for a multitude of benefits, including increased active bioavailability, decrease active metabolism and degradation, lymphatic transport of actives, transport of actives across the BBB, extended and biphasic active release, multiple routes of administration, and tissue-targeted active delivery. Increased research and development of these drug delivery platforms will continue to advance therapeutic efficacy and safety for emerging difficult-to-deliver actives.◆

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BIOGRAPHY

Dr. John K. Tillotson research areas include functional lipids, SEDDS development, and direct-compression tableting. He joined ABITEC Corporation in 2015, and currently serves as the Pharmaceutical Technical Business Director for the Americas, responsible for business development and product technical support in the US, Canada, and Latin America. He has extensive experience in the development of solid oral dosage forms, including the development of multiple direct-compression, drug delivery systems, and formulations. He earned his BS in Pharmacy (Ferris State University, MI) and his PhD in Industrial Pharmacy (University of Cincinnati, OH). He can be reached at (614) 429-6464 or jtillotson@abiteccorp.com.

Drug Development
EXECUTIVE

Taras Seniuch

Director, Business Development

SHL Group

SHL GROUP

SHL Group: Expansion Driven by Our Partners

SHL Group's contract manufacturing services (CMO) is the latest edition to the vast and vertically integrated network of SHL, adding final assembly, labeling, and packaging services for SHL's designed devices. For SHL's partners, this translates into a full turnkey solution, from device design and development to clinical and commercial assembly, labeling, and packaging, which reduces timelines to clinic, market, and most importantly, to those patients in need. *Drug Development & Delivery* recently interviewed Taras Seniuch, Director of Business Development at SHL's contract manufacturing organization, SHL Pharma, to learn more about this unique service offering for their partners.

Q: SHL Group has been a leader in the auto injector industry since the early 90s. Why did SHL Group decide to add contract manufacturing services and what determined the service offerings?

A: SHL's contract manufacturing services opened its doors in 2011 to address the evolving business needs of the pharma/biotech industry. As devices vary in shapes, sizes, and industrial designs, our partners require unique manufacturing capabilities. Therefore, SHL took the opportunity to add value to our partners by building an infrastructure that meets these unique requirements while ensuring maximum flexibility across the different device designs. This self-invested infrastructure also minimizes or even eliminates any capital expenses required by our partners.

Pharmaceutical and biotechnology companies have a difficult decision to make during the device development process: invest in an internal infrastructure to support the specialized manufacturing processes of device assembly or leverage existing expertise and outsource these activities. This is where SHL can make a difference. By

"Our experienced team members have custom-built the manufacturing facilities for maximum flexibility to accommodate multiple high-quality operations and processes. This flexibility allows SHL to manage all programs from lower clinical volume to higher commercial volume. Also, for those companies that choose to build internal infrastructure, our services can offer these flexible operations for risk mitigation and redundancy to ensure business continuity for our partners."

offering design and development of the devices through to assembly, labeling, and packaging, SHL can now provide a comprehensive service offering for our partners. As industry continues to evolve, SHL will also continue to expand its offerings. One most recent example is the significant number of combination product stability studies added over the past 2 years. Our contract manufacturing facilities have also self-invested in an extensive number of stability chambers to meet the needs of our partners in managing these complex, regulatory mandated studies.

Q: How does SHL's vertical integration affect the timeline for your partners and ultimately the patients?

A: Vertical integration is the backbone of SHL's business model, which ranges from device design, tooling fabrication, molding, and now contract manufacturing. This vertical integration provides SHL with the opportunity to minimize or eliminate the need for our partners to further outsource activities during development through to commercialization of a finished product. SHL can offer parallel workstreams during development of the device by also identifying the appropriate equipment early in the design phase, utilizing our internal automation network when needed. These parallel activities inherently reduce timelines and accelerate the delivery of our partners' medicines to the clinic, and/or market for those patients in need.

Q: Can you tell me about the in-house expertise at SHL's CMO services and the flexibility you can offer to your partners?

A: SHL's CMO services employ highly skilled staff members with extensive pharmaceutical and biotech industry experience. For our partners, SHL is a device partner that understands the complex needs of drug product clinical and commercial preparation and timelines. Understanding the key differences between drug and device development requirements enables SHL to bridge the two workstreams to create a seamless transition into a combination product.

Our experienced team members have custom-built the manufacturing facilities for maximum flexibility to accommodate multiple high-quality operations and processes. This flexibility allows SHL to manage all programs from lower clinical volume to higher commercial volume. Also, for those companies that choose to build internal infrastructure, our services can offer these flexible operations for risk mitigation and redundancy to ensure business continuity for our partners.

Q: Your on-site Process Development group offers several services that partners have had to outsource in the past. Can you tell us about this team and their services?

A: Process Development was identified early on as a critical addition to the contract manufacturing operation. The Process Development team consists of four teams: Manufacturing

Sciences, Analytical Sciences, Statistics, and Project Management.

Manufacturing Sciences is responsible for equipment commissioning and process design. This group collaborates with SHL engineering, design, and automation teams to design high-quality manufacturing processes and control strategies. Analytical Sciences is responsible for test method design, development, and validation. This group also provides services such as syringe characterization, feasibility testing, transportation studies, and stability studies, which eliminates the need for our partners to manage multiple suppliers. Our Statistics team then assures optimal control strategies are in place, maximizing output of our processes and minimizing waste. Lastly, Project Management leads the design and tech transfer activities, which establishes the full tech transfer plan and monitors the completion of milestones, thus guiding our partners throughout the process to ensure a seamless transition from development into commercialization.

Q: When do your partners need to determine their final assembly, labeling, and packaging strategy?

A: Typically, when a pharma/biotech company is developing an auto injector, a decision on the assembly, labeling and packaging equipment, and processes follows final device design verification and product validation. Unfortunately, this can then put these activities on the critical path for regulatory submission, which could increase the product time-to-market.

At SHL, we collaborate with our partners at the early design phase of the auto injector to understand the critical attributes of such a device and the impact that it may have on the existing assembly and secondary packaging infrastructure. In some cases, additional infrastructure is needed (i.e.,assembly equipment, change parts, etc.). Hence, SHL can work in parallel with our in-house automation team to develop solutions for such requirements. Initiating these activities at an early stage will ensure that equipment and/or processes are in place to accommodate a timely tech transfer from development into clinical or commercial readiness.

Q: Tech transfer is challenging for many companies when outsourcing with a CMO. Can you tell our readers about your tech transfer process and how your team manages these processes?

A: SHL's CMO services have a robust tech transfer process enabled and facilitated by a cross-functional team that includes Process Development, Quality, Regulatory, and Operations. It is critical to ensure effective and efficient knowledge transfer from the development team into process development and further into day-to-day operations. SHL's tech transfer process contains a robust set of procedures, including deliverables, milestones, risk analysis and evaluation, process characterization, and validation plans, to name a few. These documents outline all requirements for the design and technology transfer of a device design to the contract manufacturing site of SHL.

Q: Given SHL's extensive experience with combination products, do you provide regulatory support to your partners?

A: As mentioned, SHL has extensive experience in the pharma/biotech industry. While working in the industry, many of our leadership team members received extensive training in authoring or reviewing regulatory submissions across multiple global jurisdictions.

As a CMO, we have also seen many different regulatory submissions across our different partners and programs. SHL can leverage this wide-ranging experience to establish the most robust set of regulatory information relevant to SHL's business of device design and development, assembly, labeling, and packaging. Ultimately, the goal is to provide a robust set of information that will minimize or even eliminate questions from the regulatory agencies, whether it relates to the submission itself or an on-site audit or inspection at SHL. ◆

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A Map to Biologics

By: William Boomershine, PhD

INTRODUCTION

Biopharmaceutical products represent up to 20% of the total pharmaceutical market and are growing at a rate of nearly 8% annually. To keep up with this impressive growth rate, many CDMOs are making strategic investments in equipment and expertise to support analytical development and structural characterization of biopharmaceuticals in more economical and efficient ways.[1] Unlike small molecule active pharmaceutical ingredients that exist as a single chemical entity, biologics nearly always exist as a mixture of molecules. Different molecules can arise from numerous sources including N-terminal variants, post-translation modifications (PTMs), glycoforms, and degradation products. Due to the potentially high amount of heterogeneity in the biologic, it is critical to demonstrate control over the drug substance (DS) manufacturing process from fermentation to purification and protein re-folding. Characterization of the various molecules is a first step in demonstrating process control. High-resolution mass spectrometry is a key component to the characterization of novel biologics and biosimilars.

INTACT MASS ANALYSIS

Intact mass analysis of biologics is an important tool for verifying that the purified drug substance was successfully expressed and purified. Intact mass analysis of monoclonal antibodies (mAbs) verify that the molecule has been assembled correctly and all expected post-translation modifications are present. While this provides a high-level confirmation of protein molecular weight, it cannot provide the location of any modifications that might present. A different tool is required to help elucidate the location(s) of modifications. This site-specific information is required to demonstrate that the entire process from protein expression and purification to drug product set on stability is under control. One such tool is peptide mapping with high-resolution mass spectrometry.

PEPTIDE MAPPING

Methods that target specific impurities that are known to reduce the activity, binding, or efficacy of the biologics are required to fully de-risk the impact of potential impurities generated during the manufacture of biologics. Peptide mapping is one technique that can provide the necessary resolution to target the specific impurities where traditional chromatographic or electrophoretic techniques prove to be difficult. Coupled with high-resolution mass spectrometry, peptide mapping can provide acceptable specificity, repeatability, and accuracy to quantitate known degrada-

tion peptides within the digested sample. Peptide mapping generally consists of the following steps:

- Denaturation of the target protein
- Reduction of disulfide bonds
- Alkylation of the free thiol groups within the side chains of cysteine residues to ensure disulfide bonds are not reformed
- Buffer exchange into digestion buffer
- Digestion with an appropriate endoproteinase
- Analysis by HPLC/UV/MS or MS/MS

Glycoproteins can be deglycosylated prior to performing peptide mapping to reduce the heterogeneity introduced by various glycoforms. Identification of peptides generated during the peptide mapping procedure can be performed using advanced mass spectrometry software tools based on intact mass and MS/MS fragmentation patterns of the peptides.

The use of peptide mapping to characterize biologics has the advantage that the protein is divided into a large number of smaller peptides. The generated peptides can then be chromatographically separated using HPLC or UPLC technology. The intact masses of the peptides can provide information regarding the type of modification that was made. MS/MS sequencing of the peptides can provide the exact amino acid residue containing the modification. This level of resolution at the individual amino acid level is simply not possible with mass spectrometric analysis of intact proteins or mAbs. Examples of the use of peptide mapping to characterize and quantitate specific post-translation modifications or degradation products are provided.

N-TERMINAL VARIANTS

Quantitation of N-terminal variants from bacterial (formyl-Met, Met, or another amino acid) expression systems, eukaryotic (ie, pyro-Glu, Gln) expression systems, or synthetic peptides (acetylation) are possible using the correctly chosen endoproteinase for digestion. Chromatographic separation of peptides that differ by a single amino acid is generally easier than separating intact proteins that only differ by a single amino acid. Given that this type of peptide mapping is targeting just one peptide from the entire protein, the chromatography can be optimized for the N-terminal peptide and its variants rather than optimized to separate all peptides generated from the peptide map. Due to the relatively large mass differences between the different N-terminal variants, quantitation can be performed using multiple reaction monitoring (MRM) detection on triple-quadrupole mass spectrometers, allowing for maximum specificity and adequate sensitivity to observe even trace levels of minor components.

