Drug Development & Delivery

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Prefilled Syringes & Parenteral Manufacturing

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

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Cindy H. Dubin
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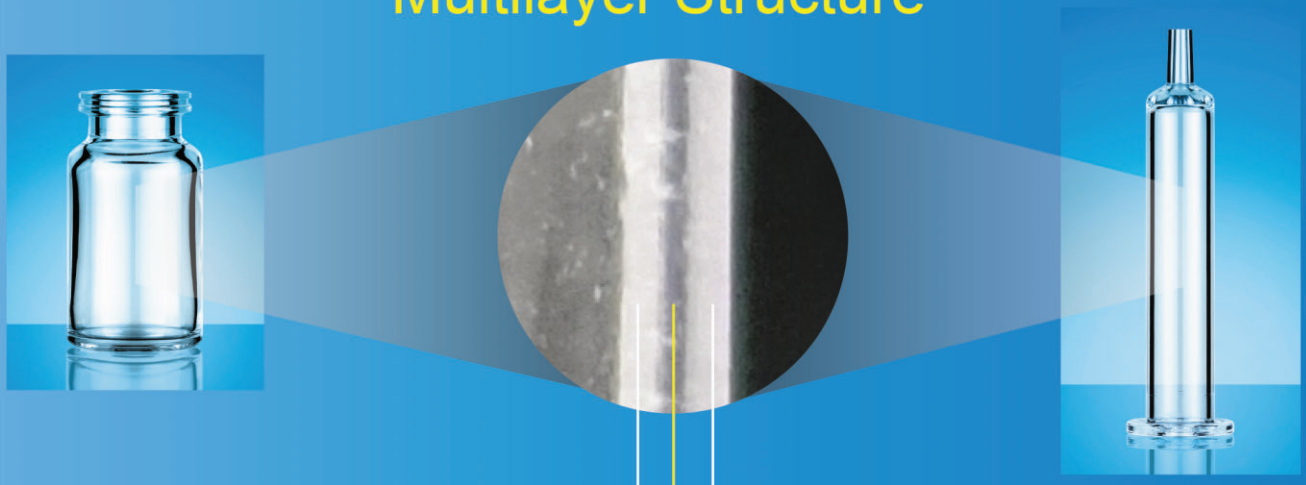

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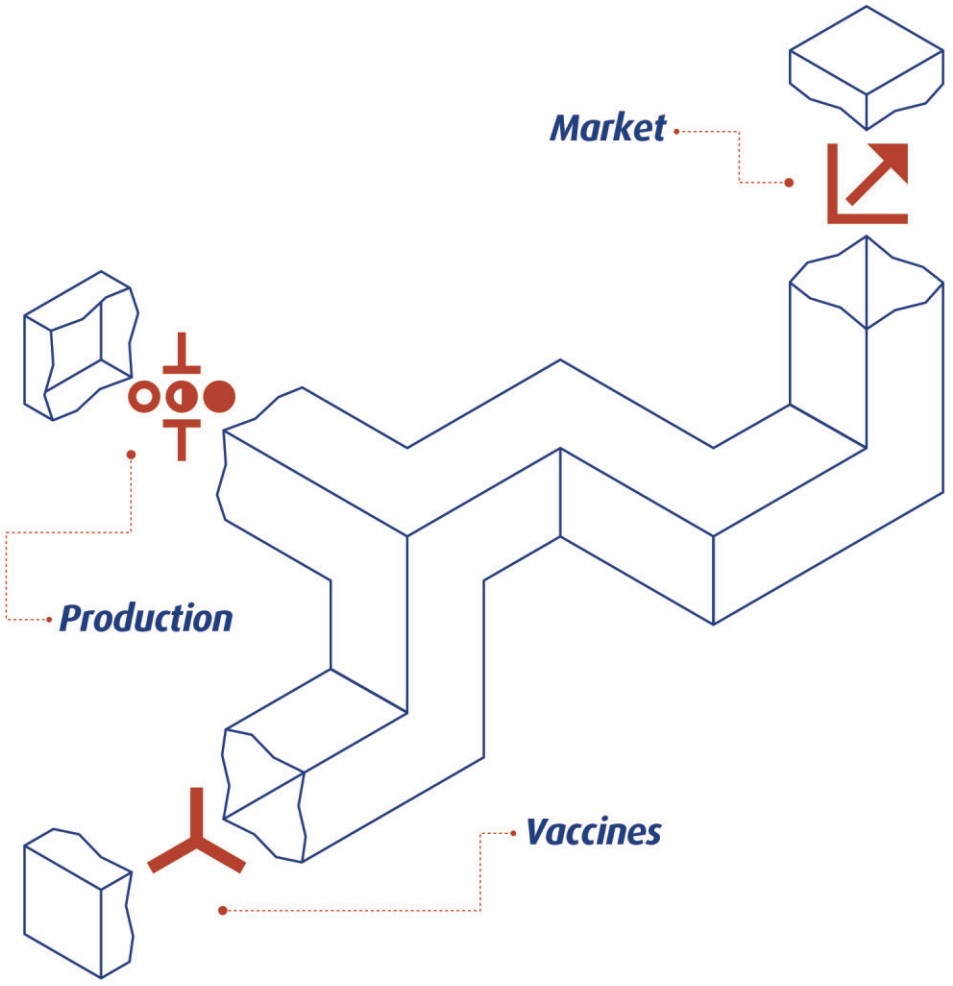

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"Fundamentally, this unique approach forces a rigorous analysis of the product requirements and the risks associated with the development upfront so likely issues can be prevented before they happen. The development approach builds the formulation up from sound foundations and crucially focuses on the physical and chemical requirements and the biological challenge."

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Catalent Invests $14 Million at its Softgel Facility

Catalent recently announced that work is underway to expand integrated turnkey softgel capabilities at its facility in Eberbach, Germany. The $14-million expansion, which is scheduled to be completed by mid-2020, includes two new softgel encapsulation lines dedicated to Catalent's proprietary Vegicaps technology. This addition is driven by the increased global demand for animal-free consumer health products, and these new lines will be completed by September 2019. The investment also includes new printing technology, a state-of-the-art vision inspection system, expansion of the facility's softgel coating capabilities, and the addition of further packaging capacity.

"The Eberbach facility is our biggest softgel development and manufacturing facility in Europe with a capacity of more than 10 billion softgel capsules per year," said Raoul Bernhardt, General Manager of the Eberbach facility. "This investment reflects the importance of the site and will enable us to better serve our customers with increased volumes and turnkey services."

In addition to these capital investments, the site is increasing its total production output by growing the workforce by more than 10% across Operations, Quality Control, and related supporting functions.

The 360,000-sq-ft facility offers integrated softgel manufacturing services that simplify supply chain management and deliver products faster to market. In addition to handling prescription pharmaceuticals, over-the counter pharmaceuticals, nutritional supplements, medical devices, and animal health products, the facility also specializes in handling highly potent and cytotoxic compounds within an isolated, self-contained cytotoxic suite. This is the latest expansion at the facility with the most recent one dating to early 2015 when it was expanded to include additional softgel coating and blister packaging equipment.

Catalent is the leading global diversified provider of advanced delivery technologies and development solutions for drugs, biologics and consumer health products. With more than 85 years serving the industry, Catalent has proven expertise in bringing more customer products to market faster, enhancing product performance and ensuring reliable clinical and commercial product supply. Catalent employs over 11,000 people, including over 1,800 scientists, at more than 30 facilities across five continents, and in fiscal year 2018 generated approximately $2.5 billion in annual revenue. Catalent is headquartered in Somerset, New Jersey. For more information, visit www.catalent.com.

ChemioCare Announces Initiation of PETT-Based (Permeation Enhanced Transdermal Technology) Lenalidomide Program

ChemioCare USA Inc. recently announced it is initiating development of a transdermal formulation of lenalidomide, which is currently marketed in an oral form. ChemioCare believes that by applying its permeation enhanced transdermal technology (PETT), it can potentially target and deliver the optimal continuous lenalidomide AUC (drug level area under the curve) that may lead to reduced drug toxicity and improvement in the overall safety profile of the drug. These improvements can be expected to allow patients to stay on their treatment longer with fewer dose interruptions while improving their quality of life. The benefits of transdermal delivery may transform lenalidomide PETT into a new superior drug profile.

Lenalidomide is the standard of care for the treatment of multiple myeloma, and is also indicated for the treatment of certain forms of myelodysplastic syndrome and mantle cell lymphoma. In 2018, revenues reached $9.6 billion globally with $6.5 billion in the US. The branded form is projected to continue to grow at double-digit growth rates in the coming years. Lenalidomide represents a major well-established blockbuster product with no clear replacement in development in the world of Oncology. Lenalidomide is expected to experience first generic entries in 2021 or 2022.

ChemioCare conducted a systematic assessment of feasibility and market potential to identify PETT transdermal reformulation targets from the thousands of potential opportunities that exist. These opportunities were further refined to select key patches that fit in the technology and may have the potential to benefit patients the most. "We are delighted to launch the first program out of the PETT prioritization project, which has the potential to transform the multiple myeloma treatment paradigm," said Pedro Lichtinger, Chairman and CEO.

The characteristics of our novel PETT platform provide a broad horizon to improve the delivery of many drugs to achieve superiority or enable new indications. Drugs delivered by PETT can be developed to target optimal blood levels for prolonged periods of time thereby minimizing the high and low blood levels associated with toxicities or treatment failure. "PETT technology works like a continuous injection of drug into the blood stream that can be precisely delivered to provide the right amount of drug to work without providing too much drug which can cause toxicity," said Dr. Jamie Oliver, CMO. Dr. Oliver further stated that "in the case of lenalidomide, both efficacy and toxicity are associated with its AUC and oral medications just are not able to precisely maintain the optimal blood levels over the dosing interval."

A biotechnology company focused on improving the profiles of medicines through its proprietary permeation enhanced transdermal technology (PETT). The platform technology uniquely combines high flux and sustained release into a matrix drug in adhesive patch. ChemioCare has three patches in development for cancer and cancer supportive care.

OmniSeq & LabCorp Extend Exclusive Distribution Pact & Complete Follow-On Investment Agreement

OmniSeq and LabCorp recently announced an extension of their exclusive distribution agreement as well as an additional investment by LabCorp. The distribution agreement and LabCorp's initial investment in OmniSeq's Series B financing round were first announced in August 2017.

The distribution agreement originally provided LabCorp with exclusive distribution rights for the OmniSeq Comprehensive and Immune Report Card clinical assays. The agreement's extension adds OmniSeq Advance, as well as the OmniSeq MSI NGS test. Together, OmniSeq's next-generation sequencing (NGS)-based assays provide comprehensive genomic and immune profiling to enable oncologists to select the most appropriate therapies or clinical trials for each patient. Pursuant to the agreement, OmniSeq's suite of advanced tests will be exclusively offered by LabCorp to US-based physicians through Integrated Oncology, a member of the LabCorp Specialty Testing Group, and globally to biopharmaceutical customers through Covance, LabCorp's drug development business.

Proceeds from LabCorp's additional investment will be used by OmniSeq to pursue FDA approval or clearance of its proprietary NGS-based comprehensive genomic and immune profiling panels, to continue the development of new panels intended to predict the response to checkpoint inhibitors and other immunetherapies, and to support the expansion of testing operations.

According to Mark Gardner, CEO of OmniSeq, "We are honored to extend our partnership with LabCorp to expand access to OmniSeq's advanced testing methodologies to help provide more precise guidance in the selection of the right therapy or clinical trial for patients diagnosed with a broad range of cancers. With LabCorp's continued collaboration and support, we will have the funding to augment the clinical utility of our testing services, and to make the best of precision medicine more readily available to physicians and patients across the US and to biopharmaceutical companies around the globe."

"OmniSeq has been an excellent partner for us in both clinical studies and clinical diagnostics," said Marcia Eisenberg, Chief Scientific Officer of LabCorp Diagnostics, and a member of OmniSeq's board of directors. "Working together, we have brought advanced NGS-based diagnostics to market, supporting more informed clinical decisions for targeted and immuno-oncology therapies. By combining the clinical trials capabilities of Covance, the single-source lab solutions services of Integrated Oncology, and the testing services of OmniSeq, LabCorp is uniquely positioned to bring precision medicine to oncology patients across the country."

OmniSeq, an innovation of Roswell Park Comprehensive Cancer Center, is a molecular diagnostic laboratory based in Buffalo, NY. OmniSeq endeavors to find the right drug or the right trial for every patient by improving access to better cancer treatment options through molecular profiling. OmniSeq offers four NGS-based assays: OmniSeq MSI NGS, Immune Report Card, OmniSeq Advance, and OmniSeq Comprehensive. For more information, call +1-800-781-1259 or visit www.omniseq.com.

Vyome Therapeutics Begins Dosing in Phase 2 Trial of Bactericidal Antibiotic Topical Gel

Vyome Therapeutics Inc. recently announced it has dosed the first patient in its Phase 2 trial of the company's lead clinical candidate, VB-1953, for the treatment of moderate-to- severe inflammatory acne vulgaris. VB-1953 is the first bactericidal antibiotic topical gel formulation for treatment of acne vulgaris capable of not only reducing infection due to P. acnes with anti-inflammation action, but also retarding antibacterial resistance.

"There are about 10 million patients in the US with moderate-to-severe inflammatory acne who are resistant to the currently approved bacteriostatic antibiotics. There is an urgent need for a new and effective therapy that yields higher clinical response than what is currently available. With its novel bactericidal and anti-inflammatory mechanisms of action, VB-1953 could potentially meet this unmet need, and we look forward to sharing the important results of this trial in early 2020," said Venkat Nelabhotla, Chief Executive Officer of Vyome Therapeutics.

The double-blind, randomized, vehicle controlled, dose ranging Phase 2 study is evaluating the safety and efficacy of VB-1953 topical gel when applied once versus twice daily for 12 weeks in subjects with moderate-to-severe inflammatory facial acne vulgaris. The company plans to enroll up to 480 patients. The primary efficacy endpoint of the study is the absolute change from baseline in inflammatory lesion counts in each treatment arm at Week 12 and the secondary endpoint is the proportion of subjects at week 12 achieving an Investigator's Global Assessment of Inflammatory Acne (IGA) score of 0 (clear) or 1 (almost clear) with at least a 2-point improvement from baseline.

"Today, patients who are not responding to current medicines have no option outside of oral systemic acne treatments which are well-known for their potential adverse events. VB-1953 has the potential to not only serve as an effective topical therapy for these patients, but also to delay the onset of resistant bacterial strains, serve as a potent anti-inflammatory agent, and prevent patients from needing systemic acne treatments," said Dr. Angelo Secci, Chief Medical Officer of Vyome Therapeutics.

Vyome's lead molecule, VB-1953, is a first-in-class topical bactericidal antibiotic clinical drug candidate with a novel mechanism of action that includes inflammation-reducing capabilities as well as the demonstrated ability to treat antibiotic resistant P. acnes strains. VB-1953 is currently being studied in a Phase 2 clinical trial in the US. In preclinical studies, VB-1953 showed activity against clindamycin-resistant P. acnes bacteria, a low emergence of resistance and the ability to reduce inflammation. VB-1953 is delivered with a microtechnology gel system that ensures the drug is retained at the site of infection and minimizes systemic exposure. Acne caused by antibacterial-resistant P.acnes currently poses an emerging and unmet need for patients worldwide, with a potential $2B market opportunity in the US alone.

ExCellThera's Lead Technology Receives FDA Regenerative Medicine Advanced Therapy Designation

ExCellThera Inc. recently announced the US FDA has granted regenerative medicine advanced therapy (RMAT) designation to its lead technology, ECT-001, in the treatment of hematologic malignancies. The RMAT designation is based on strong data from Phase I/II clinical trials using ECT-001 to expand stem and immune cells for the treatment of blood cancers.

RMAT designation is granted by the FDA under the 21st Century Cures Act for cell therapies, tissue-engineered or similar products intended to treat or cure a serious disease, and which demonstrate preliminary evidence to address an unmet clinical need. It accords all the benefits of the FDA's fast track and breakthrough therapy designation programs, including an ability to interact with the agency to discuss the potential acceleration of regulatory approval. Under the auspices of the RMAT designation, FDA will work closely with ExCellThera and provide advice on generating the evidence needed to support approval of ECT-001 in an efficient manner.

"The FDA's RMAT designation is a clear signal of confidence in the potential of our lead cell therapy drug product, ECT-001, to treat patients with hematologic malignancies," said Dr. Guy Sauvageau, CEO and founder of ExCellThera. "We look forward to working with the FDA within the RMAT framework to advance ECT-001 through the final phases of clinical development in an expedited manner."

Various clinical studies using ECT-001 are currently ongoing in the treatment of multiple myeloma, high-risk leukemia and other hematologic malignancies. In addition, ExCellThera plans to initiate additional clinical trials, including a pivotal trial in the United States and Canada, in the coming months. ECT-001 has also received FDA orphan drug designation for the prevention of graft-versus-host disease.

The ECT-001 technology is a combination of a small molecule, UM171, and an optimized culture system. The technology, capable of expanding the number of stem and immune cells exponentially in as little as seven days, is used in novel curative cord blood transplant therapies for patients with blood cancers, allowing rapid engraftment, greatly reduced incidence of transplant-related mortality, low risk of chronic graft-versus-host disease and low risk of relapse, resulting in better outcomes for patients.

ExCellThera is an advanced clinical-stage biotechnology company delivering molecules and bioengineering solutions to expand stem and immune cells for use in novel one-time curative therapies for patients with hematologic malignancies, autoimmune and other diseases. ExCellThera's lead solution combines a proprietary small molecule, UM171, and an optimized culture system. In pursuit of better treatments for patients, the company is building out its portfolio of products, as well as supporting best-in-class clinical trials. For more information, visit excellthera.com.

Kamada Announces FDA Acceptance of Inhaled AAT Program

Kamada Ltd. recently announced receipt of a letter from the US FDA stating the company has satisfactorily addressed the concerns and questions regarding its Inhaled Alpha-1-Antitrypsin (Inhaled AAT) program for the treatment of Alpha-1 Antitrypsin Deficiency (AATD), previously communicated by the agency.

This most recent response from the FDA in connection with the development plan for Inhaled AAT follows positive scientific advice received in July 2018 from the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) in Europe. Kamada intends to conduct a unified global pivotal Phase 3 clinical trial in the US under an Investigational New Drug (IND) application and in Europe under a Clinical Trial Authorization (CTA) in order to submit marketing applications for regulatory approval in both regions. The company expects to initiate the Phase 3 study during the second half of 2019, subject to a successful completion of a Human Factor Study (HFS), to be initiated during the current quarter. The HFS is required to support the combination product, consisting of Kamada's AAT for inhalation and the investigational eFlow nebulizer system of PARI Pharma GmbH.

The Phase 3 study protocol was designed to test the safety and efficacy of the company's inhaled AAT product in patients with AATD, and is meeting the requirements provided by the FDA and EMA. The protocol includes the enrollment of up to 250 subjects who will be randomized 1:1 to receive either Inhaled AAT at a dose of 80 mg once daily, or placebo, during 2 years of treatment. The primary endpoint will be lung function measured by FEV1, and secondary endpoints will include lung density changes measured by CT densitometry, as well as other parameters of disease severity.

"We are extremely pleased to receive this feedback from the FDA regarding our Inhaled AAT for the treatment of AATD," said Amir London, Kamada's Chief Executive Officer. "We expect to initiate the trial in the second half of 2019, subject to successfully completing the required human factor study. The current global intravascular AAT market is estimated at more than $1 billion annually, and is growing at approximately 6%-8% each year. We believe that our Inhaled AAT, if approved, could capture a significant share of this growing market due to the ability of our treatment to directly reach the lungs, as well as its enhanced convenience that would improve the quality of life for patients. We are encouraged by the strong support we continue to receive from the patient population and leading AATD physicians."

Kamada Ltd. is focused on plasma-derived protein therapeutics for orphan indications, and has a commercial product portfolio and a late-stage product pipeline. The company uses its proprietary platform technology and know-how for the extraction and purification of proteins from human plasma to produce Alpha-1 Antitrypsin (AAT) in a highly purified, liquid form, as well as other plasma-derived Immune globulins.

Rexahn & BioSense Global Announce Collaboration & License Agreement

Rexahn Pharmaceuticals, Inc. and BioSense Global LLC recently announced a collaboration and license agreement to advance the development and commercialization of RX-3117 for pancreatic cancer and other cancers in Greater China.

Under the agreement, Rexahn will grant BioSense an exclusive license to develop and commercialize RX-3117 in Greater China. Rexahn will receive an upfront payment and will be eligible to receive additional development, regulatory, and commercial milestones up to a total of $226 million contingent on achieving regulatory and commercial goals related to pancreatic cancer and additional indications. Rexahn will also be eligible to receive tiered royalties in the low double digits to mid teens on annual net sales in the territory. The companies will collaborate to develop RX-3117 for pancreatic cancer and other indications. BioSense will fund all activities related to the development and commercialization of RX-3117 in Greater China and will initiate a Phase 2 study to evaluate the drug candidate in up to three additional indications not previously studied by Rexahn.

"Rexahn is focused on developing novel therapies for people with difficult-to-treat cancers. This partnership will enable us to extend the development of RX-3117 to patients in Greater China and also to evaluate RX-3117 in additional indications in collaboration with BioSense," said Douglas Swirsky, President and CEO of Rexahn. "We are excited to work with the experienced regulatory and development team at BioSense to advance the development of RX-3117 towards regulatory approval in Greater China."

Andy Li, PhD, President, and CEO of BioSense Global, added "We are delighted to partner with Rexahn to develop RX-3117 for the Greater China markets. Cancer is the leading cause of death in China with over 4 million new diagnoses and almost 3 million deaths per year. Prognosis is poor for certain cancers and treatment options are limited. Despite the significant success of immunotherapy, chemotherapy will remain a critical component of treatment regimens for many cancers. With its unique tumor-targeting mechanism, we believe RX-3117 could become a safer, more efficacious yet affordable treatment option to patients and doctors. We are excited to advance the development of RX-3117 for cancers that are especially prevalent among Chinese patients."

RX-3117 is a novel, investigational, oral, small molecule nucleoside compound. Once intracellularly activated (phosphorylated) by UCK2, it is incorporated into the DNA or RNA of cells and inhibits both DNA and RNA synthesis, which induces apoptotic death of tumor cells. Due to the high level of over expression of UCK2 in cancer cells, RX-3117 offers the potential for a targeted anti-cancer therapy with an improved efficacy and safety profile. RX-3117 is currently being studied in a Phase 2a clinical trial in combination with Abraxane (paclitaxel protein-bound particles for injectable suspension) in first line metastatic pancreatic cancer patients and a Phase 2a clinical trial in patients with advanced or metastatic bladder cancer. It has received Orphan Drug designation for the treatment of pancreatic cancer.

Bellerophon Announces Agreement With FDA on Regulatory Approval Pathway for INOpulse

Bellerophon Therapeutics, Inc. recently announced it has reached agreement with the US FDA on the regulatory approval pathway for INOpulse in patients with Pulmonary Hypertension associated with Interstitial Lung Disease (PH-ILD).

In January 2019, the company reported positive results from Cohort 1 of its ongoing Phase 2b randomized, double-blind, placebo-controlled clinical study (iNO-PF) of INOpulse for the treatment of PH-ILD. Subjects on active treatment demonstrated a statistically significant improvement of 34% in moderate to vigorous physical activity (MVPA) as compared to subjects on placebo, as well as improvements in overall activity, oxygen saturation and additional functional measures. Based on these data and INOpulse's safety profile, the FDA agreed with Bellerophon on the use of MVPA as the primary endpoint in the pivotal Phase 3 study, as measured by a medical wearable continuous activity monitor (actigraphy). In addition, the agency agreed with the company's proposal that the Phase 2b study be amended to a Phase 2/3 trial. This agreement allows a seamless transition into Cohort 3 of iNO-PF, which will serve as the pivotal Phase 3 trial.

