Drug Development® & Delivery

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

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GATTEFOSSÉ

Measuring Drug Solubility in Solid Lipids

Gelucire® | Compritol® | Geleol™

The Challenge

Solid lipid excipients are commonly applied in bioavailability enhancement and in technologies like solid SEDDS, solid lipid nanoparticles (SLN) and nano lipid carriers (NLC). A key step in formulation development is identifying suitable excipient(s) based on drug solubility and compatibility.

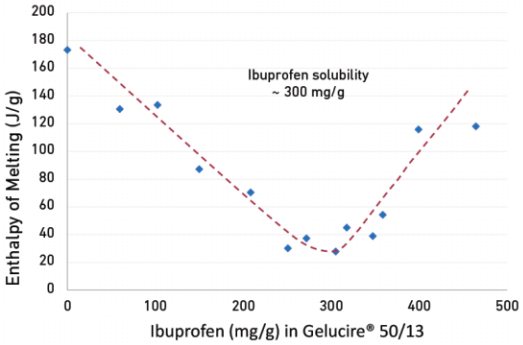
Our Solution

Combining robust analytical techniques, Gattefossé has developed a rapid screening protocol to tackle the early development hurdles. The approach helps measure saturation solubility as well as compatibility of the API in a solid/semi-solid lipid excipient within days of testing.

Solid and Semi-Solid Excipients

Gelucire® series 44/14, 48/16 and 50/13 are self-emulsifying excipients used alone or in combination with other excipients to develop SEDDS for bioavailability enhancement. Geleol™, Compritol® and Precirol® on the other hand, may be applied in SLN and NLC for a variety of drug delivery systems.

Solubility of Ibuprofen in Gelucire® 50/13 by DSC



HSM image of Ibuprofen above equilibrium solubility (375 mg/g) in Gelucire® 50/13

Contact Us

We provide the technical support you may require in various stages of drug development.

▸ gattefosse.com/measuring-saturation-solubility-in-lipid-excipients

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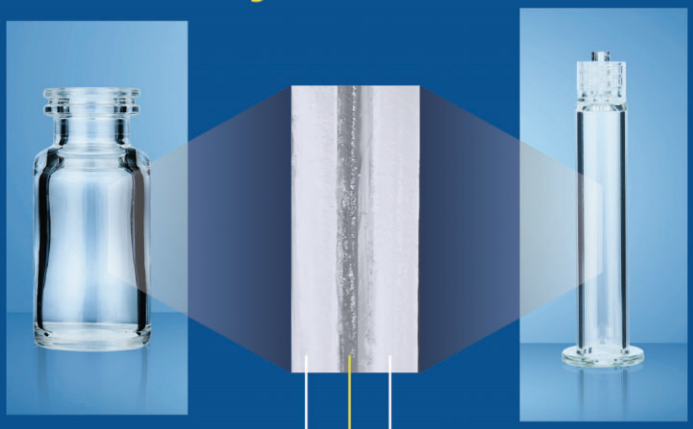
Multilayer Structure



Water Vapor Barrier Layer (COP)

Oxygen Barrier Layer (New Polymer)

Drug Contact Layer (COP)

- Excellent Oxygen Barrier
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- Very Low Extractables
- Low Protein Adsorption
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Mitsubishi Gas Chemical Company,Inc.

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

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E-mail: nb3.pharmapackage@mgc.co.jp

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LET'S MAKE A HEALTHY WORLD

WITH AJINOMOTO BIO-PHARMA SERVICES, YOU HAVE THE POWER TO MAKE.

You have the power to make a difference by delivering therapeutics that improve quality of life and inspire a healthier world. You need a manufacturing partner who has the power to make your every challenge their own and who shares your unwavering tenacity and dedication from clinical studies through commercial success. Together, we have The Power To Make.

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Prefilled Syringes & Parenteral Manufacturing

"While large molecule biologics dominate the market, the demand for small molecule parenteral products is also increasing. According to Transparency Market Research, the global small molecule injectable drugs market will expand substantially from 2017 to 2025 due to growth in generic injectables, which is outpacing that of innovator drugs, a strong pipeline of small molecule injectable drugs, and significant investment in R&D for small molecules.

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THE DIFFERENCE OF ONE READY DOSE

REDUCING MEDICATION ERRORS WORLDWIDE. Across the healthcare continuum, BD develops industry-leading technologies and parenteral delivery devices that help health systems decrease drug preparation-related medication errors. We know that providers who use industry-made, prelabeled, premeasured and ready-to-use, prefilled syringes have appreciably reduced medication errors in cases where more than 90% of parenteral drugs are in vials and ampules.[1] By working closely with more than 70 of the top 100 pharmaceutical companies worldwide, we are continuing to act on our vision to reduce medication errors, improve patient safety and efficiency and manage costs. To support this vision, we offer innovative technologies through the BD Hylok™ and BD Sterifill Advance™ prefillable syringe systems. Discover the difference one company can make. **Discover the new BD.**

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BD

1. IMS Health. IMS Health Global Midas Edition. Danbury, CT: IMS Health Inc.; 2015.

Histogen Announces Investigational Device Exemption Application

Histogen Inc. recently announced it has submitted an Investigational Device Exemption (IDE) application with the US FDA for the initiation of a Phase 1 clinical trial of HST 002 for the treatment of facial folds and wrinkles.

HST 002 is a naturally produced collagen and extracellular matrix dermal filler targeting the treatment of facial folds and wrinkles. The planned Phase 1 clinical trial is designed to assess the safety and tolerability of HST 002, as well as look for early indications of efficacy versus a placebo control.

If successful, HST 002 would be novel in the dermal filler market as it is composed of all-human and naturally produced collagen with dermal matrix proteins with the potential to reduce the risk of inflammation. In addition to clinical development of HST 002, Histogen recently announced the filing of an IND amendment for its lead product for hair loss (HST 001) and the anticipated IND filing for its joint cartilage regeneration (HST 003) product candidate in 2020.

On January 28, 2020, Histogen announced that it entered into a definitive agreement with Conatus Pharmaceuticals Inc. pursuant to which Histogen will merge with and into a wholly owned subsidiary of Conatus in an all-stock transaction. The combined company is expected to operate under the name Histogen Inc., and after closing, the combined company is expected to change its trading symbol to HSTO and trade on the Nasdaq Capital Market, and to focus on advancement of its patented technology for dermatological and orthopedic indications.

Under the terms of the merger agreement, pending stockholder approval of the transaction, Histogen will merge with a wholly owned subsidiary of Conatus, and Histogen stockholders will receive newly issued shares of Conatus common stock. The exchange ratio used to determine the number of shares of Conatus common stock issuable to Histogen stockholders pursuant to the merger will be determined using a pre-transaction valuation of $100 million for Histogen's business, based on its latest priced investment round and clinical pipeline advancement, and $35.135 million for Conatus' business, an approximately 155% premium to the 20-day volume weighted average closing share price of Conatus common stock prior to the announcement date on the Nasdaq Capital Market. As a result, current Conatus stockholders will collectively own approximately 26%, and Histogen stockholders will collectively own approximately 74%, of the combined company on a fully-diluted basis, after taking into account Histogen's and Conatus' outstanding options and warrants at the time of closing, irrespective of the exercise prices of such options and warrants, with such ratio subject to adjustment based on each company's net cash balance at closing.

The combined company, led by Histogen's current management team, will be named Histogen Inc. and be headquartered in San Diego, CA. After closing, the combined company is expected to change its trading symbol to HSTO and trade on the Nasdaq Capital Market.

Mogrify & Sangamo Announce Collaboration & Exclusive License Agreement

Mogrify Ltd and Sangamo Therapeutics recently announced they have executed a collaboration and exclusive license agreement for Sangamo to develop allogeneic cell therapies from Mogrify's proprietary induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) and Sangamo's zinc finger protein (ZFP) gene-engineered chimeric antigen receptor regulatory T cell (CAR-Treg) technology.

Mogrify's technology enables the transformation of any human cell type into any other human cell type. This transformation is achieved using transcription factors or small molecules identified using proprietary big data technologies. iPSCs and ESCs provide an evergreen starting material for the generation of Tregs, and facilitate more complex engineering and greater manufacturing scalability, potentially enabling the resulting therapies to be more cost-effective and thus more accessible to larger patient populations.

Under the terms of the agreement, Mogrify will be responsible for the discovery and optimization of the cell conversion technology from iPSCs or ESCs to regulatory T cells, and Sangamo will be granted exclusive rights to use Mogrify's technology to create Tregs from iPSCs or ESCs. Sangamo expects to then use its ZFP gene-engineering technology and therapeutic development capabilities to transform these Tregs into novel "off-the-shelf" allogeneic CAR-Treg cell therapy candidates and hopes to take them through clinical development through to registration for the treatment of inflammatory and autoimmune diseases.

Under the terms of the agreement, Sangamo will pay Mogrify an upfront payment. Mogrify is also eligible to receive potential additional payments related to development and regulatory milestones, and product sales.

The Mogrify platform takes a systematic big-data approach that leverages data from next-generation sequencing and the construction of gene-regulatory networks (DNA-protein & protein-protein), to identify, the transcription factors (in vitro) or small molecules (in vivo) needed to convert any source human cell type into any target human cell type. The Mogrify platform offers the potential to optimize cell conversions in order to deliver cells that exhibit improved safety, efficacy and scalable manufacturing profiles suitable for development as cell therapies.

Tregs are a subset of T lymphocytes and act as the key regulators of the immune system. They ensure that the immune system does not mistakenly harm healthy organs while still protecting the body from pathogenic microorganisms.

CAR-Tregs are regulatory T cells (or Tregs) which are genetically engineered with a Chimeric Antigen Receptor (CAR) to precisely target sites of autoimmune and inflammatory pathology. Sangamo's CAR-Treg platform aims to use CAR and zinc finger protein (ZFP) technologies to genetically engineer Tregs ex vivo to treat autoimmune and inflammatory diseases.

Mogrify has developed a proprietary direct cell conversion technology, which makes it possible to convert any source human cell type into any target human cell type. The platform takes a systematic big-data approach to identify, from next-generation sequencing and gene-regulatory networks, the optimal combination of transcription factors (in vitro) or small molecules (in vivo), needed to convert a cell.

Mustang Bio Receives Advanced Therapy Medicinal Product Classification

Mustang Bio, Inc. recently announced that the European Medicines Agency (EMA) has granted Advanced Therapy Medicinal Product (ATMP) classification to MB-107, Mustang's lentiviral gene therapy for the treatment of X-linked severe combined immunodeficiency (XSCID), also known as bubble boy disease. The US FDA previously granted Regenerative Medicine Advanced Therapy (RMAT) designation to MB-107 for the treatment of XSCID in August 2019.

EMA grants ATMP classifications to new therapeutics that are based on genes or cells and intended as long-term or permanent therapeutic solutions to acute or chronic human diseases at a genetic, cellular, or tissue level. The ATMP program provides specific regulatory guidelines for preclinical development, manufacturing, and product quality testing of ATMPs and offers incentives, including fee reductions for regulatory advice, recommendations, and evaluation and certification of quality and non-clinical data.

Manuel Litchman, MD, President and Chief Executive Officer of Mustang, said "We are extremely encouraged that the EMA has granted MB-107 with ATMP classification, an important step in establishing our path to market approval and commercialization in Europe. This classification complements the RMAT designation we received last year from the FDA and brings us closer to realizing our goal of commercializing MB-107 for XSCID patients, as these patients are in desperate need of innovative and potentially curative treatment options."

MB-107 is currently being assessed in two Phase 1/2 clinical trials for XSCID: the first in newly diagnosed infants under the age of 2 at St. Jude Children's Research Hospital (St. Jude), UCSF Benioff Children's Hospital in San Francisco and Seattle Children's Hospital and the second in patients over the age of 2 who have received prior hematopoietic stem cell transplantation at the National Institutes of Health. Under a licensing partnership with St. Jude, Mustang intends to develop the lentiviral gene therapy for commercial use as MB-107.

Mustang Bio, Inc. is a clinical-stage biopharmaceutical company focused on translating today's medical breakthroughs in cell and gene therapies into potential cures for hematologic cancers, solid tumors, and rare genetic diseases. Mustang aims to acquire rights to these technologies by licensing or otherwise acquiring an ownership interest, to fund research and development, and to out-license or bring the technologies to market. Mustang has partnered with top medical institutions to advance the development of CAR T therapies across multiple cancers, as well as a lentiviral gene therapy for XSCID. Mustang is registered under the Securities Exchange Act of 1934, as amended, and files periodic reports with the US Securities and Exchange Commission. Mustang was founded by Fortress Biotech, Inc. (NASDAQ: FBIO). For more information, visit www.mustangbio.com.

Esperion Announces Development & Commercialization Agreement With Otsuka Pharmaceutical

Esperion recently announced it has entered into a collaboration agreement with Otsuka Pharmaceutical Co., Ltd. for the development and commercialization of NEXLETOL and NEXLIZET tablets in Japan. Both medicines were recently approved in both the US and EU.

The collaboration advances the commitment of both companies to provide cost-effective, oral, once-daily, non-statin LDL-cholesterol (LDL-C) lowering medicines for hypercholesterolemia patients in Japan. This development and commercialization collaboration combines Esperion's expertise in lipid management with Otsuka's deep cardiovascular drug development and commercialization expertise in Japan.

Under the terms of the agreement, Esperion will grant Otsuka exclusive rights to NEXLETOL and NEXLIZET tablet development and commercialization in Japan. Otsuka will be responsible for all development, regulatory, and commercialization activities in Japan. In addition, Otsuka will fund all Japan-specific development costs associated with the program. Esperion estimates this amount to total up to $100 million over the next few years. Esperion will receive an upfront cash payment of $60 million as well as up to an additional $450 million in total development and sales milestones. Esperion will also receive tiered royalties from 15 percent to 30 percent on net sales in Japan.

"We are thrilled to partner with Otsuka, one of the leading pharmaceutical companies in Japan. Otsuka shares our vision of the potential for convenient oral, once-daily, non-statin LDL-C lowering medicines to help hypercholesterolemia patients in Japan," said Tim Mayleben, President and Chief Executive Officer of Esperion. "Otsuka's history of successfully commercializing cardiovascular medicines in Japan, and overlapping healthcare provider targets make this a highly synergistic collaboration. This collaboration continues the evolution of Esperion to a truly global research and development driven commercial pharmaceutical company and further validates the global value of our medicines."

Makoto Inoue, President and Representative Director of Otsuka Pharmaceutical, added "We aspire to become an indispensable company for patients, physicians, and others around the world. If approved in our home market of Japan, bempedoic acid will represent another step forward in our fulfillment of that aspiration."

High levels of LDL-C can lead to a build-up of fat and cholesterol in and on artery walls (known as atherosclerosis), potentially leading to cardiovascular events, including heart attack and stroke. In the US, 96 million people, or more than 37%of the adult population, have elevated LDL-C. There are approximately 18 million people in the US living with elevated levels of LDL-C despite taking maximally tolerated lipid-modifying therapy — including individuals considered statin averse — leaving them at high risk for cardiovascular events. In the US, more than 50% of atherosclerotic cardiovascular disease (ASCVD) patients and heterozygous familial hypercholesterolemia (HeFH) patients who are not able to reach their guideline recommended LDL-C levels with statins alone need less than a 40% reduction to reach their LDL-C threshold goal.

HALIX Enters Collaboration for GMP Manufacturing of a COVID-19 Vaccine

HALIX B.V. has recently joined a consortium of partners under the guidance of the University of Oxford, to provide GMP manufacturing services supporting the large scale production of a COVID-19 vaccine (ChAdOx1 nCoV-19), being developed by the University's Jenner Institute. This GMP manufacturing scale-up is taking place alongside early phase clinical trials. The trials are crucial in testing whether the vaccine is proven to be effective.

The nCoV-19 vaccine is based on the Jenner Institute's adenovirus vaccine vector (ChAdOx1) technology, which was chosen as the most suitable candidate for a SARS-CoV-2 (COVID-19) vaccine as it can generate a strong single dose immune response, and is not a replicating virus, so it cannot cause infection in the vaccinated individual.

Under the collaboration, HALIX B.V. will utilize its brand new state-of-the-art GMP facilities with capacity up to 1,000 L SUB scale, applying its viral vector bioprocessing expertise, to transfer an industrial scale drug substance process from Pall in the UK, supporting the manufacture of ChAdOx1 nCoV-19 clinical trial material. Based on this transfer, HALIX B.V. and the consortium will be in a position to manufacture at a larger scale. This is a key step in decreasing the time it would normally take to make the vaccine available for deployment and could help to halt the further spread of this pandemic.

The large-scale manufacturing project is a collaborative effort, led by Dr Sandy Douglas at the Jenner Institute. The ChAdOx1 coronavirus vaccine alliance encloses viral vector manufacturing and regulatory compliance experts from the University of Oxford's Jenner Institute and Clinical Biomanufacturing Facility, the Vaccine Manufacturing and Innovation Centre (VMIC), Pall Biotech and Cobra Biologics.

Alex Huybens, Chief Operations Officer of HALIX, states "We are committed to working as one team across the industry bringing our collective expertise, track record and manufacturing capabilities, to support the Jenner Institute's rapid clinical development of this nCoV-19 vaccine candidate to combat this evolving crisis as quickly as possible."

HALIX has an established technical and quality track record for the development and GMP manufacture of viral vectors used against infectious diseases, such as HIV, ZIKA, chikungunya and the flu. Our brand new 6,700 m2 BSL2 GMP facility, located in Leiden (the Netherlands), provides both clinical and commercial scale manufacturing capabilities in fully independent, self-contained Grade B and C cleanrooms for virus products.

The clinical trial program, led by Professor Sarah Gilbert at the Jenner Institute and Professor Andrew Pollard of the Oxford Vaccine Group, will recruit up to 510 volunteers, who will receive either the ChAdOx1 nCoV-19 vaccine or a control injection for comparison. Since March 23, 2020, The University of Oxford is recruiting individuals in the UK to take part in trialing the vaccine. For further information on the vaccine, visit: https://covid19vaccinetrial.web.ox.ac.uk/.

Catalyst Biosciences Completes Phase 2b Trial of Subcutaneous Factor IX Dalcinonacog Alfa (DalcA)

Catalyst Biosciences, Inc. recently announced completion of dosing and the 30-day follow-up period for its Phase 2b trial of SQ dalcinonacog alfa (DalcA).

"We are pleased to have successfully completed the DalcA Phase 2b trial during this challenging pandemic and remain on track to report final results later this quarter," said Nassim Usman, PhD, President and Chief Executive Officer of Catalyst." "Interim trial data presented at European Association for Haemophilia and Allied Disorders (EAHAD) 2020 earlier this year clearly demonstrated the potential for DalcA to significantly change the treatment paradigm in hemophilia B; we look forward to continuing its development."

The open-label Phase 2b study was designed to evaluate the ability of DalcA to maintain steady state protective FIX levels above 12% in six individuals with severe hemophilia B. Each subject received a single intravenous dose, followed by daily SQ doses of DalcA for 28 days. Data presented at the EAHAD Congress in February showed that daily SQ dosing of DalcA achieved effective prophylaxis with FIX activity levels ranging from 14%-28% and zero bleeds. No neutralizing antibodies were detected and the treatment was well tolerated. The half-life of SQ DalcA ranged from 70-112 hours, suggesting the potential for lower or less frequent dosing.

Catalyst is a research and clinical development biopharmaceutical company focused on addressing unmet needs in rare hematologic and systemic complement mediated disorders. Our protease engineering platform includes development programs in hemophilia and a research program on subcutaneous (SQ) systemic complement inhibitors. One of our key competitive advantages is that our product candidates made using our protease engineering platform have improved functionality and potency. These characteristics allow for SQ delivery, which is less invasive, faster to treat, and more convenient than intravenous (IV) drugs currently on the market.

Our lead asset, MarzAA has completed Phase 2 development in prophylaxis and met its primary endpoint of significantly reducing the annualized bleed rate (ABR) in individuals with hemophilia A or B with inhibitors. Our second hemophilia asset, SQ dalcinonacog alfa (DalcA) is being developed for the treatment of hemophilia B and has demonstrated efficacy and safety in a Phase 2b clinical trial that has completed dosing and all participant activities.

We have an early stage Factor IX gene therapy construct – CB 2679d-GT – for Hemophilia B that has demonstrated superiority compared with the Padua variant in preclinical models. We also have a global license and collaboration agreement with Biogen for the development and commercialization of pegylated CB 2782 for the potential treatment of geographic atrophy-associated dry age-related macular degeneration. For more information, visit www.catalystbiosciences.com.

INmune Bio Announces Initiation of Clinical Program to Determine if Company's Platform May Prevent Complications of Cytokine Storm Caused by COVID-19

INmune Bio, Inc. recently announced the initiation of a therapeutic program to treat patients with pulmonary complications from COVID-19 infection with its dominant-negative TNF inhibitor (DN-TNF) platform.

The program targets patients admitted to the hospital with hypoxia who do not yet require intensive respiratory support. If successful, treatment with DN-TNF should decrease the need to transfer patients to the ICU and the need for mechanical ventilation. The company is working closely with regulatory authorities and clinical sites to get the Phase 2 program enrolling patients as quickly as possible.

"In response to reports highlighting the role of TNF in the cytokine storm of COVID-19 and the Lancet article, Trials of Anti-Tumor Necrosis Factor Therapy for COVID-19 are Urgently Needed published earlier, INmune Bio is initiating a program to treat patients with pulmonary complications from COVID-19 infection," said RJ Tesi MD, CEO and Chief Medical Officer of INmune Bio. "DN-TNF targets one of the main cytokines involved in cytokine storm without causing immunosuppression. The trial targets patients not yet in ICU or on mechanical ventilation in an attempt to keep them from needing these scarce resources."

Targeting soluble TNF with DN-TNF in patients with pulmonary complications from COVID-19 is based on three scientific pillars. Soluble TNF is an important part of cytokine storm and is elevated in hospitalized patients with COVID-19. Soluble TNF activates immune cells that contribute to hypoxia and acute respiratory distress syndrome (ARDS), which can result in the need for mechanical ventilation. Finally, soluble TNF activates endothelial cells to express VCAM-1 and ICAM-1 that signal leukocytes to leave the blood vessel and enter the tissue where they cause damage to lung tissue.

"Soluble TNF plays at least two important roles in the cytokine storm of COVID-19," says RJ Tesi. "It signals the leukocytes to come to the lung; when they arrive, it makes sure they are activated. The company believes that neutralizing soluble TNF should prevent the recruitment of new cells to the inflamed lung and decrease the activation of leukocytes that are already there."

DN-TNF is not an anti-viral therapy and is not expected to decrease viral load, ability of the participant to infect others, or length of active infection or shedding. The goal of the study is to determine if the company's DN-TNF platform will help prevent symptomatic participants from getting worse. The new program would expand the ongoing research into the DN-TNF platform, which utilizes dominant-negative technology to selectively neutralize soluble TNF, a key driver of innate immune dysfunction and mechanistic target of many diseases. DN-TNF is currently being developed for cancer (INB03), Alzheimer's (XPro1595), and NASH (LIVNate).

INmune Bio, Inc. is a publicly traded (NASDAQ: INMB), clinical-stage biotechnology company focused on developing treatments that target the innate immune system to fight disease.

Arcutis Announces Enrollment of First Patient in Phase 1/2b Study

Arcutis Biotherapeutics, Inc. recently announced it has enrolled the first patient in Phase 1/2b study of ARQ-252, a potent and highly selective topical small molecule inhibitor of janus kinase type 1 (JAK1), in adult patients with chronic hand eczema.

"Hand eczema is one of the most common skin diseases, affecting approximately 8 million Americans, and currently there are no FDA-approved therapies for this affliction," said Howard Welgus, MD, Arcutis' Chief Medical Officer. "We are delighted to begin enrollment in this Phase 1/2b study of ARQ-252, our topical JAK1 inhibitor, in adult patients with chronic hand eczema. JAK inhibition has been shown to treat a range of inflammatory diseases including hand eczema, and we believe that, due to its demonstrated potency and high selectivity for JAK1 over JAK2, ARQ-252 has the potential to treat hand eczema without causing the adverse effects that may be associated with other less selective JAK inhibitors."

The Phase 1 portion of the study will assess the safety, tolerability, and pharmacokinetics of once-daily application of ARQ-252 cream 0.3% to both hands for two weeks in six subjects with chronic hand eczema. The Phase 2b portion of the study will assess the safety and efficacy of ARQ-252 cream 0.1% once-daily and ARQ-252 cream 0.3% once-daily and twice-daily versus vehicle applied once-daily and twice-daily for 12 weeks to patients with chronic hand eczema. The company expects to begin the Phase 2b portion of the study in the second half of 2020, and expects topline data in the second half of 2021.