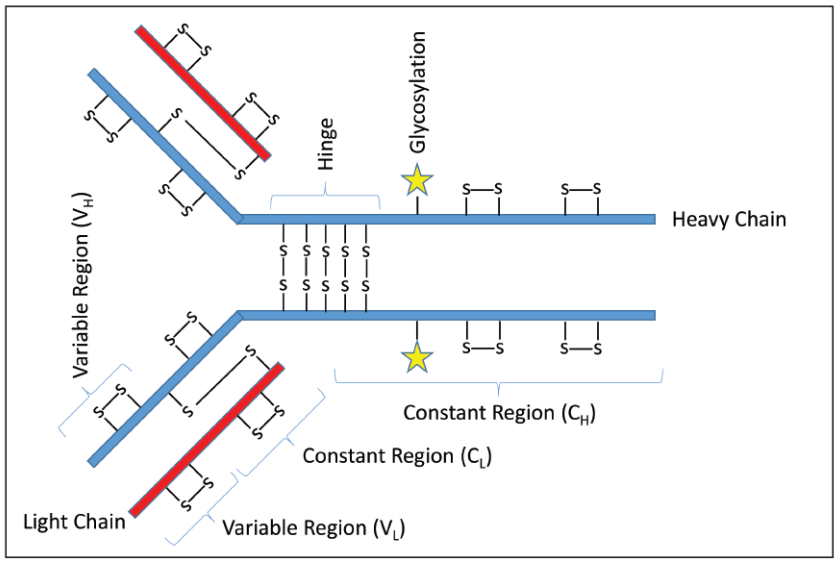
DEGRADATION PRODUCTS

Quantitation of degradation products generated during protein purification and re-folding steps or during stability assessment of the drug product, such as methionine oxidation or deamidation of asparagine and glutamine residues, can be more challenging given the potentially larger number of degradation locations and their distribution in the protein. Oxidation of methionine residues is one of the most common degradation products found in biologics. Methionine can be oxidized through oxygen dissolved in the buffer or through the formation of hydroxyl radicals upon exposure to UV light. Deamidation of asparagine residues can occur during protein purification and re-folding steps or during the shelf-life of the drug product. Deamidation occurs faster at higher pH and higher temperature and is more likely for asparagine than it is for glutamine. The amino acid following the asparagine or glutamine residue can also affect the rate of deamidation.

Selection of the proper endoproteinase is a key step in developing a method that can quantitate such a large number of potential impurities. In silico protein digestions should be performed with the goal of generating the largest number of peptides that contain only a single potential modification site. In the situation where a single endoproteinase will not generate an acceptable peptide map for the characterization and quantitation of degradation products, sequential or simultaneous digestions with multiple endoproteinases may need to be performed. Given the small mass difference between asparagine and aspartate residues that result from deamidation, quantitation is best done using high-resolution mass spectrometry. Scanning a mass range can allow for detection of multiple degradation products with a single injection using extracted ion chromatograms (XICs) of the native and modified peptides.

While mass spectrometric analysis of intact proteins can generally detect oxidation of methionine residues, it cannot determine its location within the protein. Further, mass spectrometric analysis of intact proteins, in general, cannot determine if a single deamidation has occurred due to the small mass change (+1 Da) in relation to the error in the deconvolution calculation used to convert the charge state

FIGURE 1



Monoclonal antibody showing intra-molecular and inter-molecular disulfide bonds and glycosylation sites.

envelope into the intact, deconvoluted mass. Peptide mapping with high-resolution mass spectrometry can provide both the peptide-specific location of the modification and the ability to observe small mass changes.

DISULFIDE BOND FORMATION

Correct disulfide bond formation can be critical to protein folding, enzyme activity, and proper binding in biologics. Formation of incorrect intra-molecular disulfide bonds can lead to mis-folded proteins and reduced activity or binding. Formation of incorrect inter-molecular disulfide bonds can lead to protein aggregation, which is of great immunogenicity concern to patients. A schematic of a typical mAb showing intra-molecular and inter-molecular disulfide bonds is provided in Figure 1.

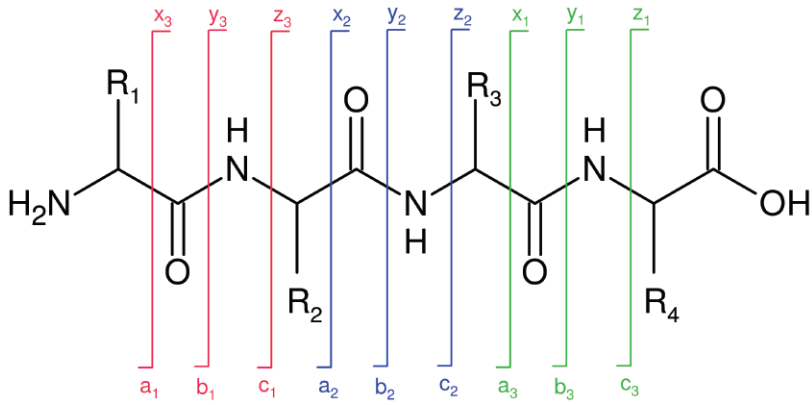
During peptide mapping, disulfide bonds are typically reduced (using DTT, TCEP, or ß-ME) then alkylated (using Iodoacetamide or Iodoacetic acid) to prevent reformation of disulfide bonds during subsequent steps. Therefore, information regarding which disulfide bonds were present in the protein prior to peptide mapping is lost. However, non-reducing peptide maps can be performed allowing information regarding which disulfide bonds are present to be retained. In the non-reducing peptide map, the protein is denatured and alkylated without first reducing the disulfide bonds (or denaturated without alkylation), which maintains the already intact disulfide bonds. The non-reducing peptide map should be performed in parallel with the traditional reducing peptide map and analyzed using the same HPLC or UPLC method with MS detection. Any peptide that is not involved in a disulfide bond will have the same retention time and observed mass in the non-reduced peptide map as it does in the reduced peptide map. Peptides that are involved in disulfide bonds will have peaks with different retention times in the non-reduced peptide map from the retention times of the corresponding individual peptide peaks in the reduced peptide map. Comparison of the chromatograms between the reduced and non-reduced peptide maps should quickly reveal which peaks were involved in the disulfide bonds. A high-resolution mass spectrometer can then determine which peptides are linked through disulfide bonds using intact mass.

CONFIRMATION OF PROTEIN SEQUENCE BY MS/MS

In order to gain amino acid residue specific information from peptide mapping, sequencing of peptides by tandem mass spectrometry (MS/MS) is required. Peptides are sequenced using collision-induced dissociation (CID) to generate product ions from a single or set of precursor ions. Peptides will fragment in predictable ways along the peptide backbone to yield a series of product ions (Figure 2). The a, b, and c-series product ions provide information toward the N-terminal side of the peptide while the x, y, z-series ions provide information towards the C-terminal side of the peptide. The b-series and y-series ions can be used to sequence the peptide, confirming the presence of each amino acid.

For ideal peptide sequencing by MS/MS, peptides should be 5-20 amino acids in length. Peptides that are shorter than five amino acids are generally not retained on reversed-phase HPLC columns while peptides longer than 20 amino acids may not have full sequence coverage. In order to observe most of the b-series and y-series ions, it is helpful to have a positive charge on the N-terminus and C-terminus of the peptide. The amino group provides the charge at the N-terminus while having an Arginine or Lysine residue can provide the charge at the C-terminus. Therefore, trypsin or endoproteinase Lys-C are generally the most useful enzymes when MS/MS

FIGURE 2



Example product ions from MS/MS sequencing of a peptide.

sequencing is required. For these reasons, selection of an appropriate endoproteinase is essential for MS/MS sequencing.

MS/MS sequencing can be used to determine the residue-specific location of a post-translation modification or degradation product. It can also be used as an orthogonal technique to N-terminal sequencing using Edman degradation. Advantages over Edman degradation are 1) MS/MS sequencing works even if the N-terminus is blocked (eg, acetylated, pyro-Glu, and 2) can provide sequencing information for most of a protein, while Edman degradation is typically limited to < 40 residues. MS/MS sequencing can even be used to identify unknown proteins by comparing peptide sequences to a protein library database.

GLYCOFORMS

One of the most complex post-translational modifications is glycosylation of proteins and mAbs. There are dozens of glycans ranging from high mannose glycans to hybrid glycans to complex glycans. Glycosylation can be important for protein function but may also play a role in immunogenicity. N-linked glycans are attached to the side-chain of an asparagine residue within the sequence Asn-X-Ser or Asn-X Thr where X is any amino acid except proline. O-linked glycans are attached to the side chains of serine and threonine residues and there is no known consensus sequence.

Monoclonal antibodies contain a single N-linked glycosylation site in each heavy chain while other proteins may contain multiple glycosylation sites. Glycan profiles are largely determined by culture conditions and the genotypes of host cells. Characterization of glycosylation is a critical step to demonstrating control over the bioprocess used to express proteins and mAbs.

Most N-linked glycans can be removed using PNGase F. The released glycans may be analyzed by MALDI-TOF or they can be labeled with a fluorescent tag and analyzed by hydrophilic interaction chromatography (HILIC) with mass spectrometry detection. Labeling of glycans with a fluorescent tag has several advantages. The labeled glycans can be chromatographically separated using HILIC and quantitated using highly sensitive fluorescence detection. The HILIC method should be compatible with mass spectrometry, allowing for the characterization of the labeled glycan by intact mass. Product ions resulting from the in-source fragmentation of glycosidic bonds are often observed. However, given the potential variation in stereochemistry, linkage site within the glycan, and the anomeric configuration of each monosaccharide, the product ions themselves are often not enough to determine the full structure of the glycan. Additional experiments are required to define the monosaccharides and their anomeric configurations. Toward this end, the glycans are treated with exoglycosidases that remove monosaccharides from the non-reducing terminus of the glycan. The exoglycosidases are specific to the stereochemistry, the anomeric configuration of the monosaccharide being released, and its linkage site within the remaining glycan. A full structural characterization of the various glycoforms is possible through this process.

Characterization of the glycosylation site within the protein can be performed using the aforementioned peptide mapping procedures. The glycosylated peptide should contain multiple masses corresponding to the various glycoforms. Deglycosylation of the protein prior to peptide mapping should result in a single peptide mass in place of the multiple masses observed for the glycosylated peptide. It should be noted that glycosylation may not change the retention time of the peptide as retention on a reversed-phase HPLC column is driven by hydrophobic interactions, to which the glycans contribute very little. The peptide map can also be analyzed using HILIC. Because the glycans are well retained in this separation technique, the glycopeptides are well separated from the non-glycosylated peptides.

SUMMARY

High-resolution mass spectrometry is a core technique for the characterization of biologics. It can provide a full range of characterization capabilities ranging from high-level analysis through intact mass analysis all the way down to residue specific information from MS/MS sequencing.◆

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BIOGRAPHY

Dr. William Boomershine is a Principal Scientist at Alcami Corporation. He earned his PhD in Biochemistry from The Ohio State University for his research on the solution structures of archaeal Ribonuclease P proteins using NMR. He has more than 11 years of experience in the pharmaceutical development and manufacturing industry characterizing small molecule APIs, peptides, and proteins using high-resolution mass spectrometry. He possesses a strong knowledge base in peptide and protein chemistry and development of analytical methods for peptides and proteins.

