Drug Development & Delivery

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

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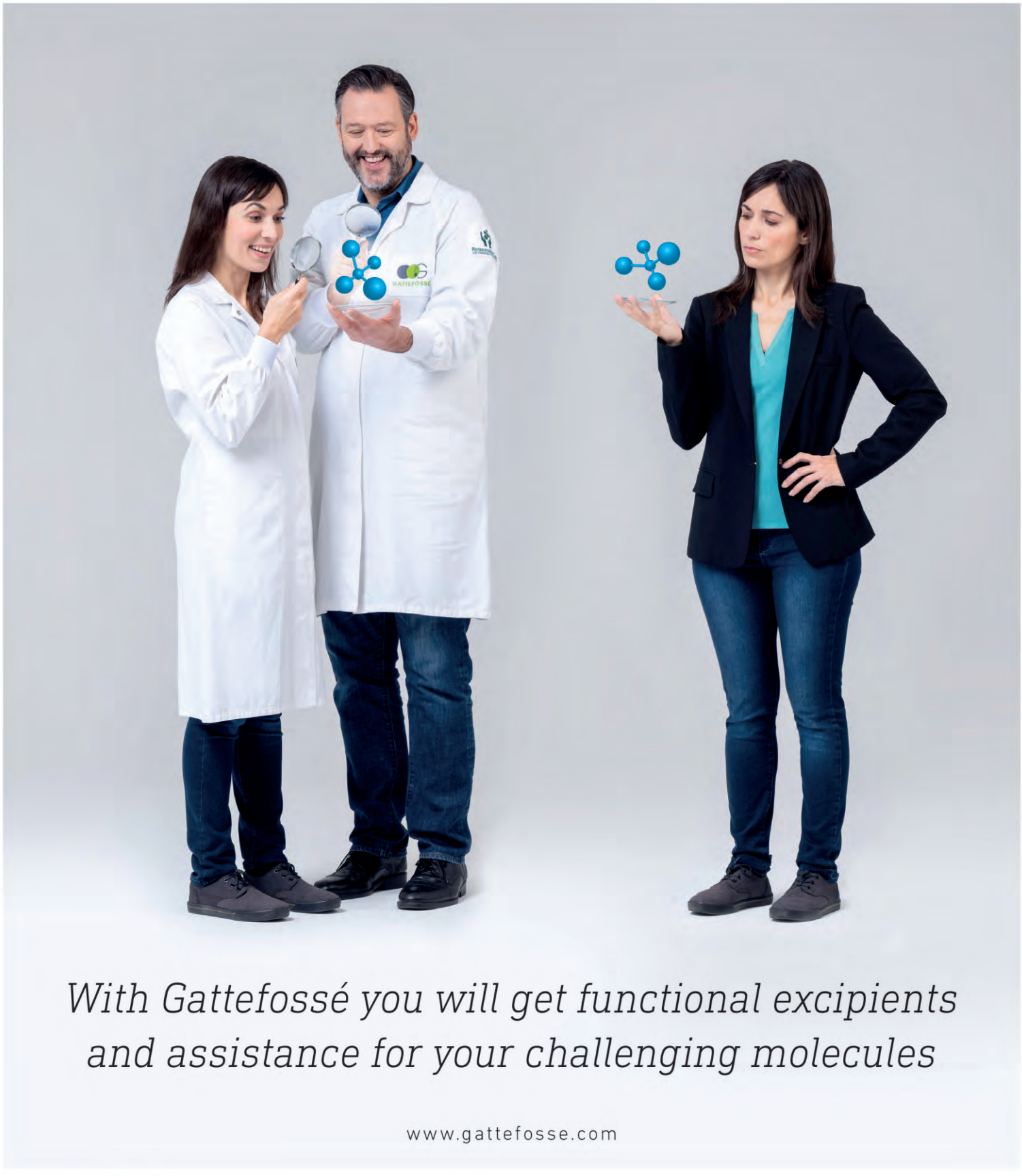

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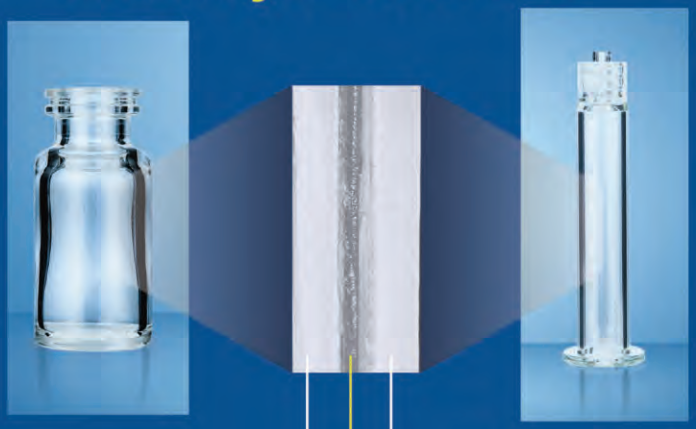

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"In addition to improving enzyme specificity, researchers have been using computational algorithms to predict which regions of the genome might be at risk for OTEs. These algorithms usually identify OTEs but often provide either too many sites to study or are filtered too much and so miss important sites. In response to these uncertainties, IDT launched a new product called rhAmpSeq™ that can be used in preclinical risk assessments."

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Injection Devices & COVID-19

"However, others expect the market to recover and reach $21.3 billion in 2023, partly due to increased demand for injection devices that can be used and monitored in the home environment. For example, treatment of chronic diseases such as diabetes, Rheumatoid Arthritis, and Crohn's disease are most commonly self-administered at home, and prefilled safety syringes and autoinjectors are typically used by these patients."

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ANA Therapeutics & Quotient Sciences Announce Manufacturing Partnership

ANA Therapeutics, a Silicon Valley-based biotech start-up, and Quotient Sciences, a leading provider of innovative drug development and manufacturing solutions, recently announced a partnership to support the manufacturing of ANA Therapeutics' drug candidate, ANA001 (niclosamide capsules), which they are developing as a potential treatment for COVID-19. As part of the collaboration, Quotient will scale up the capsule formulation, characterize and optimize the manufacturing process and ensure continuity of drug product through clinical trials.

Laboratory experiments have shown niclosamide stops SARS-CoV-2 (the virus that causes COVID-19) from replicating, making it a promising candidate for reducing the spread of COVID-19. Niclosamide was previously approved by the FDA as a treatment for tapeworm and although not currently marketed in the U.S., it is on the World Health Organization's List of Essential Medicines and has been used for decades to safely treat millions of people around the world.

"We have selected Quotient Sciences as our development and manufacturing partner and our plan is simple," said Andrew Bartynski, COO, ANA Therapeutics. "Niclosamide has the potential to be an effective antiviral agent to combat COVID-19, and our top goal is to complete a clinical trial to determine its efficacy in treating patients with COVID-19. Quotient's speed and agility will play a key role in reaching that important milestone."

Mark Egerton, PhD., CEO of Quotient Sciences, said, "We are proud to partner with ANA Therapeutics in their pursuit of a treatment to fight this coronavirus pandemic. Our experience and flexible manufacturing approaches will enable ANA Therapeutics to initiate clinical testing in an accelerated timeframe."

Under the scope of the agreement, ANA Therapeutics will access Quotient's formulation and manufacturing expertise to develop and rapidly supply drug product for pivotal clinical trials in Q3 2020. The program will be conducted at Quotient's facility in Garnet Valley, Pennsylvania.

ANA Therapeutics is a Silicon Valley-based biotech startup working to develop niclosamide as a safe, widely accessible antiviral treatment for patients with COVID-19. A low-cost, scalable, and well-tolerated compound, niclosamide has the potential to be a needed treatment to help individuals who contract the novel coronavirus to beat it.

Quotient Sciences is an innovative global pharmaceutical development, clinical, and commercial manufacturing organization providing services to the pharmaceutical and biotech industries. A combination of specialized skills and agile integrated processes enables Quotient Sciences to develop customized solutions which dramatically reduce the time and cost of getting drugs to market. Everything we do is driven by a deeply held belief, shared across the entire organization, that molecules need to become cures — fast.

Humanetics Corporation & Pharmaceutics International, Inc. Announce Partnership

Humanetics Corporation and Pharmaceutics International, Inc. (Pii) will work together to support a clinical trial of BIO 300 in COVID-19 patients.

The study will focus on patients who were treated for severe COVID-19, discharged from the hospital, and continue to recover at home. These patients face the possible risk that their respiratory complications will continue to progress, leading to long-term impairment similar to the lasting effects of Severe Acute Respiratory Syndrome (SARS).

The study will compare the lung function, exercise capacity and quality of life in COVID-19 survivors who receive BIO 300, against a group receiving a placebo. The primary endpoint of the trial will be at 12 weeks and patients will be followed for one year.

BIO-300 is a unique, highly selective modulator of inflammation, cell cycle arrest and DNA damage repair being developed for several indications including oncology and defense countermeasures. The patented formulation using suspended nanoparticle technology for improved oral bioavailability, was developed by Humanetics initially for the U.S. Department of Defense to protect military members from harm caused by ionizing radiation. The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, awarded funding to conduct the study of BIO 300.

The study will be conducted by physicians at NYU Langone Health with clinical trial material manufactured by Pii, a US-based contract development and manufacturing organization (CDMO). Humanetics and Pii have worked closely together since 2014 on the development of manufacturing techniques for BIO 300 that increase the drug's oral absorption properties. These improved characteristics allow BIO 300 to be taken by COVID-19 patients in the convenience of their homes. Previous clinical supplies of BIO 300 manufactured by Pii have been used in a clinical trial of non-small lung cancer patients receiving radiation treatments.

There is a growing concern about the long-term health effects caused by COVID-19 infection. Data from survivors show that a significant number have measurable lung damage at discharge from the hospital, which can linger and progress to additional lung abnormalities, including permanent fibrosis. BIO 300 is one of the therapies to be tested in the growing number of survivors who need treatments to mitigate this progressive lung damage.

Pharmaceutics International, Inc. (Pii) is a US-based contract development and manufacturing organization (CDMO) with a passion for solving problems efficiently with the highest quality standards. Pii's Hunt Valley, Maryland campus includes 70 manufacturing for both oral and injectable manufacturing. Our professionals have extensive experience with small and large molecule compounds, developing and manufacturing complex oral and parenteral drugs as well as extended-release formulations, suspensions, and other dosage forms.

EyePoint Pharmaceuticals Receives $9.5 Million From Ocumension Therapeutics Under Expanded License Agreements

EyePoint Pharmaceuticals, Inc. and Ocumension Therapeutics recently announced the expansion of their exclusive license agreements for the development and commercialization of YUTIQ and DEXYCU in certain Asian markets. Under the expanded agreements, Ocumension has made a one-time $9.5 million payment to EyePoint for rights to commercialize both products under their own brand names in South Korea and other jurisdictions across Southeast Asia and as the full and final prepayment of all remaining development, regulatory, and commercial sale milestone payments under the original license agreements.

"Ocumension is an important partner that shares our beliefs in the therapeutic potential of YUTIQ and DEXYCU for ocular diseases that represent growing and significant areas of unmet medical need," said George Elston, Chief Financial Officer and Head of Corporate Development of EyePoint Pharmaceuticals. "We are delighted to expand our partnership with Ocumension to include the broader Asian marketplace. The payment from the expanded license agreements will support our operations and the ongoing clinical development of our pipeline, including our lead candidate, EYP-1901, a potential six-month sustained delivery therapy for wet age-related macular degeneration."

"EyePoint's YUTIQ and DEXYCU are important programs in our portfolio of ocular disease treatments that have the potential to replace current standards of care that lack long-term activity, especially given the impact of COVID-19 on patient desire to visit the doctor," said Ye Liu, Chief Executive Officer of Ocumension. "We look forward to continuing our development efforts for both products in order to bring these innovative treatment options to patients in need across Asia."

EyePoint Pharmaceuticals, Inc. is a pharmaceutical company committed to developing and commercializing innovative ophthalmic products in indications with high unmet medical need to help improve the lives of patients with serious eye disorders. The company currently has two commercial products: DEXYCU, the first approved intraocular product for the treatment of postoperative inflammation, and YUTIQ, a 3-year treatment of chronic non-infectious uveitis affecting the posterior segment of the eye. The company's pipeline leverages its proprietary bioerodible Durasert technology for extended intraocular drug delivery including EYP-1901, a potential six-month anti-VEGF therapy initially targeting wet age-related macular degeneration. EyePoint Pharmaceuticals is headquartered in Watertown, MA, with offices in Basking Ridge, NJ.

Ocumension Therapeutics is a China-based ophthalmic pharmaceutical platform company dedicated to identifying, developing and commercializing first- or best-in-class ophthalmic therapies. The company's vision is to provide a world-class pharmaceutical total solution to address significant unmet ophthalmic medical needs in China. Since the inception, Ocumension Therapeutics has focused on building a platform integrating specialized capabilities in each major functionality involved in an ophthalmic drug's development cycle, from research and development, manufacturing to commercialization. Ocumension Therapeutics believes its platform positions it well to achieve leadership in China ophthalmology, with a first-mover advantage over future competitors.

Scioto Biosciences Receives $26.5 Million Series B Investment From Genome & Company

Scioto Biosciences recently announced the closing of a strategic investment of up to $26.5 million from Genome & Company and other investors to join in an upcoming tranche. Genome & Company is a leading microbiome company with headquarters in South Korea. The deal gives Genome & Co a majority stake in Scioto and expands its presence into the US.

Both companies have agreed to multilaterally cooperate on the research of new drug candidates. The funding will continue to support clinical development of Scioto's lead drug candidate, SB-121, which targets disorders related to the gut-brain axis like Autism Spectrum Disorder (ASD) as well as disorders related to gut-injury such as Necrotizing Enterocolitis (NEC) which affects premature infants. SB-121 is built on Scioto Biosciences' proprietary ABT (Activated Bacterial Therapeutics) Platform.

Scioto Biosciences, headquartered in Indianapolis, IN, is primarily focused on developing new drugs targeting brain and bowel diseases, and has taken an exclusive global license of the ABT Platform, which was invented by researchers at the Abigail Wexner Research Institute (AWRI) at the Nationwide Children's Hospital in Columbus, Ohio.

"We are very much looking forward to partnering with Genome and Company to continue to develop the ABT platform. We are excited to have them as a development partner with deep microbiome expertise and better access to Asian markets," said Joe Trebley, CEO of Scioto Biosciences.

Through the deal, Genome & Company is adding a new clinical-stage drug candidate, SB-121, to its pipeline which will follow its leading clinical candidate GEN-001 (immune-oncology), which is currently undergoing clinical trials simultaneously in the US and Korea. Through Scioto Biosciences, Genome & Company expands its global presence, now including the US, which will also support the company as a discovery center and facilitating communication with regulatory agencies such as the FDA for clinical studies.

"We are very pleased to be able to expand our microbiome drug portfolio through Scioto Biosciences, which is developing original technology with excellent scalability," said Dr. Pae Jisoo, CEO of Genome & Company.

RM Global Partners LLC acted as Genome & Co's advisors and Lighthouse BioPartners LLC acted as Scioto Biosciences' advisors for this transaction.

Based in Indianapolis, Scioto Biosciences is a preclinical stage company developing innovative therapies devoted to having a transformative impact on the delivery of live bacterial therapeutics (LBTs). Scioto was founded in 2017 as a partnership between Indiana business accelerator, Monon Bioventures (MBV) and AWRI with whom the company has a worldwide exclusive licensing agreement. The Scioto Activated Bacterial Therapeutic (ABT) Platform has the potential to enhance efficacy wherever LBTs are used, such as gastrointestinal health, diabetes, neurological disorders, alternatives to in-feed antibiotics (in livestock) and others.

Organicell Provides Phase 1/2 Clinical Trial Update

Organicell Regenerative Medicine, Inc. recently announced it has partnered with Alternative Research Associates, LLC and Larkin Hospital in Miami, FL, to initiate a randomized, double-blinded, placebo-controlled Phase 1/2 clinical trial against COVID-19 of its lead therapeutic candidate, which has been re-branded as Zofin.

To date, a total of five patients have been treated with Zofin under the US FDA emergency Investigational New Drug (eIND) Program. Three of these COVID-19 patients were hospitalized in critical condition and, following treatment, regained complete recovery of lung and renal function. The other two patients were treated as outpatients and both have shown significant improvements in all symptoms and will continue to be monitored.

The objective of the FDA Phase 1/2 study is to investigate the safety and potential efficacy of perinatal sourced components for COVID-19. The study will enroll 20 patients and is expected to commence within the next 2 weeks.

In addition to the rebranding of its therapeutic candidate, Organicell will be unveiling a new corporate logo, tagline and website. The new brand reflects the company's renewed focus on building and advancing a portfolio of biologics.

Albert Mitrani, Chief Executive Officer of Organicell, stated "Our team and stakeholders have worked vigilantly to make 2020 a milestone year at Organicell. We are pleased to partner with Alternative Research Associates and Larkin Hospital to advance this important clinical study to evaluate moderate to severe patients with COVID-19."

Dr. Maria Ines Mitrani, Chief Science Officer at Organicell stated "We look forward to working with our partners at Larkin Community Hospital to evaluate the treatment of Zofin in moderate to severe COVID-19 patients."

Organicell Regenerative Medicine, Inc. is a clinical-stage biopharmaceutical company that harnesses the power of nanoparticles to develop innovative biological therapeutics for the treatment of degenerative diseases. The company's proprietary products are derived from perinatal sources and manufactured to retain the naturally occurring microRNAs, without the addition or combination of any other substance or diluent. Based in South FL, the company was founded in 2008 by Albert Mitrani, Chief Executive Officer and Dr. Maria Ines Mitrani, Chief Science Officer. For more information, visit https://organicell.com/.

Larkin Community Hospital is an integrated healthcare delivery system accredited by the Joint Commission with locations in South Miami, Hialeah and Hollywood, Florida. Our network of acute care hospitals provides a complete continuum of healthcare services, including a full range of inpatient and outpatient services, home health agencies, Skilled Nursing facilities, Rehab centers and Assisted Living facilities in Miami-Dade and Broward County. For more information, visit http://larkinhospital.com/.

Ajinomoto Bio-Pharma Services Expands Small Molecule Manufacturing Capabilities at its India Facility

Ajinomoto Bio-Pharma Services recently announced a major expansion of small molecule manufacturing capabilities with the addition of a new production facility in Visakhapatnam, India. Construction of the 8,500-square-meter facility began at the end of July 2020 and is expected to be completed mid-2022.

To meet the current and future needs of customers, the new small molecule manufacturing facility doubles the production capacity at the site to 310 m3 for active pharmaceutical ingredients (API) and intermediates and has dedicated equipment to manage OEB 4 high potency ingredients. Further, the site has completed renovations on existing laboratory space to support additional R&D activities. It is estimated that the expansion will create at least 60 new jobs at the site.

The US FDA approved Ajinomoto Bio-Pharma Services India manufacturing site, which was designed, constructed and is managed based on the Aji Bio-Pharma Belgian sites' GMP operating standards and quality systems, has successfully supported a number of the world's leading biopharmaceutical companies since its formation in 2011 and continues to win awards for sustainability and quality standards.

"We are very excited to be investing in this additional production capacity to continue delivering high quality, cost-effective small molecule manufacturing services for our customers," said K.V.V. Raju, Head of Site Operations and CEO, Ajinomoto Bio-Pharma India Pvt. Ltd. "This expansion exemplifies our commitment to our vision statement of being a leading, trusted, innovative partner to our clients and our people."

"The increased manufacturing capacity at Aji Bio-Pharma India offers a significant advantage for our small molecule customers, who now have a variety of options to meet their manufacturing needs," said Peter Stuyck, Sr. Vice President and Head of European Operations, Ajinomoto Bio-Pharma Services. "This expansion optimizes capacity across all locations and further enhances Aji Bio-Pharma's commitment in being a leading global and quality-driven CDMO with comprehensive service offerings."

Ajinomoto Bio-Pharma Services is a fully integrated contract development and manufacturing organization with sites in Belgium, United States, Japan, and India, providing comprehensive development, cGMP manufacturing, and aseptic fill finish services for small and large molecule APIs and intermediates. Ajinomoto Bio-Pharma Services offers a broad range of innovative platforms and capabilities for pre-clinical and pilot programs to commercial quantities, including Corynex® protein expression technology, oligonucleotide synthesis, antibody drug conjugations (ADC), high potency APIs (HPAPI), biocatalysis, continuous flow manufacturing and more. Ajinomoto Bio-Pharma Services is dedicated to providing a high level of quality and service to meet our client's For more information, visit www.AjiBio-Pharma.com.

FDA Clears Appili Therapeutics to Expand its Phase 2 Clinical Trial of Favipiravir for the Potential Prevention of COVID-19

Appili Therapeutics Inc. recently announced the US FDA has granted the company clearance to proceed after Appili's filing of an investigational new drug (IND) application for broad-spectrum antiviral favipiravir. Appili is expanding its Phase 2 clinical trial into the US to evaluate the safety and efficacy of favipiravir tablets in controlling outbreaks following exposure to COVID-19 in long-term care (LTC) facilities. Appili's Phase 2 clinical trial is leveraging the versatility of favipiravir as an oral tablet suitable for administration across a wide variety of care settings, including long-term care. Appili intends to enroll up to 760 participants in this Phase 2 clinical trial across both the US and in Canada. Health Canada provided regulatory clearance on May 21, 2020, for Appili's Phase 2 study evaluating FUJIFILM Toyama Chemical's (FFTC) favipiravir as a preventative measure against COVID-19 outbreaks.

"The burden of illness in long-term care centers continues to be a significant problem, and finding ways to offer LTC residents and staff protection against COVID-19 with an oral treatment would be a significant advance in our fight to control the devastating effects of this pandemic," said Dr. Armand Balboni, Chief Executive Officer at Appili Therapeutics. "The limited response to vaccines often seen in the elderly further supports expanding this trial into the US. Favipiravir is an antiviral that can be administered orally as a tablet, without the need to be given intravenously or as injections, and may be an important option to avoid and/or control outbreaks in elderly residents living in LTC facilities."

"The elderly are at the highest risk for contracting the disease and the rising rates of COVID-19 infection currently seen in much of the US will likely continue to be a major threat to those living and working in long-term care facilities," said Primary Investigator Dr. Allison McGeer, senior clinician scientist at the Lunenfeld-Tanenbaum Research Institute at Sinai Health. "Through the means of a randomized control clinical trial, our team is looking forward to working with clinical partners in the US to understand if favipiravir could be an option for outbreak control in this setting."

Favipiravir was originally developed and approved in Japan as a treatment and stockpile countermeasure for pandemic influenza outbreak under the name AVIGAN. Following promising clinical studies, Russia and India recently approved favipiravir-based antiviral medications for the emergency treatment of COVID-19. Researchers are conducting additional trials evaluating favipiravir as a treatment for COVID-19 in countries including the US, Japan, China, and the UK.

Appili Therapeutics Inc. was founded to advance the global fight against infectious disease by matching clearly defined patient needs with drug development programs that provide solutions to existing challenges patients, doctors, and society face in this critical disease space. Appili has built a pipeline of assets designed to address a broad range of significant unmet medical needs in the infectious disease landscape.