ARQ-252 is a potent and highly selective topical, small molecule inhibitor of janus kinase type 1 (JAK1). Many inflammatory cytokines and other signaling molecules rely on the JAK pathway, and specifically JAK1, which plays a central role in immune system function. Inhibition of JAK1 has been shown to treat a range of inflammatory diseases, including rheumatoid arthritis, psoriasis, Crohn's disease, and atopic dermatitis. The company believes that due to its high selectivity for JAK1 over JAK2, ARQ-252 will be able to effectively treat inflammatory diseases without causing the hematopoietic adverse effects typically associated with JAK2 inhibition. In 2018, Arcutis exclusively licensed the active pharmaceutical ingredient in ARQ-252 for all topical dermatological uses in the US, Europe, Japan, and Canada from Jiangsu Hengrui Medicine Co., Ltd. of China. In mid-2019, Hengrui completed a Phase 2 study in rheumatoid arthritis that used the same active pharmaceutical ingredient as in ARQ-252 but dosed orally. The results confirmed that this active pharmaceutical ingredient is a highly potent inhibitor of JAK1 based on the drug's impact on rheumatoid arthritis, and was generally well tolerated at exposures well above those expected with topical administration of ARQ-252.

Arcutis is a late-stage biopharmaceutical company focused on developing and commercializing treatments for unmet needs in immune-mediated dermatological diseases and conditions, or immuno-dermatology.

Hovione's Inhaler for High-Dose Delivery Earns Product Design Award

Hovione Technology recently announced its innovative 8Shot Dry Powder Inhaler (DPI) enabling high-dose drug delivery to the lungs has received the Red Dot 2020 Product Design Award in the Healthcare Daily Living AIDS category. The Red Dot Design Award is an internationally recognized quality seal awarded for innovative and high-quality product design.

"The Red Dot jury's experience and expertise evaluating outstanding product design and technical innovation for more than 60 years is unparalleled. This distinction awarded to our 8Shot DPI is a great success for Hovione Technology", said Peter Villax, Hovione Technology's CEO.

8Shot is the world's first 8-puff, disposable DPI enabling drug delivery of new pharmaceutical compounds requiring very high doses delivered to the lungs. It delivers therapeutic doses up to 400 mg formulated as drug alone or engineered particles in multiple, sequential inhalation maneuvers for maximum therapeutic benefit and patient safety.

"We are extremely proud and delighted to accept the Red Dot Product Design Award, together with our design and development partner WeADD," said Dr João Ventura Fernandes, Hovione Technology's Director of Technology Development and Licensing. "The 8Shot DPI is uniquely positioned to make available off-the-shelf to pharmaceutical companies a patented high payload DPI to deliver inhaled biologics, antibiotics, anti-virals, vaccines, pain or rescue treatments requiring high-dose drug delivery."

Hovione Technology's TwinMax and 8Shot dry powder inhalers are designed to enable safe and effective delivery of large doses to the lung. Featuring patented inhaler technology, TwinMax and 8Shot are compatible with drug doses up to 100 mg and 400 mg respectively, delivered conveniently to patients from multiple inhalations. Our Large Dose DPIs are suitable for inhaled delivery of biologics, antibiotics, anti-viral, vaccines, pain or rescue treatments.

Hovione Technology offers access to a complete portfolio of innovative, cost-effective dry powder inhalation devices – disposable, capsule-based, blister-based and large dose DPIs. With over 20 years of expertise developing innovative inhaler technology, Hovione Technology's team has been behind the first market approved disposable dry powder inhaler for influenza treatment in Japan, the TwinCaps DPI. Millions of patients are being treated every year with Hovione Technology's innovative inhaler technology. For more information, visit www.hovionetechnology.com.

WeADD is a Portuguese Company specialized in innovation, development, product engineering and intelligent property in small and large appliances, machinery, functional packaging and consumer electronics in sectors such as health, sports, coffee and internet of things. For more information, visit www.weadd.com.

7 Hills Pharma Announces COVID-19 Vaccine Program Targeting At-Risk Elderly

7 Hills Pharma, a clinical stage immunotherapy company focused on development of drugs for the treatment and prevention of cancer and infectious diseases, recently announced it has launched a coronavirus (COVID-19) vaccine program for older adults.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in 2019 as the cause of COVID-19, for which a global pandemic was declared in early March. The new disease is characterized by severe flu-like symptoms, and age appears to be an important risk factor for death from COVID-19. Women and men over the age of 65 have a higher reported mortality.

In response to the urgent need for an effective vaccine, 7 Hills Pharma President and CEO Upendra Marathi said his company is launching an evaluation of its lead compound 7HP349, a next-generation small molecule integrin activator, as an oral adjuvant with a novel recombinant coronavirus vaccine, laying the foundation for potential clinical testing in late 2020.

"We are looking for collaborators with clinical-stage inactivated, live attenuated, or vectored coronavirus vaccines that may be enhanced with our adjuvant for at-risk subjects, including the elderly," Marathi said.

Integrins are cell adhesion molecules essential for a productive immune response. They are critical for antigen presentation and immune priming. Prolonged integrin mediated cell adhesion improves immunologic memory.

7 Hills Pharma has developed a novel, systemic means to improve adjuvantation by triggering integrins α4β1 and αLβ2 and augmenting any antigen-specific immune responses.

"We expect our cell adhesion agents will greatly enhance the efficacy of emerging vaccines against this coronavirus," Marathi said. "Although this approach is potentially applicable for all ages, older subjects have lower immune responses to vaccines in general, and may respond particularly well."

Working with several leading universities, 7 Hills Pharma has demonstrated that 7HP349 augments prophylactic vaccine responses against influenza, Chagas disease and tuberculosis in preclinical models. Thus, 7HP349 can facilitate a more productive immune response against a variety of antigens from infectious diseases, as well as solid tumor cancers.

7 Hills Pharma is focused on the development of novel and cost-efficient immunomodulatory agents that leverage well-known integrin biology to drive and enhance essential steps in the immune cycle. The company's lead programs are designed to improve the effectiveness of immuno-oncology therapies including checkpoint inhibitors, vaccines, and cord blood transplantation in the treatment of cancers and infectious diseases. For more information, visit www.7hillspharma.com.

Roquette Launches Online Technical Platform for Researchers & Drug Developers

As virtual collaboration and knowledge-sharing have reached a new level of urgency within the scientific community, Roquette, a trusted global supplier to life science companies for over 40 years, boost its capabilities. The company has launched an online technical search platform, called Innovation Hub, along with its virtual pharmaceutical assistant, named Rosa, aimed specifically at research scientists and drug developers requiring immediate access to in-depth research and chemical formulations.

The interactive and easy-to-use digital platform is a new innovation for the company, offering product solutions to common formulation challenges in an effort to help developers achieve optimal drug processability and enhanced tabletability while reducing a drug's time-to-market.

"We recognize that the scientific community is determined to collaborate more than ever before," said Rajeev Gokhale, Head of Pharmaceutical Sciences at Roquette. "Innovation Hub supports the digital transformation happening on the bench by more rapidly addressing formulators' challenges in preclinical stages, while allowing developers direct access to our own scientists and their deep level of know-how and scientific expertise."

"We are especially pleased to be able to offer this platform to our scientific partners at a time when it's even more critical to help shorten drug development outcomes," added Kelsey Achenbach, Head of Marketing for Roquette's Global Pharmaceutical business unit. "Starting with 13 of our most trusted excipients for direct compression, we'll be adding more products featuring our complete portfolio in the months to come. We truly look forward to helping make the formulation process faster and more efficient, while making things easier for our customers to interact with our scientists in an on-demand fashion."

Innovation Hub offers scientists and developers an opportunity to analyze formulations, read existing Roquette technical research and inquire directly to the company's Customer Technical Support team with a reply turnaround timeframe of less than 48 hours. The platform's content addresses common formulation challenges ranging from encapsulation and taste-masking, to solubilization, long-term stability and timed-release considerations. Additional Roquette functional excipient product information and specialty active pharmaceutical ingredients (APIs), application examples, novel manufacturing techniques and analytical data will be available in the near future. The web-based platform is free and available to use at www.roquette.com/innovation-hub.

Roquette's commitment to the pharmaceutical industry stems from the company's desire to help its customers save and sustain patient life. As a trusted global supplier of naturally derived, raw materials to life science and pharmaceutical companies around the globe for more than 40 years, the company today offers the widest portfolio of excipients in the world as well as APIs, in addition to providing formulation solutions and technical support to customers in the pre-clinical stage. Roquette operates manufacturing sites globally with a transparent and secure supply chain, providing end-to-end solutions along with regulatory support and assistance in the compliance process.

Samsung Bioepis Announces US Launch of Oncology Biosimilar for Early & Metastatic HER2-Overexpressing Breast Cancer & Metastatic Gastric Cancer

Samsung Bioepis Co., Ltd. recently announced today that ONTRUZANT (trastuzumab-dttb), a biosimilar of the reference biologic medicine HERCEPTIN (trastuzumab) for the treatment of HER2-overexpressing breast cancer, metastatic breast cancer, and metastatic gastric cancer or gastroesophageal junction adenocarcinoma, is now available in the US. Patients should be selected for therapy based on an FDA-approved companion diagnostic for a trastuzumab product. ONTRUZANT is available in both 150-mg single-dose vials and 420-mg multi-dose vials.

The launch follows the approval from the US FDA in January 2019 for the 150-mg vial and in March 2020 for the 420-mg vial, based on Samsung Bioepis' comprehensive data package, including analytical, nonclinical, and clinical pharmacokinetic, safety, and effectiveness data demonstrating that ONTRUZANT is highly similar to its reference product HERCEPTIN, and there are no clinically meaningful differences in terms of the safety, purity and potency of the product.

"The launch of ONTRUZANT to deliver our first oncology biosimilar in the US marks an important milestone for Samsung Bioepis, and more importantly, for the patients who are in need of this proven treatment," said Christopher Ko, President and Chief Executive Officer, Samsung Bioepis. "While we understand that this is an unprecedented time for our hospitals and healthcare workers, we at Samsung Bioepis remain steadfastly committed to the patients we serve through our efforts to ensure the continued supply of our medicines through collaboration with our manufacturing and commercial partners."

ONTRUZANT will be introduced in the US at a list price (wholesaler acquisition cost) of approximately $1,325 for the 150-mg single-dose vial and $3,709 for the 420-mg multiple-dose vial (prices are rounded), representing a 15% discount to the current list price of HERCEPTIN. Wholesaler acquisition costs do not include discounts to payers, providers, distributors, and other purchasing organizations.

ONTRUZANT will be marketed and distributed in the US by Merck (known as MSD outside the US and Canada), which announced on February 5, 2020, that it intends to spin-off certain products, amongst them ONTRUZANT and its biosimilars businesses, into a new, independent, publicly-traded company. Merck will continue to fully support the commercialization of ONTRUZANT until the spin-off, which is intended to take place in the first half of 2021, at which time ONTRUZANT will become a product of the new company.

Under terms of agreement, Samsung Bioepis is responsible for preclinical and clinical development, process development and manufacturing, clinical trials and regulatory registration while Merck is responsible for commercialization activities for products approved in its partnered territories, including the US.

Beam Therapeutics Licenses SIRION Biotech's LentiBOOST Technology

SIRION Biotech GmbH recently announced that Beam Therapeutics licensed rights to use SIRION Biotech's LentiBOOST for use in their CAR-T cell products.

CAR-T cell therapy represents a promising and future-defining shift in cancer treatment. Beam Therapeutics is developing a new generation of CAR-T product candidates using its proprietary base editing technology.

Under the terms of this agreement, SIRION agreed to provide Beam with non-exclusive access to its proprietary lentiviral transduction enhancer LentiBOOST for clinical development and commercialization of Beam's portfolio of CAR-T programs. SIRION will be entitled to undisclosed upfront and milestone payments and is eligible to receive royalties on future product net sales plus license fees tied to commercial success.

Dr. Christian Thirion, CEO and Founder of SIRION Biotech GmbH, explains "LentiBOOST was engineered to improve lentiviral transduction of difficult cell types like T-cells and hematopoietic stem cells. This technology enables robust upscaling of the T-cell production process, and helps to reduce manufacturing costs by lowering the amount of lentiviral vectors needed for production of the cell product while at the same time improving clinical efficacy by increasing vector copy numbers (VCN) per cell. We are delighted that the LentiBOOST technology may help Beam further enhance the clinical success of its CAR-T pipeline."

"LentiBOOST is used in an increasing number of clinical trials in the US and in Europe and the technology is more and more considered as a gold standard in manufacturing of cell products. Our non-exclusive licensing strategy makes our technology available to a wide range of companies and research hospitals to boost the efficiency of their various clinical programs," says SVP of Business Development & Licensing, Dr. Sabine Ott.

SIRION Biotech was founded in 2005 to lead the next generation of viral vector technologies for gene and cell therapy as well as vaccine development. Now SIRION offers one of the world's most comprehensive viral vector technology platforms based on lenti-, adeno-, and adeno-associated viruses which expedites gene therapy research and advances drug development.

SIRION is becoming a partner of choice in this growing sector. LentiBOOST has been used in a number of clinical trials from early stage clinical Phase 1/2 through late-stage clinical Phase 3 trials and demonstrated clinical success in improving transduction of the therapeutic vector.

Metrion Biosciences & International Scientific Consortium Publish Data & New Recommendations for In Vitro Risk Assessment of the Cardiac Safety of New Medicines

Metrion Biosciences Limited announced it has contributed to two new peer-reviewed papers under the US FDA CiPA (Comprehensive in vitro Proarrhythmia Assay) initiative. The papers, in Nature Scientific Reports and Toxicology and Applied Pharmacology, focus on application of improved cardiac safety testing protocols and recommendations for best practice for the drug discovery industry.

The CiPA Initiative, which began in July 2013 following a workshop at the US FDA, has the objective to revise and enhance the regulatory framework assessing cardiac safety of new chemical entities. Under current guidelines, new therapeutics undergo initial assessment of proarrhythmic risk by measuring activity against the hERG cardiac ion channel, before progressing to studies in preclinical animal models and ultimately, a thorough QT interval study in the clinic. The CiPA initiative aims to extend the use of advances in early electrophysiology-based cardiac ion channel screening, in silico predictive modelling, and human induced pluripotent stem cell-derived cardiomyocytes to improve the accuracy and reduce the cost of predicting the cardiac liability of new drug candidates. Metrion's research forms part of the first stage of the proposed harmonisation work, to provide clarity on how to standardize cardiac ion channel assays to ensure they deliver consistent data for in silico models of clinical cardiac arrythmia risk.

The first paper, published in Nature Scientific Reports on March 27, 2020, by an international group of authors drawn from 20 different commercial and academic laboratories, including Metrion Biosciences, was coordinated by the Health and Environmental Sciences Institute (HESI). It reviews data from a multi-year, multi-site collaboration across industry, academia and the FDA regulatory agency to optimize experimental protocols and reduce experimental variability and bias. The goal of the study was to guide the development of best practices for the use of automated patch clamp technologies in early cardiac safety screening. High-quality in vitro cardiac ion channel data is required for accurate and reliable characterization of the risk of delayed repolarization and proarrhythmia in the human heart and to guide subsequent clinical studies and regulatory submissions.

The second paper, to be published formally in Toxicology and Applied Pharmacology paper on May 1, 2020, but currently available online, uses automated patch clamp data from the CiPA consortium to address the lack of statistical quantification of variability, which hinders the use of primary hERG potency data to predict cardiac arrhythmia. The consortium establishes a more systematic approach to estimate hERG block potency and safety margins.

Dr Marc Rogers, CSO, Metrion Biosciences, said "The Metrion team has been a participant in the international CiPA Initiative since inception and we are now pleased to be able to announce the publication of our data from this global collaborative scientific effort. We believe these projects will make a significant contribution to the eventual revision of cardiac safety testing guidelines by the FDA and other international regulatory agencies. They also contribute to deepening our knowledge of the underlying causes of proarrhythmia, which will help prevent early attrition of potentially promising drugs."

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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2019 Global Drug Delivery & Formulation REPORT

Part Three of a Four-Part Series

Part 1: A Review of 2019 Product Approvals

Part 2: Notable Drug Delivery and Formulation Product Approvals of 2019

Part 3: Notable Drug Delivery and Formulation Transactions and Technologies of 2019

Part 4: The Drug Delivery and Formulation Pipeline

By: Kurt Sedo, Vice President Operations, and Esay Okutgen, Ph.D., Director Drug Delivery, PharmaCircle LLC

Introduction

It was not so long ago when the drug delivery business model was "simple." Big Pharma discovered the drug, and drug delivery companies provided the means to optimize its performance. Big Pharma took the risks of clinical development and commercialization, and reaped the rewards while drug delivery companies contented themselves with license fees, milestones, royalties, and hopes of landing additional partners for the same platform. The script has been flipped with the genomic revolution. For diseases with a well-understood genetic cause, discovering the "drug," increasingly some sort of nucleic acid derivative, is becoming increasingly obvious. The real challenge is delivering these generally fragile therapeutics both safely and in sufficient amounts to very specific locations in very specific cells. No longer is drug delivery and formulation an improvement, it is a necessity.

Following a generation of technology commoditization, Big Pharma is once again looking for technologies to deliver these new therapeutics. Their preferred business model in dealing with "delivery" companies remains the same; license fees, milestones, and single-digit royalties, but these "delivery" companies, eschewing the label of Drug Delivery, are increasingly looking for a bigger piece of the action. With the success of smaller companies developing and commercializing new-generation therapeutics, Big Pharma has been forced to sweeten the deal.

This doesn't mean there aren't technology opportunities for small molecule therapeutics, but the opportunities and rewards have shrunk as technologies lose exclusivity and Big Pharma brings the necessary expertise in-house. The business for low-margin technologies has shifted to Service Companies that are content with lower license-related fees in exchange for manufacturing and packaging margins.

This year, nine technologies were identified as "notable" by the Technology Team: Alnylam's ESC-GalNAc-Conjugate Delivery, Emisphere's Eligen Technology, RegenexBio's NAV Vectors, PharmaCyte's Cell-in-a-Box, DBV's ViaSkin, Ensai's ImplaVax, Beta Bionics' iLet Bionic Pancreas, Lyndra's GR Oral Delivery, and Mati's Punctal Drug Delivery. Of these, four are presented in more detail later in this review.

On the deal front, perhaps Dicerna's deal with Novo Nordisk and Codiak Biosciences' agreement with Jazz Pharmaceuticals, which are discussed further, best represent the new reality. Honorable mention goes out to Halozyme who inked another attractive Enhanze licensing deal with Argenx after stepping back from developing their own proprietary pipeline. Sometimes you need to play to your strengths.

Notable Drug Delivery and Formulation Related Technology Transactions of 2019

Technology: engEx Platform
Indication(s): Cancer
Delivery Route: Injection
Licensor: Codiak Biosciences
Licensee: Jazz Pharmaceuticals
Deal Value/Upfront: Potentially >$1 billion/$56 million
Royalty: Mid-Single to High-Teens

Deal Summary: A strategic collaboration agreement focused on the research, development, and commercialization of exosome therapeutics to treat cancer. Codiak granted Jazz an exclusive, worldwide, royalty-bearing license for therapeutic candidates directed at five targets to be developed using Codiak's engEx platform. The targets include well-validated oncogenes implicated in hematological malignancies and solid tumors, but have proven to be largely undruggable. Codiak is responsible for the execution of preclinical and early clinical development of therapeutic candidates through Phase 1/2 proof-of-concept studies, Jazz thereafter. Codiak has an option to participate in co-commercialization and cost/profit-sharing in the US and Canada for up to two products. Codiak will receive an upfront payment of $56 million, up to $20 million in preclinical development milestone payments, and milestone payments totaling up to $200 million per target, plus tiered royalties.

Notable: This is not unlike "classical" drug delivery technology deals in which the licensor provides its proprietary delivery technology for application to the licensee's specified actives. The difference here is that Codiak seems responsible for the therapeutic active as well. The engEx technology can incorporate a range of therapeutic drug classes (including small molecules, proteins, peptides, cytokines, and nucleic acids) onto the surface or in the lumen of its therapeutic exosomes. The exsomes can also be engineered to optimize potency and tropism for directed delivery to desired cell types.

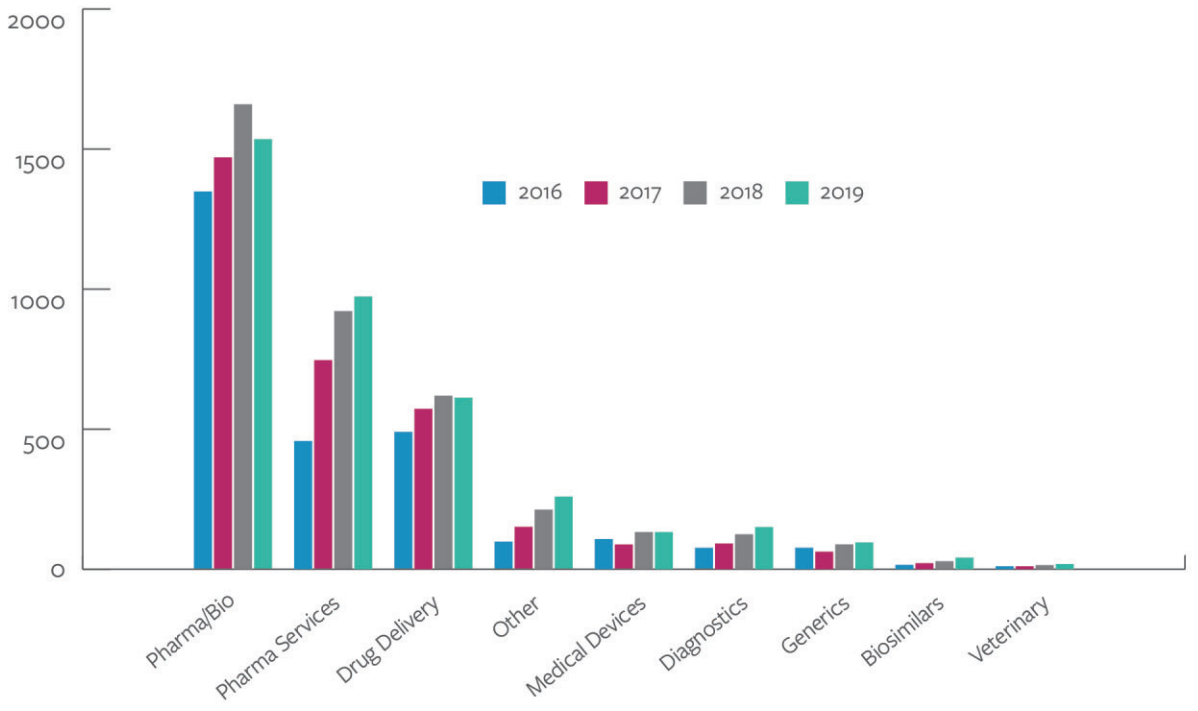
Technology: GalXC RNAi Platform
Indication(s): NASH, Type 2 Diabetes, Rare Diseases
Delivery Route: Injection
Licensor: Dicerna Pharmaceuticals
Licensee: Novo Nordisk
Deal Value/Upfront: Potentially >$1 billion/$225 million (including equity)
Royalty: Mid-Single to High-Teens

Deal Summary: The agreement is for the discovery and development of novel therapies for the treatment of liver-related cardio-metabolic diseases using the GalXC RNAi platform technology. Dicerna will conduct and fund discovery and preclinical development to clinical candidate selection for each liver cell target, and Novo Nordisk will be responsible thereafter. Dicerna receives an upfront payment of $175 million, a $50 million equity investment, $25 million annually during each of the first 3 years of the collaboration, and up to $357 million per target in milestone payments, plus tiered royalties on sales ranging from the mid-single-digits to mid-teens.

Notable: This is the second agreement signed by Dicerna with heavyweight Big Pharma companies within a month. The earlier agreement with Roche was for similar terms and targeted to Chronic Hepatitis B. The challenge addressed by Dicerna's GalXC RNAi platform is the efficient delivery of siRNA and oligonucleotide therapeutics to the targeted RNAi machinery. With the GalXC RNAi platform the challenge is handled by means of GALNAc sugars attached to the extended region of a proprietary Dicer substrate short-interfering RNA (DsiRNA-EX) molecule.