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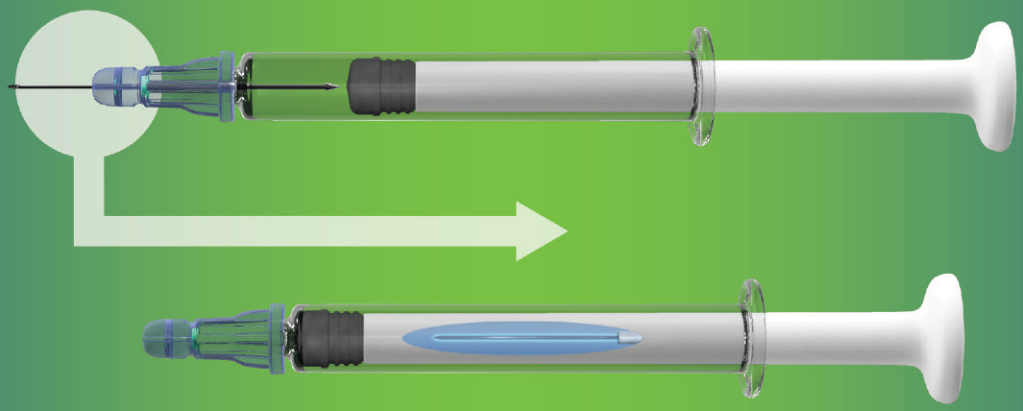

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SPECIAL FEATURE

Injection Devices: As Self-Injection Grows, Drug Delivery Gets Smarter

By: Cindy H. Dubin, Contributor

The global injectable drug delivery market is growing around 11.8% CAGR and will soon eclipse oral delivery as the primary route of administration of pharmaceuticals. The market was valued at $328 million in 2015 and is expected to reach $640 million by 2021.[1] This growth is being fueled by biologics, which are expected to grow at a clip of 26.5% to over $250 billion by 2020.[2]

The growth of chronic diseases and the requirement for repeat dosing to treat these diseases are driving the market for self-injections to grow at over 22% per year towards nearly $80 billion by 2022.[2] "This move towards injection of biologics at home is a clear trend in our society and our industry, and it presents a clear challenge for device developers," says John A. Merhige, Chief Commercial Officer, Credence MedSystems, Inc.

This annual *Drug Development & Delivery* report highlights some of the innovative and novel technologies developers are deploying to make self-injection easier and improve patient adherence.

Aptar Pharma: Developing, Manufacturing, Outlicensing Injectable Platforms

Quality improvement is continuing to drive innovation in the injectables market. The pharmaceutical companies are increasingly looking at ways to eliminate the risks associated with contamination. Specifically, the focus has been around reducing the level of particulates found in drug product. This focus on particulates is raising the bar for all players associated with the development and manufacturing of injectable products, with attention focused towards achieving a zero-defect product. Aptar Pharma has addressed this trend with the development of its Premium portfolio of injectable components: PremiumFill®, PremiumCoat™ and PremiumVision™.

"PremiumFill is a guaranteed specification to Aptar Pharma's highest quality of production, resulting in lower embedded particles, improved particulate cleanliness, and an overall reduction in defects," says Adam Shain, Global Director Business Development Injectables, Aptar Pharma. "Also produced with the PremiumFill guarantee is PremiumCoat, the new standard for film-coated stoppers. And, PremiumVision uses an in-line automated vision inspection system designed to further validate against critical defects and offers the ability to customize and further reduce the particulate level guarantee for PremiumFill."

Aptar Pharma is developing drug delivery devices. In its injectable business, it is developing and manufacturing Rigid Needle Shields (RNS). For Injectable drug delivery devices, Aptar Pharma is leveraging its expertise and outlicensing to pharma

Oval's high-viscosity autoinjector for delivery of formulations up to 1,000cP.

Aptar Pharma injectable components.

partners, such as BD. The BD Intevia™ is based on Aptar Pharma's two-step, push-on-skin autoinjector.

Through its licensing and internal development programs, Aptar Pharma is working on developing connectivity solutions for injectable devices. The company currently has connected devices for other drug delivery routes such inhalation, ophthalmic, and nasal. "We plan to leverage those technologies to develop our connected injectable device portfolio," says Sai Shankar, Business Development Director for Connected Devices, Aptar Pharma. "Our focus in the connected Injectable device space is agnostic of device. We are able to leverage our partnership with Propeller Health and bring anyone's device technology into platform."

Mr. Shain adds that Aptar Pharma is always focused on the most ideal way a syringe should interact with an Autoinjector. The RNS for Autoinjector has a proprietary design that allows for multiple gripping points on the RNS. The proprietary mushroom tip design allows for the autoinjector cap design to grip the RNS from the front, potentially eliminating current metal gripping components. This feature allows for removal by the autoinjector cap without rotating the rubber shield, a simple method to prevent coring or fragmentation. The back ledge of the RNS also provides a solution for those autoinjector designs requiring removal of the RNS from the collar.

"This patented solution provides an ideal solution to help minimize components within the autoinjector, while providing a consistent pull off force for patients," says Mr. Shain.

BD – Medical Pharmaceutical Systems

Historically, delivering small-molecule drugs used to treat chronic diseases was of little concern, as most of these medicines could be administered orally. Recent developments in biotechnology have produced a plethora of protein-based molecules that must be injected to achieve their therapeutic effects. To accommodate the volume limitations of current intramuscular and subcutaneous delivery methods, manufacturers must concentrate these formulations, thereby creating the challenge of high viscosity.

"This poses a fundamental problem with two possible solutions: increase the injection volume or increase the injection duration," says Armando Rios Jr., Senior Global Marketing Manager, BD Medical – Pharmaceutical Systems. "While these options may be feasible for IV administration, they pose significant impediments to subcutaneous delivery. Practically speaking, humans have a finite ability to self-inject over long periods with traditional delivery devices, as factors such as fatigue, concentration, and the urge to move eventually cause their ability to hold the injection device steadily in place. Physiologically, the subcutaneous tissue has a limited physical and absorptive capacity for a rapid influx of large volumes (e.g. >10mL), and associated injection pressure may lead to drug leakage and injection pain."

He says that prefilled syringes and autoinjectors are designed to administer small drug volumes (≤2 mL) in under 15 seconds. But wearable injectors, such as the BD Libertas™ large-volume wearable injector, can administer larger volumes (more than 2mL) of drug subcutaneously over an extended period.

"Wearable injectors effectively address the volume and viscosity challenges of prefilled syringes and autoinjectors, allowing highly concentrated drugs to be diluted into larger volumes and administered over longer periods without saturating the subcutaneous space," says Mr. Rios. "Although the potential benefits of these delivery systems are numerous, perhaps the most notable is the ability to self-administer

BD Libertas™ is a product in development, BD (Some statements are forward-looking and are subject to a variety of risks and uncertainties.).

high-volume, high-viscosity drugs in a non-clinical setting."

As care delivery transitions from clinic to home, BD is working on digital solutions in parenteral drug delivery. "Recognizing that truly meeting patient needs requires transitioning from a drug delivery provider to providing interconnected disease management systems, BD has invested in consolidating its digital expertise to develop fully-integrated, drug delivery solutions," says Mr. Rios.

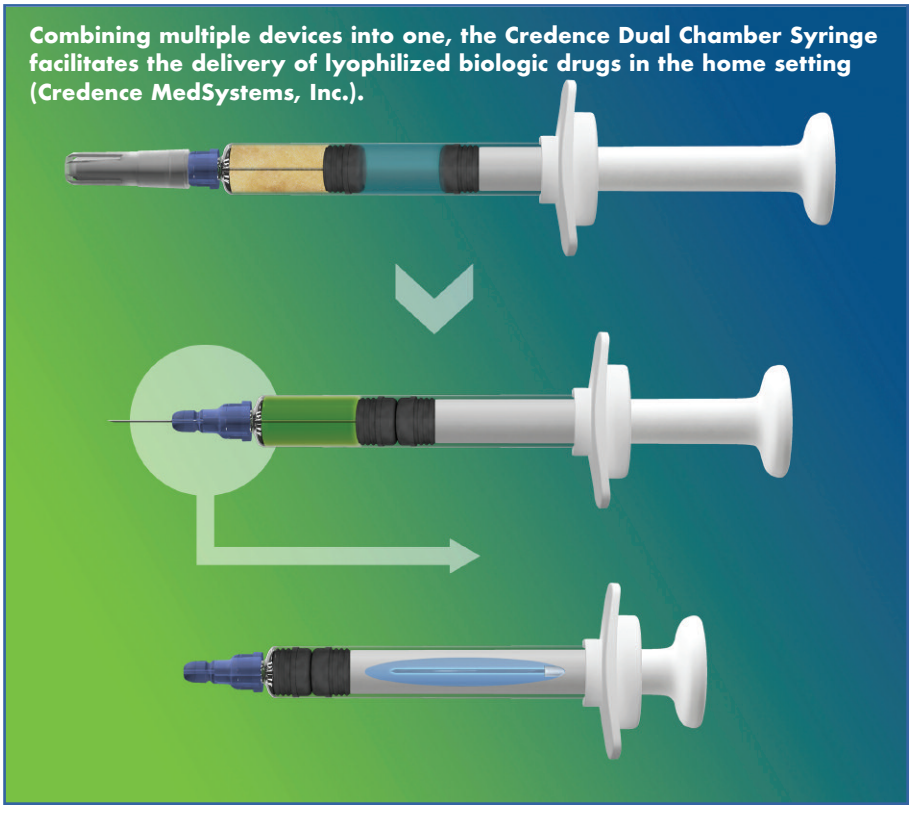
"Through their ability to collect a variety of information, smart devices have the potential to impact stakeholders positively across the healthcare continuum – patients, healthcare providers, and payers."

Credence MedSystems, Inc.: One Reconstitution Device, Multiple Features

Biologics can be difficult or impossible to formulate in a stable ready-for-injection solution and, therefore, often require storage as a lyophilized freeze-dried product that is reconstituted with a diluent at the time of injection. Yet, the conventional process of reconstitution is challenging, especially for the non-professional tasked with injecting themselves or a loved one.

"Conventional "vial-to-vial" transfer procedures provide substantial risk of dosing error, are arduous and time consuming, and expose the users to unnecessary risk of accidental needlestick," says John A. Merhige, Chief Commercial Officer, Credence MedSystems, Inc. "These factors can impact patient adherence and lead to a detrimental effect on outcomes. It is the responsibility of our industry's innovators to respond to this challenge by developing products that can be easily and successfully used to deliver lyophilized drug products in a safe and effective manner by a non-professional user in the home."

Credence MedSystems is answering this call with its Companion Dual Chamber Reconstitution System. The Companion Dual Chamber Syringe stores the freeze-dried drug in a separate chamber from the liquid diluent while the product is stored on the shelf. At the time of injection, the user pushes on the plunger rod to transfer the diluent from the rear chamber into the front chamber so that it mixes with the lyophilized cake. Once reconstitution occurs, the user continues the injection until a tactile and audible end-of-dose click confirms that the full reconstituted dose has been delivered. At this point, the pre-attached needle retracts seamlessly into the



Combining multiple devices into one, the Credence Dual Chamber Syringe facilitates the delivery of lyophilized biologic drugs in the home setting (Credence MedSystems, Inc.).

plunger rod, protecting the user and disabling the syringe from reuse.

"The Companion Dual Chamber allows pharma to impress its end users by consolidating multiple devices into one: It is a reconstitution device; a user-feedback device; a passive needlestick safety device; a reuse prevention device; and, a familiar staked-needle syringe that allows conventional syringe operations," explains Mr. Merhige.

He stresses the importance of the Dual Chamber making use of a standard syringe barrel and a standard plunger stopper. This design, he says, allows pharma to preserve the use of its preferred primary package components while also eliminating the presence of the glue that is conventionally used to affix a staked needle into a syringe. That, combined with the separation of the lyophilized drug from the diluent, serves to protect the integrity of the drug. Finally, the Credence Dual Chamber Syringe is compatible with multiple syringe sizes, reducing the package size and improving ergonomics.

Mr. Merhige concludes: "The Credence Dual Chamber Reconstitution System presents a safe and effective way to allow non-professional users to deliver lyophilized drug products in the home."