Eyenovia & Arctic Vision Announce Exclusive Collaboration & License Agreement

Eyenovia, Inc. and Arctic Vision recently announced they have entered into an exclusive license agreement for Arctic Vision to develop and commercialize MicroPine for the treatment of progressive myopia and MicroLine for the treatment of presbyopia in Greater China (mainland China, Hong Kong, Macau, and Taiwan) and South Korea.

Under the terms of the agreement, Eyenovia may receive up to a total of $45.75 million in upfront payments as well as additional payments, based on various development and regulatory milestones, including the initiation of clinical research and approvals in Greater China and South Korea, and development costs. In addition, Arctic Vision will purchase its supply of MicroPine and MicroLine from Eyenovia or, for such products not supplied by Eyenovia, pay Eyenovia a mid-single digit percentage royalty on net sales of such products, subject to certain adjustments. Eyenovia will pay a mid-double digit percentage of such payments, royalties, or net proceeds of such supply to its Asian licensee pursuant to the arrangement by which Eyenovia reacquired rights to such products in Greater China and South Korea from the original licensee.

MicroPine (atropine ophthalmic solution) is for progressive myopia, a back-of-the-eye condition commonly known as nearsightedness. Progressive myopia is estimated to affect close to 5 million children in the US who suffer from uncontrolled axial elongation of the sclera leading to increasing levels of myopia and in some cases major pathologic changes, such as retinal atrophy, macular staphylomas, retinal detachment, and visual impairment. MicroPine has been developed for comfort and ease-of-use in children. Microdose administration of MicroPine is anticipated to result in low systemic and ocular drug exposure. A recent therapeutic evidence assessment and review by the American Academy of Ophthalmology indicates Level 1 (highest) evidence of efficacy for the role of low dose atropine for progressive myopia.

MicroLine is a pharmacologic treatment for presbyopia. Presbyopia is the non-preventable, age-related hardening of the lens, which causes a gradual loss of the eye's ability to focus on nearby objects and is estimated to affect nearly 113 million Americans. Current treatment options are typically device-based, such as reading glasses and contact lenses. Pilocarpine ophthalmic solution is known to constrict the pupil and improve near-distance vision by creating an extended depth of focus through its small aperture effect. Eyenovia believes that its administration of pilocarpine using the company's high-precision microdosing technology could provide a meaningful improvement in near vision while enhancing tolerability and usability.

Eyenovia's Optejet microdose formulation and delivery platform for ocular therapeutics uses high-precision piezo-print technology to deliver 6-8 µL of drug, consistent with the capacity of the tear film of the eye. We believe the volume of ophthalmic solution administered with the Optejet is less than 75% of that delivered using conventional eyedroppers, thus reducing overdosing and exposure to drug and preservatives. Eyenovia's patented microfluidic ejection technology is designed for fast and gentle ocular surface delivery, where solution is dispensed to the ocular surface in approximately 80 milliseconds, beating the ocular blink reflex. Successful use of the Optejet has been demonstrated more than 85% of the time after basic training in a variety of clinical settings compared to 40% to 50% with conventional eyedroppers. Additionally, its smart electronics and mobile e-health technology are designed to track and enhance patient compliance.

Wearable Drug Delivery Provider Sorrel Medical Partners With Leading Global Pharmaceutical Manufacturer

Sorrel Medical recently announced it has entered into a strategic partnership with one of the world's leading pharmaceutical companies to advance the development and introduction of next-generation wearable drug delivery solutions.

The partnership will involve various molecule development initiatives across a range of configurations of Sorrel's wearable drug delivery platform. This partnership is entered in parallel to collaborations already in place for Sorrel Medical, as a provider of the device constituent of combination products.

Sorrel's discreet and versatile on-body injectors are specifically designed to enhance the patient experience and encourage adherence to treatment therapies, while reducing the risk of medication errors. The device attaches to the patient's body via a sticker patch, while multiple smart sensors – along with a series of internal system checks and visual, audio and tactile indicators – guarantee successful self-administration. Medication is injected subcutaneously through a reliable electro-mechanical pumping mechanism. The pre-filled and pre-loaded devices are available in cartridge and vial-based configurations ranging from 1 mL to 25 mL to meet a wide range of specific drug requirements.

"With the changing nature of injectable drugs, including the proliferation of biologics with higher volumes and viscosities, the world's leading pharmaceutical companies are looking to device makers for safe, versatile and easy-to-use devices," said Andrei Yosef, PhD, CEO of Sorrel Medical. "Combining our platform approach to development with our partner's extensive expertise in pharmaceutical formulation and market penetration, we can provide solutions that enhance the self-administration experience while encouraging patient adherence to treatments."

Sorrel Medical, an Eitan Group company, is a medical device company focused on the development and commercial manufacturing of platform-based, pre-filled and pre-loaded wearable injectors for the easy and efficient self-administration of large volume and highly viscous therapies. One of three privately held companies operating under the Eitan Group, Sorrel leverages core capabilities and expertise in drug delivery technology development, manufacturing and regulatory experience to offer a robust platform solution to global pharmaceutical and biotechnology companies. For more information, visit http://www.sorrelmedical.com.

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FORMULATION FORUM

Formulation Development Strategy for Early Phase Human Studies

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

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EARLY DEVELOPMENT CHALLENGES

Successful translation of discovery compounds into first-in-human (P1) and first-in-patient (P2) is one of the key challenges facing the pharmaceutical industry. To achieve these goals, a rational formulation development strategy will be critical to avoid costly drug development failures, while speeding up the development timeline in a cost-effective manner. This is particularly true for compounds with challenging properties in solubility and bioavailability.

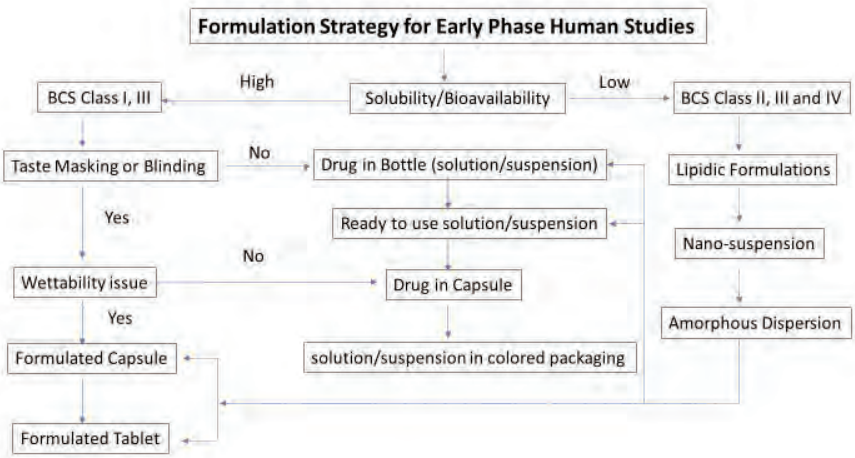
At the early phase of drug development, there is a limited supply of API available. Determination of an appropriate bioavailable formulation for animal PK, GLP toxicity, and first-in-human and first-in-patient is a challenging task. For poorly soluble and bioavailable compounds, development of formulations is usually achieved using drug delivery systems. Those development studies may involve the pre-formulation evaluation of the compound physicochemical biopharmaceutical properties, such as solubility and stability, in commonly used solvents and bio-relevant media, and permeability, etc. Afterward, optimization of solubility and bioavailability can be achieved by utilizing suitable delivery systems by screening a set of technology platforms, such as Ascendia's AmorSol®, NanoSol®, and EmulSol®, that address different compound challenges in hydrophilicity, lipophilicity, and melting point.

CONSIDERATIONS FOR EARLY PHASE DEVELOPMENT

The main goal for early phase development is to test the compound safety and efficacy for the intended therapeutic indications in animal and humans. Tremendous efforts have been placed in improving the pharmacokinetic properties of compounds and ensuring bioavailability in animal models and human Phase 1 and 2 studies. Even though a simple formulation, such as solution/suspension, drug-in-capsule is always desirable to allow for a fast transition to tox and human studies, a desired compound systemic exposure in testing subjects is prerequisite to meet the goals of early development. Therefore, time and resources might have to be allocated for compounds with poor bioavailability. Otherwise, the drug program could be at a higher risk of costly failure in first-in-man and at late stages.

It is critical to understand the compound's

FIGURE 1



properties, route of administration, animal model, patient population, and dose range, and use a phase-appropriate formulation that can meet clinical requirements on the systemic exposure, dosing flexibility, the design of the clinical studies, and project timelines. Figure 1 is a decision tree to guide in the early formulation selection.

Below are a few points for consideration during selection of early phase formulations:

1. What is the human dose range and the correspond concentration of the selected formulation at this location?

- Rout of administration, dose requirement, and compound solubility may determine whether to choose solution or suspension.

- Dose flexibility that covers low and high dose range is important as the highest dose is unknown pending the toxicity of drug candidate in human.

- Due to the wide range of doses for early clinical phase, if solution and suspension are considered, a biopharmaceutical assessment should be conducted to assess any bridging requirement between formulations.

- Handling Instructions and stability data will be required to support each dosage form.

2. Is there a requirement in blinding for the study design?

- Taste masking may be required for certain patient populations, such as pediatrics.

- Potential taste or color difference between active and placebo.

- Use of bittering agent for liquid dosage forms.

- Use of colored packaging or dosing syringe or cups.

3. Is the clinical study conducted by in-hospital dosing or out-patient dosing?

- There is different shelf life and storage requirement for different dosing strategy.

- Ready to use solutions/suspensions with room temperature or refrigeration storage is desirable for out-patient dosing.

DOSAGE FORM OPTIONS FOR EARLY PHASE CLINICAL STUDY

Drug-in-Bottle

API compound is supplied in a bottle for constitution into solution or suspension. The reconstitution is done at a hospital pharmacy. Commercial vehicles or their modified forms, such as "Ora-Sweet"" could be considered for such purpose. The dose can be further diluted into filled bottles for different doses and for patients to take home. Dose flexibility is the advantage of the approach, and stability requirement is minimum. This dosage form is suitable for in-hospital dosing. In some case, bulk amorphous solid dispersion formulations can be supplied in bottle and reconstituted by this approach.

Ready-to-Use Solution or Suspension

If the compound is not suspendable or dissolvable in a commonly used suspending vehicle but is stable for a longer time period of at least 3 to 6 months, a formulated solution, suspension, and nanosuspension filled in bottle at a CDMO can be considered. This dosage form is desirable for out-of-patient dosing. In some cases, lipidic formulation (SEDDS or Nanoemulsion) can be formulated and filled into bottle or hard capsules (as liquid-filled capsule) by this approach.

Drug-in-Capsule

If compound is readily wetted and dissolvable in GI fluids without the help of excipients, drug in capsule can be considered. Active compound is filled in hard capsules. Drug in capsule is suitable for out-patient dosing and for studies requiring blinding.

Formulated Capsule & Tablet

For chronic dosing or a clinical program that is planned to fast progress to late-stage phase, formulated capsule or tablet may be desired. API compound can be simply blended with a diluting excipient, and the blend is filled in hard capsules, or in some cases, for API that has challenges in flowability, wettability, and dosage uniformity, a formulated capsule or tablet may be considered. For poorly water-soluble compounds, it is possible that the enabling formulations, such as nanosuspensions, lipidic formulations, and amorphous solid dispersions, can be further incorporated into the capsule and tablet dosage forms.

SUMMARY

A phase-appropriate formulation development, which can meet clinical requirements on the systemic exposure, dosing flexibility, the design of the clinical studies, and project timelines, is important for successful translation of discovery compounds into first-in-human (P1) and first-in-patient (P2). To achieve these goals, a rational formulation development strategy is critical to avoid costly drug development failures, while also speeding up the development timeline in a cost-effective manner. ◆

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DRUG DEVELOPMENT

Bringing New Drugs to Patients Faster by Integrating Traditionally Separate Pharma Development Functions

By: Nutan Gangrade, PhD

INTRODUCTION

Speeding novel or improved drugs to the patients who need them is, of course, the be-all and end-all of pharmaceutical research and development (R&D). The $2.6-billion estimated cost of new drug development makes efficiency critical as well.[1] Reducing R&D project timelines saves on overhead in development while increasing the likelihood of primacy in the marketplace, which engenders significantly more sales. Therefore, increasing R&D efficiency makes sense from both humanitarian and business standpoints. The following describes new approaches drug developers are taking to streamline drug development.

SOME SENIOR PHARMA DECISION-MAKERS ARE RETHINKING HOW THEIR COMPANIES TACKLE R&D

Over time, pharma leaders have tried various ways to shorten development timelines by integrating process segments that have traditionally been separate. For instance, clinical research organizations (CROs) have integrated clinical activities with data sciences and biological and bioanalytical providers, resulting in a coordinated offering that simplifies clinical research.

Similarly, contract development and manufacturing organizations (CDMOs) have combined active pharmaceutical ingredient (API) synthesis and contract development with manufacturing of drug products to reduce downtime related to coordinating activities and transitioning from vendor to vendor.

Some companies have reorganized by expanding their API businesses to include drug product manufacturing. Meanwhile, other drug product businesses have taken on API production to streamline combined development and manufacturing. A 2017 study of one such program compared multi- and single-vendor CDMO models on cycle times and development economics.[2] The conclusion was that the single-vendor model could expedite the development of potentially life-changing therapies and save sponsors up to $45 million per drug through reduced time to market.[2]

These examples demonstrate how the industry has been employing a variety of tactics to integrate various workflows and processes, aiming to streamline drug development.

THE NEXT LOGICAL STEP: HORIZONTALLY INTEGRATE CLINICAL RESEARCH WITH DEVELOPMENT & MANUFACTURING FUNCTIONS

The latest development in this trend toward greater efficiency is the integration of clinical development and manufacturing capabilities into a single drug development program. Traditionally, multiple vendors (several CROs and several CDMOs) would be employed to undertake separate development activities. The idea behind integration is that dovetailing clinical activities with clinical manufacturing will improve decision-marking and increase speed and flexibility for developing investigational drug products. Ultimately, making therapies available to patients, faster, without compromising quality or safety.

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"Combining clinical and development with manufacturing functions addresses many of the challenges encountered in traditional drug development. In this model, production and clinical testing are integrated with single-source, small batch manufacturing. In response to emerging human data, a variety of formulation prototypes with varying technologies can be screened and clinically evaluated in short order, allowing rapid-fire selection, manufacture, and dosing."

HURDLES TO SHORTER TIMELINES & HIGHER SUCCESS RATES

In general, alongside high and ever-increasing costs, these common pharmaceutical development productivity pain points must be addressed:[3]

Challenges That Result in Long Timelines

Challenges in development and optimization of new clinical formulations - Ongoing trial results may dictate unanticipated alterations in dosing or formulations. For example, first-in-human (FIH) trials often reveal that the new drug molecule has suboptimal bioavailability — requiring time-consuming reformulation prior to use in subsequent, proof-of-concept (POC) clinical trials.

Lack of flexibility to respond to indicated changes - Changing dosages or formulations post-POC and in life cycle management activities usually means returning to the manufacturer for a new product development program and clinical trial manufacturing campaign. However, when clinical trials have begun, only clinical drug products already manufactured and approved can typically be used — in other words, it is neither simple nor easy to introduce a new dosage form partway through a trial. This lack of flexibility causes serious delays, with gaps of weeks to months between production and dosing — extra weeks or months that delay bringing an improved therapy to those in need. Additionally, the new formulation's deviation from the original protocol becomes a time-consuming regulatory issue that must be resolved.

Need to transition to a clinical cGMP process - The simple formulations for FIH studies are often prepared by pharmacies. These products may include drug-in-capsule or basic solutions or suspensions that allow maximum dose flexibility, which is important in the Phase 1 setting. However, as a molecule progresses in development toward POC patient trials, it is important to transition to a dosage form that delivers the drug optimally, is stable, and can be shipped to patient sites globally. This dosage form must also be manufactured according to good manufacturing practice (GMP) at an appropriate facility. Each product transition process entails additional time-consuming studies.

Management of multiple vendors - Simply coordinating multiple vendors takes time and effort. In addition, inevitably, there will be a time lag between a project handoff and when the recipient can begin the next stage of development.

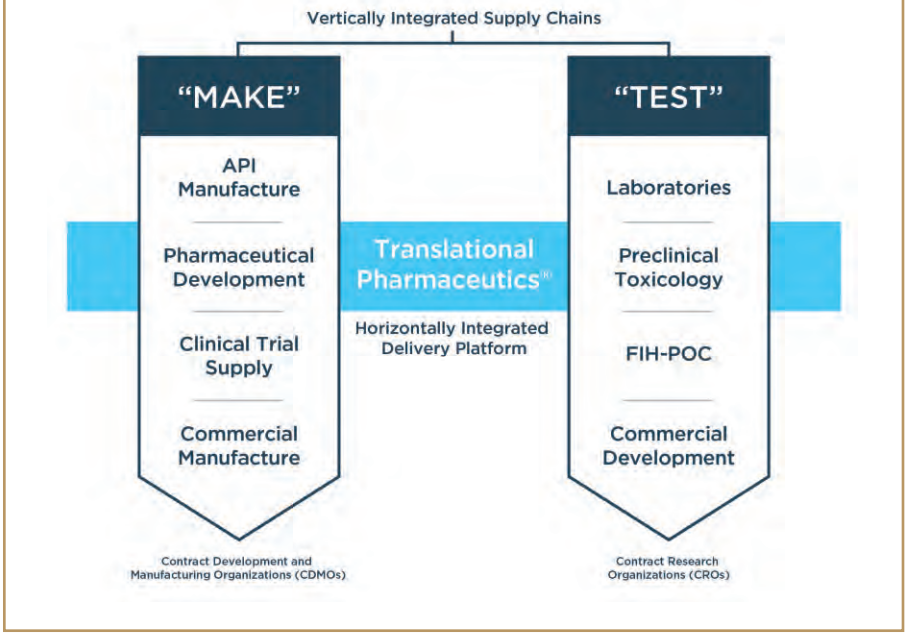
Challenges That Result in High Molecule-Attrition Rates

In drug development, early choices may be based on animal model data, which is notoriously less predictive of in-human results than human data. This suboptimal input and lack of flexibility to change course, mid-trial, lead to a high failure rate for new drugs, particularly late in the game. According to a 2018 MIT study, two out of five drugs that reach Phase 3 will fail.[4] This high failure rate factors heavily into the overall cost of drug development — a cost, one way or another, passed on to the public.

THE NEW APPROACH ADDRESSES ALL THESE CHALLENGES

Combining clinical research with development and manufacturing functions addresses many of the challenges encountered in traditional drug development. In this model, production and clinical testing are integrated with single-source, small batch manufacturing. In response to emerging human data, a variety of formulation prototypes with varying technologies can be screened and clinically evaluated in short order, allowing rapid-fire selection, manufacture, and dosing. These efficien-

FIGURE 1



cies reduce timelines significantly, lower costs, and increase a drug's chances for successfully improving human lives. Enabled capabilities include:

- Real-time decisions can be made based on the clinical results
- Formulations can be developed and optimized as the trial progresses
- Scale-up from small batch to clinical manufacturing does not require time-consuming tech transfer to another CDMO
- Costly mistakes and/or rework are avoided
- Compared with the coordination of multiple outsourced partners, assignment of a single vendor and a cross-functional project manager streamlines management
- Better-optimized therapies reach patients sooner

This integrated approach, which our company refers to as Translational Pharmaceutics®, was evaluated in a recent Tufts CSDD study.[5] This study found that, compared to industry benchmarks, an approach that integrates clinical and manufacturing functions, on average:

- Reduces development time by >12 months
- Translates into R&D cost savings of >$100 million per approved molecule
- Results in total financial gains of >$200 million per approved molecule, as products reach the market sooner

WHY AREN'T ALL PHARMA COMPANIES TAKING THESE NOVEL, INTEGRATIVE APPROACHES?

Large pharma companies have long-standing, standard ways of doing things they know work. Their focus is on keeping processes moving without complication, so aside from looking for small improvements and optimization, the less they vary their day-to-day procedures, the better able they are to remain productive.

The downside, however, is that this traditional structure is often not flexible enough in modern early drug development, where it is necessary to make swift decisions and pivot quickly. What's required today is a start-up mindset, like that of small biotech companies. Institutional features enabling the necessary speed to succeed in the current, competitive marketplace include:

- Strong scientific skills and competencies
- Flexible and agile processes
- A culture that encourages innovation, thinking outside the box, and working smarter to adopt tailored/bespoke approaches

In many cases, large pharma companies have noted that a lot of the innovation in drug development and new molecule discovery is coming from small biotech companies. In turn, large pharma is allowing small biotechs to apply their considerable energies to early drug development, and then purchasing the rights to promising new drug candidates. In fact, today, a large proportion of the molecules large pharma companies have in their pipelines were not developed in-house, but were bought from lean, agile biotech companies entirely focused on achieving the next phase of development. To illustrate, a 2019 STAT article lists the provenance of the highest-selling prescription drugs from Pfizer and Johnson & Johnson for 2017.[6]

TABLE 1

	R&D Cost Reduction	Net Revenue Gain	Total Financial Gain
Application	**Mechanism:** Drug development times shortened, resulting in R&D cost savings	**Mechanism:** Products reach market faster, affording additional sales	
FIH to POC Transitions	$135.2M	$120.8M	$256M
Modified Release Formulations	$117.2M	$103M	$220.2M
Solubility Enhancement Formulation Development	$107.7M	$93.8M	$201.5M
All Types of Projects Evaluated			$102.6M – $290.1M

Mean After-Tax Financial Gains per Approved Small Molecule, Oral Drug Developed Using a Blended, In-House Clinical/Manufacturing Approach for Various Applications, Compared With Conventional Outsourcing[7]

SOME VISIONARY LEADERS IN BIG PHARMA HAVE DEVELOPED A WORKAROUND

Large pharmaceutical companies are taking steps to bring new therapies to the world faster by addressing the problem of sluggish R&D. One approach is to carve out a start-up-like division within the larger organization. These separate business units are designed and encouraged to behave like small biotechs. For a handful of new molecules each year — especially those with time pressures or known competition — these innovative programs achieve accelerated development.

One example of this phenomenon is at Eli Lilly. This vast company set up a separate division called Lilly Chorus.[7] Chorus teams save time by not having to work with standard Lilly processes — for instance, they have a streamlined QA process especially tailored for POC development. At Lilly Chorus, molecules reach POC much faster than they would within the parent organization's system. The limited number of molecules selected for development through this model have been very successful.

Another example is Janssen Research & Development, a Johnson & Johnson company, and its WAVE early development unit. Like Chorus, WAVE is a team operating within a larger company that is specifically engineered to execute in a lean, efficient, biotech-like way. This independent unit progresses novel compounds from FIH through initial POC stages. By focusing on key compound developability questions, WAVE scientists produce data that enables robust decision-making. Through this arrangement, Janssen can discover and develop innovative solutions that address unmet medical needs.

Independently operated divisions like these can engage in the kind of agile decision-making necessary for fast, effective early development — even within the confines of a large, less flexible organization.