"Reaching this critical agreement with the FDA for INOpulse in PH-ILD represents a significant milestone for Bellerophon as it confirms the validity of MVPA as a clinically meaningful endpoint, enables us to build upon the robust data generated to date from iNO-PF and substantially shortens the regulatory pathway for our therapy in a disease with a serious unmet need," said Fabian Tenenbaum, Chief Executive Officer of Bellerophon. "We appreciate the FDA's support and their agreement on both the primary endpoint and the seamless pivotal Phase 2/3 design, creating the opportunity for INOpulse to become the first approved therapy in PH-ILD. We expect to complete Cohort 2 and initiate the pivotal Phase 3 trial in the second half of this year."

"Compared to surrogate endpoints, such as 6-minute walk distance or patient reported outcomes, change in MVPA provides a direct and continuous measure of physical activity in PH-ILD patients, who have limited ability to perform even the most basic daily tasks," said Steven D. Nathan, MD, FCCP, Medical Director of the Advanced Lung Disease and Lung Transplant Program at Inova Fairfax Hospital and Chair of Bellerophon's Steering Committee. "INOpulse is a selective vasodilator that can improve both cardiopulmonary circulation and oxygenation, increasing the ability to perform physical activities. The improvements in MVPA seen to date in iNO-PF support INOpulse's potential to address this unmet medical need. I am excited by the acceleration of this program into Phase 3 and look forward to the further evaluation of this promising therapy in the clinic."

Bellerophon Therapeutics is a clinical-stage biotherapeutics company focused on developing innovative therapies that address significant unmet medical needs in the treatment of cardiopulmonary diseases. The company is currently developing multiple product candidates under its INOpulse program, a proprietary pulsatile nitric oxide delivery system.

XOMA Acquires Royalty Rights to Five Hematology Candidates

XOMA Corporation recently announced it has agreed to acquire the rights to potential royalty payments and a portion of the potential milestone payments associated with five hematology assets from Aronora, Inc. Three of the assets are anti-thrombotic candidates that are covered by a collaboration with Bayer, a global leader in hematology therapeutics. Two of the collaboration assets are in early to mid-stages of development and the third is a Phase 2 candidate that is subject to an option. In addition, XOMA agreed to acquire the rights to potential royalty payments and a portion of the potential upfront and milestone payments associated with two unpartnered hematology programs from Aronora.

"The transaction diversifies XOMA's royalty interest portfolio by expanding into hematology indications, and these innovative anti-thrombotic candidates have the potential to address very large market opportunities. The fact that three assets are part of an ongoing collaboration between Aronora and Bayer, a company for whom we have tremendous respect, strengthens our belief in the potential of these therapies to address significant unmet medical needs," said Jim Neal, Chief Executive Officer at XOMA. "These assets possess the characteristics we have established for our royalty aggregator business model: outstanding development partner, mid-stage to early clinical stage of development, important therapeutic categories, and sizable potential royalty opportunities. Aronora's expertise in hematology, with an advanced focus on anti-thrombotic monoclonal antibodies, intrigued our team."

The five royalty interest assets XOMA acquired from Aronora are: Three Bayer collaboration monoclonal antibody (mAb) programs targeting factor XI/XIa: BAY1213790 in Phase 2 clinical development; BAY1831865 in early clinical development; and Aronora's AB023 (xisomab 3G3) in Phase 2 development; and, Two proprietary hematology programs at Phase 1 and preclinical stage: AB002, a thrombin analog, and AB054, a factor XII mAb, positioned for acute cardiovascular events, medical device associated clots, and/or inflammation.

Under the terms of the agreement, XOMA will make an initial $6-million payment subject to closing conditions defined in the agreement. XOMA will make an additional payment of up to $3 million to Aronora upon fulfillment of certain other conditions. In return, XOMA will receive, on average, low single-digit royalties on future sales of these five products and 10 percent of the milestones associated with each of the assets. In addition, XOMA could pay Aronora sales-based milestones on each asset if XOMA's royalty receipts related to each program exceed certain thresholds. XOMA expects this transaction to close within the next 90 days.

XOMA has built a significant portfolio of products that are licensed to and being developed by other biotechnology and pharmaceutical companies. The company's portfolio of partner-funded programs spans multiple stages of the drug development process and across various therapeutic areas. Many of these licenses are the result of XOMA's pioneering efforts in the discovery and development of antibody therapeutics. The company's royalty-aggregator business model includes acquiring additional licenses to partner-funded programs.

Thermo Fisher Scientific Announces Collaboration to Advance Biopharmaceutical Characterization & Monitoring Methods

Thermo Fisher Scientific and Genovis recently announced a collaborative research project to develop advanced end-to-end workflows for the preparation, characterization, and monitoring of novel and complex biotherapeutics using liquid chromatography-mass spectrometry (LC-MS).

Bringing together Thermo Fisher's leading LC-MS technology with the advanced enzyme-based sample preparation and analysis techniques of Genovis will enable the development of robust, automation-ready, magnetic bead, and chromatography-based workflows for the streamlined analysis of biotherapeutics. Expertise from Thermo Fisher's Global Customer Solution Centers will also help Genovis to determine optimal hardware/software configurations and suitable consumables for critical quality attribute (CQA) analysis of biotherapeutics during the research and development phase.

"With the shift toward large biological entities, companies are aiming to bring to market medicines with greater affinity and efficacy, but these medicines also present an additional level of analytical complexity," said John Rontree, Senior Director, Global Marketing and Strategy, Pharmaceuticals and Biopharmaceuticals, Thermo Fisher Scientific. "By collaborating with Genovis, we plan to develop comprehensive workflows that provide robust and advanced solutions for preparing and assessing complex biotherapeutics."

"We are excited to work with Thermo Fisher Scientific to continue our goal toward more automated analytical workflows," added Fredrick Olsson, Chief Executive Officer at Genovis. "Through this collaboration we will be able to develop new products and workflows on world-class instrumentation together with experts from Thermo Fisher's European Biopharma Customer Solution Center and serve the growing analytical needs of biopharma customers of both companies with meaningful innovations."

The combination of the Thermo Scientific Vanquish Duo UHPLC Systems (with Dual LC workflow) and the Thermo Scientific Chromeleon Chromatography Data System (CDS) Software with the SmartEnzyme technology from Genovis will enable the development of LC-MS-based protocols for O-glycosylation profiling and automated high-throughput workflows for CQA analysis of monoclonal antibodies at the subunit level.

Thermo Fisher Scientific Inc. is the world leader in serving science, with revenues of more than $24 billion and approximately 70,000 employees globally. Our mission is to enable our customers to make the world healthier, cleaner and safer. We help our customers accelerate life sciences research, solve complex analytical challenges, improve patient diagnostics, deliver medicines to market and increase laboratory productivity.

Neon Therapeutics Announces Completion of Enrollment in Phase 1b Clinical Trial

Neon Therapeutics, Inc. recently announced the completion of enrollment in NT-002, its Phase 1b clinical trial evaluating NEO-PV-01 with KEYTRUDA (pembrolizumab) and chemotherapy in patients with untreated advanced or metastatic non-small cell lung cancer (NSCLC). NEO-PV-01 is a personal neoantigen vaccine custom-designed and manufactured based on the neoantigens identified by Neon's proprietary bioinformatics engine, RECON, as being the most therapeutically relevant for an individual patient.

"Our NT-002 trial has the potential to demonstrate the effect that NEO-PV-01, our personal neoantigen vaccine, may have in combination with pembrolizumab and chemotherapy, the current standard of care in first-line metastatic NSCLC. While the pembrolizumab-chemotherapy regimen has shown improved clinical outcomes in first-line NSCLC, we believe NEO-PV-01 could improve the therapeutic efficacy of this combination by directing T cells to target neoantigens expressed in each patient's tumor," said Richard Gaynor, MD, President of Research and Development at Neon Therapeutics.

The trial, conducted in collaboration with Merck, is evaluating the safety, tolerability, and efficacy of NEO-PV-01 in the metastatic setting. Patients enrolled in the trial undergo an initial tumor biopsy and then begin 12 weeks of treatment with pembrolizumab and chemotherapy. They receive the NEO-PV-01 vaccination at week 12 and treatment with pembrolizumab continues throughout the trial. The primary endpoint of the trial is safety. In addition, Neon is evaluating immune responses and clinical outcomes. Neon expects to report immune and clinical outcome data from NT-002 over the course of 2020.

"This trial seeks to build on the proof-of-mechanism established in our NT-001 trial, which combines NEO-PV-01 with OPDIVO (nivolumab) in patients with metastatic melanoma, NSCLC and bladder cancer, and will highlight the impact of the addition of chemotherapy to our NEO-PV-01 and anti-PD-1 combination has on the potential to improve the suppressive tumor microenvironment found in many cancers," Dr. Gaynor continued.

KEYTRUDA is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ. OPDIVO is a registered trademark of Bristol-Myers Squibb Company.

NEO-PV-01 is a fully personal cancer vaccine targeting neoantigens that is custom-designed and manufactured for each individual patient based upon the tumor's unique mutational fingerprint. The neoantigen-targeting peptides in NEO-PV-01 are intended to generate an anti-tumor immune response that directs patients' T cells to target and kill their cancer cells. NEO-PV-01 is being studied in multiple ongoing Phase 1 clinical trials.

Neon Therapeutics is a clinical-stage immuno-oncology company and a leader in the field of neoantigen-targeted therapies, dedicated to transforming the treatment of cancer by directing the immune system towards neoantigens. Neon is using its neoantigen platform to develop both vaccine and T cell therapies, including NEO-PV-01, a clinical stage neoantigen vaccine for the treatment of metastatic melanoma, non-small cell lung cancer, and bladder cancer; NEO-PTC-01, a neoantigen T cell therapy for the treatment of solid tumors; and NEO-SV-01, a neoantigen vaccine for the treatment of a subset of estrogen-receptor-positive breast cancer.

Cambrex Completes New Quality Control Laboratory for Generic API Development in Milan

Cambrex Corporation (NYSE: CBM), the leading small molecule company providing drug substance, drug product and analytical services across the entire drug lifecycle, today announced that it had opened a new 120m2 quality control (QC) laboratory at its site in Paullo, Milan, Italy. The laboratory expands on the current QC facilities that analyze and test its generic API portfolio of products during development and manufacturing. The QC laboratory is now fully operational, having been authorized by the Agenzia Italiana Del Farmaco (AIFA).

The additional laboratory space will increase the efficiency of the QC department as the site expands the number of generic APIs in development. New instruments, including a polarimeter and infrared spectrometer, have been added, with the systems linked to secure, electronic data capturing software to allow full traceability in line with regulatory requirements.

"Our facility in Milan is the center of the Cambrex's generic API business, and this investment is the latest in a number of steps we have taken at the site to increase its efficiency and flexibility as we look to grow the portfolio of products that we offer," commented Aldo Magnini, Managing Director, Cambrex Milan. "In the last year the company has made strategic investments to expand its capabilities in research and development, manufacturing, and now QC capabilities, as we look to take advantage of the opportunities that are arising in the generic market."

Cambrex manufactures over 70 generic APIs which are produced to cGMP standards at the Milan site, where seven production departments are supported by a pilot plant, kilo scale plant and development and analytical laboratories.

Cambrex is the leading small molecule company that provides drug substance, drug product and analytical services across the entire drug lifecycle. The company provides customers with an end-to-end partnership for the research, development and manufacture of small molecule therapeutics. With over 35 years' experience and a growing team of over 2,000 experts servicing global clients from sites in North America and Europe, Cambrex is a trusted partner in branded and generic markets for API and dosage form development and manufacturing.

Cambrex offers a range of specialist drug substance technologies and capabilities including biocatalysis, continuous flow, controlled substances, solid state science, material characterization and highly potent APIs. In addition, Cambrex can support conventional dosage forms including oral solids, semi-solids and liquids and has the expertise to manufacture specialist dosage forms such as modified-release, fixed dose combination, pediatric, bi-layer tablets, stick packs, topicals, controlled substances, sterile and non-sterile ointments. For more information, please visit www.cambrex.com.

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Formulation Forum

Formulation Development From Preclinical to First-In-Human

By: Jim Huang, PhD, Founder & CEO, Ascendia Pharmaceuticals

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Winning against all odds of "one approval out of every 5,000 to 10,000 compounds"

According to PhRMA July 2013 Profile, for every 5,000 to 10,000 compounds that enter the drug pipeline, only one receives final approval. There is only a 16% probability of being approved for compounds entering the Phase 1 stage. The average R&D budget for each new medicine is $1.2 billion, with more recent studies estimating the costs to be even higher.

When a compound enters preclinical development for a GLP tox study from the drug discovery stage, we face a question of how to develop a tox and clinical formulation that ensures the success of IND and first dose in human. According to Lipper, et al, poor biopharmaceutical properties of compounds is attributed to 39% of the failure of the new drug program under development.[1] A compound with poor biopharmaceutical properties or improper formulation design could lead to a delay in the project or even program termination. The key considerations for successful tox and Phase 1 formulation development consist of the following:

- Pre-formulation of drug candidate
- Biopharmaceuticals evaluation
- Analytical method development
- Formulation development
- cGMP manufacturing for clinical trials

PRE-FORMULATION CHARACTERIZATION

One of the primary goals of preformulation studies is to identify the physicochemical characteristics of a drug candidate that predict drug product performance *in-vitro* and *in-vivo*. Pre-formulation studies usually cover the following items: pKa, LogP/LogD, pH solubility curve, pH stability curve, solvent solubility, particle size distribution, hygroscopicity, API solid-state stability under stressed temperature/humidity conditions, melting point, salts form evaluation, polymorph/hydrate/solvate evaluation, forced degradation under different stressed conditions (light, heat, oxygen, acidic, and alkaline pH, etc), stability-indicating analytical methods for characterization of active, and impurities.

Those parameters are important to guide the selection of a potential drug candidate and to determine future formulation strategies.

BIOPHARMACEUTICAL ASSESSMENT

The biopharmaceutical properties generated during the drug candidate selection process, which is critical for the next step of formulation development and for selection of formulation technologies, include compound dissolution in simulated gastric and intestine fluids, solubility, and stability in simulated GI fluids, enzymatic stability, intestine membrane permeability, and modeling and simulation of animal and human PK and bioavailability. The steps in the absorption process include the disintegration and dissolution of the compound from the solid dosage form into the gastrointestinal lumen. The potential limiting steps for absorption of the compound through the GI membrane (including dissolution, solubility, and permeability limited process) should be fully understood. A thorough biopharmaceutical characterization will minimize the risk of selection of a poorly

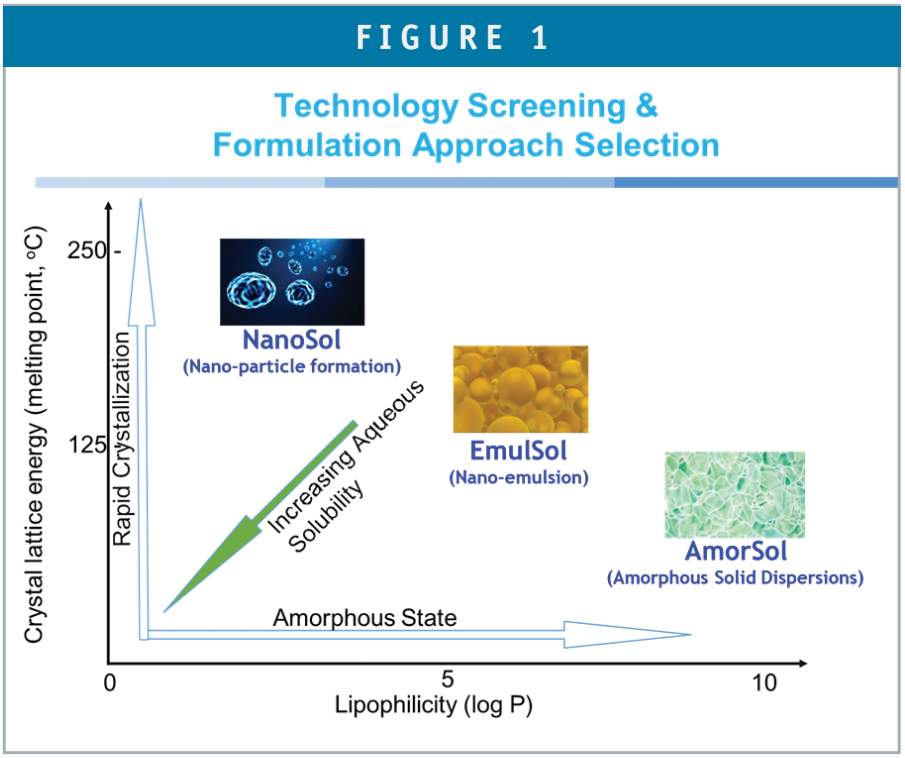
designed formulation, and allow for an efficient, science-based formulation development process.

According to the FDA biopharmaceutics classification system (BCS), drug compounds can be classified into four classes based on their solubility and permeability (bioavailability). Based on the BCS classification of the drug candidate, different formulation strategies can be explored. If a drug candidate is predicted to be BCS I (soluble and permeable), a simple formulation strategy can be employed for the GLP tox and first-in-human studies. Neat compounds can be filled in bottles (drug in bottle) or into capsule (drug in capsule). However, if a compound does not wet easily, has a low dose, has a bad taste, or has a poor flow properties, a formulated powder blend of drug-excipient, capsule-containing granulation, or immediate-release tablet could be utilized to facilitate the dissolution, content uniformity, and taste-masking.

For BCS III compound (soluble, but poor permeability), excipients with permeation-enhancing properties may be required to ensure enough oral bioavailability. For example, for soluble peptides, a lipid formulation encapsulated in a bead, or a capsule with enteric coating could help enhance absorption of the peptide in the intestine while protecting its gastric degradation in the stomach.

If a drug molecule is predicted to have challenging oral bioavailability [BCS II (insoluble, but permeable), or IV (insoluble, poor permeability)], choosing an appropriate formulation strategy for tox and human Phase 1 is critical to ensure the solubility and bioavailability of those drug candidates is maximized in order to realize its full potential for safety and efficacy evaluation in animal and human. Other routes of administration, such as injectable, topical, and nasal routes, can be considered for BCS III and IV compounds.

FIGURE 1



ENABLING FORMULATION TECHNOLOGIES

For challenging compounds, there are several enabling formulation approaches, ranging from salt form formation, solution formulation by pH control, co-solvent or complex formation, particle size reduction by micronization/nanosizing, lipid formulation (SEDDS and emulsion), amorphous solid dispersions, and nanoparticles.

A guided formulation selection tree can be followed in junction with considerations in route of administration, phase of development, target patient population, freedom of operation, available technology in house, and marketing considerations.[2] Figure 1 shows the general rule of thumb in selection of formulation technology based on compound properties in melting point and lipophilicity.

Salt Form Selection

Salt form formation is an effective way to modify the solubility of molecules with ionizable functional groups (pKa). Selection of an appropriate solid form (polymorph, hydrate, or salt) for a compound is a key activity for drug development. Salts are usually considered when the physicochemical characteristics of the free acid or base pose problems in formulation and process, including issues in solubility, stability, size reduction, polymorphism, and bioavailability of the parent compound through changes in compound solubility and dissolution rate.

Solution Formulation

Solubility of weakly acidic or basic compounds can be increased by a pH-controlled solution approach. Cyclodextrin, surfactant, polymer, and co-solvents, such as propylene glycol, polyethylene glycol, glycerin, etc, may also be added to further increase compound solubility in those media. One major limitation using pH-adjusted and co-solvent systems is potential drug precipitation once the formulation is administered into the

body by oral or IV routes, which may cause implications in injection pain, thrombophlebitis, variable PK profiles, and bioavailability. While cyclodextrin-based solution alone does not exhibit such precipitation phenomenon, the extent of solubility enhancement could be limited by cyclodextrin solubility and the maximum allowable daily dose of cyclodextrin due to its potential side effects at a high dose.

Size Reduction by Micronization or Nanosizing

For compounds with a high melting point and with a dissolution-limited absorption process, the dissolution rate and bioavailability of the drug substance can be significantly increased by reducing the particle size of the API. Micronization by fluid energy mills, such as jet milling, can efficiently reduce the average particle size down to below 10 microns, whereas using bottom-up (solution precipitation) and top-down (wet milling) processes can be used to produce nano-sized API below 300 nm. For insoluble compounds, reduction of particle size to submicron and nano levels not only could increase drug dissolution and bioavailability after oral administration, but has also demonstrated to reduce or eliminate food effect for some commercial products. Screening of polymer, surfactant, and stabilizer is required to ensure the physical stability and in-vivo performance of suspensions. Suspension is amenable to pediatric or geriatric formulations with addition of sweeter or taste-masking agents.

Lipid Emulsion Formulation

For lipophilic compounds with high logP values and a low-to-intermediate melting points, lipid formulations could be a good option for oral dosage forms of BCS II and IV compounds. Solution or liquid-filled capsules can be chosen for the first-in-human formulation. To overcome significant inter- and intra-subject variation in drug uptake observed on some macroemulsion systems (dispersion as coarse emulsion after administration to GI fluid), addition of surfactants to the lipidic excipients are frequently used to produce spontaneous self-emulsifying drug delivery systems (SEDDS) and self-microemulsifying drug delivery systems (SMEDDS) for compounds with poor water-solubility. However, there have been some challenges, such as chemical instability of compounds due to oxidation, capsule incompatibility, and tolerability issues, resulting from high level of surfactants, etc. Pre-formed nanoemulsions manufactured by a high-energy process to reduce the oil droplets to a nano level enjoys the same benefits of microemulsions, except they are more tolerable for patients due to significant reduced level of surfactant(s), which is suitable for different routes of administration, such as IV, SC, topical, oral dosage forms, and in some cases, vaccine adjuvant.

Nanoparticles

There are different types of nanostructured particles for use in the pharmaceutical field, which include nanostructured lipid carriers, solid lipid nanoparticles, liposomes, polymeric nanoparticles, and superparamagnetic nanoparticles, etc. Nanoparticles could overcome the limitations of traditional methods and bring new ways of delivery of therapeutic drugs for treatment of different disease areas, such as cardiovascular, CNS, immunology, cancer, imaging, and nutraceuticals. Through controlling the particle size, surface properties, drug loading, and release rate, drugs can be delivered to enhance bioavailability, to sustain for longer period of time with less frequent dosing (long acting delivery), or to target certain organs/tissues inside the body that are difficult to reach by conventional means.

There are different ways to prepare the nanoparticles: solvent evaporation, solvent injection, extrusion, emulsification, melt-emulsification, emulsification-solvent evaporation, milling, homogenization, microfluidization, or combined methods. Thorough understanding of the nanoparticle structure and its physical chemical properties in relationship with *in-vitro* and *in-vivo* performance is the key to further advance those technologies into the market.

