Drug Development & Delivery

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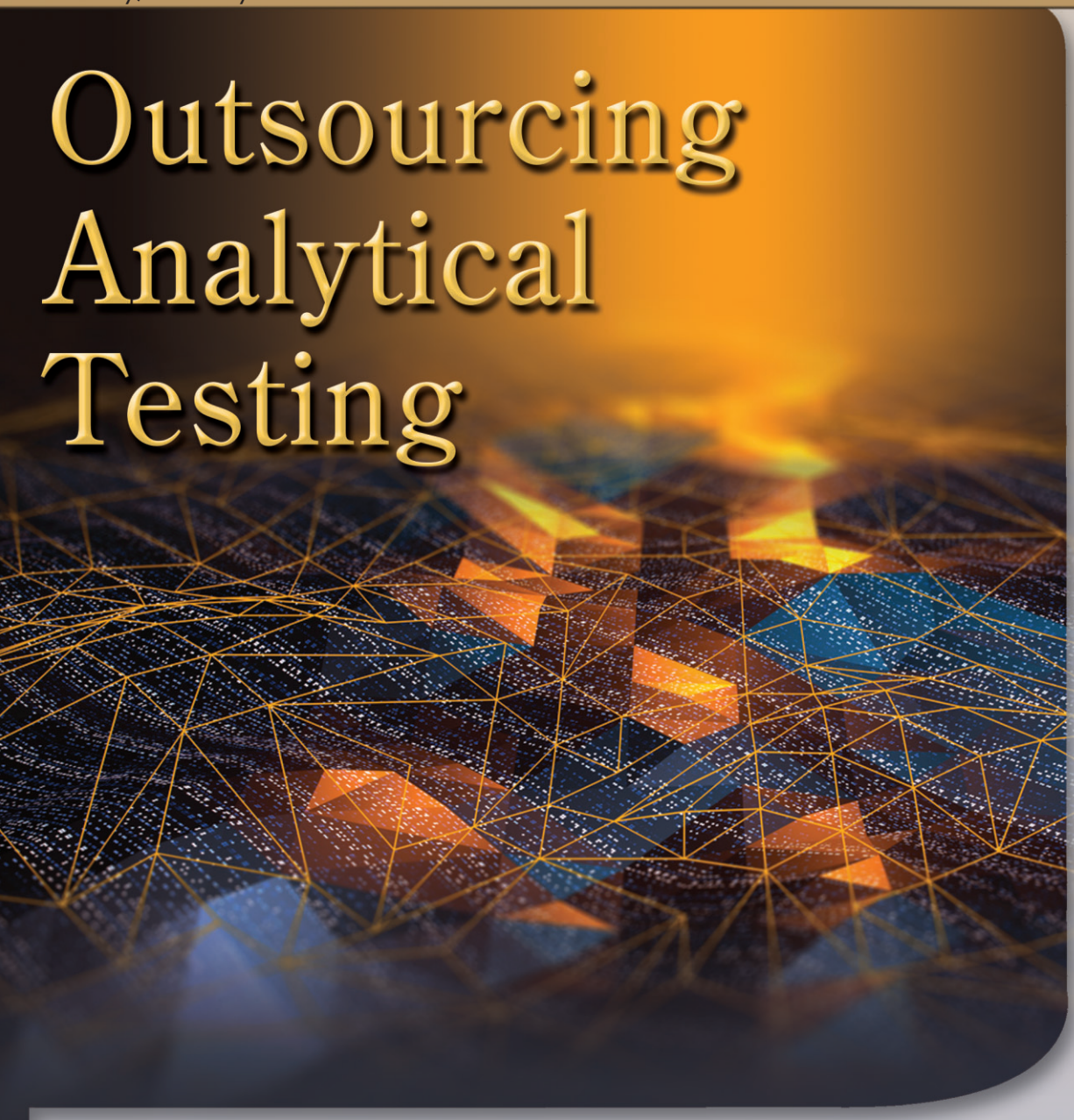
Outsourcing Analytical Testing



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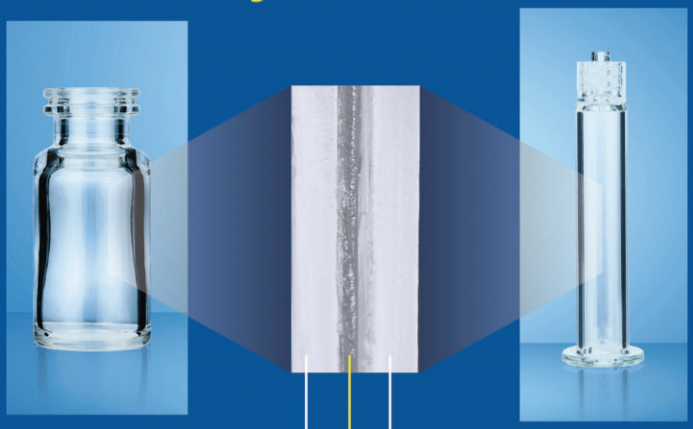

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Outsourcing Analytical Testing

"The global pharmaceutical analytical testing outsourcing market size is projected to reach $10.4 billion by 2026, according to a recent report by Grand View Research, Inc. Clinical bioanalytical testing services is projected to be the largest service segment over the forecast period. And with many big companies lacking the required manufacturing set-up and expertise to carry out in-house testing services, outsourcing is essential to remain competitive."

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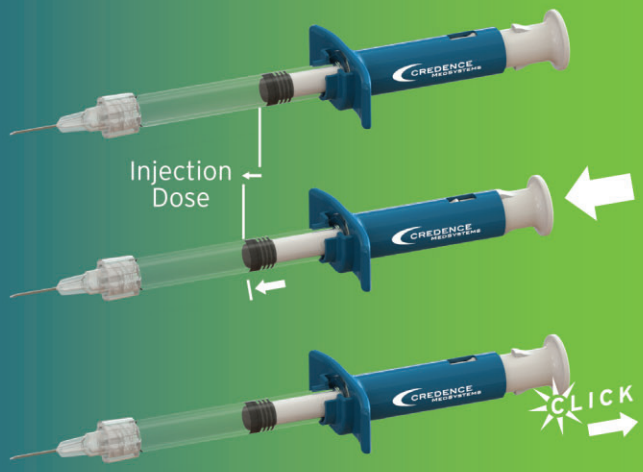

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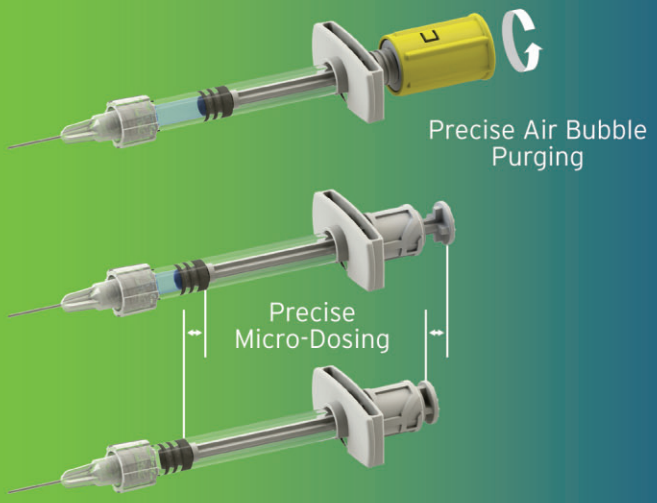

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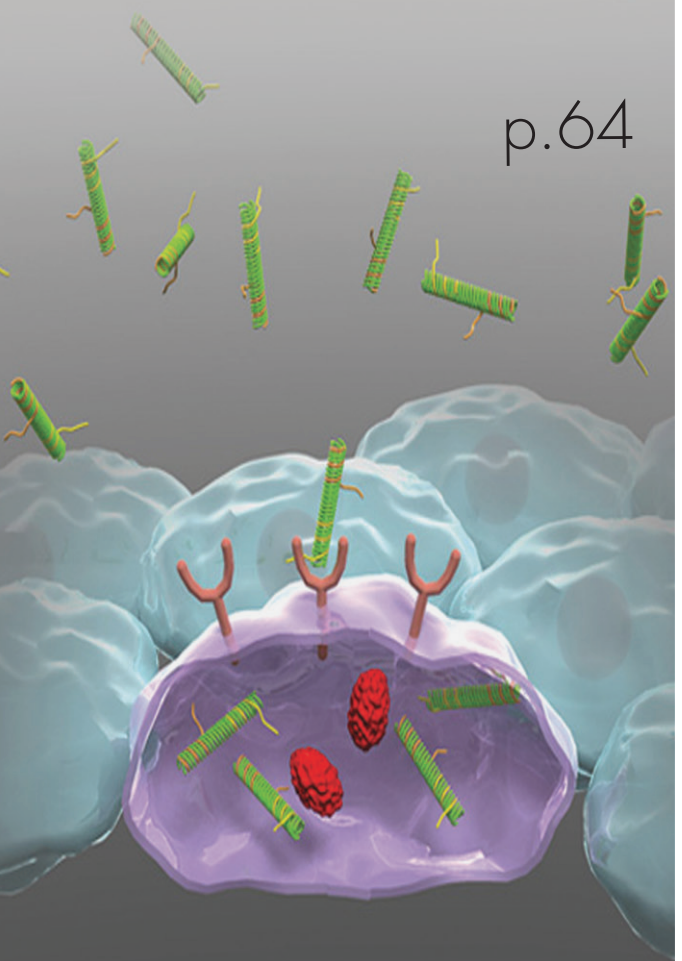
Oligonucleotide Delivery

"More than 30 years have passed since the initial development of oligonucleotide drugs; however, only eight drugs have been approved thus far. This is partially due to issues related to oligonucleotide delivery methods. We believe there is a novel delivery platform with the potential to resolve several of these complications."



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Patent Filed for Nitric Oxide Delivery Device That is Comparable to Inhalers

Nu-Med Plus, Inc., a medical device development company, recently announced that a patent has been filed for a nitric oxide delivery device that is designed for single or short-term use.

Nitric oxide delivery devices on the market today are large, electronically complex devices that are used primarily in neonatal intensive care units. Nu-Med Plus Inc realized that to extend the utility of nitric oxide delivery to a wider range of patients that could benefit from the therapy that another form factor was needed. The result was a simple mechanical device that delivers the appropriate dose of nitric oxide gas per inhalation to the patient. It is hand-held with no electronics and a variable nitric oxide dose.

A patent was filed in 2019 adding this to the stable of Nu-Med intellectual property. Dr. Craig Morrison, a member of the medical supervisory board of Nu-Med remarked, "It's a very simple device; it is used like an inhaler. One use that comes to mind is altitude sickness when the user could carry a small disposable unit to use until they could be transported to a lower altitude. Remote areas and rural areas without electrical power, patients being transferred by ambulance, patients being transported for chronic routine treatments, and patients in developing countries without access to electric power are generally groups that would need disposable delivery sources of nitric oxide therapy. This could be a real game changer."

With this new device, Nu-Med Plus will in the future seek enrollment in further studies to investigate its efficacy. Nu-Med Plus is currently in the process of submitting for FDA approval for a nitric oxide delivery system that is a fixed hospital unit. Nu-Med Plus's technology is designed to be utilized for a variety of inhaled nitric oxide treatments. Inhaled nitric oxide has been proven to stabilize blood pressure, open airways, fight infections and blood clots, combat aging, and treat erectile dysfunction.

Nu-Med Plus, Inc. founded in 2011, is a medical device development company created to explore medical applications of newly developed nitric oxide technologies. The strategy focuses on high growth potential markets where there is a clearly defined need recognized by the medical community that can be addressed by Nu-Med Plus and its technical expertise. Initial research and product development have been in the delivery of inhaled nitric oxide gas for therapeutic use. For more information, visit www.nu-medplus.com.

Bioiberica Launches Natural Origin Thyroid

Bioiberica, a world reference in the identification, extraction, and development of animal-derived APIs, recently announced the launch of its natural thyroid active pharmaceutical ingredient (API) for the treatment of hypothyroidism. Replacing or supplementing the hormones that are ineffectively produced by the human thyroid gland, the API specifically targets patients who prefer a natural origin treatment or those who continue to experience symptoms despite using the standard synthetic therapy.

Hypothyroidism is a common condition of thyroid hormone deficiency that affects up to 5.3% of the population in Europe, depending on the definition used. Thyroid hormone replacement via levothyroxine – a synthetic variation – is the standard treatment for patients with hypothyroidism. However, evidence suggests that 5%-10% of patients treated with levothyroxine exhibit persistent symptoms despite having normal thyroid-stimulating hormone (TSH) levels. These symptoms include fatigue, weight gain, and depression.

Javier Velasco-Alvarez, R&D Director at Bioiberica, said "There is a clear subset of patients suffering from hypothyroidism with persistent symptoms despite following a standard synthetic thyroid treatment. Our natural thyroid API, extracted from porcine thyroid glands, targets this unmet need. It contains the hormones – tetraiodothyronine, also known as thyroxine or T4, and triiodothyronine, otherwise known as liothyronine or T3 – that are naturally produced by the thyroid gland. Scientific evidence shows that thyroid API is an effective treatment from a natural origin."

Manufactured to European pharmaceutical standards, thyroid offers quality, safety, and regulatory compliance due to Bioiberica's vertically integrated supply chain, through which it can offer full traceability, security, and sustainability.

Jaume Reguant, Healthcare Director at Bioiberica, added "The development of our new thyroid API is the direct result of collaborative partnership with a key player in the pharmaceutical market. By combining our partner's knowledge with our leading expertise in the identification and manufacture of specific biomolecules, we have successfully developed a solution that looks to address one of today's many healthcare challenges. Above all else, we believe that collaboration and shared expertise is key to innovation in the pharmaceutical industry. The development of our new thyroid API is just one example of how such partnerships can help us explore new horizons and activate the innovation of novel pharma solutions. It's for this reason that we are actively seeking partners to investigate new opportunities in glycosaminoglycans, complex lipids, proteins, and bioactive peptides of non-recombinant origin."

Bioiberica is a global Life Science company committed to improving people, animal, and plant health and well-being. Our core business is the identification, extraction, and development of animal-derived biomolecules, which are transformed into high-quality products for the pharmaceutical, nutraceutical, veterinary, feed, and agricultural industries. This specialization has positioned us as the leading Heparin API manufacturer and a world reference in the research, production, and sale of other animal-derived APIs, ingredients, and compounds, such us chondroitin

New Publication Demonstrates GeneSight Improved All Clinical Outcomes Using HAM-D6 Analysis in Large Prospective GUIDED Study

Myriad Genetics, Inc. recently announced that a new analysis of the GUIDED clinical trial using the 6-item Hamilton Depression Rating Scale (HAM-D6) was published online in BMC Psychiatry. The key finding is the HAM-D6 scale identified statistically significant improvements in all three clinical endpoints – remission, response, and symptoms – between GeneSight-guided care and treatment-as-usual at Week 8.

"The HAM-D6 scale has been shown to be a better measure of core depressive symptoms than the HAM-D17 scale," said Boadie W. Dunlop, MD, one of the study investigators and associate professor of Psychiatry and Behavioral Sciences at Emory University School of Medicine. "This post hoc analysis provides further evidence that the GeneSight test led to significant and clinically meaningful improvements in clinical outcomes for patients with major depressive disorder relative to treatment-as-usual care."

The GUIDED study was the largest prospective study to assess the benefit of pharmacogenomics-guided treatment for depression using the GeneSight Psychotropic test versus an active therapy control arm. All patients in the GUIDED study had the 17-item HAM-D17 questionnaire administered by blinded off-site raters as part of the study protocol. The 6-item HAM-D6 score represents a subset of HAM-D17 questions that have been shown to be more directly linked to depression. For example, questions such as "have you had trouble sleeping" that could be associated with conditions other than depression are excluded from the HAM-D6 score. Clinical studies have shown that the HAM-D6 score is superior to HAM-D17 at discriminating antidepressants from placebo.

GeneSight Psychotropic is a pharmacogenomic test that analyzes clinically important variations in DNA. The results of the test can inform doctors about genes that may impact how their patients metabolize or respond to depression medications.

Myriad Genetics Inc., is a leading precision medicine company dedicated to being a trusted advisor transforming patient lives worldwide with pioneering molecular diagnostics. Myriad discovers and commercializes molecular diagnostic tests that determine the risk of developing disease, accurately diagnose disease, assess the risk of disease progression, and guide treatment decisions across six major medical specialties where molecular diagnostics can significantly improve patient care and lower healthcare costs. Myriad is focused on five critical success factors: building upon a solid hereditary cancer foundation, growing new product volume, expanding reimbursement coverage for new products, increasing RNA kit revenue internationally, and improving profitability with Elevate 2020. For more information, visit www.myriad.com.

Tetra Bio-Pharma Provides Update on its Hepatocellular Carcinoma Drug

Tetra Bio-Pharma Inc. recently announced it will be requesting a meeting with the US FDA to discuss the drug development program for its Orphan Drug candidate HCC011, inhaled delta-9-tetrahydrocannabinol (THC), in the treatment of hepatocellular carcinoma.

Hepatocellular carcinoma (HCC), also known as primary liver cancer, is the most common form of liver cancer and is responsible for 80 percent of the primary malignant liver tumors in adults. In addition to quality of life benefits to cancer patients, based on preclinical research, HCC011 should also have antitumor effects. The Phase 2 study of HCC011 will target patients with disease progression on Sorafenib, have measurable disease, and Child-Pugh Class A liver impairment. The Phase 2 trial will consist of a single arm. Patients will receive the HCC011 by inhalation three times daily, in combination with Sorafenib, until disease progression or unacceptable toxicity. The study design is similar to the ones used by recent drugs seeking accelerated approval. The Disease control rate will be assessed based on the Response Evaluation Criteria in Solid Tumors (RECIST); the overall survival and time to progression will be closely monitored over time. Patients will also beneficiate of the anti-emetic effect of HCC011, which will participate in improving their quality of life.

The company intends to file an NDA for HCC011 via the 505(b)(2) pathway. The FDA has three approval pathways by which drugs may gain approval and the 505(b)(2) new drug application (NDA) is one of the three ways created by the Hatch-Waxman Amendments of 1984, with 505(b)(2) referring to a specific section of the US Federal Food, Drug, and Cosmetic Act. The provisions of a 505(b)(2) provide manufacturers who have certain types of drugs with an opportunity to acquire FDA approval without performing all the work that's required with a standard 505(b)(1) NDA.

Additionally, 505(b)(2) pathway allows for the ability to pursue additional designations such as fast track and accelerated approval to complement its already granted Orphan Drug Designation for HCC011 in HCC. Orphan drug designation provides certain benefits and incentives, such as seven-year marketing exclusivity, protocol assistance from the FDA, tax credits of 50% of the clinical drug testing cost awarded upon approval, and a waiver of the prescription drug user fee. The company fully intends to seek out additional designations where appropriate.

The HCC011 orphan drug candidate benefits from Tetra's significant clinical data on the pharmacokinetics, safety and pharmacodynamics of inhaled cannabinoids. The company will also benefit from its previous investment in its GMP compliant manufacturing facility for these inhaled new drugs that holds an active Drug Establishment License (DEL) from Health Canada.

Tetra Bio-Pharma is a biopharmaceutical leader in cannabinoid-based drug discovery and development with a Health Canada approved, and FDA reviewed, clinical program aimed at bringing novel prescription drugs and treatments to patients and their healthcare providers.

Catalent Partners With Bridge Therapeutics on Formulation, Development & Production of New Opioid Addiction Treatment

Catalent recently announced it has completed clinical production of Bridge Therapeutics Inc.'s (Bridge) opioid addiction development therapeutic product, BT-219, and executed an Exclusive Licensing Agreement to use Catalent's proprietary Zydis orally disintegrating tablet (ODT) technology. Bridge currently intends to seek approval from the US FDA for BT-219 under the 505(b)(2) regulatory submission pathway as well as a possible future single entity buprenorphine product.

Catalent's Zydis ODT technology is a unique, freeze-dried tablet that disperses almost instantly in the mouth without water. Zydis is recognized as one of the world's best performing ODTs and has well-established advantages over conventional oral dosage forms, including improved patient compliance, adherence and convenience. Bridge's exclusive license of the Zydis technology will initially apply to the US, with the potential to expand to other nations.

BT-219, or Bunalz, is an investigational new drug (IND) which applies the Zydis delivery technology to buprenorphine and naloxone, which are the active ingredients in the Suboxone prescription medication for opioid addiction. Buprenorphine, being a Schedule III medication, is considered safer and less addictive than methadone, which is classified as a Schedule II medication. It has also been shown that buprenorphine is six-times safer than methadone with regard to overdose risk among the general population.

"Catalent has a proven track record in working with partners to bring new therapies to market quickly and we look forward to working with Bridge as they pursue approval for this important and exciting new development product," said Jonathan Arnold, President of Catalent's Oral and Specialty Delivery business unit. He added, "The Zydis technology platform has been shown to be very versatile and effective in developing easy-to-administer dose forms for innovators and to date, more than 36 products have been launched using Zydis technology in over 60 countries."

Dr. Greg Sullivan, Chief Medical Officer of Bridge Therapeutics, added "This new formulation will provide improved administration characteristics. With many formulations being unpleasant to patients, this fast-dispersing Zydis formulation could potentially increase compliance with Medication-Assisted Treatment (MAT) and thus better clinical outcomes." In addition to assisting the needs of the general population, utilizing the Zydis formulation technology lessens the chance of an institutionalized patient being able to divert the medication for untoward purposes."

Catalent's 250,000-sq-ft site in Swindon, UK, houses the company's Zydis development and manufacturing operation, which produces over one billion tablets annually and employs more than 600 people. In March 2019, Catalent announced a $27 million investment to commercialize its next-generation ODT technology, Zydis Ultra, which allows an increased drug load and taste masking to be incorporated into the Zydis dosage form.


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Tonix Pharmaceuticals Enrolls First Patient in Phase 3 RELIEF Study

Tonix Pharmaceuticals Holding Corp. recently announced that the first patient was enrolled in the Phase 3 RELIEF study (TNX-CY-F304). RELIEF is a potential pivotal study of TNX-102 SL (cyclobenzaprine HCl sublingual tablets) 5.6 mg, a non-opioid, centrally-acting analgesic, taken daily at bedtime for the management of fibromyalgia.

"Tonix is dedicated to improving the lives of the millions who suffer from fibromyalgia, and enrolling the first patient in the RELIEF study is an important step towards achieving this goal," said Seth Lederman, MD, Tonix's President and Chief Executive Officer. "Our two prior randomized, double-blind, registration-quality studies of TNX-102 SL in fibromyalgia evaluated TNX-102 SL at 2.8 mg, whereas the RELIEF study will evaluate TNX-102 SL at the 5.6 mg dose. In the prior studies, TNX-102 SL 2.8 mg was well tolerated, and the most common side effect was transient tongue numbness in a subset of patients. RELIEF is an adaptive-design study for which the primary endpoint is change from baseline in mean pain. We believe the mechanism of action of TNX-102 SL is the improvement of sleep quality. We expect results from an unblinded interim analysis in the second half of next year and topline results in the first half of 2021 based on the currently-planned sample size."

Supported by the previous safety and efficacy findings of TNX-102 SL in fibromyalgia and posttraumatic stress disorder (PTSD), Tonix believes that using the 5.6 mg dose of TNX-102 SL in the new Phase 3 RELIEF fibromyalgia study has the potential to provide clinical evidence to support the efficacy and safety of TNX-102 SL for the management of fibromyalgia. The registration of TNX-102 SL 5.6 mg for the fibromyalgia indication is expected to be supported by the long-term safety exposure data from the PTSD program for TNX-102 SL 5.6 mg. The active ingredient of TNX-102 SL, cyclobenzaprine, is not associated with a risk of addiction.

The RELIEF study is a double-blind, randomized, placebo-controlled adaptive design trial designed to evaluate the efficacy and safety of TNX-102 SL (cyclobenzaprine HCl sublingual tablets) in fibromyalgia. The trial is expected to enroll approximately 470 patients across approximately 40 US sites. For the first two weeks of treatment, there will be a run-in period in which patients will start on TNX-102 SL 2.8 mg (1 tablet) or placebo. After the first two weeks, all patients will have the dose increased to TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) or two placebo tablets for 12 weeks. The primary endpoint is daily diary pain severity score change from baseline to Week 14 (using the weekly averages of the daily numerical rating scale scores), analyzed by mixed model repeated measures with multiple imputation.

The RELIEF study is expected to have one unblinded interim analysis when the study has results from approximately the first 50% of efficacy-evaluable patients, pending agreement with the US FDA.

LEO Pharma & Portal Instruments Announce Collaboration to Develop Needle-Free Drug Delivery Device

LEO Pharma A/S and Portal Instruments recently announced a global collaboration and license agreement to develop Portal's innovative needle-free drug delivery system for use in combination with LEO Pharma's portfolio of investigational and approved medicines.