INTEGRATING CLINICAL & MANUFACTURING ACTIVITIES IS ANOTHER WAY

Engaging a single organization that can undertake multiple development activities may enable pharmaceutical companies to develop their own new medicines and bring them to patients significantly faster. This approach is illustrated by two stages of development, as shown in a recent Tufts whitepaper (referenced in Table 1). The first stage encompasses the initial clinical studies to achieve POC — the transition from Phase 1 to POC. The second stage is the post-POC , in which drug products are optimized for pivotal trials in late clinical development.

Pre-approval R&D cost benefits from faster initiation were substantial. Rate of return analysis on costs and sales found further gains attributable to earlier launch. Through these mechanisms, notable time and monetary savings can be achieved across a broad range of study types, as

quantified in Table 1.

Enlisting the aid of a company focused on getting work done very quickly by integrating formulation, manufacturing, and clinical testing can shorten development times by more than 12 months.

REAL-TIME ADAPTIVE MANUFACTURING IS EFFICIENT & SPEEDS NEW DRUGS TO PATIENTS

In pharma development, shorter timelines are key. Integrating traditionally siloed functions is one way to streamline the process and bring novel therapies to patients sooner. Enabling research groups to function more like start-ups, regardless of how the rest of the organization operates, can help.

Engagement in real-time adaptive manufacturing can streamline R&D. Compared to a traditional development program, a flexible dosage design complemented by real-time manufacturing of changing dosages and formulations can result in efficiencies that reduce timelines significantly and increase a drug's chances for success.

The impact of this integrative approach has been quantified across a large portfolio of small molecule, oral dose, early stage clinical drug development projects. Faster initiation of POC and pivotal clinical trials engender real pre-approval R&D cost benefits. Additionally, shorter development times mean earlier arrival to market, resulting in substantial financial gains per approved new drug and streamlined access to new, life-enhancing therapies for patients. ◆

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BIOGRAPHY

Dr. Nutan Gangrade is Global Head of Pharmaceutical Sciences at Quotient Sciences and has over 30 years of experience within the pharmaceutical industry. Prior to his current role, he served as Managing Director of Quotient Sciences, Philadelphia, with responsibility for all development and manufacturing operations across two sites. He held the position of Senior Director of Formulation Development at QS Pharma, a US CDMO, where he was also a founding team member. He has previously held positions at Bristol-Myers Squibb (DuPont Pharmaceuticals) and Wyeth-Ayerst Research (American Cyanamid). In these positions, he was the CMC lead for several products in various phases of development. He earned his PhD in Pharmaceutics from the University of Georgia.

GENE-EDITING TECHNOLOGY

The Importance of Assessing Off-Target Effects of CRISPR Gene Editing

By: Mark Behlke, MD, PhD

INTRODUCTION

"It feels like my bones are being sawed with a rusty blade, for hours" says Alice (not real patient's name) – a woman in her 30s who has lived with a lifelong condition, called sickle cell disease (SCD). "I just have to tough it out. I try warm soaks, heating pads, and deep breathing to soothe the agony. It's hard to get the right care and pain relief. You go into the emergency room and you don't know if you're going to leave alive. Every time, it's a battle" she says. Pain is the hallmark of SCD, and is caused by deformed, sickle-shaped red blood cells clumping together and blocking capillaries. This results in severe pain and swelling in affected body parts. SCD can be life-threatening. In fact, half of the patients that make it to adulthood are dead by their early 40s.

THE DISCOVERY OF CRISPR

In the early 1990s, a scientist completing his PhD in Spain discovered genetic sequences in archaea that were repeated up to 600 times in a row. This corroborated a similar discovery in bacteria by Japanese scientists in the late 1980s. These repeats were later found to be part of a prokaryotic immune system. They are used to store genetic information on viruses to which the organism and its progenitors have been exposed, and prime the organism to defend itself against these threats in the future.[2] At the time, few people would have imagined that this finding, which later became known as CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), would lead to further developments that would become the dominant gene editing technology and

have a major impact on the medical sciences.

CRISPR gene editing is a technology that is being used by scientists to make precise, permanent changes to DNA in animals and plants. CRISPR can be used to make these edits at a single, specific location. It is currently being evaluated in early phase clinical trials for several disorders caused by a single gene mutation, including SCD and beta-thalassemia. As the technology evolves, we will likely see more applications beyond treating these types of disorders, as well as use of the technology in agricultural science to improve crop yields and resilience and boost nutritional value.

WHAT IS CRISPR GENE EDITING?

CRISPR gene editing is based on a natural defense mechanism, used by bacteria and archaea. It is composed of two components: a nuclease (eg, Cas9), responsible for the cleavage of double-stranded DNA, and an RNA guide, which provides specificity by aligning the nuclease–RNA complex to the desired target DNA. The technology is currently generating a lot of excitement because it is more cost effective, rapid, and easy to use than previous gene editing techniques, including zinc-finger nucleases and TALENs. As the most commonly used enzyme in CRISPR gene editing, Cas9 is often applied to target and edit precise stretches of DNA and has been a key focus of our work at Integrated DNA Technologies (IDT).

THE CAS9 ENZYME

The first case of a nuclease engineered for the CRISPR technique was the Cas9 system from Streptococcus pyogenes (S.p.), which was described in 2012.[3] This CRISPR system, composed of wild-type (WT) Cas9, and two guide RNA molecules fused into a single guide RNA (sgRNA), has been successfully used for gene editing purposes in mammalian cells.

CRISPR/Cas9 gene editing offers unparalleled genome editing efficiency and can function in various cell types and species. However, despite the improved specificity of CRISPR in recognizing target sequences when compared with previous gene editing techniques, DNA cleavage may still occur at unintended sites that are similar but not identical to the desired target site. These are known as off-target effects (OTEs) and may account for more than 50% of the editing delivered by WT Cas9.[4] Although these events mostly occur in areas of the genome believed to have no function, there is always the risk that they may lead to unintended, adverse consequences. Many researchers have tried modifying the guide RNA and created improved-specificity mutant Cas9 proteins to reduce OTEs, but these alterations also usually reduce on-target editing performance.

ENGINEERING A HIGH-FIDELITY CAS9 ENZYME

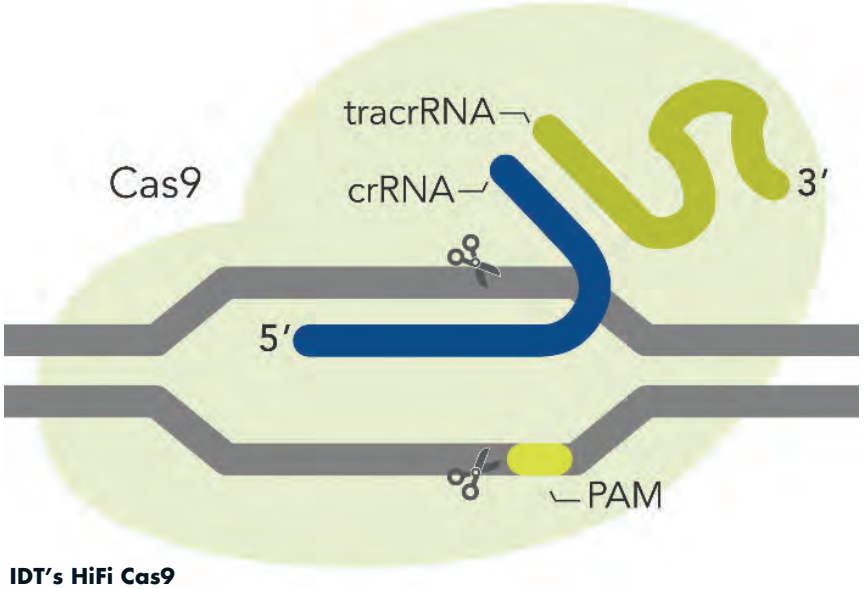
Our work at IDT has focused on developing and improving the tools available for biomedical scientists to conduct their research in the field of gene editing. A recent breakthrough was the development of a new high-fidelity Cas9 enzyme, known as HiFi Cas9. We achieved this by devising an unbiased bacterial screen to isolate ribonuclease protein (RNP)-delivered Cas9 variants that displayed highly specific cleavage with minimal OTEs, while retaining full on-target nuclease activity in line with that of WT Cas9. The results of this work and clinical applications were published in Nature Medicine in 2018.[5]

As the most active and specific high-fidelity Cas9 variant available when delivered as an RNP complex, it is ideal for use in clinical studies. This led IDT to partner with Aldevron to supply a Good Manufacturing Practice (GMP) grade of the enzyme for clinical use.

Excitingly, Dr. Matthew Porteus and his team from Stanford Medical School have been using this high-fidelity enzyme successfully in their preclinical studies, ahead of a proposed Phase I SCD clinical trial. The trial is investigating the potential for a gene-editing therapy to correct the SCD-causing point mutation in the human beta-globin gene (HBB). The HiFi Cas9 enzyme was used to show that the sickle HBB allele could be efficiently corrected, while simultaneously reducing problematic off-target editing from ~30% to less than 1%, in the preclinical studies (compared with using WT Cas9). The Aldevron GMP HiFi Cas9 enzyme provides similar impressive results and will ultimately be used in the clinical trial for SCD, as well as other monogenic hematologic disorders.

"We performed an unbiased evaluation of several versions of high fidelity Cas9 enzymes in primary human stem cells. We have been very impressed with the characteristics of this new IDT enzyme. Unlike other versions, this version consistently gives us high on-target editing activity, while having low off-target activity. Because of the retained, excellent on-target activity and improved specificity profile, we are excited to use this version in our future experiments focused on developing novel genome editing-based therapies for several diseases with unmet medical needs," said Dr. Porteus.

FIGURE 1



IDT's HiFi Cas9

A CAUSE FOR CONCERN

While CRISPR gene editing is being considered for numerous applications in animals and plants alike, and clinical trials have already begun to recruit participants and administered investigational therapies, one cause for concern remains the potential for OTEs. Such concerns in this field are not new. For viral vector-based gene editing, researchers were worried about the potential for a mutagenic vector to integrate into the genome. For zinc-finger nucleases, there was concern that the method could cause OTEs according to cell-based experiments.[6]

For CRISPR, research continues to suggest that OTEs require further analysis and review. The nucleases used in CRISPR gene editing cut the DNA and create double stranded breaks, and the sgRNA directs the enzyme complex to the correct location in the genome. However, these guides may also cause breaks to occur at unintended sites. While these may not have a noticeable impact and may not even be detected, it remains important to understand the frequency and nature of these effects and more accurately predict occurrence to minimize risk when using this technology for medical purposes.

To that point, there are numerous solutions being investigated by scientists. In early 2018, the US National Institutes of Health (NIH) announced the launch of the Somatic Cell Genome Editing (SCGE) program. The program will run for 6 years and will support researchers bringing gene editing therapies to patients and developing novel assays for assessing OTEs.

WHERE WE ARE TODAY?

In addition to improving enzyme specificity, researchers have been using computational algorithms to predict which regions of the genome might be at risk for OTEs. These algorithms usually identify OTEs but often provide either too many sites to study or are filtered too much and so miss important sites. In response to these uncertainties, IDT launched a new product called rhAmpSeq™ that can be used in preclinical risk assessments. A number of pharmaceutical and biotech companies as well as academic centers doing translational medicine studies are already using rhAmpSeq to help reduce the work-load of monitoring OTEs while optimizing the performance of their CRISPR therapeutic protocols. The technology enables a researcher to rapidly characterize hundreds to thousands of individual off-target and on-target sites from a single DNA sample using modern multiplex next-generation sequencing (NGS) methods.

Even with tools like rhAmpSeq, we are still in the early years of CRISPR technology, and there is still much to learn. As the technology is optimized to minimize OTEs, there will still be a need to acknowledge that a certain degree of risk is inherent in many promising potential and proven successful treatments and that CRISPR is no different.

HOW MUCH RISK ARE WE WILLING TO ACCEPT?

With the first human trials using CRISPR to treat several diseases already underway, a key question remains: what does greater awareness of OTEs mean for clinical applications of CRISPR and how might it improve safety profiles for investigational and approved therapies?

It is not uncommon for new medical therapies to be approved for use despite their potential to cause harm. This is because of the benefit/risk ratio, whereby benefits of the therapy in addressing the burdens and harms of disease – including the likelihood of death, are weighed against the potential risks and actual burdens and harms of the treatment. Should the benefits exceed the risk, the therapy is deemed appropriate and acceptable. An example of such an approved treatment is

the chemotherapy drug, cisplatin. Although a known mutagen, cisplatin is used to treat several ailments, including life-threatening cancers.

A challenge for CRISPR will be that adverse effects may not become known for many years, and risks may vary between individuals because all of us have our own unique genome (different DNA = different risk profile). Despite these and other challenges, the potential of CRISPR gene editing is too great to ignore. It offers people suffering from debilitating and uncurable diseases the hope that one day there may be a one-time treatment that proves to be a lifetime cure. It also offers these same individuals the hope that their disease may one day have a treatment plan unique to them and their genetic code, realizing the dream of truly personalized medicine. In addition to applications in human medicine, CRISPR gene editing has implications and potential uses for agriculture and food security, which could be particularly important considering the challenges expected with projected population growth and climate change. However, with such great hope and promise, comes challenges both in the laboratory and beyond.

OVERCOMING THE CHALLENGES OUTSIDE OF THE LAB

CRISPR is currently being evaluated by researchers, clinicians, and ethicists to assess the potential repercussions of the technology. It will be important that these discussions involve laypersons so that public opinion of the technology is based on informed facts and not uninformed rumors. A paper issued in Frontiers in Public Health in 2017 published results from an online survey of 2,493 respondents and found that while the mention of explicit risks dampened enthusiasm for the use of CRISPR technology, respondents remained largely supportive of the research.[7] Interestingly, the researchers noted that the use of common metaphors (editing, engineering, hacking, modification, and surgery) used to describe genetic modification did not influence attitudes. However, these findings only represent a snapshot of attitudes and it is important to remember that the discussion and information available will evolve over time. A key question remains: will the discussion and information available keep up with the pace of scientific discovery?

Publicly available scientific information can be difficult to navigate, sometimes inaccurate and oftentimes complicated to understand for the non-expert reader. We have seen before, in the case of genetically modified organisms (GMOs) for example, that an uninformed or misinformed public can have negative implications for scientific progress. It is therefore paramount that the societal debate keeps up with the rapid pace of research and that the public understands both the benefits and risks of the technology and is confident that it will be used to reduce the global burden of disease and suffering associated with disorders like SCD, cystic fibrosis, and Huntington's disease.

Like other potentially powerful technologies and scientific breakthroughs, gene editing raises legitimate questions and fears about possible risks and misuse. Given the relative technical ease and low cost of CRISPR gene editing, this technology is likely to find widespread use in both medicine and agriculture. To alleviate fears and benefit from the opportunities afforded, open, transparent and continuous debate is required, as well as education of stakeholders – from scientists and governments to civil society and local communities. Without these discussions, and additional efforts to ensure consumer education and engagement, we run the risk of failing to unlock CRISPR's true potential. As leaders in the provision of CRISPR technologies, we strongly promote and support efforts to raise awareness, education, and discussion regarding CRISPR technology among both multidisciplinary experts and the general public. ◆

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BIOGRAPHY

Mark Behlke, MD, PhD, is Chief Scientific Officer at Integrated DNA Technologies (IDT) and is an internationally-recognized expert in the field of nucleic acid technologies and an inventor cited on more than 50 US Patents. In nearly 25 years at IDT, Mark has overseen research programs and new product development in the areas of DNA thermodynamics, gene synthesis, probe chemistry, qPCR, NGS, antisense, RNA interference, and CRISPR genome editing. Mark joined IDT as an R&D consultant in 1995 and was named VP R&D in 1996. He was promoted to CSO in 2013.

DEVICE DEVELOPMENT

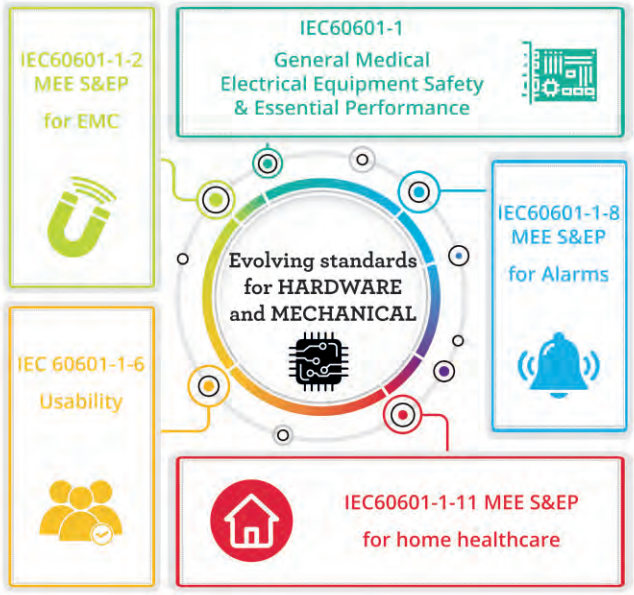
Mapping the Regulatory Strategy to Better Navigate Electronic Drug Delivery Device Development for Patient Safety & Security

By: Ahmed Mallek, Hadrien Gremillet, and Audrey Chandra

ELECTRONICS ALTER STAKEHOLDERS' PARADIGM & TRENDS IN DRUG DELIVERY DEVICES

Along with technology advancement in the medical industry, the behaviors and needs of different stakeholders also evolve. As a matter of fact, there is a clear interest in electronic drug delivery devices for a wide range of reasons. Patients need smart, interactive, and automated devices to help them administer their treatment on a regular basis in the home setting, without the need of other peoples' assistance. Indeed, it is without a doubt there is a strong digital adoption by patients as they want to become more independent. Moreover, through drug delivery digitalization, patients may have the opportunity to significantly improve their treatment adherence, which has become one of the major issues in self-administration today. For instance, patients' adherence in glaucoma treatment can be as low as 37%.[1] Nevertheless, through digital reminders, some studies show that patient adherence can be multiplied by three.[2] In addition, as there is an increase in the number of new molecules, there is an obvious need of advanced delivery systems to help patients administer their drugs in the most convenient way possible. As a matter of fact, newly developed molecules, such as biologics and formulations with high viscosity, can require specific administration conditions. Consequently, the electronics are increasingly used to obtain this specific condition. Taking wearables as an example, these devices are developed to help patients inject viscous formulations that require time-consuming drug administration. This situation thus explains why industrial players continue innovating in digitalized health solutions.

FIGURE 1



Different Evolving Standards & FDA Guidance for Hardware

Different healthcare stakeholders will be able to benefit from the emerging trend of electronic drug delivery devices. Patients may improve their quality of life as they can better monitor their chronic diseases. In addition, both healthcare providers and caregivers may also have the possibility to check their patients' adherence and compliance to optimize treatment efficacy. Researchers have a high interest in monitoring patient behavior to obtain more reliable data, particularly in the case of clinical trials. At last, the data that will be generated by the electronic de-

Real World Challenges
in *Drug Delivery and Formulation*

The Objective

Need to understand the changing dynamics of clinical-stage pipelines by indication, molecule type and most advanced phase to present to senior management

The Challenge

How do I obtain this information in a format that will allow me to quickly evaluate overall trends in pharmaceutical development?

The PharmaCircle Solution

1. PharmaCircle's intuitive interface allows for rapid data extraction and analysis.
2. Track pipeline landscape changes of key parameters, including by indication, molecule type, route, dosage form and most advanced phase, over the past five years.
3. Data snapshots from previous years can be compared with the current data to see how the pipeline landscape has changed over time.

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vices will help pharmaceutical companies and payers to also access better quality of statistical analysis on patient behavior. Moreover, this may help them to better adapt their solutions to the real needs of the patients.

UNDERSTANDING THE COMPLEXITY OF THE REGULATORY EXIGENCE

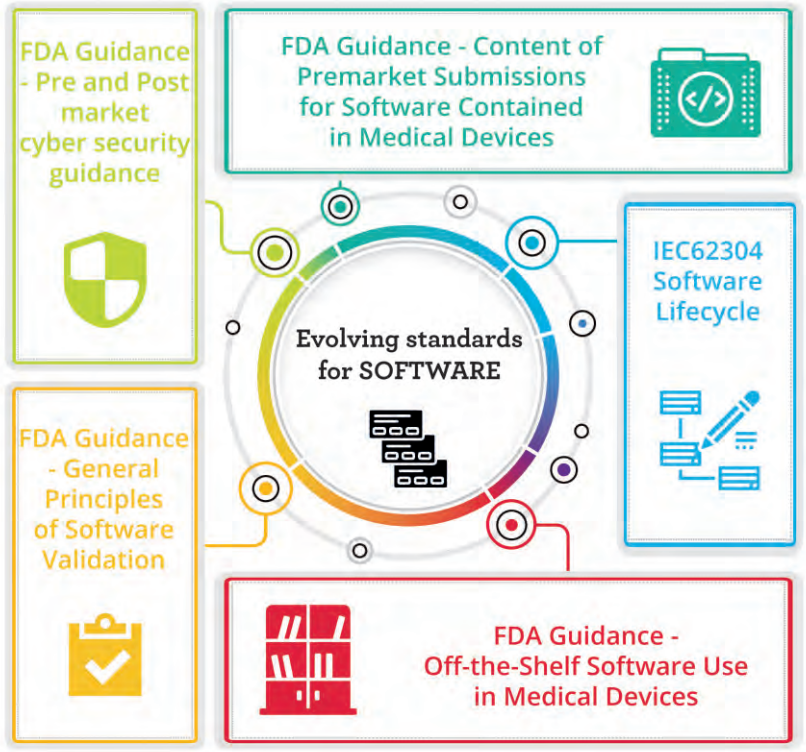
In spite of the fact that electronic devices offer real added value and opportunities, there is a slower adoption of this innovation trend than expected due to various factors: one of them being the exigent and thorough regulatory requirements that have to be completely well interpreted. In fact, the regulatory requirement for electronic device development can be split into three categories, namely concerning mechanical, hardware and software, human factors, and cybersecurity.

CONSIDERING HARDWARE & SOFTWARE FACTORS IN ORDER TO COMPLY

Regarding these aspects, IEC 60601-1 series of standards - including Collateral Standards, Particular Standards, and National Deviations - have to be taken into account as these may impact the development of the Medical Electrical Equipment (MEE). Indeed, the most important standard when developing an MEE is the General IEC 60601-1 for electrical safety and essential performance published by the International Electrotechnical Commissions.

On the other hand, if the embedded software provides support for basic safety or essential performance or its failure may lead to an unacceptable risk, section 14 of the IEC 60601-1 about Programmable Electronic Medical Systems and the IEC 62304 will be needed to design the software in the MEE. The IEC 62304 is all about software process lifecycle, and it elaborates the requirement as well as necessary documentations for software development based on three safety classes. The second edition of this standard will normally be published in 2020. In addition, the FDA has provided some different guidance that is highly recommended. For instance, we can list guidance on general principles of Software Validation (Issued in January 2002); guidance for the Content of Premarket Submissions for Software Contained in Medical Devices (Issued in May 2005), and guidance on Off-the-Shelf Software Use in Medical Devices (Issued in September 2019).