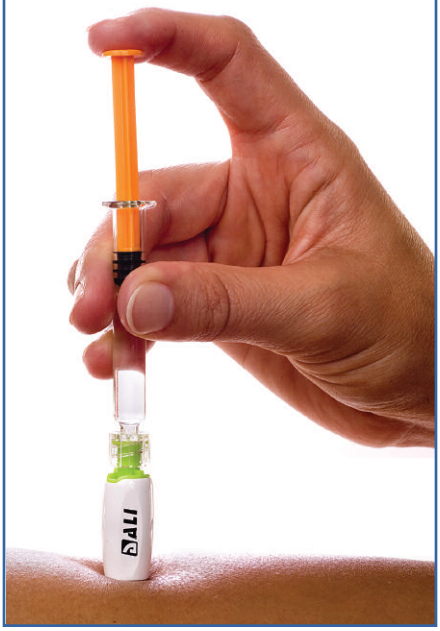
DALI Medical Devices™: Connectivity Keeps All Interested Parties in the Loop

One of the major challenges affecting the injection device market is applying connectivity features that can enhance patients' compliance and adherence to treatment, provide reminders and training to the user, and adherence/non-adherence data to payers, healthcare providers, regulatory authorities, and the pharmaceutical manufacturer. Benefits of connected injection devices for the pharma include clinical trial data (pre- and post-market), reimbursement evidence, market understanding, adverse events, product and training improvements, and increased sales by increased adherence.

"DALI Medical Devices is developing novel connectivity features and systems that can be integrated to its existing Safe Auto-Needles™ (SANs) product line, but also to other injection devices such as pens and autoinjectors," explains David Daily, DALI's CEO & Cofounder. Target therapeutic applications we collaborate on include endocrine disorders, autoimmune diseases, emergency drugs, CNS diseases, cancer-related treatments, back-of-the-eye diseases, and others.

DALI's Safe Auto-Needle products offer a combination of features from both autoinjectors and prefilled/safety syringes, such as automatic needle insertion, hidden needle, and passive sharps protection, all in an effort to reduce anxiety and perceived pain associated with needles. Mr. Daily says that, unlike conventional autoinjectors, while using the SANs, patients have manual control of injection speed, reducing pain associated with fast injections.

The DALI SAN-L™ disposable autoinjector can be used with luer syringes to combine automatic needle insertion, passive sharps protection, and a hidden needle.

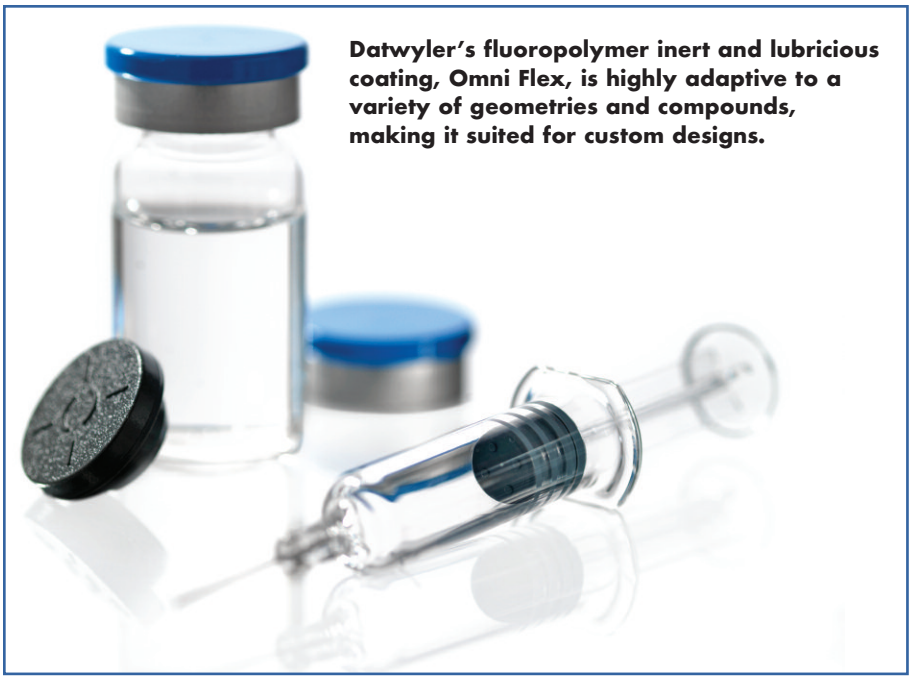


SANs are customizable for use with all types of syringes and primary drug containers, including conventional plastic hypodermics, single- or dual-chamber prefilled syringes made of glass or plastic, or vials. Depending on the configuration and pharma clients' preferences, the SANs are packed either in a blister pack or an injection-molded cap sealed with a Tyvek® lid. These designs allow either separate unit package or kit-packaging together with the drug, depending on the pharma client's preference.

Datwyler: Coatings & Closures Cater to a Range of Device Designs

As a component supplier, Datwyler caters to prefilled syringe, cartridge, and vial drug delivery systems. The company develops novel coatings that enable elastomeric compounds to make these systems more efficacious, and also focuses on the custom design of elastomeric closures to suit unique devices.

Products are available in a variety of elastomeric compounds designed for sterilization stability and drug compatibility. These chemically clean and functionally reliable compounds and designs are especially critical for biologics. According to Megan Williamson, Head of Sales, Americas, Datwyler: "Delivery of biologics presents a challenge for high viscosity drug products and our custom design capabilities and finite element analysis can provide component design and geometry optimization to meet these needs. With biologics being sensitive drugs with less resilience to extractables, leachables, and silicone, our



Datwyler's fluoropolymer inert and lubricious coating, Omni Flex, is highly adaptive to a variety of geometries and compounds, making it suited for custom designs.

compounds and coatings provide the cleanest E&L profiles with consistent, reliable functionality." For example, Datwyler's fluoropolymer inert and lubricious barrier coating, Omni Flex, is highly adaptive to a variety of geometries and compounds.

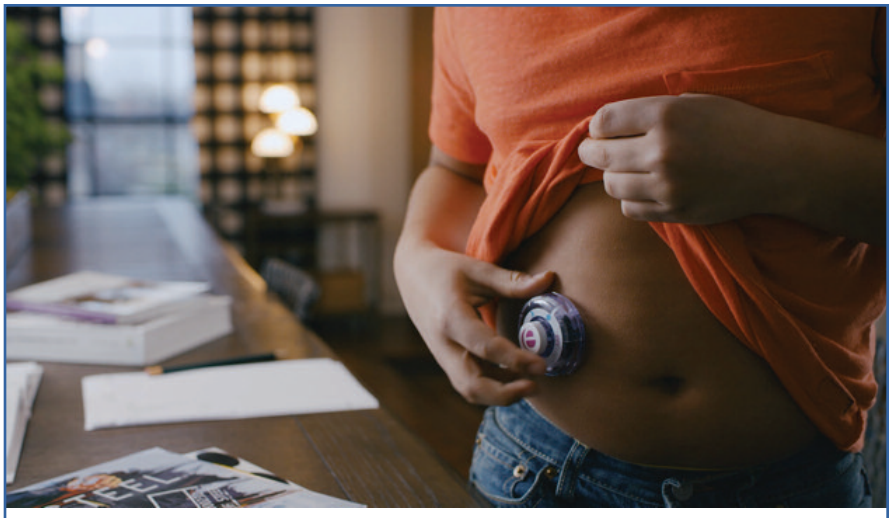
In addition, she says Datwyler's First Line automated manufacturing reduces human intervention and significantly reduces particulates and bioburden for industry-leading specifications. "This entails strict gowning protocols as well as personnel and material flow, which result in the lowest endotoxin, bioburden, particulate, and defect levels available in the industry," she says. "When a pharmaceutical company develops sensitive biologics that cannot withstand the presence of silicone lubricant in the system because visible and subvisible particles are a major concern, the Omni Flex coating, paired with First Line manufacturing, provides best-in-class particle specifications and the lowest risk for their drug product. With the rising cost of healthcare and expensive unit price of certain biologic drug products, Datwyler products can help to reduce the overall cost of ownership to our clients."

As an elastomeric component supplier, Datwyler is involved in the design and development of many custom products for novel drug delivery devices and systems, including pens, autoinjectors, pumps, and needle-free injection devices. All components are available in a variety of packaging options, including: Ready-for-sterilization, ready-to-use, and bulk packaging.

Enable Injections: Large-Volume Drug Delivery Made Simpler with Wearable Connected Device

The delivery device is the most influential factor in defining the treatment experience. Consequently, pharma companies are evaluating delivery device options for their large-volume drugs at the earliest stages of drug development. "It is now well accepted that conversion to subcutaneous delivery of high-volume (3-50mL) doses can improve patients' quality of life significantly, and even more so, if patients can easily, painlessly, and reliably treat themselves at home or work," says Jeannie Joughin, PhD, Executive VP & Chief Commercial Officer, Enable Injections.

Biologic drugs vary in dose requirements, viscosity, and desired rate of infusion, among other variables. In response to the needs of its pharmaceutical partners, Enable Injections has created variations, which have entered clinical trials, to suit specific pharma needs. The focus on improved patient experience for improved adherence is the top priority. At the core of its platform technology is the enFuse™ On-Body Delivery System (OBDS), a small device that patients can easily fill with any



The enFuse™ On-Body Delivery System improves patient monitoring while delivering high-volume (3-50mL) doses.

WHAT DOES IT MEAN TO BE NOBLE?

Well, it means a world of difference.

Noble is changing the future of adherence and onboarding through research-driven insights, innovative technologies and patient-focused solutions. Our products drive innovation to make a true impact, and our advanced strategies – from development to commercialization to utilization – are purpose-built to help transform your bottom line. **Visit Booth #413 October 8-9 at PDA Universe of Pre-filled Syringes and Injection Devices or GoNoble.com to find out how Noble can help make a world of difference for your brand.**

syringe or vial and wear unobtrusively under clothing during treatment, while carrying on with their activities. The enFuse platform is useful across the range of diagnostic categories for any drug required in volumes between 3 to 50mL. To address the increasing demand for improved patient monitoring, HIPAA-compliant connectivity has been added as an option. The enFuse Smart Device platform includes Bluetooth Low Power connectivity that transmits information to a smartphone app via a secure connection:

- When the device is powered on;
- When the device has begun dose delivery; and
- When delivery has been completed.

One of Enable's clients is developing a therapeutic for an orphan indication. Dr. Joughin explains that the client is conducting clinical dose-ranging studies and needs to deliver high volumes – in excess of 20mL. "Delivering varying volumes at different delivery rates resulted in observations of leakage, back flow, and skin irritation using a conventional delivery pump," she says. "Utilizing the clinic-ready syringe-transfer enFuse OBDS – which supports filling of variable doses – the company will be able to efficiently determine the optimal delivery rate, dose, and user experience prior to committing to the final fixed-dose product configuration for commercial launch."

Dr. Joughin adds that "Companies partnering with Enable to utilize the developed syringe-transfer 10mL or 20mL OBDS are able to enter the clinic earlier and cost-efficiently, reducing some of the financial risk associated with drug development."

To add connectivity to the all-mechanical enFuse LVWI, a small, simple power source well known for its long operation and shelf life, is added and a microprocessor embedded.

Additionally, the Enable Smart Device is pre-integrated into the Flex Digital Health Platform, medical-regulated, HIPAA-compliant, open architecture platform of connected medical devices. This provides Enable's pharma partners and healthcare providers with the ability to:

- Easily integrate with the platform;
- Gain immediate access to patient data across multiple devices;
- Gain more direct engagement with patients;
- Drive adherence; and
- Avoid high upfront development and ongoing maintenance costs.