Portal Instruments has developed a needle-free jet injector platform to address the increasing needs of patients to self-administer biologics without the need for needles. This simplifies administration, eliminates the need for "sharps containers" in the home, and reduces the time needed to perform self-injections. This technology is particularly timely in light of the increasing use of monoclonal antibodies and therapeutic proteins in drug development. Initially developed by Prof. Ian Hunter's Group at the Massachusetts Institute of Technology (MIT), the Portal drug administration technology has the potential to transform the way injectable medicines are administered across a wide range of therapeutic indications.

The Portal needle-free system is composed of a re-usable, software-controlled handheld injection device and a proprietary, single-use, pre-filled cartridge. It delivers the medicine through a pressurized liquid jet instead of a needle and has been clinically shown to be less painful and preferred by patients as compared to a standard needle-based injection.1

"LEO Pharma's novel therapies in the field of medical dermatology combined with Portal's innovative approach to drug administration offer hope to people living with debilitating skin diseases," said Christian Antoni, Senior Vice President, Global Development at LEO Pharma. "It is our ambition that this collaboration will lead to new and easier ways for people with skin diseases to administer our treatments on their own in the comfort of their home with a needle-free solution."

"We are excited at the prospect of working closely with LEO Pharma and support their ambition to empower people with skin diseases with a next-generation drug delivery platform for self-administration," said Patrick Anquetil, CEO of Portal. "This commercial collaboration gives us the opportunity to lead with innovation in the field of medical dermatology by combing novel medicines with a patient-preferred needle-free drug delivery system."

LEO Pharma helps people achieve healthy skin. The company is a leader in medical dermatology with a robust R&D pipeline, a wide range of therapies and a pioneering spirit. Founded in 1908 and owned by the LEO Foundation, LEO Pharma has devoted decades of research and development to advance the science of dermatology, setting new standards of care for people with skin conditions.

Portal Instruments is a venture-backed medical device company, developing and commercializing a connected, needle-free drug delivery platform to transform the administration of medications for chronic diseases. Portal aims to improve the patient experience and outcomes through an innovative needle-free injector with connectivity, analytics, and a companion digital experience. Portal partners with pharmaceutical companies to develop unique drug delivery solutions for their therapies. Its first commercial partnership is with Takeda Pharmaceuticals in the field of Inflammatory Bowel Diseases.

Acceleron & Fulcrum Therapeutics Announce Pulmonary Research & Discovery Collaboration Agreement

Acceleron Pharma Inc. and Fulcrum Therapeutics, Inc. recently announced they have entered into a collaboration and license agreement to identify small molecules designed to modulate specific pathways associated with a targeted indication within the pulmonary disease space.

"This collaboration brings together Fulcrum's skill in identifying drug targets based on modulation of genetic pathways associated with disease and Acceleron's deep expertise in TGF-beta superfamily signaling in an effort to generate potentially disease-modifying therapeutics," said Habib Dable, Chief Executive Officer of Acceleron Pharma. "With this agreement, along with the advancement of the Acceleron-discovered assets sotatercept—in Phase 2 trials in pulmonary arterial hypertension—and ACE-1334, we underscore our growing commitment to the development of novel therapies for patients with pulmonary diseases of high unmet medical need."

Under the agreement, Acceleron will have access to Fulcrum's unique, proprietary product engine and target identification platform with the potential to identify small molecules that control the expression of genes known to impact specific pathways associated with a pulmonary disease of interest. Acceleron and Fulcrum will collaborate on the identification of therapeutic targets and small molecule drug candidates for those targets. Acceleron will be responsible for all development and commercialization activities for any potential therapeutics identified via this platform. Fulcrum will receive a one-time, upfront payment of $10 million as well as reimbursement for relevant R&D costs. Fulcrum will also be eligible to receive research, development and commercial milestone payments of up to $295 million for a first product commercialized and up to a maximum of $143.5 million in additional milestone payments for all subsequent products commercialized. Fulcrum will additionally receive tiered royalty payments in the mid-single-digit to low double-digit range on net sales.

Acceleron is a biopharmaceutical company dedicated to the discovery, development, and commercialization of therapeutics to treat serious and rare diseases. Acceleron's leadership in the understanding of TGF-beta superfamily biology and protein engineering generates innovative compounds that engage the body's ability to regulate cellular growth and repair.

Acceleron focuses its research and development efforts in hematologic, neuromuscular, and pulmonary diseases. In hematology, Acceleron and its global collaboration partner, Bristol-Myers Squibb, are co-promoting newly approved REBLOZYL (luspatercept-aamt), the first and only approved erythroid maturation agent, in the US and are developing luspatercept for the treatment of chronic anemia in myelodysplastic syndromes and myelofibrosis.

Fulcrum Therapeutics is a clinical-stage biopharmaceutical company focused on improving the lives of patients with genetically defined rare diseases in areas of high unmet medical need. Fulcrum's proprietary product engine identifies drug targets which can modulate gene expression to treat the known root cause of gene mis-expression.

WuXi STA Opens Oligonucleotide Large-Scale Manufacturing Facility

STA Pharmaceutical Co., Ltd., (WuXi STA) – a subsidiary of WuXi AppTec – recently announced the opening of its large-scale oligonucleotide active pharmaceutical ingredient (API) manufacturing facility in Changzhou, China. This significant milestone marks WuXi STA's establishment of a comprehensive one-stop platform to support the process R&D and manufacture of oligonucleotide APIs from preclinical to commercial. It enables customers around the world to advance promising new oligonucleotide therapies more rapidly to market for the benefit of patients.

Nucleic acid drugs have gradually become a hot area in the global innovative drug industry and many nucleic acid drugs have been approved by the US FDA in recent years. To help customers accelerate new drugs to market, WuXi STA is continuously strengthening its oligonucleotide platform. The new facility, with over 30,000 square feet, is located at WuXi STA's Changzhou site. With its operation, the Changzhou site can manufacture oligonucleotide APIs up to 1 mol/synthesis run, to better meet the increasing demand of our customers.

WuXi STA's comprehensive platform covers the development and manufacturing of a variety of oligonucleotide modalities, including DNA, RNA, Morpholino oligonucleotide (PMO), and peptide conjugates (PPMO). In addition, the company's industry-leading small molecule process chemistry organization adds further value in handling complex conjugation chemistry that involves oligonucleotide and other molecular modalities, as well as a combination of solid and solution phase chemistry to support next-generation oligonucleotide manufacturing technology development.

"By leveraging our small-molecule CMC (Chemical, Manufacturing, and Control) technology and capability platform as well as global standard quality system, WuXi STA provides a robust one-stop shop for oligonucleotide innovators. The opening of this large scale manufacturing facility will empower more global partners to expedite the development and commercialization of oligonucleotide drugs to benefit patients worldwide," commented Dr. Minzhang Chen, CEO of WuXi STA.

WuXi STA's Changzhou site can now provide services involving small molecule, oligonucleotide, and peptide process R&D and manufacturing from laboratory to commercial scales. During the past years, it has successfully passed multiple inspections from the US FDA and the National Medical Products Administration (NMPA), adhering to the highest regulatory standards.

STA Pharmaceutical Co., Ltd., a subsidiary of WuXi AppTec (WuXi STA), is a leading pharmaceutical development and manufacturing capability and technology platform company serving the life sciences industry, with operations in China and the US. As a premier Contract Development and Manufacturing Organization (CDMO), WuXi STA offers our worldwide partners efficient, flexible, and high-quality solutions for integrated CMC (Chemical, Manufacturing, and Control) solutions from preclinical to commercial uses. For more information, please visit: http://www.STApharma.com.

WuXi AppTec provides a broad portfolio of R&D and manufacturing services that enable companies in the pharmaceutical, biotech and medical device industries worldwide to advance discoveries and deliver groundbreaking treatments to patients.

Opiant Pharmaceuticals Announces Development Collaboration With National Center for Advancing Translational Sciences

Opiant Pharmaceuticals, Inc. recently announced it has signed a Letter of Intent with the National Center for Advancing Translational Sciences (NCATS) to collaborate on the development of OPNT004 (drinabant), a novel cannabinoid receptor antagonist, for the treatment of Acute Cannabinoid Overdose (ACO). NCATS is one of 27 divisions and centers of the National Institutes of Health (NIH). NCATS will provide development resources around certain pre-clinical activities and studies in order to support Opiant's planned filing of an Investigational New Drug application for OPNT004. This collaboration will be carried out under a Cooperative Research and Development Agreement between Opiant and the NIH.

Opiant licensed exclusive global rights for the development and commercialization of drinabant for the emergency treatment of ACO from Sanofi in December 2018. The companies subsequently expanded their partnership in July 2019, whereby Sanofi will be responsible for manufacturing OPNT004.

"There is an urgent need for a product for the rapid reversal of ACO, and the extensive safety data of orally administered drinabant are encouraging regarding the prospects of an injectable version of the drug to better meet this need in the ER," said Roger Crystal, MD, Chief Executive Officer of Opiant. "We view this collaboration with NCATS as an important validation of the need for this product."

"During 2020, we expected to incur approximately $4.5 million in expenses related to our OPNT004 program," said David O'Toole, Chief Financial Officer of Opiant. "Although the exact amount of in-kind funding from NCATS is yet to be determined, with this collaboration, we now anticipate that our R&D expenses for the development of OPNT004 will decrease significantly in 2020. We are grateful that our programs continue to be validated and funded by government agencies."

ACO is most often linked to the ingestion of edible products containing large quantities of delta9-tetrahydrocannabinol (THC), as well as the use of synthetic cannabinoids. ACO is characterized by panic and anxiety, feelings of paranoia, agitation, visual and auditory hallucinations, and nausea, and these last several hours to days. There are no US FDA-approved medications that treat ACO; treatment is currently symptom-driven, requiring emergency medical attention and in some instances, hospitalization. ACO is particularly problematic in children, who inadvertently consume edibles, which are often sold as brownies, cookies, and candies. Opiant estimates that cannabinoid consumption will be responsible for more than 1 million emergency department visits in 2019.

Opiant Pharmaceuticals, Inc. is a specialty pharmaceutical company developing medicines for addictions and drug overdose. NIDA, a division of the National Institutes of Health, describes addictive disorders as chronic relapsing brain diseases that burden society at both the individual and community levels. Opiant's first drug overdose product, NARCAN Nasal Spray, is approved for marketing in the US and Canada by its licensee, Adapt Pharmaceuticals, now owned by Emergent BioSolutions Inc. For more information, visit www.opiant.com.


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AUTOINJECTOR PLATFORM

Identifying New, Enhanced Device Delivery Solutions for Chronic Diseases

By: Karima Yadi, MSc, and Lionel Maritan, MSc

ABSTRACT

Biologics now constitute a significant element of available medical treatments. Owing to their clinical and commercial success, biologics are a rapidly growing class and have become a dominant therapeutic modality.[1] This, and the increased demand for home healthcare, driven by the ever-increasing prevalence of chronic diseases, is fueling increased demand for self-injection devices.[2]

For manufacturers, while many are turning their attention to devices that support injection of higher volumes and greater viscosities, there remains a need to further innovate in the 1-mL space and provide innovative injection solutions for viscous drugs in the 2-mL space to improve delivery outcomes, patient quality of life, and adherence to treatment.

Reducing injection frequency is one of the strategies implemented by pharmaceutical companies. To reach this objective, they will be looking to increase their drug dosage and potency, either by increasing the drug concentration and/or delivery of larger volumes.[3,4] Needle innovations, including the usage of shorter needles with ultra-thin wall technology for prefilled syringes, supports the delivery of drugs with greater volumes and viscosities, which greatly enhances end-user experience.

CHRONIC DISEASE MARKET, SELF-INJECTION DEVICES

Self-injection devices are designed for multiple injections of biologics and hormones for patients requiring frequent dosage for the long-term management of medical conditions, such as diabetes and rheumatoid arthritis. As the population ages, the incidence of these diseases increases.

Today, more than 70 million Americans aged 50 and older – four out of five older adults – suffer from at least one chronic condition, while 11 million live with five or more chronic conditions.[5] As the population ages, the prevalence of chronic diseases will increase. In the US, these persistent conditions are the nation's leading cause of death and morbidity.[6]

Globally, chronic diseases have affected the health and quality of life of many citizens. In addition, chronic diseases, and poorly managed chronic diseases have important societal costs as they depress wages, workforce participation and labour productivity, as well as increase early retirement, high job turnover, and disability.[7] Poorly managed chronic diseases have an even greater impact. The increase in the incidence of chronic conditions, as well as the increase in home healthcare, are two of the key drivers of growth for drug injection delivery solutions.

In the attempt of improving self-injection experience for chronic disease patients in the home setting, pharmaceutical companies often develop self-injecting devices combining primary container (eg, prefilled syringes) with needle stick safety guard or autoinjector solutions. These are usually administered by a skilled medical professional, a formal or informal caregiver, or by the patients themselves.

The use of a drug delivery device will improve patient concordance and persistence to treatment, and it can reduce the total cost to payers. For drug delivery manufacturers, a relentless focus on patient centricity helps customers enhance patient injection experience, ease of use of the drug delivery solution, and patient adherence.

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PATIENT-CENTRIC PRODUCT DEVELOPMENT

Human factor engineering has become an integral part of the product development cycle. As a result, human factor considerations are playing an ever-increasing role as innovative drug delivery systems are coming to market (Figure 1). The goal of product development should be the design of robust drug delivery systems that are effective and easy for patients to self-administer every time. Healthcare professionals, patients, and caregivers need to safely prepare, place, activate, and remove the device with minimal difficulty. Human factor engineering should therefore be adopted to improve safety, reduce risk, ensure ease of use, and verify that a product design will be effective.

For manufacturers, human centered design principles should be at the heart of development of drug delivery devices. Usability should be considered throughout the development process, starting with design input, to ensure product effectiveness, efficiency, and user satisfaction in the intended use environment. The aim is to minimize user-related risks and improve user adherence by checking on ease of use, patient comfort, concordance, and persistence, and by providing easy instructions and solutions for patients with limited dexterity and reduced eye sight.

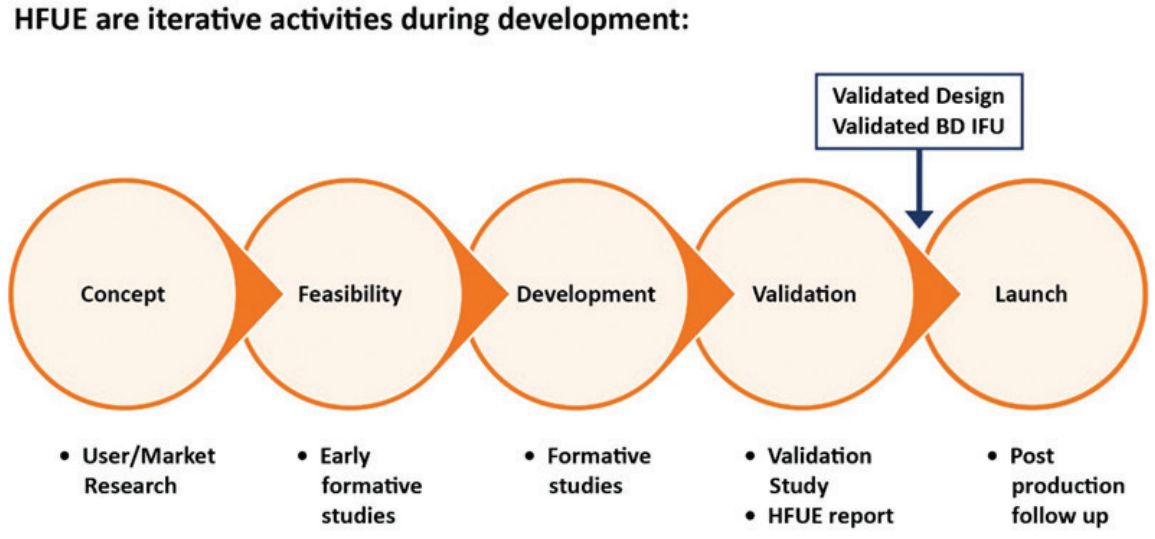
A patient-centered design approach combines clinical data, usability engineering, and patient insights that meet the needs of customers and their patients. Increasing the focus on patient centricity enables patients greater freedom to live their lives without being restricted by their drug delivery regimen.

ADDRESSING THE TREND TOWARD MORE VISCOUS DRUGS

There is an increasing trend for viscous biologic drugs to be developed in the chronic disease space. As a consequence, there is a high need for performant and robust drug delivery solutions that can administer highly viscous drugs to improve delivery outcomes and patient adherence to treatment.

The actual biotech market is driven by the 1-mL subcutaneous injection delivery solution, where there is a high need to increase drug potency and thus reduce injection frequency. To reach this objective, biotech companies will be looking to increase their drug concentration, which in turn can lead to exponential increase in viscosity. When viscosity becomes very high, they might consider reformulating the drug in a higher volume. Consequently, today, we can see more drugs developed in a 2-mL volume. To administer these viscous drugs within an acceptable injection time that a patient can tolerate – approximately between 10 and 15 seconds – there is a need for a reliably performing and robust delivery solution, especially when these drugs are administered with manual delivery needle standards, as pharmaceutical companies may not want to compromise on patient injection experience.

FIGURE 1



Human Factors during product development at Becton Dickinson (BD)

INNOVATIVE SHORT NEEDLE TECHNOLOGY

Standard needles for chronic disease treatment and administration are historically 12.7 mm long. Reducing needle length to 8 mm enables the delivery of larger, more viscous drugs, while enhancing end-user injection experience. Moreover, the risk of reaching the intramuscular (IM) layer during a subcutaneous (SC) injection is considerably reduced with an 8-mm exposed needle length versus 12.7-mm needles without increasing the risk of accidental intradermal (ID) injection, which in turn could lead to adverse immune responses.[8] This risk reduction is especially important in the absence of a skin pinch, which is usually recommended with the 12.7-mm standard needle, or when done with populations with thin SC fat or with children (Figure 2).

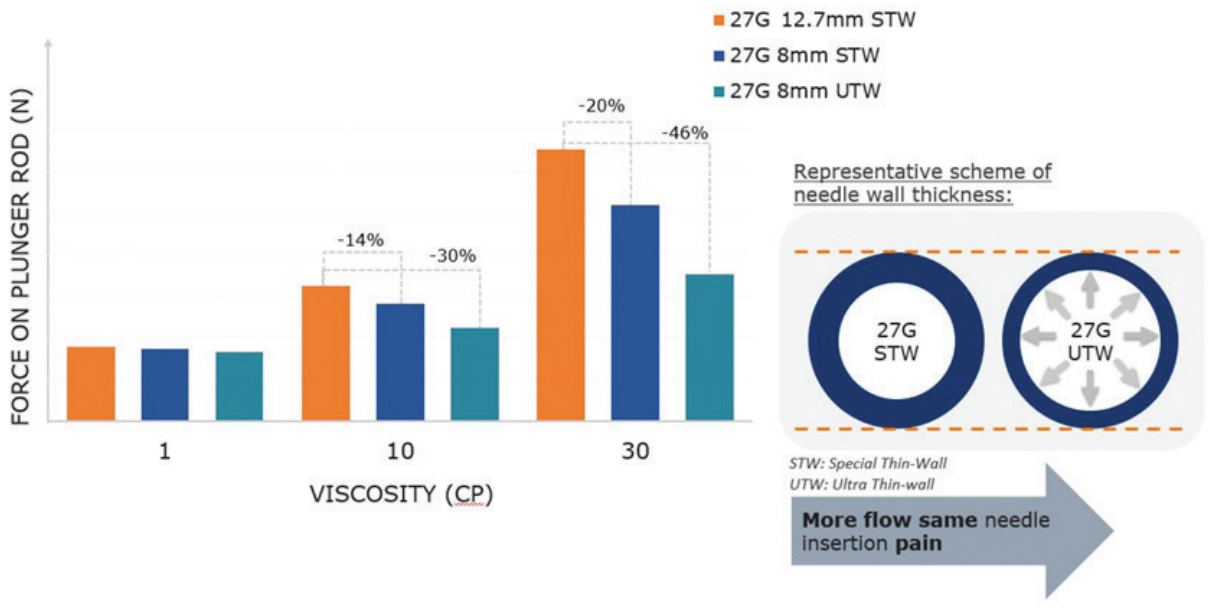
To address the specific needs of pharmaceutical companies developing viscous high-volume biologics, BD has launched a short needle technology based on its advanced BD Neopak™ 2.25-mL glass prefillable syringe platform, which is available with 12.7-mm and 8-mm needle solutions (Figure 3).

Another way to improve the performance of viscous drug delivery without increasing injection force is to work around critical needle parameters, such as needle inner diameter. To address this, BD is developing a prefilled syringe solution combining shorter needle length (8 mm) with ultra-thin wall (UTW) needle technology for use in combination products. This technology increases the inner diameter of the needle by reducing the thickness of the needle wall without having to increase the external diameter (Figure 2). The outer diameter of a needle is known to be an important feature as it influences needle insertion pain perception and the level of injection-related anxiety experienced by patients.[9] Mathematical simulations show that using an UTW needle can reduce injection force by 46% for highly viscous solutions (Figure 2). This innovation combining short 8-mm exposed needle with UTW technology therefore reduces the injection force, especially for viscous solutions, without compromising on needle robustness, insertion pain, and pain perception.

In order to further enhance patient experience and improve compliance to treatment, pharmaceutical companies will often integrate an autoinjector to the manual delivery container. However, it is increasingly difficult to develop a single designed autoinjector that can effectively and safely inject the variety of parenteral drugs with different viscosities developed by a single pharmaceutical company.

What we see today in the market are autoinjectors designed and customized to target a narrower range of drug viscosities. So effectively, multiple autoinjector devices are being used to deliver different drugs by one single pharma company. There is therefore a need for biotech companies to have a "platform" autoinjector device that can deliver a wide-range of viscosity drugs without customizing the system components.

FIGURE 2



Combination of short 8-mm and thinner needle wall technology contributes to reduce injection force

INTRODUCING BD INTEVIA™ AUTOINJECTORS

Becton Dickinson has recently launched Intevia™ 1-mL autoinjector, a platform technology solution intended for use in a home setting by patients living with auto-immune and chronic conditions. The platform provides a new solution for drug manufacturers that not only supports patients, but it supports the efficiency of the manufacturing process itself.

Intevia™ autoinjector platform includes a 1-mL and a 2.25-mL version (Figure 4). They are both two-step push-on-skin autoinjectors that are designed to effectively and safely inject a variety of drugs of different range of viscosities up to 35 cP and different fill volumes, without customizing the components.

In terms of patient centricity, the Intevia™ platform enables ease of use and has a patient-friendly design, while its unique feedback indicator and audible click provide assurance to patients when the correct dose has been delivered.

Intevia™ system integration with prefilled syringes reduces the risk of dosing errors, drug wastage, and needlestick injuries. Post-injection, the needle is protected, further safeguarding patients and caregivers. Indeed, all of its features provide patients with the confidence and convenience to self-inject as prescribed by their doctor.

The Intevia™ platform is the only push-on-skin autoinjector that is designed with proprietary knowledge of primary container process controls, integrating all the functionalities to maximize product performance. It is a well-integrated system that ensures robust performance to help manage development process risks and optimize time to market of combination products.

FIGURE 3

BD Neopak™ 2.25-mL Glass Prefillable Syringe Platform with 12.7-mm and 8-mm needle solutions addressing the needs of viscous and high-volume biologics

BIOTECH MARKET, DRIVEN BY 1-ML DELIVERY SOLUTIONS

The biotech market is driven by the 1-mL subcutaneous injection delivery solution and typical autoinjectors available on the market use a 1-mL syringe. However, many of these are not integrated platforms, and this provides some system integrated challenges for pharmaceutical companies. BD's new injection device helps overcome these.

In designing a robust and performing autoinjector, device manufacturers need to ensure a high compatibility between biotech drug, primary container, and secondary packaging. To ensure that, there is a need to master the engineering process and generate a robust set of data that bring the primary container (eg, prefilled syringes) and the secondary packaging (delivery systems) co-operating together in one performing system that will safely and effectively deliver the drug to patients, with reproducible performance across millions of units.

Becton Dickinson has developed deep domain knowledge to support the development of more robust, well-designed systems, such as the new Intevia™ platform. This means that biotech companies have a "platform" autoinjector device with the potential benefits this offers in terms of manufacturing efficiency and time to market. To offer a seamless integration, BD has de-

FIGURE 4

BD Intevia™ 1 mL and BD Intevia™ 2.25 mL*

*This product is in development, the design is subject to small changes

signed its latest BD Intevia™ 2.25-mL large-volume autoinjector around its latest UTW 8-mm needle technology. This combination will allow pharmaceutical companies to push the boundaries of viscosities further and enhance patient injection experience.

SUMMARY

In addition to wider uptake of home care, an increase in the number of biologics being manufactured, many by the same company, is driving ongoing innovation in drug delivery systems. While the ultimate aim is to improve patient experience and health outcomes, innovation can also offer the pharmaceutical industry savings in terms of assembly costs and time to market.