FIGURE 2

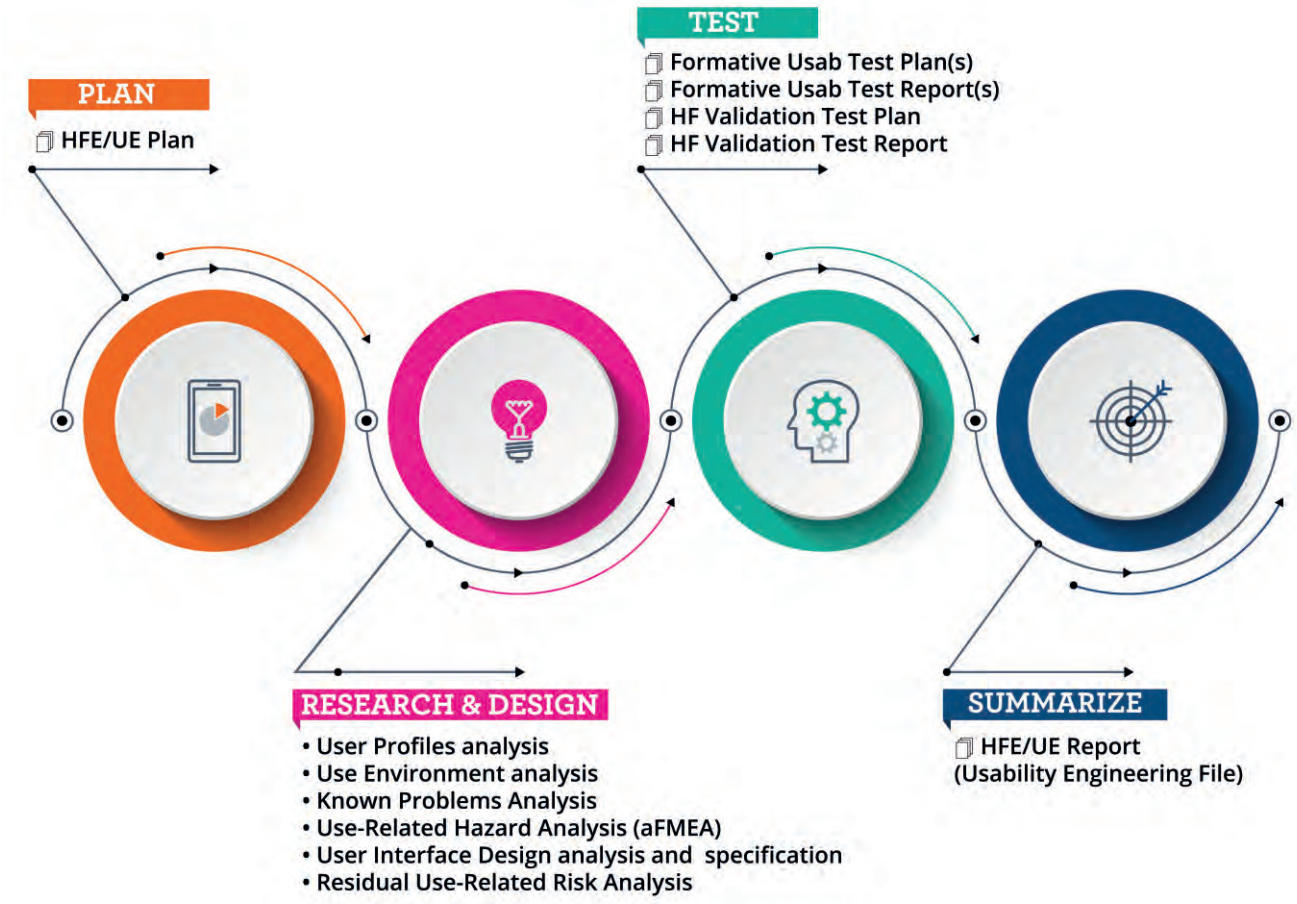


Different Evolving Standards & FDA Guidance for Software

TAKING INTO ACCOUNT REGULATORY DEVIATIONS TO STAY ON-TRACK

As mentioned earlier, depending on the targeted markets, national deviations of IEC 60601-1 Standards may exist that might lead to the variation of the recognized standard version. Therefore, it is more than crucial to consider this country deviation in electronic device development and conduct testing as early as possible to help reach the targeted markets. Nonetheless, most major countries, such as the US, Canada, and European Union, recognize the general IEC standards. They may also have some modifications, by removing or adding requirements, which are specifically related to their regulation or national standards. For example, the US recognizes the National Deviation of IEC 60601-1, which is known as the ANSI AAMI

FIGURE 3



Workflow for Human Factors/Usability Engineering Activities

ES60601-1 (More information regarding the CDRH's consensus standards can be found on the FDA website). For instance, while speaking about the differences, the US version requires different leakage current limit, flammability rating requirement for enclosure material, and different certification requirement for critical component, etc. In order to avoid bad surprises in the product development and wasting time during different dossier submissions, CB Scheme test reports are recommended. Developed by the IEC System of Conformity Assessment Schemes for Electrotechnical Equipment and Components, it is the world's first international system for mutual acceptance of test reports and certificates dealing with safety of electrical and electronic components equipment and products. (More information regarding the CB Scheme can be found on the IECEE.org website). This will make sure the device conforms to the distinct targeted markets and regulation exigence.

OPTIMIZING DEVICE USABILITY THROUGH HUMAN FACTORS VALIDATION TESTS

To ensure the usability of an electronic device, human factor and usability studies have to be conducted according to different standards and applicable guidance. This study highlights the interaction between the device and the users. In light of this, there are a few evolving standards, such as the IEC 62366-1 on the application of usability engineering to medical devices and FDA guidance on Applying Human Factors and Usability Engineering to Medical Devices. Moreover, these standards must be taken into account for such studies. Nonetheless, the innovators often make typical mistakes. In fact, they might poorly conduct Human Factors Validation Tests by having test scenarios that are not linked to the critical tasks, or they have no subjective data related to the performance. In addition, the human factors validation tests (Summative) requires at least 15 participants per user group, thus having insufficient numbers of test participants may question the reliability and the viability of the generated data. Most importantly, keep in mind that Human Factors Engineering (HFE) reports should be found easily in the dossier submission as the authority

might challenge and create hurdles when the materials are not correctly structured in the right format.

Normally, the workflow for HFE and usability engineering (UE) activities consist of planning, research and design, tests, and ultimately reporting. The objective of these activities is to provide detailed results in an HFE/UE report, which is supposed to be compliant to the FDA requirement while also proving electro-medical device conformity to the technical standards. As a matter of fact, the most critical step is to list and carry out the research and design activities. Moreover, there are six main axes that have to be considered to meet the regulatory prerequisites:

1. To ensure full understanding of the device users, the user profile analysis must be done based on the intended use and user characteristics provided in section 5.1 of the FDA guidance. It can list physical size, strength, literacy, and language skills, etc.

2. Furthermore, the use environment analysis will guarantee the understanding of the device usage environment as the healthcare setting differs from the homecare environment. The device use environment characteristics are provided in section 5.2 of the FDA guidance.

3. In addition, lighting level, noise level, etc can be listed. Also, by investigating logged incidents and putting user at risk on comparable systems through known problem analysis, there is room to develop better risk mitigation as well as to better understand how to avoid problems in a practical example and concrete situation.

4. To analyze the consequences of use error, the use-related hazard analysis can be done by performing a Use-Related Hazard Analysis based on the Fault Tree Analysis.

5. Also, in regard to establishing the device specification, the user interface (UI) analysis and specification must be held to assess the existing UI and standard.

6. Last but not least, the residual use-related risk should include the analysis of use errors, close calls, assistance, and any difficulties identified during formative and summative studies. In the final analysis, these six axies become the essential elements to bringing patient-focused design solutions.

MITIGATING THE RISKS OF CYBERSECURITY TO ULTIMATELY ENSURE ELECTRONIC DEVICE CONFORMITY

To ensure data security in developing electro-medical devices, there are some evolving standards and guidances that have to be integrated in the design process. Taking a step back to software development, the software lifecycle is regulated by IEC 62304 as mentioned earlier. Also, IEC82304-1 plays a role in the validation of health software used on smartphones or computers (Stand-Alone Software). In light of this, the FDA guidance previously mentioned acts as a crucial and fundamental element for the design steps. And through risk management, we will have a clear understanding of the security risks and also identify some hazardous situations that might occur on the safety of the user and patient. Eventually, we may picture the mitigations of the identified risks for data security and ultimately perceive the impacts on the patient/user safety. Most important, a highly secured device will be guaranteed through obtaining certifications of the software based on the recognized UL standards, such as UL2900-1 for general requirement for soft cybersecurity network-connectable products and UL2900-2-1 for particular requirement for network connectable components of healthcare and wellness system.

Speaking of cybersecurity guidelines, the FDA, Health Canada, TGA (Australia), ANSM (France), MDCG (Medical Device Coordination Group in Europe), and IMDRF (International Medical Device Regulators Forum) provide guidance on pre-market and post-market to help manufacturers address cybersecurity issues. In the pre-market phase, authorities recognized more consensus standards for conformity and provide the application of the standard TIR57 on Principles for medical device security Risk management, which therefore reinforce the relation between safety and security risk management. They also share the information on how to implement National Institute of Standards and Technologies (NIST) cybersecurity network (identify, protect, detect, respond, and recover). In addition, regulators also recommend device labeling and gives further information on additional required documentation on cybersecurity. On the other hand, in the post-market phase, authorities focus more on the life cycle aspects in which the core of this topic is to implement a proactive and comprehensive security risk management program. As an example, the FDA emphasizes NIST framework application, communication of vulnerabilities and limits,

post market surveillance process, and deployment of software updates to avoid cybersecurity issues.

Based on these guidances and standards, a general cybersecurity plan has to be elaborated according to the device being developed. First, there is a need to clarify the clinical context, such as the intended use of the device. Next, we have to define the cybersecurity activities during the device life cycle, be it in the design, manufacturing, distribution, usage, or even withdrawal. After knowing all the activities, there is a need to define the cybersecurity study and risk security management around availability, integrity, and confidentiality. In addition to define the verification strategy, there is a need to plan the tests for the identified mitigations whose results can be explained in the cybersecurity report. This documentation will become a key element for certification. At the end of the day, through post-market review and surveillance strategy, we will be able to identify the problems encountered to develop an improvement plan. Bear in mind the FDA welcomes possible modifications and changes in the post-market review and planning with the objective of improving the cybersecurity for the patients.

MEETING REGULATORY REQUIREMENT TO EVENTUALLY LEVERAGE PATIENT SAFETY & SECURITY

In accordance with the growing interest toward the electronics in drug delivery devices that offer real added values in comparison to mechanical devices, it is absolutely crucial to understand the regulatory requirement thoroughly from the beginning of product development. Patient safety has to be the priority while patient security must be the key driver of the electro-medical devices' development. That being said, innovators must therefore anticipate the problems that may occur in the future by bearing in mind the entire regulatory requirement starting from mechanical, hardware and software, human factors, and ultimately cybersecurity. To cater to the regulatory exigence, it is important to de-risk through well-designed and meticulous steps of activities that may eventually prevent hurdles during dossier submission to authorities. In view of this, Nemera understands the significance of regulatory requirement and has a clear respect to the related standards and guidances to ensure smooth product development and submission process.◆

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BIOGRAPHIES

Ahmed Mallek is a Regulatory and Compliance Project Manager at Nemera, responsible for the quality department to guarantee conformity and compliance of Nemera's electronic projects. Prior to Nemera, he worked as a Regulatory Specialist in the medical device industry and Biomedical Technician in a hospital. After he graduated from Institut supérieur d'ingénieurs de Franche-Comté, he worked as a Quality and Regulatory Engineer for electro-medical device companies, including X-Ray tables, Infusion Pump Systems, and Cryogenic devices.

Hadrien Gremillet is a Senior Marketing Analyst at Nemera, responsible for the company's electronic strategic project. Prior to Nemera, he spent 3 years as an entrepreneur in the mobile internet sector and 3 years as a consultant at McKinsey.
He graduated from Ecole des Mines de Saint Etienne and ESSEC business school.

Audrey Chandra is a Global Category Manager at Nemera. She believes the ease of use of the device plays an important role toward patient quality of life. She is in charge of identifying the pain points and the unmet needs of patients, and also accompanying product development in parallel. She joined Nemera in 2019 and graduated from Faculty of Medicine in Indonesia. She pursued her Master studies in Strategy and Business Development in Toulouse School of Management, France.

PEPTIDE THERAPEUTICS

Oral Peptide Therapeutics – Opportunities Abound as Barriers Fall

By: John S. Vrettos, PhD

INTRODUCTION

Proteins and peptides are the building blocks of life and are a very promising basis for targeting a range of diseases. Throughout the past 30 years, and especially the past 10 years, there has been a rapid growth in the development of therapeutic proteins, with a significant increase in the number of protein-based drugs on the market.

The cornerstone of protein therapeutics was laid with the regulatory approval of insulin by the US Food and Drug Administration in 1982. As the first commercially available recombinant protein, insulin soon became the gold-standard therapy for patients suffering from diabetes. Almost four decades have passed since insulin's market introduction, and its success has inspired the development of myriad new therapeutic proteins for a wide range of ailments.

The advent of peptide-based therapeutics can be traced to the success of the initial protein biologics, with proteins and peptides now being utilized across numerous indications, including cancer, autoimmune, neurological, and endocrine disorders. Currently, there are more than 200 approved therapeutic proteins and more than 100 peptides on the market, accounting for approximately 10% of the pharmaceutical market at a value of $40 billion per year. With hundreds of protein and peptide drugs in clinical trials and many more in preclinical development, this market is expected to continue to grow substantially throughout the next 5 to 10 years. A significant percentage of this growth is expected to come from peptide-based drugs.

Peptides occupy a therapeutic niche between small molecules and large biologics, and are generally classified as being a chain of amino acids containing 40 amino acids or less. Currently, the disease areas driving the therapeutic use of peptide drugs are oncology, driven by a rising mortality and need for chemotherapy replacement, and metabolic diseases. The treatment of metabolic diseases via peptide therapeutics has largely centered around the epidemic growth in type 2 diabetes. In addition to metabolic disease and oncology, the movement of the pharmaceutical industry into rare diseases and orphan drugs has also been extended to peptides, and peptides are being further targeted at infectious diseases and inflammation.

Peptides serve highly specific functions in the body that are extremely difficult to mimic by small chemical compounds. Compared with small-molecule active pharmaceutical ingredients, peptides are able to exhibit increased potency and selectivity due to specific interactions with their targets. As a result, peptides have the potential for decreased off-target side effects and decreased systemic toxicity. Moreover, because the body naturally produces peptides, peptide-based therapeutics are often well tolerated and are less likely to elicit immune responses. Furthermore, peptide therapeutics are typically associated with lower production complexity compared with protein-based biopharmaceuticals and small molecules.

That being said, recent evolution in the advancement of small molecule drug targeting has enabled the introduction of several new technologies that offer considerable promise. Among these are macrocyclic therapeutics, which represent a nexus between classic small molecules and peptides. The growth of these and similar technologies has resulted in a "blurring of the line" between peptide and small-molecule APIs, as more "peptide" drugs incorporate D-amino acids, non-natural amino acids, and are

being made as cyclic compounds.

Though peptide and hybrid-peptide therapeutics offer numerous advantages, and the growth of such drugs is strong, there remains a significant gulf between "market actual" and "market potential." This is largely attributable to challenges with the route and method of delivery of peptide drugs.

Peptides are large, polar, water-soluble biopolymers containing both hydrophilic and hydrophobic appendages in their structure. These properties make it difficult for peptides to be absorbed by the intestines. Peptides also degrade in the stomach and small intestines, given the digestive roles of these organs, so they may not even be available for absorption by the intestines. Simply said, our bodies recognize peptides as food when ingested.

Macrocyclic therapeutics and peptide-like molecules, due to their flexible composition, are resistant to breakdown by proteases in the digestive system. However, as with peptides, macrocyclic and peptide-like therapeutics suffer from poor permeability. As such, oral delivery of these therapeutics is generally not possible without an enabling formulation technology.

Given these barriers, most peptide and peptide-like drugs are administered parenterally, with approximately 75% given via injectable routes, such as subcutaneous, intravenous, and intramuscular administration. While the market for injectables is strong and growing, alternative administration forms are gaining increasing traction.

This trend is guided by three dynamics – patient compliance, prescriber preference, and market expansion. As one can appreciate, frequent injections, inconsistent blood drug concentrations, and low patient acceptability make parenteral administration of peptide-based drugs less desirable. As a result, pharmaceutical developers continue to explore alternate routes of delivery for peptide therapeutics that have the potential to maintain the drug's potency, while enhancing the ease of administration, patient compliance, and market penetration.

Against this backdrop, the oral delivery of peptides has caught the imagination of drug developers far and wide. The majority of drugs on the market today are administered as a pill or capsule, and thus, represent the form most patients are accustomed to taking. Orally administered peptides offer vast potential but also present considerable development challenges.

CHALLENGES & OPPORTUNITIES IN ORAL PEPTIDE THERAPEUTIC DEVELOPMENT

Numerous technologies are currently in development that are designed to enable the oral delivery of peptides. Though each has its unique set of properties and capabilities, all must overcome key obstacles to successfully deliver peptides via the oral route. First, the oral formulation has to remain intact in the highly acidic environment of the stomach. Once through the stomach, the dosage form design must then promote dissolution in the higher pH environment of the small intestine, while simultaneously protecting the peptide payload from degradation by protease enzymes. Finally, mechanisms must be present that facilitate the absorption of the peptide across the relatively impermeable intestinal epithelium. This factor is also critical for peptide-derived therapeutics, which may be protease resistant but are poorly permeable.

However, before any technology is applied to confront these challenges, developers must first target therapeutic peptides that are appropriate for oral delivery. Practical considerations, such as whether the orally delivered drug will enhance patient compliance, increase treatment options, and boost marketability, should have priority since, without clear medical and business advantages, there is little motivation to transition from an injectable.

Yet, even if these boxes are checked, oral delivery may not be an option unless one can achieve therapeutically relevant bioavailability. Numerous factors impact bioavailability, some of which technology can mitigate.

Illustrative of the challenges and potential of orally delivered, peptide-derived therapeutics are the ongoing development of an oral leuprolide tablet for the treatment of various endocrine disorders and the clinical development of an oral formulation of difelikefalin, a peripherally acting kappa opioid receptor agonist (KORA). Both oral formulations were engineered utilizing a technology platform, Peptelligence®, developed by Enteris BioPharma, a biotechnology company that specializes in the oral delivery of peptide and small molecule therapeutics.

Leuprolide, marketed under the brand name LUPRON DEPOT® (leuprolide acetate for depot suspension), has demonstrated in the clinic and practice to be an efficacious treatment for certain endocrine diseases. However, the drug's parenteral route of administration limits its utilization due to the irreversibility of the depot injection, which stays in the body for 30 to 90 days, and the pain and inconvenience of the injections. A daily oral le-

uprolide tablet could offer a more patient-friendly alternative to monthly depot injections, potentially encouraging physicians and patients to utilize the medication earlier and more often.

Difelikefalin (KORSUVA™), is under development by Cara Therapeutics and is the subject of several clinical studies in a number of indications. Initially, Cara Therapeutics advanced difelikefalin as an intravenous agent for the treatment of postoperative pain. The company is also developing IV difelikefalin for chronic kidney disease-associated pruritus (CKD-aP), which recently completed a Phase 3 clinical trial.

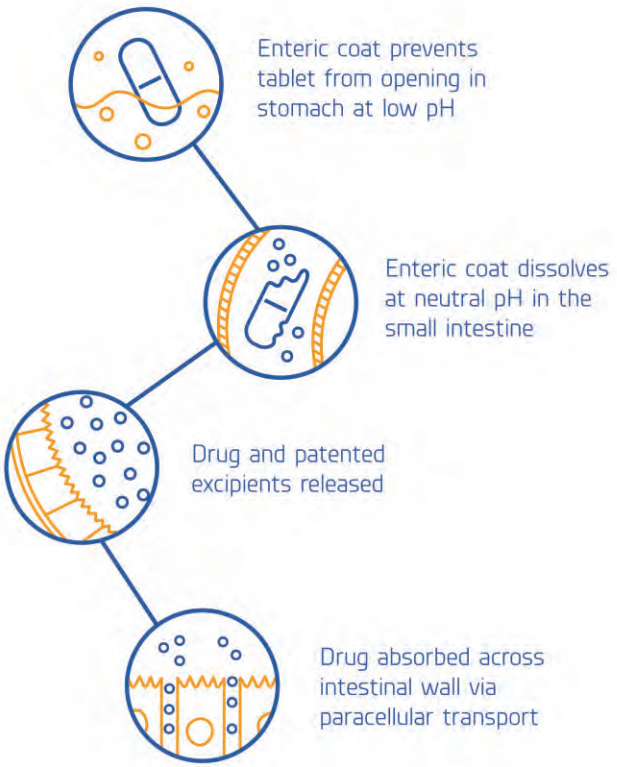
In order to advance a non-parenteral formulation of difelikefalin, Cara has partnered with Enteris to develop an oral formulation of the drug (Oral KORSUVA™). Cara initially developed oral difelikefalin for the treatment of CKD-aP. In December 2019, Cara reported that a Phase 2 clinical trial of oral difelikefalin for the treatment of CKD-aP produced positive top-line results. In addition to CKD-aP, Cara has initiated additional oral difelikefalin programs targeting chronic liver disease-associated pruritus (CLD-aP) and atopic dermatitis-associated pruritus (AD-aP). Each oral difelikefalin program is currently the subject of individual Phase 2 clinical trials, as reported by Cara.

In developing oral peptides, Enteris BioPharma utilizes its Peptelligence platform to provide protection against the harshness of the digestive system and then promote absorption of each API into the bloodstream. First, to overcome the stomach's highly acidic environment, the oral tablets were encapsulated in an enteric coating (Figure 1). Simple in concept, an enteric coating is a polymer barrier applied to an oral medication that prevents its dissolution in the gastric environment.

Enteric coatings work by presenting a surface that is stable at the highly acidic pH found in the stomach, yet dissolves at the higher pH of the small intestine and at locations within the intestinal tract to enable optimal drug absorption. A variety of materials can be utilized as an enteric coating, provided the material shields the peptide drug in the stomach and enables its release in the intestine where absorption into the bloodstream can occur.

Protecting against the acidic gastric environment and enabling dissolution in the small intestine is but the first hurdle that must be addressed. The next, limiting proteolytic degradation in the jejunum, is a considerably more difficult (and critical) proposition as peptides, including leuprolide, are highly vulnerable in the soluble form to peptidases in the lumen prior to reaching the systemic circulation. As noted previously, non-natural peptides are generally tolerant of breakdown by proteases in the digestive system; however, the ability to significantly limit this effect is important to ensuring optimal bioavailability.