Amorphous Solid Dispersion

For compounds with low-to-medium melting points, amorphous solid dispersions, where drug exists as a discrete particle dispersed within a polymer matrix, has dual strategy to enhance the aqueous solubility of a compound: 1) conversion of compound to an amorphous state, 2) reduction of compound particle to a molecule level, both of which enhance drug kinetic solubility and dissolution rate. Amorphous solid dispersion can be manufactured by spray drying, hot-melt extrusion, milling, or solvent-evaporation process. An excipient screening study should be employed to select polymer(s) or surfactant(s) that are not only miscible and chemically compatible with drug compounds, but also enhance compound solubility and physical stability at its amorphous state. Amorphous solid dispersions can be an effective approach for oral, transdermal, or inhalation routes to achieve greater exposure for drug compounds with poor solubility and high dose requirement. ◆

REFERENCES

1. Lipper et al. J. Pharm. Sci., 89(2) 145, 2000. https://jpharmsci.org/article/S0022-3549(16)30559-7/fulltext
2. Huang et al. Drug Development and Delivery, March 2019. https://drug-dev.com/formulation-forum-formulation-research-strategy-for-discovery-stage-new-drug-candidates/

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2018 Global Drug Delivery & Formulation REPORT

Three of a Four-Part Series

Part 1: A Global Review of 2018 Product Approvals

Part 2: Notable Product Drug Delivery and Formulation Approvals of 2018

Part 3: Notable Drug Delivery and Formulation Transactions and Technologies of 2018

Part 4: The Drug Delivery and Formulation Pipeline

By: Kurt Sedo, VP of Operations, and Tugrul Kararli, PhD, President & Founder, PharmaCircle

Introduction

It feels as though 2018 was a subdued year in terms of notable drug delivery product and technology deals. There were some of the typical deals as exemplified by Halozyme adding on to their partnership with Roche on the same terms as the past few years. Where things deviated from the usual was in the area of gene and cell therapy. The objective with many gene and cell therapy technologies parallels that of more traditional small molecule technologies, targeted delivery with customized pharmacodynamic properties. The Voyager Therapeutics agreement with AbbVie, for example, is intended to harness the Voyager technology to selectively target and deliver AbbVie's antibody transgenes across the blood brain barrier. The modern drug delivery and formulation toolbox needs to make room for these new gene and cell therapy technologies.

Quantitatively, Pharma transactions as a whole rose a respectable 6% in 2018 with a bit of a shift to Technology deals, up 19%, while Product Deals were up a more modest 5%.

In terms of drug delivery and formulation technologies, 2018 saw another 500 or so Active Technologies added to the toolbox, bringing the total to a little over 5,300. The majority of these technologies are still applicable to Injection-related applications, although its share dropped a point in 2018. The difference was made up by Medical Devices and the category of All Other as described later in this report.

This short overview of drug delivery and formulation transactions includes some of the numbers that color the trends of 2018 along with some thoughts on Notable Transactions and Technologies.

Special Thanks to Esay Okutgen, PhD, Director, Drug Delivery, PharmaCircle LLC for technical input.

Overall Transactions Were Up a Modest 5% in 2018

Table 1. Pharma Transactions 2018 and 2017 by Business Category

Business Category	2018	2017	Change (Y/Y)
Drug Delivery	**415**	**408**	**2%**
Company Acquisitions	4	12	
DD Technology Deals	169	136	24%
Discovery Technology Deals	5	13	
Joint Venture Deal	5	2	
Option Agreement	11	5	
Product Acquisitions	13	14	
Product Deals	207	225	-8%
Technology Acquisitions	1	1	
Generics	**49**	**20**	**145%**
Company Acquisitions	6	8	
Product Acquisitions	11	4	
Product Deals	32	8	300%
Pharma Services	**873**	**852**	**2%**
Company Acquisitions	137	150	-9%
DD Technology Deals	1	0	
Discovery Technology Deals	13	14	
Joint Venture Deal	1	2	
Pharma Services Deals	720	684	5%
Product Deals	0	2	
Technology Acquisitions	1	0	
PharmaBio	**1194**	**1118**	**7%**
Company Acquisitions	74	123	-40%
DD Technology Deals	8	2	
Discovery Technology Deals	279	201	39%
Joint Venture Deal	12	13	
Option Agreement	34	26	31%
Product Acquisitions	33	41	-20%
Product Deals	751	707	6%
Technology Acquisitions	3	5	
Other	**17**	**5**	
Total	**2548**	**2403**	**6%**

Source: PharmaCircle Strategic Deals Analyzer Module

Table Notes:
1. PharmaBio figures include Specialty Pharma transactions.
2. Transactions do not include Amendment or Termination Agreements.
3. Other includes Biosimilars.
4. Drug Delivery transactions are those where at least one element (technology, product) or one party to the transaction involves a drug delivery labeled asset.
5. Percentages are not provided where the underlying numbers are low.

- There was an overall 6% increase in transactions between 2017 and 2018. PharmaBio Company Acquisitions dropped (-40%). Does this suggest companies, been picked over or are the premiums too high?
- Drug Delivery transactions saw a perhaps significant shift from product related deals (-8%) to technology deals (+24%). Discovery Technology deals increased (+39%) perhaps reflecting an interest in doing more internal pipeline development.
- While there is only limited public data, Generics Product Deals were up a robust 300%. Pharma Service deals were up 5% and represented a bit more than a quarter of all transactions.

Product Related Deals Accounted for Almost Half of All Pharma Transactions in 2018

Table 2. Pharma Transactions 2018 and 2017 by Deal Type

Transaction Type	2018	2017	Change (Y/Y)	Share of Total (2018)
Pharma Services Deals	**720**	**684**	**5%**	**28%**
Product Deals	**1,061**	**1,006**	**5%**	**42%**
Product Acquisitions	58	60	-3%	2%
Product Deals	1,003	946	6%	39%
Technology Deals	**480**	**372**	**29%**	**19%**
DD Technology Deals	178	138	29%	7%
Discovery Technology Deals	297	228	30%	12%
Technology Acquisitions	5	6		
All Other	**287**	**341**	**-16%**	**11%**
Total	**2,548**	**2,403**	**6%**	**6%**

Source: PharmaCircle Strategic Deals Analyzer Module

Table Notes:
1. PharmaBio figures include Specialty Pharma transactions.
2. Transactions do not include Amendment or Termination Agreements.
3. Drug Delivery transactions are those where at least one element (technology, product) or one party to the transaction involves a drug delivery labeled asset.
4. Percentages are not provided where the underlying numbers are low.

- Product deals accounted for a little more than two fifths of all Pharma related transactions in 2018, an increase of 5% over 2018.
- Technology deals in 2018 accounted for a fifth of all transactions with a sharp 29% increase over 2017.
- Discovery Technology deals accounted for 62% of Technology deals, up a solid 29%.
- Pharma Service deals remain an important segment for both established and emerging PharmaBio companies.

Notable Drug Delivery and Formulation Related Technology Transactions of 2018

Technology: Open-Inhale-Close, Lever Operated (LOMI) DPI
Indication: Asthma, COPD
Delivery Route: Inhalation
Licensor/Licensee: Vectura Group/Hikma
Deal Value/Upfront: $95 million/$15 million
Royalty: Mid-teens
Deal Summary: An agreement to pursue generics of GSK's Ellipta franchise. Vectura to develop and deliver prototypes to Hikma for development and commercialization.
Notable: After dodging Advair generics for what seems a decade, GSK is facing the prospect of aggressive generic development to its Ellipta platform from Vectura, a previous formulation technology partner.

Technology: GalXC platform
Indication(s): Neurodegenerative, Pain, Cardiometabolic
Delivery Route: Injection
Licensor/Licensee: Dicerna/Eli Lilly
Deal Value/Upfront: >$550 million/$200 million (License fee and equity)
Royalty: Mid-single to low-double digits
Deal Summary: The deal covers up to ten targets with little information provided beyond selected financial terms and general targets. Terms include up to $350 million per target in milestones.
Notable: The deal involves RNAi therapeutics using Dicerna's GalXC liver targeted platform that attaches sugars to Dicer substrate short-interfering RNA (DsiRNA-EX) molecules to deliver and silence specific gene targets within the cells.

Technology: Afibromer technology
Indication: Type-1 Diabetes
Delivery Route: Implant
Licensor/Licensee: Sigilon/Eli Lilly
Deal Value/Upfront: $473 million/$63 million
Deal Summary: Sigilon will be responsible for development activities and costs related to the collaboration until submission of an investigational new drug application (IND). Post IND Lilly will be responsible for all clinical development and commercialization activities and costs.
Notable: The holy grail of Type-1 Diabetes is being pursued using the cell encapsulation of islet cells with Sigilon's Afibromer polymer, an implantable biomaterial that is claimed to minimize immune response.

Technology: Calix Exsomes
Indication: Undisclosed
Delivery Route: Oral
Licensor/Licensee: PureTech Health/Roche
Deal Value/Upfront: >$1 billion $36 million
Deal Summary: Under the terms of the agreement, PureTech Health will receive up to $36 million, including upfront payments, research support, and early preclinical milestones. PureTech will be eligible for development milestone payments of over $1 billion and additional sales milestones and royalties.
Notable: Another approach to the oral delivery of biologicals, in this case Roche's antisense oligonucleotides. The Calix Exosomes are extracellular cell-derived nanovesicles intended to deliver contents to the intestine where they can be absorbed. The milk-derived exosomes have evolved to permit oral transport of complex biological molecules, as well as small molecule drugs that are intrinsically not orally bioavailable.

Product: AXO-Lenti-PD
Indication: Parkinson's Disease
Product Stage: Preclinical
Licensor/Licensee: Oxford BioMedica/Axovant Sciences
Deal Value/Upfront: $842 million/$30 million
Deal Summary: Oxford BioMedica receives $30 million upfront and is eligible to receive $812 million upon the achievement of development, regulatory and sales milestones, plus 7% to 10% tiered royalties. Axovant will fund all clinical development and scale-up costs and receives full commercialization rights.
Notable: Significantly extended therapeutic activity. Referred to as second-generation gene therapy AXO-Lenti-PD is intended to deliver three genes that encode dopamine synthesis enzymes for a period of years.

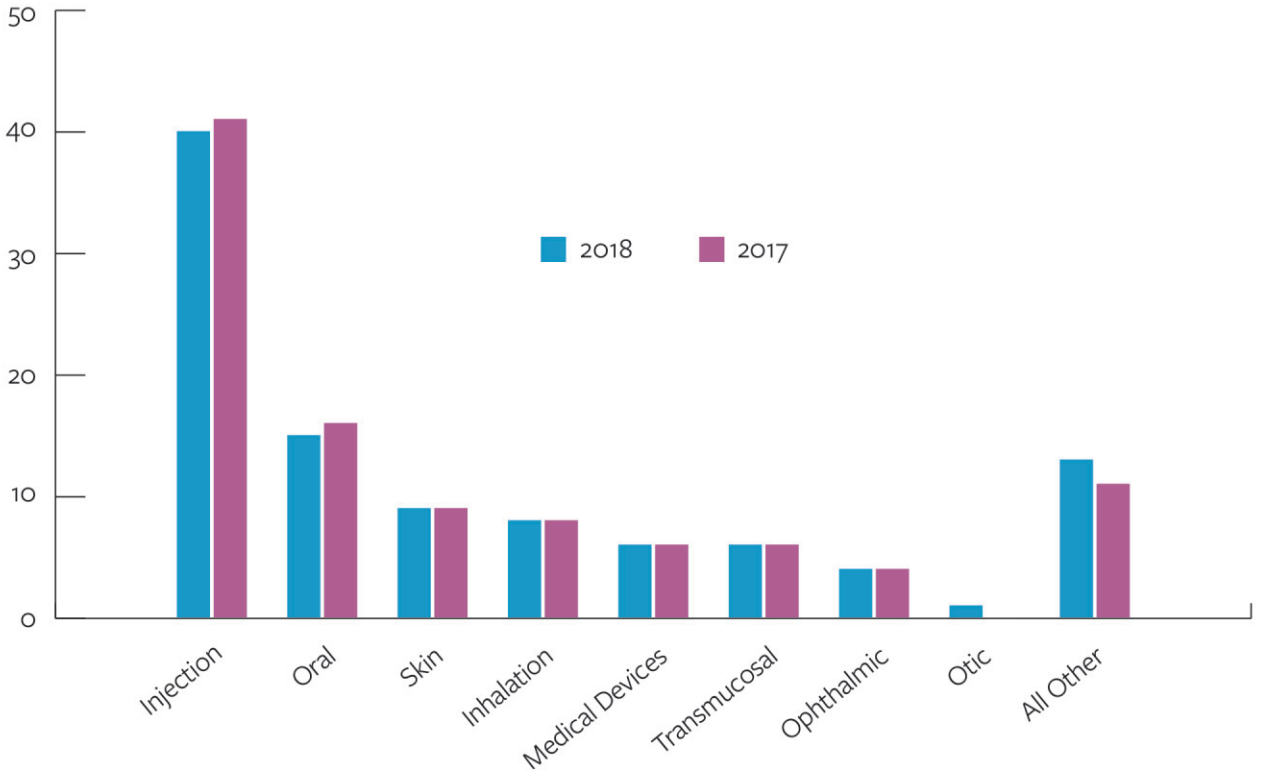
Product: TOBI Podhaler and TOBI Solution
Indication: Cystic Fibrosis
Product Stage: Marketed
Licensor/Licensee: Novartis/Mylan
Deal Value (Total): $463 million
Deal Summary: A simple transaction in which Mylan acquires the two assets worldwide in exchange for a staggered payment of about $460 million.
Notable: The circle of life in the pharmaceutical business. First approved more than 20 years ago as an inhalation solution, and refreshed six years ago with the Podhaler formulation, the TOBI franchise is intended to provide support for Mylan's respiratory franchise.

Product: Inhaled formulation of treprostinil ("TreT")
Indication: Pulmonary Arterial Hypertension
Product Stage: Phase 1
Licensor/Licensee: MannKind/United Therapeutics
Deal Value/Upfront: $45 million/$95 million
Deal Summary: MannKind will manufacture clinical supplies and initial commercial supplies. United Therapeutics is responsible for global development, regulatory and commercial activities with respect to TreT. MannKind will receive an upfront payment of $45 million, potential milestone payments of up to $50 million, and low double-digit royalties.
Notable: MannKind, with their high-performance Technosphere technology has seemingly found a therapeutic target, and partner, capable of exploiting the commercial potential of the technology. It's also notable that Al Mann was an inventor of the MiniMed technology used with United Therapeutics first approved treprostinil product – Remodulin.

Product: Tau Program
Indication: Alzheimer's Disease
Product Stage: Preclinical
Licensor/Licensee: Voyager Therapeutics/AbbVie
Deal Value/Upfront: >$1 billion/$69 million
Deal Summary: Voyager will perform preclinical development of vectorized antibodies directed against tau and be responsible for costs up through Phase 1 studies. AbbVie has an option to lead further clinical development and commercialization. Voyager will receive an upfront payment of $69 million and up to $155 million in potential payments through Phase 1 and receive up to $895 million in development and regulatory milestones, plus tiered royalties.
Notable: More barriers being crossed? This product deal sees the Voyager AAV9 variant technology that incorporates a modified gene fragment encoding for a small loop on the surface of the capsid of the virus being used to cross the blood-brain barrier and transduce the adult mouse brain following intravenous injection.

The Focus of Drug Delivery & Formulation Technologies Changed Little in 2018

Chart 1. Share of Active Drug Delivery and Formulation Technologies by Category



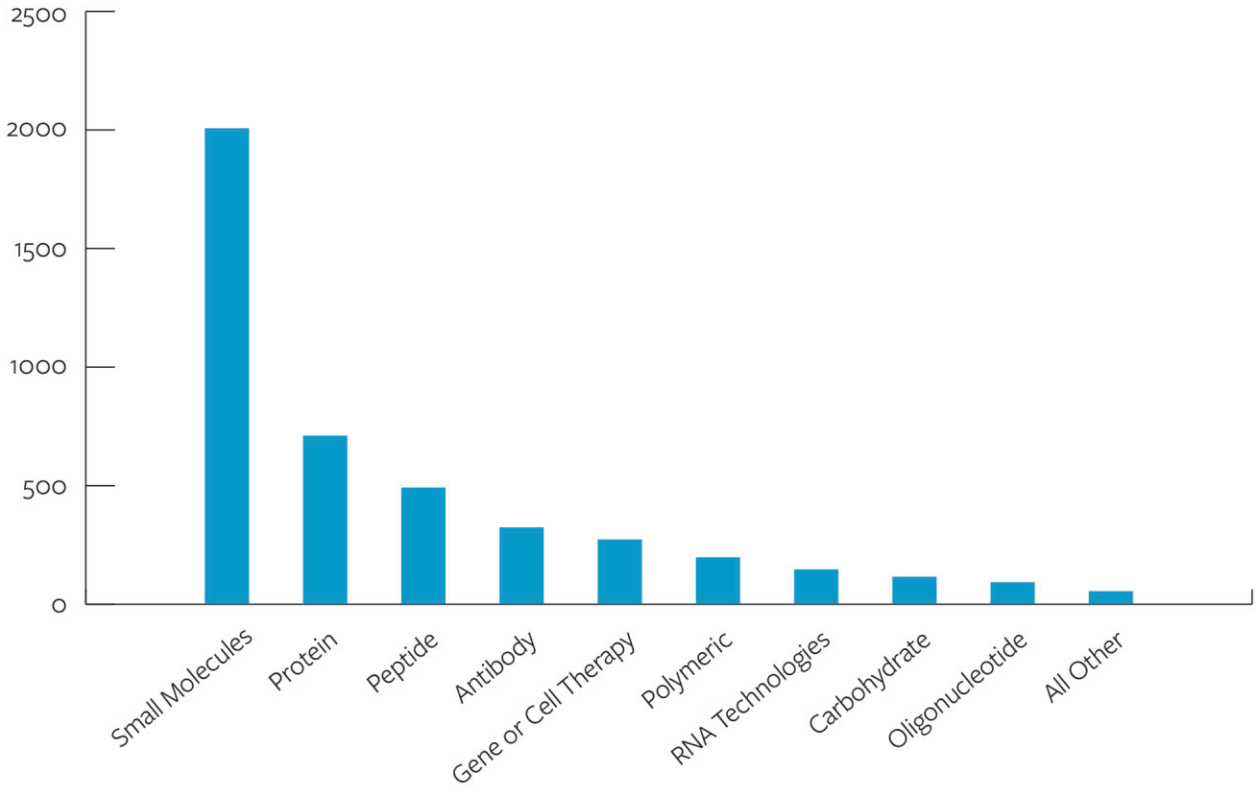
Source: PharmaCircle Drug Delivery Technology Analyzer Module

Chart Notes:
1. Only Active Drug Delivery and Formulation are included.
2. Technologies are summed by PharmaCircle Drug Delivery Categories. Technologies may be included in more than one Drug Delivery Category as appropriate.
3. Medical Devices refers to devices used for the delivery of pharmaceuticals, not standalone devices such as pacemakers.
4. All Other includes Compliance, Stabilization, Veterinary, 3D Printing and Implant technologies.
5. Data sourced March 2019 and March 2018

- There are 5,302 identified Active Drug Delivery Technologies (2019-03) versus 4,800 a year earlier.
- Injection (40%) continues to be the most important area of technology development followed by Oral (15%) and Skin (9%).
- Of the 5,302 Active technologies, 2,177 are not associated with an identifiable pipeline product.
- There were an additional 1,674 technologies identified by PharmaCircle as no longer being active.

Non Small Molecule Technologies Account for the Majority of Applications

Chart 2. Active Technology Applications by Molecule Type



Source: PharmaCircle Drug Delivery Technology Analyzer Module

Chart Notes:
1. Active drug delivery and formulation technologies only.
2. Technologies are summed by PharmaCircle Drug Delivery Categories. Technologies can be applicable to more than one Molecule Type.
3. RNA Technologies include siRNA, mRNA, miRNA.
4. All Other includes Virus, Stem Cell Microbiome and Tissue.
5. Data sourced March 2019.

- Of the identifiable molecule applications, 2007 technologies were applicable to Small Molecules.
- As a group there were 2,409 active technologies applicable to non-small molecule actives.
- Antibodies showed one of the largest year over year increase, percentage wise, in active technologies.
- Active RNA technologies, up 25%, also showed a strong year over year increase.

Notable Drug Delivery and Formulation Technologies of 2018

Technology: Triozan Nanomedicine Delivery Platform
Application(s): Oncology, CNS, Antibiotic Resistance
Most Advanced Stage: Preclinical
Technology Category(s): NP polymer, Tight Junction Modifiers, Oral Peptide/Protein/Macromolecule, Brain Targeting, Nasal Formulations
Company: Ovensa Inc.
Notable Pipeline: TRIOZAN/PTX Oral (Preclinical, Oncology)
Technology Summary: A chitosan based nanocarrier that can reach the brain via oral dosing with large molecules/biologics. TRIOZAN can cross various membranes opening the possibility for other routes of delivery (nasal, inhalation, ophthalmic, buccal etc.). Triozan formulated therapeutics can also be stored intracellularly for example in tumors, and act as a reservoir for long term release.
Notable: Old becomes new again with this new twist on chitosan-based carriers to improve delivery to various cell and tissue types. A recent agreement with Takeda, March 2019, is focused on delivering antibodies to the brain.

Technology: G-Technology
Application(s): Brain Diseases, Retinal Diseases
Most Advanced Stage: Phase 2
Company: 2-BBB Medicines
Notable Products: 2B3-101 (Phase 2, Brain Cancers), 2B3-201 (Phase 1, Multiple Sclerosis)
Technology Summary: A PEGylated liposomal technology with glutathione as a targeting ligand at the ends of the PEG molecules to mediate safe targeting and sustained delivery of systemically administered across the blood-brain and blood-retinal barriers. Liposomal delivery increases the metabolic stability while PEGylation increases the plasma half-life of the active which is loaded into the center of the liposome.
Notable: Technologies such as G-Technology are increasingly demonstrating the ability to effectively and efficiently deliver actives across the blood-brain and blood-retinal barriers to treat challenging brain conditions. A partnership with Mireca Medicines has a preclinical candidate in development for retinal disease.

Technology: OraFuse
Application(s): Multiple
Most Advanced Stage: Phase 2
Company: SynAgile
Notable Products: DopaFuse Oral Paste (Phase 2, Parkinson's Disease)
Technology Summary: A proprietary miniature, disposable, intraoral delivery system carried on a small tooth-attached retainer that continuously infuses medication into the mouth. The device can incorporate a variety of stop/start mechanisms.
Notable: A technology that can provide an infusion type constant delivery through the oral route but unlike the current buccal systems that attach to the inner cheek and which have had relatively limited market acceptance.

Technology: Print Ocular Implant
Application(s): Ophthalmic Diseases
Most Advanced Stage: Phase 2
Company: Aerie Pharmaceuticals
Notable Products: AR-1105 Implant (Macular Edema, Phase 2)
Technology Summary: A precision nanomoulding technology platform for ocular sustained release drug delivery that uses imprint lithography techniques and DSM polyesterimide polymers to produce monodisperse (uniform) nano (or micro) particles. These polymers are liquid at room temperature and are UV-cured to form clear "PTFE-like" elastic solids.
Notable: Aerie's implants are remarkably versatile as they can be administered to the posterior (intracameral, intravitreal) and anterior (subconjunctival) segment of the eye to deliver most actives.