Identifying enhanced needle solutions and offering integrated system solutions to serve the chronic disease market is a great step toward addressing improved patient outcomes and adherence. The Intevia™ platform sits among BD's vast portfolio of drug delivery solutions and affords this opportunity as it can accommodate different fill volumes and different level of viscosities without having to change any component in the delivery system. As the market further develops over the coming years, we should expect to see further innovations to meet the growing need for self-injection devices. ◆

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BIOGRAPHIES

Karima Yadi is the Global Marketing Lead for the autoinjector platform at BD Medical-Pharmaceutical Systems. She provides commercial leadership to BD's delivery system platforms and defines, develops, and launches patient-centered injection solutions in collaboration with cross functional, commercial, and regional teams. She has held different roles of increasing responsibility within Pfizer Inc. in Marketing and Business Development and at Zoetis in Regional Marketing in the Companion Animal Business Unit. She has deep experience in product launches and product life cycle management, from the development phase to the commercialization phase. She earned her BSc (Hons) in Management Science from University of Warwick Business School, and her MSc in International Business Management from London South Bank University.

Lionel Maritan is R&D Associate Director at BD, responsible for Design, Development, and Life Cycle Management activities for Autoinjectors and Safety solutions. He joined BD in 2005 and held roles of increasing responsibilities within R&D. He has deep experience in Drug Delivery Systems Design and Development from the innovation stage to commercialization. He developed, in particular, the BD Physioject™ Autoinjector and is listed on many patents. Prior to BD, he worked in the automotive industry. He has a MSc in Engineering with a specialization in plastic parts design and manufacturing.

PERSONALIZED MEDICINE

Personalizing Cancer Immunotherapy: Trends in Biomarker Discovery

By: Emile Youssef, MD, PhD

INTRODUCTION

Throughout the past few decades, research has provided significant breakthroughs that have enhanced our understanding of the complex mechanisms and pathways that regulate the immune system's response to cancer. These advances have led to great leaps in the field of cancer immunotherapy, and in recent years, immune checkpoint inhibitors and chimeric antigen receptor (CAR) T-cell therapeutics have revolutionized cancer treatment. However, the response rates and side effects associated with existing immunotherapies limit the number of patients who may benefit from these therapies. There remains an unmet need to enable selection of patients who would most benefit from a specific treatment option and exclude those who are unlikely to respond, especially given the price tag associated with many immunotherapies.

Every tumor is unique, and biomarkers have the potential to help both researchers and clinicians select the right treatment for each patient at every stage of cancer therapy. The identification of biomarkers will help to fill critical knowledge gaps by providing not only predictive and prognostic information, but also insight into the underlying mechanisms of patient response or resistance to immunotherapy.[1] However, due to tumor heterogeneity, the plasticity and diversity of cancer cells, and a multitude of other factors, biomarker development is a challenge. In this article, we explore four trends in cancer biomarker discovery.

USE OF PD-L1 AS A BIOMARKER

Programmed death 1 (PD-1) is a key immune checkpoint inhibitory receptor expressed on activated tumor-specific CD4+ helped and CD8+ killer T lymphocytes. The main PD-1 ligand, programmed death ligand 1 (PD-L1), is a transmembrane protein expressed on a variety of cell types, including the dendritic cells, which play a critical role in both innate and adaptive immunity. PD-L1 binding inhibits the function of activated T-cells. By co-opting the PD-1/PD-L1 regulatory mechanism via expression of PD-L1, tumor cells are able to bind to PD-1, inhibit T-cell activation, and evade the immune system.

Therapeutic antibody-mediated blockage of PD-1 or PD-L1 removes the suppressive effects of PD-L1 on cytotoxic T-cells, restoring host immunity against the tumor. To date, two PD-1 inhibitors [nivolumab (marketed as Opdivo®) and pembrolizumab (marketed as Keytruda®)] and three PD-L1 inhibitors [atezolizumab (marketed as Tecentriq®), avelumab (marketed as Bavencio®) and durvalumab (marketed as Imfinzi®)] have been approved for cancer immunotherapy. Consequently, defining biomarkers that predict therapeutic response to PD-1/PD-L1 blockade is important for appropriate patient selection.

Detection of tumor cell PD-L1 protein expression using immunohistochemistry (IHC) has been evaluated in clinical studies for correlation with response to PD-1 and PD-L1 immune checkpoint inhibitors. Currently, PD-L1 IHC 22C3 pharmDx (manufactured by Dako A/S, now Agilent Technologies), which is used to select patients for treatment with pembrolizumab, is the only FDA-approved companion diagnostic. The other three FDA-approved PD-L1 IHC assays serve as complementary diagnostics that may provide additional data that can be used to inform physician-patient dialogue around treatment decisions.

Recently, a Blueprint Working Group established in cooperation with the pharmaceutical industry compared the different IHC tests and cell scoring methods for PD-L1 expression. The Group concluded that more data are needed before an alternative assay

can be used to read different specific therapy-related PD-L1 cut-offs.[2] Thus, for now, PD-L1 IHC positivity is an imperfect biomarker of response and is not suitable as a definitive biomarker for selection for therapy with PD-1/PD-L1 inhibitors.[3]

Moreover, studies have shown that PD-L1 negativity is unreliable, as results may differ depending on the antibody, assay, or tissue sample. Low expression, tumor heterogeneity, and inducible genes can also lead to sampling errors or false negatives. In addition, it has been found that the treatment benefits of PD-1/PD-L1 inhibitors are not limited to patients whose tumors express PD-L1. In two pivotal trials of nivolumab, 20% to 30% of PD-L1-negative patients responded to treatment, compared with 50% of PD-L1-positive patients, suggesting that biomarkers other than PD-L1 may be predictive of response to nivolumab.[4,5] Given these finds, it is likely that a more complex, multi-component predictive biomarker system will be required to refine patient selection.

CLINICAL UTILITY OF TUMOR MUTATION BURDEN

Tumor mutation burden (TMB) is a measurement of the mutations carried by tumor cells. Typically, DNA sequencing is used to determine the number of acquired mutations in the tumor and TMB is reported as the number of mutations in a specific area of genetic material, such as mutations in a single cell, mutations in an entire tumor, or mutations per megabase. Currently, numerous studies are evaluating the association of TMB with response to immuno-oncology therapy.

It is thought that tumor cells with high TMB may have more neoantigens, cell surface molecules that are expressed solely on cancer cells and not on normal cells. These neoantigens can be recognized by T-cells, activating an anti-tumor immune response both in the tumor microenvironment and beyond. As such, it is hypothesized that a high TMB may correlate with a higher likelihood of responding to immunotherapy. In fact, research has shown that patients with high TMB have better overall survival when treated with PD-1/PD-L1 inhibitors, compared with patients with low TMB.[6]

More recently, at the 2017 International Association for the Study of Lung Cancer (IASLC) 18th World Conference on Lung Cancer, researchers presented data from CheckMate-032, an ongoing Phase I/II open-label trial evaluating the safety and efficacy of nivolumab monotherapy and nivolumab plus ipilimumab (marketed as Yervoy®) combination therapy in pa-

tients with advanced small cell lung cancer patients. The data demonstrated that response rate and 1-year overall survival nearly doubled in patients with a high TMB who were treated with combination therapy versus monotherapy. In addition, a high TMB predicted better outcomes, regardless of the treatment arm.[7] These new findings provide compelling evidence supporting the clinical utility of TMB as a biomarker for treatment with nivolumab, both alone and in combination with ipilimumab.

NOVEL TECHNOLOGIES FOR ACCELERATING BIOMARKER DISCOVERY AND DEVELOPMENT

The GVK Biosciences Online Clinical Biomarker Database, developed in collaboration with the US Food and Drug Administration, has identified tens of thousands of biomarkers. However, only a very small fraction of these have been developed into validated genomic biomarkers for FDA-approved drugs. So far, none have become in vitro companion diagnostics.[1] For a predictive biomarker to be applied in the clinic, it must have analytic and clinical validity, in addition to clinical utility. Many organizations have published guidelines for the validation of diagnostic tests, with guidance and recommendations regarding analytic sensitivity, specificity, reproducibility, and assay robustness.[8,9]

The process of translating biological data into a predictive biomarker is complicated by the myriad host- and cancer-related factors that influence the complex interactions between the tumor and the immune system. The emergence of powerful genomic and proteomic technologies, along with advanced bioinformatic tools, has made it possible to simultaneously analyze thousands of biological molecules. These techniques are paving the way to truly personalized cancer therapy by enabling the discovery of new tumor signatures, which are both sensitive and specific enough for early cancer detection, monitoring of disease progression, and appropriate treatment selection.

The availability of novel technologies and high throughput approaches, such as mass cytometry, whole exome sequencing, gene expression profiling, and sequencing technology for T-cell receptor clonality assessment, opens new doors for immune biomarker development. However, it also brings new challenges. With these techniques, a single sample can be used to address a multitude of questions, but the resulting quantity and complexity of data creates new analytical and cost considerations. The Society for Immunotherapy of Cancer (SITC) convened a working group which published a white paper that evaluated new technologies and emerging biomarkers relevant to cancer immunotherapy and provided recommendations on best practices.[10]

PROFILING THE TUMOR MICROENVIRONMENT

Metabolic considerations, the tumor microenvironment, the microbiome, and signaling pathway modulation all affect the immune system. The tumor microenvironment refers to the network of cells and structures surrounding a tumor, including stroma, connective tissue, and immune regulatory cells. A substantial body of research shows that cross-talk occurs between cancer cells and immune cells in the tumor microenvironment, and that this communication influences tumor progression and immune or drug resistance. Data has also shown that conditions such as hypoxia, nutrient stress, and tumor cell death can alter the phenotype of immune cells, inducing a tumor-promoting reprogramming.[11]

Profiling tumor microenvironment at a genetic, molecular, and even metabolic level may help elucidate the mechanisms associated with resistance and guide the design of cancer immunotherapeutics. Unlike predictive or prognostic biomarkers, immune targets are biomarkers that might not correlate strongly with response to treatment, but may help direct the development of cancer therapies.

For example, in one study, Ras mutations were used as immune target biomarkers. Patients with advanced solid tumors bearing Ras mutations were given a cancer vaccine comprised of autologous peptides along with interleukin (IL)-2, granulocyte-macrophage colony-stimulating factor (GM-CSF), or both. Although the majority of patients developed antigen-specific immune responses, only one patient out of 57 generated productive immunity that went on to eliminate the tumor cells.[1,11]

This disparity led to the discovery that there is significant expansion of regulatory T-cells (Treg) in patients with colon cancer with mutated Ras, compared to both healthy individuals and patients with colon cancer with wild-type Ras. Mutant Ras activates the MEK-ERK-AP1 pathway to induce secretion of high levels of IL-10 and transforming growth factor (TGF)-β1, which generate local induction of Treg in the tumor microenvironment.[13] Induction of Treg serves to support tumor immune escape by creating a suppressive tumor microenvironment that inhibits the anti-tumor response. Thus, the efficacy of a cancer vaccine in patients with Ras mutations may

be increased by adding an agent that targets Treg.

More recently, researchers at the Wistar Institute and the Medical University of Vienna described the role of tumor-associated B cells (TABs) in melanoma progression and therapy resistance. They showed that TABs, which represent up to one-third of all tumor-infiltrating immune cells that, can promote tumor heterogeneity and are prevalent in advanced, therapy-resistant tumor tissues, suggesting that B-cell depletion might have therapeutic potential. The therapy-resistant tissues also showed increased expression of insulin-like growth factor (IGF)-1 and fibroblast growth factor receptor (FGFR-2), which could represent new therapeutic targets.[14]

SUMMARY

Biomarkers are the foundation for personalized cancer therapy, but very few biomarkers have been successfully translated into clinical diagnostics for patient care. The challenges associated with biomarker development are outweighed by the opportunities inherent in the potential of biomarkers to guide treatment selection and therapeutic development. presented by the use of biomarkers. Ideally, biomarkers will enable the development of truly personalized cancer treatment plans, which could help avoid selection of ineffective therapies, unnecessary toxicities, and the subsequent need to treat those toxicities. In addition, the rational design of combination therapies will only be possible with an even greater understanding of the mechanisms of action and resistance in different tumor cells.[1] ◆

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BIOGRAPHY

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DEVELOPMENT TIMELINES

Drug Development Times, What it Takes - Part 1

By: Josef Bossart, PhD

INTRODUCTION

It seems simple, you define the various clinical development steps, estimate the time for each step, look for opportunities to overlap the steps, and there you have it, a plan and schedule for clinical development through to approval. But it never works out as you planned, reality always intrudes. Accurately estimating a product's clinical development timelines is more than simply adding up the individual timelines, almost always optimistic. You need to "know" the numbers, not just calculate them. The good news is that the numbers are knowable if you invest the time to find them and understand what they are telling you.

THE COLLEGE EXPERIENCE

If there ever was a simple timeline forecast situation, it must be estimating the time to complete college, either a 2-year Associate's or 4-year Bachelor's program. The very definition of these programs tells you everything that you need to know. Start a 2-year program and you graduate in 2 years. Start a 4-year program and you graduate in 4 years.

That of course is not the reality. On average, only 5% of students complete their Associate's degree in 2 years. For Bachelor's degrees, the numbers are a little better, with 19% to 41% of full-time students graduating in 4 years.[1]

What explains the discrepancy between forecast and reality? The short answer is life and circumstances. Look a little bit closer, and the reasons could be mistaken for the same reasons that clinical development timelines are delayed – unexpected failure, issues of financing, and changing priorities.

TABLE 1

Approval Type	Category	Approvals
Biologic (BLA)		
- NME	Single Active	85
	Biosimilar	16
- New Dosage Form	All	3
- New Formulation or Other Differences	All	2
Small Molecule (NDA)		
- NME	Single Active	239
	Combination	20
- New Active Ingredient	Single Active	13
	Combination	1
- New Dosage Form	Single Active	216
	Combination	9
- New Combination	All	72
- New Formulation or Other Differences	All	227
- Over the Counter	All	8
- Previously Unapproved Active	All	24
Medical Gas	All	8
Tentative	All	7
Other*	All	6
Total		**956**

* - Other includes New Indications and other undefined.

FDA – BLA & NDA Approvals 2010-2018

THE PHARMACEUTICAL DEVELOPMENT EXPERIENCE

Why then do companies, particularly emerging biotech and drug delivery companies, continue to plan financings and resource allocations around the often overly optimistic estimates of their development teams without consideration for the experience of those who have gone before?

It has been my experience that development teams, especially in emerging companies, chart the shortest most optimistic path through development and approval for their products. This optimism is reinforced by management who want to present investors and partners with the best possible product scenario. It's easier to make a business case for clinical development and approval in 4 rather than 6 years. The trouble is that a product re-

sourced for 4 years will struggle if the program takes 6 years. While it might be argued that the actual out-of-pocket costs will be the same regardless of the actual clinical development timeline, there remain the pesky overhead expenses related to facilities and personnel. In the end, a program always costs more if it takes longer. If not properly anticipated, a longer-than-expected development program can cripple, or even kill, a product and the sponsoring company.

Limited, easily available information may also contribute to why companies rely only on their internal forecasts of development and approval timelines. While the relevant information is available in the public domain, it can be hard to find, process, and properly apply to a particular product development program.

The clinical and regulatory teams may build their plans based on their professional expertise, but it behooves management and investors to have their own forecast of timelines and the related expenses. If the development team expects to complete development through to filing in 4 years and the industry average is 5 years, it would be wise to understand the resources, public relations, and financial implications of the program actually taking the average of 5 years. Even with an industry average of 5 years, half of the programs will take longer than this. How much longer is also an interesting piece of information. Are development times for similar products clustered or spread out around the average? What accounts for the shorter and longer development times?

OVERVIEW - NDA & BLA APPROVALS 2010-2018

Many articles track and discuss New Molecular Entity (NME) approvals in hopes of defining what this means for the industry and investors. This three-part review instead examines the development and review times for all of the FDA's Drugs Division NDA and BLA approvals in the period 2010-2018 for which public information is available; 900-plus approvals.

One last word, the devil is in the details. As best as possible, I will try and simplify the analyses and provide relevant details associated with these development and review times. In all cases, it is recommended that people who need to understand the details dig into the primary data sources.[2]

APPROVAL CATEGORIES & TYPES

NDA and BLA approvals can be categorized into two major groups: NME approvals (Drugs and Biologics), and products using previously approved molecular entities. This latter group includes New Dosage Forms, New Formulations, and a limited number of NDA approvals related to New Indications, Approvals for Previously Marketed Products, and Medical Gases.

The distribution of approvals for the 2010-2018 period, a total of 956 approvals, is presented in Table 1 (this does not include approvals from the Vaccine, Blood & Biologics Division of the FDA). The definition of the various Approval Types can be found in FDA reference documents.[3,4] Where the FDA product record does not include an assigned Approval Type an appropriate assignment was made consistent with the nature of the approval and other FDA assignments.

NDA and BLA approvals have averaged a little more than 100 annually for the past 9 years. Of this total, NMEs, either as single entity or combination product approvals, accounted for a little less than 38% of the total. New Dosage Form and New Formulation approvals combined accounted for the largest number of approvals, each representing about 24% of the total.

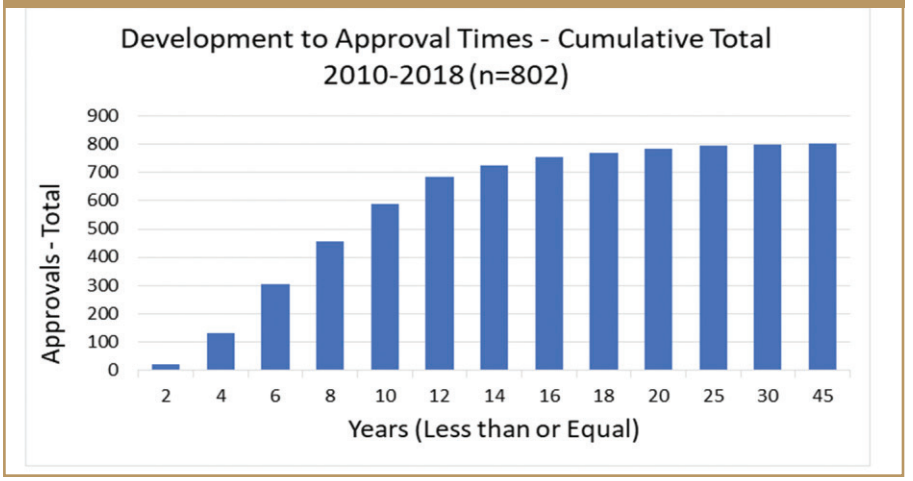
DEVELOPMENT & REVIEW TIMES

Both Development Time and Review Time require a brief definition. The easy definition is Review Time. For the purpose of this article, Review Time is the time that has elapsed between the first submission of a new drug filing, an NDA or BLA, and the date the product is granted first approval by the FDA. In the case of rolling submissions, the "clock" starts on the date of the filing of the first portion of the submission. In the case of a Tentative Approval, the approval date is the date the product is first approved by the FDA, not the second approval granted when patents and other restrictions on commercialization have expired.

Development time as presented in this article is considered as the time elapsed from the start of significant clinical investment. Because the available public information is incomplete and inconsistent, the following definition of Development Time will be used. Development Time is the elapsed time between the earliest of either: Pre-IND Meeting, first IND filing, or the start of the first human clinical trial and the filing of an NDA or BLA.

This loose definition is necessary

FIGURE 1



because of data limitations. In some cases, only one of the three dates is available. In the case of products first developed or approved in Europe, it is obvious that any Pre-IND, IND, or first US clinical date is not relevant to how long the product took to get US approval because of the previous overseas development work. Very few approvals fall into this group.

Development and Review Time is the time elapsed from the start of development as previously defined and first FDA regulatory approval.

OVERALL DEVELOPMENT & REVIEW TIMES

As a reward for getting this far, here is the number you have been hoping for: 8.2. This is the mean average Development and Review Time in years for a company to successfully move a product from the start of the clinical development process through to approval. The median is 7.2 years. This is for the 802 approvals for which the information is available and applicable. The cumulative distribution of the Review and Development Times is presented in Figure 1.

Here are a few more numbers. The mean average Development Time was 6.7 years, and the median was 5.6 years. The mean average Review Time was 1.5 years, and the median was 0.9 years.

The mean average Review Time of 1.5 years is deceiving. For the past decade, a complete submission package is reviewed by the FDA in 10 months or less. The 1.5-year mean average is distorted by the many companies that submitted applications that were kicked back or delayed by the FDA for reasons that ranged from data issues to failed facility inspections.

This is just enough information to confuse and distort any quick conclusions you hoped to make regarding Development and Review Times. It's like measuring the heights of all the people in a town and determining the average height is 4'6". An interesting data point, but it is much more useful to understand average heights in the context of age and sex. In much the same way, Development and Review Times are only relevant in the context of the well-defined product types described earlier.

In the next two articles, I will tease apart Development and Review Times as a function of the various Submission Classifications (Table 1). Within these classifications, it will be necessary to further parse approvals into those that required safety and efficacy trials, those that depended only on pharmacokinetic and bioavailability studies, and those that required only a literature review. Some received Priority Review, many did not. All of this is important in properly understanding Development and Review Times and their application to real-world development programs. ◆

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3. Drugs@FDA Glossary (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page).
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BIOGRAPHY

Dr. Josef Bossart serves as Managing Director at The Pharmanumbers Group. He has 4 decades of experience in the biopharmaceutical industry, having held senior sales, marketing, operations, and business development positions within Big Pharma and emerging Specialty Pharma companies. His activities include analyzing corporate, technology, and product development strategies in the area of Drug Delivery. Dr. Bossart earned his PhD in Medicinal Chemistry from The Ohio State University.

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IMAGE-BASED CHARACTERIZATION

Non-Invasive, Quantitative Characterization of Lyophilized Drug Product Using Three-Dimensional X-Ray Microscopy Analytics

By: Shawn Zhang, PhD, Johnathan Goldman, PhD, Xiaodong Chen, PhD, Jasmine Rowe, PhD, Sam Sheng Lin, Liping Zhou, PhD

ABSTRACT

Lyophilization is a freeze-drying process that removes water from a drug product via sublimation. It is a common and important processing method for pharmaceutical products that are not stable in liquid or frozen state, or when cold supply chain strategies are not applicable. Thorough characterization of drug product quality, such as cake moisture content, API purity, and cake appearance has to be conducted before market release. Cake appearance can be a simple way to elucidate critical product defects, but visual inspection may not detect impactful changes in the cake microstructure. An innovative image-based analytical method uses 1) high-resolution, non-invasive three-dimensional imaging with X-Ray Microscopy, 2) artificial intelligence-based image processing, and 3) image-based physical property modeling with direct numerical simulations. This new method can not only characterize quantitatively the microstructures of the lyophilized drug samples, but also presents the potential to correlate the microstructures with physical properties to optimize parameters in drug formulation, cycle development, process scale-up, stability control, and administration.