FIGURE 1

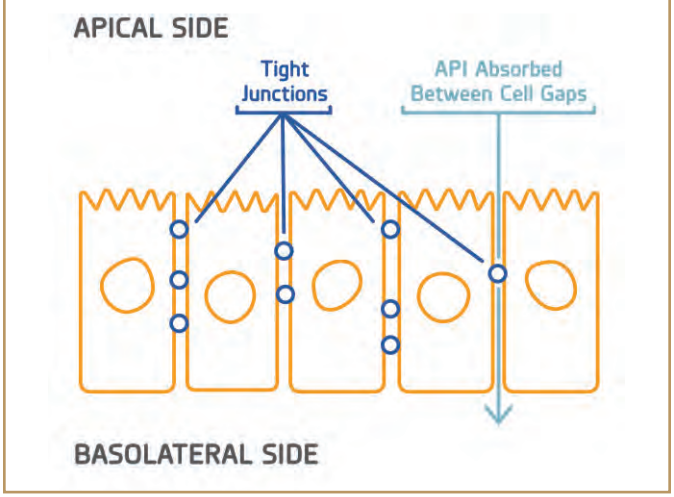


Though it is difficult to completely inhibit the actions of luminal proteases, scientists at Enteris BioPharma utilized protease inhibitors to create a protective microenvironment for its oral leuprolide tablet. Without such protective measures, the protease enzymes would immediately act upon the leuprolide, breaking it down for ingestion into the bloodstream; no different than protein consumed as food.

Despite the clear need for protease inhibitors in the oral delivery of a peptide, caution must be heeded when selecting a protease inhibitor, as many are not considered safe for use as excipients and inhibition of such a ubiquitous biological function can be risky. Developers, therefore, are encouraged to utilize technologies that limit the effects of such inhibitors to the GI lumen locally, and transiently, to avoid systemic toxicity.

Though shielding against the digestive system is paramount to administering a peptide orally, success in developing an efficacious oral peptide (one that elicits the desired therapeutic response comparable to or exceeding the standard of care) ultimately hinges on whether the API is absorbed through the intestine and enters the bloodstream as an intact chemical species. This may be the most challenging barrier to oral peptide delivery.

FIGURE 2



As peptides reach the intestinal epithelium, they first encounter an exogenous mucus gel layer containing proteases and antibodies, which together reduce the rate of diffusion to the epithelial surface. Attempts to overcome mucoadhesion have focused on incorporation of mucolytics or use of hydrophilic PEGylated nanoparticles, which avoid entrapment in mucus glycoprotein meshes. An alternative approach is to exploit mucoadhesion to increase the residence time of the dosage form in the small intestine.

However, greater success has been achieved via the use of permeability enhancers. Often, these are surfactants or emulsifying agents, such as acyl carnitines, sucrose esters, or anionic surfactants. Such permeability enhancers function by enabling the transport of peptide molecules through the epithelium via passive movement across the epithelial tight junctions (Figure 2).

In developing oral peptides, Enteris' Peptelligence platform utilizes a combination of enhancers. The first, citric acid, is more commonly recognized as a protease inhibitor because of its ability to modulate pH levels. However, citric acid also functions as a potent permeation enhancer by making the mucus layer less viscous, thus removing a diffusion layer to permeation. Additionally, citric acid makes the tight junctions more porous through multiple pathways, enhancing paracellular transport.

In combination with citric acid, Enteris employs surfactants, such as lauroyl-L-carnitine, as enhancers, which work by increasing the number of loose tight junctions. Citric acid makes these loose tight junctions even more porous. Thus, the two excipients work together.

SUMMARY

Even after overcoming these obstacles, the successful development of an oral peptide must accept that the bioavailability of an orally delivered peptide will be less than that of a comparable dose of a parenterally delivered peptide. Even the best oral peptide formats are known to have relatively low bioavailabilities of ≤10%. As such, higher doses are required to obtain the same therapeutic effect in an oral formulation.

Given such differentials, developers must carefully consider the practicality of transitioning a peptide to an oral form based on the cost per goods. Simply put, the cost of the additional API (and production) must be less than the expected market expansion for an oral formulation.

While this may seem discouraging on the surface, there has been significant investment in the development of oral peptide dosage forms by specialized drug delivery companies. This is based on the clear advantages that such medications offer patients, prescribers, and pharmaceutical developers, alike.

Ultimately, not all peptide therapeutics are appropriate for oral administration due to various constraints, from physiochemical to economic. However, for those that meet the necessary criteria, advances in formulation technologies coupled with favorable market dynamics will continue to drive interest across the entire prescription drug spectrum for safe and effective orally administered peptide therapeutics. ◆

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BIOGRAPHY

Dr. John S. Vrettos is the Senior Principal Scientist and Head of Formulation Development at Enteris BioPharma, a privately held, New Jersey-based biotechnology company offering innovative formulation solutions built around its proprietary drug delivery technologies. Dr. Vrettos earned his BA in Chemistry from Haverford College, his PhD in Biophysical Chemistry from Yale University, and was a National Academy of Sciences/National Research Council Postdoctoral Fellow at NIST. He has more than 17 years of experience in protein, peptide, and small molecule drug formulation and delivery.

Drug Development
EXECUTIVE

Michael Snape, PhD
Chief Scientific Officer
AMO Pharma

AMO Pharma: Identifying & Developing Cancer Pathway Therapeutic Candidates for Use in New Neurological Indications

For much of the past century, clinical research targeting the neuropathology and neurochemistry of childhood-onset disorders associated with developmental delays has been very limited. The few clinical research programs that have advanced in disorders, such as Rett syndrome, congenital myotonic dystrophy, and Phelan-McDermid syndrome, have focused mainly on symptom management as a supplement to other forms of patient support, including special education and speech and physical therapy.

The research team at AMO Pharma includes globally recognized leaders of research in central nervous system (CNS) disorders associated with developmental delays. In the early 2000s, AMO Pharma began a collaboration with researchers at Case Western University to investigate how the RAS-ERK signaling pathway (a target for many cancer drugs) could also potentially be applied to treatment of fragile X syndrome (the most common inherited cause of intellectual disability and the leading genetic cause of autism) and Phelan-McDermid syndrome, an ultra-rare disorder characterized by cognitive deficits, autism and severe, often intractable epilepsy. Their research showed aberrant activation of the RAS-ERK pathway in brain tissue samples of people with autism and fragile X syndrome. This increase in RAS-ERK activity was also seen in neurons and in glial cells that support neuronal function. Not long after AMO Pharma was founded in 2015, the company identified and acquired a promising investigational anti-cancer therapy, now known as AMO-01, which was engineered to inhibit activation of the RAS protein and ERK pathway. Early stage clinical data showed that this drug could inhibit RAS-ERK activity in cancer patients at doses that were shown to be safe and generally well tolerated. More importantly, data showed that the drug could penetrate the brain. Based on this mechanism of action and their new insights about the role of the RAS-ERK pathway, the team recognized the potential applications of this investigational therapeutic in the

treatment of both fragile X and Phelan-McDermid syndromes.

Drug Development & Delivery recently interviewed Michael Snape, PhD, AMO Pharma's Chief Scientific Officer, about the company's research focus and efforts to understand and target the mechanism of action of CNS disorders associated with developmental delay with the potential to target neurogenetic disorders at their root cause.

Q: Can you describe AMO Pharma's drug development strategy and how you are able to identify therapies that can be oriented toward indications in the developmental disorders field?

A: First, we work to understand the mechanism of action of the developmental disorders we target as well as the areas of unmet need and the experience of living with these conditions. We then work with research foundations and academics who are experts in the disorders to understand whether molecular targets for new therapeutic approaches have been validated by these groups. During this process, we will seek to identify druggable targets that relate to the underlying biology of the disorders. We do this because we are seeking novel therapeutic approaches that have the potential to provide benefit across the core clinical characteristics of the disorder in question. We are less interested in purely symptomatic approaches.

With an identified target, we then use our industry contacts to acquire or license a potential novel medicine. We usually seek an investigational medicine that has been advanced through a certain stage of clinical development for another indication. We do this to de-risk our programs by virtue of being able to work with novel therapeutics with an understood human safety profile. We also seek to ensure that these medicines will be able to cross into the CNS given that brain function is at the heart of the characteristic clinical presentation of many developmental disorders we are targeting. Before progressing into clinical development, we conduct preclinical assessments to confirm whether the investigational medicines we are interested in can reverse the underlying biology of our target indications.

These insights play a central role in planning clinical research protocols that will deliver clear assessments of safety and efficacy. We then apply a range of innovative clinical trial assessment tools and methodologies to identify therapies that seem well-suited to address our target indications. In many cases, these therapies have been previously studied in preclinical or clinical-stage research, and thus have established safety profiles and data supporting assessments of their mechanisms of action. Our team's extensive global experience positions us to identify therapies that target the specific pathways associated with onset and progression of disease and that present the strongest opportunities for improving clinical outcomes and receiving regulatory approval.

Q: Why did the team choose to focus on developing treatments for neurogenetic disorders?

A: Our passion for drug development in this area is strengthened and inspired by many personal connections to the rare and genetic disease communities held by members of our senior team. As the father of a son with autism, I developed a strong interest in researching genetically determined and mainstream idiopathic forms of autism, which has been the focus of my career for about 25 years. During this time, I have had the privilege of working with pioneer researchers in this field. I have been involved with work to evolve research approaches that may be the key to better treat and manage developmental disorders.

The AMO team has a shared knowledge of several key points that have inspired us to move forward in researching potential treatments for developmental disorders. First, we understand that there are many neglected developmental disorders and that these patient populations suffer from an unrecognized medical need. Following an unbiased review of available data on these disorders, we also recognized that these data challenge many pre-conceived negative notions about the potential for treatment response in patients and showed that our general understanding of the biology of developmental disorders is actually very advanced. Lastly, our team recognized that measurement approaches and tools we had previously used in clinical research of pediatric neurology products that ultimately achieved FDA approval were readily applicable to research in many developmental disorders. This meant our team had the right experience and methodologies to advance clinical development in developmental disorders with a high degree of confidence.

Q: How was a connection made between the RAS-ERK pathway and developmental disorders?

A: I became aware of the potential role of cancer pathways like the RAS-ERK pathway in brain disease while collaborating with the late Professor Mark Smith, a neuropathologist at Case Western University. Mark had previously researched the role of cancer pathways in Alzheimer's disease. We began researching the neuropathology and neurochemistry of genetically

determined forms of autism and the role of the RAS-ERK pathway using brain tissue samples from patients with autism and fragile X syndrome. The results of this research were very clear — the pathway was aberrantly activated in the brain tissue of patients with autism and fragile X syndrome, including in the glial cells that support neuronal function. We now know that abnormal behavior of glial cells is commonly reported in patients with certain developmental disorders.

These findings were an extension of research highlighting the role of the RAS-ERK pathway in the progression of cancer. Mutations of the proteins involved in RAS-ERK signalling cause a loss of control of cell division and tissue growth. Neurons in the brain generally do not divide — their equivalent of cell division is the production of new synapses. As a learning event occurs, new synapses and synaptic connections are formed. Each new synaptic connection can be thought of as representing the coding of a piece of information. Control of synapse production is thus critical to brain function and the clinical presentation of individuals with developmental disorders.

A key finding here is that consensus neurobiology points to RAS-ERK pathway signaling as being a key controller of synapse production and thus the process by which the brain codes information. In a sense, the RAS-ERK pathway controls the production of new synapses in the non-dividing tissues of neurons in parallel to controlling growth of tissues outside the brain. Therefore, dysregulation of the RAS-ERK pathway would disrupt control of tissue formation in the body and synaptic plasticity in the brain. It is therefore not surprising that this pathway could be disrupted in neurodevelopmental disorders like autism and fragile X syndrome in which the brain has a reduced capacity to make new connections and code information.

Q: What are the potential implications of AMO Pharma's studies in other disorders?

A: We hope our work identifies and confirms new approaches in clinical research in the CNS space that can transform the sector and lead to improved quality of research and more targeted therapies designed to reduce disease burden or slow disease progression. While we will continue to focus our efforts on ultra-rare neurological disorders, including congenital myotonic dystrophy and Rett syndrome, we see potential applications of our approach in treating other developmental disorders that collectively affect many more patients around the world. We say this because as we continue to conduct our research, we are learning the biological pathways we are interested in affect synapse production and brain function in more neurogenetic developmental disorders than we initially anticipated.

Q: What is next for AMO Pharma?

A: We are planning now for presentation of the results from our Phase 2 study of AMO-01 in Phelan-McDermid patients, which will present insights on efficacy and safety, including duration of benefit.

We also recently initiated our pivotal Phase 2/3 study for our AMO-02 program in children and adolescents with congenital myotonic dystrophy type 1 (CDM1) after a $35-million capital raise and coordination with the FDA on the trial design, including special parameters during the COVID-19 pandemic. If these trial results are positive, these data should support a submission to bring AMO-02 to market for the treatment of CDM1. We anticipate a pivotal data readout in 2022.

Our AMO-04 clinical program also shows significant promise. We acquired AMO-04 in 2017, and research thus far indicates it could provide clinical benefit to patients with Rett syndrome, which is a debilitating rare disease that can lead to problems with cognitive, sensory, emotional, motor, and automatic function. AMO-04 received orphan drug designation from the FDA in 2018, and we are currently conducting a Phase 1 study. We look forward to updating on this program soon.

Q: What advice can you offer to other companies that may be pursuing a similar business model?

A: One of the biggest takeaways from our journey and business strategy has been the need to be flexible and consider innovative new approaches in clinical research for CNS disorders. With the RAS-ERK pathway for example, we had to invest time and resources in understanding the mechanism of action and then develop an approach in clinical research that could deliver the results we need for regulatory review. Our experience has also shown that when trying to identify promising investigational therapies for potential licensing or acquisition opportunities, companies should do their due diligence to fully understand the disease mechanism of action and impact on patient health and quality of life in addition to assessing the safety and efficacy data for each asset. ◆

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Injection Devices: Will COVID-19 Deliver Growth to the Market?

Self-administration and digital connectivity keep patients out of healthcare settings and enable social distancing.

By: Cindy H. Dubin, Contributor

In May, Project Jumpstart, a public-private initiative, was announced that will pump $138 million into the production of 100 million prefilled syringes by the end of this year and another 500 million in 2021, should a COVID-19 vaccine become available.[1] Yet, industry gurus do not necessarily agree that the pandemic will have a positive impact on the injection delivery market.

According to one report, the global injectable drug delivery devices market is expected to decline from $16 billion in 2019 to $15.4 billion in 2020, in part due to the COVID-19 outbreak.[2] Some experts attribute this downturn to a slow down in clinical trial recruitment, which in turn has slowed down bringing new products and therapies to market.

Others attribute the decline to patients delaying their care for fear of going to healthcare settings for treatment. "Plastic hypodermic syringes and needles are used in great quantities in acute care settings so these would naturally be impacted by any change in overall service demand," says George I'ons, Head of Product Strategy & Insights – Owen Mumford Pharmaceutical Services. "Or if diagnostic procedures such as medical imaging declines, then the syringes specifically designed for use with contract media could be impacted. And, if cancer services and treatment is delayed, as has been reported, this could affect the pharmacy prepared prefilled syringes of cytotoxics and other anti-cancer agents."

However, others expect the market to recover and reach $21.3 billion in 2023[2], partly due to increased demand for injection devices that can be used and monitored in the home environment. For example, treatment of chronic diseases such as diabetes, Rheumatoid Arthritis and Crohn's disease are most commonly self-administered at home, and prefilled safety syringes and autoinjectors are typically used by these patients.

Multilayer syringes and vials ensure drug stability (Mitsubishi Gas Chemical).

The increasing prevalence of chronic diseases is leading to a rise in the overall use of syringes, particularly disposable syringes.[3] "Chronic disease products already on the market are expected to be largely unaffected by COVID-19," says Amy Boyle, Vice President Strategy, Planning and Marketing, Flex Health Solutions Segment. "This includes insulin delivery devices, rheumatoid therapeutics delivery devices, and well established cancer therapies." Consequently, the rise in the incidence of chronic diseases is expected to continue to drive the growth of the market.

Furthermore, technological advancements in self-administration, coupled with a rise of biologics in the pharmaceutical market, are some of the other factors propelling the growth of the market. Wearable injectors, for instance, capable of delivering high-volume biologics, are poised to grow $4 billion through 2024.[4]

"We believe we may be entering a new era where global pandemics become more common, which will only increase global reliance on pharma," says William Fortina, Business Development Director, Duoject Medical Systems. "Hence, we do not see a long-term decline of the need for injectable devices. Quite the opposite. Society will ask for pharma companies, their device suppliers, contract fillers, and regulators to be more agile to face such circumstances. That said, COVID-19 has delayed drug and device pipelines, which is affecting short-term investments. Business leaders who continue to invest in innovation and who continue to push projects forward despite COVID-19 will put their companies in a stronger competitive position post-crisis."

As an example, BD is working closely with the industry to identify and anticipate supply for large COVD-19 immunization campaigns to support vaccine developers in predicting drug-container compatibility before scale-up and in developing regulatory filing dossiers, explains Marie-Liesse Le Corfec, Global Portfolio Marketing Head, BD Pharmaceutical Systems.

In this annual *Drug Development & Delivery* magazine annual report on Injection Devices, we highlight trends in autoinjectors, pen injectors, wearable devices and connectivity, and prefilled syringes.

BD Pharmaceutical Systems: Platform Technologies Support Broad Design Space

BD supplies prefillable syringes as well as safety devices, autoinjectors, pens, and wearable injectors, all suitable for delivering medications such as injectable or nasal vaccines, hospital drugs, and chronic disease drugs. BD aims to develop integrated systems to meet customer expectations for smoothly interfacing components and subsystems to enable large-scale industrialization and effective commercial use.

"With our commercialized platforms such as glass or plastic prefilled syringes (BD Neopak™, BD Sterifill™ Advance), BD UltraSafe™ passive needle guard, BD Vystra™ disposable pen, BD Physioject™, and BD Intevia™ 1mL autoinjectors, or products in development, such as BD Intevia™ 2.25mL, BD Libertas™ wearable injector, and BD Evolve™ onbody injector, our customers can start their development choosing from platform technologies that support a broad design space (e.g. volume, viscosity, usage)," says Marie-Liesse Le Corfec, Global Portfolio Marketing Head, BD Pharmaceutical Systems. Customers can narrow their selections over time within those options, as tradeoffs are requiring balancing formulations, volumes, drug-container compatibility, and ergonomics.

The BD Libertas wearable injector has been designed to deliver subcutaneously 2-10mL dose volumes of drugs with up to 50cP viscosity. BD has conducted >50 pre-clinical and clinical studies to measure its performance, demonstrate feasibility of 2-10mL s.c.

The BD Libertas wearable injector has been designed to deliver subcutaneously 2-10mL dose volumes of drugs with up to 50cP viscosity.

injections, and characterize tissue response. And, BD Evolve onbody injector, a ≤3mL variable dose system, is capable of wear over a multiday period.

BD is also working on digital solutions for traceability in manufacturing and supply chains, all the way up to patient administration. Though the basic technical foundations of device connectivity are now relatively established, secure end-to-end solutions, integrated with existing industrial and clinical monitoring systems, are still not widely available on the market, she says. "We feel BD can contribute significantly here, given our breadth of experience in the digital monitoring of drug delivery systems with our infusion pumps or automated drug cabinets as well as our familiarity with the collection and reporting of healthcare data by our hospital data management and analysis systems," says Ms. Le Corfec.

Catalent produces around 300 million prefilled syringes annually at its Brussels, Belgium and Bloomington, Indiana facilities.

Catalent Biologics: Demand for Autoinjectors Amid Pandemic

Unlike industry experts' prediction that the injectable drug delivery devices market is expected to decline as a result of COVID-19, Catalent Biologics is not seeing such a decline, and specifically not in the subset market for autoinjectors. "Instead we have observed steady autoinjector demand from our customers since the start of the pandemic," says Brian Galliher, Lead Process Engineer, Catalent. "This is possibly due to the fact that autoinjector products are typically administered in-home by the patient themselves. Patients using autoinjectors do not need to leave their homes to receive health care, which is helpful when trying to social distance during the pandemic."

One of Catalent Biologics' core businesses is the filling of vials, syringes, and cartridges, while also providing safety device and autoinjector assembly for its partners. Many of its partners are transitioning their therapeutics into autoinjectors or safety devices to increase patient compliance and healthcare-provider safety.

"The usability of an autoinjector positively changes the patient experience by allowing them to administer the medicine in their own home safely and reliably," says Mr. Galliher.

SHL Medical: Preconfigured Autoinjector Technology Supports Customization

SHL's Medical's Molly® autoinjector has seen various commercial launches in the past few months. As a combination product, Molly has recently enabled therapeutics for diseases such as diabetes, Rheumatoid Arthritis, osteoporosis, and atopic dermatitis, to name a few. In hindsight, this reflects the increasing development and approval of complex biologics made available for patient self-administration, says Magnus Fastmarken, Director of Marketing at SHL

Built upon a robust preconfigured technology, SHL Medical's Molly® 2.25 has enabled a regulatory-approved autoinjector for systemic therapy in the higher volume range (≥2.0mL).

Medical. Case in point, a 2.25mL autoinjector built upon the Molly technology is the first regulatory approved and commercially available combination product in the higher volume range (≥2.0mL), he says.

First offered to pharma partners as a preconfigured solution, the Molly technology has since supported various customized device iterations due to the mature infrastructures that support it. From device design and engineering, process development through to ensuring quality and facilitating regulatory approval – various elements have been built upon the Molly technology, enabling industrial design customizations as well as manufacturing flexibility and scalability.

SHL Medical aims to improve patients' lives by providing them with innovative technology-enabled health solutions. "The circumstances brought about by COVID-19 have been a strong driver for the industry to continue developing connected devices," says Mr. Fastmarken. "For us, investing in connected devices and digital ecosystems to support remote services, as well as remote monitoring, is a cornerstone," he says. "This supports our endeavors to enable remote medication treatment encompassing patient onboarding, engagement, adherence, as well as retention. It is our belief that such a fully developed digital ecosystem must support our existing portfolio of commercialized as well as upcoming devices."

To make this happen, SHL has been actively collaborating with digital healthcare companies to develop and establish connected devices and remote care services that will help improve disease management. At present, SHL partners with Innovation Zed to develop connected solutions for pen injectors.

One connected device solution that SHL launched on the market is the InsulCheck Connect add-on device. "Our commitment to creating enhanced services in the drug delivery market, along with the expertise and quality systems in place, enabled the commercialization of this device," Mr. Fastmarken says.

Further, SHL has acquired Weibel CDS, expanding its portfolio with solutions like the Mini Bag system – a primary packaging technology and wearable delivery system for high-volume parenteral drugs. "This puts SHL in a unique position to offer a primary container solution for drugs in the range of 2- to 30/50mL, while addressing the need for wearable solutions that outline usability, compactness, and flexibility," he says.

Mitsubishi Gas Chemical: Multilayer Syringes & Vials Ensure Drug Stability

Mitsubishi Gas Chemical has been focusing on developing staked needle multilayer plastic syringes for autoinjectors. The targeted applications are biologics and regenerative medicines that are sensitive to oxygen and ultraviolet light.

OXYCAPT™ multilayer advanced material integrates plastic and glass for plastic syringes and plastic vials. The material features a water vapor layer made from Cyclo Olefin Polymer and a glass-like oxygen barrier layer with an oxygen absorbing polymer.