Transactions in the Pharma Sector Largely Flattened Out in 2019

Chart 1. Pharma-Related Transactions by Category (2016-2019)



Source: PharmaCircle Strategic Deals Module

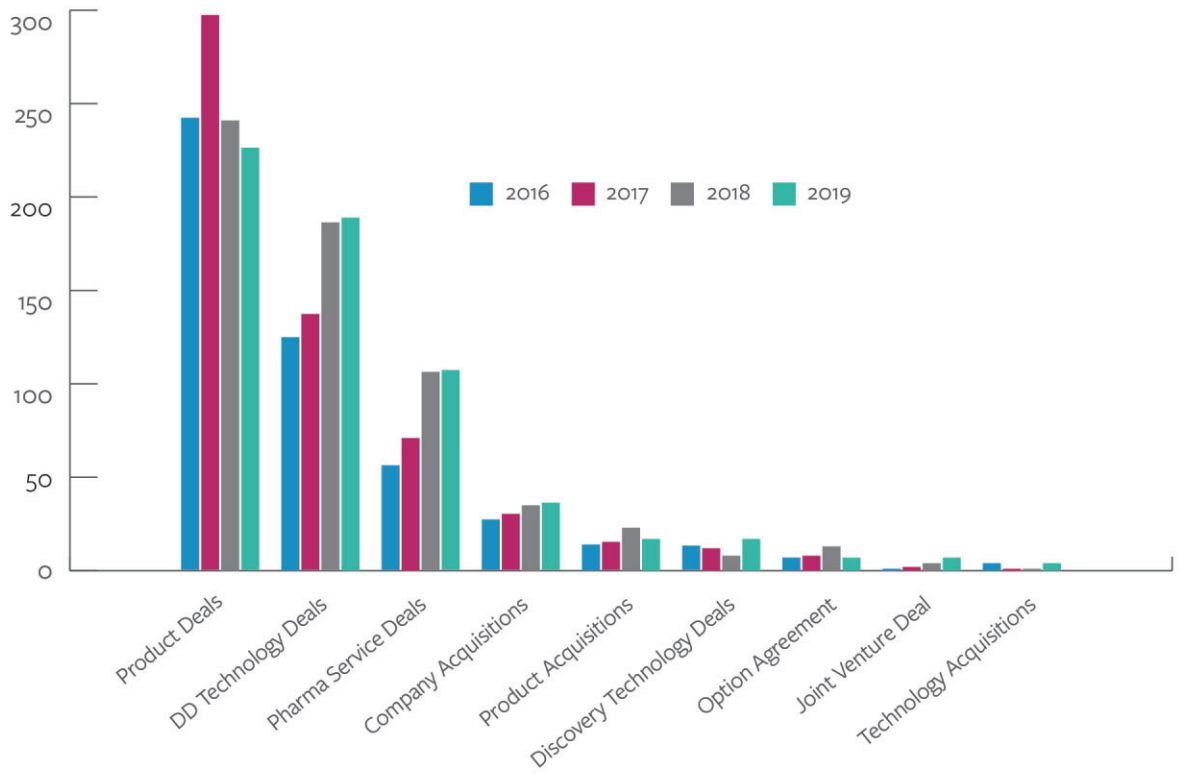
Table notes: Transaction assignments are made by PharmaCircle analysts. The transaction numbers do not include amendment or termination agreements that generally account for 10%-15% of all transactions.

This chart summarizes announced transactions, excluding termination and amendment agreements, for the past 4 years. Transactions in general showed a sharp uptick in 2017 (+20%) and 2018 (+18%) that flattened out in 2019 (0%).

- Pharma/Bio transaction totaled 1,533 in 2019 versus 1,660 in 2018.
- Pharma Services transactions continued to climb in 2019 with a total of 974 announced deals. This reinforces the sense that companies are doing more and more outsourcing, especially for access to more specialized services like vector production. The service companies are doing their part to accommodate the needs with announced expansions of facilities and the acquisition of smaller, more specialized, technology-focused companies.
- Drug Delivery transactions, 610 in 2019, have largely remained constant after a jump of 17% in 2017.
- Medical Device transactions, only those related to patient managed pharmaceutical administration, have remained relatively flat over the past few years.

Drug Delivery Technology Transactions Remained Robust in 2019

Chart 2. Drug Delivery Transactions by Transaction Type (2016-2019)



Source: PharmaCircle Strategic Deals Module

Table notes: Transaction assignments are made by PharmaCircle analysts. The numbers do not include amendment or termination agreements that generally account for 10%-15% of all transactions.

Drug Delivery-related transactions totaled 610 in 2019, little changed from 2018 (-1%), largely paralleling the overall Pharma trend. This was a change from the solid increases experienced in both 2017 (+17%) and 2018 (+8%).

- Product Deals fell in 2019 (226) falling well short of the 297 in 2017. There has been less interest on the part of drug delivery companies to take the expense and risk of developing products to advanced stages in hopes of licensing them out. Recent experience has not been kind to drug delivery companies that ventured out into product development with limited commercial success or outright portfolio failures (Nektar and Halozyme).
- The solid figures for Drug Delivery Technology Deals seen in 2019 were in large part accounted for by biologicals with an increase in gene and cell therapy-related technologies.
- The Pharma Services transactions were not necessarily associated with traditional drug delivery companies, but rather service companies that have acquired or developed their own suite of technologies and capabilities.
- Technology Acquisitions accounted for effectively nothing in 2019 (four transactions) as product development companies preferred to acquire technologies as part of a larger company acquisition or by contracting with Service Companies.

Notable Drug Delivery & Formulation Technologies of 2019

Technology: Alnylam ESC-GalNAc-Conjugate Delivery
Most Advanced Stage: Marketed (US, Europe)
Technology Category(s): Conjugates, Carbohydrate, Receptor/Carrier, Liver Targeting, Brain Targeting
Company: Alnylam Pharmaceuticals
Notable Pipeline: Lumasiran (Alnylam) Registration

Technology Summary: The technology uses novel carbohydrate conjugates and RNAi agents to target the parenchymal cells of the liver. RNAi is conjugated to an asialoglycoprotein receptor (ASGPR) ligand derived from N-acetylgalactosamine (GalNAc) via a cleavable linker. The Enhanced Stabilization Chemistry (ESC)-GalNAc-conjugate delivery platform enables subcutaneous dosing of RNAi therapeutics with increased potency and durability, and a wide therapeutic index. Once-monthly and less-frequent SC dose regimens might be possible. The technology is based on the discovery that conjugation of a carbohydrate moiety to an RNAi agent can optimize one or more properties of this agent. For example, the ribose sugar of one or more ribonucleotide subunits of an RNAi agent can be replaced with another moiety, ie, a non-carbohydrate (preferably cyclic) carrier to which a carbohydrate ligand is attached. The carbohydrate ligand is selected specifically as GalNAc for liver targeting.

Notable: This technology is the first and only one among GalNAc-RNAi conjugate technologies to have received regulatory approval, November 2019 in the US and March 2020 in Europe, (GIVLAARI for the treatment of acute hepatic porphyria). The technology has been tested for other delivery routes including oral and ocular with promising results reported for CNS delivery.

Technology: iLet Bionic Pancreas by Beta Bionics
Most Advanced Stage: Phase 2
Technology Category(s): Insulin Pumps, Combination/Incompatible, Drug Delivery Compliance
Company: Beta Bionics
Notable Pipeline: iLet Bionic Pancreas, Insulin Only (Novo Nordisk) Phase 2, Dasiglucagon Dual-Hormone Pump Therapy (Zealand Pharma) Phase 2

Technology Summary: The iLet is a pocket-size, wearable medical device that autonomously controls blood sugar in people with diabetes and other conditions. The iLet is a bihormonal system leveraging machine learning and artificial intelligence to deliver insulin and glucagon analogs for the autonomous treatment of Type 1 Diabetes. In addition to dosing insulin, the iLet doses dasiglucagon, a glucagon analog with a unique stability profile in a ready-to-use aqueous solution.

Notable: In 2019, unprecedented glycemic control was demonstrated in a first Phase 2 home-use clinical trial testing the iLet Bionic Pancreas with dasiglucagon for autonomous management of T1D. There was no device training period and no physician intervention to optimize therapy. In December 2019, Beta Bionics received Breakthrough Device designation from the FDA for the iLet Bionic Pancreas System in all configurations (insulin-only, glucagon-only, and bihormonal).

Technology: Lyndra GR, Oral Ultra Long-Acting Drug Delivery
Most Advanced Stage: Phase 1
Technology Category(s): Gastro Retentive, 3D Printing
Company: Lyndra Therapeutics
Notable Pipeline: Lyndra Ivermectin (Malaria) Phase 1, LYN-057 (Alzheimer's) Phase 1

Technology Summary: A polymeric, multi-arm device that unfolds and expands to assume a star shaped geometry when delivered to the stomach in a capsule. Upon entering the stomach, the multi-arm configuration extends, preventing further passage through the GI tract, allowing gastric residence for 7 days, potentially longer. The Lyndra GR technology enables ultra-long-acting oral therapeutic delivery, delivering small molecule therapies weekly and potentially monthly. The novel internal microarchitectures are achieved with 3-D printing technology. The arm linkages break/dissolve based on hydration pH to deliver compound in the stomach. The active is released from the system through controlled polymer matrix release technology. Following breakdown, the device residue is safely passed through the gastrointestinal system.

Notable: The technology is the result of work in the Langer lab at MIT with early and ongoing funding from the Gates Foundation. Despite the many oral sustained-release products available, there remains a significant need for therapeutics and the underlying technologies that can further simplify oral dosing particularly for compliance challenged indications. The technology may also be applicable to other delivery routes including urethral, rectal, intrauterine and vaginal.

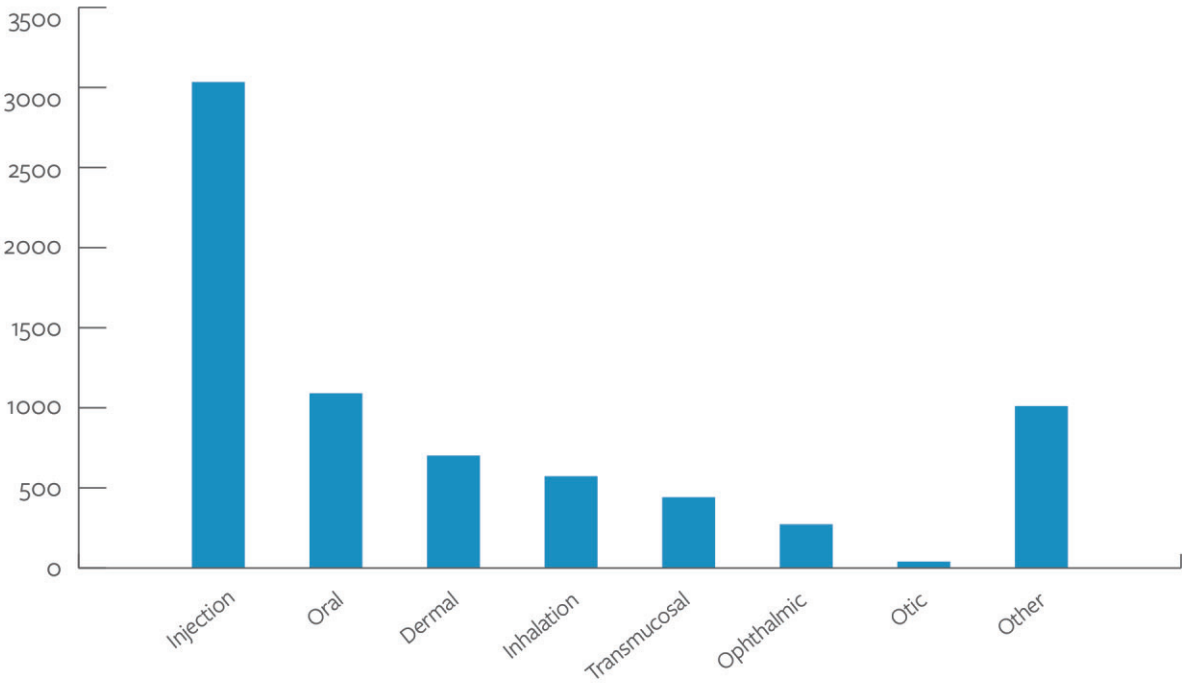
Technology: ImplaVax
Most Advanced Stage: Phase 1
Technology Category(s): Needle-Free Injectors, Reusable, Solid Dose Injectors, Biodegradable Non-PLGA Microcaps/Implants
Company: Enesi Pharma
Notable Pipeline: Shigella Vaccine (Walter Reed Army institute) Phase 1, Mumps Rubella Vaccine (Gates Foundation) Preclinical

Technology Summary: Enesi Solid Dose Injector (SDI) is a novel spring- powered needle-free injector allowing the injection of solid formulations. For vaccine delivery applications, this device/formulation combination platform is called ImplaVax. The SDI utilizes a disposable, dissolvable tip/drug cassette combination that can create a channel in the skin prior to the delivery of the drug. Features include automatic actuation and resetting mechanisms.

Notable: ImplaVax-enabled solid dose vaccines have the potential to eliminate the need for reconstitution as well as needlestick and cross-contamination hazards. Improved thermal stability would also be a major added benefit in countries where cold-chain issues and access to target populations for vaccinations can be challenging. The company has received grant funding from the Bill & Melinda Gates Foundation to support a new project to evaluate ImplaVax technology platform for enabling the development and delivery of solid dose vaccines for Measles and Rubella. In February 2020, ImplaVax was nominated in the Best New Vaccine Technology/Platform category, at the 13th Annual Vaccine Industry Excellence (ViE) Awards.

Injection Continues to be the Focus of Technology Development

Chart 3. Active Technologies by Drug Delivery Category



Source: PharmaCircle Drug Delivery Technology Analyzer Module mid-March 2020.

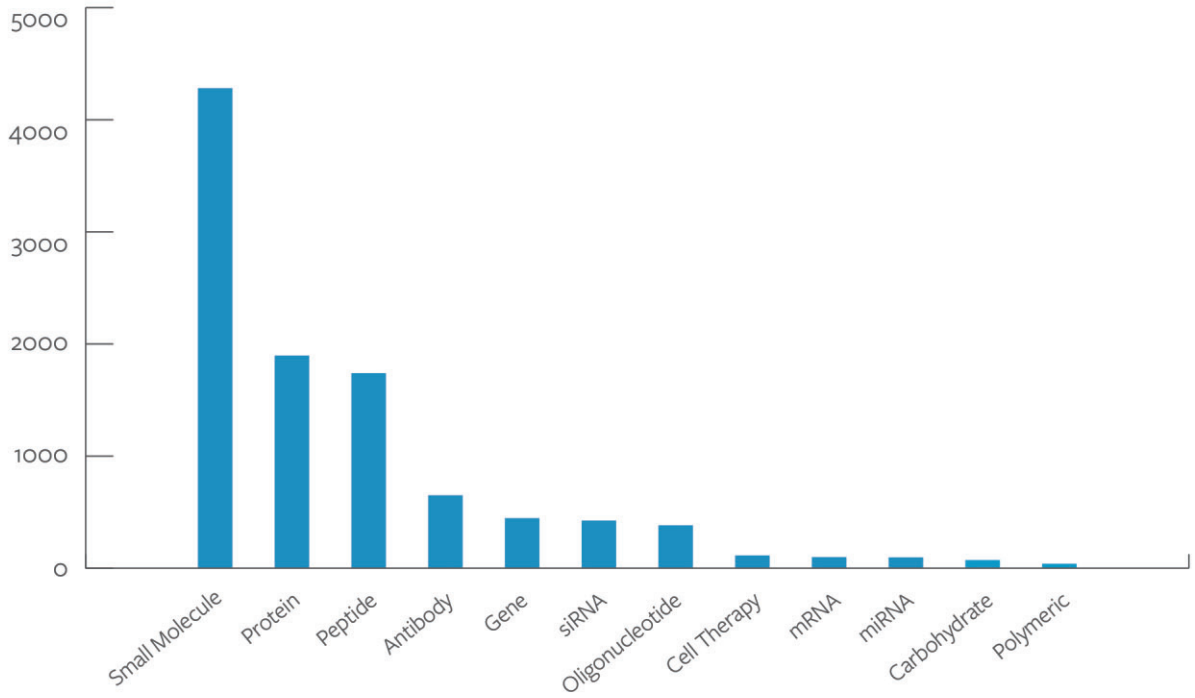
Table notes: Technology assignments are made by PharmaCircle analysts. Only technologies identified as currently active are included. Technologies can be applicable to more than one Route. Other includes a variety of technologies, such as compliance, stabilization, and production processes.

Injection technologies unsurprisingly continue to represent the largest number of active technologies perhaps because of fewer physical limitations, such as molecule size, bioavailability, stability, that represent significant challenges for other delivery routes.

- PharmaCircle has identified 5,650 discrete active drug delivery and formulation technologies. There are an additional 1,827 technologies that are considered to be inactive.
- Some 3,030 technologies are applicable to delivery by Injection. About 1,650 of these technologies are being used in products that are identified as approved or in active development at a research, preclinical, or clinical stage.
- There are 1,090 technologies applicable to Oral delivery of which 630 are associated with one or more products that are approved or in development.
- The number of active technologies applicable to Transmucosal (442) is somewhat surprising given the relatively small number of products and opportunities.
- Other refers to a variety of technologies that are not directly assignable to a delivery route and span a range of applications from compliance to super critical fluids to low dose formulations

Small Molecules Unsurprisingly Are Associated With the Most Active Technologies

Chart 4. Active Technologies by Molecule Type



Source: PharmaCircle Drug Delivery Technology Analyzer Module mid-March 2020.

Table notes: Technology assignments are made by PharmaCircle analysts. Only technologies identified as currently active are included. Technologies can be applicable to more than one Molecule Type.

Somewhat more surprising is the number of active drug delivery and formulation technologies that are identified as being applicable to peptides considering the relatively few peptide based products approved and in development.

- There are 4,282 active technologies identified as being applicable to small molecule pharmaceuticals. Almost exactly half, 2,138, are identified as being associated with one or more approved products or products in active development.
- 1,879 protein and 1,740 peptide applicable technologies have been identified. They are associated with 734 and 492 products respectively that are approved or in active development.
- There is a considerable drop-off in the number of active technologies applicable to antibody (651), gene (447), siRNA (425), oligonucleotide (383) and cell therapy (114) therapeutics.

Becton, Dickinson Leads all Companies with 69 Active Technologies

Table 1. Top Three Technology Companies by Route

Route (Number of Technologies)	Company	Active Technologies by Route	All Active Technologies
Inhalation (573)	Philips Respironics	29	35
	Vectura	20	30
	Pari	18	18
Injection (3,034)	Becton, Dickinson	63	69
	SHL	34	34
	Ypsomed	31	31
Ophthalmic (273)	EyePoint	10	13
	Alcon	10	10
	Allergan	9	11
Oral (1,091)	Teva	25	50
	Capsugel	19	22
	Catalent	16	24
Otic (56)	Aero Pump	3	7
	Mystic	3	8
	Silgan	3	7
	Ursatec	3	7
Dermal (702)	LTS Lohmann	13	16
	Foamix	10	11
	Corium	7	9
	Inovio	7	17
	Nemaura	7	8
	DJO Global	7	7
Transmucosal (442)	Aptar	16	27
	Silgan	6	7
	Nemera	5	14
	Teva	5	50
	Aero Pump	5	7
	Ursatec	5	7
	Mystic	5	8
All Technologies	Becton, Dickinson		69
	Teva		50
	Philips Respironics		35

The drug delivery and formulation space is characterized by multiple companies competing in each delivery route, with most specializing in one or at most two areas.

- Two companies that work at the interface of devices and pharmaceutical delivery, Becton, Dickinson (Injection) and Phillips Respironics (Inhalation), are the number one and three companies in terms of identified active technologies.
- Perhaps surprisingly, Teva sits in the number two position with multiple technologies in a variety of areas, including Oral, Inhalation, Injection, and Transmucosal.
- Service Companies like Aptar (27) and Catalent (24) are associated with leading positions in terms of drug delivery and formulation technologies.

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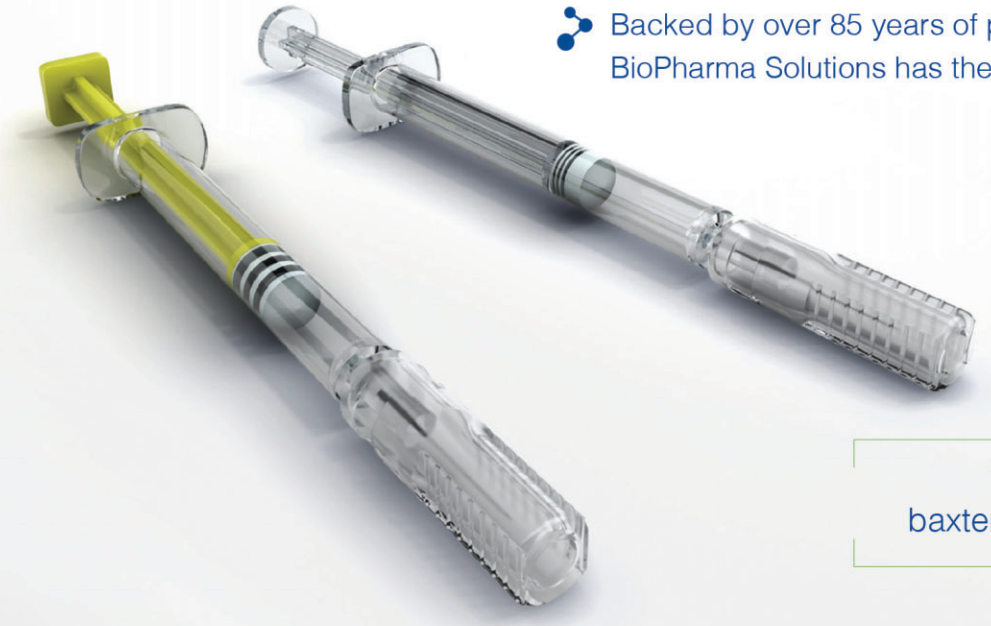

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Formulation Forum

Application of Nano-Emulsion Technology to Address Unmet Medical Needs: A Case Study of Clopidogrel IV by 505(b)(2) Pathway

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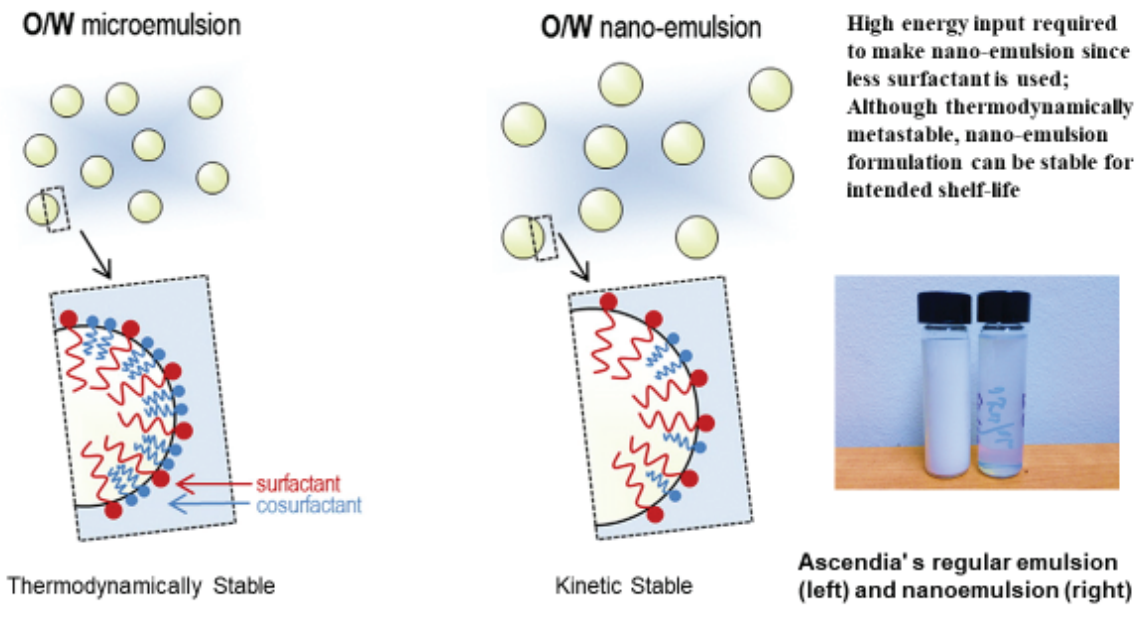
Emulsions, which are composed of nano-sized droplets dispersed in a continuous phase, can be classified into either oil-in-water (O/W) or water-in-oil (W/O). Emulsions have many practical applications in the agriculture, food, cosmetic, pesticide, and pharmaceutical industries. Emulsions can be used to deliver active ingredients by multiple routes of administration, such as topical, oral, nasal, ophthalmic, or injectables. Oil-in-water emulsions have gained significant application in the drug delivery of lipophilic drugs or nutrition supplements by parenteral, oral, and topical routes of administration, whereas water-in-oil emulsions have increased their application for delivery of hydrophilic small molecules and biologicals, such as large molecules, DNA, RNA, and peptides.