DRUG DEVELOPMENT

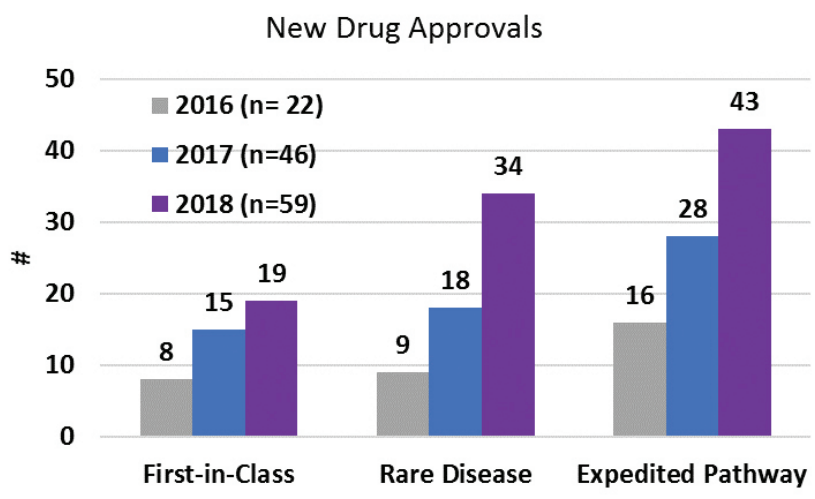
Softgel Technology for Fast-Tracked Development Programs

By: Jeff Browne, PhD, and Ronak Savla, PharmD, PhD

INTRODUCTION

Throughout the past few years, the pharmaceutical industry has undergone a significant change in terms of companies' R&D strategic areas of focus and the resulting new drug products that they intend to bring to market. In the past, R&D efforts were primarily aimed at the development of products for the treatment of widespread disease states consisting of large patient populations in hopes of "blockbuster" products with large and lucrative sales. While pharmaceutical companies still devote significant resources to these larger target therapeutic areas, in recent years, there have been considerable developmental efforts to bring new drug products to market for the treatment of rare or orphan diseases. In many cases, these new products represent "first-in-class" therapies. As such, there is often a high level of public interest in getting these new, potentially life-saving drug products approved and to patients as quickly as possible. This is illustrated in Figure 1, which highlights the total number of new drug approvals (NDAs) by the FDA, and how many each year represent "First-in-Class" therapies, "rare disease" indications, and receiving "Expedited Pathway" review between 2016 and 2018. The number of drug products that were designated in one or more of the four FDA expedited categories of Fast Track, Breakthrough, Priority Review, and Accelerated Approval has steadily increased in number in that time.

FIGURE 1



Novel Drug Approvals in Expedited Categories From 2016-2018[1,2,3]

According to the FDA's most recent data, 43 of the 59 novel drug approvals in 2018 (73%) were designated in one or more of these four expedited categories.[4] While standard times for new product approval have greatly improved throughout the past few years as a result of the Prescription Drug User Fee Act (PDUFA), the FDA review process for new products designated for expedited review can be 6 to 10 months shorter.

Given the trend toward more expedited-review designated products, project development teams are being challenged to complete their Chemistry, Manufacturing, and Controls (CMC) development work necessary for NDA submission in much shorter timeframes, often 18-24 months earlier than typical development timelines. Failure to meet these aggressive timelines not only carries serious business implications for com-

"Given the trend toward more expedited-review designated products, project development teams are being challenged to complete their Chemistry, Manufacturing, and Controls (CMC) development work necessary for NDA submission in much shorter timeframes, often 18-24 months earlier than typical development timelines. Failure to meet these aggressive timelines not only carries serious business implications for companies, but more importantly, means that patients will not receive medicines they critically need as soon as possible."

panies, but more importantly, means that patients will not receive medicines they critically need as soon as possible.

Whereas in the past, regulatory filing dates were often predicated on the completion of clinical studies, for those drugs being given expedited review, there is a greater likelihood that the timely completion of CMC development activities will be on the critical path of timelines for the submission of NDAs. These shorter development cycle times leave little room for error. Having to repeat development work because, for example, a suboptimal formulation approach was initially pursued and resulted in poor bioavailability or unacceptable stability, can result in significant delays for new product programs. Forging ahead with a suboptimal formulation approach may jeopardize the success of the program at later stages of development, or ultimately, the agency's approval of the drug as a result of CMC and/or quality issues. For these expedited programs, getting it right the first time is paramount. Having to switch formulation technologies midstream in a development program can mean additional time and costs for the project, and often requires bridging (clinical and/or stability) studies. From the formulator's perspective, being able to zero-in on a suitable formulation approach based on the API's chemical properties, such as solubility, permeability, pharmacokinetics, and stability, and the API's solid state properties, including its crystallinity, polymorphism, and salt form during the early phases of development, is preferable to trying to identify the best approach after the drug has already undergone several years of development. This is best achieved as a collaborative effort between the medicinal chemist and the formulator. Ideally, the same formulation approach selected for the early phases of development can also be used in later development, and ultimately, for the commercial manufacturing of the product. By doing so, it is more likely the NDA submission dates called for in tight project timelines for expedited programs can be met.

SOFTGEL TECHNOLOGY FOR FAST-TRACKED DEVELOPMENT PROGRAMS

Given the accelerated timelines associated with these expedited programs, lipid-based drug formulations, encapsulated in softgel capsules, provide an attractive option for addressing the challenges facing formulators. Importantly, this technology offers formulators the advantage of an approach that addresses challenges faced during early development, such as improving drug absorption as well as those challenges encountered in later development including the ease of scalability. Lipid-based formulation allows for the timely completion of early and late-phase development activities, and provides relatively straightforward scale-up dosage form manufacturing to meet the commercial volume demand requirements for newly launched products. In doing so, the risk of having to switch to another formulation approach during development, and ensuing costly time delays, can largely be avoided.

Early-Stage Development

The majority of new drugs slated for expedited review are classified as Biopharmaceutical Classification System (BCS) II and Developability Classification System (DCS) IIa/IIb compounds, mirroring the types of compounds in today's pharmaceutical pipeline.[5,6] Many of these challenging compounds will likely require an enabling technology to overcome poor bioavailability resulting from their limited aqueous solubility. The benefits of utilizing lipid-based formulations to improve bioavailability of poorly water-soluble compounds have been well documented, and

lipid-based formulations as solutions are often better absorbed compared to other solid oral dose form approaches.[7] In particular, the development of lipid-based solutions for hydrophobic drugs, which can undergo digestion *in vivo*, and/or self-emulsify to very fine dispersions (self-(micro)emulsifying drug delivery systems; SEDDS or SMEDDS) upon contact with aqueous gastrointestinal contents, can provide significantly improved solubility. The result can be improved absorption (exposure) as well as reduced absorption variability caused by intra- and inter-patient variability or food effects.

GLP toxicology formulations of BCS II (DCS IIa/IIb) compounds often utilize traditional aqueous-based suspension or "powder-in-a-bottle" approaches for early animal safety studies. As a consequence, target exposure levels are not achieved during dose escalation studies and a threshold dose in which adverse effects are observed is unattainable.[8] The utilization of lipid-based formulations of the drug to achieve adequate exposure allows for the successful and timely execution of these early safety studies, as well as being an approach that can be maintained throughout early bioavailability/pharmacokinetic studies and first-in-human studies, thereby obviating the need for the development of multiple formulations.

The lipid-based formulations and softgel technology address numerous other challenges that can arise during early development and can potentially delay project timelines. Ensuring dose uniformity can be problematic for highly potent, low-dose drugs. For example, the process challenges faced in trying to achieve acceptable content uniformity of a very low-dose drug - micrograms or milligrams per dosage unit - during the mixing of a powder bed, especially during scale up to larger batch sizes, can be difficult and potentially extend process development timelines. While uniformity of dose typically manifests itself during the scale-up of manufacturing processes for a new product, variable dosing in early development can be equally troublesome and can result in questionable data. To overcome these dose uniformity issues, it is best that they are dealt with as early as possible in development. Ensuring API uniformity in the formulation via the development of fill solutions represents a more effective means than the reliance on processing equipment. Furthermore, once the fill solution is manufactured, it is encapsulated on an encapsulation machine using a highly accurate positive displacement pump allowing for a uniformity of dosage of +/- 1% to be achieved. Another challenge frequently encountered and relating to highly potent or toxic new drug compounds is their safe handling. As with uniformity issues, safety typically becomes a major consideration for larger scale manufacture. However, even during the manufacture of lab-scale batches in early development, the potential for dust generation and exposure to personnel is reduced given that the drug is wetted during the fill formulation preparation. This provides an added degree of comfort and often means less aggressive measures need to be taken for employee protection, such as full personal protective equipment and engineering controls for isolation and containment.

In addition to the aforementioned issues, there are other API challenges that are best addressed during early development to avoid significant delays later in the product's development. Despite showing promising activity, unfortunately, many new drugs are unstable and can often be prone to oxidation, hydrolysis or light degradation. As shown in Table 1, the softgel technology can be used to improve the stability of these drugs.

To meet the aggressive timelines for expedited programs, many pharma companies, contract research organizations (CROs), and contract development and manufacturing organizations (CDMOs), including Catalent, have looked for ways to reduce formulation development times required for producing Phase I clinical supplies. For expedited softgel programs, it is now possible to provide clinical supplies within 4 to 6 months, as shown in Figure 2.

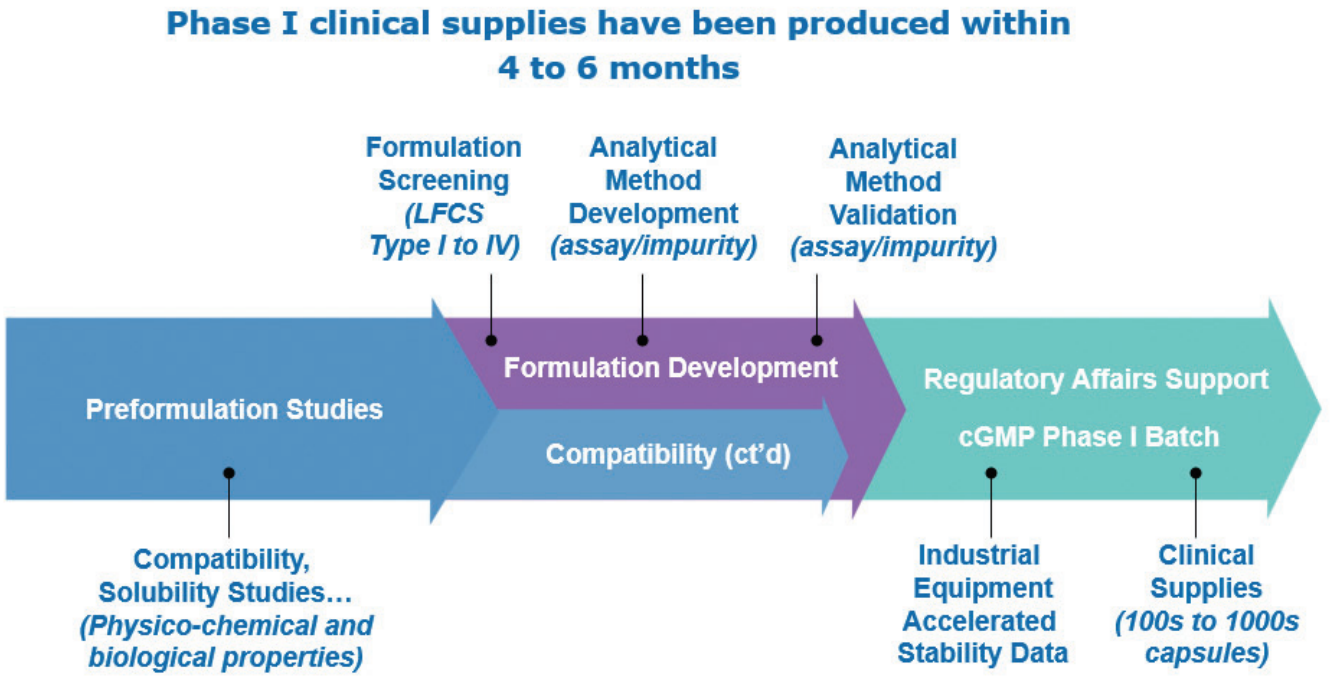
The standard time for the development

TABLE 1

Stability Challenge	How Softgel Technology Addresses
API is prone to oxidation	Gelatin shell has low oxygen transmission rates and softgel manufacture takes place in closed processing vessels with inert headspace (N_2)
API undergoes hydrolysis in the presence of water	Lipid solution or semi-solid fill formulation limit exposure of API to water
API is subject to photo degradation	Manufacture of fill under yellow lights and incorporation of opacifying agents such as titanium dioxide into gelatin shell
API has multiple polymorphic forms	Development of a stable fill so that the API remains in the solubilized state

Softgel Technology for Improving API Stability

FIGURE 2



Parallel Development to Meet Accelerated Timelines

of softgel prototype fill formulations for screening in animal pharmacokinetic (PK) studies is 6 to 8 weeks. Shortened times for fill formulation development are possible through the utilization of robotic systems and generic high-performance liquid chromatography (HPLC) methods, which allow for the rapid screening of drug solubility in selected excipients. Similar approaches have been employed to generate drug-excipient compatibility data. These studies are performed with a few grams of API, which in the early phases of development, is often only available in very limited quantities.

Pharmacokinetic analysis and modeling using in silico software, such as GastroPlus™ during the early phases of development, have also proven to be valuable tools, often identifying true bioavailability issues, whether that be poor solubility, poor dissolution, or high first-pass metabolism, and assessing the importance of parameters, such as drug particle size. These insights can aid formulators in making sound scientific judgements regarding their formulation efforts.

Based on initial animal PK data and *in vitro* development studies, one or more viable candidate fill formulations can quickly be selected for further testing. These studies are typically performed in higher species of animals, such as dogs or monkeys, or directly into humans. It is at this phase of development that fill formulations are typically encapsulated to facilitate unit dosing of the drug. This includes the selection of a shell, which is compatible with the fill formulation, and given that the shell has negligible impact on the fill properties, such as dispersion and digestion of lipid-based fills, similar in vivo performance data as well as stability to that observed in early studies, would be anticipated throughout the development of the product.

Late-Stage Development

Avoiding time delays can also be achieved with the softgel technology during the later stages of development, thereby enabling tight timelines to be met. While other technologies can often require major changes to formulation and processing steps to deal with challenges that arise during scale-up, this is not normally the case with softgels. The fill formulation and shell selected during early development will essentially remain the same throughout scale-up and commercial manufacture, and the same can be said for the process. The same equipment train and process, including the mixing equipment for the preparation of the fill and shell (gel mass) as well the encapsulation machines for manufacture of the softgels, are also used when scaling-up to production-scale batch sizes. The time needed for scale-up activities can be considerably less for the softgel technology compared to processes required, and challenges, such as uniformity

and safety, faced for other dosage form technologies.

The fact that softgel fill formulations and their encapsulation normally do not normally undergo significant changes during the later stages of development is important for several reasons when dealing with accelerated timelines. This allows for the upfront identification of critical formulation and process parameters, and the establishment of rationale ranges, during early development. It can be easily adapted to meet initial commercial volumes for a new product and scaled-up to larger batch sizes to cover increased demand as label indications expand. These same parameters and ranges tend to apply as batch sizes increase to larger scale. It also minimizes the risk of unwanted stability changes that can occur due to major changes to formulation or process late in the development of a product as is often the case with other technologies. Stability data generated on the softgel fill and shell during the early phases of a development program are usually applicable to stability data obtained for larger scale and registration batches manufactured in the later phases of development. As such, early phase stability studies often offer excellent longer-term supporting stability data for establishing a new product's shelf-life.

SUMMARY

There are many factors and challenges that can potentially extend development timelines. In the early phases of development, many of these often relate to properties of the new drug compound. Lipid-based formulations encapsulated using softgel technology offer an attractive option for reducing development times in the early and later phases of fast-tracked or expedited product development programs. Benefits include improved bioavailability of poorly water-soluble drugs, improved stability, better content uniformity for potent or low dose drugs, and the safer handling of potent or toxic compounds. Delays can be avoided against accelerated product development timelines because softgel formulations and manufacturing processes established early in development can also be used without major modifications in the commercial manufacture of the product. Finally, the scale-up and manufacture of new drug products to meet commercial demand using the softgel technology is relatively straightforward and will not affect quality or performance of the product.◆

REFERENCES

1. https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ReportsBudgets/UCM591976.pdf.
2. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM629290.pdf.
3. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM536693.pdf.
4. FDA Center for Drug Evaluation & Research, "Advancing Healthcare Through Innovation-2018 New Drug Therapies", Jan 2109, www.fda.gov.
5. Butler JM, Dressman JB. The developability classification system: application of biopharmaceutics concepts to formulation development. J Pharm Sci. 2010; 99: 4940-4954.
6. Bayliss et al., 2016. Quality guidelines for oral drug candidates: dose, solubility and lipophilicity. Drug Disc Today, 21(10), 1719-1727.
7. Ronak Savla, Jeff Browne, Vincent Plassat, Kishor M. Wasan & Ellen K. Wasan (2017) Review and analysis of FDA approved drugs using lipid-based formulations, Drug Development and Industrial Pharmacy, 43:11, 1743-1758, DOI: 10.1080/03639045.2017.1342654.
8. Pointeaux T et al. Fast-tracking time to market in the early stages of drug development. Drug Development & Delivery. 2011;11(8):60-66.

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BIOGRAPHIES

Dr. Jeff Browne has 40 years of experience in the pharmaceutical industry and held various positions in drug delivery R&D and pharmaceutical manufacturing. Since he joined Catalent Pharma Solutions (formerly RP Scherer) in 1994, he has worked in the softgel technology area and held a variety of positions including his most recent role as Director of Science & Technology. Dr. Browne earned his bachelor's degree in Pharmacy and his doctorate in Industrial and Physical Pharmacy from Purdue University in West Lafayette, Indiana.

Dr. Ronak Savla is the Scientific Affairs Manager at Catalent Pharma Solutions and a Co-Chair of the Catalent Applied Drug Delivery Institute. Dr. Savla is responsible for the strategy and execution of the scientific communications plan, management of external collaborations, identification and nurturing relationship with key opinion leaders, and scientific assessment of novel drug delivery technologies. Dr. Savla is an author on more than 60 papers, articles, posters, and abstracts and has given dozens of conference presentations that cover a wide range of drug delivery topics.

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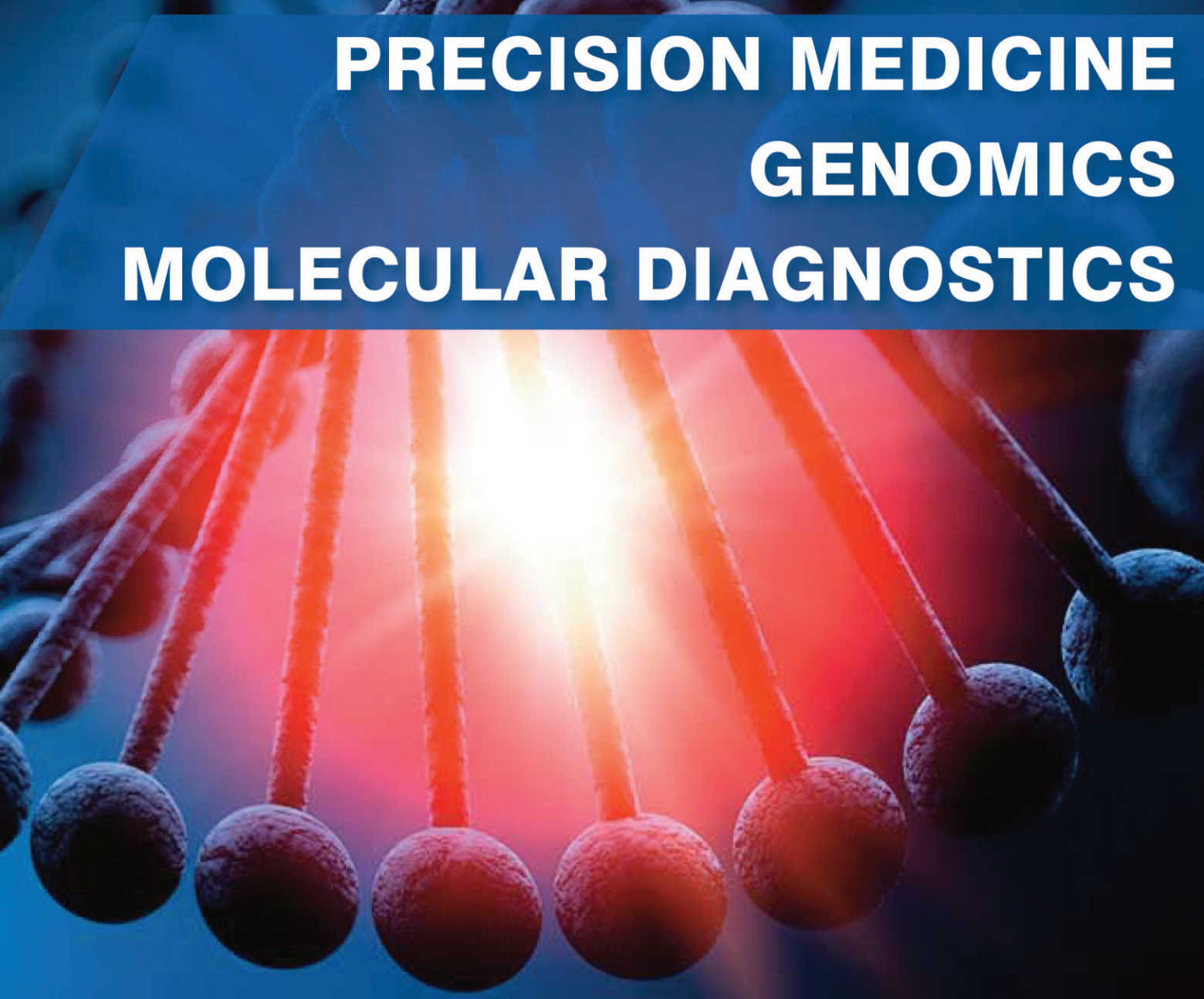

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Which are emerging technologies and growth opportunities for NGS informatics and services?

DRUG DELIVERY

ENHANZE®: An Efficient Way to Optimize Biologic Therapies for Subcutaneous Administration

By: Michael J. LaBarre, PhD

ABSTRACT

Halozyme Therapeutics, Inc. has developed the ENHANZE® drug delivery technology that enables and optimizes subcutaneous drug delivery for a range of therapies typically administered intravenously or by frequent subcutaneous injection. The technology uses Halozyme's patented enzyme recombinant human hyaluronidase PH20 (rHuPH20) that acts locally and transiently to degrade hyaluronan (HA) in the extracellular matrix. Degradation of HA in the subcutaneous space with rHuPH20 allows for a larger injection volume than is possible with traditional subcutaneous delivery. This results in increased dispersion and absorption of subcutaneously co-administered injected drugs and fluids, thus enabling the delivery of targeted therapies for oncology, autoimmune conditions, hematologic diseases, and other disease states. The transition from intravenously administered therapies to subcutaneous delivery and the optimization of subcutaneous delivery have been demonstrated to improve patient experiences, increase efficiency in drug administration, and reduce overall healthcare costs.