OXYCAPT plastic syringe features reduced leachable impurities and low extractables made possible by the PTFE stopper coated with slight silicone oil, a Polypropylene (PP) plunger rod, and the silicone-oil free OXYCAPT syringe barrel. OXYCAPT plastic vials are suited for parenteral pharmaceutical liquid medication storage. The multilayer construction preserves drug stability and shelf life in plastic vials, with reduced oxidation.

"By replacing a glass syringe with our OXYCAPT, pharmaceutical companies can solve problems such as glass breakage, pH shift caused by inorganic extractables from glass, and protein aggregation by silicone-oil on

The Credence Connect™ captures information about the injection and provides user feedback in real-time.

the glass barrel," says Tomohiro Suzuki, Associate General Manager, Mitsubishi Gas Chemical.

Credence MedSystems: Digital Connectivity Benefits Commercial & Clinical Settings

Credence MedSystems introduced the Credence Connect™ Auto-Sensing Injection System at the Pharmapack conference in Paris this past February where it was awarded Best Innovation in Drug Delivery Devices.

The Credence Connect brings digital connectivity to any prefilled syringe, explains John A. Merhige, Chief Commercial Officer, Credence MedSystems. The system is compatible with the Credence Companion® Safety Syringe System or any other standard prefillable syringe. The automatic or 'passive' function of the system allows the seamless capture and communication of injection information without requiring additional actions by the user to verify administration. Injected volume, time and date of administration, and duration of injection are measured, automatically transmitted, and recorded as dose history. The Connect provides real-time monitoring of an injection while it is taking place, allowing automatic measurement and communication of the volume injected over time. This allows the user to receive critical real-time feedback on the injection as it occurs.

The Connect embeds the connectivity in a reusable ergonomic finger flange that enhances usability and minimizes the environment footprint of the system. In addition to measuring data about the injection, it links to an app on a smartphone via Bluetooth Low Energy. The system will integrate with customer-specific or third-party platforms. The user can track the progress of the injection by viewing a counter or meter that provides the user visual confirmation and feedback. The meter advances when the injection is occurring and pauses when the injection is paused, providing positive reinforcement to the user. If the injected volume and duration/time match the prescribed parameters, the injection is determined to be a success. The app allows reminders, alarms, instruction, and guidance.

While the Connect has applicability to the commercial-use setting, the immediate shorter-term impact is likely greater in the performance of clinical studies, says Mr. Merhige. "Most significantly, the Connect can help allow the results of a study to be a true measure of a drug's safety and efficacy, as opposed to a potentially misinformed result stemming from poor or unknown compliance," he says. "The Connect can trigger early intervention when non-compliance is observed and allow safety and efficacy data to be mapped to dose history. These capabilities can minimize the risk of losing the development cost associated with a failed study and the revenue that could have come from an otherwise missed approval. Further, the Connect provides remote monitoring, enabling more efficient performance of these studies and allowing studies to be executed within the confines of social distancing."

Datwyler's NeoFlex™ plungers offer an optimized extractables and leachables profile to secure the integrity and safety of the customer's drug.

Datwyler: Coated Plungers for Compatibility and Protection

Datwyler has produced a range of cartridge components, such as plungers and combiseals, to seal the cartridges used in insulin pens. Offering the same rubber compound for both the plunger and the septum helps pharmaceutical companies when analyzing extractable and leachables, says Carina van Eester, Global Platform Leader, Prefilled Syringes and Cartridges, Datwyler.

"Datwyler offers very clean, uncoated compounds that guarantee good compatibility with injectable drugs like insulin," she says.

Pen injectors are used increasingly for multi-dose therapies requiring the injection of a fixed dose, she says. "Due to the rise of biologic drugs being delivered in pens, we have seen more demand for coated plungers to protect these highly sensitive large-molecule drugs."

In addition to pen injectors, other devices for subcutaneous self-injection continues to grow to accommodate biologicals and biosimilars. To meet this growing demand, Datwyler offers NeoFlex™ coated plungers for 1- and 2.25mL prefilled syringes. "With biologics being costly to manufacture and highly sensitive to extraneous contaminants, it is essential that packaging suppliers provide coated solutions that protect the drug product at all costs," says Ms. Van Eester.

DDL: Injection Device Tests Mimic Real-Use Conditions

In the last year, DDL has grown its testing capabilities for prefilled syringes, autoinjectors, and pen injectors. Matt Pasma, Test Engineer, DDL, says there has been a shift from the use of vials and single-use syringes for a drug product to either prefilled syringes that have a set dose in the syringe that gets fully injected or to a pen or autoinjector.

"These devices allow the user to set the dose and then inject it much like the traditional vial and single-use syringe method," Mr. Pasma says. "These unique devices have very specific FDA requirements that need to be met. We have expanded our testing capabilities to handle these requirements."

DDL has the capability to perform the preconditioning in various environmental conditions, drop testing, and vibration testing prior to dose accuracy testing requirements. Mr. Pasma says "We have equipment and expertise needed to perform each test, and we have also installed an Instron universal tester that is designed to test all of the components of an autoinjector in one setup, which is more in line with how the product is used. This will allow our customers to feel more confident in the results when testing their pen and autoinjectors."

DDL's most recent initiative to serve the rapidly growing injectable market is the launch of the company's Container Closure Integrity (CCI) program. This program offers a suite of

DDL conducts performance and mechanical testing of prefilled syringes, autoinjectors and pen-injectors per the recommendations set by the FDA and the related industry standards.

All Sonceboz devices are intended to be body-worn and feature integrated connectivity.

deterministic testing technologies that include electrical conductivity and capacitance (high-voltage leak detection), laser-based gas headspace analysis, helium tracer gas detection in vacuum mode, and vacuum decay to help meet USP-NF<1207> deterministic CCI requirements for virtually any product-package system, including injectables.

Sonceboz: Accurate Dosage of High-Volume Drugs

The Sonceboz platform technology delivers high volumes of biologics, such as checkpoint inhibitors and other immune-oncology treatments. The technology enables patients to receive large volumes of biologics in a home setting, in a convenient way, by adhering an easy-to-use patch pump to the skin and until dosage is complete. "This way patients do not have to necessarily go to a hospital or clinic, can save time, and avoid potential exposure to disease such as COVID-19," says a Sonceboz spokesperson.

All Sonceboz devices are intended to be body-worn by either an adhesive patch or by the use of a belt-clip or strap. All devices come with an integrated connectivity interface that provides data such as delivery status, time of injection, potential error messages, etc. In some cases, the device provides the patient with data, in other cases data needs to be collected by a CRO during clinical trials.

Depending on the lifecycle of a drug product, and the customer's specific needs, the spokesperson says. Sonceboz can provide a matching solution with its interface. "We are helping pharma companies deliver very high volumes of drugs in excess of 25mL," the Sonceboz spokesperson says. "For such volumes, an electromechanic device that connects directly to vials is an optimal solution because the electromechanic drive mechanism offers consistent dosing accuracy and performance across the whole delivery cycle."

Owen Mumford Pharmaceutical Services: Platform Suited to Range of Drugs

At Owen Mumford Pharmaceutical Services the focus has been on creating and marketing a platform based on UniSafe®, an intuitive passive safety device for prefilled syringes. UniSafe uses the same technique as a standard syringe, and the safety shroud – which completely covers the needle – is deployed automatically. With a 1mL device on market, a 2.25mL soon to be available, and an autoinjector in development, this platform will be used for a variety of drugs and biologics for a range of diseases that require treatment by subcutaneous administration, explains George I'ons, Head of Product Strategy & Insights –

UniSafe® safety device for prefilled syringes is a spring-free device delivering safety and simplicity (Owen Mumford Pharmaceutical Services).

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"Our UniSafe passive safety device for prefilled syringes is the first device of its type to have a design that is spring-free," says Mr. I'ons. "This provides a clearer view of the dose in the syringe, is less intimidating for patients, and prevents pre-activation of the device."

The design also helps to prevent removal of the plunger and helps to eliminate reuse, drug wastage, and spillage. He says there will be increasing demand for reusable products so Owen Mumford is developing a reusable autoinjector based on its UniSafe platform. This device will have the option of connectivity where the electronic components, often containing precious metals, are housed in the reusable part of the device. "We have seen growing concerns around the use of plastics and challenges with the ability to recycle them," he says. "The addition of electronics for connected devices presents an even greater sustainability challenge."

Enable Injections: On-Body Infusor Incorporates Connectivity

Enable Injections continues to be focused on the development of the enFuse® platform and its biopharma partner combination product programs, and has completed two clinical studies with its biopharma partners.

The enFuse on-body infusor is a small wearable device capable of delivering large volumes of medicine subcutaneously in a single administration, currently in the investigational stage. Once approved, it will accommodate infusion of high-viscosity biopharmaceutical and pharmaceutical therapeutics from 3-50mL. The platform is designed to leverage existing primary container closure systems, which eliminates the need for additional drug compatibility testing, additional filling and manufacturing lines, and additional stability testing risk.

The enFuse® On-Body Infusor by Enable Injections is designed for patient self-administration of high-volume drugs from 3-50mL.

Jennifer Estep, Associate Director, Marketing, Enable Injections, says that enFuse is designed to offer several benefits to patients, including the potential for at-home self-administration by the patient or caregiver. This allows the potential to reduce the risk of exposure, the time and inconvenience of travel to and from administration in a healthcare facility, and the need to have home infusions administered by a healthcare provider.

"Our partners also appreciate the benefits the enFuse platform offers such as product differentiation through an improved patient experience, while minimizing development costs and time," she says. "The next generation enFuse is in development to incorporate connectivity for patients to communicate treatment information and track infusions on their smartphone."

West Pharmaceutical Services, Inc.: The Growing Trend of Self-Injection, Less Frequent Dosing

West is working with customers to ensure supply of the right components and solutions to help resolve the COVID-19 pandemic. "The process for selecting the best high-quality packaging components and devices for use with injectable medicines, including vaccines, is a complex one driven by years of science that West has pioneered," says Aileen Ruff, Vice President, Services and Solutions, West Pharmaceutical Services, Inc. "We help customers in the selection, testing, and verification of components and devices to prepare for future commercial scale-up and launch of successful vaccine candidates."

In the biologics space, there is a clear trend toward higher delivery volumes, less frequent dosing, and the conversion from intravenous to subcutaneous delivery. Ms. Ruff says this is driving demand for wearable technologies. West's wearable solution is the SmartDose® drug delivery portfolio, which includes 3.5mL and 10mL user loaded injectors, as well as a 3.5mL preloaded injector.

The SmartDose 3.5 injector is commercialized with Amgen's Repatha, to provide a single, monthly dose delivery option. "Our SmartDose devices can address multiple disease states from oncology and autoimmune to CNS, and empower patients to treat themselves in the comfort of a clinic or their own home vs. a hospital setting, with fewer injections than a multiple autoinjector alternative," says Ms. Ruff.

scPharmaceuticals Inc. announced its intent to go to market with West's 10mL SmartDose 10 injector for FUROSCIX®, a proprietary, subcutaneously delivered furosemide solution, for the treatment of worsening heart failure due to congestion. West's SmartDose wearable injector provides an outpatient alternative for the treatment. The FDA accepted scPharmaceutical's New Drug Application resubmission of FUROSCIX in July 2020.

Alexion has also announced its adoption of the SmartDose injector for two blood disorder products. ULTOMRIS® utilizes the SmartDose 3.5 injector to help facilitate at-home self-administration for ease of use. The SmartDose platform helps to provide patients confidence in their therapy and help reduce and prevent frequent visits to infusion centers, she says.

"To further strengthen the offering to our customers, West is partnering with Swissfillon for an integrated solution for clinical filling of the SmartDose Platform Cartridges," says Ms. Ruff. "Taking away possible challenges in the supply chain around upscale of fill-finish activities help simplify the journey to approval for our pharma clients."

West also partnered with Accord Healthcare Limited to develop a delivery device for a weekly single-dose injection of its drug Methofill™ (methotrexate) SELF INJECT. The incorporation of West's SelfDose™ injector supports the required dosing level and ergonomic design, which allows Rheumatoid Arthritis patients with dexterity issues to self-inject outside of a healthcare setting. West's SelfDose patient-controlled injection technology is for volumes lower than 3.5mL.

West's SmartDose® portfolio and SelfDose™ injector have options to partner with customers and help enhance the self-injection experience for patients while mitigating risk.

Bespak by Recipharm: Autoinjector Technology is Customizable

Over the last year, Bespak's injectables unit has been largely focused on autoinjector technology due to its ability to improve patient experience and increase treatment adherence. The increasing number of treatment options for chronic diseases involving biologics has shifted towards reducing injection frequency, which often leads to increased concentration and higher viscosities.

With this in mind, the company has been scaling up the Vapoursoft®-powered Syrina® AS autoinjector to commercial-scale manufacturing. In parallel, Bespak is engaged in a number of client programs developing Syrina-based delivery devices.

"As we transfer to the manufacturing stage, we leveraged our design for manufacturing capabilities to develop robust processes and tools," says Reenal Gandhi, Business Development Director, Bespak. "Multi-cavity tooling and an assembly line equipment have been installed and are being validated to support clinical studies and low-volume commercial supplies. As we transition from design and development to validation and manufacturing, our experience of high-volume medical device manufacturing and process design creates robust and repeatable processes."

The Syrina AS is ready for low-vol-

Powered by VapourSoft® technology, the Syrina® AS is Bespak by Recipharm's most advanced autoinjector, featuring automatic needle insertion and audible end-of dose-indication.

ume manufacturing, and design verification testing has been completed with delivery of 2mL 50cP fluid with a 27G STW needle in less than 10 seconds. This verification is one variation of the Syrina AS platform, which is designed to be customizable to 2.25mL and 1mL syringes, as well as different fill volumes, viscosities, and needle gauges. "We selected this configuration based on the market trend toward 2mL injection and higher viscosity drugs, while maintaining a thinner needle for patient comfort," says Ms. Gandhi. Our devices can work with multiple therapeutic areas and are suitable for a range of biologic drugs and immunology/autoimmune drugs. The device also works with high-concentration, small-molecule formulations and covers a range of viscosity drugs."

Bespak by Recipharm has several customer programs leveraging the Vapoursoft technology moving through the development and scale up process. One example is a drug delivery requirement for a 2mL product with viscosity of 30-40cps. Working with a traditional autoinjector demanded a larger needle and a stronger spring that introduced other risks to the device, explains Ms. Gandhi. Having already performed stability studies with a 27G syringe, there was a strong preference to avoid changing the primary container. Moving to a larger needle also meant impacting patient comfort. "By leveraging the Syrina AS platform product, the need to evaluate a new syringe configuration could be eliminated, saving time and avoiding the risk of reformulating down to a lower viscosity," she says. The autoinjector is currently being evaluated and compatibility tested with the product.

Bespak by Recipharm can also develop bespoke devices based on customer requirements. A global biopharma company had a unique formulation, which, due to its ultra-high viscosity, could not be administered using conventional autoinjectors. Bespak by Recipharm partnered with the company to develop a VapourSoft-driven autoinjector based on an adaption of the Syrina AS platform. "This allows the company to offer users a simpler and easier option to deliver the drug than with a traditional syringe and manual injection process," she says.

To meet the industry's growing demands for "connected devices," Bespak by Recipharm is developing a connectivity option for its autoinjectors. The option can sense and transmit data to a patient's smartphone, such as when an injection was taken and if the injection was completed. The connectivity module is designed to allow integration with customers' preferred connected health systems by using an open architecture compatible with technical solutions offered by a range of connectivity solution providers.

DALI Medical Devices: Bringing Clinical Trials to the Home Environment

DALI Medical Devices develops a variety of injectable drug delivery devices, and has spent the last year focusing on the Synnect® Smart Injection Solution. Synnect transforms a standard syringe into a smart syringe by replacing just the plunger rod, explains Ziv Cahani, Vice President of Business Development and Marketing, DALI Medical Devices.

Synnect connects to a dedicated mobile device app and transmits injection data to a secure cloud in real

The Synnect® Smart Injection Solution from DALI Medical Devices transforms a standard syringe by just replacing the plunger rod.

time. Including sensing and connectivity technologies, the Synnect enables accurate and continuous measure of injected drug volume, tracking the start and end of the injection, and integrates with existing data management platforms (reimbursement evidence, adverse events, product, and training improvements).

Among other relevant usages, the Synnect is suited for an injectable drug's clinical trials happening in the home environment. "The COVID-19 pandemic has underscored the need for reliable at-home treatments as one way to prevent overwhelming hospitals and other healthcare facilities," says Mr. Cahani. "In addition to improving patient convenience, self-administration of injectable drugs at home protects high-risk patient populations and improves compliance. These are all relevant needs of clinical trials, especially in times a pandemic when, for example, older people want to eliminate visits in hospitals due to the risk, when there is a quarantine."

Synnect allows pharma companies and CROs to remotely monitor the clinical trial's process at different sites, which can reduce the costs of the clinical trial, he adds.

The Maverick Emergency Autoinjector technology, developed by Duoject Medical Systems and manufactured by Stevanato Group, is intended for life-saving injections.

Duoject Medical Systems: Autoinjector Lessens Risk, Saves Lives

Duoject has continued developing its Maverick Emergency AutoInjector in collaboration with Stevanato Group. This device offers higher levels of reliability and user-friendliness to patients who find themselves in a life-threatening situation, says William Fortina, Business Development Director, Duoject Medical Systems.

"It is well documented that patients have had issues with marketed epinephrine autoinjectors: struggling to take them out of their casing; triggering the system in the wrong orientation; or simply having to carry bulky systems with them at all times," he says. "When someone's life depends on receiving their injection, pharma companies and patients should expect a system that is designed with the primary goal of minimizing the chances of misuse. We developed the Maverick Emergency AutoInjector after careful evaluation of existing systems' shortcomings. We believe its patented sequential activation, ergonomic design, and robust automated injection mechanism will make it a strong alternative to current market offerings."

The Flex reference-design platform for an autoinjector.

Flex Health Solutions: Wearability & Connectivity Go Hand in Hand

Amy Boyle, Vice President Strategy, Planning and Marketing, Flex Health Solutions Segment, sees the injectables market growing with new biologics and a trend to personalized medicine that is delivered only through wearable injectors. Wearability, she says, is multifaceted, from biocompatibility, to device shape, to user interface, to connectivity.

"We have extensive expertise in connectivity and sensor technologies that drive form, function, cost, and data capability as well as the software to support it," she says.

She adds that connectivity strategy needs to match the data set and clinical constraints. "Connectivity can drive significant real estate demands and power demands of a product, but often a better strategy is available to suit the data packet and use case," she says.

With connectivity comes concern about cybersecurity and the remote connection between medical devices and backend application. Flex has developed a team of cybersecurity experts to ensure that, as a contract design and manufacturing organization, it is addressing any concerns, and fulfilling compliance requirements in design, development, and verification.

"Our expertise in connectivity and power management facilitates the transition to smart and communicative devices," says Ms. Boyle. "We have created smart inhalers, autoinjectors, connectivity modules for existing injection pens, and new innovative platforms."

The SG Alina® Pen, a new user-friendly self-injection device for diabetes care, is based on intellectual property and technology licensed from Haselmeier.

Stevanato Group: Providing Optimized Primary Containers & Integrated Solutions

Primary containers are at the heart of what Stevanato Group offers. It is a leading supplier of cartridges to the pen injector market for insulin and the second largest glass syringe producer globally. In recent years, it has become recognized as an integrated solution provider for drug delivery systems, offering contract manufacturing of devices as well as a growing portfolio of its own proprietary and licensed devices. Expanding its US presence is also a key strategy with a Technical Excellence Centre opening Boston this year to provide testing and analytical services related to drug, primary container and device.

To help fight the COVID-19 pandemic, Stevanato Group offers a range of glass primary packaging solutions for vaccines and drugs under development by its pharmaceutical customers, primarily vials and syringes, some with integrated safety systems, which can be used in hospitals and in some cases for self-administration. The possibility to use these solutions at home allows patients to be treated in more comfortable and familiar surroundings, says Steven Kaufman, Vice President, Drug Delivery Systems at Stevanato Group.

In the past year, Stevanato Group signed agreements with two key players in the medical device sector. First, a partnership and collaboration agreement with Duoject Medical Systems for the promotion and contract manufacture of Maverick™, an emergency-use autoinjector for overcoming life-threatening situations. Maverick is designed to be an intuitive, user-friendly cartridge-based device that provides full dose delivery visual, audible, and tactile feedback with no exposed sharps throughout the injection process. Maverick integrates Stevanato Group's highly resistant Nexa® glass cartridges as the primary container of choice, providing greater robustness, making the device even more reliable when an emergency intramuscular injection is required, explains Mr. Kaufman.

Additionally, Stevanato Group has an exclusive licensing agreement with Haselmeier related to its Axis-D intellectual property and technology to be the basis of the SG Alina® pen injector for diabetes care. In this framework, Cambridge Design Partnership is working closely with the R&D team of Stevanato Group to develop and bring the pen injector to market for clients looking for alternatives to existing devices.

"Due to a number of upcoming

patent expirations and other new injectable drugs coming to market, there is a growing demand by pharma clients for robust and user-friendly pen injectors," says Mr. Kaufman. "The SG Alina pen injector features an appealing and functional design, including an easy-to-dial mechanism, optimized injection force for patient comfort, and a readable display."

Stevanato Group is strengthening its drug delivery systems' portfolio by also developing EZ-be POD®, a discreet and comfortable wearable device for adjustable regimens, such as for diabetes treatment, pain management, and others. The company is also active in the respiratory therapeutic area with ICOcap®, a capsule-based inhaler used for asthma and COPD, licensed from partner Iconovo.

Ypsomed: Focusing on Devices so Partners Can Focus on Therapy

Ypsomed's main focus is in the areas of large-volume patch injectors and smart connected reusable add-ons. The company is is focused on developing the large-volume 3-10mL YpsoDose prefilled patch injector, which is being industrialized for clinical trials. The main benefit of the YpsoDose patch injector is to allow users to perform infrequent injections in an efficient and convenient way, saving significant costs for the healthcare system, explains Ian Thompson, Vice President Business Development, Ypsomed.

The electromechanical, cartridge-based, connected device is centered around a versatile platform customized into product-specific variants to provide a reproducible injection for each drug. YpsoDose automatically inserts the injection needle at the start and retracts the needle at the end of the injection process.

Ypsomed's YpsoMate 2.25 is the first approval and launch of a ready-to-use autoinjector compatible with a 2.25mL prefilled syringe for Teva's AJOVY® migraine drug.

"As YpsoDose illustrates, connectivity will become instrumental in effective self-management of chronic diseases," says Mr. Thompson. For instance, the reusable add-on SmartPilot for YpsoMate with built-in sensor technology and wireless communication capabilities, transforms the standard two-step YpsoMate autoinjector into a fully connected digital health system. SmartPilot monitors device use and provides therapy-relevant injection data to providers, caregivers, and healthcare stakeholders, as well as patients, through the self-injection process. "SmartPilot for YpsoMate is being industrialized for first customers, allowing our partnering pharmaceutical firms to rapidly develop therapy solutions that address non-adherence in clinical trials and post-market introduction," he says. "In short, Ypsomed addresses the device-oriented challenges so that our pharmaceutical partners can focus on the therapy-oriented challenges."