As a result of small droplet size as low as <100 nm, the large surface area, and a reduction in surface tension, nano-sized emulsions can provide unique solutions for overcoming drug solubility, permeability, and stability problems. There are two types of nano-sized emulsions: nano-emulsions, which are a kinetic stable system that only require low level of surfactant of below 10%, and micro-emulsions, which are thermodynamic system, but require a high level of surfactant up to >50%. The distinction between micro-emulsions and nano-emulsions relates to their thermodynamic stability. Micro-emulsions are thermodynamically stable due to the use of sufficient co-solvents and surfactants to prevent Ostwald ripening – essentially the coalescence of the droplets into larger particles. Ostwald ripening is the most frequent instability mechanism, although gravitational separation can also occur with larger particles.[1] Nano-emulsions contain much less of the surfactants, and as such, are meta-stable

FIGURE 1



Comparison of Regular, Micro-, and Nano-Emulsions

TABLE 1

Product	Generic Name	Route of Administration	Therapeutic Area
Diprivan®	Propofol Emulsion Injectable	IV	Anesthetic
Restasis®	Cyclosporin Emulsion Eyedrop	Ocular	Dry-eyes
Cleviprex	Clevidipine Butyrate Emulsion Injectable	IV	Hypertension
Diazepam-Lipuro®	Diazepam Emulsion Injection	IV	Anxiolytic & Sedative
Fluosol-DA®	20% Intravascular Perfluorochemical Emulsion	IV	Blood Substitute
Vitalipid®	Multivitamin Oily Injection	IV	Nutrition Supplement

Example of Marketed Emulsion Products

and more susceptible to Ostwald ripening. In addition, nano-emulsions require greater kinetic formation energy, and are usually prepared using high-pressure homogenization, microfluidics, or ultrasonic generators. However, a well-formulated nano-emulsion will maintain its physical-chemical stability through its shelf-life of at least 2 to 5 years. Because of the undesirable side-effects caused by many solvents and surfactants (in fact, the FDA places daily intake limits on such ingredients), micro-emulsions are disadvantageous compared to nano-emulsions for use in human by parenteral route.

In addition, nano-emulsions possess benefits in improving drug solubility, loading and stability, reduction of injection pain and thrombophlebitis, enabling of targeted drug delivery, and reduction of drug toxicity. A few lipid-based nano-emulsion pharmaceutical products have been marketed in the past years (Table 1).

EMULSOL™ TECHNOLOGY

A drug's low solubility often presents a serious challenge to developing bioavailable dosage forms. This challenge can be exacerbated for drugs with chemical stability issues when solubility-enhancing approaches utilize excipients that are incompatible with the drug substance. To overcome these challenges, many technologies have been developed, including particle size reduction to nanometer-size drug crystals with greater surface area for dissolution, production of amorphous solid dispersions for reducing the energy required for dissolution, and lipid-based drug delivery systems for dissolving a hydrophilic drug in either a lipid or oil phase. However, not all of these technologies are suitable when the drug is both poorly soluble and chemically unstable. In particular, the use of nano-emulsions is a growing area due to their ability to formulate poorly soluble drugs for multiple routes of administration – drops or creams for topical products, suspensions for pediatric products, and sterile, parenteral forms for injection, and to potentially shield the active ingredient from chemical degradation.[2]

Despite their advantages, nano-emulsions have certain limitations. The oil droplet particle size may increase over time via Ostwald ripening – this physical instability can lead to loss of optical clarity and potentially a decrease in drug solubility as the interfacial surface area decreases. In order to achieve physically stable nano-emulsions, long-chain triglyceride oils are sometimes employed, but typically require the use of organic co-solvents or toxic co-surfactants (eg, Cremaphor). The addition of co-solvents and co-surfactants significantly reduces the safety and tolerability profile of the pharmaceutical formulation. These excipients may not be suitable for pediatric administration, may cause injection site pain and irritation, and are becoming less acceptable in general for use in pharmaceutical formulations. With deep understanding of lipid chemistry and its interaction with drug and utilizing a tailored formulation approach, Ascendia developed a proprietary technology, EmulSolTM for production of novel oil-in-water nano-emulsions.

Ascendia's EmulSol technology produces stable, optically clear nano-emulsions without the use of organic solvents and with minimal use of surfactants using a high-pressure or microfluidic homogenization process. By selecting a specific lipid carrier in combination with a surfactant and/or co-surfactant and a unique process, Ascendia has eliminated the use of organic solvents in its formulation approach. EmulSol formulations are prepared using a robust, commercial-scale homogenization process, but with a proprietary combination of lipid carrier and surfactants – the resulting emulsion of oil droplets in the water phase is physically stable and safer for IV administration. The elimination of solvents from the formulation reduces injection site irritation and is more acceptable for pediatric, IV, and ocular products; and the minimization of surfactants improves the safety and chemical stability of the resulting nano-emulsion formulation. Ascendia has used its EmulSol technology to formulate its lead

FIGURE 2

	Aqueous Concentration (mg/ml)	Comments
Clopidogrel Free-Base	7 mg/ml @ pH 1 buffer	Highly pH dependent solubility
	0.002 mg/ml @ pH 7.4 buffer (simulated plasma pH)	Solubility crashes at higher pH
ASD-002 Nano-emulsion	> 200 mg/ml in oil phase	Formulation suitable for 505(b)(2)
	> 20-50 mg/ml loading in total volume of nano-emulsion	300-1200 mg dose can be delivered with a ~10-25 ml injection

Enhancement of Clopidogrel Solubility & Drug Loading by EmulSol™ Technology

pipeline products – ASD-002, a novel injectable form of the anti-thrombotic drug clopidogrel, and ASD-004, a clear emulsion cyclosporin eyedrop for dry eyes.

CASE STUDY OF ASD-002: INJECTABLE CLOPIDOGREL

Clopidogrel, first approved in 1997, was co-developed and co-marketed (as Plavix®) by Bristol-Myers Squibb and Sanofi. Clopidogrel is one of the leading anti-thrombotic drugs in use today, and as recently as 2011, was the second best-selling drug product in the world, achieving over $7 billion in sales that year. Clopidogrel is indicated for Acute Coronary Syndrome (ACS), and also following recent myocardial infarction, stroke, or in established peripheral arterial disease. In particular, ACS refers to unstable angina or when blood supply to the coronary arteries becomes suddenly fully or partially blocked (ie, heart attack). However, in the current medical practice, there is unmet medical need in the fast onset of P2Y12 agent in patients prior to urgent PCI procedure. When a patient presents with a suspected coronary event, a 300- to 600-mg loading dose of clopidogrel is frequently administered. However, the only commercially available dosage forms of clopidogrel are oral tablets in 300-mg and 75-mg strengths – not ideal for administration in an emergency setting. Also, when delivered orally, there is a significant delay in the time (2 to 5 hours) required for the medicine to become effective, although clopidogrel is rapidly absorbed, the time to reach peak concentration and at a low dose therapeutic effect can require several hours. Therefore, in an acute, emergency setting, for a higher dose of 300-600 mg a more rapidly acting, injectable clopidogrel dosage form is desirable.

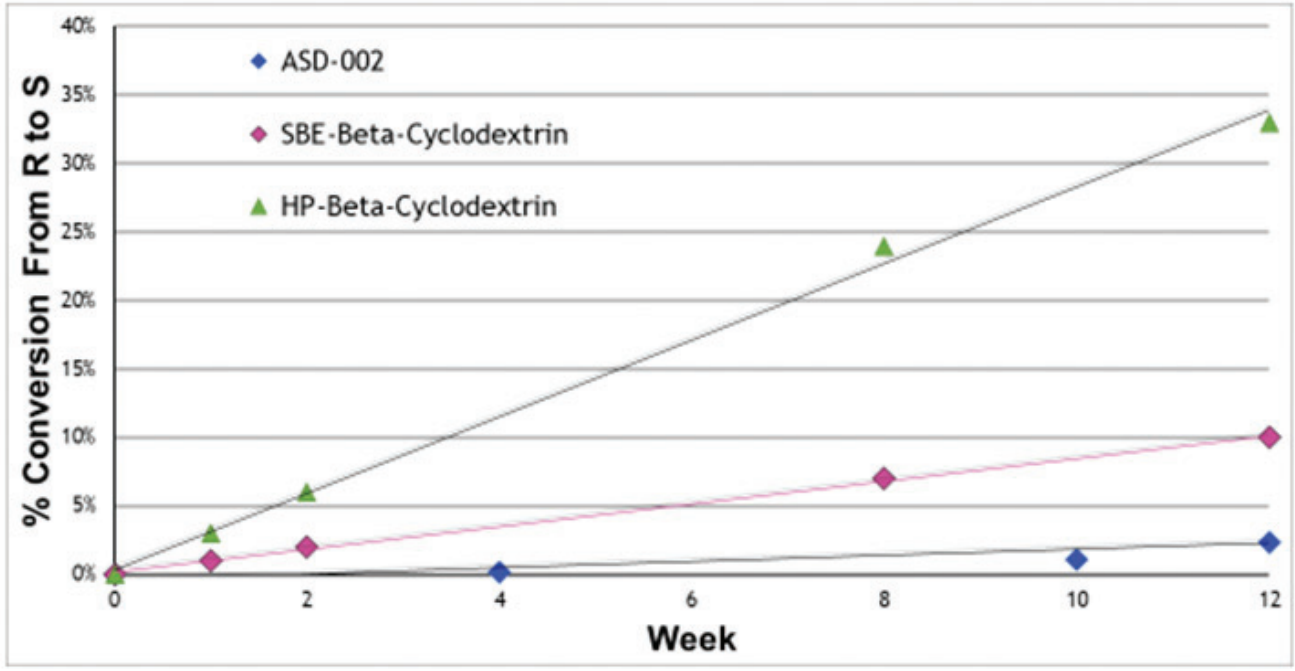
The barrier to developing such a product is due to clopidogrel's challenging solubility, physical form, and chemical stability properties. Clopidogrel is a weak base with a pKa of 4.5, and it is practically insoluble in water at neutral pH (the oral tablet composition uses the bisulfate salt form of clopidogrel, which is soluble at gastric pH, but not suitable for injection). Clopidogrel free-base is a semi-solid, viscous, oily form, thus presenting difficulties in storage, dispensing, and processing. Moreover, the free-base form is chemically unstable and undergoes both hydrolysis and oxidation. In addition, clopidogrel is a chiral molecule: only the s-enantiomer is biologically active, and chiral conversion to the r-enantiomer can easily occur in a liquid dosage form.

There have been development efforts to formulate and clinically test an injectable clopidogrel dosage form. Ligand licensed an injectable clopidogrel formulation (developed by Prism using Cydex's cyclodextrin-based technology platform) to The Medicines Company in 2011.[3] Other injectable formulations have been studied clinically.[3] And the patent literature also discloses attempts to formulate stable parenteral dosage forms.[4] However, despite the development efforts to date, and the clear unmet medical need, an injectable form of clopidogrel has not been successfully developed and approved.

Using its EmulSol technology, Ascendia has developed a novel oil-in-water nano-emulsion formulation of clopidogrel. The goal of the development program has been to demonstrate successful formulation of clopidogrel free-base in a nano-emulsion suitable for injection, having acceptable chemical and physical stability properties. Because the formulation contains no solvent, the risk of injection site pain is greatly reduced. And, even though the free-base is poorly soluble at plasma pH, when contained in the oil phase of the nano-emulsion, the clopidogrel drug substance becomes much more soluble as shown in Figure 2.

The ASD-002 nano-emulsion is prepared by a unique high-pressure and high-shear process using Ascendia's proprietary technology. Another challenging aspect of this development program is the demonstration of chemical and physical stability. Clopidogrel has several degradation pathways, including oxidation (Impurity A), hydrolysis (Impurity B), and chiral conversion (Impurity C). Ascendia has investigated the degradation pathways of clopidogrel free-base and clopidogrel bisulfate

FIGURE 3



Enhancement of Clopidogrel Chemical Stability by EmulSol™ Technology Versus Cyclodextrin Solution at 40°C/75%RH

in aqueous solution, and developed stability-indicating analytical methods. Ascendia has demonstrated physical stability of the formulation by showing minimal change in oil droplet particle size following either autoclaving the formulation, or a freeze-thaw cycle for the formulation – the mean particle size remains a consistent nano-range size. Chiral conversion to the r-enantiomer is the predominant chemical impurity. Ascendia has shown in accelerated stability studies that chiral conversion is kept within USP limits for sufficient time to provide a commercially acceptable product shelf-life. ASD-002's stability profile has been compared to other aqueous-based liquid formulations (eg, cyclodextrin-based liquid forms) of clopidogrel and demonstrates superior chemical stability with respect to all three major impurities – chiral degradation, oxidation, and hydrolysis (Figure 3).

SUMMARY

Emulsion drug delivery systems have tremendous potential for customized delivery of both lipophilic and hydrophilic drugs in different routes of administration. Nano-emulsions are particularly useful in developing liquid formulations of poorly water-soluble drugs for injectable administration. Oil-in-water nano-emulsions can be used to stabilize drugs, to increase drug loading, to reduce injection site reaction, and to achieve unique drug PK/PD profiles.

Despite the past challenges that prevent development of a soluble, stable form of the anti-thrombotic drug clopidogrel in a suitable parenteral form, using its EmulSol technology, Ascendia has successfully developed a novel oil-in-water nano-emulsion formulation of clopidogrel, whereby the insoluble and unstable free-base form of clopidogrel is converted to a form with acceptable drug loading and is protected from chemical degradation.

A ready-to-use, nano-emulsion, parenteral form of clopidogrel with a faster and higher PK/PD effect and a higher single dose >300 to 1200 mg is moving forward into development for human BA/BE studies under the NDA 505(b)(2) pathway. Ascendia is exploring further clinical development and partnering opportunities for this unique product. ◆

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LYOPHILIZATION

Process Monitoring During Freeze-Drying

By: Gregory A. Sacha, PhD

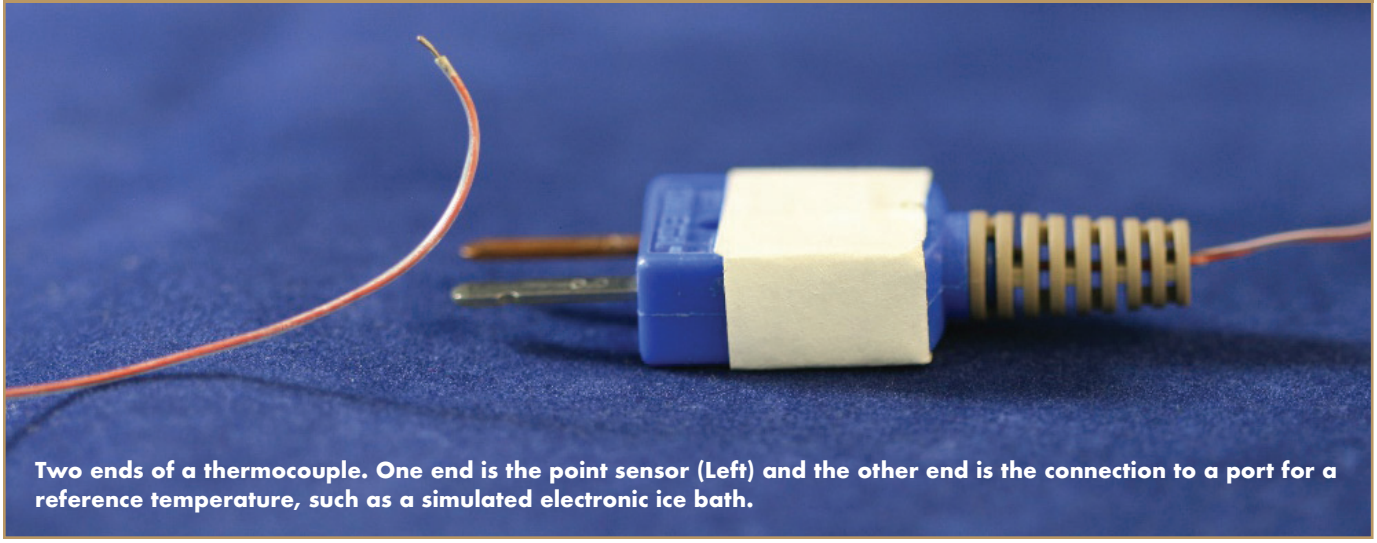
INTRODUCTION

Freeze-drying, also known as lyophilization, is the process of removing ice from a formulation through sublimation. This typically consists of three different steps during the process. First, the solution is cooled to freeze the material. Next, primary drying is conducted to remove bulk ice by establishing a pressure differential between the vapor pressure of ice at the sublimation front and the vapor pressure of ice in the condenser. This is established through manipulation of the shelf temperature and chamber pressure to control the product temperature. The temperature of the product is increased after removing bulk ice to provide energy to remove unfrozen water during secondary drying. In-process data are needed during each step to understand the effect of shelf temperature, product temperature, and chamber pressure throughout the process. These data and other types of data provide information to ensure the product temperature remains below the failure point and provide information on when each processing step is complete. The conventional methods of process monitoring include using devices that measure temperatures and pressure within the freeze-dryer. These include, but are not limited to, thermocouples, resistance temperature detectors (RTDs), capacitance manometers, and Pirani gauges. The following describes the devices used for process monitoring and how they can be used to detect end points during the process.

INSTRUMENTS FOR MONITORING TEMPERATURE

Temperature is monitored at many different locations on the freeze-dryer and may also be used for monitoring the product. There are a few different types of sensors that are used for the equipment and the product. One type of sensor is a thermocouple that consists of two wires constructed of different metals joined at the ends (Figure 1). A voltage difference is created when the ends of the wires are placed at two different temperatures and a current flows. This is known as the Seebeck effect.[1] There are different types of thermocouples that are used for different purposes (Table 1). Type T thermocouples are most often used in freeze-dryers for monitoring product temperature. Thermocouples sense temperature at the point where the wires form a junction. Therefore, they are considered point sensors. The advantage is that they are easy

FIGURE 1



Two ends of a thermocouple. One end is the point sensor (Left) and the other end is the connection to a port for a reference temperature, such as a simulated electronic ice bath.

to use and the wires are narrow and flexible.

Another type of temperature sensor is a resistance temperature detector (RTD) (Figure 2). They typically consist of a coil of fine wire, such as platinum, copper, or nickel, wrapped around a glass or ceramic core. The resistance of the metal changes in a precise, linear way with temperature. An RTD senses temperature throughout the area of the wire. Therefore, they are considered area sensors. They are bulkier than thermocouples, but are more accurate, precise, linear, and have less drift than thermocouples. Freeze-dryers are typically equipped with RTDs for all fixed temperature measurements.

A third type of temperature sensor is the Tempris® system (Figure 3).[3] It is a wireless sensor consisting of a handmade quartz crystal that oscillates in a temperature-dependent frequency. The sensor is excited by a modulated microwave signal, and the response is overlaid with the carrier signal leading to a frequency shift from which the product temperature is derived. The crystal is attached to an antenna that is threaded through the stopper. The data is transferred from the individual sensor to another antenna connected to a data recording device located outside of the lyophilizer. However, designs are available that include placing the data collection antenna inside of the lyophilizer to improve signal collection.

The Tempris sensor and RTDs are both available as wireless sensors and are amenable to steam sterilization. The wireless format allows for placement of the sensors in vials along the conveying line so they can be located in different locations across the shelf without risking sterility assurance.

Temperature sensors are necessary for monitoring product temperature at laboratory-scale. The goal is to place the sensor touching the bottom center of the vial because that is the location of the last quantity of ice before sublimation is complete. Temperature sensors are used in the laboratory to collect information on product temperature as a function of chamber pressure and shelf temperature and as a method of determining when sublimation is complete in the monitored vials. The challenge is that sensors placed in the vials may act as seeds for ice nucleation. Vials equipped with sensors exhibit less supercooling than the rest of the batch before ice nucleation and, therefore, behave differently than the rest of the vials.

Product temperature is often monitored during scale-up batches in the manufacturing area. Some manufacturing sites also monitor product temperature during routine batches. Wireless sensors are more

FIGURE 2

A resistance temperature detector placed in a vial. (Courtesy of Steve Nail)

TABLE 1

Type	Material of Construction	Comments
S	Platinum / Plantinum + 10% Rhodium	Loses sensitivity at low temperature
T	Copper / Constantan	Used in freeze-dryers
K	Chromel / Alumel	Most common general purpose
E	Chromel / Constantan	Good for low temperatures
J	Iron / Constantan	Lower limit of about -40°C

Common Types of Thermocouples.[2]

FIGURE 3

Tempris wireless sensor placed in a vial.

amenable to routine use than thermocouples that must be attached to a data collection port. This restricts the use of thermocouples to vials located on the front edge of a shelf due to the connection to a port and to reduce the risk to sterility assurance. The challenges with routine monitoring of product temperature are that the monitored vials do not behave the same as the rest of the vials in the batch, and sensors may not remain in the solution in the vial or the desired location within the vial. The data received from sensors that do not remain in place are no longer valid, but still must be explained during evaluation of the in-process data.

INSTRUMENTS FOR MONITORING PRESSURE

Pressure is another in-process measurement that can be used to evaluate the progress of the cycle. Pressure within the lyophilizer is often monitored using a capacitance manometer and may also include a Pirani gauge. A capacitance manometer measures the setpoint pressure in the lyophilizer. This is possible because the output for the capacitance manometer is independent of gas phase composition. The device consists of a diaphragm that moves due to small changes in pressure and results in changes in the recorded capacitance.[2]

Another device used to monitor pressure is known as a thermal conductivity gauge or Pirani gauge. The gauge uses a heated filament that carries current that is surrounded by the gas being measured. The thermal conductivity changes as the pressure changes or in the case of lyophilization, as the level of water vapor changes in the product chamber. The pressure during the main portion of primary drying appears higher than detected by the capacitance manometer, indicating there is a high level of water vapor in the chamber. The pressure detected by the Pirani gauge decreases toward the end of primary drying and becomes similar to the pressure detected by the capacitance manometer. This phenomena makes comparing the differences in pressure detected by the two gages an easy method for determining the endpoint of primary drying.

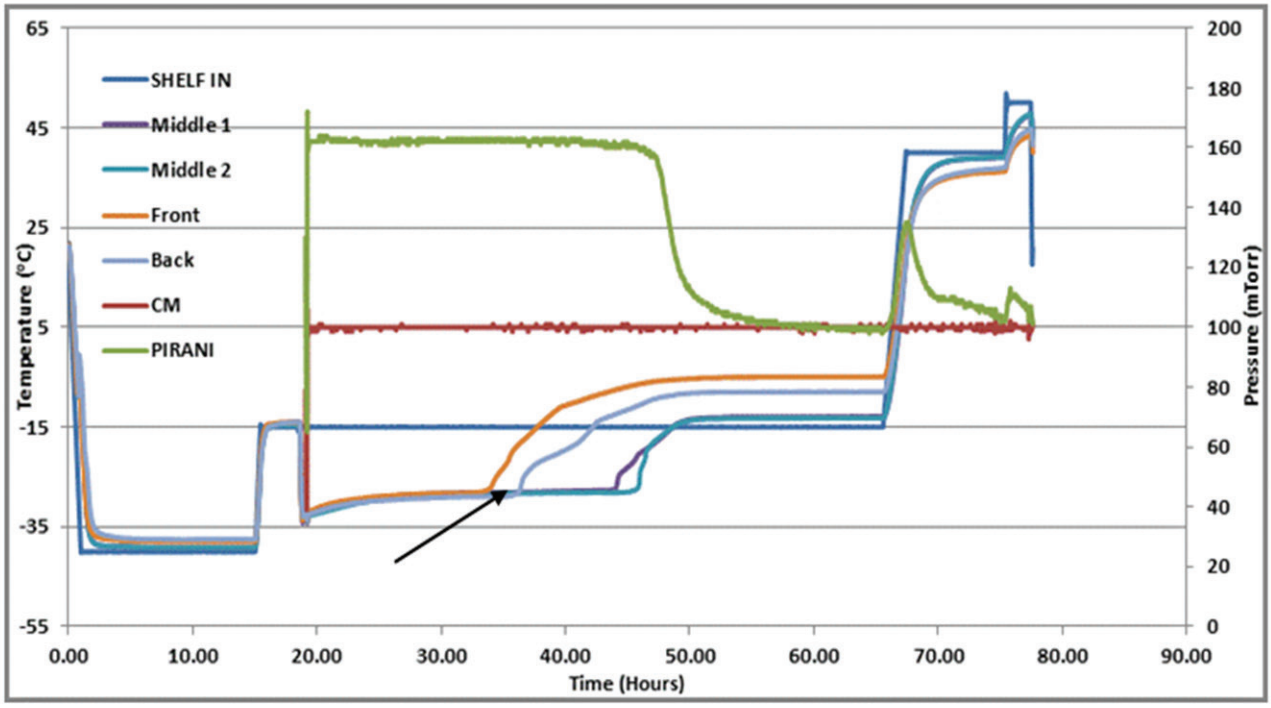
The filaments within the Pirani gauges can be constructed of different metals, and some of the metals are not as amenable to repeated sterilization cycles as others. It is important to know the materials of construction for the filaments and to choose gauges equipped with platinum–rhodium filaments if they will be subjected to sterilization cycles.