INTRODUCTION

Biologics are revolutionizing modern medicine by providing new approaches for treating diseases, such as cancer, autoimmune diseases, and other chronic or inheritable conditions. Biotherapeutics are also the fastest-growing sector in the pharmaceutical industry; in 2016, 8 out of the top 10 best-selling drugs worldwide were biologic agents.[1] Recent market research has indicated that the global market for biologic drugs may reach $580.5 billion in sales by 2026.[2]

Although biologic therapies offer the potential for tremendous progress in medical care, challenges may exist in terms of administration routes, formulation properties, dosing regimens, and safety. Large molecule biologics often require administration of large doses, which results in many of these biologic therapies being delivered by intravenous infusion, with only some designed for multiple and/or subcutaneous self-injections. The need for parenteral administration of these agents may also limit the development of new biologic therapies because of restrictions on viscosity, pH, and osmolality.[3]

Halozyme Therapeutics, Inc., a biotechnology company based in San Diego, CA, has developed a novel drug delivery technology (ENHANZE drug delivery technology) that may overcome some of the challenges associated with subcutaneous drug delivery. Subcutaneous administration of therapeutics may enable a better experience for patients and has the potential to increase healthcare system efficiencies and decrease overall healthcare expenses.[4]

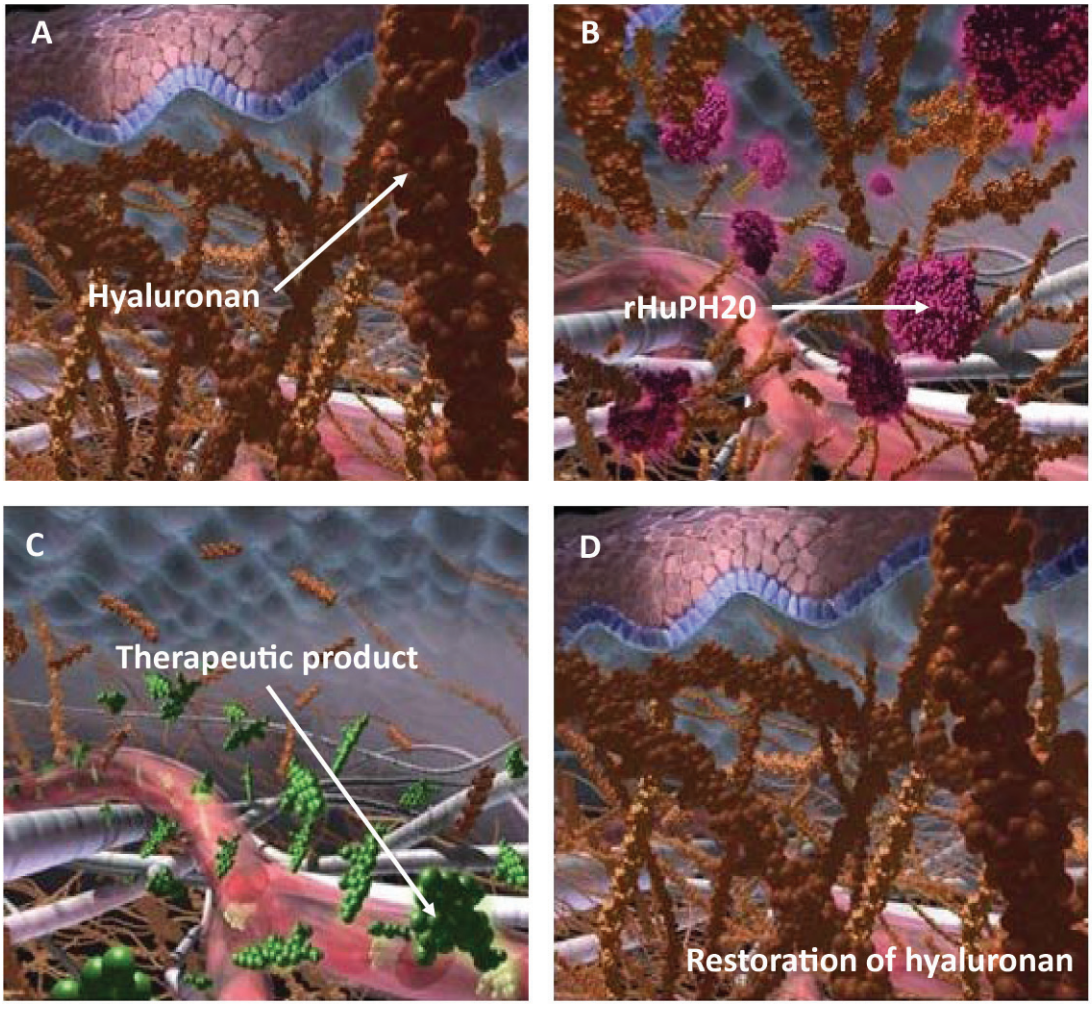
HOW RHUPH20 WORKS

The subcutaneous space comprises the extracellular matrix and various cell types, such as adipocytes, fibroblasts, and macrophages. The fibrous network contains both long-lasting structural components, such as collagen and elastin, and short-lived components, such as hyaluronan (HA).[5] Hyaluronan, a naturally occurring glycosaminoglycan with repeating disaccharide

subunits of D-glucuronic acid and N-acetyl-D glucosamine, is a crucial component of the extracellular matrix. Hyaluronan controls tissue water content and is crucial for cellular homeostasis.[6] Approximately 30% of HA (up to 15 g distributed across the body) is replaced on a daily basis.[6] Hyaluronan acts as a barrier to prevent bulk fluid flow and is one of the reasons why subcutaneous drug delivery methods are typically restricted to small-volume injections.[7]

Central to the ENHANZE drug delivery technology is Halozyme's proprietary recombinant human hyaluronidase PH20 enzyme, rHuPH20, which works locally and transiently to degrade HA in the extracellular matrix of the subcutaneous space by cleaving the linkage between the disaccharide units that comprise HA.[7] Hyaluronan is restored at the local site within 18 to 24 hours after injection with rHuPH20.[8,9] By temporarily degrading HA at the injection site, rHuPH20 enables subcutaneous bulk fluid flow and increased dispersion and absorption of co-administered therapeutics. The ENHANZE drug delivery technology may enable reformulation of existing intravenous (IV) drugs for subcutaneous injection. Additionally, rHuPH20 may be added to existing subcutaneous drug formulations to optimize dosing and administration, providing the opportunity for a wide range of therapies to have expanded delivery options beyond IV infusions or multiple subcutaneous injections.

FIGURE 1



Effect of rHuPH20 on HA

A. Resistance to bulk fluid flow and limited large volume SC drug delivery, dispersion, and absorption due to hyaluronan accumulation
B. rHuPH20 depolymerizes hyaluronan
C. Increased subcutaneous bulk fluid flow, resulting in increased dispersion and absorption of co administered therapeutics
D. Restoration of hyaluronan ~24 hours post-administration of rHuPH20

REDUCING THE TREATMENT BURDEN FOR PATIENTS

Owing to the increased costs of administering drugs intravenously versus subcutaneously or intramuscularly, it may be advantageous to further develop subcutaneous drug delivery approaches for biological agents.[10] The ENHANZE drug delivery technology can potentially reduce the time and/or the frequency of dosing required for IV administration or subcutaneous injection as compared with those same treatments when they do not use rHuPH20.

STUDIES EVALUATING THE DELIVERY OF THERAPEUTIC AGENTS IN COMBINATION WITH RHUPH20

Although the ENHANZE drug delivery technology can aid in the subcutaneous administration of drugs for a broad range of therapeutic areas, several current applications involve co formulations with oncology therapies. Several studies have found that rituximab (MabThera®) and trastuzumab (Herceptin®) co formulated with rHuPH20 for subcutaneous administration demonstrated reduced administration times compared with IV formulations while maintaining similar safety and efficacy profiles.[11] Recent data presented at ASCO 2018 from an investigational study in patients with multiple myeloma demonstrated that a subcutaneous formulation of daratumumab with rHuPH20 enabled a dosing time of 3 to 5 minutes compared with a typical IV administration time of 4 to 6 hours.[12]

One study compared the time commitment required for IV delivery of the biologic drug trastuzumab versus the time commitment for a subcutaneous injection of trastuzumab with rHuPH20. Trastuzumab is a targeted therapy that is used to treat HER2-positive breast cancer in both early and metastatic settings.13 Patients treated with intravenous trastuzumab typically receive infusions lasting 30 to 90 minutes. By contrast, the subcutaneous formulation of trastuzumab with rHuPH20 can be administered within 2 to 5 minutes.[4,14]

Another study evaluated the treatment preferences of patients with HER2-positive breast cancer who received trastuzumab either through the standard IV formulation (n=235) or the subcutaneous formulation with rHuPH20 (n=232). Results indicated that 88.9% of patients preferred the subcutaneous formulation, 9.6% preferred the IV formulation, and 1.5% had no preference. "Time saving" was given as the main reason for preferring the subcutaneous formulation over the IV formulation.[15]

Patients with primary immunodeficiency disease (PID) generally prefer subcutaneous injections to IV administered drugs; however, subcutaneous injections of immunoglobulin (Ig) replacement therapy require weekly or biweekly small-volume infusions (15 to 30 mL) at multiple injection sites.[16] rHuPH20 can be used to improve the dispersion of Ig replacement therapy, thereby enabling the subcutaneous administration of large volumes (up to 300 mL) of Ig at a single site and potentially enabling the interval between treatments to be expanded from weekly/biweekly to every 3 to 4 weeks.[17,18]

Early collaborations with Roche and Baxter (now Takeda) have been followed by more recent clinical research efforts in partnership with Pfizer, Baxter (now Takeda), Janssen, AbbVie, Eli Lilly, Bristol-Myers Squibb, and Alexion using the ENHANZE drug delivery technology.[19,20]

SUMMARY

Drug developers are working to develop new products and improve existing therapies to help patients manage their diseases effectively while reducing their treatment burden.

The ENHANZE drug delivery technology has the potential to improve the pharmacokinetic profiles of co-administered drugs through increased dispersion, absorption, and bioavailability. Also, it may have an important role in reducing treatment burden by enabling at-home self-administration or by decreasing administration times and allowing patients to undergo treatment in a physician's office instead of at an infusion center.[16,18] Furthermore, the use of the ENHANZE drug delivery technology may help reduce local swelling and induration when compared with subcutaneously administered therapeutics that do not contain rHuPH20.[17] All these benefits could lead to increased health system efficiencies by reducing administration time versus IV drug delivery, resulting in increased patient throughput, reduced product waste, and decreased overall healthcare expenses.

Although the subcutaneous delivery of therapeutic agents has long been explored as a means to deliver biologic agents more effectively and efficiently, the presence of HA in the subcutaneous space has thus far prevented large volumes of liquid from being injected and quickly absorbed. The patented enzyme rHuPH20, which is the central component of the ENHANZE drug delivery technology, has proven effective in addressing this challenge by temporarily

modifying the subcutaneous space. The ENHANZE drug delivery technology may enable large volumes of biologics and other agents to be rapidly delivered to their relevant target tissues and has the potential to improve the drug delivery experience for a wide range of patients. ◆

REFERENCES

1. Ngo HX, Garneau-Tsodikova S. What are the drugs of the future? Medchemcomm 2018;9:757-8.
2. Biologics Market is Expected to Grow at the CAGR of 9.5% During 2018-2026. 2018. (Accessed July 20, 2018, at https://globenewswire.com/news-release/2018/04/16/1471980/0/en/Biologics-Market-is-Expected-to-Grow-at-the-CAGR-of-9-5-During-2018-2026-Credence-Research.html).
3. Škalko-Basnet N. Biologics: the role of delivery systems in improved therapy. Biologics 2014;8:107-14.
4. Jin JF, Zhu LL, Chen M, et al. The optimal choice of medication administration route regarding intravenous, intramuscular, and subcutaneous injection. Patient Prefer Adherence 2015;9:923-42.
5. Turner MR, Balu-Iyer SV. Challenges and Opportunities for the Subcutaneous Delivery of Therapeutic Proteins. J Pharm Sci 2018;107:1247-60.
6. Viola M, Vigetti D, Karousou E, et al. Biology and biotechnology of hyaluronan. Glycoconj J 2015;32:93-103.
7. Frost GI. Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration. Expert Opin Drug Deliv 2007;4:427-40.
8. Hompesch M, Muchmore D, Morrow L, Vaughn D. Accelerated Absorption and Reduced Glycemic Variability in T1DM Patients Human Hyaluronidase-Facilitated Coinfusionof a PrandialInsulin Analog. European Association for the Study of Diabetes; 2011; Lisbon, Portugal. p. 1043.
9. Morrow L, Muchmore D, Hompesch M, Jiang P, Jadin L, Vaughn D. Addition of Human Hyaluronidase to Rapid Analog Insulin Reduces theAbsolute Variability of Early Insulin Absorption across Infusion Set LifeLINDA. American Diabetes Association Scientific Sessions. San Diego, CA2011:Abstract 27-LB.
10. Tetteh EK, Morris S. Evaluating the administration costs of biologic drugs: development of a cost algorithm. Health Econ Rev 2014;4:26.
11. Shpilberg O, Jackisch C. Subcutaneous administration of rituximab (MabThera) and trastuzumab (Herceptin) using hyaluronidase. Br J Cancer 2013;109:1556-61.
12. Ajai Chari, Saad Zafar Usmani, Maria-Victoria Mateos, et al. Subcutaneous daratumumab (DARA) in patients (Pts) with relapsed or refractory multiple myeloma (RRMM): Part 2 update of the open-label, multicenter, dose escalation phase 1b study (PAVO). J Clin Oncol 2018;36:suppl; abstr 8013.
13. HERCEPTIN Prescribing Information. Genentech, Inc., South San Francisco, CA. 2017. (Accessed September 25, 2018, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s5250lbl.pdf).
14. Sanford M. Subcutaneous trastuzumab: a review of its use in HER2-positive breast cancer. Target Oncol 2014;9:85-94.
15. Pivot X, Gligorov J, Muller V, et al. Patients' preferences for subcutaneous trastuzumab versus conventional intravenous infusion for the adjuvant treatment of HER2-positive early breast cancer: final analysis of 488 patients in the international, randomized, two-cohort PrefHer study. Ann Oncol 2014;25:1979-87.
16. Wasserman RL. Overview of recombinant human hyaluronidase-facilitated subcutaneous infusion of IgG in primary immunodeficiencies. Immunotherapy 2014;6:553-67.
17. Kang DW, Jadin L, Nekoroski T, Drake FH, Zepeda ML. Recombinant human hyaluronidase PH20 (rHuPH20) facilitates subcutaneous infusions of large volumes of immunoglobulin in a swine model. Drug Deliv Transl Res 2012;2:254-64.
18. Wasserman RL, Melamed I, Stein MR, et al. Recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulins for primary immunodeficiency. J Allergy Clin Immunol 2012;130:951-7 e11.
19. ENHANZE® DRUG DELIVERY TECHNOLOGY. 2018. (Accessed November, 2018, at https://www.halozyme.com/technology/enhanze/default.aspx).
20. Baxter Launches HYQVIA in the United States for Adult Patients with Primary Immunodeficiency. 2014. (Accessed November, 2018, at https://www.halozyme.com/investors/news-releases/news-release-details/2014/Baxter-Launches-HYQVIA-in-the-United-States-for-Adult-Patients-with-Primary-Immunodeficiency/default.aspx).

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BIOGRAPHY

Dr. Michael J. LaBarre is Vice President of Product Development at Halozyme. His career comprises more than 2 decades of biotechnology drug discovery and development experience, including work on successful approvals of commercial therapies such as Rituxan® in 1997 and more recently, RITUXAN HYCELA® with Roche in 2017. Prior to joining Halozyme in 2008, he served as Vice President, Product Development at Paramount BioSciences LLC; Director, Analytical and Protein Biochemistry, Discovery Research at Biogen Idec; and Director, Analytical and Formulation Sciences, Research and Development at IDEC Pharmaceuticals. He earned his BS in Chemistry from Southampton College of Long Island University and his PhD in Bioinorganic Chemistry from the University of Arizona.

Drug Development EXECUTIVE

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PAREXEL

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PAREXEL: Advancing Patient-Centric Drug Development to Improve Clinical Trial Success

A recent report from The Economist Intelligence Unit (EIU) commissioned by PAREXEL found that drugs developed across the industry using patient-centric trial designs had faster study enrollment times and were 19% more likely to be launched. However, only 5.2% of Phase II and III trials utilized patient-centric designs. For this reason, PAREXEL announced the creation of its Patient Innovation Center this past September to help sponsors improve the drug development process and optimize patient involvement and engagement. *Drug Development & Delivery* recently spoke with Sy Pretorius, MD, Senior Vice President, Medical & Scientific Services at PAREXEL, about the new Patient Innovation Center and how it is helping to improve the patient experience, enhance study recruitment and retention, reduce costs, and deliver better data.

Q: Tell us more about how you define patient-centricity and why it's so important in clinical trials.

A: Patient-centricity keeps patients at the center of what we do, incorporating their input into all aspects of clinical development to enhance patient satisfaction and simplify the journey to new treatments. PAREXEL has been practicing a patient-centric approach for years and recently introduced our Patient Innovation Center, which takes patient-centricity and being patient-centric to the next level. One of our main goals is to empower patients to become active participants in the study planning process, using their feedback and ultimately simplifying the patient journey to enhance their experience, satisfaction, and increase compliance with study requirements. Without patients, we are unable to advance

"Without patients, we are unable to advance the development of new therapies. To this end, as an industry, we need patients to be interested in clinical trials and to participate in clinical trials. The reality is that less than 0.002% of the global population participates in clinical trials. To increase awareness and participation them, we need to partner with patients, their families, and caregivers in ways that align what we need to accomplish as an industry with their needs."

the development of new therapies. To this end, as an industry, we need patients to be interested in clinical trials and to participate in clinical trials. The reality is that less than 0.002% of the global population participates in clinical trials. To increase awareness and participation them, we need to partner with patients, their families, and caregivers in ways that align what we need to accomplish as an industry with their needs. We need to address the barriers to participation in clinical studies. It starts when and where patients hear about a study - how do we make it as easy as possible for them to obtain and understand information related to clinical trials. Constantly thinking about creative ways to reduce the burden of participation, while maximizing the benefits associated with participation.

Q: Can you elaborate on what motivated the launch of the Patient Innovation Center (PIC) and what your goals are for the PIC?

A: While the evidence is clear that patient-centric approaches can improve the drug development process, many sponsors face challenges when attempting to apply these strategies. Knowing how critical patient engagement and retention are to successful clinical development, PAREXEL launched the PIC to help sponsors implement patient-first strategies and decrease barriers to implementation. PAREXEL is also looking forward to seeing how the PIC can foster innovation in patient-centric approaches, such as virtual (or at-home) trials and direct-with-patient studies. Even more, PAREXEL's goal is to uncover practical challenges within trial design that can be addressed proactively to achieve the right balance between scientific rigor and feasibility for patients. Further on is an example of what a patient-centric trial might look like as part of PAREXEL's PIC.

Before the study begins, PAREXEL uses its innovative patient-centric protocol optimization approach to identify and address practical challenges to patient participation. PAREXEL helps design a protocol through a combination of web listening and, patient, caregiver, and site staff input to optimize the clinical study experience for participants, leading to more engaged patients, lower drop-out rates, and greater compliance with study requirements. Simultaneously, PAREXEL also proactively seeks opportunities to address the needs of commercial stakeholders and build a better value story. The company's regulatory experts incorporate guidance to address agency requirements from a patient-centric perspective.

During the study, PAREXEL leverages feedback from patients to select the tools and services necessary to enhance the patient experience and reduce the practical, financial, and geographic barriers to participation. This may include enhancing the informed consent process to implementing a virtual study solution that incorporates elements such as at-home nurse visits, telehealth visits to reduce the number of trips to the trial site, direct-to-patient drug shipments, and PAREXEL's Patient Sensor Solution that utilizes wearables to remotely capture, transmit, and store data in a secure platform powered by the Perceptive Cloud.

As a patient's involvement in the study concludes, PAREXEL deploys a closure plan to help patients feel valued and understand the next steps. This includes trial summaries with clear terminology patients can understand, and a thank you card to show appreciation for their efforts. In addition, PAREXEL considers ways to transition them to a post-study treatment plan. In some cases, PAREXEL's managed access program can help patients obtain access to treatments based on compassionate use.

Q: How is recruitment and retention affected by a patient-centric strategy?

A: Studies show that only about a third of clinical trial sites meet their accrual enrollment targets, and 50% are forced to extend their enrollment periods beyond their original projections. There are various factors contributing to patient recruitment failure,

including overly optimistic projections, restrictive inclusion/exclusion criteria, intensive protocol leading to high patient burden, and a focus on outcomes that are not important to patients. However, according to PAREXEL's recent research with the EIU, patient-centric trials took just half the time to recruit participants.

Patient-centric strategies can help recruitment and retention by reducing the practical, financial, and geographical barriers patients and caregivers often face, and optimizing patient involvement and engagement. For example, these trials may offer options for patients to stay at home during trials and continue treatment with familiar caregivers, instead of traveling to the trial site. These types of accommodations can make trials more manageable for patients and reduce drop-out rates.

Q: How does PAREXEL recommend companies implement a patient-centric strategy?

A: To set up a patient-centric trial for success, you must incorporate the patient perspective into the design. PAREXEL's recommendations include, but are not limited to:

Create a Patient Profile: Having a detailed profile of a trial's patient population and understanding who they are as people can lead to the creation of a more specific protocol that makes the difference between the success and failure of a trial. In addition to demographics of the target patient population, companies should consider such real-world elements as the type of treatment being tested, payment, and disease impact. For example, companies should consider such questions about their population as: "Are they elderly and may have difficulty leaving home?" "Are they young adults who can travel easily?" "Are they small children who must be supervised by parents?" "Is the treatment curative or palliative?" "What is life like with this disease?" "Are there routine hospitalizations?"

Crowdsource Patients & Caregivers: Survey patients, caregivers, and nurses/physicians to understand how a study may be received. These parties have a practical view on the impact of the study design as well as the participant's ability to join and remain in a trial. Eliciting this feedback can result in great value.

Scan the Web to "Hear" the Patient Voice: There has been an explosion of open online forums, tweets, blogs, and other social media where patients share stories about their disease and treatment options. "Listening" to the web through key search terms, and dipping into online chatter can give companies an unfiltered insight into what it's like to live with a disease in non-medical terms —and what matters to patients.

Consult With Experts to Mitigate Study Burdens: Patients know a lot about living with their disease, but they are inexperienced in planning clinical research logistics. It is the organizers' job to probe further into what exactly participation in your trial would mean for the participant. Nurse specialists with experience at high-performing investigative sites, for example, are a good resource in judging the burdens a clinical trial can impose on patients. Their analysis of the potential benefits and challenges should be taken into account when sponsors are evaluating the patient journey.

Simplify & Standardize Informed Consent: A typical informed consent form is notoriously long and can include a lot of terminology that patients are unfamiliar with. Make the core document easier for patients and caregivers to understand, for example, by breaking the elements of a study into short video modules.

Q: Despite the advantages of a patient-centric trial, why do you believe patient-centric strategies are so rarely implemented?

A: PAREXEL's recent research with the EIU found that between 2012 and 2017, only about 5% of Phase II and Phase III trials included patient-centric themes, which is surprisingly low given all the attention that this topic is getting throughout the industry. Many are hesitant to take that leap because of the resources required upfront, although these costs could save time and money in the end. This approach also requires improved communication between all stakeholders and additional training to those onsite, both of which can be difficult to coordinate, especially among legacy processes. Even if companies want to implement patient-centric strategies, most often they do not know where to start.

This is where PAREXEL hopes the PIC will make a meaningful impact. Our dedicated team is passionate about understanding patient needs and reducing patient burden, making the clinical trial journey more streamlined for all involved. To accompany this effort, PAREXEL is investing heavily in innovative technology, including at-home monitoring with wearable devices, which make it easier for patients to participate in trials they otherwise would not have been able to geographically access. ◆

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Special Feature

Prefilled Syringes & Parenteral Manufacturing: Flexibility for Faster Development

By: Cindy H. Dubin, Contributor

A new generation of patient-centric prefilled syringes and autoinjectors can deliver a range of parenteral drug volumes and support flexible dosing regimens. Designed with human factors in mind, today's devices present pharma companies a variety of delivery options: wearable, smart, needle-free, single-use, combination products, and packaging. Both the parenteral products and delivery technologies are being produced with flexible manufacturing lines, flexible filling, flexibility dosing, and flexible packaging options – all with the goal of getting product to market and in users' hands faster.