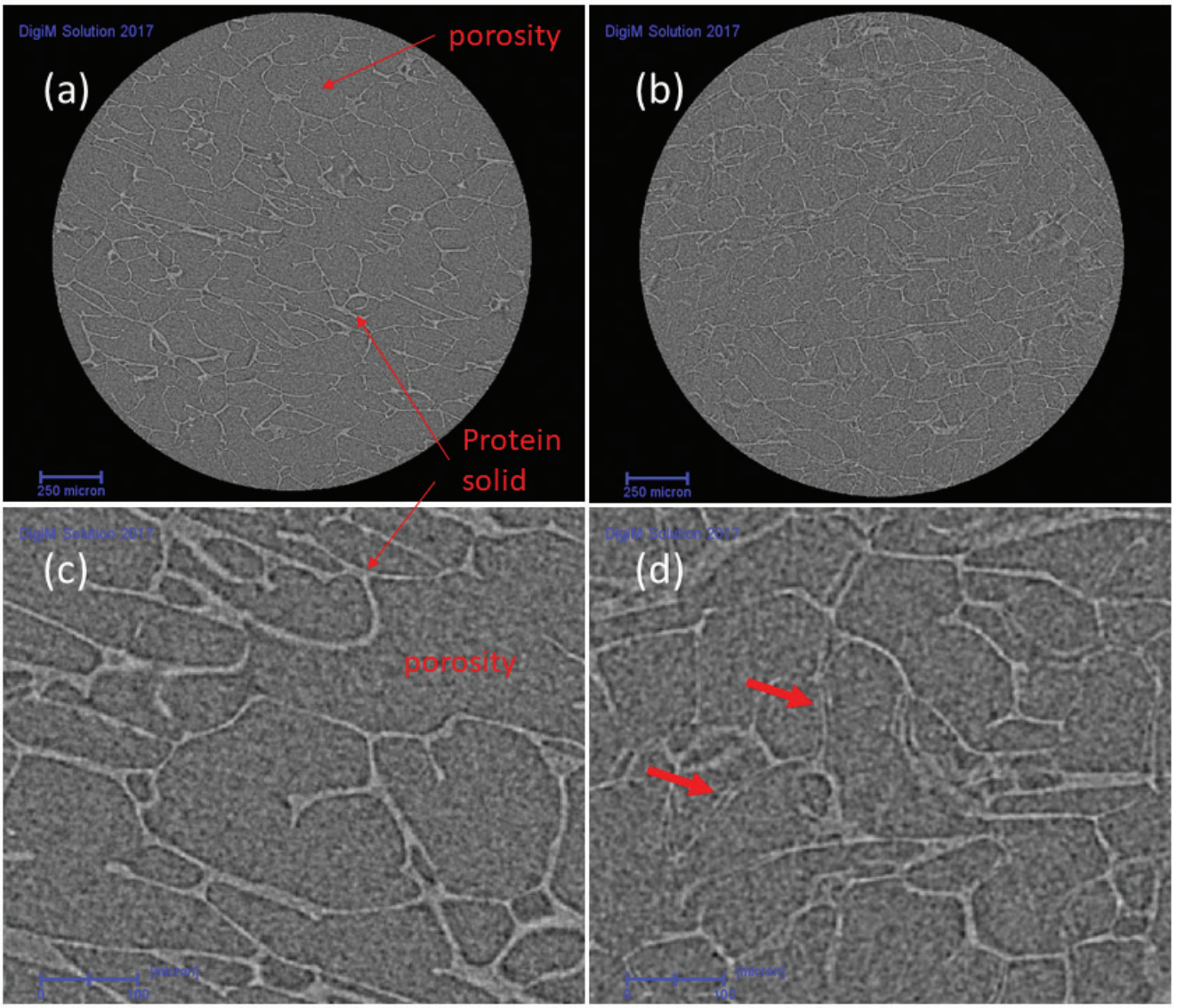
LYOPHILIZED DRUG PRODUCT

To enhance storage stability of biopharmaceutical products, lyophilization is often used.[1,2] Lyophilization is a freeze-drying process that removes water from a drug product via sublimation. It is a common and important processing method for pharmaceutical products that are not stable in liquid or frozen state, or when cold supply chain strategies are not applicable. In addition to sterility and endotoxin testing, physical characterization, such as cake moisture content, reconstitution time, integrity, homogeneity, uniformity, potency, and cake appearance, is often employed to confirm drug product quality. Despite decades of commercialization, lyophilization remains to be time-consuming and costly in both development and scale-up phases due to the challenges in cycle development, process optimization, and cake characterization, particularly when trouble shooting, such as understanding inadequate reconstitution times, is necessary.

An innovative image-based analytical method for cake structure analysis uses high-resolution, non-invasive imaging with X-Ray Microscopy (XRM) collecting three-dimensional (3D) volume data from lyophilized drug samples in the vial. It is important that the cake structure is determined in situ within the vial to avoid impacting any measured cake parameters, such as pore size and porosity, due to manual manipulation. Common structural analysis techniques, such as Brunauer-Emmett-Teller (BET) specific surface area testing or Mercury intrusion capillary porosimetry (MICP), typically require the cake is removed from the vial for analysis. The reconstructed 3D dataset is then quantified with an artificial intelligence (AI)-based image processing method. Image-based modeling with direct numerical simulations are conducted to predict multiple physical properties that are otherwise difficult, or impossible, to measure.

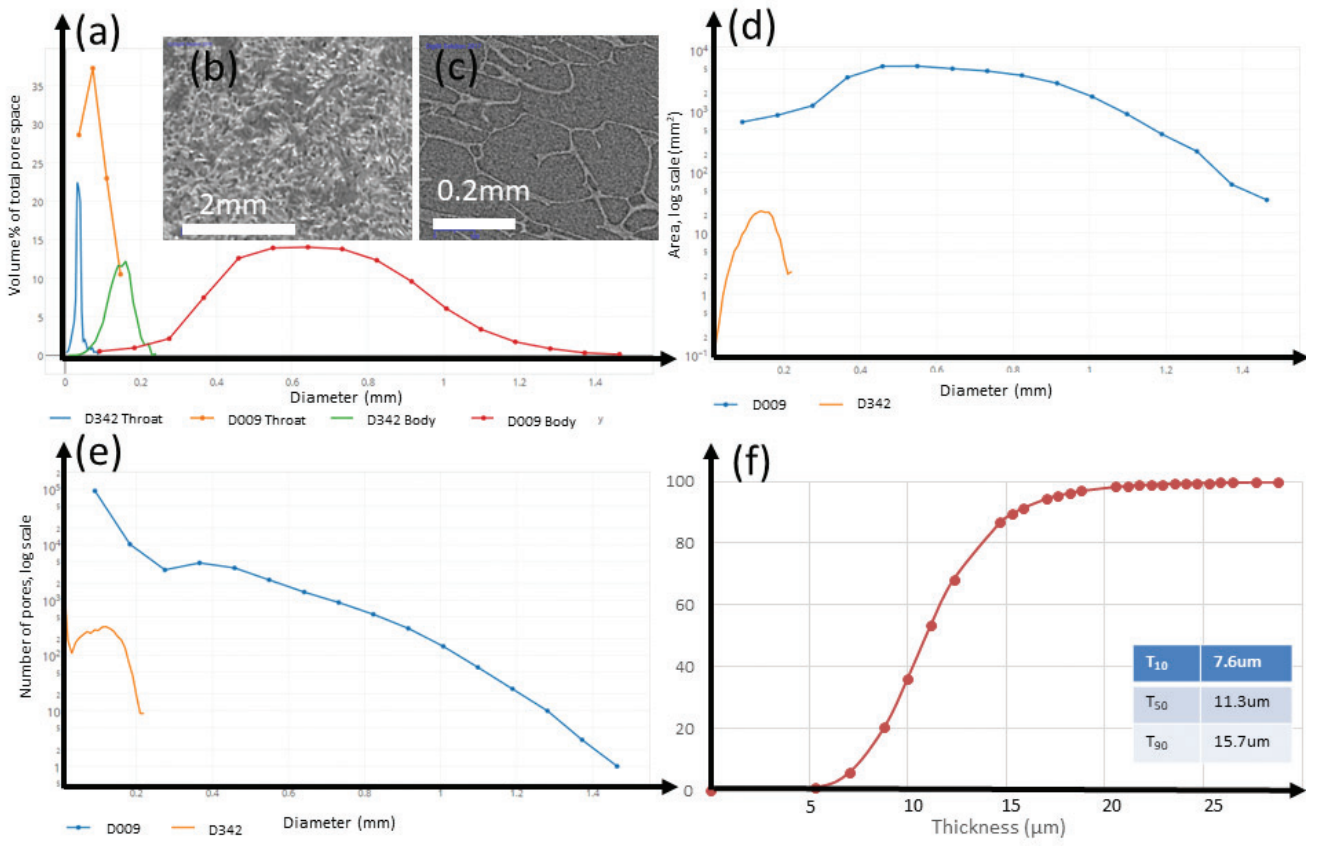
This new image to simulation (I2S) method not only characterizes quantitatively the microstructure of the lyophilized drug samples, but also presents potential to correlate the microstructures with physical properties and process parameters. For example, Pisano, et. al had explored mass transfer characterization using X-Ray micro-computed tomography images.[3] Further enhancement of the method could be used to optimize parameters in drug formulation, cycle development, process scale-up, transfer, and stability.

FIGURE 1



Cross sections of two 3D XRM scans of the same cake sample inside a glass vial versus removal of glass vial, using spatial resolution of 1µm. (a) Low magnification of the sample imaged inside a glass vial. (b) Low magnification of the sample after the glass vial is removed. (c) High magnification cross section image corresponding to (a). (d) High magnification cross section image corresponding to (c). Note the double edge artifact due to cake wall deformation when absorbing environment humidity during a few hours of XRM scan.

FIGURE 2



Quantitative micro-porosity geometry analysis of two freeze cake samples. (a) Pore size and pore throat size distribution of cake D009 and cake D342. (b) Cake sample D009 scanned at 18-µm resolution by Vendor A. (c) Cake sample D342 scanned at 1-µm resolution by DigiM. (d) Pore surface area distribution of D009 and D342, note log scale of Y axis. (e) Pore court distribution of D009 and D342, note log scale of Y axis. (f) Cumulative distribution of cake solid thickness, with insert table showing thickness 10%, 50%, and 90% values.

XRM NON-INVASIVE VISUAL INSPECTION

The opaque nature of lyophilized products makes visual inspection of the cake structure difficult. Removal of the cake from container, required by light microscopy and scanning electron microscopy imaging techniques, is undesirable, as the cake product is highly sensitive to humidity and temperature fluctuations. X-Ray micro-computed tomographic (MicroCT) imaging offers an attractive solution, as it can visualize internal cake structures non-invasively.[4] Popular MicroCT systems used in the pharmaceutical industry, however, have a few limitations. First, these MicroCT systems, originally designed for small animal imaging, are limited to 5- to 10-µm resolutions, insufficient to elucidate the sub-micron sized cake microstructures. Second, these MicroCT systems only support geometrical magnification, i.e., they can only obtain higher resolution scans by moving the sample closer to the X-Ray source. For larger samples, their dimension limits nearness to the X-Ray source, and ultimately limiting resolution. Cutting the samples smaller is not always desirable, and often impossible for the lyophilized product. Third, popular small animal imaging MicroCT systems are calibrated to handle small animal tissues and organs. They suffer from a severe beam hardening artifact when imaging cake directly inside a glass vial, due to the high-density gradient between the wall of the vial and the cake.

X-Ray Microscopy (XRM), in comparison, removes all of these limitations. Spatial resolutions of 0.5 to 1 µm, or an order of magnitude improvement from small animal MicroCT imaging systems, is routinely achieved. A multi-stage magnification optics design allows a 3D scan focus on an internal sub-volume of the sample digitally, thus, it supports high resolution at constant distance from the X-Ray source. Beam hardening can be mitigated to obtain artifact-free cake

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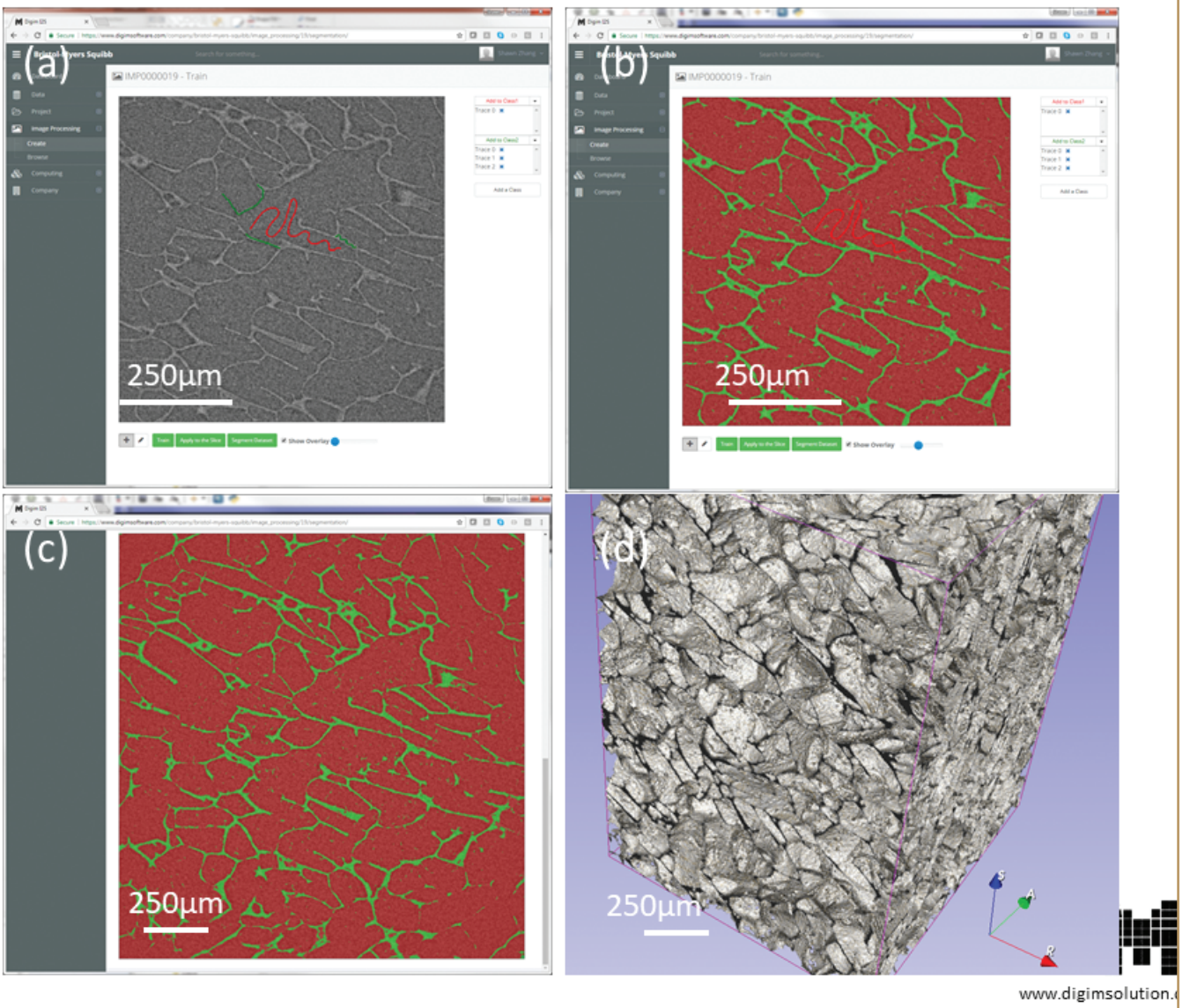
FIGURE 3



DigiM I2S cloud-based artificial intelligence segmentation on a XRM image volume. (a) Training phase where a small image with all features of interest is interactively seeded with lines of pixels representing the phase: red line is a seed line for the air phase; green line is a seed line for the cake solid phase. (b) Machine learning segmentation on the small training image. (c) Machine learning segmentation applied to the full 2D image where the small training image is cropped out (d) Machine learning segmentation applied to the full 3D volume, with 3D cake solid visualized in grey.

microstructure. XRM is traditionally only considered feasible with a synchrotron facility.[5] In recent years, however, it has become increasingly available in a laboratory environment and is more accessible to broader pharmaceutical community.

Figure 1 shows two XRM scans of cake sample D342, where the cake microstructures with and without glass vial during the imaging experiments are compared. To better visualize the detail of the microstructure, only one 2D cross section from the 3D volume is shown. Both scans are 1 µm in resolution. Figures 1a and 1c shows a successful cake-in-vial scan without any beam hardening artifact. Porosity and a thin wall of protein solid are both resolved clearly. Figures 1b and 1d show a scan of the same cake sample taken out of the glass vial. Small deformation of the protein solid is captured during the scan as double-edged features, denoted by the red arrows in Figure 1d. The comparison clearly indicates that the scan corresponding to 1b, where the cake is taken out of the glass vial, is undesirable. However, subtle change of the protein solid layers is captured and can be correlated with the mechanisms of cake collapses, due to the high resolution and contrast of XRM.

Resolution is very important to how a lyophilized microstructure may be eluci-

TABLE 1

	Cake D009	Cake D342
Analyzed volume (mm^3)	15x11x18.6	1.37x1.35x2
Resolution (um)	18	1
Porosity (%)	38	84.9
Peak pore body (um)	640	130-170
Peak pore throat (um)	70	32-40
Diffusivity (% of bulk)	8.4, 12, 3.7	44, 35, 27
Permeability ($10^{-12}m^2$)	98.4, 201.4, 35.6	63.6, 52.5, 47.8

Characterization of micro-structure geometry and physical properties of two cake samples.

dated, as in any imaging study. Figure 2b and 2c show two lyophilized cake samples imaged at 18-μm and 1-μm resolution, respectively. In Figure 2b, a cake sample D009 was imaged at 18-μm resolution. Only the large pores are visible, while a fair amount of micro-porosity cannot be fully resolved, leaving a lot of voxels (3D version of pixels) with a mixture of cake solid and porosity. In Figure 2c, a cake sample D342 imaged at 1-μm resolution, in comparison, can resolve the thin cake filament with very good contrast and resolution, which is essential for quantitative analysis.

As the first advantage of image-based lyophilized product characterization method, XRM imaging provides direct, non-invasive, explicit and full 3D visualization of lyophilized samples, at resolutions as high as sub-micron.

AI MICROSTRUCTURE QUANTIFICATION

High-resolution 3D imaging, including but not limited to XRM and MicroCT, produces massive volumetric image data with rich microstructure information for lyophilized drug and other solid and semi-solid dosage samples. The management, analysis, and quantification of these data become a non-trivial task. Conventional desktop-based analysis software solutions, commercial or open source, fall short on dealing with these data effectively.

Using a cloud computing interface, DigiM I2S, thousands of 3D volumes can be easily accessed, visualized, searched, and managed via a web-based browser, from anywhere, at any time, using any kind of computing devices.[6]

Figure 3a shows a snapshot of DigiM I2S' AI-based image segmentation interface. The user interactively draws traces of lines as the seed to train the DigiM I2S AI engine. The red trace is the training seed for the porosity, and green trace is the training seed for protein solid. Figure 3b shows the results where the image is classified into two phases, red phase for porosity and green phase for protein solid. If the classification is unsatisfactory, the user can revise his/her seeding strategy by removing, adding, or modifying trace lines.

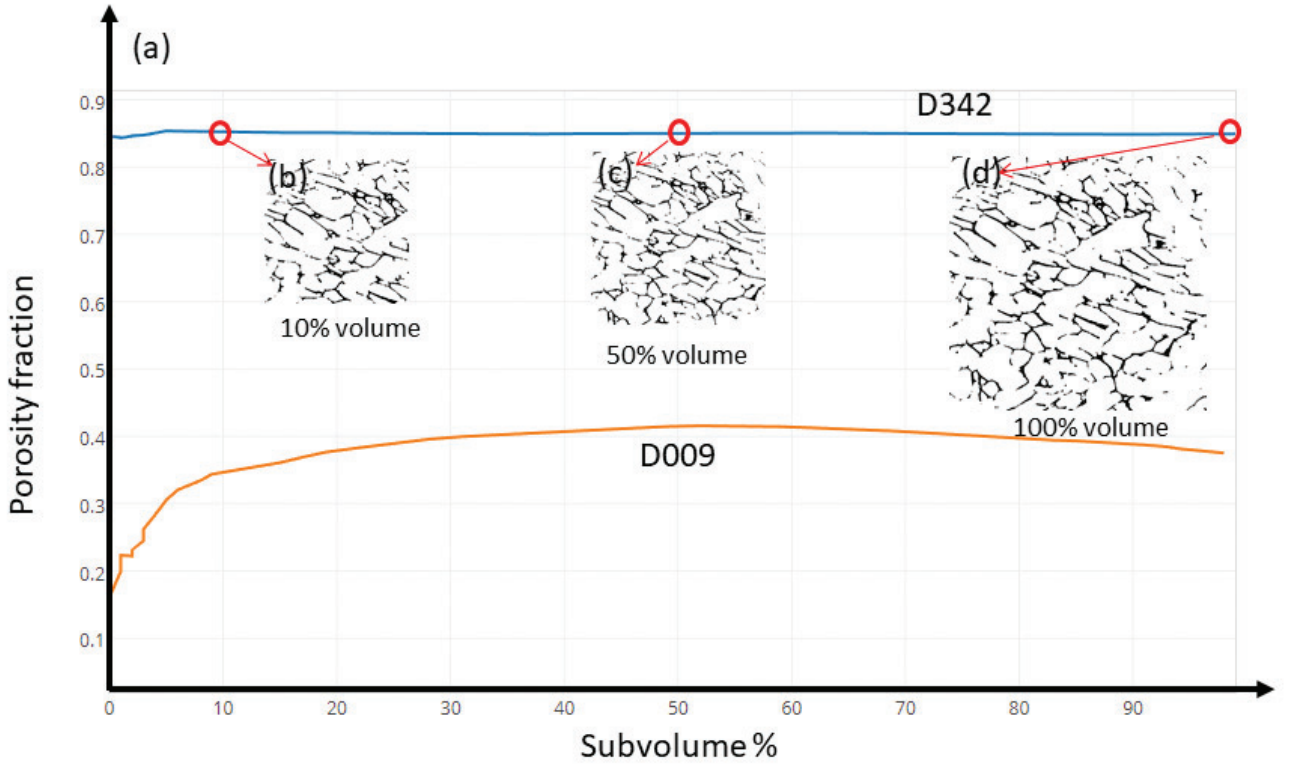
When the user considers the supervised AI segmentation on the training image is acceptable, Figure 3c, a cloud computing batch session can be launched on the full image volume, through which the 3D cake structure can be reconstructed, as shown in Figure 3d. These 3D reconstructions fully digitize the cake microstructure. Thus, they can be visualized, digitally edited, and quantified.

QUANTIFICATION

With reconstruction of 3D microporosity and cake structure, quantification is possible. Table 1 summarizes the quantifications computed from the two 3D imaging scans corresponding to Figure 2b and 2c. Resolved porosity of the two cakes are 38% and 84.9%, respectively. Figure 4 shows how porosity varies within each cake sample. Starting with a small sub-volume (eg, 10% of total cake volume image), porosity is computed for each incremental sub-volume. When the porosity reaches a constant volume, i.e., it does not further increase with the increase of sub-volume size, a representative elementary volume (REV) is considered to be obtained. D342 has reached REV with about 30% of total volume, while D009 has not achieved REV even with the full volume. Hence, high resolution XRM imaging compared to MicroCT offers the advantage of more accurate pore structural quantification by capturing more representative REVs.

The reconstructed 3D microstructure can be quantified in various ways, such as pore body size distribution and pore throat distribution (Figure 2a), pore surface area distribution (Figure 2d), pore number distribution (Figure 2e), and cake solid thickness distribution (Figure 5f). With the digital microstructure data, a large suite of geometrical characterization can be computed, including but not limited to shape, orientation, aspect ratio, and ferret diameter of pores. While

FIGURE 4



Representative elementary volume (REV) analysis. (a) Comparison of REV analysis on cake samples D009 and D342. (b) Cross section of a sub-volume of cake D342 that is 10% of total scanned cake volume. (c) 50% of total scanned cake volume. (d) 100% of total scanned cake volume.

porosity can be obtained with other laboratory measurement methods, with arguably higher uncertainty and more difficulty than imaging analytics methods, pore size distribution, surface area distribution, and cake solid thickness cannot be measured otherwise at all. Full 3D quantification capability is the second distinctive advantage of the image-based lyophilized product characterization workflow.

PHYSICAL PROPERTY PREDICTION

Qualitative visualization at high resolution and quantification in 3D, as discussed in previous sections, are both extremely valuable. However, they are characterizing the structures that are captured at one particular time instance, under fixed physical conditions. By combining the microstructures from the images with computational physics methods, properties under variable physical conditions can be predicted. Variable physical conditions include, but are not limited to, pressure, temperature, fluid flow, and electromagnetic field.