METHODS OF MONITORING THE PROGRESS OF FREEZE-DRYING CYCLES

The instruments for measuring temperature and pressure during a lyophilization cycle provide data for interpretation of the progress of the cycle. The easiest method of detecting the endpoint of primary and potentially secondary drying is by comparing the pressure measured by the capacitance manometer and Pirani gauge. The pressure detected by the Pirani gauge decreases toward the end of primary drying and matches closely with the pressure detected by the capacitance manometer (Figure 4). Their convergence indicates the end of sublimation. Figure 4 also provides product temperature data measured using thermocouples. The end of sublimation in the individual vials is indicated by the steep increase in product temperature and varies depending on the location of the vial on the shelf. Note that the product temperature of the monitored vials increases approximately 10 to 20 hours sooner than convergence of the pressure data. Basing the endpoint of primary drying on the rise in product temperature detected by the monitored vials could lead to prematurely advancing the cycle to secondary drying.

Similarly, pressure rise testing can be used to detect the endpoint of primary drying. This method also compares the pressures detected by the capacitance manometer and the Pirani gauge. However, the comparison is made after closing the isolation valve located between the product chamber and the condenser and

FIGURE 4



In-process lyophilization cycle data showing comparison of the Pirani Gauge (green) with the Capacitance manometer (red) and product temperature (Arrow).

monitoring the rise in pressure. The method relies on defining the time at which testing begins, defining the number of times the valve can be closed and opened, and determining the acceptable extent of pressure rise.

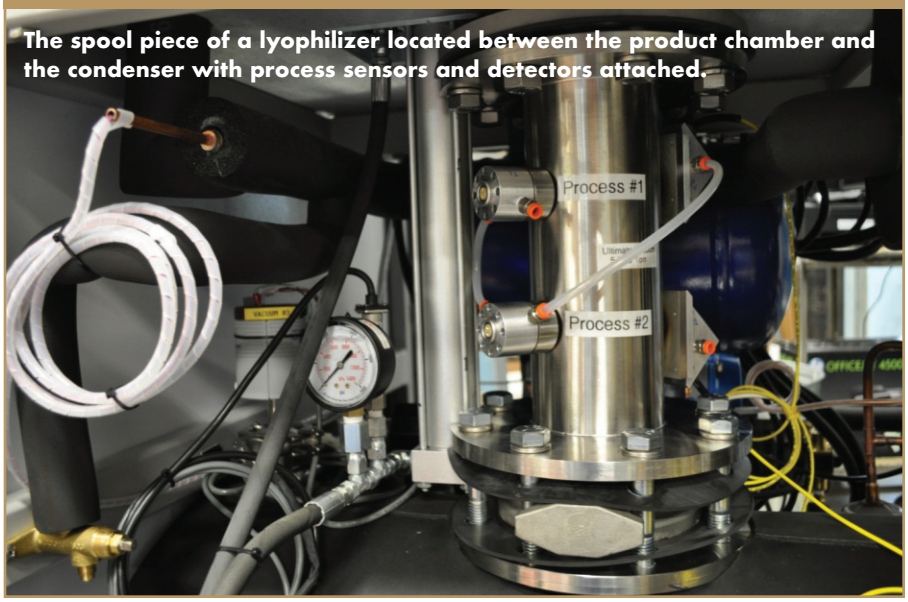
Manometric temperature measurement utilizes the data from pressure rise testing to calculate product temperature, vapor pressure of the ice at the sublimation front, and the resistance to mass transfer (R_p). Programs are available on some laboratory-scale lyophilizers, such as the SMART freeze-dryer that uses an algorithm to manipulate the setpoint shelf temperature to maintain the desired product temperature.[4] This method automatically determines the endpoint of primary drying while using the most efficient processing conditions.

ALTERNATIVE METHODS OF PROCESS MONITORING

Tunable Diode Laser Absorption Spectroscopy (TDLAS) optically measures the mass flux of water vapor from the product chamber to the condenser. TDLAS is an instrument and method developed by Physical Sciences Inc.[5] The measurement is made using sensors and detectors that are attached to the spool piece of the lyophilizer (Figure 5).

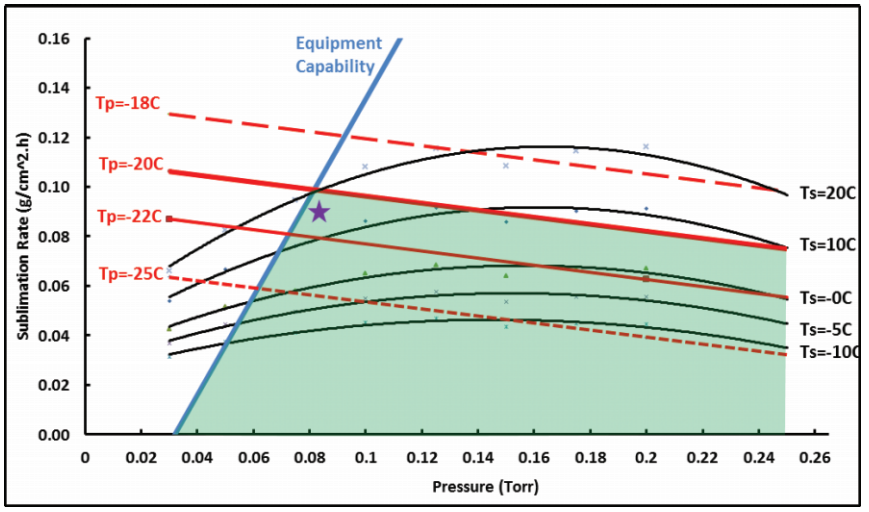
The water vapor concentration and gas velocity data are used to solve equa-

FIGURE 5



The spool piece of a lyophilizer located between the product chamber and the condenser with process sensors and detectors attached.

FIGURE 6



Example of a Primary Drying Design Space Graph. The Star Represents the Processing Conditions that will Produce the Most Efficient Primary Drying Cycle.

tions for the first principles of heat and mass transfer.

$$dq/dt = K_v A_v (T_s - T_b)$$
$$dq/dt = \Delta H_s \, dm/dt$$

Where dq/dt is the heat flux in calories per square centimeter, K_v is the vial heat transfer coefficient, A_v is the area of the outside of the vial, T_s is the temperature of the shelf surface, T_b is the temperature of the product in contact with the bottom of the vial, dm/dt is the mass flux in grams per hour per square centimeter, and ΔHs is the heat of sublimation of ice (670 calories per gram).

Resistance to mass transfer of the dried product layer is also done using TDLAS and the following equation:

$$R_p = A_p (P_i - P_c)/dm/dt$$

Where A_p is the cross sectional area of the product (the area of the inner diameter of the vial), P_i is the vapor pressure of ice at the sublimation front, and P_c is the chamber pressure. We base design space calculations on the resistance of the dried layer at the end of primary drying, since this represents a maximum value. Thermocouples are placed in the bottom of the vial and, as the sublimation front approaches the bottom, the measured temperature closely approaches the temperature of the sublimation front. The vapor pressure, P_i, is calculated from the product temperature using the following relationship:

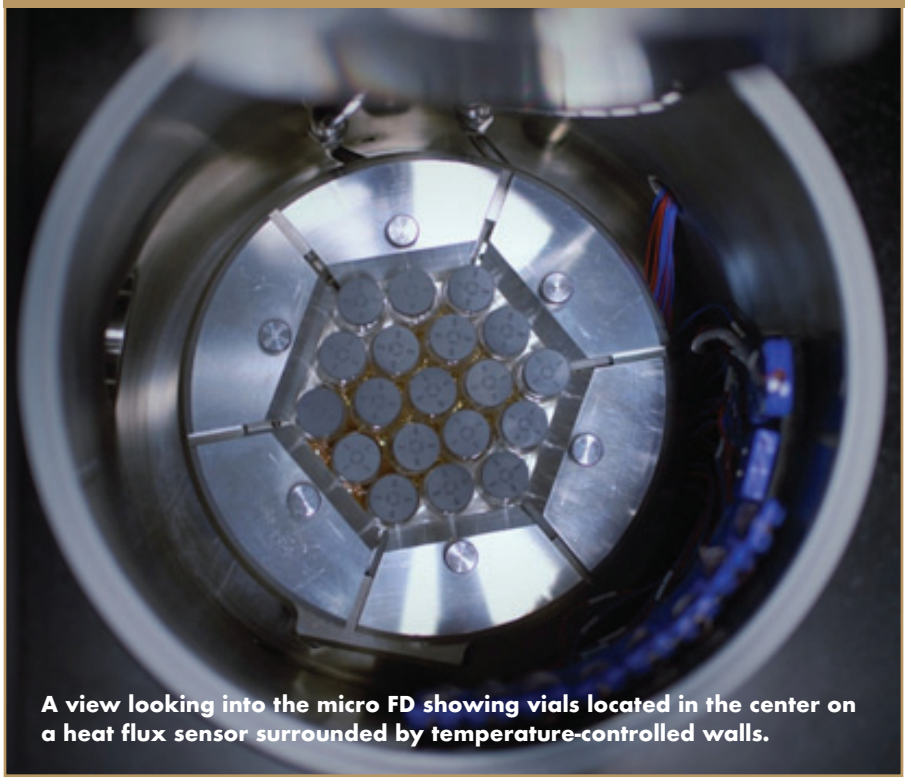
$$P_i \text{ (in Torr)} = 2.698 \times 10^{10} \exp(-6144.96/T_b)$$

Where T_b is the temperature at the bottom of the frozen layer.

The aforementioned equations are used in combination with values of K_v, R_p, and the maximum, allowable product temperature to construct the design space (Figure 6). Note there are two types of temperature isotherms – shelf temperature and product temperature. The product temperature above which the product fails becomes a boundary of the design space. The other boundary is equipment capability, since every freeze-dryer has a maximum sublimation rate that it will support.

Another method of collecting data to solve the equations for the first principles of heat and mass transfer is using a heat flux sensor developed by Millrock Technol-

FIGURE 7



A view looking into the micro FD showing vials located in the center on a heat flux sensor surrounded by temperature-controlled walls.

ogy.[6] The heat flux sensor is located on a shelf of a lyophilizer, and vials are placed directly on the sensor (Figure 7). The sensor directly measures heat flow from the shelf to the vial to obtain K_v for the vial and calculates R_p using the data collected using the sensor.

Finally, mass spectrometers, such as residual gas analyzers, can be attached to lyophilizers to monitor materials flowing from the product chamber to the condenser. This can be used to detect water vapor to determine the endpoint of primary drying, but it is quite useful for monitoring the removal of organic solvents that may be used in a formulation, monitoring for leaks of silicone from the equipment and monitoring for leaks that can lead to a loss of sterility assurance.

SUMMARY

Multiple methods are available for process monitoring during freeze-drying. The methods are useful for assessing challenges that may occur, but they are even more useful for detecting the endpoint of primary drying and for improving the efficiency of a freeze-drying cycle. Comparative pressure measurement is an easy and inexpensive method for monitoring primary drying that poses no risk to sterility assurance unlike product thermocouples. Advanced methods are available for monitoring mass flux and heat flux to solve for the first principles of heat and mass transfer equations. Solving the equations can support the development of a process design space and improve the understanding of conditions that can lead to product failure during primary drying. ◆

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BIOGRAPHY

Dr. Gregory A. Sacha is a Senior Research Scientist in the Research and Development department at Baxter Healthcare in Bloomington, IN. He is responsible for the formulation and process development of parenteral dosage forms that include both large and small molecules. His work resulted in several patents for formulation and process development of large molecules. His interests and expertise are in lyophilization and thermal characterization of pharmaceutical products. Dr. Sacha developed and leads a workshop for the study of formulation and process development for lyophilized products in collaboration with the McCrone Group and Millrock Technology.

Storage and Distribution Support for Clinical Trials Worldwide

Aricle by Gulam Jaffer, president of Yourway

Patient centricity has moved to the forefront of clinical trials. Direct-to-patient (DTP) services provide convenience, and lead to greater participation and retention, addressing two key challenges that face study sponsors. Yourway has the resources and expertise to devise tailored clinical logistics solutions for decentralised/virtual trials anywhere in the world, for even the most sensitive medications.

Evolving challenges of clinical trials

Efficiently and effectively managing the supply of speciality clinical materials and patient samples used in international trials has become more challenging. Navigating the varying and rapidly evolving complex and stringent regulations in each country requires detailed knowledge. Compliance with data protection laws, which are also rapidly changing and vary among regions, is complicated, as is ensuring data security and protection against digital attacks. Access to advanced packaging solutions that provide active temperature management combined with real-time tracking capabilities has become essential.

The two biggest challenges are patient recruitment and retention. A 2012 study estimated that more than 60% of trials fail to fully enroll their intended participants and approximately 30% of patients drop out of the studies.

The consequences are significant. Nearly 80% of clinical trials do not finish on time, with 20% delayed for six months or more. For a blockbuster drug, each day a trial is delayed causes a loss in revenue of roughly $8 million. For orphan and other specialized therapies, the loss in revenue opportunity is approximately $600,000 per day of delay.

Direct-to-patient solutions

Patient centricity has thus moved to the forefront, with trial protocols focused on patient convenience and incorporating patient input. It is also driving the adoption of DTP services in virtual clinical trials.

DTP services include delivery and administration of clinical trial drugs to participants in their homes, as well as pickup of patient samples, so patients can avoid travel and widely dispersed patient populations can participate in a single trial. DTP services are ideal for trials enrolling patients in remote locations or with mobility issues.

For sponsors, DTP services can boost participation and retention, and potentially lower trial costs. The

ability to access real-time data from remote monitoring devices enables trending and more rapid identification of potential safety issues.

These benefits have been confirmed in various studies. For instance, one survey found that over half of the patients indicated that they would be more likely to participate in a clinical trial if they could receive care at home. Another study found that the use of DTP services increased patient retention rates – with rates above 95% in some cases.

The move towards decentralised/ virtual trials

Despite the limitations of virtual or decentralized trials, such as varying international regulations or the need for nursing assistance, approximately 24% of clinical studies conducted in 2017 included DTP services. A total of 30% of respondents in a 2017 study indicated that their companies were considering the incorporation of DTP services in trials over the next 12–18 months. The FDA, meanwhile, recently published a draft guidance on the use of electronic media to facilitate the informed consent process for clinical trials and has endorsed DTP services and virtual clinical trials.

A solution-based approach

Partnering with a clinical logistics provider that has an established, global network of depots, demonstrated knowledge of the regulations in these regions, centralized management, and tracking systems, and a highly trained workforce is the key for successful virtual clinical trials and DTP studies.

Yourway BioPharma Services offers – in addition to the comprehensive transport capabilities – comparator drug sourcing, primary and secondary pharmaceutical packaging services, warehousing and distribution support, unused product return services, and assistance with logistics project management for all types of clinical trials, including decentralized studies that rely heavily on DTP services.

As the only truly integrated premium courier and clinical packager in the market, Yourway is uniquely positioned to support DTP clinical trials. The ability to access packaging services and courier/ shipping services from a single provider creates unique opportunities to find solutions that will protect the integrity of the drug products and increase the efficiency of the trials.

Yourway's integrated packaging and shipping services mean that the decisions about packaging design are made with comprehensive understanding of the conditions that the shipment will encounter.

Understanding the full scope of a client's needs allows it to apply a solutions management approach to eliminate the inefficiencies that can result from a complicated supply chain involving multiple discrete service providers. Integrating packaging and shipping services at Yourway means that decisions about packaging design – from primary and secondary packaging through temperature-controlled shippers and beyond – are made with comprehensive understanding of the conditions that the shipment will encounter on the way to the patient. Likewise, routing, shipping, and temperature-controlled decisions are made with a unique and complete understanding of the capabilities of the clinical packaging.

Furthermore, because the relevant drug products and related materials remain in Yourway's hands from the initial packaging steps in the temperature controlled packaging facilities, all the way through to the last mile to patients, it can ensure an unbroken temperature controlled chain. It maximises the use of supplies, and minimizes waste and shipping costs while ensuring that products stay within specifications (for example, temperature, pressure, and vibration), creating efficient and effective solutions for even the most complex supply chains. Additionally, since no handoffs are required between packaging and shipping, we can eliminate lags and enhance the efficiency of the entire trial, which is critical given that all lost time can cause loss of profit.

Unlike the few big players in the clinical trial logistics space, Yourway offers highly personalized services that can only be found with small to mid-sized companies. It has the bandwidth of a large company but is responsive to the customers' individual needs in a way that only small companies can be. It offers true one-on-one customer service that ensures high-quality, responsive, tailored support from start to finish.

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RISK-BASED MONITORING

Making the Move to RBM: Improving Patient Safety & Data Quality With Real-Time Insights

By: Crystal Stone and Amanda Coogan

INTRODUCTION

In an era in which the time- and resource-intensive business model of developing blockbuster drugs has been supplanted by a push to move drug candidates through the pipeline with greater speed, accuracy, and quality, risk-based monitoring (RBM) and real-time data analytics are becoming a must-have for clinical trials. Taking a risk-based monitoring approach can help enhance the safety, quality, and efficiency of clinical studies, while supporting regulatory compliance.

WHAT IS RBM?

In traditional monitoring, clinical research associates (CRAs) check every data point reported by an investigator against source records with the goal of achieving 100% source data verification (SDV). However, studies have shown that SDV is not necessarily synonymous with data quality.

RBM represents a paradigm shift from traditional monitoring methods. RBM utilizes a combination of monitoring strategies, including a greater reliance on centralized monitoring and statistical assessments to guide site monitoring visits and a focus on advanced technical capabilities. The goal of RBM is to bring together the relevant metrics and data necessary to increase efficiency, safety, and quality and to make data-driven decisions. Targeted monitoring replaces pre-scheduled site visits with data-triggered ones, concentrating on sites with a higher workload and a greater need for support and monitoring. Centralized remote monitoring and risk-based SDV helps reduce the number of data points CRAs must verify against source data on site, reducing workload and time.

TRENDS BEHIND THE RISE OF RBM

RBM has been hotly debated since the US FDA published its industry guidance *Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring* in 2014. However, adoption has been slow and industry has been uncertain about implementation. In recent years, the trend toward RBM has been accelerating, fueled by a number of key factors.

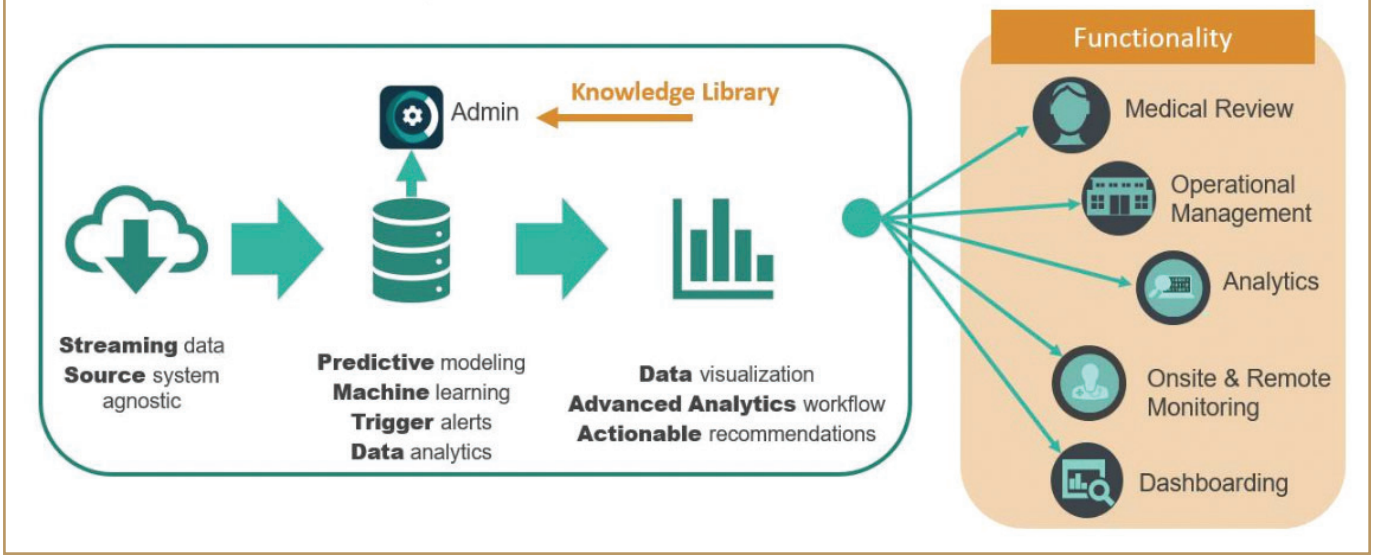
Changes in the Regulatory Environment

RBM is becoming the regulatory standard for clinical monitoring. With the 2016 updates to the ICH Guidelines for Good Clinical Practice, sponsors are now tasked with a greater responsibility for trial oversight, including the use of a formal approach to quality management that integrates technology and leverages real-time information to drive a more structured approach to risk.[1] In April 2019, the FDA published the draft guidance *A Risk-Based Approach to Monitoring of Clinical Investigations: Questions and Answers*, providing additional direction to help industry operationalize and implement risk-based monitoring.[2]

Shifts in Development Priorities

Throughout the past few years, changes in policy and a greater emphasis on developing new therapies for rare diseases

FIGURE 1



have changed the clinical trial landscape, as an increasing number of studies are being launched with fewer participants. According to a study from the 2019 National Organization for Rare Diseases (NORD) and Orphan Products Breakthrough Summit, 34 of the novel drug approvals in 2018 were for rare or orphan diseases, representing a historic high since the Orphan Drug Act was passed in 1984.[3] The small patient populations and low data volume in rare disease trials underscore the importance of making every data point count.

Drive Toward Digitization

Industry-wide emphasis on modernizing and improving the efficiency of clinical trials is driving digitization of the entire development process, from recruitment and data collection to adherence and data analysis. In January 2019, then-FDA Commissioner Dr. Scott Gottlieb indicated that modernization of the clinical trial process would necessitate the pairing of real-world data with advances in machine learning to "help expand the sources of evidence [used] to make more reliable treatment decisions."[4]

Exponential Increases in Data Volume

The volume, velocity, and variety of data generated by clinical trials is increasing exponentially. Despite advances in technology, time spent collecting, cleaning, and organizing data sets still accounts for 50% to 80% of data scientist time, leaving little time for data analysis.[5] Automated solutions can help address this pain point.

Demand for Data Quality

Outside of investigator fees, clinical monitoring is the biggest driver of clinical costs, accounting for over 60% of labor costs and approximately 30% of total expenses.[6] However, research has shown that expenditures related to source data verification do not necessarily correlate with improved data quality.[7]

BENEFITS OF IMPLEMENTING AN RBM TECHNOLOGY

RBM offers a responsive, real-time approach to clinical trial monitoring and risk management. Beyond providing a way to view and visualize risks, a comprehensive RBM solution provides insight into what the data mean in the context of the study and offers actionable steps to make optimal use of that data for in-trial decision making. Comprehensive implementation of RBM has the potential to bring a number of clear, measurable benefits.

From a compliance standpoint, regulators are seeking more rigorous assurances of patient safety and data quality. Selecting a robust RBM platform with assurance, traceability, and a built-in audit trail helps drug developers stay compliant with current and emerging regulatory requirements.

More advanced RBM software may utilize machine learning to alert decision-makers about potential risks that were not previously identified during trial set-up. These technologies analyze prospective data collected during the trial on an ongoing basis to detect patterns and anomalies, automating the time-intensive process of data analysis.

RBM technology can track trend information and make actionable data readily available to sponsors and CROs so they can take corrective action, which can improve both patient safety and data quality. In addition, by determining when it

makes sense for monitors to perform site visits based on study-specific risk thresholds, RBM analytics can help reduce unnecessary on-site monitoring and focus resources on sites that require more support.