The Enable Smart Device is designed to be simple to use. The user opens the Enable app on their smartphone and the delivery device does the rest to ensure delivery of the therapeutic. That includes automatic warming in seconds and push-button simplicity in a device developed to enable painless subcutaneous drug delivery.

Gerresheimer: New Integrated Safety System Eliminates Assembly Steps

The continued focus on safety and user friendliness led Gerresheimer to introduce its new integrated safety system, Gx Innosafe®, for prefilled syringes. "Integrating safety into our staked-in needle syringes, with an intuitive design, improves the ease of use," says Maximilian Vogl, Global Head of Product Management, Gx Solutions, Gerreshimer. "Gx InnoSafe eliminates the necessity of additional assembly of safety devices after filling the drug. Based on that, our customers will experience benefits regarding total cost of ownership, reliability, and reduction of errors."

With the Gx® InnoSafe™, Gerresheimer now offers a syringe with an integrated passive safety system that avoids needlestick injuries, prevents repeated use, and is designed with pharmaceutical companies' production processes in mind.

Gerresheimer also offers a broad portfolio of injection systems with several targeted to biologic drugs, self-administration, and needlestick prevention. These include wearable injectors with electronically controlled drug delivery, as well as fully passive and integrated safety syringes.

With regards to packaging, Gerresheimer uses glass and plastics for sensitive biologic drugs to address challenges like free silicone and tungsten deposition. Most of the primary packaging is ready-to-fill. "Our new Gx® RTF Vials are washed and sterilized and offered in a nested configuration for direct filling," says Mr. Vogl.

Kahle: Custom Syringe Assembly for Complex Designs

Kahle designs and builds custom assembly, inspection, and process equipment for medical devices and drug delivery products with complete equipment valida-

Kahle glass syringe assembly machine.

tion services. Kahle works with customers' device/requirements regardless of the design, the processes, or the production rate required. As a manufacturing equipment supplier, Julie Logothetis, President of Kahle, says the company faces challenges posed by the complexity of new injection/drug delivery devices. "Some of the "traditional" packaging and processing equipment companies work off of standard platforms and designs and do not have the flexibility to meet the requirements of the new, more complex devices," says Ms. Logothetis. "Gone are the days of a simple syringe and needle. A new safety injection device can have 12 or more components that need to be assembled, compared to a three-piece syringe and basic needle."

In the past year, Kahle built equipment to assemble standard and basic safety syringes, a new safety needle that is going to be on the market soon, as well as components for wearable pump devices. Kahle Needle Assembly Systems are available in various machine configurations, depending on product design and assembly requirements.

Mitsubishi Gas Chemical: Multilayer Material Address Pitfalls of Glass & Plastic

Traditional glass and plastic materials for syringes and vials are filled with problems. Glass suffers from a range of issues — such as high-breakability and poor PH stability — while plastic has an insufficient oxygen barrier and UV barrier. The US FDA and pharmaceutical companies have searched for solutions, and many companies have launched advanced material products, but oxygen barriers and stability have been met with criticism, explains Tomohiro Suzuki, Associate General Manager, Mitsubishi Gas Chemical (MGC).

This led to the creation of OXYCAPT™ — MGC's new, lightweight, multilayer material, which Mr. Suzuki says has all the benefits of glass and plastic. "OXYCAPT unites the best qualities of glass and plastic in a three-tiered, multilayer, advanced material that features an excellent water vapor layer made from COP (Cyclo Olefin Polymer) and a glass-like oxygen barrier layer with an oxygen absorbing polymer," he says. "With low extractables, low protein absorption, and low breakability, all components come together to produce the best high oxygen barrier material on the market."

One of MGC's targeted therapeutic application is biologics. Mr. Suzuki points out that the ICH guideline for Stability Testing of Biotechnological/Biological Products Q5C mentions oxidation as one of the causes for protein instability. Thus, he says, MGC has tried to improve the oxygen barrier of the polymer containers. "If the drug is sensitive to oxygen, the multilayer container will be the best candidate."

OXYCAPT™ Multilayer Plastic Vial and Syringe from Mitsubishi Gas Chemical.

The Safelia® 2-step autoinjector from Nemera delivers biologics and reduces needlestick injuries.

The OXYCAPT plastic syringe features reduced leachable impurities and low extractables. This is made possible by the PTFE stopper coated with slight silicone-oil, a Polypropylene (PP) plunger rod, and the silicone-oil free OXYCAPT syringe barrel. Each component works together to produce a high break resistance syringe with glass-like transparency.

"The catalyst for OXYCAPT were pharma clients looking for specially designed containers with a high gas barrier for autoinjector," says Mr. Suzuki. "As the glass was not customizable and existing polymer syringes had no oxygen barrier, we offered customized containers made by the multilayer technology."

Nemera: Autoinjector & Safety Devices Ensure Easy Delivery of Biotherapeutics

The challenge for manufacturers is to offer a device with high technicity without compromising patients' comfort and experience. With this in mind, Nemera developed the Safelia® two-step autoinjector platform to optimize the self-injection experience while offering the ability to tailor the injection to deliver even the most challenging (high volume/high viscous) drugs.

Séverine Duband, Global Category Manager, Parenteral, Nemera, says the Safelia autoinjector is robust enough to handle fluid or viscous formulations (biologics), in 1mL or 2.25mL injection volumes, and enables injection parameters to be tailored, such as needle insertion and injection speed, to fit the drug's constraints.

"Biotherapeutics tend to be more viscous, concentrated, and administered in larger volumes," explains Ms. Duband. "In order to deliver the right dose of these types of formulations, at the right depth, in 15 seconds or less, a robust delivery engine is required. Safelia meets these challenges as it injects large-volume, and high viscosity drugs, in a convenient way for the patient."

The patient removes the cap and then applies the device to the injection site. Throughout the injection process, the needle is hidden, reducing the risk of needlestick injuries as well as anxiety. "Overall, it can improve the patient's experience thanks to reduced needle diameters, reduced injection times, and design-controlled delivery for viscous injections."

Also designed to improve the patient experience is Safe'n Sound®, a range of safety devices for prefilled syringes. This customizable platform of passive, one-handed add-ons, significantly reduces the risk of needlestick injury during injection while being robust and ergonomically designed for both novice and experienced users, Ms. Duband says. Safe'n Sound is for low fill volumes and higher viscosity formulations. It features a large thumb-pad for ease of use, clear visibility of the tip for easy inspection of the drug, and a rounded shape for increased labeling surface.

Noble International Inc.: Trainers Improve the Patient Experience, Support Compliance

Several studies have suggested that without proper training during the onboarding process — defined as the first 30 to 90 days of treatment — patients who have been instructed to use self-injecting drug delivery devices (including autoinjectors, prefilled syringes and onbody devices) are more likely to drop off from therapy or incorrectly use their devices. To address this challenge, Noble is collaborating with pharmaceutical companies to develop trainers that replicate the form and function of a variety of self-injection devices and provide the patient the opportunity to train at home, gain familiarity with proper device use, and help reduce needle anxiety. Noble has already developed trainers for the autoinjector, prefilled syringe, onbody, and respiratory markets.

Within the past year, Noble announced plans to launch its prefilled syringe demonstrator platform, based on safety and shielding system technologies. "This platform offers brands a speed-to-market, onboarding solution aimed at improving the patient experience and confidence," says Paul Sullivan, Associate Director, Business Development at Noble International Inc.

Noble offers customization of AdhereIT™ to fit a variety of autoinjector platforms.

Separately, Noble launched its own connected device platform, AdhereIT™, designed to help improve patient experiences and outcomes by providing real-time feedback for autoinjector training and injection sessions. AdhereIT incorporates proprietary technologies and fits onto an autoinjector device or trainer with capabilities including the detection of contact with the injection site and the beginning and end of training or injection sessions. It can also send scheduling reminders to patients and wirelessly transmit collected data — including usage errors — to smartphones or tablets.

"The trainers replicate the design, tactile feedback, and actuation force of a self-injection device while also simulating injection speed," says Mr. Sullivan. Additional mechanical features vary by trainer type. For example, Noble's onbody injection devices replicate the volume and viscosity of the drug as it is delivered.

Some of Noble's trainers incorporate smart features such as wireless connectivity, sensors, audio cues, and error detection/simulation. "These are designed to work in tandem with smartphone apps and can provide real-time feedback to the patient. In this fashion, the patient is kept informed of any errors associated with their use of the device as they occur."

Oval Medical Technologies Limited: Overcoming the Challenges Viscous Formulations Pose to Autoinjectors

An increasing number of long-acting injectables (LAIs) developed by pharma increase the time between injections to improve patient acceptability. These products consist of formulations that are highly viscous (between 100cP and 1,000cP) with high drug loadings of biologics, supporting once per month, once every two months, and in some cases, once every three months dosing. Many of these products are being designed for self-administration and require autoinjectors that can be used easily and safely by patients and caregivers.

However, highly viscous formulations can be non-Newtonian (their viscosity varies when subjected to shear forces), resulting in inconsistent injection times and variability in dose dispensed. Also, the drug may be suspended in the formulation, which can result in clogging, inconsistent injection times, and inconsistent bolus shapes, which in turn result in variable pharmacokinetic profiles.

"To achieve reliable and consistent delivery by an autoinjector, it is critical to understand and characterize the fluidic behavior of the formulation early in the specification process," says Barbara Lead, Chief Executive Officer, Oval Medical Technologies Limited. "Failure to do this early enough can increase development costs and time scales, and reduce the reliability and likely commercial success of the final product."

Oval has developed methodologies to characterize formulations to understand the relationships between delivery force and viscosity, factors effecting clogging, and the shape and consistency of the delivered bolus. These data are used to generate a specification for an autoinjector. "If final formulations are not available early in the development process, characterization of placebo formulations over a range of viscosities can provide very useful data for input to the autoinjector specification," she says.

Oval has a specific delivery technology using a 'damped' delivery mechanism that provides consistent delivery speed for formulations that have non-Newtonian viscosities, non-homogenous consistency, or viscosity with high susceptibility to temperature variations. Oval can provide "works like" injection rigs that can be used to investigate bolus shapes in animal cadaver tissue in conjunction with MRI scans. These injection rigs have been used in pharmacokinetic studies in dogs, resulting in consistent pharmacokinetic profiles.

"Manual injection of highly viscous formulations can be very difficult for scientists and inconsistent bolus shapes will give rise to inconsistent pharmacokinetics," says Ms. Lead. "In situations where the pharmacokinetics are required to choose between formulation options, consistency is very important."

Product family from Sensile Medical: The SenseCore rotary pump technology allows tightly delivered dose tolerances combined with small volume increments as low as 1µl.

Sensile Medical: Acquisition Extends Business to Further Support Pharma & Biopharma Customers

With the acquisition of Sensile Medical back in July, Gerresheimer is extending its business model in the direction of an Original Equipment Manufacturer (OEM) for drug delivery platforms with digital and electronic capabilities for pharmaceutical and biopharmaceutical customers. As a result, Gerresheimer has become the main supplier to a large heparin producer and will supply this customer with prefillable syringes.

One of the main technologies to come out of the acquisition is the SenseCore rotary pump for drugs that need precise dosing, "SenseCore allows tightly delivered dose tolerances combined with small volume increments as low as 1µl," says Sandra de Haan, Chief Business Officer, Sensile Medical. "Exact dosing is possible even for very viscous aqueous solutions."

She adds that the technology is an integral part of Sensile's pump family, open to a variety of drugs, regardless of volume or therapy. Furthermore, these electronically controlled devices offer a variety of options for dosing that can be pre-set or adjusted by healthcare providers or patients.