This annual *Drug Development & Delivery* special feature highlights contract manufacturers and device developers responsible for creating next-generation parenteral drug delivery.

Ajinomoto Bio-Pharma Services: Flexibility to Get Biosimilars to Market Quickly

A challenge with biosimilars is they require manufacturers who can produce the drugs quickly with little historical knowledge from which to draw. Most of these products need to be filled for Phase I trials then quickly move to Phase III and commercial manufacturing shortly thereafter. "Without this data, the manufacturer and client must work closely together to deliver a product that can be commercially available after only manufacturing a handful of batches," says Scott Goldstein, Associate Director, Drug Product Manufacturing, Ajinomoto Bio-Pharma Services. "The competitive market for these drugs means that every day matters in clinical trials to be first to market."

A newly built Gerresheimer facility for small-batch scales provides prefillable container production in a flexible manner.

"While it is not technically feasible to produce particle-free injectable products, the objective should be to improve whatever is possible to meet this expectation." – Carina Van Eester, Global Platform Leader, PFS and Cartridges, Datwyler.

The relationship between contract manufacturer and client needs to be flexible in a variety of ways. For example, flexibility in scheduling is critical if stability issues are discovered or if emergency batches are needed to avoid delays in clinical trials. Flexible manufacturing lines are also important to fill the same drug that may be needed in different applications. "Many drugs may begin clinical trials in vials but transition to a syringe in Phase III," says Mr. Goldstein. "Clients want to know that, if needed, they can change the product presentation without having to change the manufacturer. A contract manufacturer with experience making these adjustments can allay a client's fears and assure them changes can be handled without compromising quality."

Baxter BioPharma Solutions: Prefilled Diluent Syringes Reduce Contamination

Baxter BioPharma Solutions offers prefilled syringes containing diluents in a range of fill volumes. The diluents include sterile water for injection and sterile 0.9% sodium chloride solution. According to Gregory A. Sacha, PhD, Senior Research Scientist, the prefilled diluent syringes are innovative to the PFS market for a couple of reasons. "First, a prefilled diluent syringe eliminates one step in the reconstitution process for lyophilized solids," he explains. "The clinician does not have to locate a vial of diluent, remove a specific volume of diluent from the via and transfer it to the vial containing the dried solid. Reducing the steps involved in reconstitution reduces the potential for contamination of the product."

A diluent syringe can be packaged with the dried solid product to ensure the correct diluent at the correct volume is readily available for the product.

Sterilization became an issue for one of Baxter BioPharma's clients. Dr. Sacha says the client wanted to use a polymeric syringe for a terminally sterilized product. "Polymeric syringes become opaque after terminal sterilization using an autoclave. Studies were needed to identify the correct cooling conditions for terminally sterilized polymeric syringes to prevent them from becoming cloudy."

Polymeric syringes from three manufacturers were compared based on the stability of the product and the appearance of the syringes after sterilization. The main challenge was the change in appearance after sterilization. Investigation of the sterilization and cooling conditions identified a process that prevented problems with appearance. Dr. Sacha says: "The client could begin to use any of the syringes available and not worry about changes in appearance."

Catalent Biologics: Parenteral Manufacturing That Supports Personalized Therapies

Industry insiders can agree that prefilled syringes are flexible, convenient, and provide caregivers and patients with a safer parenteral delivery mechanism compared to administration from vials. Yet, clinical parenteral products are still often developed in a vial format. Alyson Norrick, Director, Manufacturing Technology, Catalent Biologics, believes this may be because vials typically have a lower unit cost or because of the dosing flexibility that vials allow during clinical phases, when the therapeutic dose is still being optimized.

"Once a clinical product advances to late-stage trials and is approaching commercialization, the cost and time associated with transitioning the product from vial to syringe may seem prohibitive," she says. "To mitigate potential vial to syringe issues, Catalent works with its customers to position products for long-term success, from the outset of a project and throughout the product's lifecycle. We offer pre-qualified, quick-to-clinic, PFS configurations that are compatible with many early-phase clinical products and are economically feasible."

Catalent also collaborates with clients and device vendors to develop formulations and container closure solutions that support simpler administration, helping to improve patient compliance and adherence, and reducing the burden on healthcare systems. "We have observed an increased number of license holders focusing on development of self-administered dosage forms," says Ms. Norrick. "For example, instead of requiring patients to make frequent visits to an infusion center or doctor's office for treatment, combination products are being developed that allow for administration of therapies at

home either by simple injection, autoinjectors, or bolus injection devices."

Also being developed is flexible parenteral manufacturing to support personalized therapies. Personalized medicine often translates into smaller batch sizes, varied delivery volumes or presentations for a single product, diverse packaging configurations, more immediate need for product and, hence, more frequent shipments to a diverse number of global markets. "The challenge for CDMOs is to consistently offer the flexibility to develop patient-centric manufacturing solutions for any given product, whether working with commercialized products that require high-volume semi-automated or automated processing or personalized, low-volume products that require small-batch formulation, filling, and manual product assembly and packaging," says Ms. Norrick.

To that end, Quality by Design (QbD) has become a fundamental component of biopharma product design. "Astute biopharmaceutical teams are incorporating QbD elements from the infant stages of product development, and it is imperative that Catalent be equipped to support continuation of this design investment over the course of a product lifecycle," she says. "QbD leads to optimized process development and manufacturing timelines, and comprehension and command of a product's design space leads to implementation of robust, sustainable manufacturing processes that yield more product with fewer deviations."

CordenPharma International: Compounding-Filling Provides Compatability & Flexibility

The emergence of disposable/single-use-system injectable technologies provides alternatives to traditional compounding-filling in stainless steel devices. State-of-the-art compounding-filling suites handle compounds that are prone to oxidation or are not compatible with standard contact material, where traditional stainless steel mixing vessels and usual transfer lines cannot be adopted.

"Options in compounding-filling technology allow the customer to have the best "compatibility" set-up, as well as receive a good range of batch sizes to be driven into their targeted container," says Fabio Stevanon, Director, Global Injectables Platform, CordenPharma International.

"As dose volumes go up and the frequency of dosing associated with new therapeutic regimens goes down, we've seen a trend toward the use of combination products." – Karen Flynn, SVP & Chief Commercial Officer, West Pharmaceutical Services, Inc.

CordenPharma also focuses on the importance of flexibility for clients to make the best choice in using either glass or plastic cyclo-olephins containers, and to cope with specific requirements connected to their formulation where non-ionic – no-metal release is needed, or non-polar contact surface is required. "The ability to utilize traditional or fully-disposable compounding systems, coupled with a range of containers with various material compatibility, expands the concept of flexibility for customers facing specific formulation requirements," Mr. Stevanon says.

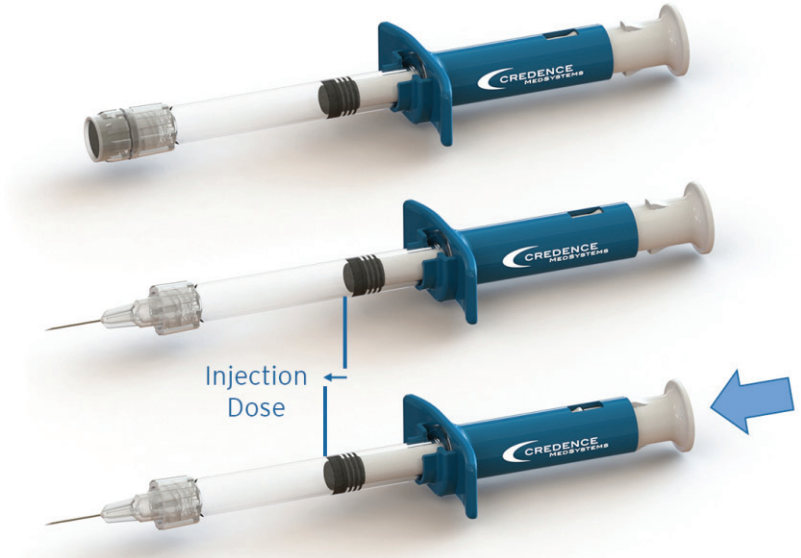
CordenPharma's Injectables Platform offers customers a range of injectable services. Its injectable manufacturing capability covers both terminal sterilization and aseptic filling technologies for PFS, vials, ampoules, and lyophilized vials, with a range of filling volumes (aseptic from 0.5 to 10ml; terminally sterilized from 5 to 100ml). "With multiple process and filling lines, and an overall annual capacity of ~100 million units, the platform offers the flexibility to support multiple programs and customers in parallel, at any scale and stage of drug development and commercialization," says Mr. Stevanon.

The Italy-based injectable facility, CordenPharma Caponago, has two flexible injectable filling lines: One line that manages 1 to 10ml PFS and 3ml cartridges had successful FDA and EU inspections in 2018; and the second line – which focuses on both liquid and lyo vials in ranges from 1 to 10ml – will be validated this spring and approved by the end of the year.

Credence MedSystems: Multiple Injections to Multiple Sites Without Overdosing

There is a growing need for customized injection systems to support the increase of specific therapeutic applications, such as the global dermal filler market. This sector is forecasted to surpass $8.5 billion by 2024.[1] Administering dermal fillers and botulinum toxin therapies involves multiple injections of finite low-volume boluses into multiple target sites. Certain segments of the market already use PFS, while other subsets will soon transition from the classic vial presentation to a PFS, says John A. Merhige, Chief Commercial Officer, Credence MedSystems, Inc.

"Vials force the user to draw the solution into a hypodermic syringe and then attach a fine needle for administration," he explains. "The user must attempt to gauge the correct injection volume by reading and responding to the dose line markings on the syringe. This is challenging enough when the syringe diameter is small and there is reasonable distance between dose lines. But as these products transition to PFS, which have a larger diameter, it becomes untenable to meter the injection because the distance between the dose lines



The Credence Multi-Site™ Injection System, designed for the dermal filler market, administers multiple injections of a precise small-volume dose into multiple target siteswithout fear of over- or underdosing.

is too short. Therefore, the benefits of a prefilled syringe, which include reduced user steps and diminished potential for error or contamination, are offset by the difficulty in performing the injections accurately."

Credence has responded with the Credence Multi-Site™ Injection System. The Multi-Site System allows the user to administer multiple injections of a precise small-volume dose into multiple target sites without fear of over- or underdosing. With Multi-Site, the user presses on the plunger rod until it advances and hits a hard stopping point, which corresponds to the desired injection dose. Mr. Merhige says this is especially important on the first injection, where the momentum from overcoming the break-loose force can cause the plunger rod to advance too far and result in overdosing. When the user releases the plunger rod, it resets by retracting back to its original position and is ready for the subsequent injection. The process is repeated until the syringe has been fully dosed.

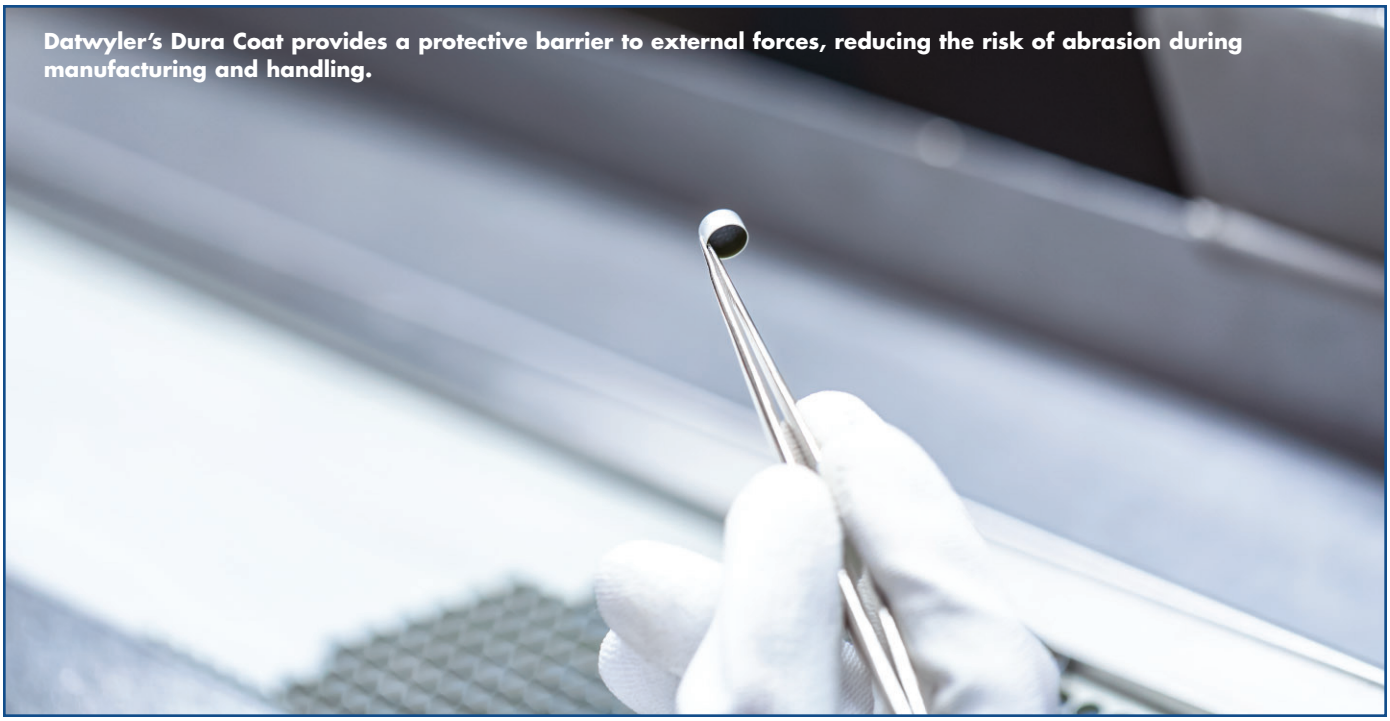
The Multi-Site System has flexible options that are customizable to specific applications and manufacturer preferences. The injection dose volume and number of doses per syringe can be adjusted, and there is flexibility to include the Credence proprietary needle retraction system on the last dose if desired to comply with needlestick prevention laws. And, because the functionality of the system is entirely on the 'back end,' the system is compatible with a variety of closure components and PFS, including multiple sizes and materials.

Assembling the components occurs post-filling in secondary assembly and requires only minimal change to existing equipment, says Mr. Merhige. An additional option exists to implement Force-Assist™, which provides a mechanical advantage to the user. "This is relevant because dermal filler administration is characterized by injection of highly viscous substances through very fine-gauge needles," he says.

Datwyler: Next-Generation Aluminum Reduces Particle Generation

A lot of attention is paid to particles in injectable drug products. The general expectation is that injectables are produced essentially free of extraneous matter. "As there is limited direct evidence of patient risk due to sterile, inert particles, it is reasonable to conclude zero tolerance should not be the requirement but instead considered as a goal in manufacturing of injectable drug products," says Carina Van Eester, Global Platform Leader, PFS and Cartridges, Datwyler. "While it is not technically feasible to produce particle-free injectable products, the objective should be to improve whatever is possible to meet this expectation."

When considering a filled cartridge, Ms. Van Eester says there are four main contributors to the particles in the drug solution: combiseal, plunger, cartridge barrel, and drug. As a rubber component manufacturer, Datwyler has delivered First Line plungers that provide the lowest parti-



Datwyler's Dura Coat provides a protective barrier to external forces, reducing the risk of abrasion during manufacturing and handling.

cle levels in the industry, both visible and subvisible, she says.

"The combiseal, however, has a rather bad reputation with regard to particle generation," she continues. Combiseals are traditionally produced out of lacquered aluminum, which is not very resistant to washing, leading to a weak adhesion of the lacquer on the aluminum. During production, transport, and crimping of the combiseal, the lacquer can detach, leading to shedding of particles that can end up in the cartridge and contaminate the drug.

To guarantee the durability of the combiseals, they have to be extremely robust throughout the manufacturing process. Datwyler is addressing this challenge with a new generation of aluminum: Dura Coat. This proprietary material consists of an epoxy lacquer and polypropylene laminate that is applied to standard aluminum seals to meet customer and authority requirements. "Once these two layers are applied to a standard aluminum seal, the result is a durable and robust packaging solution," says Ms. Van Eester. "This technology uses high-quality materials and, therefore, enables a clear reduction in particles during processing and handling."

DDL, Inc.: PFS Testing to Ensure ISO Compliance

The FDA is challenging pharmaceutical companies to develop and bring more generic drugs to market. Injectable therapies constitute a sizeable share of the generic drug product market. Additionally, there is a growing number of novel compounds slated for a parenteral format. This combination signals there will be a need for more testing services for prefilled syringes and other injection devices.

The bulk of the requirements surrounding the physical and mechanical performance of a prefilled syringe is covered by the ISO 11040 series of standards, says Joseph Wojcik, Program Manager, Combination Products, DDL, Inc. Most of the testing that DDL conducts pertains to Parts 4 and 6 of ISO 11040, which govern glass and plastic syringe subassemblies, respectively, and Part 8, which defines the method requirements for fully finished prefilled syringes.

Mr. Wojcik explains that the ISO 11040 series of standards consists of a number of mechanical tests to measure attributes such as leakage, break loose, extrusion force, burst resistance, etc. on the syringe. For example, to test break-loose and extrusion force, each syringe is placed in a vertical syringe-holding fixture with a safety needle attached and expelled at 50mm/minute. The break-loose force and extrusion force data is then recorded and included in a report, which ultimately goes into an FDA submission.

Another of the key aspects of ISO 11040 for glass Luer syringes is the subject of connectivity. The manufacturing process produces a slippery and slightly irregular Luer taper, which may not form a secure connection with some components. The ISO standard addresses this issue by recommending that certain Luer tests from ISO 80369-7 are conducted to demonstrate adequate connectivity to the same components that will be attached to the syringe in the actual use situation. Note that ISO 80369-7 is the replacement for ISO 594 and the FDA will no longer accept submissions showing conformance to ISO 594 beginning in 2020.

"ISO 80369-7 tests are done to measure attributes such as leakage by pressure from liquid and air, stress cracking, resistance to separation from axial load, unscrewing, overriding, etc," he says. "There are a number of procedures that DDL does to assure that the syringe is meeting all the requirements outlined in the standard."

DDL assists a variety of customers with performance and mechanical testing of their prefilled syringes per the recommendations set out by the FDA and the related industry standards such as ISO 11040.

Both ISO 11040 and 80369-7 standards contain the information needed to conduct a technically valid test, Mr. Wojcik says. "When supplemented with information provided by a drug manufacturer, the data ensures that the manufacturer, when presented to the regulatory authority, understands all judgements and rationales for the testing data."

Gerresheimer: Small-Batch Production for Biologics

Biologics are competing to be first to market for narrower therapeutic classes, such as orphan indications, specialized medicines, and personalized treatments.

Nemera's Safelia® two-step autoinjector combines two PFS sizes in one device.

These niche and targeted therapies call for smaller-scale, more diverse types of production.

"Gerresheimer's newly built production environment for small-batch scales combines state-of-the-art technologies for prefillable container production in a more flexible manner," says Maximilian Vogl, Global Head of Product Management, Gerresheimer. "The small-batch production enables us to react faster and better to the needs of the drug manufacturer, like potential variations in gliding behavior with specific coated surfaces like reduced silicone or baked-on silicone. Furthermore, we involve the innovative metal-free formed glass syringe to overcome the issue of tungsten for sensitive drugs. This offers several advantages in designing the most suitable prefillable container."

Flexibility in fill-and-finish means that the packaging used for that process has to fulfill the same level of flexibility. "As a supplier of pharma packaging, Gerresheimer focuses on a standardized, ready-to-fill packaging concept for aseptic fill/finish to reduce unnecessary efforts based on format changes or interchanges between different types of containers like vials, syringes or cartridges," he says.

Packaging and delivery systems should be designed to meet exact patient needs and performance requirements, ensuring product quality and optimal storage conditions. Mr. Vogl says Gerresheimer's risk-based approach for new devices and packaging optimizes product quality and eliminates risks from development to series production.

Nemera: New Autoinjector Delivers Viscous, High-Dose Drugs

With homecare treatment for chronic diseases on the rise, a new generation of autoinjector platforms is being developed to offer more comfort to the patient while bringing more flexibility to the pharmaceutical companies to administer a larger dose (2ml and above) of biologic formulations.

Nemera has designed a new autoinjector specifically for biologic drugs. The two-step autoinjector, Safelia®, is an adjustable platform suited for either 1ml or 2.25ml-long PFS.

"Combining these two sizes of prefilled syringes with the same device platform enables flexibility in drug development, as choice of final fill volume and syringe size can be made at a later development stage," explains Séverine Duband, Global Category Manager – Parenteral, Nemera. And, she says there is a synergy in the manufacturing and the supply chain as the core device components are identifical.

Using Safelia is a two-step injection process: The patient removes the cap then applies the autoinjector to the injection site. Features include: a cam-based mechanism to deliver more viscous formulations through thinner needles; a disconnected needle insertion and injection system to deliver the right dose at the right depth; reduced risk of glass breakage because

Noble's BD Onboarding kit simulates an injection for syringe users.

force is transmitted onto the syringe shoulder instead of the flange; tailored needle insertion and injection speed; and a hidden needle for increased safety.

"With drugs becoming more viscous, the risk of glass breakage with self-injection devices becomes a critical consideration as a pressure is exercised on the syringe flange, during either insertion into the device or the release of the spring to deliver the drug," explains Ms. Duband. "Thanks to plastic's robustness, risk of breakage is prevented and high forces can be applied on the syringe. Plastic gives pharmaceutical companies the opportunity to use very thin needles (e.g. 29G) even with viscous drugs, which improve patient comfort."

While Nemera doesn't supply primary drug containers, it ensures full compatibility of its standard device delivery platforms with syringe components. As an illustration, its Safe'n'Sound add-on safety device platform is compatible with prefilled ISO standard glass syringes as well as Plajex COP plastic syringes.

Additionally, Nemera holds a pharmaceutical drug manufacturing certification for primary packaged pharmaceutical drugs and medicinal products. This enables handling, assembling, sterilizing, and storing drug products for autoinjectors.

Noble: Helping Patients & Manufacturers Close the Training Gap

Ninety-two percent of patients prefer self-paced learning at home with training devices when onboarding to drug delivery systems, according to a longitudinal study conducted by Noble, a a drug delivery device trainer focused on patient onboarding. This type of training was found to significantly increase patient engagement and performance by applying multiple blended and multimodal learning techniques, explains Joe Reynolds, Research Manager, Noble.

Several novel training technologies are available to create hyper-realistic training experiences for patients and other stakeholders to overcome needle anxiety and build confidence. Examples include Noble's proprietary training-needles and agitators that were designed to safely decrease needle anxiety and reduce wet injections. "These features can be applied to syringes, injection pens, and

autoinjectors to help patients build skills, knowledge, and adherent behaviors," he says.

Noble recently launched a new line of training products in partnership with BD. The new products mirror two of BD's syringe systems and help health professionals, caregivers, and patients practice injection before using the actual drug delivery systems, which have needles. The training devices have faux needle tips that simulate the feel and forces of injection with a needle. The platform incorporates an extensively tested, proprietary lockout mechanism. Designed for repeated use, this resettable locking needle guard simulates the lockout forces of BD safety and shielding systems for prefillable syringes, with the capability for patients to reset the mechanism for multiple refresher sessions prior to actually injecting.

"We believe these results can assist pharmaceutical manufacturers in creating effective combination product onboarding programs that can help healthcare professionals and patients close the training gap, thereby reducing patient errors when using autoinjectors," says Mr. Reynolds.