Finally, RBM can help shorten the timelines for evaluating study data. Data cleaning at the end of a study can be time-consuming, typically requiring three months or more. With RBM technology, data are evaluated on an ongoing basis throughout the course of a clinical trial, which helps minimize the time from study end to the reporting of study results.

SELECTING AN RBM TECHNOLOGY

A comprehensive RBM system approaches risk in all of its layers (operational, safety, and quality), from initial risk identification and assessment all the way through to ongoing risk review.

Risk Identification & Assessment

The system should allow users to identify and log critical study-related data and processes. It should also let users evaluate and characterize risk both at the start and throughout the course of the study using a built-in risk register.

Risk Control & Mitigation

For each of the risks identified, the RBM technology should have the ability to control and mitigate the risk through a variety of automated or manual risk management strategies. For example, the software should be able to issue alerts when risks approach pre-defined thresholds and when safety or data quality is at risk. By remotely monitoring for signals that might require an in-person visit to a trial site, sponsors and CROs can be more judicious about how and when they deploy their staff to sites. Consequently, on-site visits can be scheduled only when the RBM technology signals that such visits are needed, rather than scheduling site visits at regular intervals.

More advanced RBM software may utilize machine learning to alert decision-makers about potential risks not pre-identified during trial set-up. Rather than relying on historical data, which can be misleading and/or out-of-date, a robust RBM system should be able to analyze the prospective data collected during the trial in an ongoing manner to find patterns and anomalies. Furthermore, all of the information in the system should be fully traceable through audit trails.

Risk Communication & Action

Risk detection is only one part of the risk management continuum. The system should also allow for streamlined, centralized review of the risks detected by offering statistical models, intuitive data visualization, and the ability to drill down into the data. The software should also let users act on and close out risks through built-in workflows and ticketing functionality. This functionality should allow for targeted actions to follow-up, close, and prevent such signals in the future.

Risk Review & Updating

Finally, the RBM software must accommodate regular and ongoing risk review and modification, enabling sponsors and CROs to monitor the effectiveness of risk management activities and ensure that these activities remain effective in the context of emerging knowledge and experience. As such, the Risk Assessment and Risk Mitigation plan undergo periodic changes that may include additions, modifications, and deletions of items.

MAKING THE TRANSITION TO RBM

RBM technology can help sponsors and CROs implement comprehensive monitoring strategies from an integrated platform with automated workflows and advanced analytic capabilities. Navigating the transition to RBM can be complex, especially as RBM software solutions become more sophisticated. To help make the transition more seamless, below are strategies for addressing some of the key challenges associated with adopting an RBM approach.

Overcoming Resistance to Change

Drug developers may feel cautious about or even resistant to transitioning to RBM. This resistance may be due, in part, to uncertainty about how the FDA will respond to the use of these newer techniques. However, sponsors and CROs should also consider how regulatory agencies might respond if RBM modifications are not made. For companies that are cautious about making the shift to RBM, it may be useful to evaluate the factors underlying that hesitation and to determine how to address it.

Even for companies that are ready to transition to RBM, the change can be daunting. The move toward an RBM approach requires change management related to people, process, and technology. Commitment at the executive level, along with comprehensive staff training and a clear understanding of each team member's roles and responsibilities, helps

"RBM offers a responsive, real-time approach to clinical trial monitoring and risk management. Beyond providing a way to view and visualize risks, a comprehensive RBM solution provides insight into what the data mean in the context of the study and offers actionable steps to make optimal use of that data for on-trial decision making. Comprehensive implementation of RBM has the potential to bring a number of clear, measurable benefits."

ensure that RBM is incorporated into the fabric of both the company and the clinical trial.

Clarifying Uncertainty About Implementation

As clinical trials become more complex, RBM technologies have also become more sophisticated. Unlocking the full value of RBM technology requires proactive planning, thoughtful implementation, and ongoing strategic execution following deployment. The process of implementation involves requirements gathering, planning, and testing, and should cover five key areas:

1. **Project Scope** - The scope should be aligned with the needs of the end user(s) and should include clear definitions of roles and responsibilities. Sponsors may want to consider starting with a pilot of the technology, so they have an opportunity to familiarize themselves with the implementation process, test the system, and validate internal processes on a small scale.

2. **SOP/Plan Impact** - This entails reviewing existing procedures and plans and updating them or creating new processes, if needed. This is also a good time to document the internal escalation process for handling issues identified by the system.

3. **Communication** - This describes how the sponsor will communicate with both the technology vendor and the end user(s).

4. **User Acceptance Testing (UAT) Plan** - This is an area many sponsors overlook. UAT should be performed at both the system level and the study-specific level.

5. **Oversight Plan** - This involves outlining success and value metrics, and how these metrics will be communicated to all stakeholders.

Training Algorithms for Machine Learning-Based RBM Systems

In some RBM technologies, machine learning is being used to support data processing, analytics, visualization, and decision-making. The use of machine learning creates an opportunity for researchers to process, analyze, and visualize more data than ever before, but it is not intended to replace human resources. Machine learning-based RBM technologies are only as effective as their algorithms, and their outputs still need to be interpreted and contextualized by trained trial management staff. In short, machine learning is a complement to, rather than a substitute for, human judgment. Machine learning algorithms "learn" from their users by observing their interaction with the results and gathering feedback. This will further help improve the algorithm's accuracy and effectiveness. This is especially important for clinical trials on rare diseases, where historical data is lacking or limited.

Sponsors should keep in mind that the accuracy and efficacy of machine learning algorithms are dependent on the quality of the data. In computer science, "garbage in, garbage out" describes the concept that flawed input data produces nonsense output. As such, machine learning algorithms will generate signals based on any valid raw data format, regardless of what those data are. In the context of a clinical trial, a false positive or a false negative could have significant downstream impact on patient safety and study integrity. Consequently, it is important to never act on a result without questioning it first. Algorithms are designed to facilitate decision-making, not to dictate action, so their outputs should always be validated by researchers.

KEY TAKEAWAY

When implemented and managed appropriately, RBM technologies are powerful tools for monitoring risk and improving both patient safety and data quality. Comprehensive RBM technologies approach risk from all angles, alerting users when risks approach predefined thresholds and when safety or data quality is at risk of compromise. In addition to making on-site monitoring more efficient, RBM software provides ongoing oversight of patients, sites, and the study as a whole to facilitate informed decision-making. By combining risk-based approaches with dvancements in technology, RBM helps sponsors implement comprehensive monitoring strategies and focus resources towards the monitoring practices that have the greatest impact on the quality of both patient safety and clinical trial data. ◆

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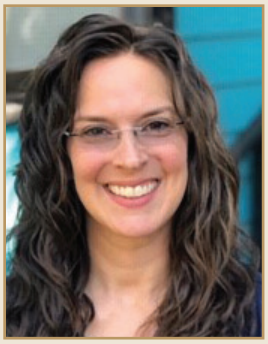
BIOGRAPHIES



Crystal Stone is Risk-Based Monitoring Director, Customer Engagement at Remarque Systems. After a 12-year career in the medical device industry, she transitioned to the software industry to support Quality Risk Management/Risk-Based Monitoring. Her role includes management and oversight of customer engagement as well as consultant and subject matter expert to small and large pharma, medical device, and CROs, which has given her broad exposure to how companies are implementing risk management/RBM.

Amanda Coogan is Risk-Based Monitoring Senior Product Manager at Remarque Systems. She worked for 12 years in university hospitals and medical device firms supporting domestic and international studies across a range of disease states, then transitioned to the software industry. There she serves as consultant, subject matter expert, and project manager to small and large pharma, medical device, and CRO customers supporting the implementation of Quality Risk Management/Risk-Based Monitoring. In addition to working with customers, she provides RBQM and clinical trial operation expertise to support software product development.

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Prefilled Syringes & Parenteral Manufacturing: Innovations, Challenges & Solutions

By: Cindy H. Dubin, Contributor

The prefilled, pre-loaded, connected, wearable injector from Sorrel Medical.

The global injectable drug delivery market was valued at $331 billion in 2015 and is expected to reach $931 billion by 2024.[1] The market is segmented by product: pen injectors, autoinjectors, wearable Injectors, and needle-free injectors. An increase in home self-administration and the projected growth for biologics therapies to treat these chronic conditions are driving these sectors.

While large molecule biologics dominate the market, the demand for small molecule parenteral products is also increasing.[2] According to Transparency Market Research, the global small molecule injectable drugs market will expand substantially from 2017 to 2025 due to growth in generic injectables, which is outpacing that of innovator drugs, a strong pipeline of small molecule injectable drugs, and significant investment in R&D for small molecules.[2]

Additionally, the global Prefilled Syringes Market (PFS) market is projected to reach $9.53 billion by 2026[3] because of their ease at delivering injectable drugs to treat chronic diseases.[4] PFS materials include glass and plastic. Glass has strong barrier properties, which make it the preferred material for the manufacturing of prefilled syringes. Additionally, glass is highly compatible with different filling drug machines. However, certain concerns over breakage and the reaction of glass ions with the drugs could shift the preference from glass prefilled syringes to plastic prefilled syringes. The plastic segment is anticipated to be the fastest-growing segment owing to technological innovations.[5]

This annual *Drug Development & Delivery* report features several leading companies' innovations in delivery devices as well as how contract parenteral manufacturers are addressing the ever-demanding challenges, issues, and opportunities related to delivering biologics and small molecules.

Ajinomoto Bio-Pharma Services: Manufacturing Complex Formulations

As no two manufacturing processes are identical, the Ajinomoto Bio-Pharma Services drug product manufacturing team works with a range of processes, from a simple formulation, filtration, and fill to high-potent complex formulations, which can take place over several days and require non-standard filling operations, explains Megan Owen, Senior Manager, Drug Product Manufacturing, Ajinomoto Bio-Pharma Services.

"We offer scheduling and component flexibility with five automated vial filling lines and two automated prefilled syringe filling lines. Additionally, we offer hundreds of qualified container closure configurations, ensuring that we have a configuration that is compatible for each of our clients' product requirements."

She says the company also looks to industry trends as decisions are made regarding investing in new technologies and capabilities. For example, as the market for highly potent APIs is steadily growing so is the need to safely manufacture and fill these highly potent products. "To that end, we have installed a dedicated, fully contained and integrated fill line at our San Diego location that not only mitigates the inherent risk of exposure but also efficiently handles a range of fill volumes," she says.

Additionally, the CDMO has invested in a flexible fill line, the Optima VFVM 7000, to support the aseptic fill of drug substance APIs. "This new line increases our capacity by 50% and enables us to process larger batch sizes and volume ranges for vials, syringes, and cartridges," says Ms. Owen. "The new multi-purpose line also allows us to utilize Ready-to-Use (RTU) vials, cartridges, and syringes to reduce requirements for the manufacturing process."

The Optima VFVM 7000 aseptic vial filling line at Ajinomoto Bio-Pharma Services maximizes filling accuracy, enables larger batch sizes, and provides a broader range of filling volumes.

In 2019, Aji Bio-Pharma guided nine clients through their PPQ campaigns and established parameters for commercial production of their drug products. One of the campaigns was particularly challenging as it was a complex formulation of a viscous product. In addition to the formulation challenge, viscous products can be difficult to fill, while maintaining final dosage accuracy. Multiple departments across Aji Bio-Pharma (Drug Product, Quality Control, Quality Assurance, and Validation) collaborated with its client to produce a robust and repeatable process to support its commercial manufacturing campaign. This involved using specialized formulation equipment and custom fill tubing assembly coupled with engineering runs to optimize the filling parameters.

AMRI: Overcome Common PFS Challenges with a CDMO Partnership

The increase in biologic drugs presents particular obstacles, primarily attributed to viscosity. Different products have differing viscosity, or centipoise levels, requiring unique processing solutions. A major challenge is cleanly dispensing product into the syringes, as product will often stick to the tip of the filling needle and create a trail of product along the syringe after dispensing.

CDMOs must work with both clients and equipment manufacturers to overcome such challenges, necessitating product-centric solutions and high levels of expertise. For example, collaborative efforts with key equipment vendors were conducted at AMRI's Albuquerque, NM, facility to engineer, reprogram, and test the Programmable Logic Controller (PLC) for the motion and timing of fill curves, allowing for better process parameter predictability of the equipment.

"Having completed media fills and scaled up commercial manufacture for two existing lines, AMRI can offer cGMP aseptic processing and enable pre-approval inspections for commercial products, transferring capabilities at speed to new commercial drug product manufacturing requirements," says Anish Parikh, Vice President, Sales & Marketing - Drug Product, AMRI.

Handling controlled substances is an-

other challenge intensified by viscosity. A robust reconciliation process is needed to track and trace batches to quantify the controlled substance deployed. At AMRI, compliance managers account for product usage levels from start to final packaging, including product quantity used in preparation and flushing of production lines. "Such robust processes are critical in assuring compliance and successfully clearing rigorous DEA auditing," says Mr. Parikh.

AMRI also supports clients in product material selection. "We've seen an increasing demand for plastic over glass, but selection rests on more than the inherent properties of the base materials being filled," he says. "Our analytical team expert in extractables and leachables, container testing, and heavy metal detection, significantly aids in optimizing container closure design for a given product and is a valuable resource for our clients."

Baxter BioPharma Solutions: Automated Inspection Identifies Particulates

One of the largest challenges in parenteral manufacturing is preventing particulate matter from entering the product. While the particulate matter can be reduced with careful inspection, it is almost impossible to eliminate. Baxter BioPharma Solutions takes a two-pronged approach to this challenge. First, the R&D laboratory located onsite is fully equipped for isolating and identifying particulate matter. This aids in rapidly identifying the possible sources and in progressing with the batch. Next, a team was established that includes representatives from manufacturing and R&D that evaluate all possible sources for contamination. The evaluations pinpoint areas for improvement and reduction of particulate matter.

"All parenteral products must undergo 100% visual inspection to eliminate units that appear with defects or particulate matter," says Gregory A. Sacha, PhD, Senior Research Scientist, Baxter BioPharma Solutions. "The goal is to utilize automated inspection machines because they are tremendously faster than manual inspection. This is challenging for syringes that are filled with dispersed systems used as vaccines because the dispersed material can appear as particles or can settle within the syringe and appear as a defect. Baxter BioPharma Solutions is well equipped with automated inspection equipment that is followed by automated container closure integrity testing."

The automated inspection equipment is qualified using prefilled syringes from a defect library that are placed randomly within acceptable units. The goal is for no more than one defect to be accepted and to ensure that the number of false rejects does not exceed an established threshold percentage of the total defective units identified, he explains.

"It is advantageous for the Baxter BioPharma Solutions to have automated container closure inspection equipment attached to the inspection line," advises Dr. Sacha. A particular challenge with syringes that are equipped with pre-staked needles is for the needle to protrude through the cap. The protrusion is often difficult to detect with the naked eye. Automated container closure inspection equipment aids the identification of defective syringes from multiple batches.

While syringes are available in glass and polymeric formats, terminal sterilization of polymeric syringes can be challenging, says Dr. Sacha. A recent client desired to use polymeric syringes and terminally sterilize its product. He explains that initial trials produced prefilled syringes with a haze that was not visually appealing. Baxter BioPharma Solutions developed a method to terminally sterilize the polymeric syringes while preventing development of the haze. This required adjusting the parameters to slowly cool the syringes post-sterilization.

BD: Optimizing Administration for Multiple Stakeholders

There has been increased use of traceability of injection devices, in the manufacturing process, the supply chain, and even in terms of patient use. Though the basic technical foundations of these solutions are now relatively established, robust end-to-end solutions, integrated with existing industrial and clinical monitoring systems, are still not widely available on the market.

"We feel very strongly about this at BD, given our breadth of experience incorporating smart capabilities into devices and in the digital monitoring of drug delivery systems, as well as in the collection and analysis of healthcare data," says Marie-Liesse Le Corfec, Head of Global Portfolio Marketing at BD Pharmaceutical Systems.

As market needs evolve, BD is shifting from providing products to providing full solutions that address the needs of the multiple stakeholders involved in the healthcare ecosystem. BD's range of platforms span the vaccine, drug volume, and viscosity continuum.

"Our customers can start their development in our injection containers and devices with a broad design space that they can then narrow over time, as their drug development evolves, constraints emerge,

BD's portfolio of prefilled syringe injectors.

and decisions are made about formulations, volumes, possible drug container compatibility issues, and ergonomics," she explains. This can be achieved through commercialized platforms such as our range of prefillable glass or plastic syringes and stoppers for various usages (BD Neopak™, BD Sterifill™ Advance, BD Hylok™, BD Hypak™ for Vaccine), BD UltraSafe™ passive needle guards, BD Vystra™ disposable pens, BD Physioject™, and BD Intevia autoinjectors, as well as products in development, such as BD Libertas™ wearable injectors and BD Evolve™ programmable on-body injectors.

BD also works with customers to recommend the best packaging solution for their applications. Typically, Ms. Le Corfec says for medication in volumes over 10mL, which are often infused through pumps, the recommendation is to use polymer prefillable syringes such as BD Sterifill Advance, which is designed to be automatically recognized by pump software, and benefit from a light weight and a high resistance to breakage.

She adds that for volumes under 5mL, glass remains the best-in-class material relative to inertness, permeability to O_2, transparency, and resistance to scratches during the manufacturing process. And for volumes between 5 and 10mL, the optimal syringe material, either glass or plastic, depends on several criteria such as drug compatibility, syringe format, manual vs. power-driven delivery, emergency use, etc.

Catalent Biologics: High-Speed Filling Lines Get Products to Patients Faster

Companies are demanding more capacity as their products continue to go straight into syringe presentations rather than vials during clinical trials. The growth in syringe demand earlier on has necessitated that many manufacturing partners, such as Catalent Biologics, reconsider their internal capacity. Catalent has addressed this by undertaking a $100 million expansion to its drug product manufacturing facility in Bloomington, Indiana, which includes the addition of a new high-speed syringe filling line, due to be completed in 2021. Additionally, that same facility recently completed a $14 million packaging

Catalent has experience handling small molecules, biologics, and vaccines from automated filling lines, offering a high degree of aseptic processing.

expansion, while the Brussels, Belgium site completed a $13.5 million packaging expansion in 2018.

"With these packaging investments, our sites have expanded their safety device and autoinjector capabilities and capacities, brought about by an increase in demand as more commercial products move towards self-administration devices," says Brian Galliher, Senior Process Engineer, Catalent.

He says the high-speed filling lines in Brussels and Bloomington can meet a combined annual capacity of up to 290 million syringes for biologics, small molecules, vaccines, and diluents. Across these two sites, other options include containment (barrier isolator or restricted access barrier system), different filling mechanisms (time pressure, peristaltic pump or rotary piston), and varying component sizes (ranging from 0.5mL to 20mL).

"Additionally, by having secondary packaging integrated within the two sites, including autoinjector and safety device assembly, Catalent Biologics can expedite the packaging process, allowing quality products to get to patients faster," says Mr. Galliher.

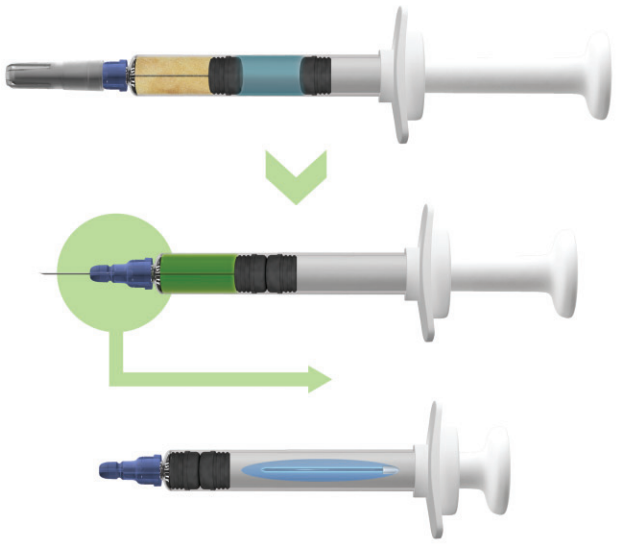
In fact, a customer recently asked Catalent to help introduce a new product to market far quicker than is typical. "Due to our longstanding relationship with this customer and familiarity with each other's needs, we were able to support its project from filling to device assembly and launch," he explains. "An agreement was quickly reached that it was imperative to launch this product into the market rapidly. With a cross-functional, cross-company team, we were able to fill, assemble, and launch the customer's product into market within just 30 days."

Credence MedSystems: Enabling Broad Access to Dual-Chamber Fill-Finish Processing

Last October, Credence MedSystems was awarded a grant from the Bill & Melinda Gates Foundation to support the development of Credence's Dual Chamber Reconstitution Syringe tailored for use in developing nations. The project will solve a major problem in the global health setting by allowing last-mile administration by untrained users of vaccines and contraceptives requiring reconstitution.

John A. Merhige, Chief Commercial Officer, Credence MedSystems, says macro market dynamics are driving growing demand for Credence's Dual Chamber Reconstitution Syringe, resulting in numerous pharma collaborations and development advances. These dynamics include growth in the biologics and self-injection markets. "The fact that many of these injectables and particular biologics require storage in dry form introduces the added complexity of needing to reconstitute at the time of use," he says. "These dynamics result in the need for an intuitive delivery system that promotes successful reconstitution and injection by less-experienced users."

He asserts that the Credence Dual Chamber Syringe is unique in the industry due to its simplicity of use, its flexibility to use off-the-shelf syringes of varying sizes and materials, its ergonomic design and compact environmental footprint, and its safety features. To enable mixing, the user pushes on the plunger rod; after mixing, the user delivers the medication and receives end-of-dose tactile and audible cues, signaling that the full dose has been delivered. Upon completion of the injection, the needle automatically retracts into the syringe barrel, preventing accidental needlestick and reuse. Further, incorporating the dry form and the liquid diluent into the chambers of one primary package enhances the likelihood of appropriate reconstitution ratios and dos-



The simplicity of use, flexibility, and safety of the Credence MedSystems Dual Chamber Syringe enable the administration of complex drug products by inexperienced users.

ing, while minimizing environmental footprint and added supply chain complexity.

Credence is working on derivatives of its Dual Chamber System, encompassing glass and polymer barrels, as well as barrel sizes ranging from 1mL to 20mL. "The flexibility of the technology enables system customization," he says. The Dual Chamber System can be used with a pre-attached needle or in a luer lock configuration for alternative routes of administration. Additionally, Credence is working with numerous large and small biopharma customers to advance the Dual Chamber System towards clinical use.

Broad access to dual-chamber fill-finish capabilities requires a supply chain that continues to advance and serve the expanding needs of patients. "Traditional limitations in the supply chain for dual-chamber fill-finish capabilities have hindered the ability to meet the pent-up and growing demand for this system," says Mr. Merhige. "This has kept solutions that can help patients from the market. However, as that market need and potential have become more obvious, there has been significant progress. Credence is working actively with partners in the supply chain towards the goal of enabling broad access to dual-chamber fill-finish processing. This includes *in situ* lyophilization as well as off-line lyophilization approaches."

Datwyler: Plunger Designed with Functionality in Mind

While low break loose and gliding forces have been the main factors in determining PFS component design, the list of functional user requirements has become much longer and continues to grow with the introduction of new applications and therapies. For manual applications, a low break loose force makes it easier for the user to inject the drug. This requirement has resulted in plungers designed with very low compression, causing the risk for leakage has increased greatly. In addition, a low break loose force and a low compression also means that the plunger will move more easily during air transport. If the plunger moves too much, it might move into the non-sterile area of the barrel, which can increase the risk for drug contamination.

For automatic injections, the break loose force value is not as much of a concern as in manual applications because the device can be developed to cope with higher forces. The consistency over time is more important in automatic injections to guarantee good device performance throughout its life cycle.

Although there is no clear ISO guideline with regard to acceptable break loose forces, market research indicates that most customers prefer a break loose force below 10N, with 15N being an acceptable value, and 20N being the absolute maximum, explains Carina van Eester, Global Platform Leader, PFS and Cartridges, Datwyler. For gliding forces, the values are mostly dependent on drug viscosity, needle size, and the impact of the drug on the siliconization of the barrel.

"If we consider all of these requirements, some compromises have to be made to develop a PFS component that can guarantee

Datwyler's NeoFlex™ coated plunger guarantees drug sterility and component functionality.

Cleanroom production of Gx RTF® glass syringes at Gerresheimer Bünde in Germany.

drug sterility and component functionality for both manual and automatic injections," she says. "The new NeoFlex™ coated plunger from Datwyer was developed with all of these requirements in mind. The compression of the plunger, the shape of the rills, and the finishing of the trim edge were optimized to create a fully coated plunger that offers a high safety margin of sterility and a consistent break loose force over time."