Figure 5 shows a Mercury intrusion capillary porosimetry (MICP) simulation result conducted with DigiM I2S on samples D342 and D009. MICP is based on the premise that a non-wetting liquid (one having a contact angle greater than 90°) will only intrude porous capillaries under pressure. The relationship between the pressure and capillary diameter is described by Washburn as: P=-2*gamma*cos(theta)/r, where P is pressure, gamma is surface tension of the liquid, theta is contact angle between the liquid droplet surface with the solid wall, and r is the radius of the pore.[7]

As a non-wetting liquid to most materials, mercury must be forced using pressure into the pores of a material. The pore size distribution controlled by pore throats is determined from the volume intruded at each pressure increment. Total porosity is determined from the total volume intruded. The MICP technique is used widely in the industry because of its ease and simplicity. However, for most pharmaceutical materials, it is very difficult to keep sample integrity when it is subjected to high pressure. The sample can deform under moderate-to-high pressure, thus changing the geometry being measured. The sample can also fracture, leading to measurement inaccuracy and failure. These challenges are more pronounced

FIGURE 5

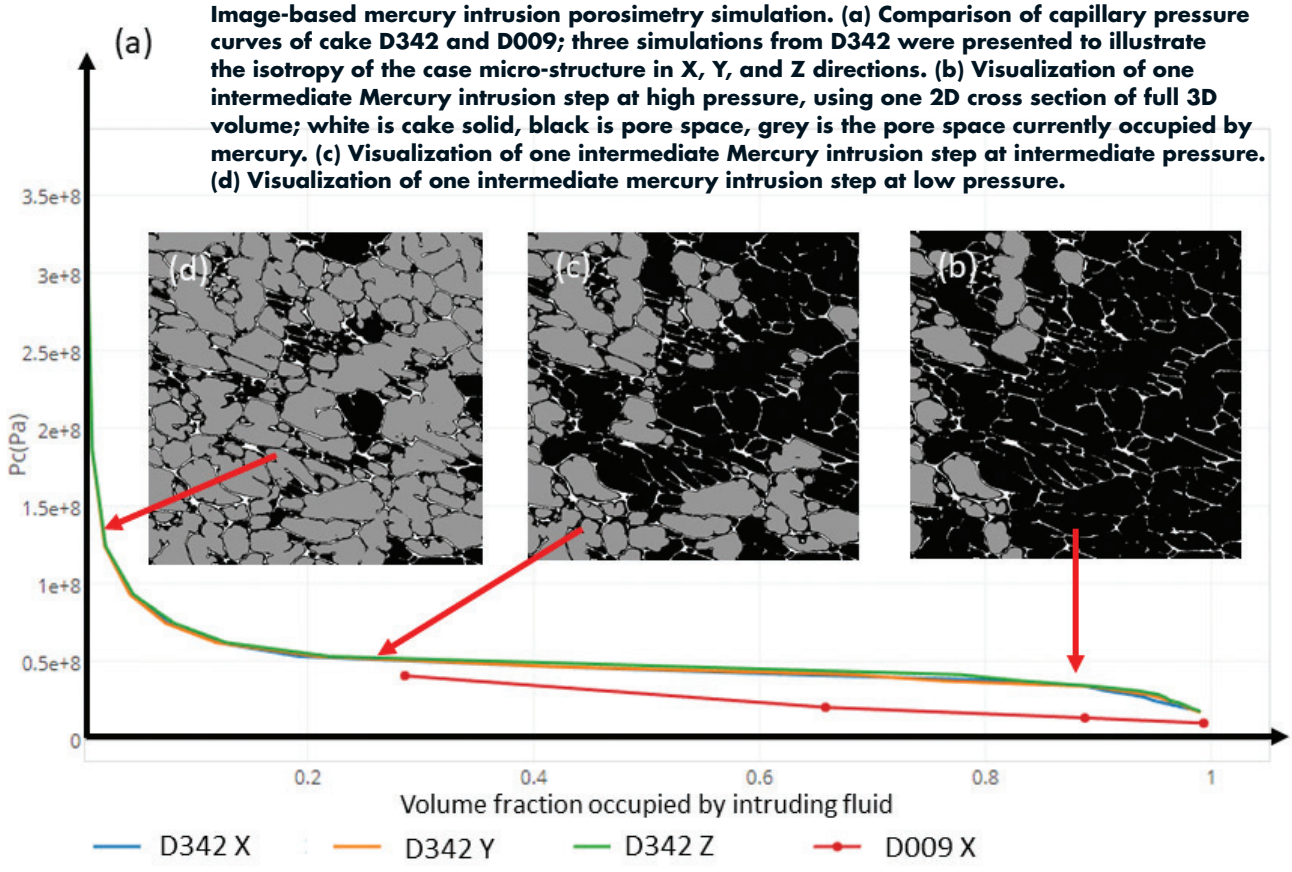


Image-based mercury intrusion porosimetry simulation. (a) Comparison of capillary pressure curves of cake D342 and D009; three simulations from D342 were presented to illustrate the isotropy of the case micro-structure in X, Y, and Z directions. (b) Visualization of one intermediate Mercury intrusion step at high pressure, using one 2D cross section of full 3D volume; white is cake solid, black is pore space, grey is the pore space currently occupied by mercury. (c) Visualization of one intermediate Mercury intrusion step at intermediate pressure. (d) Visualization of one intermediate mercury intrusion step at low pressure.

on lyophilized drug samples. An image-based MICP simulation method adapted to the cloud computing environment DigiM I2S circumvented all of the aforementioned problems and avoided the use and disposal of Mercury entirely.[8]

Figure 5a shows four MICP simulations performed by DigiM I2S. The three curves correspond to the three directions of D342 sample. The three curves have nearly identical shape, indicating isotropic micro-porosity structure of D342. The result corresponding to the X direction of D009 is also shown. Due to the bigger pores resolved with relatively lower resolution in cake sample D009, only four pressure points are captured with this simulation with much lower threshold entry pressure.

Figure 5b, 5c, and 5d show three intermediate saturation states associated with their corresponding pressure in the MICP simulation of X direction for sample D342. One cross-section is shown from the full 3D simulation at each saturation state. In the simulation, mercury is pushed into the cake sample from left to right. The simulation result curves run from right to left with increasing pressure. At low pressure, Figure 5b, only a small portion of the pore space near the inlet is saturated with mercury (grey), while the majority of the pore space is still empty with only air (black). Cake solid is visualized as white voxels. When pressure increases, Figure 5c, more Mercury is pushed into the cake sample, thus mercury saturation is increased and occupies 70% of the total pore space. Near the final stage at high pressure, Figure 5d, more than 95% of the total pore space is occupied.

Image-based simulation can produce not only pore space distribution characterization of lyophilized samples without risking sample integrity, but also direct visualization to allow elucidation of dynamic transport processes. Other simulations, such as Navier-Stokes-based permeability, Second Fick's law-based molecular diffusivity, Ohm's law-based electrical conductivity, Fourier's law-based thermal conductivity, and linear element-based Young's modulus, can be computed. With the image-based method, physical properties are derived from the exact same microstructures, which is very difficult, if not impossible, to do otherwise.

FURTHER POTENTIAL & LIMITATIONS

Image-based characterization has great potential in a number of lyophilized drug product characterization situations. Cake integrity and purity can be non-invasively monitored. Inter-batch and intra-batch homogeneity can be quantified. Correlations of sample microstructure with lyophilization process can be mechanistically understood, parameterized, and optimized, including sublimation rate, primary and secondary drying optimization via annealing, and controlled ice nucleation. Specifically, if we can derive mass transfer and heat transfer coefficients from the cake structure and couple them with lyophilizaiton modeling tools, the results would be extremely helpful for cycle development and scale up.[9] Optimistically, this approach could be used for stability prediction and failed batch diagnostics.

Like any characterization effort, a number of limitations need to be kept in mind. A successful image-based characterization project requires an optimal balance between resolution and the number of samples studied to ensure representativeness. Finite resolution limits the smallest feature that can be studied. Furthermore, due to the high price of imaging devices, sophistication in the imaging experiment, and the massive amount of data derived, the cost of image-based analysis is not trivial. However, as the image data progressively develops into a digital drug database, with more insight, faster drug evaluation, and facilitation of new formulation design, the initial imaging cost will be marginalized. Last but not least, the management, visualization, and quantification of simulation of massive amount of data is often overlooked and limits the utility of 3D imaging data. A dedicated software and computing hardware platform is often required, where a cloud computing solution, such as DigiM I2S, offered both as software as a service (SaaS) and on-premise installation, has a great advantage. ◆

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BIOGRAPHIES

Dr. Shawn Zhang is Founder and Managing Partner of DigiM, where he leads DigiM to becoming the platform technology pioneer in microstructure physics, characterization, and design with applications. He earned his PhD Computational Physics from Rutgers University.

Dr. John Goldman is a Process Development Scientist at Moderna Therapeutics, leading its mRNA lipid nanoparticle drug product lyophilization development. Dr. Goldman earned his PhD in Chemical Engineering from Carnegie Mellon University.

Dr. Xiaodong Chen is a Senior Research Investigator at BMS, responsible for developing, recommending, and implementing development strategies of biologics drug product formulation, device and primary packaging, tech transfer to commercial manufacturing, and registrational filing. He earned his PhD from the Ohio State University.

Dr. Jasmine Rowe earned her PhD in Chemical Engineering from the University of Texas at Austin. She leads an Applied Engineering group within drug product development at BMS, where her group focuses on the development and integration of engineering tools and models for both oral solids and parenteral products.

Sam Lin is a Software Development Manager with DigiM. As one of the chief architects of the first cloud-based image processing platform, he leads the design and development of DigiM I2S. He also champions AI-based image processing platform technology since he joined DigiM in 2015. He earned a Computer Science degree from QingDao University.

Dr. Liping Zhou joined DigiM Solution with 15+ years of experience in the pharmaceutical and biotech industry, including Novartis and Ipsen. She earned her PhD in Chemistry from the University of Connecticut and has nearly 20 publications in peer-reviewed journals and book chapters to her credit.

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BIOPROCESSING

A New Era: Why the Time Has Come for Biopharma to Move to Continuous Bioprocessing

By: Martin Smith, PhD

INTRODUCTION

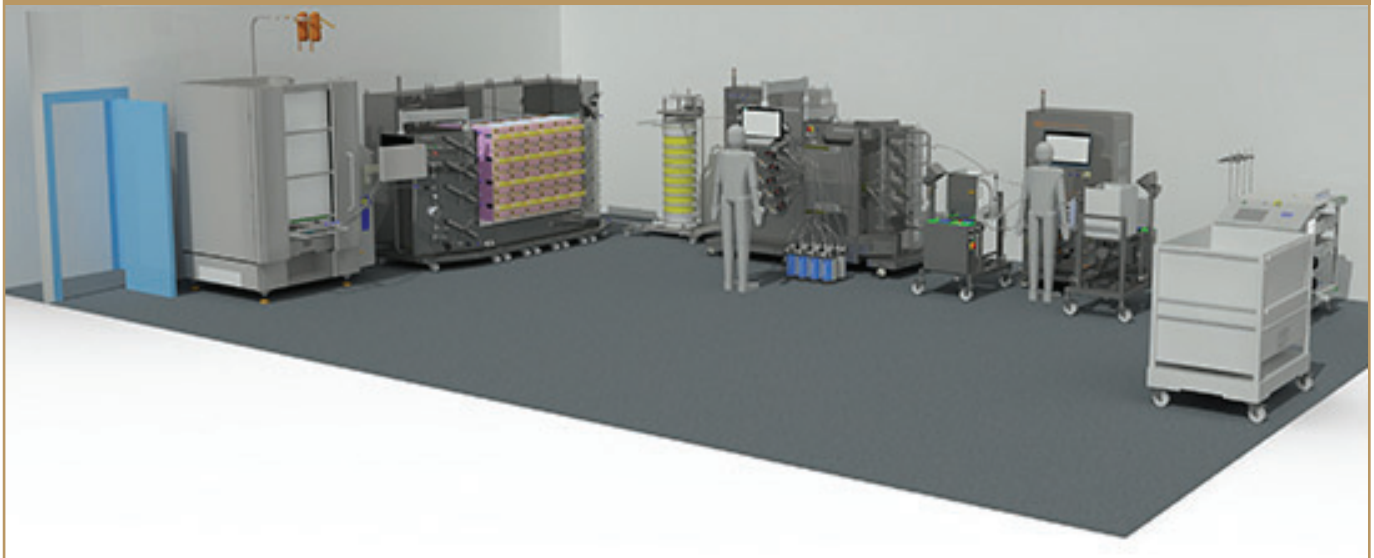
The pharmaceutical industry is approaching a watershed moment when it comes to drug manufacture. Rising cost pressures, market paradigm moves toward outcome-based medicine, fierce competition, and the ever-greater demand created by a growing and aging population are all putting unprecedented pressure on the sector. More complex therapeutics in greater numbers must be produced quicker and more cost effectively than ever before – and the industry is struggling to keep up.

One of the fundamental reasons for this growing strain is that despite billions of dollars being invested into the industry every year, the methods used in drug manufacture haven't changed substantially in decades, resulting in an ever-decreasing return on investment for R&D efforts within the pharma sector. While other manufacturing arenas have embraced continuous flow manufacturing or continuous processing and seen huge improvements in efficacy, reliability, control, and cost reduction, biopharma is in danger of falling behind.

There are myriad reasons for this. In such a highly regulated sector, manufacturers have often voiced fears of contamination risks and control issues, both of which are – often incorrectly – associated with continuous processes. There are practical financial considerations too: significant capital has been invested in stainless steel plants throughout the years, and large manufacturers are understandably reticent to shift to continuous manufacturing, which largely uses single-use systems.

But times are changing. Biopharmaceutical companies, finding themselves in an increasingly precarious position and concerned about the efficiency of their manufacturing operations, are

FIGURE 1



Pall's Cadence BioSMB system and Cadence Virus Inactivation system integrate together to provide combined continuous unit operations. The first-to-market combination of multicolumn chromatography and continuous low pH virus inactivation meet the market need for process intensification through parallel single-use operations.

"One of the fundamental reasons for this growing strain is that despite billions of dollars being invested into the industry every year, the methods used in drug manufacture haven't changed substantially in decades, resulting in an ever-decreasing return on investment for R&D efforts within the pharma sector. While other manufacturing arenas have embraced continuous flow manufacturing or continuous processing and seen huge improvements in efficacy, reliability, control, and cost reduction, biopharma is in danger of falling behind."

looking beyond traditional batch processing to a new way of creating complex and diverse new drugs.

The question is how much potential does continuous bioprocessing really hold for the biopharmaceutical industry, and will manufacturers be able to navigate the perceived obstacles and truly move beyond batch processing to a continuous future?

FINANCIAL DRIVERS

From a purely financial perspective, it's hard to argue against the move from traditional batch processing to continuous manufacturing. Industries like automotive, aerospace, food, and metal product have been using continuous manufacturing processes for many years, and the benefits have been remarkable. Increased efficacy and reliability, reduced capital costs and failure rates, improved process control, and accelerated speed of bringing new products to market are just some of the improvements that continuous processes are driving in manufacturing companies around the world.

Now, the biopharmaceutical sector's early adopters of continuous are beginning to reap similar financial rewards; already demonstrating that continuous bioprocessing offers the single greatest opportunity for large-scale cost-savings in biomanufacturing on a number of levels. Drug manufacturers that have adopted continuous have seen a huge reduction in the size of single-use components. The implementation of more purification cycles to produce more product, as an alternative to scaling up, can decrease consumable spending by remarkable proportions.

Chromatography – usually the most cost-intensive aspect of downstream bioprocessing – offers perhaps the most striking example of the potential savings offered by continuous. Protein A sorbents used in the primary capture step, for example, can cost over $10,000 per litre. However, by optimizing the number of columns needed to operate this process, manufacturers can enable reductions in reagent use of up to 90%. This vastly improves the efficiency of consumable use, while also reducing the need for large tanks, buffer-storage bags, and other equipment – all of which takes cost out of the manufacturing process.

The improvements in utilization and efficacy that continuous brings can have significant knock-on effects on manufacturers' capital expenditures. When using traditional batch processing in a large stainless steel production bioreactor, as much time will be spent cleaning and on changeover as on production. With continuous, where manufacturing assets can be running 24/7, 365 days a year, manufacturers will quickly find their footprint needs are reduced. This means fewer large manufacturing sites and smaller workforce requirements which, coupled with reduced spend on consumables, will contribute to a significant reduction in capital expenditure.

PERCEIVED REGULATORY RISK

The single biggest reason why these financial rewards haven't been seized with both hands is the perception that continuous processing comes with significantly higher regulatory risk than batch processing.

There is some justification for this concern. It wasn't until 2015 that we saw the first continuous process for a small-molecule drug product gain regulatory approval with Vertex's Orkambi. And there are aspects of continuous processing – for example, the fact that unit operations run for significantly longer periods than in batch systems – that lead to concerns around bioburden management and process consistency, while the use of more complex instrumentation in continuous has

FIGURE 2

The Allegro STR 200 bioreactor, Cadence Acoustic Separator, Cadence BioSMB 350 system, and Cadence VI system integrate to make up the Pall suite of single-use technologies that enable fully continuous bioprocessing at manufacturing scale.

led some to believe there will be a higher risk of equipment failure.

Of course, manufacturers and regulators must understand the differences between traditional batch processing and continuous manufacturing and be attune to possible risks. But the reality is there is no greater inherent risk in continuous than in batch processing, and the current regulations make no distinction between the two. This challenges the belief held by some that continuous, being a step-change from batch processing, will require an entirely new regulatory approach. In fact, there is no need for specific guidelines around continuous because these guidelines already exist in current regulation.

From a regulatory perspective, continuous systems actually present regulators with an opportunity, rather than a challenge. The sophisticated instrumentation of continuous systems will enable manufacturers to gather far more data than was possible with batch systems. This data will provide a better understanding of the process and enable regulatory bodies to confirm that operations are consistent and within acceptable ranges in a far more expedient and efficient way.

For the industry, it's important not to see this as a one-way process. Biopharmaceutical companies have an important job to do in helping to educate regulatory inspectors and reviewers on the implementation of continuous bioprocessing. At Pall, we've spent a great deal of time engaging with regulators to get them comfortable with the manufacturing changes that are occurring and to provide as much information as possible about continuous; the rest of the industry needs to do the same.

TECHNOLOGICAL ADVANCES

One driving force behind the adoption of continuous in other sectors has been the rapid advance of technology, in particular their ability to harness the power of data. But while others have embraced AI, robotics, and data analytics technologies as a matter of course for many years now, the pharmaceutical laboratory has remained largely unchanged for decades. Only now is the industry genuinely talking about the "Lab of the Future" with real conviction.

This has hindered the sector's move to continuous processes. As was the case with single-use components, pharmaceutical manufacturers want the reassurance of hard data and evidence of scalability before they make a change. But because adoption of cutting-edge technology had been slow, data on continuous exists on a very small scale, making it a challenge to demonstrate production-scale viability.

This cycle was very hard to break. Throughout the past 5 or 6 years, however, we've seen the industry taking a new approach to data. There is now greater emphasis on statistical methods and a

commitment to make use of manufacturing data as a means by which to improve quality-by-design and quality risk management. This has paved the way for a shift to continuous, as the industry has gone down the path with batch processing and now feels more confident about mitigating risks in continuous bioprocessing.

From a technology perspective, it is critical that equipment and analytics work together to support real-time decision making and continue to build confidence in continuous. We made the decision at Pall to invest heavily in modelling to ensure all our continuous innovations are supported by robust data, particularly around scale-up. We believe this is one of the main reasons we've become the industry leader on continuous technologies and why more and more companies now approach us to develop an end-to-end continuous process for them – because the viability and value of the continuous approach is now irrefutable.

There also needs to be recognition from technology suppliers, Pall included, that greater collaboration and cooperation is needed. If manufacturers are to be able to integrate multiple continuous operations, they must be able to combine our technologies with other systems available in the market. For this, we need open communication and open data sharing – something our industry has historically been bad at, but which is vital if our customers are to realize the true potential of continuous.

TRANSFORMING WORLDWIDE HEALTHCARE

Setting aside the financial and commercial advantages that continuous bioprocessing can bring to biopharma companies, it's important to remember the ultimate beneficiary of this shift in the manufacturing status quo: the patient.

We see medicine shortages around the world, with healthcare systems perpetually challenged by the fact that we can't bring new drugs to market fast enough to meet demand. Continuous bioprocessing can deliver a substantial reduction in the time it takes to deliver a product compared to traditional batch processing – vastly improving the speed at which biopharmaceutical companies can evaluate the viability of a new product, produce clinical trial material, and reach potential failure points will help tackle some of the world's most pressing medicine shortages.

It also will enable biopharmaceutical companies to decentralize drug manufacture. Large, expensive, immobile plants can in time be replaced by smaller, more flexible continuous facilities, deployed in strategic locations with ready access to markets, where there is high demand. This will reduce the logistical burden and associated cost of transporting medicines around the world, but more importantly, it will enable us to move toward a true "drugs-on- demand" model, driving outcome-based medicine provision, where new medicines are manufactured nimbly, more consistently, and flexibly in locations closer to the patients who need them.

The industry is on a journey, and in truth, we are only at the beginning. Giant leaps have been made compared to where we were just 5 years ago, but it will take time for manufacturers, regulators, and the supply chain to fully commit to a continuous future. There is no doubt now, however, that the tide has turned, and things will only continue to pick up pace in the coming years. The simple truth is that the benefits for the industry and for patients are far too great to be ignored – in 5 years, we will look back and wonder why we didn't do this sooner.◆

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

BIOGRAPHY

Dr. Martin Smith was appointed Pall Chief Technology Officer (CTO) in August 2014 and is responsible for the management of all central technology groups. In addition, his department provides Research and Product Development oversight, governance, and framework for the technology groups residing within Pall's Business Units. Prior to his appointment, he led Pall Media (materials) R&D. Joining Pall in 2006, he has previously led R&D for Pall Medical. Dr. Martin spent a number of years at GE-Whatman, holding R&D and Business Development positions of increasing responsibility, ultimately attaining the senior technical position within the company. Prior to joining Pall, he was VP of Clinical Diagnostics at Intelligent MDx Inc. He has held several technical and product development positions at various diagnostics and laboratory supply companies in both the US and Europe. He earned his PhD in Biochemistry from University College London, UK, and is the holder of multiple US-granted patents in the area of separations science.

Special Feature

Outsourcing Analytical Testing: Novel Services Elicit Consistent, Quantifiable, & Faster Results

By: Cindy H. Dubin, Contributor

The global pharmaceutical analytical testing outsourcing market size is projected to reach $10.4 billion by 2026, according to a recent report by Grand View Research, Inc. Clinical bioanalytical testing services is projected to be the largest service segment over the forecast period.[1] And with many big companies lacking the required manufacturing set-up and expertise to carry out in-house testing services, outsourcing is essential to remain competitive. In addition, ancillary services, such as registration, storage and testing, process and facility validation, and cleaning validations, are being outsourced and will only boost the market growth.

This exclusive annual *Drug Development & Delivery* report describes some novel analytical testing services aimed at ensuring quality and safety, and in some cases, speeding the process and saving money.

Catalent provides stand-alone assays from its facilities in Research Triangle Park, NC, and Kansas City, MO.

ARL Bio Pharma: Test Services for Drug Discovery, Launch, and Access

ARL Bio Pharma is a contract laboratory that provides analytical and microbiological testing to pharmaceutical companies and research scientists. The laboratory provides guidance and test services for all phases of the product lifecycle following USP, FDA, and ICH guidelines. "ARL's approach to industry quality requirements, analytical systems, and data integrity provides the scientific results needed to launch small molecules, biologics, proteins, and peptides to market," says Thomas C. Kupiec, PhD, President and CEO, ARL Bio Pharma. "Our team maintains awareness of quality, safety, and changing regulations to comprehensively understand clients' drug product goals, provide results, and help interpret data for each stage of the lifecycle."

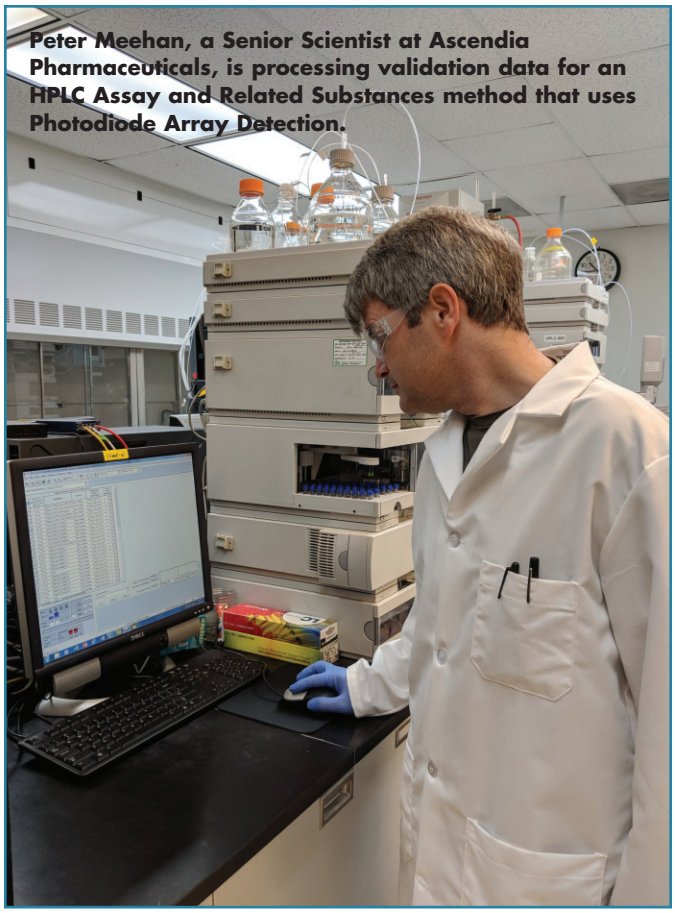
Analytical method development and validation is important to develop safe and effective drug products and improve efficiencies in the drug discovery process. ARL validates analytical methods based on ICH and USP guidelines and high-quality industry practices. Method parameters may include precision, limit of detection, limit of quantitation, accuracy, linear range, specificity, robustness, system suitability, ruggedness and freeze-thaw. "Analytical method parameters help establish accurate and reliable acceptance criteria," says Dr. Kupiec.

ARL's laboratory also works with pharmaceutical companies to perform Y-site compatibility studies. These studies ensure that the mixing of two product formulations does not impact the physical or chemical properties of the drugs. Dr. Kupiec says: "The data is used in product packaging so administrators know what other drug products can be clinically administered with the packaged product to ensure patient safety."

Ascendia Pharmaceuticals: Phase-Appropriate Method Validation

Ascendia Pharmaceuticals provides analytical support for all stages of the drug development process, from discovery to approval. Analytical support includes method development, method validation, and testing drug products, drug substances, excipients, components, etc.

"Ascendia's analytical support model is based on providing our clients with reliable data," says Muhammad Asif, PhD, Sr. Director, Analytical R&D and Quality Control, Ascendia Pharmaceuticals. "To ensure accurate results, Ascendia has developed internal systems and processes that fulfill this promise throughout the development process."