Sonceboz: Connected Wearable Delivery Ensures Patient Compliance, Alleviates Fears

"Connectivity is a prominent topic toward providing adherence monitoring of medication use," says Tom Mayer, business Development Manager, Medtech, Sonceboz. "As a result, there is a clear demand for device platform technology that enables pharma to adapt and use wearable injection devices starting in clinical trial applications from early phases onward, as well as demand for devices to perform lifecycle management activities," he says. "To achieve this goal, one has to design a robust platform that offers flexibility and technological synergies to reduce complexity and cost." Mayer believes electromechanical systems are ideal because they can offer, for example, programmable delivery profiles and dosing. This, he says, allows for adaptation across different drug products.

Sonceboz offers the Medtech wearable injection device platform for pharma companies that can't address their challenges using traditional PFS technology. For example, if a drug is stored in a vial as primary container during clinical trials or early commercial phase, a PFS cannot be used as the injection device, explains Mr. Mayer. "In contrast, our technology works with vials as well as cartridges as the primary container. And, should a drug be in a lyophilized form, our device technology allows for automatic reconstitution at point of use."

Connected wearable devices also address needle fears. "Visible injection needles are one of the challenges for PFS," he says. "By using wearable devices with a hidden needle and an automated insertion and retraction system, one can circumvent objections by patients with needle phobia."

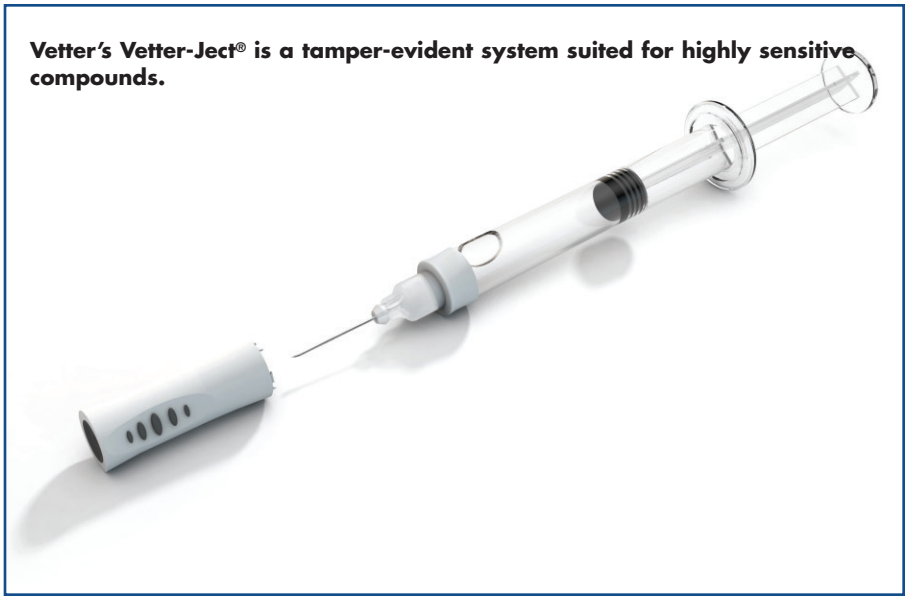
Mr. Mayer adds that wearable devices can deliver higher viscosity and higher delivery volumes. "PFS are typically limited to a payload of 2.25ml, but a wearable injector can inject those highly viscous formulations."

Vetter: Supporting Early Development to Commercial Manufacturing

"The mainstream approach toward simple-to-manufacture molecules is yesterday's thinking," says Claus Feussner, PhD, Senior Vice President Vetter Development Service. "This is because more drugs are targeted towards small, specific subgroups such as RNA and DNA therapeutics.

Vetter acts as a solution provider for large and small pharma as well as biotech companies in the field of injectables. Its patented dual-chamber syringe, Vetter Lyo-Ject®, allows different ingredients and solvents to be prefilled and stored separately, then mixed and administered right before use. "Dual-chamber systems can be used

Vetter's Vetter-Ject® is a tamper-evident system suited for highly sensitive compounds.



for lyophilized/solvent drugs and liquid/liquid drugs, and offer many advantages for sensitive compounds," says Dr. Feussner. "Benefits include enhanced product safety provided by an all-in-one closed system, precise dosing because the drug is premeasured, and simple administration users."

Vetter also offers a syringe closure system, Vetter-Ject®, which is a tamper-evident system for prefilled syringes. The device combines an integrated staked needle with a baked-in siliconization process for standard glass barrels that is suited for highly sensitive compounds.

As a CDMO, Vetter's services span early development support, including clinical manufacturing, through to commercial manufacturing and secondary packaging services. Vetter works with customers by asking a variety of questions to determine how to move forward. Is the product liquid or lyophilized? What are the therapy requirements? Is it a self-administered therapy? What does the product lifecycle and competition look like? What are the different drug concentration presentations to be brought to market? Other critical issues to be considered include the use of nonflurotec or flurotec stoppers, glide and release forces, and shelf-life issues.

West Pharmaceutical Services, Inc.: Systems to Deliver High Volumes and High Doses

Combination products, those that combine the drug, its primary packaging, and delivery system, are becoming more prevalent as biologic drugs present the challenges of higher viscosities and increased dose volumes. "As dose volumes go up and the frequency of dosing associated with new therapeutic regimens goes down, we've seen a trend toward the use of combination products," says Karen Flynn, SVP & Chief Commercial Officer, West Pharmaceutical Services, Inc. "Manufacturers of injection technologies are addressing this trend by developing systems that are capable of delivering up to 2.5ml using systems such as autoinjectors and volumes even greater than 10ml using on body wearable technologies."

West is addressing this trend by extending the platform of its wearable injector technology, SmartDose®, to include doses of up to 10ml. "West developed the SmartDose platform of devices to meet a variety of delivery needs," says Ms. Flynn. "With three device options, the platform features pre-programmable user-loaded and preloaded variations."

Additionally, West is commercializing its patient-assisted injector, SelfDose®, in collaboration with several pharmaceutical customers. The SelfDose injector offers a self-controlled injection option to patients. "An off-the-shelf delivery system that is ergonomically designed for optimal patient administration, the SelfDose injector was developed using extensive human factors studies that helped to confirm the intuitive design, and support ease of use and patient acceptance," she says.

Primary containment systems are also trending towards specialized components that are engineered to enhance functional performance. West supplies elastomer components used with glass prefilled systems, and also supplies Daikyo Crystal Zenith® PFS systems. For complex molecules, West provides NovaPure® syringe plungers for PFS/autoinjector delivery systems across various injection volumes and higher viscosity ranges in glass systems. "NovaPure plungers are designed to maintain container closure integrity while minimizing the contact area between the plunger and syringe, reducing friction and break-loose force," explains Ms. Flynn. "When a non-glass system is preferred, West offers Crystal Zenith syringe systems to maintain purity, integrity, and efficacy of biopharmaceutical therapies. It minimizes potential contamination issues associated with glass systems and reduces breakage, protecting high-value drugs."

Aptar Pharma: Ready-to-Use Program Facilitates Development Time

Pharma customers serving the biologics market require smaller runs as these markets have a smaller subset of patients. As a result, contract partners must be able to provide Ready-To-Use (RTU) products that allow for faster and more flexible runs.

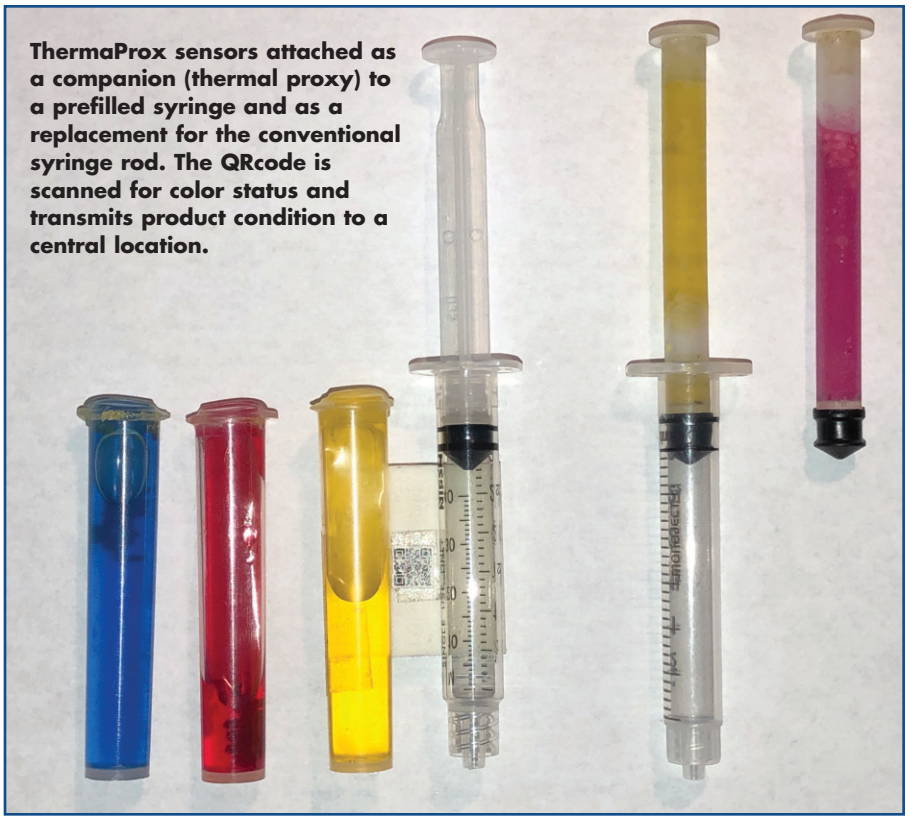
Aptar Pharma fulfills this request for customer by providing RTU stoppers. The stoppers, along with vials, and seals are available through Aptar's recently launched QuickStart™ for Injectables, a one-stop-shop, ready-to-use sterile solution, designed specifically to accelerate the development time for start-ups and early-stage development, R&D, biotechs, and university research organizations.

Launched in October 2018, this injectable development package comes with gamma-sterilized stoppers and push-off caps from Aptar Pharma and EMA Pharmaceuticals respectively, and ETO sterilized vials from Schott.

"We facilitate customers who require speedy developments with an immediatly available and easy-to-use online ordering platform," says Adam Shain, Director, Global Business Development - Injectables, Aptar Pharma.

Addtionally, as the developer and

manufacturer of Rigid Needle Shields (RNS) for autoinjectors, Aptar fulfills customers' mandate for optimal performance. Mr. Shain says that customers are choosing the design of their RNS early in the process to ensure optimal removal in the device. "Previously, the device was designed around the RNS; today customers realize that they can remove gripping features in their autoinjectors by utilizing the right RNS," he says. "Our patented RNS allows for optimal gripping by any autoinjector and minimizes components within the device while providing a consistent pull-off force and a prevention method for fragmentation during removal."



ThermaProx sensors attached as a companion (thermal proxy) to a prefilled syringe and as a replacement for the conventional syringe rod. The QRcode is scanned for color status and transmits product condition to a central location.

ThermaProx, Inc.: Navigating the Cold Chain's Last Mile with a Prefilled Syringe

Much effort is being placed on the quality control of the containers in which a medication will reside. However, little has changed in the transport of finished, prefilled medications from manufacturer to patient. The same technology for vial shipments stands for prefilled syringes. They are packaged and shipped, with coolants, inside insulated containers and handled multiple times under all types of storage and weather conditions.

Nat Cooperman, CEO, ThermaProx Inc., explains that large quantities (pallets) of syringes are shipped with electronic recorders measuring the temperature and shock to which the syringes are exposed, but once the pallets are broken down to the carton level those recorders disappear and reliance is now on label or card indicators to record temperature and limit occurrences. "Shipments get broken down further to the box level and, often, no temperature or shock records are available. Even worse, when the box arrives at a pharmacy or patient's home ("the last mile"), there is little record of how the syringe is handled or stored."

The challenge becomes even greater with regard to highly temperature-sensitive biologics, gene therapies, vaccines, and cancer chemotherapeutics becoming more prevalent. The more of these products being sent directly to a patient's home, where receipt and storage conditions are often unknown, the greater the possibility for unknown temperature limit excursions to occur, says Mr. Cooperman.

ThermaProx, Inc. has developed a multi-patented temperature excursion sensor that mimics the temperature characteristics (thermal mass) of the monitored medications up to the point of the injection site. "Existing sensors (electronic, card or label) monitor the ambient temperature surrounding the medication, resulting in many false positives indicating temperature excursions that the product never experienced," says Mr. Cooperman. "The ThermaProx sensor is triggered only when the medication is definitely questionable."

Reference

1. Dermal Filler Market Worth Over $8.5 Billion by 2024, Global Market Insights, December 11, 2018, https://www.globenewswire.com/newsrelease/2018/12/11/1664912/0/en/Dermal-Filler-Market-worth-over-8-5-Billion-by-2024-Global-Market-Insights-Inc.html.

BIOGRAPHY

Cindy H. Dubin is an award-winning journalist who has been reporting on the pharmaceutical industry for more than 18 years about a variety of topics, including formulation development, drug delivery, and drug quality.

Drug Development & Delivery

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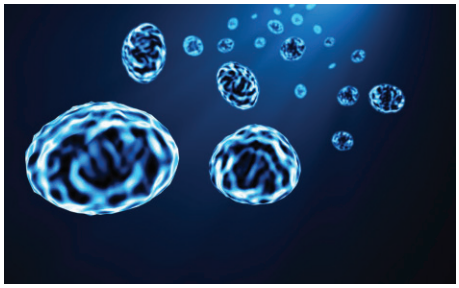
Ensuring Quality Commitment

Prioritizing quality control in drug delivery and reducing human contamination is critical to pharmaceutical customers. **Aptar Pharma's** Injectables division fulfills this need with its unique offering, PremiumVision™, a guaranteed quality commitment using in-line, automated vision inspection systems designed to validate against critical defects in elastomeric components. With PremiumVision, Aptar Pharma is setting new standards for particulate reduction and molding consistency. Aptar Pharma has further shown its commitment to serving the market with the expansion of its facility in Congers, New York, which features the ability to manufacture with the PremiumVision offering when requested. This state-of-the-art facility is dedicated to the exclusive provision of elastomeric components for the US market. Its recent launch has provided Aptar Pharma with additional resources and local capabilities to better respond to customers' requirements in quality, support, and project turnaround. For more information, visit Aptar Pharma at **www.aptar.com/pharma.**

Nanoparticle Formulations



Ascendia Pharmaceuticals is a contract development and manufacturing (CDMO) company offering services for formulation development of poorly soluble drugs and other challenging development programs. Our formulation options include nanoemulsions, amorphous solid dispersions, nanoparticles, liposomes, and oral controlled release. These technologies are suitable for oral, topical, or injectable dosage forms. NanoSol is our technology for production of nanoparticle formulations. Ascendia has the capability to make nanoparticles from native drug crystals using ball milling, or lipid-based nanoparticle composites for lipophilic drugs. When the nanoparticle is delivered to the body there is greater surface area for dissolution, and by using enhancers in the formulation higher bioavailability can be more readily achieved. Ascendia can optimize nanoparticle formulations and produce clinical trial materials for first-in-man studies. For more information, contact Ascendia at (732) 640-0058 or visit **www.ascendiapharma.com.**

CDMO Services - Vaccines

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A unique full-service biotech partner for innovation and manufacturing of GMO2/BSL2 sterile liquid and lyophilized products. **Bavarian Nordic** is a globally integrated biotechnology company focused on in-house executed research, development, manufacturing, and marketing of innovative and safer vaccines against cancer and infectious diseases for which the unmet medical need is high and for which we can harness the power of the immune system to induce a response. Based on this in-depth experience, we are now entering the CDMO market, making the complex simple for you. As innovators and developers of live virus vaccines, our combination of 25 years of expertise and state-of-the-art facility can guide and accelerate your biological therapeutics from development to commercial and beyond. For more information, visit Bavarian Nordic at **www.cdmo.bavarian-nordic.com.**

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Technology & Services Showcase

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Technology & Services
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Exelead is a CDMO dedicated to the development and commercialization of therapeutics to treat life-threatening diseases. Exelead's core technologies focus on the manufacture of sterile drug products specializing in liposomal and PEGylation formulation technologies. Exelead has development capabilities that can be utilized to improve drug delivery and drug product characterization. The Indianapolis, Indiana manufacturing facility produces proprietary parenteral pharmaceuticals for oncology and enzyme replacement treatment, as well as for the treatment of numerous infectious diseases. Exelead manufactures drug products that are distributed globally and offers solutions at every phase of the drug development process (Pre-Clinical, Phase I/II/III, and Commercial). For more information, visit Exelead at **www.ExeleadBioPharma.com.**

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Wearable Micro Pump

Sensile Medical, a Gerresheimer company, specializes in the development of key technologies for the patient-oriented delivery of liquid drugs. The company has developed a new kind of patented micro pump, which is the key component of all product platforms. SenseCore is small and very precise in dosage. Consisting of only two plastic parts, it can be produced at a low cost. Due to its high degree of flexibility, it is compatible with a variety of drugs. A wearable micro pump of this type designed specifically for the treatment of Parkinson's received the EU certificate only recently. A European pharmaceutical company has obtained the CE declaration and will now launch the product on the market. For more information, contact Sensile Medical AG at + 41 62 209 71 00 or visit **www.sensile-medical.com.**

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TOPICAL DEVELOPMENT

Fast Tracking Your Way to Success

By: Marc Brown, PhD, Jon Lenn, PhD, and Jeremy Drummond, PhD

THE RISK CHALLENGE

Recent reviews have suggested that it takes the evaluation of 10,000 compounds to produce one approved medicine containing a new chemical entity (NCE), and the development time is typically between 10 and 14 years with costs in excess of $1billion.[1,2] Nevertheless, the continual discovery of new potential target pathways, the re-purposing of drugs, and advantageous regulation focused on orphan drugs is stimulating companies from the largest multinationals to the smallest single drug biotech start-ups to continue to invest time, effort, and resource in the development of the next commercially successful drug product. The development strategies taken by these companies can be very different, and a fundamental consideration is their attitude to risk. It is typically dependent on their funding structure and the funds they have available, the markets they are aiming for, their corporate culture as it relates to risk tolerance, and regulatory agencies assessment of the medical need for the product.

This is especially true in the development of any topically applied medicine, in which performance is intimately linked to formulation and the attitude to risk impacts the decision as to whether to develop either a simple Proof of Concept (PoC) prototype formulation or a fully market-ready, commercially viable product early in the development process.

Small single drug biotech companies are typically funded by external investment and must raise large sums of money as they complete specific milestones in their project. These companies will be usually focused on taking their drug candidate into a formulation development program for a single geographic market (eg, EU or US). They will often target the development of a simple or prototype formulation, addressing problems as they arise, so they can evaluate the asset in a preclinical or clinical PoC study within their initial budget. Investors, whether venture capitalists or Big Pharma, are aware of the risks of early drug development and want clear demonstrations of safety and/or efficacy before committing further funds.

The challenge with this approach is that if the early studies are successful, then further development will likely involve reformulation and extensive bridging safety studies. In the worst-case scenario, it can involve starting again because the formulation needed to proceed to final Marketing AuthoriSation Application (MAA) or New Drug Application (NDA) enabling clinical studies can be radically different from the PoC prototype formulation. The time and money initially saved in the early stages of the project is often lost and/or exceeded later in the project. Any pharma company that is considering in-licensing from or investing in a small biotech start-up, will always factor in the commercial readiness of the formulation into their due diligence process, and the risks of only having a simple PoC formulation will reduce their evaluation value.

Large pharma organisations have detailed processes and procedures for assessing the development risks of their internal pipeline and ensuring that any formulation meets a well-defined quality target product profile (QTPP). They want to ensure it is an optimized, patient-friendly, stable, clinically-safe, commercially viable and approvable, often global market-ready formulation be-

fore any preclinical/clinical evaluation. This approach invariably takes longer and requires more investment earlier in the project, but it does significantly reduce the risks of taking a suboptimal, patient unfriendly, and non-commercially viable formulation into the clinic. Any key impacts of formulation on performance, so crucial for a topical product, will have been identified upfront, and this will greatly reduce the chances of making changes later in clinical evaluation when it will be costlier and have a larger impact to the overall development timelines. Furthermore, the risks of having to do bridging studies or even repeat early clinical studies, typical in the order of $5 to $10 million for Phase II trials, are significantly reduced.[3]

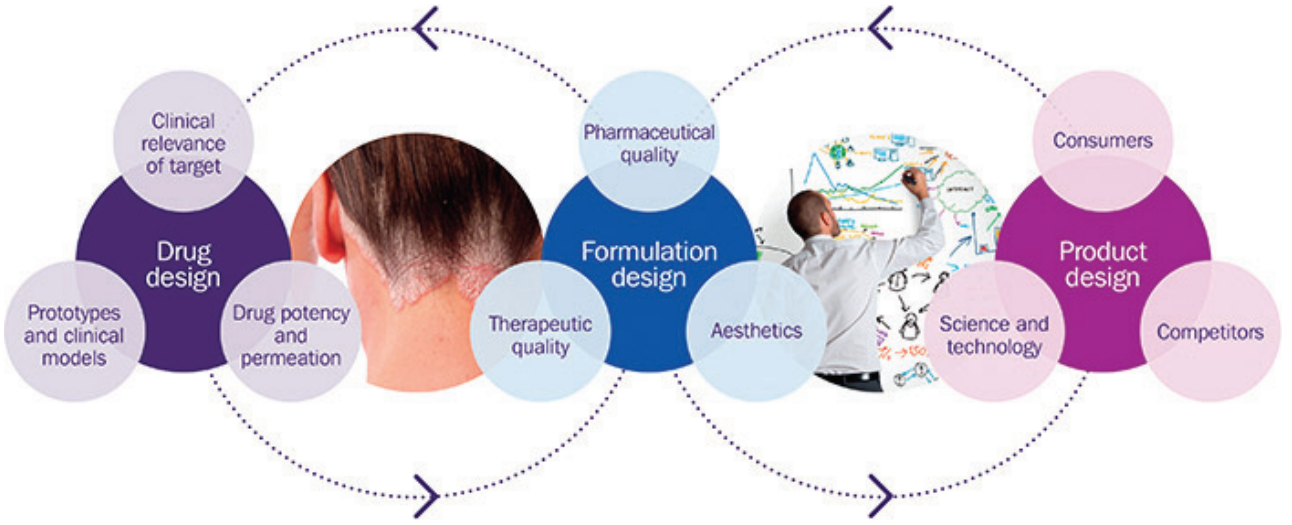
It is likely that significant numbers of "topical therapeutically effective" and commercially viable drugs have had their development stopped because a suboptimal simple formulation did not show the necessary safety and efficacy during the PoC stage of the project when an optimized formulation would have shown otherwise. With the odds so great and upfront investment so high no companies want to be in this situation. Conversely, there are undoubtedly topical products on the market developed by biotech or small pharma companies and subsequently out-licensed to large pharma companies that might easily have been culled because of their risk profile in the early stages of development was less favorable when compared to other candidates in a large company pipeline. Having only a single drug candidate focuses the mind of a small company's management to "how can we address this risk" rather than "that is a significant risk" and if they hadn't taken the risk and proceeded into PoC studies, the patient benefits and commercial value needed to justify the investment in money and time would never have been identified.