Additionally, connectivity and sensor technologies are part of the modular device concepts that Sensile provides. For example, Sensile's onbody devices have a mechanism that enables automated needle insertion and retraction before and after drug administration. "This reduces the risk of needle injuries and contamination before or after administration," says Ms. De Haan. "The aim is to provide the greatest possible safety and comfort for patients thanks to a reliable drug delivery device that is easy to use." She adds that Sensile Medical is exploring data exchange options such as apps, RFID, and cloud technology for all of its platform solutions.

SHL's Needle Isolation Technology (NIT®) is a safety solution that is changing the way cartridge-based autoinjectors are handled.

SHL: Preconfigured Autoinjector Maximizes Speed to Market

With the number of biological treatments going off patent, challenges have shifted from overcoming regulatory hurdles, such as safety and efficacy, to challenges related to intellectual property and patent expirations. SHL Global Director of Marketing Magnus Fastmarken points out that this can be a tremendous opportunity for both the drug manufacturer and the delivery device developer. "We see an increased request for preconfigured devices for biosimilars that can be easily developed and quickly launched for commercial use."

Molly® is SHL's first preconfigured autoinjector program designed to help pharmaceutical companies minimize initial investments and maximize speed to market. Molly has already been commercialized in a range of shapes, colors, and labeling textures. These low-level customizations, says Mr. Fastmarken, enable pharma companies to create differentiation for branding and product identity. He adds, "Because it comes in both 1mL and 2.25mL volumes, Molly can also support therapies with less frequent injections in higher volumes."

The development of innovative treatments also calls for technologies that look beyond current autoinjector standards in terms of volume and viscosity. Cartridges, which have primarily been used for pen injectors, expand fill volume choices and offer dual-chamber options for formulations that need to be separated before use, says Mr. Fastmarken. "Until now, the most significant limitation with cartridge-based systems was the need for the patient to manually attach the needle, a risky step regarding drug safety and needlestick injuries. SHL's Needle Isolation Technology (NIT®) eliminates this risk in that the needle is pre-installed in the device and automatically attached with just a simple twist of the needle cap."

Earlier this year, a pharmaceutical company successfully relaunched its cartridge-based drug product equipped with SHL's NIT. "The NIT is a true problem solver," says Fastmarken. "Cartridges open up a world of opportunities for pharma companies, and offer patients a safe and intuitive experience without sacrificing usability."

Fastmarken believes that the industry

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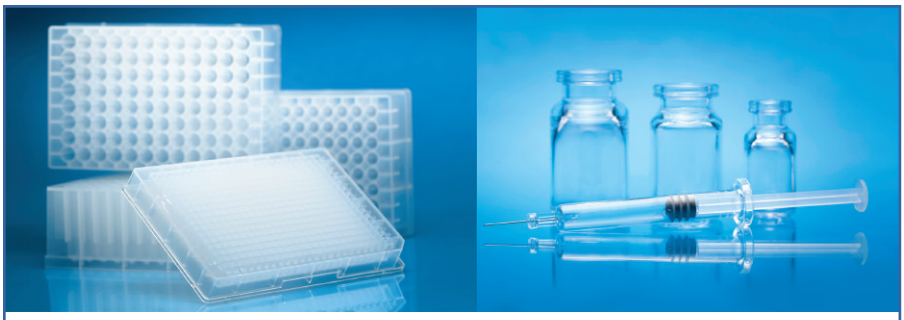

A platform of coating technologies from SiO_2 Medical Products, Inc. enable drug and container compatibility.

has only scratched the surface of the autoinjector's true potential. "In the future, a new generation of connected autoinjectors will prove to be the perfect sensor for collecting dose-level data based on real-world patient experiences. Data collected from these devices will deliver insights that support adherence and outcomes for patients and stakeholders."

SiO_2 Medical Products, Inc.: Parenteral Containers Optimize Development and Delivery through Advanced Material Science

A common device for self-administration of injectable biologics is the autoinjector, which contains, at its heart, a prefilled syringe. These syringes must meet very stringent requirements for fit, performance, and drug compatibility, and must protect the drug formulation and maintain its potency over an extended period of time. The predominant choice for drug storage is a silicone-lubricated glass, 1mL-long prefilled syringe. However, such a syringe is known to require numerous design and performance compromises for the overall injector design. Specifically:

- Poor dimensional control of the syringe leads to autoinjector design concessions;
- Fragility of the syringe has led to catastrophic injection failures;
- The mobile lubricant has created formulation stability challenges; and
- The mobile lubricant can lead to variable injection performance.

Parenteral containers supplied by SiO_2 Medical Products, Inc. (SMP) overcome these and other observed shortcomings of existing prefilled syringes, says Holger Krenz, Director Corporate Account Management, SiO_2. The SMP syringe is constructed of high purity engineered polymers (such as COP) with an insert molded needle for improved dimensional control over traditional glass alternatives. Additionally, engineered polymers provide improvements over glass for break-resistance, including critical design elements such as the syringe neck and flange – mitigating common failures of glass syringes, Dr. Krenz adds.

The inner surface of the SMP Primary Container is plasma coated via a proprietary process to ensure oxygen impermeability, superior drug compatibility, and extremely low levels of particulate. The SMP syringe is also offered as a silicone-free system. "These configurations provide a reliable and consistent product that truly meets design requirements for the storage and delivery of the emerging portfolio of biologic products." SMP syringes are packaged in a ready-to-use (RTU) format to enable consistent filling processes and implementation into existing fill/finish lines.

Additionally, the SMP Primary Containers provide the benefit of a truly common drug contact surface. Michael Chiappetta, Advisor for SiO_2 Medical Products, says: "Because the contact surface of the SMP microplate, vial, and prefilled syringe are the same, the need to account for drug compatibility when transitioning the biologics through the drug development cycle from a microplate to a vial and subsequent syringe is eliminated. This is generally not possible for glass syringes because commonly used manufacturing processes for glass syringes and glass vials differ greatly – resulting in uncommon or varied contact surfaces."

Further, SMP's proprietary platform of plasma coating technologies enable advances in drug and container compatibility, Mr. Chiappetta says. "The coating process enables the drug contact surface to be modified when required. In brief, the coating can be adjusted to better match with the stored biologic. SMP molded syringe combined with a controlled interior coating provide improved autoinjector fit and reliability for numerous biologics, including highly viscous formulations."

As methods of self-administration and disruptive improvements in autoinjectors continue to grow in the drug delivery industry, Mr. Chiappetta stresses that the prefilled syringe must similarly undergo significant material and design improvements."

Sonceboz: Device Platform Handles a Variety of Applications

The increasing number of biologic drugs designed in the space of Immuno-Oncology require more tailored and capa-

ble injection systems to allow for complex therapies such as drug combinations or automatic reconstitution. "We are providing a technology platform, Your Platform, that enables a variety of therapeutic applications – covering large-volume, high-viscosity, reconstitution, and dual-container," says Tom Mayer, Sales and Application Manager, Sonceboz. "The platform is ideally suited for treating Rheumatoid Arthritis."

The large-volume injector is designed to deliver up to 6mL or more of highly viscous drug formulations subcutaneously in bolus or programmed delivery. Dual-cartridge injection is designed to carry two standard containers, enabling complex drug combination therapies through sequential or simultaneous injection into the subcutaneous spaces. Additionally, automatic reconstitution injection enables the in-device reconstitution of lyophilized drug formulations, carrying both the drug and the diluent in separate preloaded/prefilled primary containers. There is no need to connect external drug containers.

We believe that patient-centric design with intuitive usability are key to allow patients to safely administer injections in their known environment," says Mr. Mayer.

He says that Sonceboz' goal is to design an integrated, automatic reconstitution system that will help pharma simplify the administration of lyophilized drugs at home.

The Sonceboz wearable drug delivery systems dispense high volumes of viscous medications.

West Pharmaceutical Services, Inc.: Developing Products with Simplicity & Functionality in Mind

One challenge that is becoming more complex for pharmaceutical companies is navigating the regulatory landscape, especially for therapies that will be offered as a combination product. While quality and risk mitigation expectations continue to be a focus for regulatory bodies globally, agencies are now increasing attention on ensuring that drug delivery technologies are developed with not only functionality, but usability in mind to promote both safety and adherence among end-users.

For a successful path to approval, essential performance requirements for a therapy's delivery technology must be established early in the development process so that the testing regimen maps to those requirements and all necessary data is included when filing with a regulatory body.

"West recognized this direction several years ago, working collaboratively with pharmaceutical partners and regulatory agencies to understand expectations for a delivery system in a combination product filing, and ensuring products in a self-injection portfolio are tested and validated accordingly to have readily available data and challenge studies demonstrating safety, functionality, and usability," says Eric Resnick, Vice President & Chief Technology Officer, West Pharmaceutical Services, Inc.

A successful self-injection system combines engineering and design to ensure that the therapy is not just delivered, but is delivered in a system that addresses both the potential physical and emotional barriers to patient adherence, says Mr. Resnick. As therapies evolve requiring new delivery and dosing options, demand has increased for flexibility in delivery technologies to meet the needs of the drug and the patient.

To that end, West has built upon the success of the first generation of its wearable self-injection technology — the SmartDose™ drug delivery platform — to address market needs for higher-dose volumes and enhanced functionality and usability. All versions of the SmartDose platform incorporate extensive human factors testing and analysis, and offer a variety of integrated solutions for delivery and containment featuring a silicone oil-free Daikyo Crystal Zenith® cartridge and a FluroTec-coated piston containment system. A second-generation (Gen. II) device includes enhanced usability and adherence features, and can accommodate injection volumes of up to 10mL, as well as both glass and Daikyo Crystal Zenith containers. Additionally, the Gen. III device integrates a preloaded cartridge to reduce user steps and simplify the supply chain for West's pharmaceutical partners, Mr. Resnick says.

In its effort to continually simplify drug delivery, and make it less intimidating, West offers the ergonomically designed SelfDose™ patient-controlled injector, which incorporates a simple, two-step operation to deliver a subcutaneous injection, as well as audible and visual end-of-dose indicators to confirm administration of a prescribed dose. Additionally, a passive safety system covers the needle before and after injection to help prevent needlestick injuries. Extensive human factors studies have been performed with the SelfDose injector, confirming the intuitive design and supporting its ease of use and patient acceptance.

West partnered with Accord Healthcare Limited to develop a delivery device for a weekly single-dose injection of its

drug Methofill™ (methotrexate) SELF INJECT. "They selected SelfDose because not only could it support that dosing level, but the device's ergonomic design improves the patient experience for those suffering from Rheumatoid Arthritis by allowing those with dexterity issues to self-inject outside of a healthcare setting," says Mr. Resnick. "Even SelfDose was designed to be used as a platform system for pharmaceutical partners like Accord. As a result, even viscous drug dosages up to 1mL can be used without modifying the product."

The patient experience can also be improved via connected health, which drives greater patient adherence by integrating the self-administration process with technologies patients use in their everyday lives, such as smart devices. "West's collaboration with HealthPrize Technologies is an example, as it allows patients to use electronically connected drug delivery systems to track in real-time when they take their medication, and uses gamification to reward patients for compliance," explains Mr. Resnick. The platform is designed to be accessed through a mobile app or Web portal and can gather information such as dosage and device history use for trends and analytics.

"The future of connected health, though, will be incorporating universal technology in drug delivery systems to allow pharmaceutical partners to customize data collection to address the needs of a therapy and its corresponding patient population," he continues. "This could include transmission of data in real time through low-energy Bluetooth technology."

Ypsomed AG: Embedding Connectivity to Transform Autoinjectors Now & in the Future

Ypsomed has been focused on the new area of prefilled patch injectors. The YpsoDose patch injector attaches to the skin during injection to deliver large-volumes (3-10mL). Targeted therapeutic indications are biologic drugs that require the injection of higher volumes with potentially reduced injection frequency compared to a treatment with autoinjectors, says Ian Thompson, Vice President Business Development at Ypsomed.