In March 2020 Teva announced the launch of its drug product AJOVY® in the prefilled YpsoMate 2.25 autoinjector for the preventive treatment of migraine in adults. The collaboration with Teva marks the first commercial market entry of Ypsomed's larger 2.25mL autoinjector YpsoMate 2.25, says Mr. Thompson. AJOVY (fremanezumab-vfrm), a humanized monoclonal antibody, is the first and only anti-CGRP treatment for the prevention of migraine with monthly and quarterly dosing options, he says.

"To date, Teva had marketed AJOVY in a standard syringe," says Mr. Thompson. "With the launch of the drug in an autoinjector, Teva now offers AJOVY in a format that is more convenient for patients. This was the first approval and launch of a ready-to-use autoinjector compatible with a 2.25mL prefilled syringe." ◆

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Drug Development
EXECUTIVE

Nora Khaldi, PhD
Founder & CEO
Nuritas

NURITAS

Nuritas Pharma: Life Changing Peptide Drug Discoveries for a Changing World

Peptides are the major signaling molecules in the human body (most bodily functions communicate via peptides) and as a result have both significant therapeutic potential and the highest probability of clinical success compared to other modalities. While there are now about 60 approved peptide drugs, we believe the landscape of opportunity is vast and largely unexplored. Enabled by artificial intelligence, our scientists are able to interrogate vast numbers of peptides and identify first-in-class therapeutics that meet or surpass industry standards, overcoming previous peptide delivery challenges. *Drug Development & Delivery* recently interviewed Nora Khaldi, PhD, Founder and Chief Executive Officer of Nuritas, to discuss the company's innovative approach to accelerating the discovery of novel therapeutic peptides that address unmet patient needs in multiple disease areas.

Q: The category of infectious disease is now on everyone's minds with the challenges we face in global pandemics. How does your platform help address the challenges we are facing today and in the future?

A: Peptides have long demonstrated exceptional utility against a host of micro-organisms, with drugs like Vancomycin remaining one of the last effective bulwarks against antibiotic-resistant bacterial species. Using AI to take the serendipity out of drug discovery in this space should enable a rapid, systematic response to the global challenge of infectious disease opening the possibility of bringing many diseases that have historically been economically unattractive to drug developers (eg, tropical diseases or diseases endemic to developing nations) into the frame for real, concerted development efforts.

We're excited by two opportunities that we believe Nuritas can offer to address these significant challenges. The first is rapid response. Our KRAS work is a great example of the power of Nuritas' AI platform to identify peptides in a matter of months that may be able to serve as therapeutic options for development against a known target. The same strategy can be applied to target new bacterial, fungal, and viral challenges as they arise.

As a proof of concept in the anti-infective space, we identified peptides that kill bacteria, yeast, and molds by creating predictors to address each microbial subtype; identifying more than 20 such peptides from the millions searched in our database. The selected peptides offer exceptional potency and highly specific activity to each targeted microbial type. In fact, data on one of our patented antimicrobials was published in September 2019 in the peer-reviewed journal Frontiers of Microbiology. We also have compelling data on other compounds that have anti-fungal properties.

Our success to date in the infectious disease space represents just the tip of the iceberg, and by channeling the power of our AI platform to address the unique challenges in bacterial resistance and the frightening task of tackling unknown bacteria, viruses, and fungi, Nuritas will realize its mission of delivering life-changing drug discoveries to people around the globe.

Q: In this era of remarkable new technologies like CRISPR, stem cell and regenerative medicine, and organ bioprinting, why has Nuritas chosen to focus on peptides for drug discovery?

A: Peptides are the major signaling molecules in the human body (most bodily functions communicate via peptides) and as a result, have both significant therapeutic potential and the highest probability of clinical success compared to other modalities. While there are now about 60 approved peptide drugs, we believe that the landscape of opportunity is vast and largely unexplored. From a bioactivity standpoint, peptides offer a "goldilocks" solution that neither small molecules nor large biologics can offer:

- Peptides have broader reach than small molecules because they can engage with a huge target population that small molecules cannot. For example, peptide-peptide and protein-protein interactions (PPIs) are key to most cellular processes, and small molecules have limited ability to interfere with PPIs in a meaningful way – they are simply too small. Additionally, many proteins have broad shallow binding sites or are unstructured, which makes them much more suited to binding peptides than small molecules.

- Peptides are a more attractive modality than biologics because peptides can enter cells and interact with intracellular targets (approx. 75% of all known druggable targets) – while biologics (antibodies) are too big to get into cells.

- Peptides are safer than small molecules because they are generally exquisitely specific for their target and display far fewer off-target or side effects. Additionally, they are less likely to generate an immune response than large biologics.

- Peptides are easier and less expensive to manufacture than large biologics, cell therapies, or gene therapies.

Q: What is Nuritas' approach to peptide drug discovery?

A: Enabled by the Nuritas AI platform, Nuritas scientists can interrogate vast numbers of peptides and identify first-in-class therapeutics that meet or surpass industry standards – specifically, unmodified peptides with demonstrated potency, cell penetration (if needed), lengthy half-life, and other characteristics necessary for successful development.

Q: There are many companies using AI to enable drug discovery. How is your AI platform different?

A: Unlike most other AI platforms, Nuritas has a legacy benefit that exceeds many other companies in the space. Our machine-learning infrastructure and algorithms have been trained on proprietary data generated throughout the past 5 years.

The company has built a large collection of plant, animal, and marine proteomes, analyzing them using mass spectrometry and using the resulting data to train our AI. This process has given us what is arguably one of the largest natural peptide databases in the world (both pure peptides and peptide networks). In addition, we have generated large quantities of proprietary assay data on peptide performance in a wide variety of cell-based bioassays, in vivo animal models, and human clinical studies. The human clinical data derives from studies conducted with GRAS peptide networks that we have been able to rapidly get into the clinic. As much of the biological "low-hanging fruit" in the target landscape has been picked, our

ability to generate validated bioactivity predictions even in low data environments addresses the biopharma industry's huge appetite for novelty and allows development against previously considered "undruggable" targets.

In contrast to other AI drug discovery companies, Nuritas can uniquely provide evidence of its powerful discovery capabilities in PeptAIde™, an anti-inflammatory to support exercise recovery, discovered by AI, marketed by BASF, and backed by human clinical data. Additionally, we are developing a broad proprietary biopharma pipeline, with the most advanced programs in fibrosis and cancer. Our fibrosis program is built on a novel target that is implicated in the major pathophysiologies of NASH (steatosis, inflammation, and fibrosis) and which has the potential for broader anti-fibrotic use. Next in the pipeline is a program targeting oncology indications driven by the previously undruggable KRAS G12D mutation.

Q: Do you have plans to develop your own products, or are you focused on commercialization through partnerships?

A: Both. One of the benefits of the AI platform is the ability to rapidly generate multiple discovery programs, at a pace that none but the largest pharma companies could hope to develop themselves. The prolific nature of the platform allows us to choose only the best of the best to advance and affords us the luxury of being able to design the best path forward for each program. For instance, with the KRAS peptide, we may be able to quickly demonstrate proof of concept internally using in vitro and PDX models, enabling rapid advancement for our own pipeline, perhaps retaining US rights and partnering ex -US. ◆

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THERAPEUTIC FOCUS

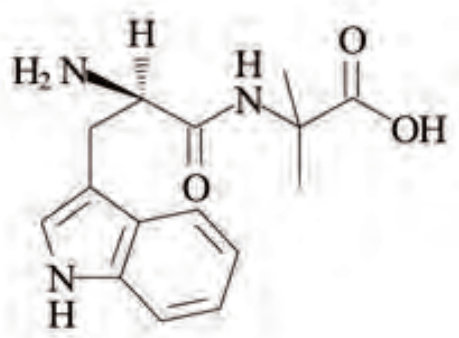
The Future of Treating Alzheimer's Disease: Aducanumab & Beyond

By: Hermann Russ, MD, PhD, and Alexander Gebauer, MD, PhD

ABSTRACT

A final analysis of data from Biogen's larger Phase 3 dataset of the EMERGE study with aducanumab for treatment of Alzheimer's disease (AD) demonstrates that this investigational antibody reduced clinical decline in patients on several clinical endpoints and biomarkers. Aducanumab uniquely and specifically binds to aggregated toxic amyloid beta monomers that are thought to be primarily responsible for the cognitive decline and neurodegeneration seen in AD patients. A small molecule, GAL-101, currently in clinical development by Galimedix Therapeutics for treatment of glaucoma and dry macular degeneration, has similarly demonstrated the ability to fight these toxic amyloid beta oligomers, the same targets as aducanumab, in a particularly sophisticated way. GAL-101 has the advantages of a small molecule compared to an antibody, which include easy manufacturing, oral availability, good brain penetrance and no immunological adverse effects. As such, Galimedix Therapeutics believes studies of GAL-101 in AD are warranted to develop it as a future convenient oral drug treatment for many millions of AD patient around the world.

FIGURE 1



Chemical Structure of GAL-101

VALIDATION OF AMYLOID BETA AS AN AD DRUG TARGET

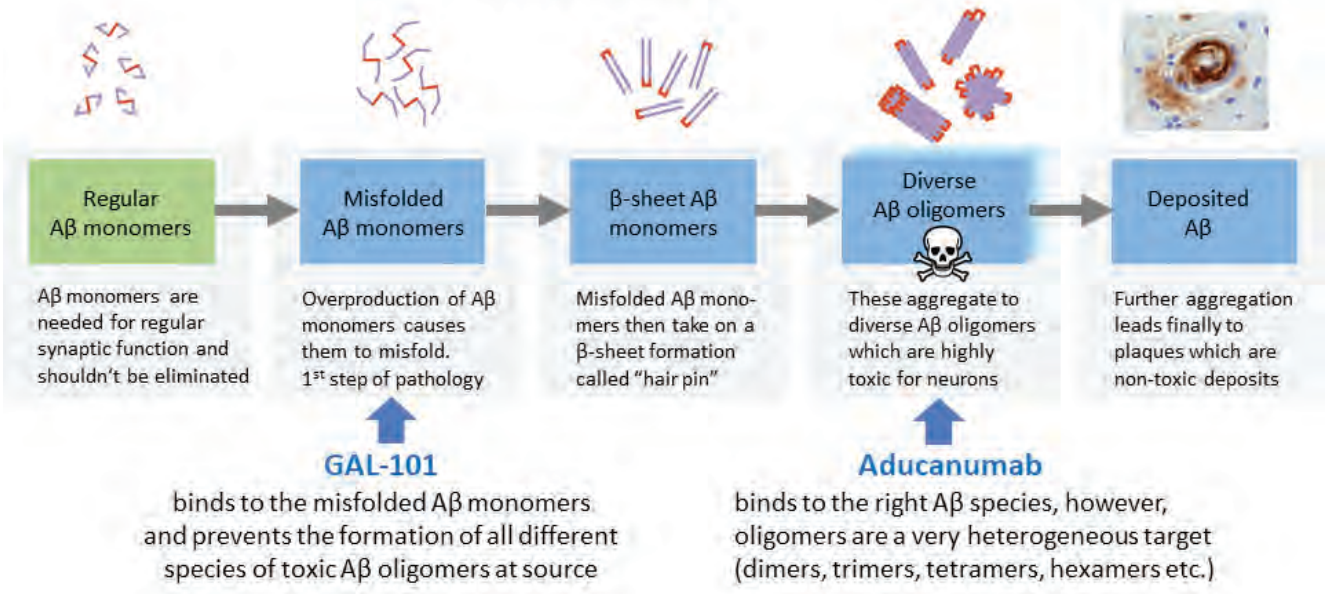
The times when amyloid beta as a drug target have been dubbed a dead horse in the race for treatment of AD are now over. In October 2019, Biogen announced a new analysis of the larger Phase 3 dataset showing that its investigational compound aducanumab reduced clinical decline in patients with early AD on multiple measures of effectiveness. Aducanumab is an antibody that specifically binds to aggregated amyloid beta monomers, which are also called soluble amyloid beta protofibrils or amyloid beta oligomers. Biogen plans to submit their data to the FDA for approval.

After decades of failure in large Alzheimer's disease neuroprotection trials, the results from the EMERGE study with aducanumab can be considered a breakthrough and a validation of amyloid beta as a target for new Alzheimer's drugs. However, the question remains why other amyloid beta approaches failed in so many clinical studies.

WHY WAS ADUCANUMAB SUCCESSFUL?

There are obviously some challenges with amyloid beta as a drug target and with antibodies as drugs for AD. The scientific community more and more recognizes that several forms of amyloid beta exist and that not all forms are harmful. Monomeric amyloid beta, for instance, is known to be necessary for proper synaptic functioning and amyloid beta plaques are, in fact, rather inert deposits. Secretase inhibitors and monoclonal antibodies against amyloid beta monomers causing undesired clearance of this species led to functional deficits. Antibodies targeting plaques caused immunological reactions and could release the encapsulated toxic amyloid beta species inducing additional neurodegeneration. Therefore, these are wrong approaches to new AD drugs. However, the aggregated species of amyloid beta monomers

FIGURE 2



The 5 different species of amyloid beta

have been identified as the real neurotoxic agent causing death of neurons and cognitive decline. These amyloid beta oligomers can now, following the EMERGE study results, be considered as a validated drug target for AD. Aducanumab and GAL-101, a small molecule in clinical development by Galimedix Therapeutics, share this target.

HOW TO ADDRESS AMYLOID BETA RIGHT

Amyloid beta oligomers are formed by aggregation of misfolded amyloid beta monomers and are known to be highly toxic to neuronal cells, killing them in low nanomolar concentrations. The elimination of the amyloid beta oligomers should also indirectly reduce the load of deposited amyloid beta in the brain tissue and the density of plaques during long-term treatment. However, removal of plaques is not the neuroprotective mechanism.

The toxic amyloid beta oligomers are a highly heterogeneous target consisting of dimers, trimers, quadrumers, hexamers, octamers, etc. Some of the smaller aggregates are probably more toxic than others. That is the precise situation where antibodies face their limitations because their strength is an extremely high specificity to a single, well-defined target. It is difficult to fathom the possibility of designing an antibody that binds selectively to all the different toxic species of amyloid beta oligomers and does not interact with the regular monomers and plaques. This likely is the reason why some of the supposed oligomer-specific antibodies failed in the clinic. Aducanumab succeeded since it is obviously capable of eliminating at least some of the most toxic amyloid beta oligomer species.

The importance of the aducanumab results cannot be overestimated. The courage and the staying power of the developers at Biogen and the originator company Neurimmune deserve the highest appreciation. With unrelenting determination, they finally paved the way for the first disease-modifying treatment for probably the worst known medical threat to humankind.

AD GROWTH CALLS FOR PRACTICAL SOLUTIONS

There are currently at least 30 million Alzheimer's patients around the globe suffering from this devastating disease, and there are no satisfactory treatment options. There is probably a high number of unreported cases because making an early diagnosis with no meaningful treatment options to offer isn't in the best interest of patients. Now, there is hope for all these patients. However, how many of them can realistically get access to a high-tech antibody drug like aducanumab?

In an ideal world, an Alzheimer's drug would be an orally available small molecule that is easy to manufacture, that can by taken at home as tablet, and that effectively eliminates toxic amyloid beta oligomers. Ideally, such a small molecule not only eliminates some of the already formed toxic amyloid beta oligomers, but is also prevents the formation of all species of the toxic amyloid beta oligomers at their source. The aspect of prevention is

important here in the sense that it is in general the superior way to prevent a health problem rather than waiting until the problem has manifested in the form of toxic amyloid beta oligomers in the tissue and only then try to eliminate them.

Drug candidates with such a profile exist but to date have been broadly neglected as just another amyloid beta approach doomed to fail. In fact, there is enormous potential with smart small molecule approaches that specifically eliminate the toxic amyloid beta oligomers. One of these non-antibody approaches is GAL-101 (Galimedix Therapeutics, Inc.), a so-called amyloid beta aggregation modulator, which showed significant cognitive improvement in the typical animal models of AD.

A FUTURE ORAL ALZHEIMER DRUG TARGETING AMYLOID BETA

GAL-101 specifically fights the toxic amyloid beta oligomers, the same target as aducanumab, in a particularly sophisticated way. GAL-101 binds with high affinity to only the misfolded form of amyloid beta monomers even before they can aggregate to toxic amyloid beta oligomers. Then a rapid conglomeration happens, forming amorphous, non-beta-sheet species, so-called "clusters," which are innocuous. Interestingly, once GAL-101 concentration reaches effective levels, it triggers formation of the "clusters," which then have shown the capacity to collect additional misfolded amyloid beta monomers even in the absence of additional GAL-101 molecules, through a self-propagation mechanism. This novel "trigger effect" results in a sustained effect lasting far longer than the time a single administration of the drug remains at therapeutic levels in the brain, potentially allowing for a convenient once- or twice-per-week intake regimen for patients. Thus, GAL-101 may provide sustained prevention of formation of toxic amyloid beta oligomers in the Alzheimer brain leading to a slowing of disease progression and a possible restoration of neural function depressed by the chronic toxic attack. The latter has been demonstrated in astonishing in vitro long-term potentiation experiments with GAL-101.

An eyedrop formulation of GAL-101 is currently under development as treatment for glaucoma and dry macular degeneration (AMD). Both these diseases are currently understood as an Alzheimer-like pathology of the retina. The proven efficacy of aducanumab in Alzheimer's disease is also an indirect validation for drugs like GAL-101 targeting the same pathology in the retina, ie, dry AMD and glaucoma. The oral formulation of GAL-101 intended for use in AD is currently in the phase of IND-enabling studies.

The introduction of antibodies eliminating toxic amyloid beta oligomers will doubtlessly be a breakthrough in the treatment of AD and a blessing for many patients in need. However, antibodies will be dispensable when the first orally available small molecules enter the market. When Big Pharma companies undertake their strategic portfolio planning for future Alzheimer drugs, the consideration of small molecules like GAL-101 in addition to the biologicals may be the safest, and most profitable bet.◆

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BIOGRAPHIES

Dr. Hermann Russ is a board-certified clinical neurologist and experimental pharmacologist. He is Chief Scientific Officer and Co-Founder of Galimedix and inventor of the use of GAL-101 in neurodegenerative retinal diseases. He earned his PhD in Neuro- and Biochemistry and his MD in Neurology from the University of Wurzburg, Germany. Until 1999 he held several academic positions, including Professor of Pharmacology (University Giessen) and Consultant of Neurology (University Clinic of Regensburg). Dr. Russ served 21 years in several executive roles in Pharma industry, eg, at Merck Serono, Merz, and Teva. His scientific focus is on neurodegenerative diseases, specifically Alzheimer's, Parkinson's, and degenerative retina diseases. He is (co)inventor of about 25 patents and (co)author of about 50 peer-reviewed scientific publications.

Dr. Alexander Gebauer is a medical doctor and earned his PhD in Experimental Pharmacology at the University of Mainz, Germany. He is Executive Chairman and Co-Founder of Galimedix. Dr. Gebauer served 28 years in several executive roles in the pharma industry, eg, at sanofi, Merz, and Sun Pharmaceuticals. His scientific focus is on translational medicine and innovative clinical development programs. He has achieved regulatory approval for several drugs and medical devices in many countries. He is (co)inventor of several patents, (co)author of about 20 peer-reviewed scientific publications and co-edited the handbook of methods in clinical pharmacology.

COMBINATION PRODUCTS

Development Challenges & Solutions

By: Tom McLean

INTRODUCTION

Combination products have made a tremendous impact on the healthcare landscape in recent years, offering powerful and novel treatment options and approaches across many disease states – and the acceleration of growth in this sector of science and medicine is expected to continue propelling forward.

To meet the needs of drug developers and patients alike, the packaging and device industry has targeted its innovation specific to combination therapeutics. These drug products require a particularly nuanced approach from development through delivery that is essential to ensuring optimal outcomes can be achieved.

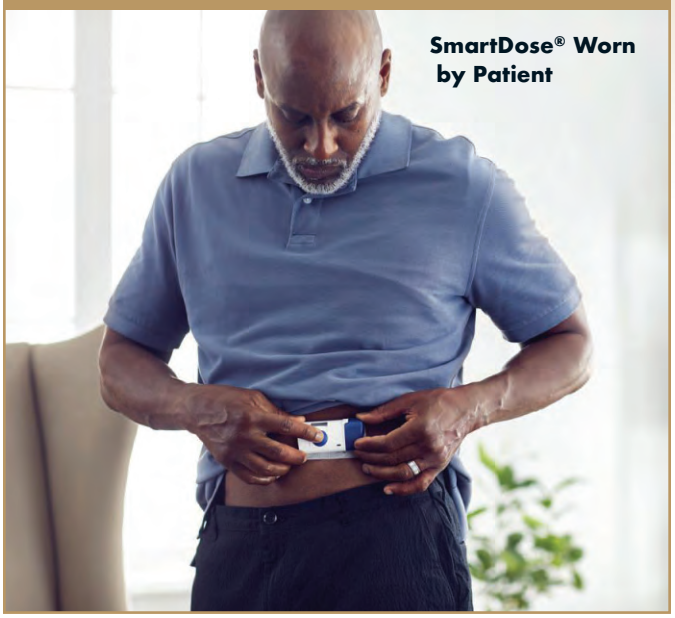
KEY CONSIDERATIONS

When assessing challenges that impact combination product development, the following relevant topics should be of central concern: maintaining the integrity and quality of the medicine; following regulatory standards and guidance; accounting for human factors and user needs; containment; and delivery/administration modality.

CHALLENGES

While many of the challenges relevant to the development and delivery of combination products are also applicable to individual therapies, potential risks can be heightened given the inherently complex nature of such products. Common challenges include:

FIGURE 1



Regulatory Landscapes around the world are complex and constantly evolving; it can be difficult to feel fully informed on current regulations and guidance particularly around combination products. In fact, a customer survey conducted by West revealed that the dynamic regulatory landscape is often the greatest challenge pharmaceutical companies face specific to combination products.

The final rule on current Good Manufacturing Practice (cGMP) requirements for combination products (21 CFR Part 4) was issued in January 2013, and since then, many draft guidances and other regulations have been introduced, including the EU Medical Device Regulations (MDR) being implemented in 2020. Staying abreast of and responding to these changes is a significant and common hurdle for many of our customers.

Similarly, different regulatory definitions exist for medical devices and combination products, and these definitions and distinctions can be confusing. When bringing a combination product

to the market, it is imperative that definitions and terminology are understood to ensure that the development team stays on the same page. Further, different regions/countries have unique standards and processes for regulatory submission, so developers must have an understanding of the relevant standards for those locations in which a combination product is intended to be launched.

Today's combination products also mean that device and drug(s) must be developed in parallel. This relates to regulatory requirements in terms of the process for defining a product's primary mode of action (PMOA), which serves to establish its regulatory and product development framework.

Also, as appropriate, the Design History File (DHF) must be updated to validate and maintain a device throughout its lifecycle. It is important to ensure that all DHFs are compliant to new regulatory requirements and standards. This has particular importance for legacy products.