She adds that the NeoFlex plunger works in different siliconized barrels – from standard siliconized, to low siliconized, and cross-linked siliconized barrels. And, NeoFlex is suited for use in COP/COC barrels. "Traditional uncoated plungers chemically react with COP/COC, causing the break loose force to increase over time, particularly at higher temperatures," says Ms. van Eester. "If a plastic barrel is used in an autoinjector where consistency of break loose forces is vital, or for a manual application where the break loose force has to be kept at the lower end, it is recommended to use a fully coated plunger, such as NeoFlex."

Gerresheimer: The Importance of Primary Packaging

Wenzel Novak, Global Senior Director, Business Development at Gerresheimer. says primary container capacity is one of the greatest market issues right now. With commercialization of its Gx RTF® Vials, the company offers nested and pre-sterilized vials.

Smaller batch sizes are often requested when filling biological products, hence Gerresheimer has invested in small batch production at its facility in Wackersdorf, Germany, improving flexibility and time to market. When the filled biological agent is sensitive to its storage environment, the container must be individually adapted to its properties. Therefore, Gerresheimer developed a range of different specific technologies such as tungsten-free forming.

Gerresheimer has also commercialized Gx InnoSafe®, an integrated passive Safety Device, which is offered in a standard nest-and-tub configuration. As it is already assembled, no additional assembling at the fill and finish site is needed.

Furthermore, Gerresheimer expanded its polymer syringe platform Gx RTF ClearJect® and now supplies a 2.25mL COP-staked needle 27G ½-in. syringe. Mr. Novak says COP is suitable for sophisticated medications, especially for sensitive or biological products, offering inert material properties and minimized leaching and extractables profiles.

In addition to COP syringes, Gerresheimer offers syringes made of type I glass in a variety of configurations. "Glass has always been the preferred container material for parenteral pharmaceutics," he says. "Increasingly, strict drug product requirements and the trend toward customized products, reveal the limits of this material. COP, on the other hand, is suit-

able for cold storing of pharmaceuticals, and is recommended for aggressive agents or emergency uses that require shatterproof packaging. Finally, biopharmaceuticals necessitate excellent low leachables and extractables profiles. Comparatively new materials such as COP create new options for prefilled syringes. While cyclo olefins will not replace the other materials, they do serve specific requirements of some parenteral drug products."

During clinical development, Gerresheimer advises clients about how to choose the right primary packaging, syringe, or drug delivery device, as well as with regulatory approval processes.

Nemera: Device Platform Accommodates up to 2.25mL Fill Volume PFS

Growing biologics pipelines and the shift from an intravenous to subcutaneous route of administration require drug delivery devices to accommodate high-volume and viscous formulations. Patients and caregivers need reliable, robust, and easy-to-use devices to administer treatment at home, independently, with optimized convenience. With this in mind, Nemera has launched a passive safety device based on design research, human factors, and user-experience studies.

The Safe'n'Sound® needle safety device platform is a premium add-on to prefilled syringes; a passive, one-handed safety device intended for use by non-experienced users for self-administration and by healthcare professionals. Safe'n'Sound is commercially available to accommodate 1mL and 2.25mL fill volume prefilled syringes. "The new 2.25mL size is specifically relevant to administer complex, high-value drugs such as monoclonal antibodies or other biological therapies," says Audrey Chandra, Category Manager, Nemera. "It offers a reliable and intuitive design for user safety, and is compatible with any type of ISO standard 2.25mL prefilled glass syringe, including various flange types."

In addition, patients who need a large injection volume may opt to use on-body injectors to administer their treatment at home, without having to go to the hospital to get their dose regimen. Nemera is actively working on the smart wearable, which is intended to improve and ease patients' lives. "Our innovative wearable concept consists of disposable and reusable parts," explains Severine Duband, Global Category Manager, Nemera. "The electronics are reused and only the drug is disposed off after administration. This on-body injector can adjust flow rate and has automatic needle insertion, as well as smartphone connectivity for treatment information, reminders, and compliance features."

Nemera ensures the compatibility of its drug delivery platforms with a range of PFS components, including non-siliconized stoppers and other materials such as glass and plastic. "Particle formation from adhesive, silicon, or other residuals has to be minimized as this may trigger protein aggregation and eventually undesirable reaction with highly sensitive drugs, such as biologics," says Ms. Duband. "This reaction may decrease drug stability and affect delivery consistency as well as trigger adverse reactions of the patients."

Alcami: Component Selection Equates to Successful Manufacturing

As a contract manufacturer, Alcami provides experience in all aspects of the manufacturing process, including fill volume accuracy, plunger placement, material compatibility, and, reduction in line loss. "Many of the prefilled syringe products in the contract manufacturing space are high value, low volume, so assessment of manufacturing capabilities with components selected by the client during the device design process is critical to ensuring our success during an individual manufacturing run or campaign," says Jacquelyn Uribe, Vice President, Quality Operations, Alcami.

She says engineering runs are the most comprehensive way to approach this assessment. "Because they are performed on equipment used at scale, this allows us to assess additional considerations associ-

Sterile fill-finish capabilities from Alcami provide flexible manufacturing solutions for liquid and lyophilized products.

PremiumCoat™ stoppers from Aptar Pharma represents a step change by significantly reducing particulate levels.

ated with the introduction of a new process/components that may have been lost if this was conducted in a laboratory setting."

Alcami's focus on filling services is two-fold: to ensure component offerings align with current client demand; and to ensure filling technology can support a variety of product types. The company's site in Morrisville, NC, offers 1mL long, 1mL standard, and 2.25mL and 3mL syringe capability with a variety of needle configuration options. The filling technology on the syringe line currently utilizes a positive displacement pump technology that can fill high viscosity products with planned expansion for peristatic filling to support more shear-sensitive formulations.

Aptar Pharma: Line of Elastomeric Stoppers Reduce Particle Contamination

Particles are a major source of concern for injectable drugs manufacturers, coming from multiple sources including the elastomeric components. And as more complex proteins and expensive drugs are developed, the challenge for elastomeric components manufacturers is to deliver higher standards of cleanliness in elastomeric components, maintaining the integrity of the container closure, while minimizing interaction between the formulation and the components of the elastomeric closure system.

To meet this challenge, Aptar Pharma's PremiumCoat™ range of elastomeric stoppers is designed to protect sensitive and high-value drugs, including biopharmaceuticals. "PremiumCoat stoppers significantly reduce particulate levels," says Arnaud Fournier, Senior Business Manager, Aptar Pharma Injectables. "In fact, the Particulate Count Index (PCI) achieved with PremiumCoat has a PCI of 1.3."

The surface of the elastomer is coated during the manufacturing process with a thin fluoropolymer film (ETFE). This delivers a completely homogenized coating. The process targets only the area that comes into contact with the drug, ensuring that overall integrity of the container closure is secured, explains Mr. Fournier.

PremiumCoat is available in Ready-to-Sterilize (RTS) and Ready-to-Use (RTU) variants. The RTS product is compatible with steam sterilization and uses Aptar Pharma's proprietary washing process, designed for operations that have sterilization facilities in place. The RTU product is sterilized by gamma irradiation. The RTU offering reduces the number of human product interactions and allows the product to be introduced to the manufacturing line at the point of use. Additionally, the RTU stoppers ease the project transfer from the development laboratory to in-house production or to a CMO, he says.

"Our customers' manufacturing productivity is improved as the stoppers may be used immediately upon receipt and be directly introduced into RABS or isolators," says Mr. Fournier.

While PremiumCoat supports gamma-irradiation sterilization, it also maintains a similar leachables profile as stoppers sterilized by steam, he says. With gamma-irradiation, vial stoppers can be sterilized in their packaging, limiting contamination risks during transfer, improving productivity, and controlling exposure.

PremiumCoat RTU stoppers can be supplied in Aptar Pharma's QuickStart™, a solution that provides components to aid research and development labs in small-volume filling of high-value formulations. Co-developed alongside Schott and EMA Pharmaceuticals, Aptar Pharma QuickStart can be configured to different sizes and configurations of vials, stoppers, and caps.

Aztech Sciences Inc.: Guiding Clients to Make Proper PFS Selections

Robustness in device design and improvement in dosing accuracy and precision has been a significant step in the evolution and application of multi-chamber PFS. Their benefit is multi-drug device packaging when incompatibility is a concern between drug candidate platforms that are formulated together for long-term shelf life.

"In addition to offering accurate dosing, target efficacy, and reduced contamination potential, multi-chamber PFS offer

Using risk management principles for PFS, Aztech Sciences Inc. helps drive its clients' projects into the clinic.

the advantage of prefilled product and reconstitution parenteral solvents to be packaged together," says Alphonso Higuera, PhD, Vice-President/Cofounder, Aztech Sciences Inc. "The combination of drug administration into one regimen using multi-chamber PFS also provides dosing flexibility for healthcare providers, which can lead to improvement in patient compliance."

Robustness is critically important to the biotechnology space, which demands sterile and compatible finished product environments. Thus, extractable and leachables aspects of PFS are a area significant concern for many biological therapeutic agents and formulations. "While developments continue towards providing plastic resins with high product compatibility, glass resins are still a preferred choice for biologics and sensitive small-molecule product packaging," says Dr. Higuera.

He says Aztech recently worked with a consultant whose client was not clear about the importance of extractables and leachables with PFS. "Using a pragmatic and scientifically sound approach, we guided the client in the proper selection of PFS for their development program aligned with compendial and regulatory requirements," he says. "The outcome from this approach allowed our client to establish a successful product risk assessment leading the project into a viable IND-enabling track."

Novocol Pharma: Cartridge Manufacturing for Combination Products

This CDMO, based in Cambridge, Ontario, specializes in sterile cartridge manufacturing, which has witnessed increased interest driven by trends for combination products with novel drug delivery systems to allow self administration. The shift towards reducing healthcare burden through self administration has led to the development of new drug delivery devices, including wearables, pen injectors, and autoinjectors for both new therapeutics and life cycle management of products previously found in other dosage forms like syringes and vials, says Atif Zia, President of Novocol Pharma.

Additionally, the growth in biologics and biosimilars has resulted in an increasing need for larger volume injections and multi-dose injections, as well as a need to handle formulations with higher viscosity.

"All of these issues have made the cartridge an attractive format," Mr. Zia says. "For example, 3mL cartridges exceed the volume of the traditional 1mL prefilled syringe and the expanded 2.25mL prefilled syringe, allowing for more doses per container." He adds that cartridges can be customized for container geometry and have the benefit of a lined seal that can reduce drug product oxidation and enable multi-dose applications.

As novel drugs are being developed both for single-use and multi-use indications, the cartridge provides flexibility and robustness for both situations. In emergency autoinjectors, cartridges have a track record of safety for intra-muscular emergency applications such as anaphylaxis, opioid overdose, and military ountermeasures. In multi-use indications, the cartridge is commonly paired with a patient-centric pen injector for variable- or fixed-dose subcutaneous self injection of drug products for chronic illnesses. Here, the cartridge system is favorable as a multi-dose platform where patients can use a disposable needle for each dose.

"Given the close coupling of injector devices and the cartridge, it is an imperative for manufacturers to have expertise in developing and achieving the critical-to-quality attributes for the filled cartridge," says Mr. Zia. "Turnkey contract manufacturers such as Novocol provide value by combining cartridge fill-finish operations with drug delivery device assembly as a seamlessly integrated manufacturing operation. Device reliability and patient safety are affected by manufacturing controls for cartridge attributes such as siliconization, break loose/glide force, break force, container-closure integrity, cap geometry, and plunger insertion depth."

SCHOTT: Glass and Polymer Packaging Options Ensure Drug Stability

The importance of partnerships between pharma packaging suppliers and device manufacturers allows for integrated

solutions. One example is compatibility testing of SCHOTT's syriQ BioPure® PFS with Ypsomed autoinjectors and Nemera Safe'n'sound® safety devices.

SCHOTT's product range includes glass and polymer solutions. On the glass side, syriQ BioPure syringes were specifically designed to keep sensitive drugs stable over shelf life and shorten time to market while making administration more convenient for patients, says Anil Kumar Busimi, Senior Global Product Manager for SCHOTT iQ Platform. "The 1mL- and 2.25mL-long borosilicate glass containers are manufactured under improved processes to lower tungsten and adhesive residuals and to ensure a uniform silicone layer," he says. "A safe and easy administration with superior functionality is further enhanced by a seamless device integration. The syriQ BioPure silicone-free PFS have the additional benefit of being the world's first glass PFS without any silicone in the barrel."

Some drugs, especially biologics are ultra-sensitive to silicone and may interact with silicone oil in the PFS, which could impact the stability and efficacy of the drug. "Pharma companies struggle to shift such drugs from a vial to PFS," says Mr. Busimi. "With the availability of syriQ BioPure silicone-free, the seamless transition from vial to PFS is now possible even for the most sensitive biologic drugs. This is particularly relevant for ensuring drug stability of formulations that are ultra-sensitive to silicone."

On the polymer side, syringes within the SCHOTT TOPPAC® Polymer Design platform are made of cyclic olefin copolymer (COC), which provides drug stability i.e. barrier properties, no ion release or heavy metals, low free silicone amount, low protein adsorption, and no pH shift, explains Tom van Ginneken, Global Product Manager for Polymer Platform at SCHOTT. "SCHOTT TOPPAC is approved in more than 90 countries worldwide and has helped bring two blockbuster drugs to the market. The manufacturing process is based on highest quality standards with a state-of-the-art fully automated production."

SCHOTT offers the possibility to customize the design of the container to the pharma's drug, application or device needs. "By building the primary packaging around the most ergonomic shape of device, the usability of the device is not compromised," says Mr. van Ginneken. "This approach is supported by a four-stage sampling process (first-hand samples, functional prototypes, FHU samples, and fully automated production samples) to accelerate time to market for drug product and optimizing project completion."

Sorrel Medical: Connected Drug Delivery Shares Treatment Data With Caregivers

Connectivity in drug delivery devices and the demand for solutions that facilitate the sharing of data between stakeholders – patients, HCPs, and others – is essential. And developing these devices to optimize self-administration, using human factors studies and experience from on-market devices, minimizes use errors and makes the devices as simple and user-friendly as possible, claims Mindy Katz, Director of Product, Sorrel Medical.

Sorrel Medical's wearable drug delivery platform is designed for simple and efficient administration of large-volume and high-viscosity medications via a body-worn wearable injector. The device utilizes an electro-mechanical pumping mechanism for accurate and controlled drug delivery, and is primary container-agnostic to accommodate a range of drug reservoirs. Current configurations in development include a 1mL with internal drug reservoir, filled at point of care, and a 3-, 5-, 10-, and 20-, and 25mL with a prefilled and pre-loaded cartridge or vial.

"The pre-filled and pre-loaded device configuration enhances the patient experience and encourages adherence to therapies, while reducing the risk of medication errors," says Ms. Katz.

The devices are fully connected, via Bluetooth and near-field communication (NFC), allowing patients to share treatment data. The device utilizes UV LED technology for disinfection at point-of-care, overcoming the challenge of maintaining sterility in pre-loaded wearable devices. It also incorporates multiple smart sensors, including air detection, occlusion, needle positioning, and on-body attachment. "Those sensors, together with a series of internal system checks and visual, audio, and tactile indicators, guarantee a successful and confident self-administration experience," she says. ◆

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Raza Bokhari, MD

CEO

FSD Pharma, Inc.

FSD PHARMA

FSD Pharma Inc.: Is Ultra Micro-PEA the Best Untold Story in Pharma?

In 2019, the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) both formally expressed their commitment to advancing research on the potential benefits of cannabis for therapeutic uses. NIH's research portfolio on cannabinoids has provided early basic and preclinical work on CBD as an epilepsy therapy; in June 2018, FDA fast-tracked approved Epidiolex, a cannabidiol oral solution for treatment of seizures associated with Lennox-Bastaut syndrome or Dravet syndrome. The FDA claims it continues to support companies' drug development programs for drugs derived from cannabis or containing cannabinoids.

One such company is FSD Pharma Inc., a Canadian-domiciled specialty pharma that came on the scene in May 2018 by raising $53 million Canadian on the CSE. At that time, its focus was to build a hydroponic facility to grow medicinal-grade cannabis and supply it to prescription users in Canada and the rest of the world, except for the US. In 2020, FSD became one of 12 Canadian-domiciled companies to trade on NASDAQ, and is now focused on advancing research and development of synthetic compounds, including cannabinoid compounds that target the endocannabinoid system of the human body, which helps regulate key physiological and pathological processes. Endocannabinoids are natural, lipid-based signaling molecules that act through the cannabinoid receptor 1 (CB1) and 2 (CB2). Research has shown that the endocannabinoid system serves important protective functions in the body. For example, it stops pain signals before they reach the spinal cord and it boosts the body's ability to adapt to stressful situations.

In that quest, FSD acquired Prismic Pharmaceuticals, a US-based specialty pharma developing non-addictive prescription drugs for the treatment of pain and inflammation, at the end of 2019 for $17.5 million. The outcome of that acquisition

is the launch of FSD Pharma Biosciences Division, led by Edward Brennan, MD. The group has a Phase 1 first-in-human safety and tolerability trial for its lead candidate, FSD-201 ultra-micronized palmitoylethanolamide (micro-PEA), currently underway in Alfred Hospital, Australia. FSD-201is a potent anti-inflammatory agent that has widespread application to treat certain diseases of the central nervous system and autoimmune disorders of the skin, GI tract, and the musculoskeletal system.

Drug Development & Delivery recently interviewed FSD Pharma's CEO Raza Bokhari, MD, about how acquiring Prismic will benefit FSD, what makes the ultra-micronized platform unique, and how ultra-micro-PEA could be the answer to ending the opioid epidemic.

Q: Why did FSD acquire Prismic Pharmaceuticals and what doors does that open for you?

A: We now have the worldwide license, except in Italy and Spain, of ultra-micronized-PEA, which is a naturally occurring fatty acid. Prismic secured its license from its parent company, Epitech, a European privately held company. Epitech had developed the ultra-micronized version of PEA into 6 to 10 microns and then developed a 600-mg tablet. That tablet has been prescribed for more than a decade as a medical-grade supplement for inflammation in Italy. Prismic's initial interest was to expand into a nutraceutical, but FDA guidelines changed and Prismic was left with no option but to develop ultra-micronized-PEA as a prescription drug. Prismic ran out of capital and engaged with us in early 2019. We acquired these rights from Prismic with the acquisition. We are confident the outcome will be positive and similar in the response of all the hundreds of thousands of patients to whom Epitech has been selling to as a prescription medical supplement.

Q: What is the ultra-micro-PEA development platform? What makes it unique?

A: Micronization allows PEA to be orally bioavailable, but as we advance forward, there is a possibility it could take another form. The micronization technique was invented by Epitech and is protected by patents until 2034. As a potent analgesic and anti-inflammatory agent, ultra-micro-PEA is expected to be effective in many inflammatory diseases, such as chronic pain, arthritis, endometriosis, and various auto-immune disorders. In addition, there is some published data to suggest that ultra-micro-PEA may also have the potential to be an opioid-sparing agent.

Q: How does ultra-micro-PEA work in the body?

A: PEA directly and indirectly targets several receptors involved in inflammation and pain. One such receptor, PPAR-α, belongs to the peroxisome proliferator-activated receptor family of transcription factors regulating the expression of genes involved in cellular differentiation, development, metabolism, and inflammation. PPAR-α is found in the intestine, heart, liver, kidney, muscle, and fat tissue.

Another target, the GPR55 receptor, is homologous with CB1 and CB2, the principal cannabinoid receptors, and is also activated by Δ9-tetrahydrocannabinol, the principal psychoactive ingredient in cannabis, and possibly by at least two endocannabinoids. PEA also interacts indirectly with CB1 and CB2. CB1 receptors are found in the brain and throughout the body while CB2 receptors exist mainly in the gastrointestinal and immune systems.

The endocannabinoid system, including CB1 and CB2, is a key regulator of pain sensation and pain processing pathways. Endocannabinoids active at CB1 down-regulate neurotransmission, while CB2 agents regulate CNS immune cell activity. The combined activity at CB1 and CB2 receptors affects normal nociceptive processing and resolution of acute pain.

Q: Where do you see ultra-micro-PEA having the biggest benefit?

A: We are looking at the therapeutic effects of ultra-micro-PEA on its own. Pain is an outcome of inflammation. By reducing inflammation, it reduces pain. Instead of prescribing opioids, for some conditions, in which non-steroidal anti-inflammatory treatments are not enough, and there is nothing in-between, this micronized formulation of PEA could be the go-to drug before opioids are prescribed. There could be a reduction in the global increasing number of opioid addicts. It could also possibly slow down the disease progression through a reduction in cytokines. Additionally, as ultra-micro-PEA is a potent anti-inflammatory agent, it could likely become a safer and more effective NSAID for early-stage osteoarthritis, in lieu of non-steroidals.

Q: What is the market potential for the ultra-micro-PEA platform?

A: By Q4 2020 or early-Q1 2021, we will be in a position to be in front of the FDA with an IND to start looking at the value and impact of an ultra-micronized version of PEA in some

disease conditions, particularly early-stage osteoarthritis. We expect that to garner the interest of Big Pharma and get them talking to us.

Q: Do you envision licensing ultra-micro-PEA?

A: Drug development is a team sport. As a specialty R&D pharma, our expertise is to conduct Phase 1 and Phase 2 trials. Phase 3 and commercialization is the job of the big boys. We are a public company, so we have to respond to market realities in real time. As Chairman of the Board of FSD Pharma, I have the pulse of our board, and current thinking is that it's best to pass on the baton to bigger players who are more adequately capitalized to conduct the other studies. Our comfort level is to initially invest up to $50 million on this compound. At that point, we will have sufficient data to tee it up and possibly pass it on to bigger players.

Q: Once you pass the baton on ultra-micro-PEA, what's next for FSD?

A: We are actively looking to expand our pipeline by looking at other compelling compounds that target the endocannabinoid system. One investment banker at the JP Morgan Healthcare Conference told us that ultra-micro-PEA is the best untold story in the pharma industry. There are companies out there struggling to raise capital, and we could have an opportunity to acquire them.

FSD has signed a letter of intent with Solarvest to develop and test pharma-grade cannabinoids out of algae. The pharma-grade process could reduce the production time for targeted cannabinoid molecule(s) by up to 95%. Solarvest has completed a feasibility study for the expression of CBD and THC as a way to produce cannabinoids in sterile GMP facilities. Our belief is that the cannabinoid molecule potential is truly unmarked.

Q: What advice can you offer to other CEOs in niche and nascent markets?

A: You need strategic and financial partners. Be flexible enough to embrace them at the right time to create sustainable shareholder value. And, if you have to fail, fail fast in early-stage assets, and move onto the next compound. Companies tend to get caught when they receive data points that weren't as expected. So, reposition yourself and move on quickly. This is a thousand-mile journey. We have taken the first few steps, but they are definitive steps. We don't carry long-term debt on our books, and our balance sheet has capacity to raise capital. We believe we are well-positioned to move forward, but we are always learning from our own and others' mistakes. ◆

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ANALYTICAL SERVICES

Applying Innovative Thinking & Techniques to Reduce Time-to-Market

By: Ramesh Jagadeesan, PhD

INTRODUCTION

Applying an innovative approach to analytical chemistry can help to drive efficiencies and reduce critical timelines in successfully delivering vital medicines to patients. While contract development and manufacturing organizations (CDMOs) have the capacity to support pharmaceutical companies with their analytical requirements for both small and large-scale projects, the opportunity exists to increase speed to market with innovative thinking. The following explores the importance of innovation during analytical chemistry and discusses how time to market can be reduced during the analytical testing stage. In addition the value of understanding the drug development and manufacturing process during analytical testing is reviewed.

THE ANALYTICAL SERVICES MARKET

Greater preference from drug developers to redirect their resources in order to focus on core capabilities is creating growth in the outsourced analytical services market. Time pressures and in-house capacity issues have led many organizations to turn to stand-alone service providers and CDMOs that can support them in building a more strategic approach to their analyses and testing processes. At the same time, stricter demands from regulatory agencies for more analytical details on medicines and process development is also driving the need for better and more efficient analytical strategies.

INNOVATIVE APPROACHES TO ANALYTICAL CHEMISTRY

CDMOs strive to continuously identify innovative solutions that can bring increased value to their customers. As more systematic approaches are introduced, the automation of analytical instrumentation is simplifying. As a result, the volume of data being created is increasing while the level of resource required to generate this data is reducing, which has significant benefits for companies given the ever-increasing market demand.

The development of quality products is only possible with a forward-thinking, innovative mindset, along with close monitoring of emerging technological advancements. Increasingly, it is not only about estimating the expected but also about estimating the unexpected. Traditionally, analyses have been used to quantify the active ingredient and the impurities. Innovation has now led to the ability to estimate unexpected additions in formulations, for example, elemental impurities generated due to manufacturing vessels, reactants, etc.