YpsoDose is a prefilled and preassembled, electromechanical, cartridge-based connected device, based on a versatile platform that can be customized into product-specific variants. A key feature of YpsoDose is the motor-controlled needle insertion and retraction mechanism that ensures that the injection needle is not exposed except during the injection process.

Additionally, Ypsomed has developed smart, reusable add-ons such as SmartPilot for the YpsoMate autoinjector. "SmartPilot transforms the standard YpsoMate autoinjector into a fully connected device, detecting and communicating different use states of the autoinjector to the smartphone, providing real-time, step-by-step instructions in written, animated, and audible formats, all the while improving patient adherence and therapy outcome," explains Andreas Schneider, Business Development and Innovation Manager, Ypsomed. "In a commercial setting, SmartPilot connects the patient with different stakeholders (doctors, pharma industry, payers) that may take advantage of the collected data."

Both YpsoMate and YpsoDose are designed for the existing and new wave of monoclonal antibody-based biologics used in treating autoimmune diseases and immuno-oncology therapies.

Furthermore, Ypsomed is addressing a set of key device-oriented challenges to effectively embed connected devices into the broader digital ecosystem. For example, Ypsomed is developing a turnkey digital solution to simplify adherence monitoring and provide secure smart device integration. These interrelated managed services ensure simple access to device and therapy-relevant data via standardized web-based interfaces, fully secured device-to-cloud communication, and complete connected device life cycle management that provides control of, and insights into, marketed devices. ◆

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DRUG DELIVERY

Targeted Delivery of Submicron Particle Cancer Chemotherapy: Helping Shift the Immunotherapy Paradigm

By: Marc A. Iacobucci, BS, Pharm, MBA

INTRODUCTION

Chemotherapy (CT) has been used in the treatment of cancer since the late 1940s. A new class of chemotherapeutic agents called taxanes were introduced in the 1990s and remains one of the key advances in the fight against cancer.

Most CT agents are administered intravenously or orally, with very little drug ultimately delivered to the site of disease to cause a therapeutic effect. Additionally, systemic administration of these cytotoxic agents can lead to system-wide toxicity. As such, dose and frequency of dose must be carefully monitored to cause a therapeutic effect while attempting to limit toxicity. Too often, however, a suboptimal clinical outcome is the result in the form of incomplete tumor response or unacceptable adverse effects.

The subsequent emergence of biotechnology and genomics signaled the future promise of immuno-oncology therapy (IOT). However, the early generations of IOTs have their own drawbacks with only selective effectiveness and significant side effects, and more promising therapies are still years from market approval and widespread use.

Research has shown that CT and IOT in combination are synergistic and may become a mainstay of cancer therapy in the future. Unfortunately, their side effects are additive as well, which is problematic when considering how to optimize their use together.

NanOlogy™, a clinical-stage pharmaceutical development company, was formed in 2015 to increase the effectiveness and safety of CT through targeted delivery. Based on a proprietary submicron particle production technology, the company has developed stable, uncoated submicron particles of the taxanes, paclitaxel and docetaxel, as investigational drugs, which can be administered directly to the site of disease via injection, instillation, or inhalation.

These particles of pure drug are so unique in terms of size and surface area, they have recently been granted a composition of matter patent. When injected locally, via intratumoral injection for example, research has shown the particles become entrapped at the disease site, releasing drug over several weeks. This high, sustained concentration of drug at the disease site has been shown to significantly decrease or eradicate tumors in preclinical studies. Because of gradual clearance at very low levels, systemic side effects have been shown to be negligible. Moreover, the enhanced tumor kill drives a significant immune response that is being investigated to determine whether the response contributes to tumoricidal activity either alone or in combination with IOT. With five Phase 2 clinical trials underway and more on the horizon, NanOlogy investigational drugs are aiming to help shift the paradigm for IOT.

LIMITATIONS OF SYSTEMIC DELIVERY

Paclitaxel and docetaxel were game changers in the fight against cancer following their market approvals in the 1990s. They are in the taxane class of antimitotic compounds that work by inhibiting cell division leading to cell death. Their impact is

TABLE 1

NanoPac	Pancreatic Cancer	Intratumoral (ultrasound guided)
NanoPac	Pancreatic Cysts	Intracystic (ultrasound guided)
NanoPac	Prostate Cancer	Intratumoral (ultrasound guided)
NanoPac	Ovarian Cancer	Intraperitoneal infusion
NanoPac	NSCLC	Nebulized inhalation
NanoDoce	Bladder Cancer	Instillation/resected tumor bed injection (cystoscope-guided)
NanoDoce	Renal Cancer	Intratumoral (ultrasound guided)

greater on rapidly dividing cells, a characteristic of cancer cells but also of some normal cells. The drugs do not discriminate between the two and when administered systemically lead to significant side effects in some patients like bone marrow suppression, nausea, vomiting, and hair loss.

These side effects limit the amount of drug that can be given in a single dose and time until the next dose can be given so a course of CT typically involves administration in 2- to 4-week intervals for up to six cycles. Paclitaxel and docetaxel half-life in the body are both less than 1 day and are normally cleared from the body in only 2 or 3 days. Because of this, drug is at the disease site for a very short time, and multiple cycles are given with the goal of eliminating the tumor over the course of therapy. Too often, tumor burden decreases during treatment, but the disease is not eradicated, or patients cannot tolerate an entire course of therapy. Unfortunately, recurrence or spread of the cancer, or resistance to new treatment, may result.

Nonetheless, paclitaxel and docetaxel are effective cancer killing agents for a wide range of cancers and researchers have long searched for ways to deliver large, sustained amounts of these drugs to the disease site to enhance their efficacy. This has proven to be difficult via systemic administration because no effective ways have been developed to substantially concentrate drug at the disease site for long periods of time. Both drugs are also hydrophobic and solvents and further dilution are required to administer the drugs via intravenous infusion. The solvents themselves are toxic, requiring pretreatment with steroids and antihistamines to prevent allergic reactions. Some success has been achieved in micronizing CT drugs to increase the amount of drug that can be administered, but these require coating agents like albumin or carriers like liposomes to keep them stable. In fact, when researchers refer to "nanoparticles," they are often referring to the coating or carrier agents upon which drug is placed to enable better oral or systemic bioavailability.

LOCAL DELIVERY OF PURE SUBMICRON DRUG PARTICLES

Pharmaceutical nanoparticle research has mainly focused on increasing the oral or systemic bioavailability of drugs. Making small drug particles is complicated because conventional means, such as milling or microfluidization, impart static energy to the particles causing them to clump together and be difficult to work with. To solve this dilemma, coating agents are used to prevent clumping or carriers are used to complex the drug molecules. Either way, the goal is typically to increase system-wide bioavailability.

The NanOlogy technology turns this around by using local delivery of submicron particles of pure drug using the drug particles as a depot for sustained release to increase local drug concentration and residence time at the disease site. Allowing this is a proprietary submicron particle production technology that uses supercritical fluid carbon dioxide and sonic energy in a nonmechanical process that imparts very little static charge to the particles. As such, the particles remain stable and free-flowing in powder form allowing them to be suspended (not dissolved) in simple diluents at time of use for local delivery in high concentration directly to the disease site.

Unlike intravenous solutions of paclitaxel or docetaxel, which would quickly diffuse out of the tumor if given locally, the NanOlogy submicron particles become entrapped at the disease site, releasing active drug at therapeutic levels for several weeks. Drug clearance from the disease site is gradual, at subtoxic levels, causing negligible systemic adverse effects.

The simple elegance of this approach belies the complexity of production process and the particle specifications including size, geometry, surface area, density, and dissolution that are essential for this effect. Outside the lower specification limit does not allow for sufficient entrapment. Outside the upper limit does not allow for sufficient drug release. The uniqueness of these characteristics is described in a composition of matter patent (US 9,814,685) on the particles that is valid until 2036.

"NanOlogy™, a clinical-stage pharmaceutical development company, was formed in 2015 to increase the effectiveness and safety of CT through targeted delivery. Based on a proprietary submicron particle production technology, the company has developed stable, uncoated submicron particles of the taxanes, paclitaxel and docetaxel, as investigational drugs, which can be administered directly to the site of disease via injection, instillation, or inhalation."

EXTENSIVE PRECLINICAL & CLINICAL DEVELOPMENT PROGRAM

After completing preclinical toxicology and pharmacology studies to support IND approvals, NanOlogy is in clinical evaluation of two investigational drugs including submicron particle paclitaxel suspension identified as NanoPac® and submicron particle docetaxel suspension identified as NanoDoce®. NanoPac is under clinical evaluation for safety and efficacy in Phase 2 trials for the treatment of prostate cancer, pancreatic cancer, mucinous pancreatic cysts, and ovarian cancer with orphan drug designation. The prostate trial will complete in late 2018 and the others within 12 to 18 months. A Phase 2 clinical trial is planned for NanoDoce in bladder cancer in late 2018 and renal cancer in mid-2019. Findings from preclinical pharmacokinetic and pharmacology studies of an inhaled version of NanoPac for non-small cell lung cancer (NSCLC) were presented at ASCO in June. IND-enabling work is underway to allow for a human clinical trial in 2019.

NanOlogy clinical trials are designed to provide human proof of concept to enable delivery optimization and pivotal clinical trials. To date, more than 50 patients have been administered the investigational drugs. NanoPac and NanoDoce are designed for local delivery as described in Table 1.

In the Phase 2 prostate cancer trial, for example, patients undergoing planned prostatectomies have received an intratumoral injection of NanoPac 28 days before surgery. Early data from the open label trial show evidence of tumor reduction, tumor cell death, an immune response, drug in lymph nodes, and no significant drug-related adverse events.

The initial excitement surrounding NanoPac was based on published findings from a Phase 1 clinical trial for ovarian cancer and other peritoneal malignancies. Twenty-one patients, who were suffering from Stage 3 and 4 cancer and had failed all other treatments, received up to 6 cycles of intraperitoneal NanoPac.

The findings showed high and prolonged concentration of drug in the peritoneum via pharmacokinetic analysis with gradual clearance at subtoxic levels with peritoneal concentrations 450-2900 times greater than peak plasma drug concentrations. No bowel obstruction or other significant drug-related adverse events were observed, and five of the seriously ill patients survived at least 400 days after receiving NanoPac. The encouraging results led FDA to grant orphan drug status to NanoPac for ovarian cancer.

Because paclitaxel and docetaxel are FDA approved with more than 20 years of clinical experience, the FDA also allowed its streamlined 505(b)2 regulatory pathway for NanoPac and NanoDoce. It is rare for a company to have a composition of matter patent on products following a 505(b)2 regulatory path.

AN UNEXPECTED IMMUNE RESPONSE

Research has demonstrated that taxanes like paclitaxel and docetaxel can exert a modest immune response as part of their activity, and clinical research is underway using these drugs systemically in combination with IOT to evaluate their value in combination therapy. Unfortunately, systemic CT is fraught with significant adverse effects that add to the side effects of IOT.

Upon histological examination of lung tissue during preclinical lung cancer research, NanOlogy discovered a profound immune response to inhaled NanoPac versus systemic paclitaxel. This enhanced immune response has now also been seen preclinically in bladder, renal, and breast tumors, and clinically in prostate tumors. Immunohistochemistry has demonstrated substantial macrophage and lymphocyte infiltration in and around the tumor site in all cases and tumor eradication in some

cases. The scientific rationale for this effect is that large, sustained concentration of drug at the disease site substantially increases tumor kill and local accumulation of dead tumor cell debris. This debris contains tumor specific antigens, which elicit a strong immune response.