Peter Meehan, a Senior Scientist at Ascendia Pharmaceuticals, is processing validation data for an HPLC Assay and Related Substances method that uses Photodiode Array Detection.

As the drug development process is becoming more involved and sophisticated due to increasing complexity of new drug moieties, Ascendia has developed a niche in developing marketable formulations of drugs that otherwise have low solubility and/or bioavailability, claims Dr. Asif. "Development of good analytical methods not only has helped streamline the formulation development, but, in some cases, showed that a stable formulation was indeed feasible," he says. Ascendia uses a phase-appropriate method validation process. For example, during early development, accuracy and specificity of a method are ensured, while during later stages of product development, a full method validation package is offered for NDA/ANDA submissions that fulfils ICH and FDA requirements. Ascendia also offers a full method-transfer package to a commercial Quality Control laboratory.

Catalent: A One-Stop Lab for Stand-Alone Method Development

The analytical services division at Catalent conducts analytical chemistry and microbiology tests to determine and ensure the identity, purity, potency, and performance of drug substances and

"Development of good analytical methods not only has helped streamline the formulation development, but, in some cases, showed that a stable formulation was indeed feasible." – Muhammad Asif, PhD, Sr. Director, Analytical R&D and Quality Control, Ascendia Pharmaceuticals.

drug products. In addition, this division provides stand-alone method development and validation, structural characterization (including extractables/leachables and heavy metals/elemental impurity testing), solid state preformulation, and clinical and commercial-scale stability studies, in compliance with international standards. Catalent's analytical chemists and technicians handle highly potent, cytotoxic, light-sensitive, temperature-sensitive, and DEA-regulated compounds.

In addition to its suite of small-molecule testing capabilities, Catalent also possesses large-molecule capabilities, including bioassay, binding assay, master/working cell bank storage, and sterile formulation development. And, Rekha Patel, Director, Biologics Analytical Solutions, adds that Catalent's Kansas City team has comprehensive capabilities, enabling a one-stop lab for clients, minimizing the client's need to manage logistics with multiple labs.

But when it comes to managing regulations, Catalent has made some internal adjustments. "We have seen changing regulations in the area of testing/qualification of plastic packaging systems and components for pharmaceutical use," says Dontae Solomon, Director, Analytical Development, Catalent. "A recent review of our existing USP 661.1/661.2 capabilities led to us developing a plan to generate a preset quote that could cover all the variations of the testing that might be needed."

Mr. Solomon explains that USP 661.1/661.2 comes into full effect in May 2020, so requiring addressing shortly. The chapters have various LC, GC-HS, and TLC methods that are specific to the plastic being tested and the additives in the formulation. Catalent is currently establishing whether verifications are necessary, whether these could be performed in advance using an in-house method, or whether the method standards and controls in the chapter obviate the need for a separate verification.

Frontage: Integrated Service for Drug Development

The Frontage analytical service department in its CMC division offers a variety of analytical testing to support API and reference standard characterization, preformulation, formulation, and finished drug product characterization. In addition to performing regular pharmaceutical analysis for both small and large molecule products, Frontage also performs special analytical tests, such as unknown degradation product identification, extractable/leachable analysis, host cell protein, and protein mapping. Other services include diffusion studies for semi-solid

CMC scientists at Frontage Laboratories, Inc. in Exton, PA.

product development, and ICP/OES and ICP/MS tests for metal analysis.

With metal impurity testing being a recently added requirement for drug products, Frontage used both ICP/OES and ICP/MS instruments to test one client's injectable product on multiple elements. "Together, with other chromatographic and wet chemistry tests, Frontage completed full ICH stability assessment on the product and leachable tests for the container/closure," says Kang Wang, Vice President of Analytical Services. "A comprehensive data package supported a successful NDA submission."

And, as a full-service analytical lab, Frontage developed and validated an *in vitro* release test method for one customer's ointment product. Mr. Wang says Frontage supported product selection activities and a final *in vitro* bioequivalence study between reference listed drug and test products per Good Laboratory Practice regulation. The study results helped the client gain ANDA approval from FDA, he says.

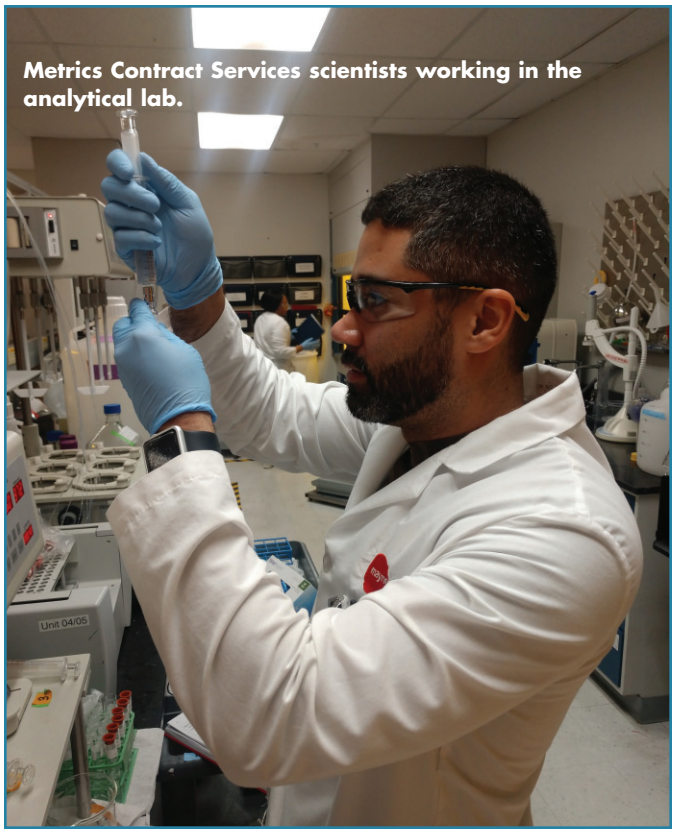
Mr. Wang adds that Frontage's analytical lab is continually evolving with new technology/instruments to meet challenges required for product development. "A highly sensitive accurate mass spectrometer will be installed in our lab in December," he explains. "With this addition, we can test low-level genotoxic impurity to satisfy regulatory requirements."

Metrics Contract Services: Methods for Testing Drug Substance & Drug Product

Metrics Contract Services has 150 chemists who provide method development, method validation, sample analysis, release testing, stability study storage and testing, physical characterization, trace metals analysis, and microbiology. A dedicated quality control laboratory to test commercially manufactured drug product made at its Greenville facility and a 17,000 square-foot facility provides storage space for clients' products requiring specified environmental conditions.

Once development is complete, the validation group works with clients to develop a phase-appropriate validation for the methodology that is in line with current FDA guidelines. Speaking of guidelines, the implementation of USP 232/233 led Metrics Contract Services to expand its metals analysis capacity by purchasing an additional ICP-MS and expanding its metals staff.

Metrics Contract Services performs a variety of analysis testing, including charged aerosol detection (CAD). As an example,



Metrics Contract Services scientists working in the analytical lab.

one client asked Metrics Contract Services to perform the release testing of Phase II clinical trial material and provided a validated HPLC method for the assay and identification of Compound X by UV detection. The method demonstrated consistent chromatography with the validating laboratory and met the requirements for precision and linearity.

During UV analysis, one peak was observed to have no impurities, explains Holly Horton, Senior Analytical Chemist, Metrics Contract Services. A review of the chemical structure of Compound X showed that no major chromophores were present and that the compound was a maleate salt. "This observation, as well as the lack of impurities, led our team to conduct another analysis using CAD," Ms. Horton says. That analysis showed two peaks, suggesting the peak identified as Compound X in the original method using UV detection was the maleate salt and not the active ingredient. The identities of both peaks were later confirmed by HPLC-MS.

A thorough investigation into the structure and chromatography of Compound X revealed that UV detection was not a suitable means for quantifying the main compound or the impurities, Ms. Horton says. Analysis performed using CAD displayed the presence of two peaks, which drew concern to the initial identification of Compound X by UV detection. LC-MS was used to properly identify these peaks.

MilliporeSigma's BioReliance® Services offer risk-mitigating approaches, testing, critical services, and customized solutions to help biopharmaceutical manufacturers bring therapies to market.

"These findings resulted in the development and validation of HPLC-CAD methods for assay, identification, related substances, and dissolution of Compound X prior to the release testing of Phase II clinical trial material to ensure the safety and efficacy of the clinical trial material," she says.

MilliporeSigma: Using LC-MS As An Orthogonal Approach To Verify ELISA Data

MilliporeSigma provides a comprehensive range of analytical, bioanalytical, and biosafety testing as part of its BioReliance® Services portfolio for biopharmaceuticals. Using a combination of analytical techniques and cell-based immunological assays, MilliporeSigma provides clients with a detailed understanding of the physical and structural attributes of their drug and its biological activity. "Our experience in method development and validation enables us to support projects from early development through to GMP lot release," says Andrew Bulpin, Head of Process Solutions, MilliporeSigma.

In addition to analysis of the molecule of interest, there is a regulatory requirement to characterize the various process-related impurities present in the drug substance or drug product. These residuals can arise from both upstream and downstream processes. Of particular concern are host cell proteins (HCPs), which pose a potential risk to patient safety and product stability.

"Generally, the level of HCPs is quantified by an enzyme-linked immunosorbent assay (ELISA) by using either a generic kit-based approach in the early stages of development, or by using polyclonal antibodies specific to the process," explains Mr. Bulpin. "This yields a numerical value equating to the total quantity of HCPs that produce an immunological reaction. However, it does not distinguish between the different HCPs present, some of which may cause concern. Also, it is necessary to demonstrate sufficient antibody coverage against all potential HCPs, which provides an additional challenge. There is increasing awareness of the limitations of HCP quantification for ELISA by regulators and manufacturers alike, leading to a need for orthogonal approaches."

Recently, MilliporeSigma established a liquid chromatography-mass spectrometry (LC-MS) platform for HCP analysis. In this approach, the sample is first digested using trypsin and the resultant peptides are analyzed by LC-MS. Proteins are then identified and quantified on the basis of the peptides detected. Mr. Bulpin says: "The combination of two-dimensional liquid chromatography and high-resolution mass spectrometry overcomes the analytical challenge of detecting low (ppm) level HCPs in a high concentration of therapeutic protein."

He says that a key benefit of the LC-MS approach is the ability to identify, as well as quantify, individual HCPs. "This knowledge enables a proper evaluation of the potential risk of specific residual HCPs," he says. "Furthermore, as a platform method, it can be applied to different products/processes without the need for extensive development, unlike an ELISA that requires specific antibodies to be raised."

The relative simplicity and ease of validation means that ELISA is unlikely to be replaced by LC-MS as a lot release test for HCPs in the near future. However, as regulators demand a better understanding of a product/process as part of the principle of Quality by Design, it is likely that more thorough characterization of the HCP profile will be required. "Several of our clients are now looking to use LC-MS as an orthogonal approach to verify their ELISA data and demonstrate suitable coverage," says Mr. Bulpin.

Quotient Sciences: Biorelevant Dissolution Assesses Different Formulations

Quotient Sciences develops and manufactures a range of dosage forms and conducts analytical testing to support preformulation, drug product formulation development, clinical, and commercial manufacturing operations. Analytical techniques such as DSC, TGA, XRPD, and Raman for solid state characterization are used. For drug product development and release, assay and content uniformity testing are typically performed via HPLC. UV, dissolution, aPSD, emitted dose testing, enzyme assays, and microbiological testing are also routinely performed. Some novel techniques are also used to support formulation development, such as biorelevant characterization.

Quotient Sciences routinely uses biorelevant dissolution testing (using biorelevant media) as an analytical tool for assessing the performance of different formulations. A recent study performed on behalf of Boston Pharmaceuticals Inc. involved developing three different formulations of BOS172767, representing different strategies (micronized capsule, lipid capsule, and spray dried dispersion tablet). "We assessed each formulation in a pH shift biorelevant dissolution test using fasted state simulated gastric fluid and fasted state simulated intestinal fluid," says Justin Holland, Senior Director (Analytics), Pharmaceutical Sciences, Quotient Sciences.

Data presented at the 2019 American Association of Pharmaceutical Scientists Meeting in San Antonio, TX, showed that dissolution testing demonstrated that all three formulation technologies had a greater release compared to the immediate release (IR) reference formulation. "All three formulations were dosed in a Phase I clinical study that successfully identified the micronized capsule as the new lead formulation with superior exposure to the IR reference formulation," he says. Furthermore, a Level C *in-vitro in-vivo* correlation (IVIVC) was achieved with the biorelevant dissolution test, providing valuable information for future formulation development and setting of product specifications.

Analytical testing is a key component of dosage form development, manufacturing, and release of drug products (Quotient).

Recipharm: Stand-Alone Analytical Service Meets Timelines, Saves Costs

In addition to offering analytical services, Recipharm launched Recipharm Analytical Solutions™ in 2019. The stand-alone service supports pharmaceutical companies with capacity for their analytical requirements, including method development, method validation, and stability program design and implementation. "By providing additional capacity for customer QC labs, we can reduce their timelines and any associated costs," says Maria Lundberg, Vice President of Global Analytical Development, Recipharm.

One leading pharma company came to Recipharm to sub-contract the routine analysis of a marketed antibiotic product. During this standalone analytical project, Recipharm established a team to conduct two series of experiments at the customer's site and one of Recipharm's facilities.

"Due to the development and validation work carried out in parallel with the stability study, we met the intended timelines established at the start of the project," says Ms. Lundberg. "We were also able to meet all the requirements of a quality control routing analysis."

In addition to launching the stand-alone analytical solutions offering, the company recently invested into expanding its laboratories in Bengaluru, India. "At Recipharm, we use a QbD approach to guarantee high quality, robust, and transferable methods," says Ms. Lundberg. "And, as an end-to-end CDMO that supports customers globally on a range of projects, we develop methods with commercialization in mind to minimize delays later down the line."

From HPLC methods development to semi-solids characterization, Aztech Sciences supports preclinical to life cycle management sample analytics.

Aztech Sciences Inc.: Remaining Versatile In Handling Complex Formulations

Aztech Sciences Inc. provides scientific rationale and customized analytical services to support analytical testing for pharmaceuticals, preformulation, and formulation, analyzing pharmaceutical raw materials, formulation prototypes, drug delivery systems, and finished products.

"Understanding that each client's project requirements vary, our approach is not a one- size-fits-all methodology, so we are focused and versatile to the project deliverables," says Alvin Persad PhD, President/Co-founder, Aztech Sciences Inc.

He says that Aztech also handles complex formulations, where the importance of recognizing a robust extraction process is essential to sample preparation and reproducibility. "Identifying the stages of the project's complexity, timelines, and milestones will allow for the level of scientific creative rationale to proceed with the project, as in the case of an early-stage analytical method development followed by pre-validation testing, eventually leading to a full method validation," he explains.

One Aztech client expressed concerns about an assay result and needed Aztech to perform a different chromatographic assay method to correlate the results. Note that this molecule does not have any chromophores. Dr. Persad says that Aztech suggested that an HPLC assay method could be developed using a refractive index detector to determine the peak (molecule) of interest. "The extraction, sample preparation, and HPLC assay were completed within a week and the client was able to correlate and confirm that both assay results are within specification from two completely different chromatographic methods," he says.

ENCO Pharmaceutical Development, Inc.: Method Remediation Leads To Successful Testing & Materials Release

Analytical services at ENCO Pharmaceutical Development, Inc (EPDI) are at the core of company operations, moving customers from early phase to commercial with phase-appropriate qualification and validation. Full instrumental capabilities include assay, related substances, and impurities, using HPLC, GC, IC, and ICP-MS. Additional offerings include full compendia testing, dissolution, disintegration, particulate testing, and thermal characterization.

While method Development and validation have been long-standing capabilities at ENCO, the application of Quality by Design (QbD) principles to analytical methods has increased their importance. "QbD requires more up-front investment in development, but returns significant benefits when implemented correctly," says Richard Camp, President of EPDI. "A strong knowledge of method capability gained though QbD is key to ensuring ongoing method suitability as projects and products evolve."

One project involved a client that was implementing a novel formulation that included several non-compendial raw materials, each of which was subject to a significant amount of analytical characterization. Mr. Camp explains that gaps were identified in the supplier's technical packages related to analytical method validation. "EPDI performed an assessment of the existing validation information to determine if it was either incomplete or non-compliant with current industry practices, performed method remediation, and subsequent validation. These activities led to the successful testing and quality release of 13 materials and 30 methods, both at the lab and manufacturing facility."

Recro Gainesville: QbD Method Development Results In Shorter Run Times

As a CDMO, Recro Gainesville offers method development, validation, and routine testing using analytical techniques needed for oral solid dosage form development, release, and stability testing. The industry's increasing awareness about product quality, safety, and changing regulations has re-

"Using a Quality by Design system and appropriate Design of Experiments, we can decrease the total method development times to less than a week compared to a traditional one-factor-at-a-time approach of six to eight weeks." – Richard Sidwell, PhD, Senior Vice President and Chief Scientific Officer, Recro Gainesville.

emphasized the need for strong analytical science capabilities. As such, Richard Sidwell, PhD, Senior Vice President and Chief Scientific Officer, Recro, says the company stays up to date on new and changing regulatory requirements, and provides support for successful regulatory submissions and drug product approvals. Some examples include modifying or developing new sensitive and selective methods for low level impurities, setting specifications based on the ICH guidelines, designing forced degradation studies to understand the degradation pathways, and conducting stability studies to provide shelf-life projection for client projects and subsequent regulatory submissions.

"In addition, we write and review CMC sections, including justification of specifications (JOS) for NDA submissions using various statistical tools," he says.

Analytical scientific staff use a variety of column chemistries (reverse-phase, chiral, HILIC, size-exclusion, and normal phase) for pharmaceutical applications to support the development and characterization work.

To accelerate the method development timelines for its clients, Recro recently acquired a Quality-by-Design (QbD) method development system that can run six different columns and scout several unattended conditions (gradient slope, % organic, temperature, flow, pH, selectivity, total run time, etc.) to develop a robust new method, explains Dr. Sidwell. "Using this QbD system and appropriate Design of Experiments (DOE), we can decrease the total method development times to less than a week compared to a traditional one-factor-at-a-time (OFAT) approach of six to eight weeks," he says. "Also, the QbD approach allows us to define the design space, which is very useful for future method changes, if required, without any additional method development time."

Recently, one Recro client requested use the same analytical method for both its API and finished dosage formulation of various strengths (5 mg, 10 mg, 20 mg, and 40 mg) to monitor and quantitate all process-related and other related substances. Dr. Sidwell explains: "By evaluating a shorter column from the same column type, and optimizing the mobile phase gradient, we decreased the run time by over 70% without changing the selectivity of the API method for more than 10 related substances. We successfully validated the method for this client's drug product as well, which resulted in substantial cost savings in addition to the shorter run time."

Frontida Biopharm, Inc.: Quality & Safety With Regulatory Compliance

Frontida Biopharm's analytical services include method development, troubleshooting, validation, qualification, product testing, stability storage, and testing for products from IND, NDA, and ANDA to commercialization. APIs, excipients, finished products, and packaging materials can all be tested, and Frontida provides reverse-engineering services and physical characterization. Frontida's analytical services are expanding beyond supporting the development and technology transfer programs to provide stability storage and testing, material release, and individual testing.

Increased requirements for quality and product safety have made development capacity more important. "Heightened quality requirements for tests not only increase the cost of a product because of a higher batch failure rate, but the regulatory risk also expands and could result in deficiency letters," says Tony Liu, Vice President, R&D, Frontida. "Response to a defi-

Alcami specializes in all phases of pharmaceutical development and testing – from preformulation studies to commercial product lifecycle management.

ciency letter could be costly and delay product approval. Both will result in financial losses, so ensuring that testing is performed correctly the first time is critical."

Frontida's ability to rapidly correct potential issues can be illustrated by its work with one client that produces bisect scored tablets. "To comply with regulations, we needed to conduct a splitting study," explains Dr. Liu. "The client's original validation protocol did not cover the ranges for this type of study. We immediately informed the client and worked with them to modify the dissolution method to cover the very low concentration of the quarter tablet dissolution profile range. The method was successfully validated and the product has been filed. Due to a series of successful FDA inspections over the last three years, FDA has waived the pre-approval inspection and the product is currently on the market."

Alcami: Expanding Services to Enhance Support of Complex Formulations

Alcami's end-to-end analytical testing platform supports clients' programs through every stage of a product's life cycle, from early-phase development activities to commercial support for both small and large molecule products. As a fully integrated CDMO, Alcami has expanded its services by adjusting to market and regulatory changes. The expansion of its Extended Workbench offering, development of a quality system with third-party audit reports, and the addition of capabilities like rapid sterility testing address client needs.

"Our Extended Workbench is a Full-Time Equivalent (FTE) program tailored to a client's specific needs," explains Michael Freeman, Commercial Development – Laboratory Services. "Dedicated employees focus solely on individual client projects to provide a flexible and controlled outsourcing laboratory service package. An Extended Workbench program can be customized based on product phase and number of products."

Clinical phase development platforms can be designed to be adaptable, granting clients the freedom to adjust priorities based on their needs and results. Programs can also be designed for short-term use with a fixed-cost schedule, providing cost control during a product's riskier development phase, says Mr. Freeman. Conversely, the Extended Workbench also provides clients with a single vendor laboratory resource for their analytical needs during the established phases of a product and portfolio. He says: "In these stages, where quality control analysis is needed, clients can control their costs and priorities while still performing routine product release, stability, and raw material evaluations."

Alcami's efforts to expand its range of services include the introduction of rapid sterility technology and biosimilar analytical capabilities. "We can release clients' products to market faster, reduce inventory holding times, and provide more robust computer-generated sterility results, eliminating subjectivity and individual analyst observations," he continues. "Also, as the industry continues to transition to more complex formulations and more biologics come off-patent, our ability to handle complex entities in the coming years is critical."

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BIOGRAPHY

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

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CYBERSECURITY

Why Pharmaceutical Companies Are Vulnerable to Cyberattacks & What You Can Do to Protect Your Company

By: Andrew Douthwaite

INTRODUCTION

The cybersecurity landscape is continually changing and evolving, and cybercriminals are increasingly targeting private companies. This means that having good cybersecurity strategies and practices in place is more important than ever. A cybersecurity breach can wreak havoc on any company, compromising proprietary digital assets, exposing private information, and potentially damaging the critical systems your company relies on to function. When a breach does occur, it also requires both time and energy to contain the breach and mitigate the damage, eating up resources, people hours, and funds that could have been deployed elsewhere. According to the 13th annual Cost of a Data Breach Study conducted by the Ponemon Institute in 2018, the global average cost of a data breach is up 6.4% over 2017 and cost companies a total of $3.86 million.[1] The average cost for each individual lost or stolen record also increased to about $148.

CYBERSECURITY & THE PHARMACEUTICAL INDUSTRY[2]

The data collected by pharmaceutical companies, including proprietary information about patented drugs, data related to pharmaceutical advances and technologies, and patient information are all incredibly sensitive and valuable, which means that losing control over that data can have catastrophic consequences and erode patient and consumer trust.

Having a comprehensive cybersecurity strategy in place to safeguard those digital assets has become an essential part of any company's security protocols. Companies that do not prioritize creating robust, flexible, and comprehensive cybersecurity strategies leave their valuable data vulnerable.

A successful cybersecurity attack against a company can result in stolen intellectual property, lost revenue, and even litigation. Valuable research data can be lost or damaged, which necessitates repeating entire clinical trials and absorbing the associated costs. Share prices can plummet, and a brand's image can become tarnished.

In general, the pharmaceutical industry as a whole has not been on the cutting edge in terms of cybersecurity practices, though the high profile and highly publicized cybersecurity attacks in recent years have acted as a wake-up call to many companies. Though there has been a surge in interest, and a new sense of urgency, when it comes to improving cybersecurity protocols at individual companies, there are still a few challenges that many pharmaceutical companies face.

DIGITAL ASSETS

A pharmaceutical company's most valuable assets are typically secret formulas for proprietary drugs and other large amounts of strictly confidential data. This makes pharmaceutical companies attractive to criminals because this data is incredibly valuable and can easily be sold on the dark web or ransomed back to companies that are desperate to protect the intellectual property their company has built its business on.

PEOPLE

Even the most airtight and well-designed cybersecurity strategy is only effective if your employees know how to implement it correctly, what their role is when it comes to safeguarding your company's assets, and who they should report potential problems to. Improperly trained employees are a challenge faced by many companies both inside and outside the pharmaceutical industry.

MERGERS & ACQUISITIONS

Mergers and acquisitions are a part of daily life in the pharmaceutical industry, and this poses a unique challenge from a cybersecurity perspective. When a company is acquired by another company, or the two companies merge, there can be a lot of shuffling, which means that cybersecurity strategies and approaches can change overnight. It also means that if a company's data is compromised, or they are found not to have taken enough care to safeguard their assets before a merger or acquisition is finalized, it could compromise the deal and leave the company vulnerable to legal problems.