Previously, elemental impurities were estimated using classical analysis, such as heavy metals tests and limits of arsenic. This is now being phased out in favor of more modern analytical techniques, including Raman spectroscopy, inductively coupled plasma mass spectrometry (ICP-MS), optical emission spectroscopy (OES), nuclear magnetic resonance (NMR) spectroscopy, and ultra-performance liquid chromatography (UPLC). Using different detectors, such as a refractive index detector, a fluorescence detector, an evaporative light scattering detector (ELSD), and Quadrupole Dalton (QDa) detectors during method develop-

ment, allows companies to ensure product safety and efficacy. This helps to provide substantial data for regulatory authorities. Furthermore, orthogonal analytical techniques facilitate a fuller understanding of the product composition, in terms of compliance both Q1 (qualitatively) and Q2 (quantitatively). The use of these techniques is helping to reduce timelines and, in turn, allowing medicines to be delivered to market more quickly.

OPTIMIZING ANALYTICAL TESTING TO REDUCE TIME TO MARKET

Innovations in analytical testing are helping to reduce time to market and regulatory burden, whilst also improving patient safety. In R&D, these advancements are proving valuable in the selection of the most stable and effective forms of drug substances, offering improvements in solubility and enabling identification of most compatible excipients.

Automation and the emergence of new techniques are lessening time for quality control testing, while stability testing has been transformed through the use of simulating chambers for freeze thaw, photostability testing, and chambers for all temperature zones.

The process of selecting packaging materials has also been enhanced with the introduction of extractables and leachables (E&L) testing, as well as the compatibility testing of materials. New technologies are also reducing regulatory burden by meeting the requirements of newer guidelines, including Quality by Design (QbD), elemental impurities, and data integrity requirements.

INNOVATION EXAMPLE – TITRIMETRIC ANALYSIS, THE NEED TO CONSIDER DRUG DEVELOPMENT & MANUFACTURING PROCESSES DURING TESTING

Some CDMOs bring understanding of the complete drug lifecycle, using experience of commercial manufacturing and quality control (QC) testing into the development of robust methods. The broad understanding and experience of how different analytical methods can impact formulation development and timelines within QC is vital to establish new methods accordingly.

Several points should be considered in method selection. Methods should be stability indicating and sensitive enough to detect and quantitate as per current regulations. Methods should be robust enough to be transferred from the scientific environment in a development lab to the highly efficient and LEAN oriented environment in a QC lab.

The development of analytical methods for genotoxic impurities also needs to be considered as this will be critically reviewed by regulatory agencies.

Breakability tests as per the guidelines of various countries should be conducted for the tablets having the score-lines. Additionally, alcohol dose-dumping studies need to be considered for extended-release dosage forms, and stability studies should be conducted as recommended by the regulators.

Working with a CDMO that is experienced in QbD-based analytical method development can ensure innovative approaches in developing high-quality, robust, transferrable methods.

METHOD DEVELOPMENT CASE STUDY

This case study demonstrates method life cycle management. A customer's previous contract services provider was conducting three analytical methods with poor resolution and sensitivity. As a result, Recipharm was approached to develop better methods for a fixed dose combination (FDC) product. Using the team's knowl-

TABLE 1

Contract provider method	Developed method

• Three separate HPLC methods
  • Assay of actives (gradient elution, 25 minutes run time)
  • Assay of preservative (25 minutes)
  • Related substances (gradient elution, 50 minutes run time)
	• Single HPLC method was developed
	  • Assay of actives, assay of preservative and related substances (gradient elution, with a run time of 80 minutes)

• Three separate HPLC systems and columns needed	• One HPLC system and one column is sufficient
• Placebo interference observed due to re-formulation	• All peaks are well resolved
	• Turn-around time and cost per analysis had been reduced two times
	• Efficiency on resource utilisation

Method Development Case Study Results

edge data base and expertise a single method was developed with the required pre-determined reproducibility and resolution. This brought considerable cost-savings during each stability run. The results are presented in Table 1.

METHOD VALIDATION

Validation documents are a window into regulatory agencies. High-quality documents and the ability to respond to queries quickly will reduce a product's time to market. A strict GMP environment, custom field calculation, and the capability for electronic data back-ups can help ensure error free data. QbD-based method validations provide a better understanding of the critical parameters of the analytical method and help to provide trouble-free methods throughout the product life cycle.

THE VALUE OF OUTSOURCING

CDMOs are leading the way in the development of shorter/fewer methods, which is contributing to considerable reductions in testing times. Their ability to offer both the necessary capacity and scale frees up their customers' QC and analytical laboratories to focus on other activities, while CDMOs can offer the expertise and resources to perform multiple analyses in parallel - something many pharma companies struggle to cope with in-house.

A successful analytical testing strategy is reliant on a thorough understanding of current techniques. Working with a CDMO alleviates much of the burden from pharmaceutical companies and their teams. This is because a reputable partner will be adept at staying up to date with today's trends, providing a better solution for its customers. They will also have ingrained processes in place for knowledge-sharing during technology transfer as well as throughout the product lifecycle. Staying at the forefront of regulatory updates and pharmacopeial changes is also fundamental to their service offerings and enables them to develop (and validate) methods based on current needs.

Working with a CDMO will provide a dedicated team that will have broad experience acquired across a wealth of varied development projects. Bringing this type of expertise to the table means that CDMOs are ideally positioned to deliver under specific timelines. For example, documents can be turned around in as little as two to 3 days, while knowledge and use of the latest techniques can help reduce analytical run time to 2 to 3 minutes. Method development generally takes between 4 to 6 weeks. CDMOs will be able to provide previous examples of their capacity to innovate, as well as the experience to suggest new solutions.

Working with different molecules across many different clients allows a CDMO to apply insight that has been acquired through the development of many formulations. Not only are they able to easily understand when issues arise related to analytical method development, but they are accustomed to identifying root causes. Access to this type of experience and expertise can optimize lifecycle management and ensure products are delivered to market in a specific timeframe.

FINAL THOUGHT

Working with a CDMO that has a dedicated understanding of innovations in analytical science can help at all stages of the product lifecycle. By bringing innovations in analytical chemistry combined with knowledge of product development, a CDMO partner can help overcome complex challenges and improve time to market for novel drug products. ◆

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

BIOGRAPHY

Dr. Ramesh Jagadeesan is Senior Director, Analytical Development, at Recipharm is currently heading the Analytical Excellence Centre at Recipharm, Bangalore, India. He has 20 years of experience in analytical research and development. He has authored numerous research publications in the areas of analytical development, controlled- release technology, and stability studies. He is an expert in stability studies for NCE, ANDA, and commercial and clinical stability. Dr. Jagadeesan earned his PhD in Pharmaceutical Analysis.

Technology & Services Showcase

Specialty CDMO

Adare Pharmaceuticals is a global specialty CDMO providing product development through commercial manufacturing expertise focused on oral dosage forms for the Pharmaceutical, Animal Health and OTC markets. Adare's proprietary technology platforms specialize in ODT, taste masking and customized drug release. With over 30 years of proven legacy, Adare has successfully developed and manufactured more than 40 products sold by partners in more than 100 countries globally. For more information, visit Adare Pharmaceuticals at **www.Adarepharma.com.**

CDMO Services

Ajinomoto Bio-Pharma Services iis 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.**

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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.**

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Technology & Services
Showcase

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.**

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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.**

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Catalent Biologics provides advanced technologies and tailored solutions for biologics, biosimilars, cell and gene therapies, and antibody-drug conjugates, from DNA to commercial supply across its network, including locations in North America and Europe. Its comprehensive offerings for customers include GPEx® cell line development, SMARTag® bioconjugation technology, process development, integrated or stand-alone analytical, drug product formulation development, fill/finish, clinical and commercial manufacturing, and primary and secondary packaging. In 2019, Catalent Biologics launched OneBio® Suite, a single solution from cell line development through supply to address the challenges facing biologic development companies looking to accelerate programs to clinic or market. This integrated service can reduce timelines, risk, and complexity by providing customers with a single contract, a global program manager, and harmonized quality systems. For more information, contact Catalent Pharma Solutions at (888) SOLUTION or visit **www.catalent.com.**

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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.**

Technology & Services Showcase

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Testing experts.
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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.**

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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.**

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Technology & Services
SHOWCASE

ANALYTICAL TESTING

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INNOVATIVE CDMO

Quotient Sciences
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Technology & Services Showcase

CDMO Solutions

Recipharm is a leading Contract Development and Manufacturing Organization (CDMO) in the pharmaceutical industry employing almost 9,000 employees. Recipharm offers manufacturing services of pharmaceuticals in various dosage forms, production of clinical trial material and APIs, and pharmaceutical product development. Recipharm manufactures several hundred different products to customers ranging from big pharma to smaller research and development companies. The company operates development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US and is headquartered in Stockholm, Sweden. The Recipharm B-share (RECI B) is listed on Nasdaq Stockholm. For more information, visit Recipharm at **www.recipharm.com.**

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DRUG DISCOVERY

Disrupting Drug Discovery From Assay Development to Lead Compound

By: Zack Gurard-Levin, PhD

A PATH FOR DRUG DISCOVERY

High-throughput screening remains one of the most powerful, unbiased approaches for small molecule drug discovery. Compound libraries, many featuring millions of diverse molecules, are rapidly tested against a therapeutic target to identify the most promising leads for preclinical and clinical development.

Today, the high-throughput screening toolbox features traditional label-dependent approaches and novel label-free technologies. Researchers select the most promising methodology based on assay sensitivity, data quality, costs, and speed. Moreover, many companies outsource drug discovery to contract research organizations (CROs) with expertise and an established infrastructure to manage hit identification and hit-to-lead programs.

IDENTIFYING THE RIGHT ASSAY FOR YOUR TARGET

When a target has been validated for drug discovery, the first step is to develop a robust assay suitable for measuring its activity and revealing small molecule modulators. Assay development aims to address:

- How sensitive and robust is the assay?
- What is the linear range of the enzyme activity?
- What are the kinetic parameters to achieve balanced conditions?

Every high-throughput assay methodology claims to provide answers and a sensitive and reproducible assay suitable for hit identification. However, before selection, two additional questions apply:

- What limitations and/or restrictions could impact data quality?
- Will extensive false-positive and/or false-negative results delay progress and increase costs?

Answering these questions is paramount to foresee potential obstacles and to determine measures of success for a drug discovery program.

Let's explore these questions in the context of different approaches: label-dependent, emerging label-free, and self-assembled monolayer desorption ionization label-free formats.

DON'T BELIEVE IN LABELS, BELIEVE IN RESULTS

Label-dependent assays are prevalent in drug discovery. They measure a change in radioactivity or optical readouts, such as fluorescence or luminescence. Popular optical-based assays take advantage of energy transfer between a donor and acceptor reagent, such as a bead or fluorescent probe.

These formats are generally simple and inexpensive to run. However, possible limitations and significant opportunities for false-positive data make them potentially problematic.

CHALLENGES OF LABEL-DEPENDENT ASSAYS

- Raising antibodies and synthesizing labeled substrates can delay projects by several months to a year.
- Antibodies are often not specific, introducing assay artifacts.
- Expensive reagents can double overall costs.
- Fluorophores may interact with enzymes and alter activity and specificity.[1]
- Dimethyl sulfoxide (DMSO) may impact the interaction between reagents and beads, affecting data quality.
- Library compounds may quench optical signals or exhibit auto-fluorescence, generating high rates of false-positive and false-negative results.

LABEL-FREE ASSAYS: SEEING IS BELIEVING, OR IS IT?

Label-free assays eliminate the false-positive and false-negative results that derive from optical interference of library compounds. This advantage alone can expedite drug discovery by avoiding the need to rule out false positives through orthogonal assays. Mass spectrometry (MS) has emerged as a powerful, label-free readout to analyze biochemical reactions. MS reveals the precise mass of substrates and products, providing an information-rich, quantitative readout that eliminates questions surrounding the data. This also opens avenues to identify unanticipated reactions.

Electrospray Ionization Mass Spectrometry

Conventional MS instruments, such as electrospray ionization, offer high sensitivity well suited for analyzing biochemical reactions. However, reactions require processing often by solid-phase extraction prior to analysis. This time-consuming step raises significant limitations for screening applications:

- Costly consumables are needed.
- Required reaction volumes may be 10+ times higher than other formats, driving up reagent consumption and costs.
- Not amenable to 1536 geometries.
- Low throughput: a 384-well plate takes over an hour to read.

Acoustic Dispense With Mass Spectrometry

An emerging strategy integrates acoustic transfer with MS.[2] Directly injecting biochemical reactions into the MS instrument eliminates the rate-limiting sample preparation step. Prototype instruments achieve a throughput of 100,000 samples per day, useful to researchers screening millions of compounds.[2] Interestingly, what enables the rapidity introduces potential limitations:

- Critical reaction components — salts, detergents, and carrier proteins — lead to ion suppression.
- Ion suppression introduces noise, and data quality suffers, with Z′-factors falling below 0.5.[2]
- Certain reaction components may impact MS hardware, necessitating frequent maintenance.
- Low-sensitivity challenges detection of nanomolar analytes.

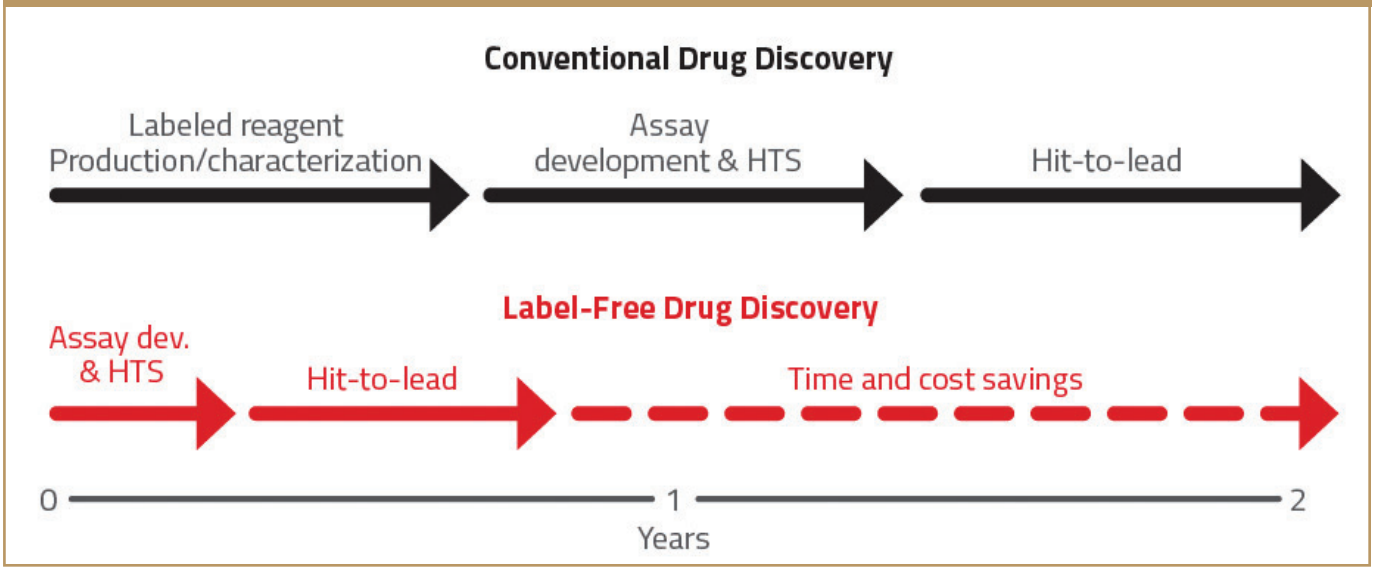
As a solution, researchers may exclude the salts, detergents, and carrier proteins. However, this can impact enzyme activity and aggregation of proteins or screening compounds. At low or zero salt concentrations, can activity be measured? Is the assay sensitive enough to work under balanced conditions (at substrate Km)? Commercial instruments integrating acoustic dispense with an open port interface along with MS are expected in 2020, and while preliminary data is encouraging and eliminates the tedious sample preparation steps, it remains to be understood whether inherent restrictions with ESI MS limit wide scale drug discovery applications.

Matrix-Assisted Laser Desorption/ Ionization Time-of-Flight Mass Spectrometry

An alternative to electrospray ionization, MALDI-TOF MS generates a rapid readout useful for high-throughput applications. It measures diverse analytes, including small molecules, peptides, oligonucleotides, and proteins (including antibodies). MALDI samples are prepared by introducing a matrix molecule to the analyte to assist with ionization to enable detection. As with acoustic MS, ion suppression due to salts, detergents, and carrier proteins is a significant limitation. These components must be removed or excluded prior to analysis, resulting in the same issues as for acoustic MS. Finding a buffer system that both the enzyme and instrumentation can tolerate is time-consuming: Some researchers report yearlong assay development programs.

Considering the aforementioned op-

FIGURE 1



tions for drug discovery, researchers must still decide which matters more: biochemical relevance or speed and take time to validate and further test their results through orthogonal approaches.

A DISRUPTIVE LABEL-FREE SOLUTION FOR SUCCESSFUL DRUG DISCOVERY

Self-assembled monolayers for matrix-assisted laser desorption/ionization — a technique termed SAMDI — was first reported in 2002.[3] In 2011, this innovative assay methodology had already achieved a throughput capable of screening 100,000 compounds in 1 day and it continues to evolve with proven assays for high-throughput screening of diverse targets and biochemical activities, affinity selection assays, and cell-based assays.[4-7]

A significant advantage of this unique surface chemistry is that drug discovery researchers are free to optimize assay conditions according to their targets, rather than having the analytical method dictate how to run their reactions. The result is more biochemically relevant assay conditions, more relevant data, and higher confidence in results. These key innovations accelerate assay development, hit identification with high-throughput screening, and hit-to-lead optimization.

SURFACE CHEMISTRY: LAYING A FOUNDATION FOR SUCCESS

Self-assembled monolayers (SAMs) of alkanethiolates on gold offer a structurally well-defined and synthetically flexible surface that enables key advantages for biochemical reactions:

- SAMs presenting short oligomers of ethylene glycol are inert to non-specific protein adsorption.[8]
- SAMs can be tailored with functional groups to specifically immobilize distinct ligands, including small molecules, peptides, oligonucleotides, proteins, and antibodies. Other reaction components are washed away, purifying up to 1,536 samples in seconds and eliminating ion suppression.
- SAMs are efficient substrates for MALDI-TOF MS, the basis for the ultra-high-throughput and label-free readout.

The assay platform is simple to utilize: The assays start with a homogenous biochemical reaction in a 384- or 1535-well plate. When the reactions are quenched, complex reaction mixtures are transferred to high-density 384 or 1536 biochip arrays. There, substrates and products are specifically captured to the SAM, while other reaction components are washed away. This innovation enables researchers to include any salt, buffer, detergent, carrier protein, or other component in the biochemical reaction.

Following immobilization of the specific analytes, matrix is applied to the biochip array and analyzed in a MALDI instrument. The resulting spectra are clean, with peaks corresponding primarily to singly charged species with virtually no fragmentation for simple data interpretation and minimal background.

BENEFITS OF COMBINING SAMs & MALDI

- Eliminate labels and associated false positives
- Amenable to any buffer system
- Fast assay development
- 384 or 1536 geometries
- Quantitative analysis
- Reduced reagent costs
- High-throughput readout
- Multiplexing capabilities

ASSAY DEVELOPMENT: SMARTER QUESTIONS, FASTER ANSWERS

Assay development with self-assembled monolayer desorption/ionization starts ahead of other assay formats: There is no need to synthesize fluorescent reporters, raise antibodies, or optimize a compatible buffer. Regardless of the analyte, assays that reveal balanced conditions suitable for hit identification and characterization can be developed in days.

One aspect to consider is that the analyte of interest must be amenable to immobilization on the SAM array. For this, several immobilization chemistries have been established, with new, traceless innovations opening avenues to immobilize challenging molecules.[9]

DISRUPTING THE HIGH-THROUGHPUT SCREENING MARKET

Researchers can now be assured that speed AND biological relevance are not compromised when running biochemical assays. The use of MALDI TOF MS provides an ultra-high-throughput readout, with the newest instruments reading a 1536-spot plate in less than 10 minutes. Meanwhile, the self-assembled monolayers provide a flexible platform for virtually any buffer, any analyte, and any target, making this combination the gold standard for drug discovery.

Another innovation is the ability to multiplex assays. Not only can this platform distinguish multiple products from a single enzyme, but it can also be used to measure multiple activities from distinct enzymes. Provided the substrates and products are mass resolvable, the reactions can be run with two or more enzymes in a single well, or run in separate plates and multiplexed prior to immobilization and analysis. In this manner, twice the data is generated in half the time. The method can also shed light on compound potency and selectivity simultaneously by screening compounds against different targets.

HIT-TO-LEAD: AN OPTIMIZED ASSAY GENERATES OPTIMIZED RESULTS

When initial hits have been identified, revealing structure-activity relationships (SAR) and optimizing for potency and selectivity are simple and streamlined. The clean dose-response data resulting from the self-assembled monolayers and MALDI MS drives medicinal chemistry programs. The platform's flexibility enables experiments that elucidate mechanism of action, defining competitive, uncompetitive, noncompetitive, or mixed inhibition. This innovation allows total characterization of lead compounds from hit identification to inhibition mechanism and generates data to drive decisions for further development.

BINDING ASSAYS: RAPID, LABEL-FREE SOLUTIONS FOR CHALLENGING PROBLEMS

Many drug discovery programs seek small molecules that bind a specific target. When binding does not change functional activity or the target itself does not possess enzymatic activity, binding assays must be developed to reveal small molecules that engage a therapeutic target of interest. Long-established binding assay types include low-throughput biophysical approaches such as surface plasmon resonance and isothermal calorimetry.

Affinity selection mass spectrometry has emerged as a powerful tool for revealing non-covalent small molecule binders. It informs on the compound mass rather than on a signal change, where metabolites or impurities may generate false-positive results. Conventional MS binding assays utilize chromatography to isolate a target and bound small molecule from nonbinders. A second column dissociates the small molecule from the target. Finally, the small molecule is analyzed by MS. This approach is suited for measuring binding events, provided that the target is stable throughout the protocol.

In addition, requisite high target concentrations (often > 1 µM), increase costs — a challenge for difficult to express/synthesize targets. Lastly, to increase throughput, hundreds of compounds are often pooled in a single well. Mixing so many compounds in a single reaction may impact target and compound behavior.

Alternatively, innovation with self-assembled monolayers has opened avenues to ultra-high-throughput, label-free assays that reveal non-covalent small molecule binders for diverse analytes. After the target and one or a pool of small molecules

incubate, target-compound complexes are rapidly and selectively immobilized on the SAM-presenting biochip arrays and then directly analyzed to identify the binding molecules. Importantly, the monolayer molecule itself, at a constant density across the arrays, provides an internal standard to compare mass accuracy and binding across large-scale screens. Data analysis includes comparing the area under the curve (AUC) of any binding compound to the AUC of the monolayer molecule. This rapid analysis identifies potential binders. Dose response experiments rank-order the binding molecules to guide development efforts.[6]

SUMMARY

For many years, drug discovery researchers have been forced to compromise certain scientific assay goals — sacrificing data quality and costs to achieve high-throughput labeled assays, sacrificing speed to use biochemically relevant reaction conditions with slow label-free readouts, or sacrificing optimal assay conditions to use rapid label-free readouts. With new innovations in assay methodologies, scientists no longer have to make sacrifices to do quality drug discovery research. The combination of high-density self-assembled monolayer biochip arrays and mass spectrometry disrupts the market by allowing researchers to use optimal reaction conditions with a label-free and ultra-high-throughput readout. This solution accelerates assay development, hit identification, and hit-to-lead characterization, taking discovery research one step closer to the clinic.◆

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BIOGRAPHY

Dr. Zack Gurard-Levin has served as Chief Scientific Officer at SAMDI Tech, Inc. since June 2016. He brings more than 10 years of multidisciplinary research experience with expertise in chemistry, biochemistry, cellular biology, and translational research. Dr. Gurard-Levin was a pioneer user of SAMDI technology and co-developed SAMDI as a high-throughput, label-free solution for drug discovery research. Prior to SAMDI Tech, he was a research scientist at the Institut Curie in Paris, France, leading epigenetics drug discovery and diagnostics projects in oncology. He has authored numerous peer-reviewed articles and has been awarded multiple research grants. He earned his PhD in Chemistry from the University of Chicago and completed a post-doctoral fellowship at Institut Curie.

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