NanOlogy is conducting extensive research to confirm these findings because its potential represents a paradigm shift in the treatment of some cancers. That is, local delivery of the NanOlogy investigational drugs by themselves or prior to IOT may jumpstart the immune system and response to therapy without adding to adverse effects associated with systemic CT.

PRODUCING PARTICLES AT COMMERCIAL SCALE

FDA approval of a new drug not only requires proof of safety and efficacy but the ability to reliably manufacture the drug at commercial scale. NanOlogy is related to a company called Phyton Biotech, which is the pioneer in plant cell fermentation (PCF®) for the development and commercial manufacture of plant-derived active pharmaceutical ingredients (APIs) and has become the largest producer of paclitaxel and docetaxel via PCF in the world. With GMP facilities in Hamburg and Vancouver, Phyton sells its APIs in every major geography, including the US, Europe, Japan, and China.

Importantly, because its paclitaxel and docetaxel are uniquely derived via PCF, Phyton is the only company in the world that controls the entire production process of these APIs in house without the negative environmental impact and supply risk associated with harvesting vast yew tree plantations for the API starting material. All other API suppliers in the world rely on harvesting yew tree plantations to source 10-DAB, their common starting material for both paclitaxel and docetaxel.

Engineering plans are in place to transfer the commercial submicron particle production process of NanoPac and NanoDoce to Phyton's Vancouver facility to take advantage of the facility's space, infrastructure, and engineering, operational, and quality personnel. Through Phyton, NanOlogy will be able to control API and bulk finished product production in one FDA-inspected facility to facilitate the CMC review and approval of the products.

SUMMARY

With much attention and research investment into IOT, NanOlogy is shaping a new paradigm for cancer treatment by attempting to improve the safety and effectiveness of tried and true CT through local delivery. The standalone potential of NanOlogy investigational drugs is noteworthy. However, the promise of these drugs to help optimize IOT cannot be overstated and could be transformational for the treatment of some cancers by reducing doses and/or cycles of IOT and resulting in better overall clinical outcomes. Because of the streamlined regulatory pathway of the NanOlogy investigational drugs, market approval and access to patients for successful drug candidates could be just a few years away. This paradigm shift has the potential to save more lives, increase patient quality of life, and reduce overall cancer care costs, and provides a pharmaceutical development area with significant investment potential.

AUTHOR'S NOTE

The NanOlogy investigational drugs described in this article are undergoing the preclinical, clinical, and CMC studies required by the US FDA for NDA submission. None of the drugs have been proven to be safe and effective or are approved for commercial distribution in the US or any other jurisdiction.◆

BIOGRAPHY

Marc Iacobucci, is an officer and board member of NanOlogy, Managing Director of DFB, and serves on the executive committee of Phyton Biotech, a company wholly owned and operated by DFB. He is part of a small team responsible for identifying new healthcare investment opportunities and leading them through development to value creation for DFB. Currently, he is primarily involved in advancing a broad clinical program in oncology for DFB affiliate, Nanology, LLC, which was formed in 2015. Prior to his current role, Marc led establishment of Phyton as a commercial operation. Marc has been with DFB since 1993 with leadership roles in business development, marketing, project management, and operations across DFB's family of companies. Earlier in his career, Marc worked for Procter & Gamble as a market analyst, Merck as a pharmaceutical representative, and as a clinical pharmacist in Ohio and Texas. A graduate of the Ohio State University with a Bachelor of Science degree in Clinical Pharmacy, Marc received his Master of Business Administration from the University of Texas at Austin. For more information about NanOlogy, please visit www.nanology.us.

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COP RTF Syringe

Gerresheimer already offers a range of ready-to-fill COP syringes manufactured by its long-standing partner, Taisei Medical Co. Ltd., in Japan. In this partnership, Gerresheimer's role is to market the ClearJect syringes and provide technical support to customers in Europe and America. Now the company has extended its COP syringe portfolio by combining its glass RTF (ready-to-fill) concept with ClearJect to create the new Gx RTF ClearJect brand. The new syringe will be manufactured at the Gerresheimer Medical Systems plant in Germany in close collaboration with the Japanese partner. The first Gx RTF ClearJect product to be manufactured is the 1-ml long syringe with staked in needle. For more information, contact Gerresheimer at +49 211 6181 246 or visit **www.gerresheimer.com.**

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Noble works with drug delivery device manufacturers and biopharmaceutical companies to develop self-injection training devices, including autoinjectors, prefilled standard and safety syringes, wearables, and respiratory platforms to provide biopharmaceutical companies improvements in launch strategies and patient adherence. Noble's training and onboarding platforms are built true to form and function to device specifications and are available as off-the-shelf and customized solutions, with the optional inclusion of proprietary technologies for products ranging from mechanical training devices to smart error-correcting training platforms. These devices are designed to emulate a device's form factor and functionality, including tactile feedback, operational forces, and administration steps to provide patients with accurate simulation of actual delivery devices while being a low-cost reusable solution to safely and effectively onboard users. Companies providing reusable, device-comparable training products will be well positioned for competitive differentiation through improved patient satisfaction, adherence, and outcomes. For more information, contact Noble at (888) 933-5646 or visit **www.gonoble.com.**

Technology & Services Showcase

DPI Technology Portfolio

Dry-powder inhalation (DPI) technology offers a favorable drug development opportunity for respiratory or systemic drug delivery. Delivering a uniform dose in a portable, easy-to-use system, capsule-based DPI device is a simple and cost-effective way to deliver inhalable medication. Capsugel's customized capsules, in both gelatin and hypromellose (HPMC), are optimized to provide superior performance and compatibility between the capsule/device and capsule/formulation. For more information or to request samples or speak with experts, visit Capsugel (Now a Lonza Company) at **https://www.capsugel.com/biopharmaceutical-products/dpi-capsules.**

Advanced Delivery Devices

SHL GROUP

SHL Group (Scandinavian Health Ltd) is a world-leading solution provider in design, development, and manufacturing of advanced drug delivery systems. We work with leading biotechnology and pharmaceutical companies to develop drug delivery devices, including compact disposable auto injectors, reusable pen injectors and complex inhaler systems. Significant investment in R&D has allowed us to enhance our broad pipeline of "next-generation" drug delivery systems. These include a range of disposable and reusable injectors with fixed or variable dosing, high dose accuracy, and the ability to accommodate high volumes and high viscosities. With locations in Taiwan, Sweden, China, and the US, our experienced engineers and designers develop product enhancements and breakthrough drug delivery solutions for pharma and biotech clients globally. For more information, visit SHL Group at **www.shl.group.**

Mechatronic Drive Systems

SONCEBOZ

Sonceboz core competencies consist of design, development, and production of mechatronic drive systems. Since 1936, our focus has been on innovation, best-in-class quality, and service, which is our key to success for worldwide OEM customers. Sonceboz is ISO 13485 certified and active in wearable drug delivery, medical devices, and laboratory industry. Pharma companies looking for Large-Volume Injectors for high- viscosity drugs, Dual-Cartridge, or Auto-reconstitution Injectors will find interesting solutions in Sonceboz's new drug Delivery Device Platform. Customized technology modules like motor-drives, electronics, pumps, and needle insertion systems are available for medical device manufacturers. Sonceboz's activity in medical devices is based on a long experience in automotive, where top quality, reliability, and cost effectiveness is key. For more information, visit Sonceboz at **www.medical.sonceboz.com.**

Integrated Delivery Systems

West is a leader in developing and manufacturing pharmaceutical delivery systems. The company has unique technologies in self-injection systems, including the SmartDose® drug delivery platform and the award-winning SelfDose® patient-controlled injector, that enable patients to self-administer injectable medicines at home. West is also collaborating with HealthPrize Technologies on a connected health offering that is designed to improve and reward medication adherence with unique technologies. The offering integrates HealthPrize's Software-as-a-Service medication adherence and patient engagement platform into injectable drug delivery systems, providing biopharmaceutical companies and their patients with an end-to-end connected health solution. For more information, contact West at (800) 345-9800 or visit **www.westpharma.com.**

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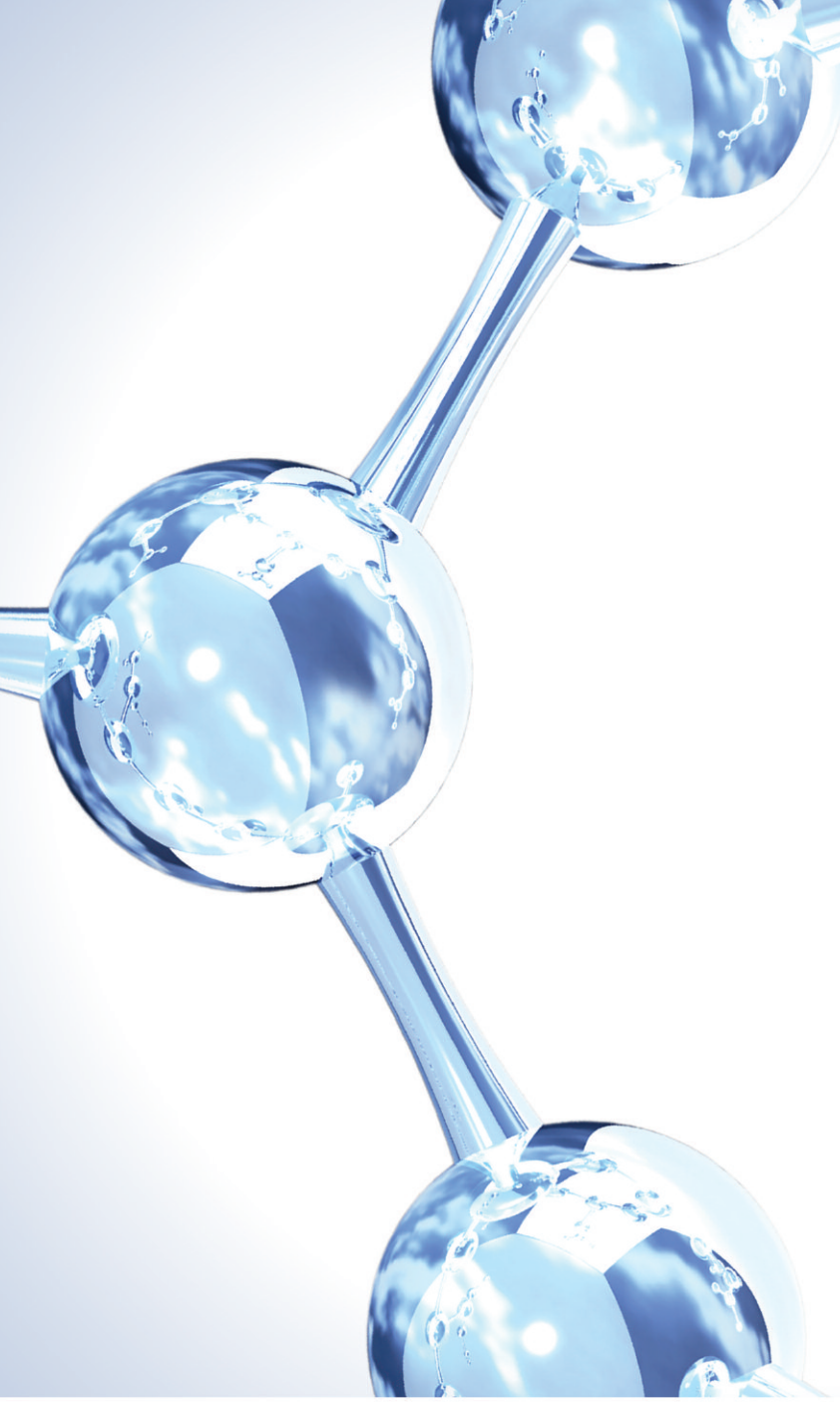

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