THE INTERNET OF THINGS

The healthcare industry, including the pharmaceutical industry, has embraced the internet of things wholeheartedly. While this makes it easy to access critical documents and patient data or use big data to track trends all of this information is about health, which comes with unique privacy challenges. Depending on where you operate, stringent new privacy regulations, such as GDPR, can mean that sloppy cybersecurity protocols could leave you vulnerable to legal litigation as well as cybersecurity attacks.

The internet of things increases your risk of experiencing a cybersecurity incident and can cause increased uncertainty around the chain of controls that follow where data is generated or created and where it ultimately ends up.

GOVERNANCE

All organizations need to have robust yet flexible cybersecurity protocols in place to protect themselves against the threat of cybersecurity attacks. This requires having an overall operating model, well-defined roles and responsibilities, robust contracts, dealing with third-party integration, monitoring threats, communicating vulnerabilities effectively, and ensuring that cybersecurity remains a top security priority.

All of this presents a significant challenge for any company, but implementing a system such as this it can be particularly onerous for pharmaceutical companies because of the extremely confidential nature of their intellectual property, the fact that their most valuable assets may be subject to strict privacy laws, and the fact that acquisitions and mergers can disrupt established ways of doing things.

WHY CYBERCRIMINALS TARGET PHARMACEUTICAL COMPANIES

Pharmaceutical and biotechnology companies are being targeted by cyber criminals more frequently than they were in the past, and according to a study conducted by Deloitte, the pharmaceutical industry is now frequently the number one target of cybercriminals around the world, particularly when it comes to intellectual property theft.[3] This is because, as these companies move toward increased digitization and storing more valuable data online, they are becoming more attractive targets. Stolen data can either be sold on the dark web or ransomed back to desperate companies who rely on their IP, as well as access to critical documents, such as

trial results and patient information, to continue running.

RECENT HACKS & WHAT THE INDUSTRY HAS LEARNED FROM THEM

Though it is unfortunate for any company to experience a cybersecurity incident such as a hack or breach, cybersecurity incidents can be used as educational tools that can better inform current company cybersecurity policies.

NotPetya Attack on Merck

One of the most significant cybersecurity attacks on a pharmaceutical company in recent history struck Merck & Co., which employs more than 69,000 people and is one of the oldest and largest pharmaceutical companies in the world.[4] Merck was one of dozens of companies hit by a massive ransomware attack in 2017 and suffered worldwide operational disruptions, forced the company to halt production of new drugs, and significantly impacted the company's revenue for the year.

Merck employees around the world opened their computers to find themselves completely locked out of the company's systems and unable to work. The incident was caused by the NotPetya strain of ransomware, which was used to attack other companies as well.[5]

The WannaCry Attacks

In 2017, healthcare networks around the world were affected by the WannaCry ransomware attacks, which locked healthcare professionals out of patient health records.[6] In all, more than 230,000 computers in 150 countries were affected causing billions of dollars of damage, virtually shutting down health systems worldwide.

Wicked Panda Uses WINNTI to Target Bayer

In 2018, drug manufacturer Bayer discovered that its computer networks had been infected with malicious software.[7] The company decided to covertly monitor and analyze the software before purging it from its systems, and though they discovered no evidence of data theft or any indication that any personal data was compromised, the incident is still unnerving.

Bayer was able to determine the hackers were using malware called WINNTI, which allowed unauthorized users to access private systems remotely and give cybercriminals the time to look for internal vulnerabilities that could be potentially exploited. According to Bayer's spokesperson, the company and their security experts believe the Wicked Panda group, which is based in China, initiated the attack.

SAFEGUARDING YOUR COMPANY'S ASSETS

Traditionally, cybersecurity was approached from an incident response perspective. This means that many companies did not review their protocols or correct vulnerabilities that could be exploited until they or another similar company had already been targeted by unauthorized users.

Once the unauthorized user was discovered, companies would work to oust them and then go through the forensics of the attack to determine how the intruder gained access by looking at things like IP addresses, domain names, and what malware was used (called Indicators of Compromise, or IoCs). Companies also need to determine what exactly was compromised, and what needed to be done to clean up the mess and patch the security hole or holes that were exploited.

The Drawbacks of the Incident Response Approach

This approach is problematic for two ways. First, it relies on your company or another company falling victim so that the IoCs could be discovered and shared with other potentially vulnerable companies and organizations. The other problem has to do with the timeframe. IoCs have a very short half-life, which means that any solutions derived from this line of defense are short lived. All an unauthorized user needs to do is reconfigure their malware or purchase a different IP address, and they can potentially regain access to your systems.

This approach leaves you and your

company trapped in a potentially endless game of cat and mouse in which each incident is dealt with in a vacuum, ignoring larger systematic weaknesses and waiting to act until after the damage has already been done.

A reactive approach also drains your company's resources unnecessarily, as your cybersecurity team spends its time chasing after the same intruders and cleaning up their messes. This drain pulls both people and resources away from other vital areas of cybersecurity, such as pre-emptively looking for vulnerabilities that could be exploited, and forces your cybersecurity personnel to dedicate themselves to minimizing damage and focusing on remediation. A Zero Trust approach would be much better suited as a preventative measure instead of the common reactive approach by not letting the original action happen and cutting off all access until a communication has been verified as trustworthy.

A Proactive, Top-Down Approach[8]

A comprehensive, robust, and flexible cybersecurity approach goes beyond updating your anti-virus software is up to date and making sure all updated security patches for your software are downloaded. While these basics are essential, they are only the beginning. A holistic cybersecurity approach seeks to uncover potential vulnerabilities before they can be exploited, keeping up to date on the latest cybersecurity threats, and continually reevaluating your cybersecurity protocols to ensure they are meeting your needs effectively.

Cybersecurity is everyone's job. Every single employee, from the CEO down to the intern in the mail room, plays an important role. In addition to the C suite working with cybersecurity experts to craft and implementing company-wide best practices, your employees need to understand what they can do to protect your company's digital assets, how to avoid falling for phishing scams or other cybersecurity attacks that could expose confidential information, and who they should report potential incidents to.[9,10] Training tools such as tabletop scenarios and pen (penetration) tests all play a critical role in honing your company's cybersecurity protocols and safeguarding assets.

Tabletop scenarios are similar to fire drills. They let your employees hone their response to a simulated cybersecurity incident in a low stakes environment. After the scenario is complete, your team can review their response, identify where improvements can be made, and formulate strategies to address any shortcomings. A pen test involves hiring an ethical hacker to stress test your cybersecurity protocols by attempting to break into your system and access your valuable digital assets. As the hacker works, they will take note of the vulnerabilities they encounter and how they were able to exploit them, then provide you with a comprehensive report at the end of the test. This valuable information can then be used to strengthen your current protocols and address any vulnerabilities before a cybercriminal attempts to gain unauthorized access to your systems and data.

THE BENEFITS OF A MSSP

For many of us, creating, implementing, and monitoring company-wide comprehensive cybersecurity solutions can seem daunting, and even overwhelming. Luckily, you can rely on a trusted MSSP (Managed Security Services Provider) to help you ensure that your company's digital assets are secure.

An MSSP consists of a team of trained cybersecurity experts who will work with you to create a custom cybersecurity solution to meet your needs and safeguard your company's digital assets. They can also monitor your network 24/7/365 for suspicious activity, offer employee cybersecurity training, and help you mitigate or even avoid damage if your company does experience a cybersecurity incident. If an incident occurs, they can also help you review the incident and learn from it so that similar breaches can be avoided moving forward. ◆

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BIOGRAPHY

Andrew Douthwaite has more than 17 years of technology experience, joining VirtualArmour in 2007 as a Senior Engineer. Now as Chief Technology Officer, Andrew focuses on leading growth in the managed security services business and ensuring VirtualArmour is a thought leader in the security industry.

Drug Development
EXECUTIVE

David Domzalski
Chief Executive Officer
Foamix

foamix®
Pharmaceuticals

Foamix Pharmaceuticals: Delivering Pharmaceuticals to the Skin Through a Foam

In the field of dermatology, topical skin medications present significant advantages over oral routes of administration. These significant advantages include direct delivery of the effective targeted therapy to the skin, easy application, and reduced risk of systemic side effects. One of the main challenges of developing topicals is ensuring that the active pharmaceutical is stable in its topical delivery vehicle. Foamix is working to address this challenge through its proprietary technology platform, which has led to the development of several unique topical foam formulations for the treatment of dermatological and other conditions. *Drug Development & Delivery* recently interviewed David Domzalski, Chief Executive Officer of Foamix, to discuss its innovative approach to drug delivery using foam to treat dermatological conditions, like acne and rosacea.

"Naturally, over the course of time, we began to develop and focus on our own research efforts. These efforts lead us to conduct two Phase 2 studies with a minocycline foam product, one in acne and one in skin infections. This was the genesis of our transition from being a partner-focused company to a fully integrated pharmaceutical company."

Q: Can you give us an overview about the company and tell us how Foamix was started?

A: Foamix is a specialty pharmaceutical company focused on the development and commercialization of innovative topical treatments for dermatological conditions. We currently have two minocycline foam product candidates, FMX101 and FMX103. FMX101 is being developed for the treatment of moderate-to-severe acne. We recently completed our third Phase 3 trial study for FMX101 (FX2017-22). We have also recently completed our clinical studies for our second minocycline product, FMX103, for the treatment of moderate-to-severe papulopustular rosacea.

Foamix was co-founded back in 2003 by Dr. Dov Tamarkin and Meir Eini to address unmet needs in the dermatology field. Our founders recognized that there was limited innovation in the field and wanted to create a company dedicated to providing solutions to patients with dermatological conditions.

The company initially adopted a partnership model - one based on working with larger and established pharmaceutical companies to develop products to help advance their product portfolios. Naturally, over the course of time, we began to develop and focus on our own research efforts. These efforts lead us to conduct two Phase 2 studies with a minocycline foam product, one in acne and one in skin infections. This was the genesis of our transition from being a partner-focused company to a fully integrated pharmaceutical company. We have established that we have the capabilities to develop our own proprietary products and successfully conduct our own clinical trials. This brings us to our next step of growth, which is to become a commercial stage pharmaceutical company. We submitted our first NDA last year for FMX101, and we intend to file our second NDA for FMX103 toward the middle part of this year. We hope to have our product candidates approved in the U.S. and subsequently launch to the physician community beginning at the turn of the new year.

Q: How was Foamix's proprietary foam technology developed?

A: Our initial foam technology was developed by our co-founders and R&D staff more than 15 years ago. Regarding our foam platform specific to FMX101 and FMX103, it took the company several years and the testing of hundreds of different foam formulations to develop the product candidates that we have today. To date, our formulation science team has developed several other different types of foams available for use. Each foam is unique and was developed based on the active pharmaceutical ingredient that would be incorporated into the final drug product. In other words, we do not have a universal foam, rather our foams are developed based on how to best preserve the chemical structure of the specific active pharmaceutical.

Our foams differ from other foam products on the market. Many available foams may break down or melt as soon as they come into contact with the skin due to body temperature. What Foamix has done is develop foams that are physically stable when they come into contact with the skin. We like to compare our foams to the consistency of shaving cream. However, unlike shaving cream that turns into a lather once applied to the skin, our foams are designed to be quickly absorbed into the skin.

Q: How does Foamix's delivery vehicle differ from other topical medications for acne?

A: Many of the topical acne medications on the market come in the form of a gel or cream and primarily contain ingredients, such as a retinoid or benzoyl peroxide. If approved, FMX101 has the potential to be the first topical minocycline foam for the treatment of acne. In addition, we believe our foam vehicle is easy to spread, readily absorbed, gentle, and does not leave a heavy residue on the skin.

Q: Oral minocycline has been around for decades. Why is it now being made into a topical formulation for the treatment of acne?

A: Minocycline is a widely used and effective oral antibiotic for the treatment of acne, but its side effects can limit its use. As an oral systemic therapy, it is associated with adverse side effects, such as headaches, dizziness, vertigo, fatigue, nausea, and photosensitivity. Dermatologists typically prescribe oral antibiotics when topical medications are not sufficient to treat the patient's acne. However, there has been a push by the American Academy of Dermatology to limit the use of oral antibiotics for the treatment of acne. Though oral antibiotics are effective, many people are concerned about their side effects especially if repeatedly used over time.

For years, researchers have been trying to develop minocycline into a topical form but have been largely unsuccessful. Minocycline is a fairly unstable molecule that will degrade quite rapidly if exposed to many of the components typically used in topical formulations, which may be why it has remained available only as an oral administration. Until now, researchers have struggled to develop a chemically and physically stable topical minocycline product, since standard delivery vehicles could not support the active drug. Our foam does not contain the components found in other topical formulations that historically have led to degradation. We identified the unmet need and developed an innovative foam compatible with minocycline.

Q: Can you tell us more about your drug development status to date and what we can expect from Foamix in the near future?

A: Foamix is using its proprietary foam technology to develop a full pipeline of drugs that are delivered locally and thus have the potential to be safer, better-tolerated, and effective treatment options for dermatologic diseases. FMX101, a 4% minocycline topical foam, is our lead product candidate. Acne is the most common skin condition in the US, affecting ~50 million people of all ages and ethnicities, a significant unmet need. We submitted our NDA for FMX101 at the end of last year, and the FDA has established a PDUFA action date for this October.

Our second lead product candidate is FMX103, a 1.5% minocycline topical foam for the treatment of moderate-to-severe papulopustular rosacea. Rosacea is a chronic skin disorder that is characterized by facial redness and inflammatory lesions, afflicting more than 16 million people in the US. We recently completed our two pivotal Phase 3 studies for FMX103, as well as a long-term safety study. Our plan is to file an NDA for FMX103 around mid-year. Finally, we are preparing to initiate a Phase 2 study in acne for our first topical combination product. We refer to this product as FCD105, and it is a combination of the retinoid adapalene and the antibiotic minocycline in a foam formulation. Adapalene is one of the most widely used retinoids in the treatment of comendonal acne. By combining both minocycline and adapalene, we believe this product could further address unmet needs of patients who suffer from acne.

Q: How do you see Foamix's proprietary foam technology adding value to a potential partner, licensor or acquirer?

A: We have evolved from being a company that focused primarily on developing products for other major pharmaceutical manufacturers to a fully integrated company. We strategically shifted our primary focus to developing our own products that we can eventually market and distribute ourselves in the US. However, we still value strategic partnerships and would certainly be open to those with the right partners. Our collaboration with Bayer Health Care is a good example. Together with Bayer, we developed Finacea® foam for the treatment of mild-to-moderate rosacea. The composition of this foam product is very different from FMX101 and FMX103, and was developed to deliver a different active molecule, azaleic acid, to the skin via one of our proprietary foam platforms. The approval of Finacea foam was an important milestone for Foamix, as it was the first prescription product developed using our technology to be FDA approved for sale in the US. In September 2018, LEO Pharma A/S acquired the worldwide rights to Finacea foam from Bayer.

With FMX101, we took a historically unstable active molecule, minocycline, and developed an innovative topical formulation that we progressed through the clinic and have now submitted for marketing approval. We are excited about potential partnership opportunities that our foam platforms may have to offer. ◆

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Dectin-1 Receptor-Mediated Delivery of Oligonucleotide Drugs Complexed With Schizophyllan Dendritic Cells & Macrophages

By: Kenji Arima, PhD, and Akihiko Watanabe, PhD

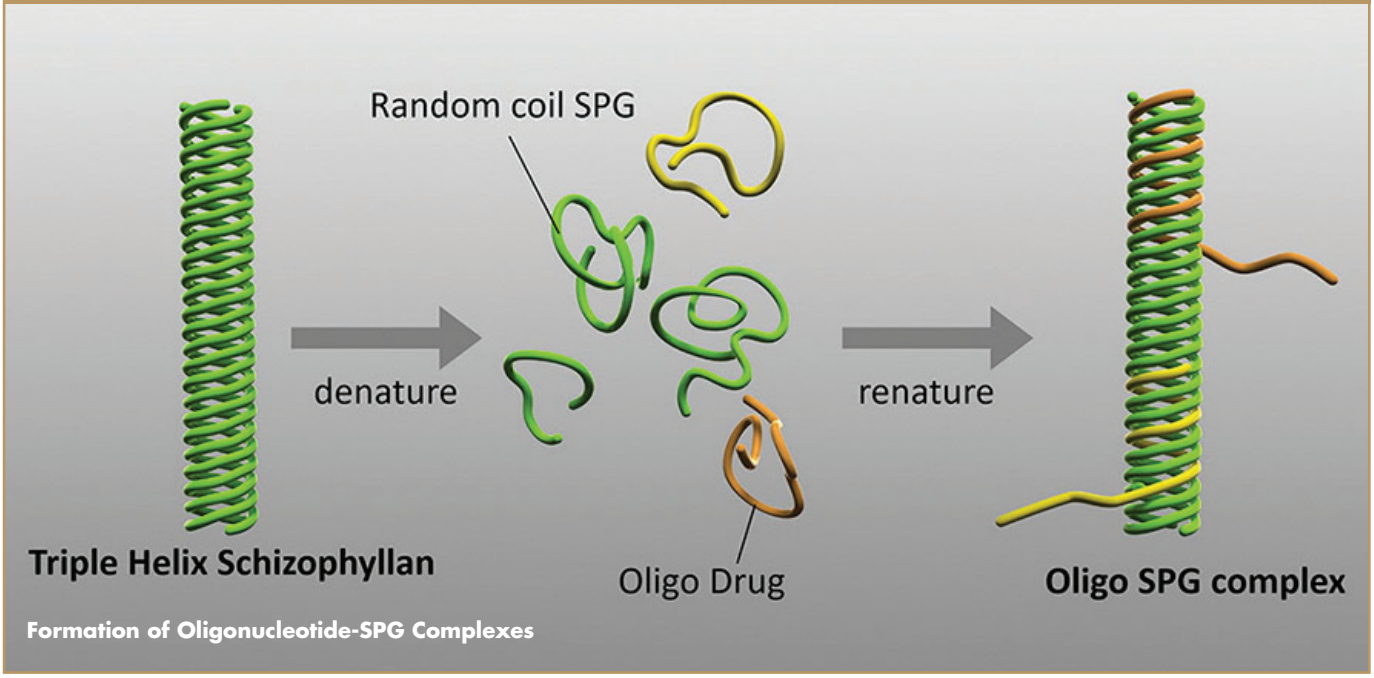
INTRODUCTION

More than 30 years have passed since the initial development of oligonucleotide drugs; however, only eight drugs have been approved thus far. This is partially due to issues related to oligonucleotide delivery methods. We believe there is a novel delivery platform with the potential to resolve several of these complications. The following introduces NapaJen Pharma's technology with a specific focus on solving some of the current challenges of oligonucleotide therapeutics. Furthermore, we outline the particular value of our company's unique ideas and systems and briefly describe its future direction.

TECHNOLOGY VALUE & UNIQUE IDEAS

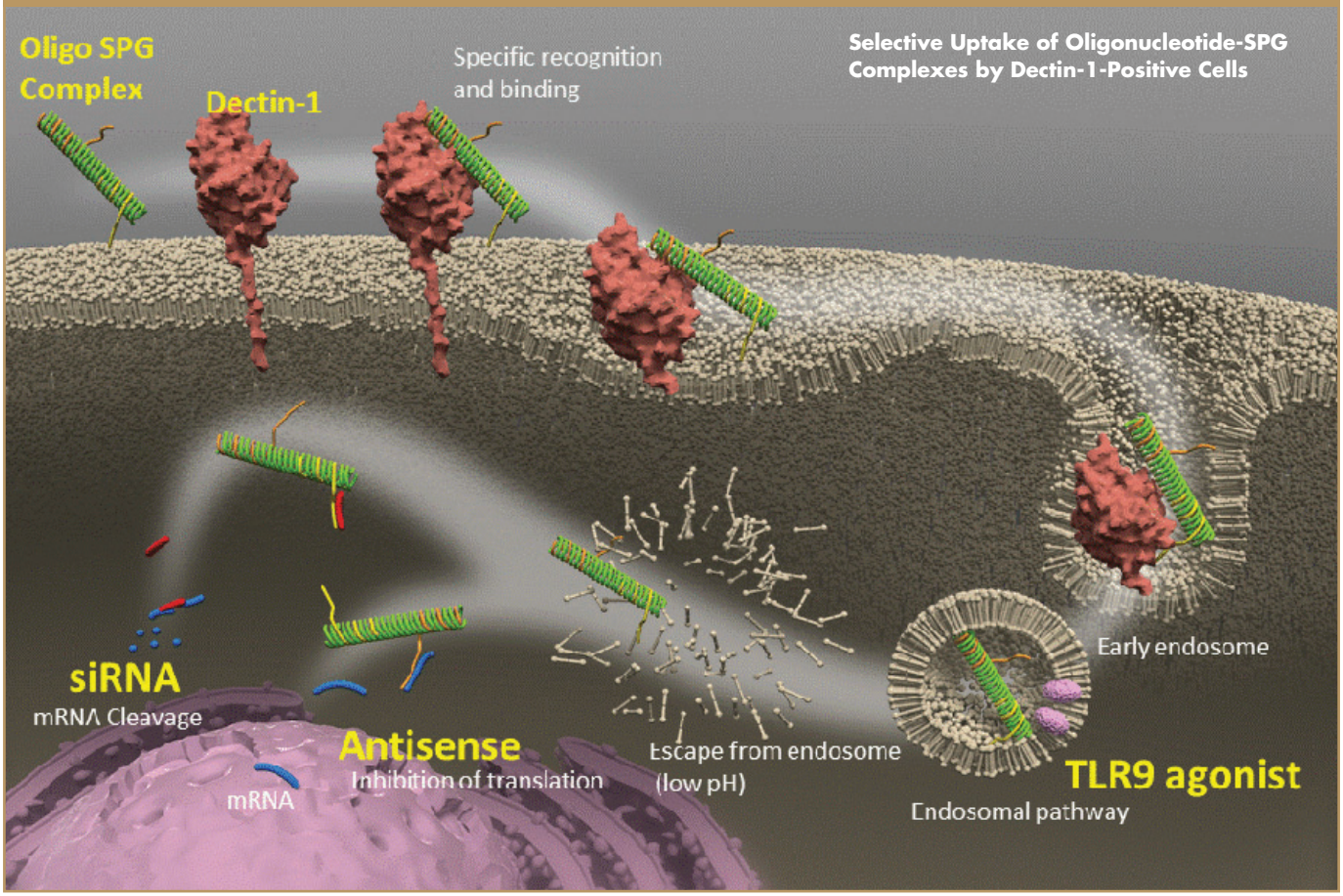
Our technology relies on forming complexes between oligonucleotide drugs and β-glucan schizophyllan (SPG) molecules, and then selectively delivering these compounds to dendritic cells and macrophages expressing Dectin-1, a specific receptor for SPG. Dectin-1 receptor is predominantly expressed on the surface of monocyte/macrophage and neutrophil cell lineages.[1] However, we have not confirmed Dectin-1 on neutrophils as functional delivery gate for oligonucleotide/SPG complex. Dectin-1 receptor belongs to the C-type lectin receptor family, and recognizes β-1,3 glucan; meanwhile, SPG consists of a triple

FIGURE 1



Formation of Oligonucleotide-SPG Complexes

FIGURE 2



helix with β-1,3 glucan chains, and is produced by *Schizophyllum commune*.

As shown in Figure 1, when SPG is exposed to alkaline environments, it denatures into separate β1,3-glucan chains. Surprisingly, after neutralization, it renatures to its original conformation. The key feature of the technology is that when neutralization occurs in the presence of poly deoxy-adenine (poly dA), a new complex is formed between two β1,3-glucan chains and one DNA strand.

By attaching an oligonucleotide, antisense oligonucleotide, such as siRNA or CpG, to the poly dA tail, it is possible to selectively direct the oligonucleotide drug to dendritic cells and macrophages expressing Dectin-1 on their cell surfaces. Cell delivery of these molecules is shown in Figure 2. In addition to siRNA, antisense oligonucleotides, and TLR9 agonists shown in the figure, delivery of peptides and other molecules has also been demonstrated.[2-5]

To note, soluble β-glucans offer advantages over particulate ones. Particulate β-glucans, such as zymosan, induce signal transduction, ie, activation of Syk and p38, and production of reactive oxygen species and TNF-α, after binding to Dectin-1. On the other hand, soluble β-glucans, such as SPG, do not induce signal transduction.[6]

Details regarding how Kazuo Sakurai, Co-founder and Chief Science Officer of NapaJen Pharma, discovered this unique idea and brought this technology to fruition are not provided here owing to word count limits; however, it can be found by reviewing Dr. Sakurai's supplemental publication on this topic.[7]

THE PITFALLS OF OLIGONUCLEOTIDE DRUG TECHNOLOGY

We believe it was 2006, the year in which Dr. Craig C. Mello won the Nobel prize for discovering RNAi, when one of the authors of this article participated in a roundtable discussion with Dr. Mello at the IBC conference held in Boston. Since then, oligonucleotide drug delivery has overcome several obstacles, but selective delivery to target cells remains a major concern. Additionally, several secondary complications hinder the development of oligonucleotide drugs, including 1) localized drug delivery, 2) high dosage required for therapeutic effect, 3) poor safety profile, and 4) high cost of goods (COGs)/Annual drug cost.