MINIMISING RISK & MAXIMISING MITIGATION

Leaders in topical product development hold an ethos that evolves around mitigating risks in product development, whatever the financial constraints on the client. These industry experts believe the optimal route to success sits somewhere between the two aforementioned extreme approaches, where it is not a drug alone that is used by a patient but a medicine (Drug Product) that needs to deliver the molecule safely and efficaciously to the site of action in a cost-effective manner. In the case of topicals, this is particularly acute because the residence time for topicals is short, wash-off is inevitable, and patients have a strong preference of what they apply to their skin or other areas of the body. The patient or consumer must always be at the forefront of any development strategy. The cosmetics and aesthetics of the final product are almost as important for a commercially successful product as the product's efficacy. The selection of a formulation for topical application is influenced by the physicochemical properties of the drug and its potency, the disease to which it is applied, and the patient who will use it (Figure 1).

Irrespective of the budget and a client's attitude to risk, the gold standard approach to drug product development has always been to follow a risk-based

FIGURE 1



Key considerations for topical formulation development.

"Fundamentally, this unique approach forces a rigorous analysis of the product requirements and the risks associated with the development upfront so likely issues can be prevented before they happen. The development approach builds the formulation up from sound foundations and crucially focuses on the physical and chemical requirements and the biological challenge. The costs are small compared to running a clinical trial, and the time required does not have to include any repeated steps."

Quality-by-Design (QbD) strategy as recommended by the FDA. Initially, this involves working with the client to develop a QTPP to define the key requirements of the product, considering the quality, safety, and efficacy of the drug product. The QTPP is an evolving document that is updated as the project progresses in which any Critical Quality Attributes influenced by Critical Material Attributes (CMA) and Critical Process Parameters (CPP) are identified, monitored, and/or controlled. In parallel to the evolution of the QTPP, performing a risk assessment is always advocated by industry leaders. This utilizes a Failure Mode and Effects Analysis (FMEA) in which the three criteria of severity, probability, and detectability are used to generate a risk register in which the appropriate proposed mitigation, control measures, and potential contingencies are described. Like the QTPP, this risk assessment document is updated as the program evolves, allowing the client to maintain a state of control over the program. Such an inexpensive process underpins the ongoing development strategy for the client, regulators, and any potential investors.

The pre-formulation stage of a new drug candidate is considered by industry leaders to be the most critical step for a topical program in which the drug's physicochemical properties and desired dosage form are considered and upon which the final optimized commercially ready formulation is built. Initially, a stability-indicating analytical method must be developed so an understanding of any potential routes of drug instability can be detected that would cause problems in later stages of the development process. For the development of topical semi-solid drug products, pre-formulation studies typically involve solubility, stability, and compatibility studies with potential excipients to be used in the final dosage form. Specialist providers perform this work using state-of-the-art automated and robotic systems to improve the efficiency of data generation. These studies enable rational formulation design and generate an understanding of drug solubility and achievable drug concentration as well as any inherent drug instability and any drug/excipient/packaging incompatibilities. If a particular risk has been identified, target screening of any excipients based on internal expertise will be carried out, and researchers will look to provide a solution to mitigate the risk of drug instability at the very start of the project.

The key to this approach is that risks are identified, either in the initial risk assessment or in the pre-formulation, right up front so the potential consequences of these risks to the project can be understood at the earliest possible stage.

The lowest risk approach to any submission is to try and keep to materials, processes, and parameters with which the regulatory authority is familiar. Industry leaders know to advocate the use of approved, and where possible, compendial excipients, in which the type and concentration of excipient used should be acceptable from a regulatory (eg, inactive ingredients database (IID) and disease perspective. Following pre-formulation, a series of prototype formulations will be developed to meet the formulation criteria defined in the QTPP, including but not limited to dosage form, strength, and packaging type, posology, any desirable aesthetic, organoleptic and/or cosmetic properties, manufacturability, and cost of

goods.

For topical products, it is essential the lead (and potentially a back-up formulation depending on any risk factors identified) has been optimized and characterised not only to demonstrate that it will maintain its quality and performance during its life on a pharmacy shelf but also that it is giving the formulation the best chance of measurable success in the clinical setting.

Throughout the years, newly developed formulations include the incorporation of a variety of proprietary and automated systems and instrumentation (Figure 2) to evaluate the future potential physical and chemical stabilities of any formulation and thus identify the risk of a product's quality, changing over the required shelf-life. For example, instrumentation like the LUMiFuge® have been introduced to predict the risk of any potential longer-term formulation physical stability issues and provide a tool to determine how they can be addressed.

Key leaders in the field have a large toolbox of performance testing models ranging from simplistic models used to select the optimized thermodynamics and release of actives from the formulations (in vitro release testing (IVRT) to skin models of drug permeation and penetration through to complex ex vivo human skin disease models involving local infections and inflammatory responses associated with these infections or pathway specific stimulation (eg, psoriasis, atopic dermatitis, acne, etc).

These models, which continue to grow in sophistication as more becomes known about molecular biology, are transforming the risk profile of the development process for topical formulations. Senior industry professionals use these models to better understand the behavior of the active drug and de-risk the formulation development process. Excellent correlations have been established between these proprietary models and the clinic, and they also help future investors or R&D management clearly understand the risks prior to authorizing expensive clinical trials.[4]

FIGURE 2

The latest Waters LC-MS/MS to be installed in MedPharm to manage increased demand for bio-analysis.

A STRATEGY FOR SUCCESS

Fundamentally, this unique approach forces a rigorous analysis of the product requirements and the risks associated with the development upfront so likely issues can be prevented before they happen. The development approach builds the formulation up from sound foundations and crucially focuses on the physical and chemical requirements and the biological challenge. The costs are small compared to running a clinical trial, and the time required does not have to include any repeated steps.

This method has proved successful for specialist contract providers and their clients. Confidence in this method is demonstrated by the increase in approved topical NDAs throughout the past decade when development has involved this unique approach. Interestingly, this approach does not end up being materially more expensive or of longer duration when the development process (ie, pre-formulation, formulation development, and per-

formance testing experiments) is appropriately designed and conducted in parallel when compared to the simple PoC approach in which a small biotech start-up initially may feel forced to consider.

The discussed "accelerated" approach addresses and provides almost immediate solutions to many of the issues highlighted previously and provides clients with confidence that their chances of success are maximized. It also provides a robust data package to allow potential investors or large pharma in-licensing teams to perform due diligence and make informed decisions about the product and its future life cycle management. ◆

REFERENCES

1. Sullivan T. A Tough Road: Cost To Develop One New Drug Is $2.6 Billion; Approval Rate for Drugs Entering Clinical Development is Less Than 12% [Internet]. Policy & Medicine. 2018 [cited 1 February 2019]. Available from: https://www.policymed.com/2014/12/a-tough-road-cost-to-develop-one-new-drug-is-26-billion-approval-rate-for-drugs-entering-clinical-de.html.
2. Sertkaya A; Wong H. H.; Jessup, A; Beleche, T (2016). Key cost drivers of pharmaceutical clinical trials in the United States. Clinical Trials. 13 (2): 117–26. doi:10.1177/1740774515625964. PMID 26908540.
3. Martinez J. Driving Drug Innovation and Market Access: Part 1-Clinical Trial Cost Breakdown | Center Point Clinical Services [Internet]. Centerpointclinicalservices.com. 2016 [cited 3 February 2019]. Available from: https://www.centerpointclinicalservices.com/blog-posts/driving-drive-drug-innovation-and-market-access-part-1-clinical-trial-cost-breakdown/.
4. L. Ring, J. Neil, A. Brink, K. Powell, J. Volmer, J. Lenn, M.B. Brown. Comparison of ex-vivo human skin model of Th2 driven inflammation as a preclinical model of acute atopic dermatitis. [poster]. Presented at AAPS Pharm Sci.

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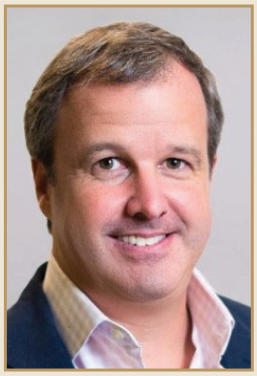
BIOGRAPHIES

Prof. Marc Brown is Co-founder and Chief Scientific Officer of MedPharm. He has been the guiding force behind all of MedPharm's scientific developments and intellectual property. He has been Professor of Pharmaceutics in the School of Pharmacy, University of Hertfordshire since 2006 and has visiting/honorary professorships at the Universities of Reading and King's College London. He has over 200 publications and 26 patents describing his work. His research interests lie mainly in drug delivery to the skin, nail, and airways. To date, he has been involved in the pharmaceutical development of over 50 products that are now on the market in Europe, America, and Japan. Prior to MedPharm, he was an academic in the Pharmacy Department at KCL.



Dr. Jon Lenn is Chief Technology Officer at MedPharm, with direct responsibility for MedPharm's operations in the United States based out of Durham, NC. Since joining in 2015, he has led MedPharm's development of cutting-edge performance models for assessing penetration and activity of clients' products targeted toward key biochemical pathways. He has over 15 years of experience in developing dermatological projects with Connetics, Stiefel, and GSK, and has been directly involved with the development and approval of 8 products. He earned his PhD on the topical delivery of macromolecules from the University of Reading.

Dr. Jeremy Drummond is Senior VP, Business Development, at MedPharm. He has spent over 20 years leading the commercial supply of product and services to pharmaceutical companies across the globe. He is responsible for leading revenue growth, key client relationships, and marketing MedPharm to its global customer base. He started his career as a technical formulator and earned his PhD in Organic Chemistry from the University of Cambridge.

CHECKPOINT INHIBITORS

Novel Targets & Global Markets

By: Laurie L. Sullivan and Cheryl L. Barton, PhD

INTRODUCTION

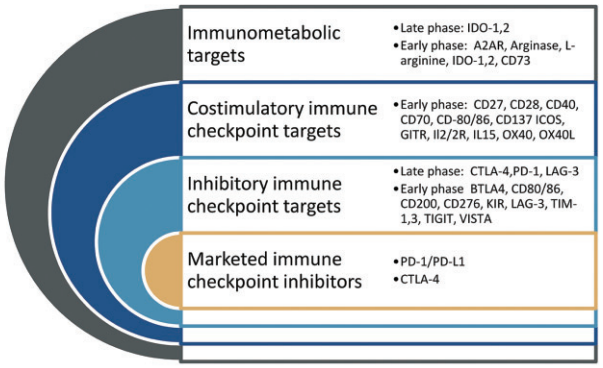
Immune checkpoint inhibitors are creating a stir among oncologists. Checkpoint inhibitors enhance the immune response to detect and target cancer cells, with a lower incidence of side effects compared with conventional chemotherapy. In addition, checkpoint inhibitors provide durable responses that last for many years. According to an analysis by BCC Research, the global market for checkpoint inhibitors is currently worth $14.9 billion. It is forecast to expand at a compound annual growth rate (CAGR) of 14.4% to reach $29.3 billion in 2023.

Seven checkpoint inhibitors have received approval from the US FDA for treatment of cancer, including three programmed cell death 1 (PD-1) inhibitors (pembrolizumab, nivolumab, and cemiplimab), three programmed death ligand 1 (PD-L1) inhibitors (atezolizumab, avelumab, and durvalumab), and one cytotoxic T lymphocyte–associated antigen-4 (CTLA-4) inhibitor (ipilimumab).

In the past 5 years, pharma companies have invested more than $3.3 billion in acquisitions, equity offerings, and venture capital. A further $1.3 billion has been spent to establish strategic partnerships for the development of checkpoint inhibitors. Therapies targeting PD-1/PD-L1 and CTLA-4 have shown remarkable success in many cancers; however, not all patients benefit from them.

This has sparked an immense effort to target other immune checkpoint receptors. Upward of 230 clinical trials are underway to evaluate checkpoint inhibitors either as monotherapy or in combination with chemotherapy or targeted therapies. Several novel agents are in early stage clinical development. These agents utilize an array of delivery technologies (e.g., small molecules, monoclonal antibodies, bispecific antibodies, and fusion proteins) to target checkpoint proteins.

FIGURE 1



POTENTIAL TARGETS FOR CHECKPOINT INHIBITION IN CLINICAL EVALUATION

Novel pathways that are being targeted include the T cell immunoglobulin and mucin domain 3 (TIM-3) and lymphocyte-activation gene 3 (LAG-3) protein inhibitors, CD47/signal regulatory protein α (SIRPα), and immunometabolic enzymes indoleamine 2,3-dioxygenase-1 (IDO-1).The following sections examine each of these targets, as well as PD-1/PD-L1 and CTLA-4.

PD-1/PD-L1

The PD-1/PD-L1 segment is maturing rapidly. Throughout the past decade, there has been mounting evidence that PD-1 and PD-L1 blockade suppresses tumor growth via the modulation of immune cell–tumor cell interaction. Developers continue to evaluate anti–PD-1/PD-L1 agents in a variety of cancers and settings in their quest to expand clinical utility and improve returns on investment.

Many PD-1/PD-L1–targeted agents are in clinical develop-

ment as monotherapies or in combination with novel checkpoint inhibitors, such as A2AR antagonists, anti–IDO-1, STING, and TLR 7 & 9 agonists. Preclinical research is underway in the development of bispecific antibodies and fusion proteins that target more than one checkpoint pathway. In addition to the six PD-1/PD-L1 inhibitors that are on the market, eight are in clinical trials, and four are in preclinical development.

By 2023 at a 5-year CAGR of 12.8%, BCC Research forecasts that marketed PD-1/PD-L1 products will generate sales of $24.6 billion. As new combinations and dosing regimens are approved, these products will become more widely available and reimbursed across the globe. The prescription of PD-1/PD-L1 agents is likely to increase as healthcare professionals become more familiar with their safety profile and new formulations ease their use. Meanwhile, among next-generation PD-1/PD-L1 agents in clinical development, several could reach the market by 2023 to generate an additional $580 million in sales.

CTLA-4

CTLA-4 is the receptor of an immune checkpoint pathway that plays a crucial role in the regulation of T-cell activation and preservation of self-tolerance. CTLA-4 is frequently overexpressed in a variety of malignancies. Ipilimumab is the only anti-CTLA-4 agent approved by the US FDA (in March 2011, for treatment of metastatic melanoma). It has since been approved for additional indications. Ipilimumab is being evaluated in numerous trials either as a monotherapy or in combination with anti-PD-1 therapies in first-line and adjuvant settings, and with other agents in advanced carcinomas.

When ipilimumab was launched in 2011, it represented a unique approach to immune checkpoint inhibition in cancer. Its use expanded when PD-1/PD-L1 inhibitors arrived on the scene, offering new combination regimens. Since that time, the safety profile of ipilimumab has been under increasing scrutiny and has limited its potential in the adjuvant setting. Bristol-Myers Squibb is developing low-dose ipilimumab, which may reduce the risk of unwanted side effects and help revitalize sales. In addition, Bristol-Myers Squibb continues to explore ways to expand the utility of ipilimumab in a variety of duplet and triplet combinations, which could help drive future sales.

Several other companies are evaluating new anti-CTLA-4 agents, six of which are in clinical development. If successful, these products will face tough competition. Next-generation products must be differentiated in terms of efficacy, safety (e.g., antigenicity), durability of response, price, ease of administration, and/or market access. BCC Research forecasts that sales of anti-CTLA-4 agents will gradually increase to nearly $2.8 billion in 2023. The clinical utility of ipilimumab will expand in combination therapies, and new anti-CTLA-4 agents will enter the market.

IDO-1

IDO-1 inhibitors, which target tryptophan metabolism, have generated a lot of interest among pharma companies and investors. Anti-IDO-1 agents offer the potential to add to existing therapies to overcome drug resistance and improve objective response rates in patients with cancer, particularly those who are refractory to checkpoint inhibitor blockade. Preliminary data suggest that IDO-1 inhibition may provide an important therapeutic opportunity to inhibit tumor metabolism and reverse evasion of the immune system.

There are nine IDO-1 inhibitors in clinical development, as well as a handful of preclinical programs. Clinical data for epacadostat showed that IDO-1 inhibitors are safe, but clinical efficacy remains questionable. Several trials of epacadostat in combination with PD-1 inhibitors have been halted. In May 2018, Roche and Pfizer returned development rights of an IDO-1 candidate back to the originators due to lack of efficacy.

Given recent clinical data, BCC Research remains cautious that anti-IDO-1 agents will enter the market. If they do, they are only likely to carve out a role in niche patient populations. Given those caveats, the global market for anti-IDO-1 therapies is forecast to reach $0.9 billion by 2023. This projection is based on the assumption that companies continue to pursue the development of anti-IDO-1 combinations and target areas of high unmet clinical needs.

LAG-3

Following the success of PD-1/PD-L1 inhibitors in cancer, developers are targeting other negative checkpoint inhibitors, including LAG-3 (CD223). LAG-3 upregulation is required to control overt activation and prevent the onset of autoimmunity. Several pharma companies have already entered this field. Innovative biotech firms have interesting products in early stage development, which may attract further pharma interest in this field.

"Manufacturers of immune checkpoint inhibitors continually push scientific boundaries to rationally design drugs and combinations that will more effectively treat patients. These include checkpoint blockers with epigenetic modulators, checkpoint blockers with costimulatory monoclonal antibodies, checkpoint blockers with cancer vaccines, and checkpoint blockers with chemotherapy and radiation. As manufacturers expand the clinical utility of these agents and healthcare professionals become more familiar with their efficacy and safety profiles, the market will continue to expand."

Blockade of LAG-3 using anti-LAG-3 monoclonal antibodies or anti-LAG-3/Ig fusion proteins is being evaluated in a number of clinical trials in patients with cancer.

Bristol-Myers Squibb, Novartis, Immutep, Boehringer Ingelheim, Merck KGaA, Shire, TESARO, and Xencor all have agents in early clinical development. Preclinical programs are underway at Incyte, Merck & Co., and Crescendo Biologics. Based on findings in preclinical animal models, anti-LAG-3 agents may have synergistic effects with PD-1/PD-L1 therapies. Crescendo Biologics and Xencor are developing bispecific antibodies that combine targeting of PD-1/LAG-3 or LAG-3/CTLA-4, respectively.

Anti-LAG-3 agents seem to have a relatively benign side effect profile and do not induce autoimmunity in preclinical models. However, LAG-3 blockade or LAG-3 deficiency accelerates diabetes in predisposed non-obese diabetic mice, which is a side effect worth watching. It will be interesting to see how this segment of the checkpoint inhibitor market unfolds over the coming years, as trials mature and more data become available. BCC Research is cautiously optimistic that anti-LAG-3 agents will reach the market and anticipates that at least three products could reach the market by 2023, generating sales of $0.2 billion.

TIM-1, TIM-3

Anti-TIM therapies represent an exciting new class of immunotherapeutic that will complement existing treatments. Drugs blocking TIM-1 or TIM-3 are being investigated as monotherapy or in combination with anti-PD-1/PD-L1 agents. Accumulating preclinical data strongly support the use of anti-TIM-3 therapies (either alone or in combination with other checkpoint-based therapies) to overcome drug resistance and achieve objective response rates in a higher frequency of patients. In preclinical models, TIM-3 blockade alone exhibits similar efficacy to PD-1 pathway blockade. However, the combination of TIM-3 blockade with PD-1 pathway blockade is remarkably more effective in these models.

Curis/Aurigene and Symphogen/Shire have preclinical programs focused on development of dual- and triple-acting agents that target multiple checkpoint inhibitors. Symphogen is exploring the potential of bispecific antibodies that combine PD-1/PD-L1 with TIM-3 activity in a single molecule. Curis/Aurigene are developing an orally bioavailable, small-molecule TIM-3 antagonist that may have improved safety and flexibility in scheduling versus a monoclonal antibody approach. Several companies are evaluating anti-TIM-3 agents in the clinic, including Eli Lilly, Novartis, and TESARO.

BCC Research forecasts that the global market for anti-TIM-3 therapies will reach $0.54 billion by 2023. This assumes that anti-TIM-3 agents will largely be used in combination with anti-PD-1/PD-L1 agents. It is anticipated that Novartis and Celldex will launch products for patients who are refractory to current treatments for solid tumors, and in the case of Novartis, also hematological malignancies. Novartis' candidate will probably be the first anti-TIM-3 agent to reach the market. Celldex' product targets TIM-1 and may have a unique profile compared with other anti-TIM agents in development. This could enable Celldex to carve out a niche in advanced renal cell carcinoma and ovarian cancer, areas that have high unmet medical need.

CD47/SIRP

Anti-CD47/SIRPα therapies, which prevent cancer cells from evading phagocytosis, are a unique approach to immune checkpoint inhibition in cancer. CD47 is a ubiquitously expressed membrane protein that binds with the SIRPα receptor on macrophages to inhibit cell phagocytosis. Cells that do not express CD47 are considered foreign, prompting attack by macrophages. Phagocytose cells displaying abnormal CD47 signals, including

cancer cells, can evade immune recognition and removal.

Accumulating preclinical data strongly support the use of CD47 antagonists/anti-SIRPα targeted therapies, either alone or in combination with other antibodies or checkpoint-based therapies. Combination therapies may have synergistic effects, with acceptable side effect profiles and better objective response rates than checkpoint inhibitors alone. Forty Seven and Boehringer Ingelheim/OSE Immunotherapeutics have preclinical programs targeting the SIRPα and CD47 pathways, respectively.

ALX Oncology and Trillium are evaluating SIRPα domain fusion proteins in Phase I trials. Forty Seven (Phase I/II), Celgene (Phase I), and Surface Oncology (Phase I) have programs targeting CD47. Preliminary data look promising. As a monotherapy, prevention of metastasis development and dramatic changes in both solid tumor/lymphoma microenvironments have been observed. This effect seems to be enhanced in the presence of anti–PD-1 agents. On the basis of positive clinical data, additional companies may enter this area of development.

Anti-CD47/SIRPα therapies could reach the market by 2023 following fast-track approvals in solid and hematological malignancies that are refractory to current therapies. BCC Research forecasts that the global market for anti-CD47/SIRPα therapies will reach $0.02 billion by 2023. This projection is based on the assumption that these agents will be fast tracked in some cancers and will be used both as monotherapy and in combination with existing therapies, such as anti-PD-1/PD-L1 agents and other targeted monoclonal antibodies.

INNOVATIVE STRATEGIES FUEL MARKET FOR CHECKPOINT INHIBITORS

Manufacturers of immune checkpoint inhibitors continually push scientific boundaries to rationally design drugs and combinations that will more effectively treat patients. These include checkpoint blockers with epigenetic modulators, checkpoint blockers with costimulatory monoclonal antibodies, checkpoint blockers with cancer vaccines, and checkpoint blockers with chemotherapy and radiation. As manufacturers expand the clinical utility of these agents and healthcare professionals become more familiar with their efficacy and safety profiles, the market will continue to expand. Indeed, checkpoint inhibitors will become the cornerstone of many cancer treatment regimens.

Not all patients benefit from PD-1/PD-L1 and CTLA-4 inhibitors, which represent the FDA-approved therapies. This has catalyzed enormous interest in the development of stimulatory and inhibitory immune checkpoint therapies. Given the heterogeneity of cancer, many approved therapies are only effective in subpopulations. Therefore, the ability to identify patients who are most likely to respond to therapy or become refractory to treatment remains a key unmet need in oncology.

Throughout the next 5 years, marketed checkpoint inhibitors will gain regulatory approval in new indications and territories. In addition, novel classes of checkpoint inhibitors will enter the market. Companies will identify clinically effective combinations and validate biomarkers/signatures to help identify patients who are most likely to benefit from treatment. Precision medicine will be a major driver for pharma to effectively deliver these innovative medicines and ensure that they are available at sustainable prices to all of those in need. ◆

This article is based on a market analysis report published by BCC Research titled Checkpoint Inhibitors: Global Markets (PHM185A) by Cheryl Lee Barton.

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

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