Device Challenges, including those that stem from disconnect between drug and device or packaging development, can lead to impaired product functionality. A patient receiving a medicine that is safe and accurate depends largely on the reliability and robustness of a device as the delivery vehicle, in addition to any other packaging components.

The testing involved in identifying and overcoming device challenges must include extensive environmental and human factors testing. How a device and a drug interact is a central consideration for combination products. In order to fully and precisely understand how one component impacts the other, drug and device producers need to work closely together from as early as possible in the development process to ensure the correct materials and mechanism of administration are utilized.

Drug volume is another key device consideration as larger doses (by volume/size) can pose greater challenges. Patient self-administration of higher volume, higher viscosity systems is a relatively new concept and has triggered the need for systems that can accommodate accordingly – but keeping up with the evolving demands can be difficult.

Consistent & Optimized Product Integrity & Quality depend on myriad factors that can be difficult to mitigate or control. Drug containers and delivery systems are deeply intertwined with the product that ultimately reaches the end-user – even more so with combination products – and all of the resources used to put a needed medicine in the hand of a user are at best for naught if the quality is diminished, and at worst can pose risk for patients.

However, where there are challenges there are not only solutions – but opportunities.

SOLUTIONS

The aforementioned challenges described are routinely experienced by pharmaceutical and device manufacturers working in the combination products space. Fortunately, meaningful solutions are possible through streamlined development processes, successful testing and control, and synergistic practices essential to success.

Paving a Smoother Road from Concept to Patient

In an ever-changing landscape, it is always important to drive innovation by keeping the end intention closely in mind. This means commencing development with a comprehensive understanding of a drug target product profile, as well as user/patient needs – and having protocols in place to keep this in sight.

Doing so also involves forethought and preparedness from a risk management standpoint – implementing practices and processes to identify hazards, anticipate and analyze potential hurdles, mitigate and manage risk, and monitor and measure outcomes.

Specific to overcoming challenges with patient-administered combination products with larger drug volumes, recent innovation is starting to transform the possibilities with wearable devices that deliver medicine subcutaneously. While combination product manufacturing and packaging challenges will continue to evolve as the type and volume of drugs change, ap-

FIGURE 2

A polypropylene plunger rod for use in combination with the Daikyo Crystal Zenith® 1 mL Insert Needle Syringe.

FIGURE 3

Daikyo Crystal Zenith® Polymer Ready-To-Use Syringe Systems

proaches that allow for more patient-centered care continue to progress.

Taking an Integrated & Collaborative Approach

Above all, therapies cannot be developed and delivered to patients in a silo. All involved parties – those creating the medicine(s), those creating the packaging, and those tasked with administration (be it healthcare professionals, patients, and/or caregivers) – must work together with cooperation and transparency to ensure alignment across health, strategic and tactical priorities, visions, and goals.

We've learned that an integrated approach can lead to a solution that overcomes any number of challenges specific to combination product development and delivery. That's why we have implemented an Integrated Solutions program in an effort to help our customers navigate the entire journey as they research, design, and deliver a combination product. This approach synthesizes our primary packaging, device, analytical testing, regulatory guidance, and contract manufacturing expertise in a single-source solution.

From a regulatory standpoint, understanding and keeping abreast of relevant governance – as it applies to a broad range of devices and containers – is essential. Drug companies can and often do look to the device manufacturer/provider for guidance and input, particularly when filing. We maintain current expertise and capabilities to support customers not only in navigating global regulations impacting combination product development, but also in designing and performing the studies needed to demonstrate required compliance from development through and post-commercialization.

It's also imperative for device/packaging manufacturers to work with clients to enhance their understanding of current regulations and standards in order to create, execute, and interpret proper study designs – covering syringes, cartridges, vials, and all related components and devices. On our side of the development equation, we, as device and packaging producers, bring expertise of industry regulations and standards to help our customers and their products succeed.

The synergy and collaboration required for combination products differs from approaches taken when drugs and devices are developed separately for individual products.

Improving Quality

Consistently producing and delivering the highest quality medicine(s) and devices requires rigorous testing that aims to identify and reduce risks, follows standards and focuses on continuity – ultimately enabling the long-term, safe, and efficient delivery of drug products to patients.

From extractables, leachables, and particle analysis to product purity and stability, rigorous and complex testing is essential to ensuring the quality and integrity of a product is upheld from creation to delivery.

Whenever possible, testing to measure these factors should be conducted per

industry standards – or, in cases when specific standards don't yet exist for a given combination, testing should be based on related standards and factor in all the critical parameters of the drug preparation and delivery process.

Design verification studies for combination products can include and focus on the evaluation of physical aspects of device component performance, evaluation of physiochemical interactions with the drug product, risk reduction, and adherence to established standards and regulatory requirements/guidances. When properly executed, highest quality and rapidly approved/marketed products are the result.

Verification testing for combination products also serves to confirm that a device has been designed correctly, functions as intended, and performs reliably against external factors specific to the intended patient population, as well as drug specifications. It also evaluates the integrity of the product in worst-case conditions – such as drops, extreme temperature swings, and exposure to moisture. Further, how and where end-users interact with a device must be closely examined to determine and finesse device reliability.

CASE STUDY: SMARTDOSE® DRUG DELIVERY PLATFORM

West's SmartDose® drug delivery platform, which was developed to allow for patient self-administration in accordance with individual prescriptions, has evolved through three generations to accommodate changing patient and combination drug delivery needs.

KEY LEARNINGS FOR CONTINUED PROGRESS

The path to bringing a combination product to market is lengthy and complex, and one best navigated through partnerships that leverage respective expertise. And, as with any medicine, the universal goals from a healthcare standpoint are to develop and deliver needed medicines that are optimally safe, effective, accessible, user-friendly, and ultimately help improve patients' lives.

While safety and efficacy are first-and-foremost paramount to the potential success of any treatment regimen, quality packaging is also highly critical and closely tied to safety and efficacy. Not only can it impact these elements, but it can also influence adherence for patient-operated products.[1] This is particularly relevant to combination therapies, which tend to involve more complex delivery systems.

A co-packaged combination product must function and be evaluated as a system, rather than individual components, and requires testing to establish successful drug delivery. Proper, comprehensive testing must be designed to account for both treatment preparation, packaging, and administration utilizing all intended components and materials. Further, functionality, compatibility, and human factors must be carefully evaluated to demonstrate that all device/container components as well as the drugs work together for a desired outcome.

Combination drug development pipelines continue to rapidly expand and diversify with differentiated molecules and formulations – which can call for nuanced as well as significant packaging and delivery system requirements. An overarching flexibility and willingness to innovate and partner are also critical to anticipating and meeting the needs of an ever-growing and expanding market. ◆

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1. Conn VS, Ruppar TM, Chan KC, Dunbar-Jacob J, Pepper GA, De Geest S. Packaging interventions to increase medication adherence: systematic review and meta-analysis. Curr Med Res Opin. 2015;31(1):145–160. doi:10.1185/03007995.2014.978939. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4562676/.

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BIOGRAPHY

Tom McLean has served as Vice President, Development Engineering, R&D Innovation and Technology at West Pharmaceutical Services, Inc. since 2016, with responsibility for the development of West delivery system products from concept through product design, verification, and validation. He has been working at West since the acquisition of Tech Group in 2005 and has held various senior leadership positions during this time in development engineering - leading product realization, program management, sampling, and business systems. He is a member of ISO/TC 84 (Devices for Administration of Medicinal Products & Catheters). Mr. McLean earned his BS in Mechanical Engineering from Purdue University.

Technology & Services
SHOWCASE

CONTRACT MANUFACTURING

AbbVie Contract Manufacturing has been serving our partners for more than 40 years across ten of our manufacturing facilities located in both North America and Europe. Our contract development and manufacturing capabilities span both small and large molecule API, including classical fermentation, chemical synthetic, biologics, and ADCs. In addition to APIs, we are offering extensive experience and technical solutions in the area of drug product manufacturing, which includes traditional tablet and capsule production with emphasis, potent and hot melt extrusion. Lastly, we can also package your product regionally and offer aseptic fill/finish including prefilled syringe & vial manufacturing capabilities.For more information, visit AbbVie Contract Manufacturing at www.abbviecontractmfg.com or email us directly at **abbviecontractmfg@abbvie.com.**

CDMO SERVICES

Ajinomoto Bio-Pharma Services is a fully integrated contract development and manufacturing organization with sites in Belgium, United States, Japan, and India providing comprehensive development, cGMP manufacturing, and aseptic fill finish services for small and large molecule APIs and intermediates. Ajinomoto Bio-Pharma Services offers a broad range of innovative platforms and capabilities for pre-clinical and pilot programs to commercial quantities, including: Corynex® protein expression technology, oligonucleotide synthesis, antibody drug conjugations (ADC), high potency APIs (HPAPI), biocatalysis, continuous flow manufacturing and more. Ajinomoto Bio-Pharma Services is dedicated to providing a high level of quality and service to meet our client's needs. For more information, contact Ajinomoto Bio-Pharma Services at **www.AjiBio-Pharma.com.**

FORMULATION DEVELOPMENT

Ascendia Pharmaceuticals is a speciality CDMO dedicated to developing enhanced formulations of existing drug products, and enabling formulations for pre-clinical and clinical-stage drug candidates. We specialize in developing formulation solutions for poorly water-soluble molecules and other challenging development projects. Combining our extensive knowledge and experience of formulation capabilities with our suite of nano-particle technologies, we can assess the feasibility of a broad array of robust formulation options to improve a drug's bioavailability. Thusly decreasing the amount of drug and the number of injections and greatly reducing in some cases the daily pill-burden from 20 to 4. Ascendia's expertise spans across (IV, SC, or IM), injection, ophthalmic, transdermal, nasal delivery, along with immediate- and controlled-release products for oral administration and complex generics. For more information, visit Ascendia at **www.ascendiapharma.com.**

PARENTERAL DELIVERY DEVICES

FOR BETTER TREATMENT OF CHRONIC DISEASES. Across the healthcare continuum, BD is the industry leader in parenteral delivery devices that help health systems treat chronic diseases. We not only continually advance clinically proven, prefillable drug delivery systems, we do so with a vision to help healthcare providers gain better understanding of how patients self-inject their chronic disease therapies outside the healthcare setting. This is why we partner with leading pharmaceutical and biotech companies worldwide to develop digitally-connected self-injection devices — including wearable injectors and autoinjectors — to capture valuable data that can be shared with caregivers. Discover how BD brings new ideas and solutions to customers, and new ways to help patients be healthy and safe. For more information, visit BD Medical — Pharmaceutical Systems at **bd.com/Discover-BD1.**

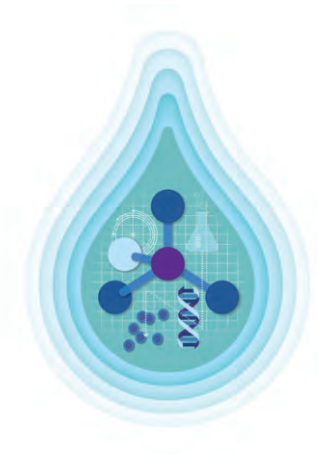
Technology & Services Showcase

Platform Technology

CAPTISOL®

Captisol is a patent-protected, chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. Captisol was invented and initially developed by scientists in the laboratories of Dr. Valentino Stella at the University of Kansas' Higuchi Biosciences Center for specific use in drug development and formulation. This unique technology has enabled 11 FDA-approved products, including Onyx Pharmaceuticals' Kyprolis®, Baxter International's Nexterone®, and Merck's NOXAFIL IV. There are more than 30 Captisol-enabled products currently in clinical development. For more information, visit Captisol at **www.captisol.com.**

Bioavailability & Development Toolkit



From its three early phase drug development centers of excellence in Nottingham, UK, Somerset, NJ, and San Diego, CA, and its network of manufacturing facilities, **Catalent** offers its customers end-to-end solutions, encompassing early drug product formulation and dose form design, through to clinical supply services, commercial-scale manufacturing and lifecycle management. For early development, these solutions include analytical, preformulation, and formulation technologies, and Catalent offers the most comprehensive bioavailability-enhancing technology toolkit, including lipid formulation, spray drying and hot melt extrusion. Its experience sees Catalent support the development and launch of over 100 new products every year. By adapting for each molecule's unique characteristics and challenges, Catalent uses its expertise and a wide range of tools and technologies to create dose forms that benefit patients. For more information, contact Catalent Pharma Solutions at (888) SOLUTION or visit **www.catalent.com.**

Differentiated Injectable Delivery

Credence MedSystems is a medical technology company focused on delivering medications safely for the benefit of our patients, caregivers and partners. The Companion Safety Syringe System was born from Credence's core philosophy of *Innovation Without Change*. By providing passive safety and reuse prevention while using existing primary package components, the Companion offers best-in-class drug delivery with a vastly simplified path to market for our biotech and pharmaceutical partners. The Companion is available in luer needle, staked needle and dual chamber reconstitution configurations. In all cases, the user performs the injection, receives end-of-dose cues and then the needle automatically retracts into the syringe, which is then disabled. For more information, contact Credence MedSystems at 1-844-CMEDSYS, email info@credencemed.com, or visit **www.CredenceMed.com.**

Testing Services

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DDL is an independent third-party, ISO 17025-accredited testing laboratory that provides package, medical device, and combination products testing. For nearly 30 years, DDL has provided extraordinary service and specialized testing expertise to the medical device and pharmaceutical industries. We employ a team of engineers, technical, and quality experts devoted to helping our customers bring medical device and combination products to market. Our single source, totally integrated approach enables organizations of all sizes from start-ups to globally recognized corporations maximize product performance, reliability, and safety while seamlessly achieving regulatory compliance. We work hard to build strong partnerships with our clients and have an unwavering commitment to assist in getting products to market on time. For more information, visit DDL at **www.DDLTesting.com**.

Technology & Services Showcase

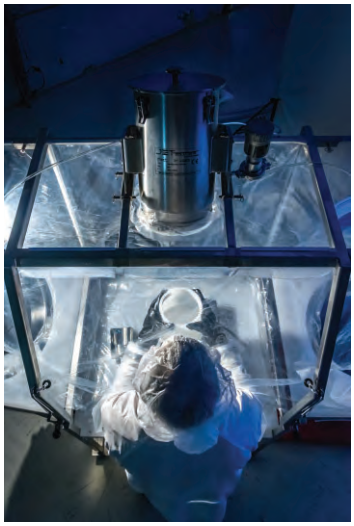
Formulation Technology

Enteris BioPharma is an independently operated and wholly owned subsidiary of SWK Holdings Corporation [NASDAQ: SWKH]. The organization's headquarters and 32,000- square-foot cGMP manufacturing facility is based within the heart of New Jersey's "Life Sciences Corridor." Through its pioneering and proprietary Peptelligence® technology, Enteris BioPharma partners with pharmaceutical and biotech organizations to develop bespoke solutions, including robust oral formulation development and clinical cGMP manufacturing. For more information, visit Enteris BioPharma at **www.enterisbiopharma.com.**

Formulation Support, Lipid-Based Technologies

With application and R&D Centers in the United States, France, India, and China, the **Gattefossé group** is providing formulation support for oral, topical, transdermal, and other routes of administration. Equipped with state-of-the-art analytical and processing instruments, we are able to support your development efforts and stay at the forefront of research both in basic and applied sciences pertaining to lipids and related drug delivery technologies. Our support covers all stages of development, from solubility screening and preclinical to late-stage formulation and "proof-of-concept" studies. Moreover, we provide extensive regulatory support, sharing toxicological and safety data, and analytical/characterization methods. For more information, visit Gattefossé at **www.gattefosse.com.**

Atmospheric Control Module



JetVent™, **ILC Dover's** atmospheric control module, provides safe, automatic, and pressurized containment for higher-potency active pharmaceutical ingredients (HPAPIs) within manufacturing-area isolators, lab areas, and for GMP chambers where airflow, temperature, humidity, and pressure differentials exist from room to room. Designed for use with isolators, including ILC Dover's ArmorFlex® Flexible Isolator, the module's precise fan speed controls negative air pressure to ensure proper flow into flexible-wall isolators, while reducing the risk of worker exposure. Key features include: Portable & Compact, Fully Automated Control, Features Vacuum Control, Includes Breach Response, and Works With Air or Nitrogen. For more information, visit ILC Dover at **www.ilcdover.com.**

Functional Chemicals

Mitsubishi Gas Chemical (MGC) is a leading company in the field of functional chemicals, such as oxygen barrier and absorbing polymers. MGC established the Advanced Business Development Division in 2015 for tackling a variety of today's problems, and the division created OXYCAPT™ Multilayer Plastic Vial & Syringe to solve some issues of existing primary packaging for injectable drugs. OXYCAPT Vial & Syringe consists of three layers. The inner and outer layers are made of cyclo-olefin polymer (COP), the most reliable polymer in the pharmaceutical industry. The middle layer is made of state-of-the-art polyester developed by MGC. The oxygen-barrier property is almost equivalent to glass and much better than COP. OXYCAPT also provides an ultra violet (UV) barrier. For more information, visit Mitsubishi Gas Chemical at **www.mgc.co.jp/eng/products/abd/oxycapt.html.**

Technology & Services Showcase

Patient-Focused Delivery Devices

With over 1,600 people and four plants across two continents, **Nemera** is a world leader in the design, development, and manufacturing of drug delivery devices for the pharmaceutical, biotechnology, generics industries. Nemera's services and products cover several key delivery routes: Ophthalmic (multidose eye droppers for preservative-free formulations), Nasal, Buccal, Auricular (pumps, valves, and actuators for sprays), Dermal & Transdermal (airless and atmospheric dispensers), Parenteral (autoinjectors, pens, safety devices, and implanters), and Inhalation (pMDIs, DPIs). Nemera always puts patients first, providing the most comprehensive range of devices in the industry, including off-the-shelf innovative systems, customized design development, and contract manufacturing. For more information, contact Nemera at information@nemera.net or visit **www.nemera.net.**

Advanced Delivery Systems

SHL GROUP

SHL Group is a world-leading solution provider in design, development, and manufacturing of advanced drug delivery systems. We work with leading biotechnology and pharmaceutical companies to develop drug delivery devices, including compact disposable auto injectors, reusable pen injectors, and complex inhaler systems. These devices use standard pre-filled syringes and cartridges, as well as novel primary containers. SHL has always invested significantly in research and development. The investment has especially intensified over the past 10 years, allowing us to upgrade our broad pipeline of next-generation drug delivery devices. These innovative devices include advanced reusable and disposable injectors that can be enhanced through digital implementations and can accommodate high volume and high viscosities. Our investments have strengthened our support in the advancement of drug development and digital healthcare. For more information, visit SHL Group at **www.shl.group.**

Versatile Platform

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

Global-Leading CDMO

VETTER

Headquartered in Ravensburg, Germany, **Vetter** is a global-leading contract development and manufacturing organization (CDMO) with production facilities in Germany and the United States. Currently employing 5,000 individuals worldwide, the company has long-term experience in supporting biotechnology and pharmaceutical customers both large and small. Vetter services range from early stage development support, including clinical manufacturing, to commercial supply and numerous packaging solutions for vials, syringes, and cartridges. As a leading solution provider, Vetter appreciates its responsibility to support the needs of its customers by developing devices that contribute to increased patient safety, convenience, and enhanced compliance. Great importance is also given to social responsibility, including environmental protection and sustainability. For more information, visit Vetter at **www.vetter-pharma.com.**

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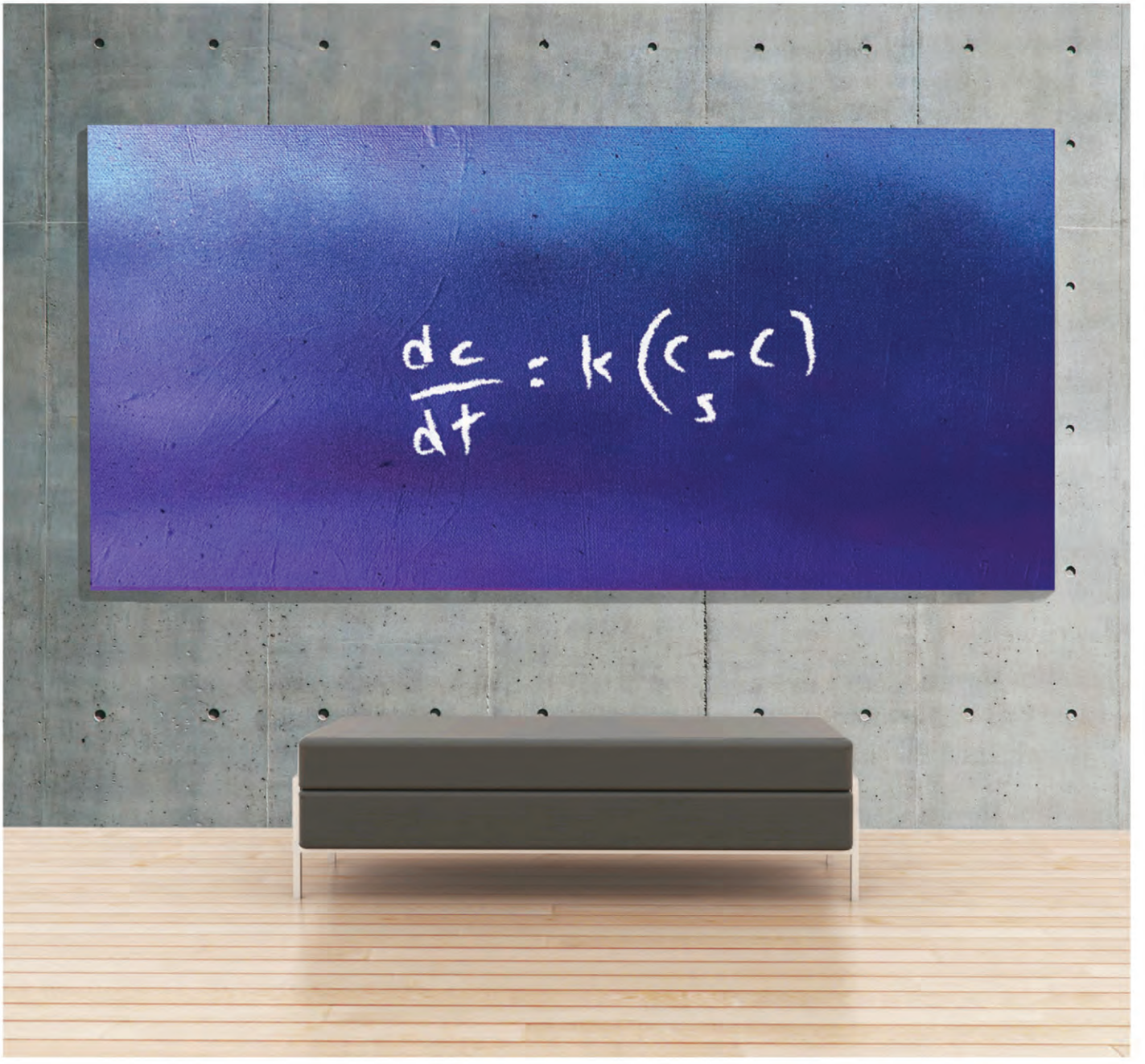

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