SELECTIVE DELIVERY OF OLIGONUCLEOTIDE-SPG COMPLEX TO DECTIN-1-EXPRESSING CELLS

The profiles of human embryonic kidney (HEK) cells not expressing, and those expressing Dectin-1 via transduction (dHEK), were compared in the presence of fluorescence-labeled oligonucleotide-SPG complexes. Transduced dHEK cells exhibited strong fluorescence, as opposed to HEK cells.

Human peripheral blood mononuclear cells (PBMCs) were cultured with different concentrations of fluorescent-tagged NJA-730 (a complex formed between CD40-targeted oligonucleotide and SPG). Fluorescence-activated cell sorting (FACS) analysis showed that the fluorescence-positive fraction corresponding to Dectin-1-positive cells, and the degree of fluorescence were dependent on the concentration of NJA-730.

EFFECTIVE DELIVERY BY INTRAVENOUS (IV) SYSTEMIC ADMINISTRATION

In a mouse model of allogenic heart transplantation, IV injection of NJA-312, a mouse homologue of NJA-730, increased the lifespan of the grafted donor heart by more than 100 days.[8] Moreover, a random amplification of cDNA end (RACE) assay was conducted on CD40 mRNA (the target of NJA-730), which was harvested from cynomolgus monkey PBMCs following IV administration of NJA-730. This assay showed the expected band corresponding to cleaved CD40 mRNA, suggesting that systemic IV administration of NJA-730 was effective in primates. In the current clinical Phase 1 trial of NJA-730, an analog RACE assay will be conducted soon. A successful result with this assay would validate NJA-730 itself, and also confirm the proof of mechanism (POM) of NapaJen's targeted delivery technology.

EFFICACY WITH LOW DOSES

In the aforementioned mouse allogenic heart transplantation model, a dosage of 2 μg per administration was effective. Therefore, doses in the order of hundred μg per administration are expected to be clinically effective, which are lower than the effective doses of Onpattro™.

HIGH SAFETY PROFILE

Following repeated toxicity testing of NJA-730 in monkeys over a 4-week period, no significant adverse effects were observed. Additionally, in the clinical Phase 1 trial that evaluates the safety profile of NJA-730, which is a single ascending dose (SAD) study in progress, no concerning events have been reported; hence, the trial has progressed toward testing multiple ascending dose (MAD) study of NJA-730.

LOW COGS/ANNUAL DRUG COST

The annual costs of the currently available oligonucleotide drugs Onpattro™ and Spinraza™ are quite high. Onpattro™ and Spinraza™ reached $450,000 and $750,000, respectively, in the first year, and $375,000 for Spinraza™ in the subsequent years.[9,10] At present, as the frequency of NJA-730 administration and the yearly drug manufacturing costs have not been determined, we are not including a direct cost comparison in this article. However, based on the value propositions of NapaJen technology previously outlined, there is a high probability that drug manufacturing would be less expensive in comparison to the aforementioned ones. For this reason, we hope that oligonucleotide drug technology, which has until now been restricted to the treatment of rare diseases and a subset of cancers due to high costs, becomes widely available for the treatment of non-orphan diseases.

FUTURE DIRECTIONS

A Phase 2 trial testing NJA-730 for acute graft versus host disease (GvHD) will start in 2020, and demonstration of proof-of-concept is expected to be achieved by the fourth quarter of 2021. The aforementioned POM is anticipated to be confirmed in a Phase 1 Extension study. Due to suppression of CD40, an important accessory molecule for antigen recognition, NJA-730 may be applicable for treating other indications, such as organ transplantation, inflammatory bowel diseases, psoriasis, and other autoimmune diseases, in addition to acute GvHD. We hope to continue our studies toward that aim, both independently and in collaboration with other companies. In addition, we are currently discussing partnerships with pharmaceutical and biotechnology companies, including a joint study with a Big Japanese pharma company that commenced in February 2019. Through these partnerships, we hope to develop numerous drug candidates, and ultimately use our oligonu-

cleotide drug technology to provide novel treatment options to patients suffering from various diseases.

SUMMARY

More than 30 years have passed since the initial development of oligonucleotide drugs; however, only eight drugs have been approved thus far because of several issues of oligonucleotide drugs. We believe NapaJen Pharma could offer technologies with the potential to resolve several of these complications. Our technology relies on forming complexes between oligonucleotide drugs and β-glucan schizophyllan SPG, and then selectively delivering these compounds to dendritic cells and macrophages expressing Dectin-1, a specific receptor for SPG. Value proposition added by NapaJen Pharma could be 1) selective delivery of oligonucleotide-SPG complexes to Dectin-1-expressing cells, 2) effectiveness by systemic administration, 3) efficacy with low doses, 4) high safety profile, and 5) low COGs/annual drug cost. These advantages will be further confirmed by upcoming clinical studies. A Phase 2 trial testing NJA-730, a complex formed between CD40-targeted oligonucleotide and SPG, for acute GvHD will commence in 2020, and demonstration of proof-of-concept is expected to be achieved by the fourth quarter of 2021. The aforementioned POM is anticipated to be confirmed in a Phase 1 Extension study. In addition, we are currently discussing partnerships with pharmaceutical and biotechnology companies, including a joint study with a Big Japanese pharma companythat commenced in February 2019. Through these partnerships, we hope to develop numerous drug candidates, and ultimately use our oligonucleotide drug technology to provide novel treatment options to patients suffering from various diseases. ◆

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BIOGRAPHIES

Dr. Kenji Arima has been in the pharmaceutical arena for more than 40 years. Most recently, he joined NapaJen Pharma as the Chief Development Officer, and became CEO in August 2019.He successfully led the NJA-730 project to the clinical stage from the research stage in a short period of time. Prior to NapaJen, he was with the Japan Agency for Medical Research and Development (AMED) from 2014 to 2016. At AMED, he proposed and established DISC (Drug Discovery Innovation and Screening Consortium), an innovative collaboration system between academia and pharmaceutical industry, where DISC makes possible for academia to use the high-throughput chemical library with 200,000 compounds collected from the industry. He worked in Suntory and then Asubio Pharmaceuticals for 35 years holding various positions, including the President of the US subsidiaries of both Suntory and Asubio Pharmaceuticals for 11 years. While at the US subsidiaries, he also contributed to the pharmaceutical industry as the President of New York Pharma Forum in 2010, whose members are major US and Japanese pharmaceutical companies, and the President of US and Japan Healthcare study team with over 40 US-based Japanese healthcare companies between 2004 and 2007. He can be reached at k.arima@napajen.com.

Dr. Akihiko Watanabe is Vice President of Research Innovations and Business Development of NapaJen Pharma. He earned his PhD in Immunopharmacology from Gifu Pharmaceutical University, Japan. He held a wide range of roles for more than 30 years in research leadership, top management secretary, marketing, and business development in Japanese organizations as well as in global pharmaceutical companies like Kyowa Hakko Kirin, Teva, Bayer, and Toyobo. Earlier in his career, he was responsible for drug discovery research mainly in immunology, in addition to oncology and CNS areas. Most recently, he contributed to in-licensing, seed finance evaluation, and out-licensing in scientific diligence and business development roles. He has also served on the editorial board of the official journal of The Pharmaceutical Society of Japan. He also showed leadership in pharmaceutical organizations, such as Human Science Foundation and Pharmaceutical Industry Forum. He can be reached at a.watanabe@napajen.com.

MARKET BRIEF

Tumor-Infiltrating Lymphocytes: A New Frontier in Cancer Immunotherapy

By: Cheryl L. Barton, PhD, and Bianca Piachaud-Moustakis, PhD

INTRODUCTION

Recent developments have demonstrated that immunotherapies are capable of achieving durable anti-tumor responses in patients with metastatic cancer. According to Yang and colleagues (2016), one modality that has been able to induce durable complete regressions in patients with melanoma has been adoptive cell therapy (ACT).[1] Adoptive cell therapy is a more technical approach in which the patient's autologous T- cells are expanded, manipulated ex vivo, and then re-infused into the patient to exert an anti-tumor response. Sometimes, immune cells that naturally recognize melanoma are used, while at other times they are modified to make them recognize and kill the melanoma cells.

Throughout the past 10 to 15 years, investigators have pursued different modalities of ACT that include:

- Tumor-Infiltrating Lymphocytes (TIL): T-cells are grown from the tumor itself
- Endogenous T-cell Therapy: tumor-specific T-cells are grown from the blood
- CAR T: a chimeric antibody/T-cell receptor gene is put into peripheral T-cells
- T Cell receptor (TCR) transduced T-cells: T-cell receptor gene engineered to recognize a tumor is put into peripheral T-cells

Of these, TIL therapies have been widely studied and demonstrated consistently favorable results in preclinical animal models, supporting their viability as a mainstream treatment for metastatic melanoma (Table 1).

TABLE 1

Cellular Therapies	Pros	Cons
Tumor Infiltrating Lymphocyte (TIL)	Shows promise in patients with metastatic melanoma and cervical cancer	Treatment turnaround minimum 5-6 weeks; moderate success rate (higher in young people and females)
Tumor-Specific T-Cell Receptor Technology (TCRT)	Show clinical efficacies	On target, off-tumor toxicity
Lymphocytes expressing chimeric antigen receptors T-cells (CAR T)	Beneficial to pre-B-cell acute lymphoblastic leukemia and diffuse large B cell lymphoma	Limited clinical efficacy; unacceptable toxicities; difficulties in penetrating solid tumors; high cost; lengthened production

Source: modified from Ding et al., 2018[7]

Adoptive T Cell Therapy (ATC) Cellular Therapies

TIL GENERATION EXPLAINED

Rosenberg and colleagues at the Surgery Branch of the National Institute of Health (NIH) pioneered the use of TILs in mice and demonstrated that the combination of autologous TIL and cyclophosphamide could induce regression of metastases.[2] This was followed 2 years later with a landmark publication that presented the first human study which demonstrated how TILs could induce cancer regression when administered to patients with metastatic cancer.

TILs are a collection of lymphocytes that have penetrated the stroma of a tumor. These TILs are largely comprised of T-cells that are actively engaged in tumor destruction. While other types of ACT utilize circulating T-cells in the blood, TIL therapy relies on a tumor biopsy taken from the patient. In this instance, a tumor at least 2 cm in diameter is first harvested by excisional biopsy and then dissected into fragments (approximately 1-3 mm^3) and placed in wells with other agents. IL-2 is added, and over the following weeks, the TILs proliferate while the adherent tumor cells disappear as they die off, or are killed by the lymphocytes.

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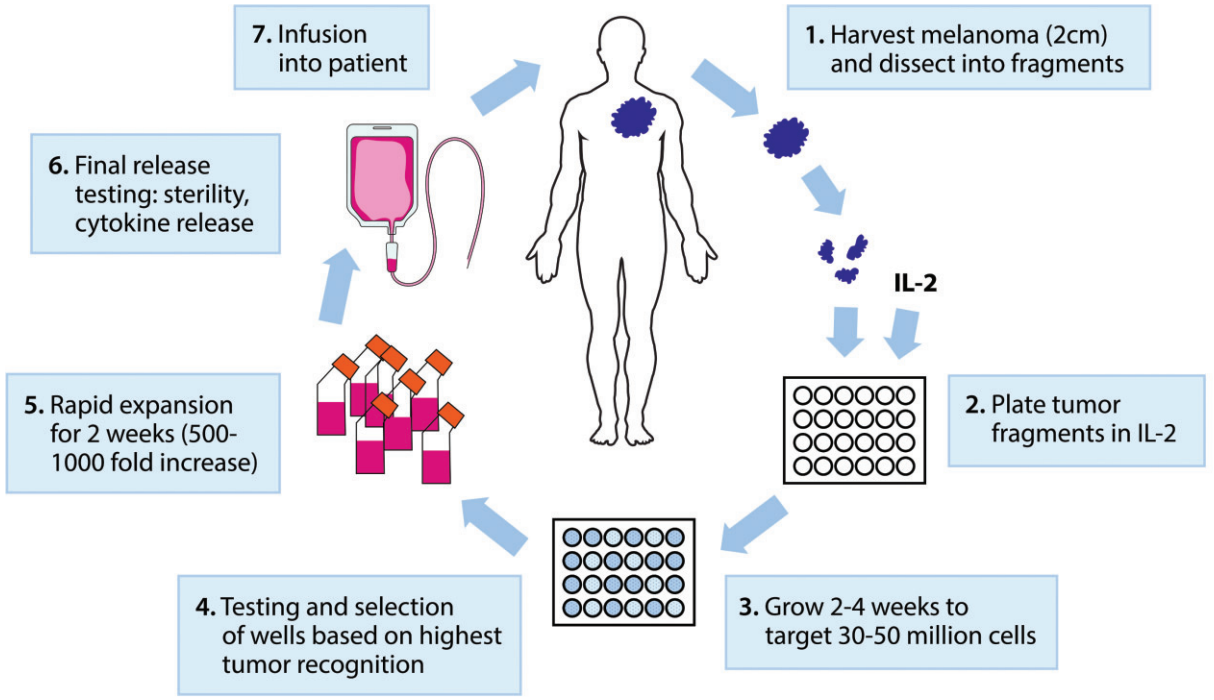
FIGURE 1



Source: Lee et al, 2012[4]

Following a growth period of 2-4 weeks, the TILs are tested for T-cell phenotype by fluorescence-activated cell sorting (FACS) and for reactivity to autologous tumor cells. The wells containing cells with the highest cytokine-release after co-culture with autologous tumor cells are selected and expanded for 2 weeks using a rapid expansion protocol with agonistic concentrations of anti-CD3 antibody, IL-2, and irradiated, allogeneic feeder cells derived from normal donor pools of peripheral blood mononuclear cells. The total generation time from start to finish is approximately 5-6 weeks (Figure 1). In essence, TIL therapy utilizes T-cells that already recognize and target a patient's tumor as a treatment for their cancer.

Studies conducted by Joseph and colleagues (2011) found that younger patients and female patients carried a higher success rate for TIL generation, with a TIL generation rate of 94% for patients less than 30 years old compared with a 46% success rate for patients over 60.[3] Female patients had a significantly higher TIL generation rate of 71% compared with 57% for men.

In addition, it was also found that patients who received systemic therapy less than 30 days before tumor harvest had a success rate of 47% compared with a 66% rate when the last therapy occurred greater than 90 days before harvest. Currently, TILs can be generated successfully from 60% to >90% of melanoma tumor samples, at different institutions.

FEASIBILITY OF TIL AS A MAINSTREAM TREATMENT OPTION

Although the clinical benefits of TIL in metastatic melanoma are well recognized, a number of questions still remain. For example, Lee and colleagues (2012) point out the clinical limitations that characterize TIL and how it is used as a treatment option includes the 5-6 week period currently required for TIL generation - a waiting time that is often too long for many patients diagnosed with aggressive metastatic melanoma.[4] In addition, Rosenberg notes that the intense myeloablative conditioning regimen associated with the highest response rates would exclude a significant number of patients who are not fit enough to tolerate the toxicities related to the treatment regime. Such patients would therefore require intense support to complete the therapy safely.[2]

Furthermore, the expense associated with TIL generation and other associated costs of inpatient care for the preparative lymphodepletion and HD IL-2, also provide a significant barrier to its uptake in the wider population. Nevertheless, it is hoped that TIL generation will become less expensive as production is scaled up for higher numbers of patients than the small groups typically treated on clinical trial programs.

Meanwhile, Weber and colleagues (2011) highlight a key logistical barrier to TIL therapy becoming a widely available treatment option, pointing to the technical requirements of TIL generation, which is currently only performed in a limited number of academic institutions.[5] Nonetheless, the authors suggest one mode of overcoming such difficulties could be through the implementation of a similar model used for hematopoietic stem cell transplantation, whereby patients travel to key specialist institutions for treatment, and then return home for follow-up care. Another proposal made by the CTEP subcommittee on the wider use of ACT is the development of a centralized TIL growth facility that would receive the tumor, grow the TIL, and transport the expanded cells out to the collaborating institutions for use in treatment.

The production and reactivity of TIL products for these other solid tumor types varies, amongst others, due to the heterogeneity in mutational load, and thus neoantigens, and lymphocytic infiltration with variations of CD4+ and CD8+ T-cells.

Despite the many promising beneficial effects, TIL therapies also have limitations. According to Rohaan and colleagues (2018), TIL is the ultimate personalized immunotherapy, given that for every individual patient, a specific infusion product needs to be manufactured, leading relatively high costs.[6] In addition, the success rates of TIL outgrowth can vary between 75% and 97%, implying a risk for every patient in that the treatment program may have to be cancelled.

Furthermore, the production time of a TIL product is more than one month, which may be too long for some patients with rapidly progressive disease. Moreover, highly specialized good manufacturing practice (GMP) facilities and production staff needs to be in place, which requires extensive investments and training. Nevertheless, the role of TIL therapy as an anticancer therapy in melanoma and possibly other solid tumors still holds great promise and could become a viable course of treatment in the future.

There are compelling reasons to follow this particular treatment modality, including the following:

- It goes without saying we want more patients to find reprieve from these brutal diseases, and TIL therapy has shown robust, reproducible clinical responses (yes, not without challenges).
- Since early 2018, just two new start-ups (profiled fully in the BCC report) actively working on this therapy have attracted more than $100 million from investors and research funds.
- Iovance Biotherapeutics Inc., which showed promising studies at ASCO 2019 using this therapy, is spending $75 million building a commercial-scale cell therapy plant, and as of June 1, the biotech's stock has nearly doubled with a market value of $2 billion.
- The logistical challenges associated with the production and delivery of these therapies are gradually being addressed, paving the way for alternative ACTs to reach the market that can target hard-to-treat solid tumors.
- Significant business opportunities exist for pharma and biotech to partner with leading institutions in the US and Europe to explore this exciting area of ACT development, where intellectual property (IP) is still in its infancy and commercial opportunities abound. ◆

This executive summary is based on the following market research report published by BCC Research: Tumor-Infiltrating Lymphocytes: A New Frontier in Cancer Immunotherapy (BIO129A). For more information, visit https://www.bccresearch.com.

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BIOGRAPHIES

Dr. Cheryl L. Barton has more than 10 years of practical pharmaceutical research experience with a leading pharmaceutical company and has served as a Pan-European Pharmaceutical analyst with a European bank. Dr. C.L. Barton Ltd. aims to provide independent, tailor-made, pharmaceutical thematic research to investment houses. Research reports combine independent scientific analysis with patients - and prescription-based models - to forecast the potential sales growth of key developmental drugs and to isolate the key drivers within the pharmaceutical sector. For more information, visit www.pharmavision.co.uk.

Bianca Piachaud-Moustakis, PhD, has more than 15 years of experience as a writer and research analyst specializing in pharmaceutical and healthcare intelligence and has worked for a number of market intelligence providers in the UK. She has a broad range of writing experience ranging from international academic and practitioner journals, to producing market intelligence reports and short articles. Areas of specialization include pharmaceuticals, healthcare, diagnostics, drug delivery systems, emerging R&D technologies, and pharmaceutical regulation.

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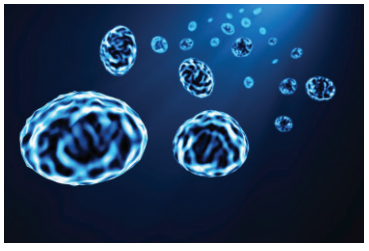
Nanoparticle Formulations



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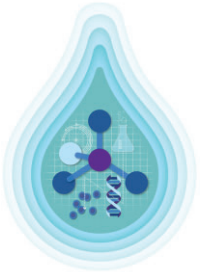

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Mitsubishi Gas Chemical (MGC) is a leading company in the field of functional chemicals, such as oxygen barrier and absorbing polymers. MGC established the Advanced Business Development Division in 2015 for tackling a variety of today's problems, and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

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

Analytical Testing

Pace Analytical Life Sciences is a network of full-service contract CMC development and GMP analytical testing laboratories. CMC development, chemistry, and microbiology central lab testing services are provided to the Pharmaceutical, Biopharmaceutical, Medical Device, and Combination Product manufacturing industries. Our investment in state-of-the-art facilities and highly trained personnel emphasizes our commitment to delivering positive customer experiences across all channels of our business. We are well-equipped to handle almost any project regardless of scope or complexity. Pace Analytical operates FDA-registered laboratory testing facilities in Oakdale, MN, San German, Puerto Rico, Woburn, MA, and Somerset, NJ. Pace Analytical Services is the largest, American-owned environmental testing company in the US. For more information, visit Pace Analytical Life Sciences at **www.pacelifesciences.com.**

Contract Service Organization

SGS Life Sciences is a leading contract service organization providing analytical development, biologics characterization, biosafety and quality control testing. With a wholly-owned network of 20 laboratories in 11 countries, services include: analytical chemistry, microbiology, stability studies, bioanalysis, extractables/leachables, virology and protein analysis. Additionally, we offer Phase I-IV clinical services. For more information, contact SGS Life Sciences at Lss.info@sgs.com or visit **www.sgs.com/lifescience.**

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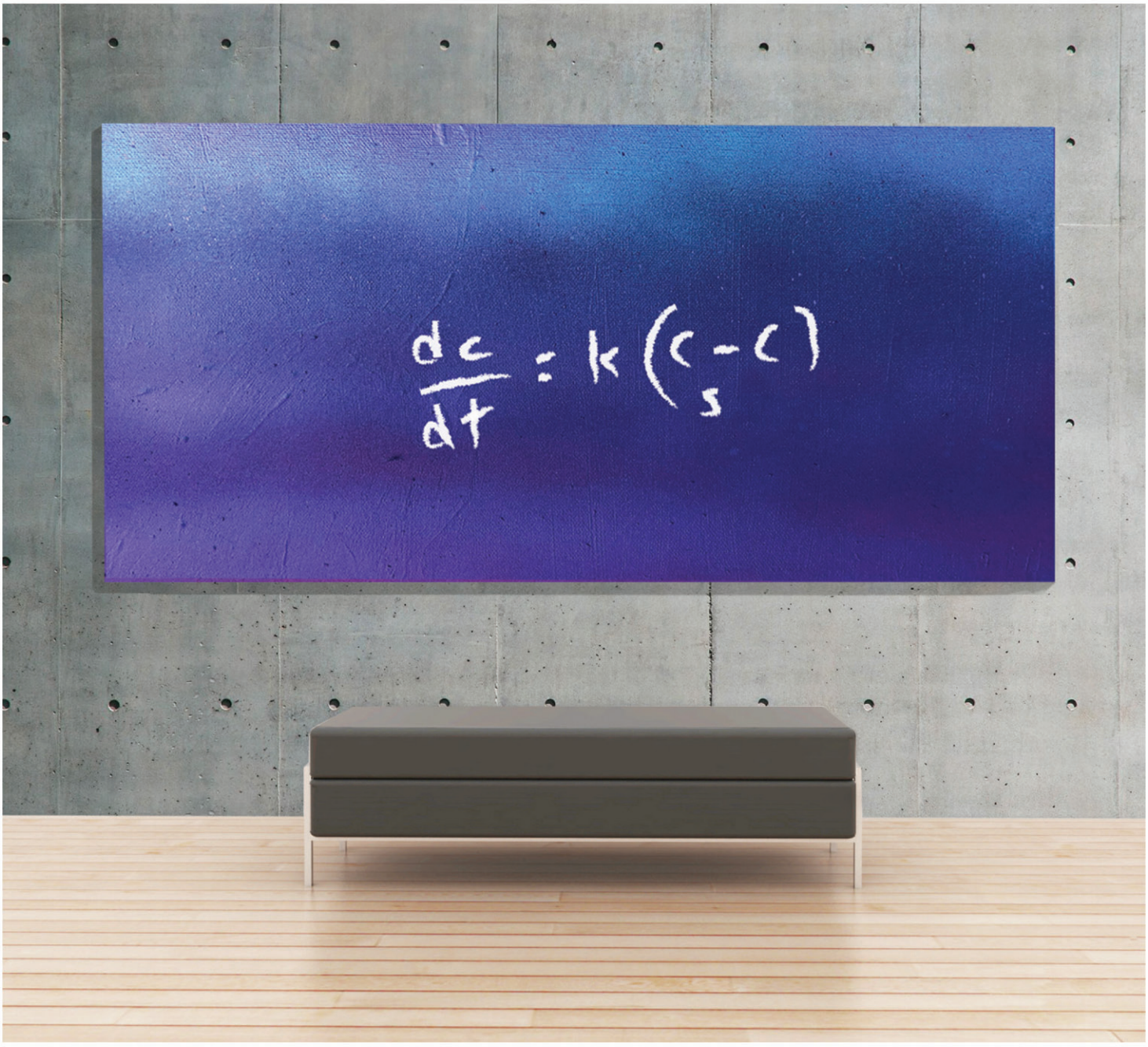

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