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Solubility & Bioavailability: Utilizing Enabling Technologies

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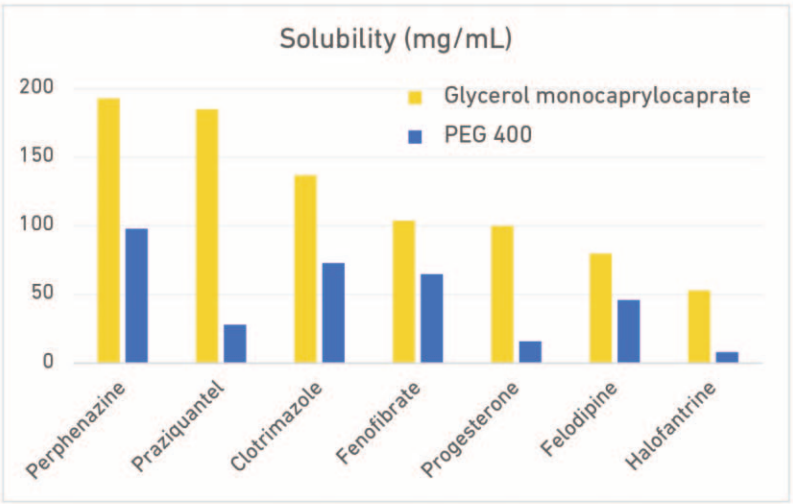

Alskar L.C. (2016) Mol. Pharmaceutics 13. 251-261

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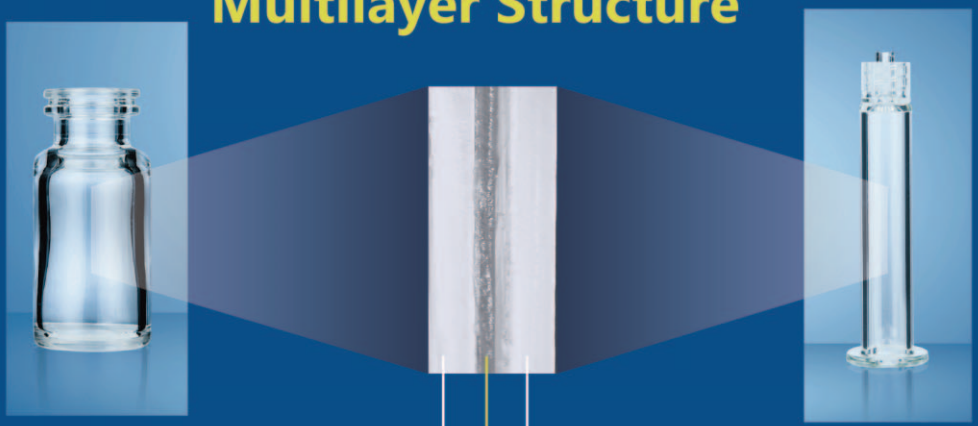

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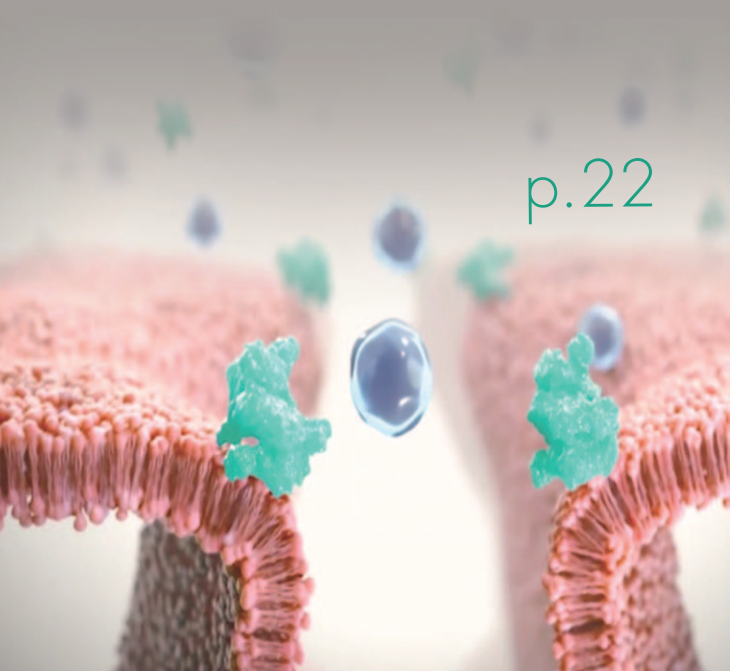
Improving Nasal Drug Delivery

"The formulation of drugs to improve suboptimal pharmacokinetics or pharma-codynamics has been an ongoing challenge in pharmaceutical development. With the growing interest in nasal delivery for its inherent advantages over other routes of administration, improvements in rate and extent of absorption are critical components for this route of delivery."



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"Solubility-limited absorption remains a key challenge in terms of bioavailability for a large number of compounds looking to progress from the discovery phase towards the clinic. Increasingly, these molecules also exhibit high melting points and poor organic solubility, making these so-called 'brick dust' compounds extremely difficult to process using conventional solubility-enhancing methods such as hot melt extrusion (HME) or spray drying."

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Contributor Cindy H. Dubin interviews several leading companies on how they are using innovative technologies, such as lipid nanoparticles to achieve a high drug loading, combining anti-solvent continuous crystallization with micro-mixing technology to control crystallization and reduce crystal size, and how a robotic capsule can improve bioavailability in the range of 47% to 78%.

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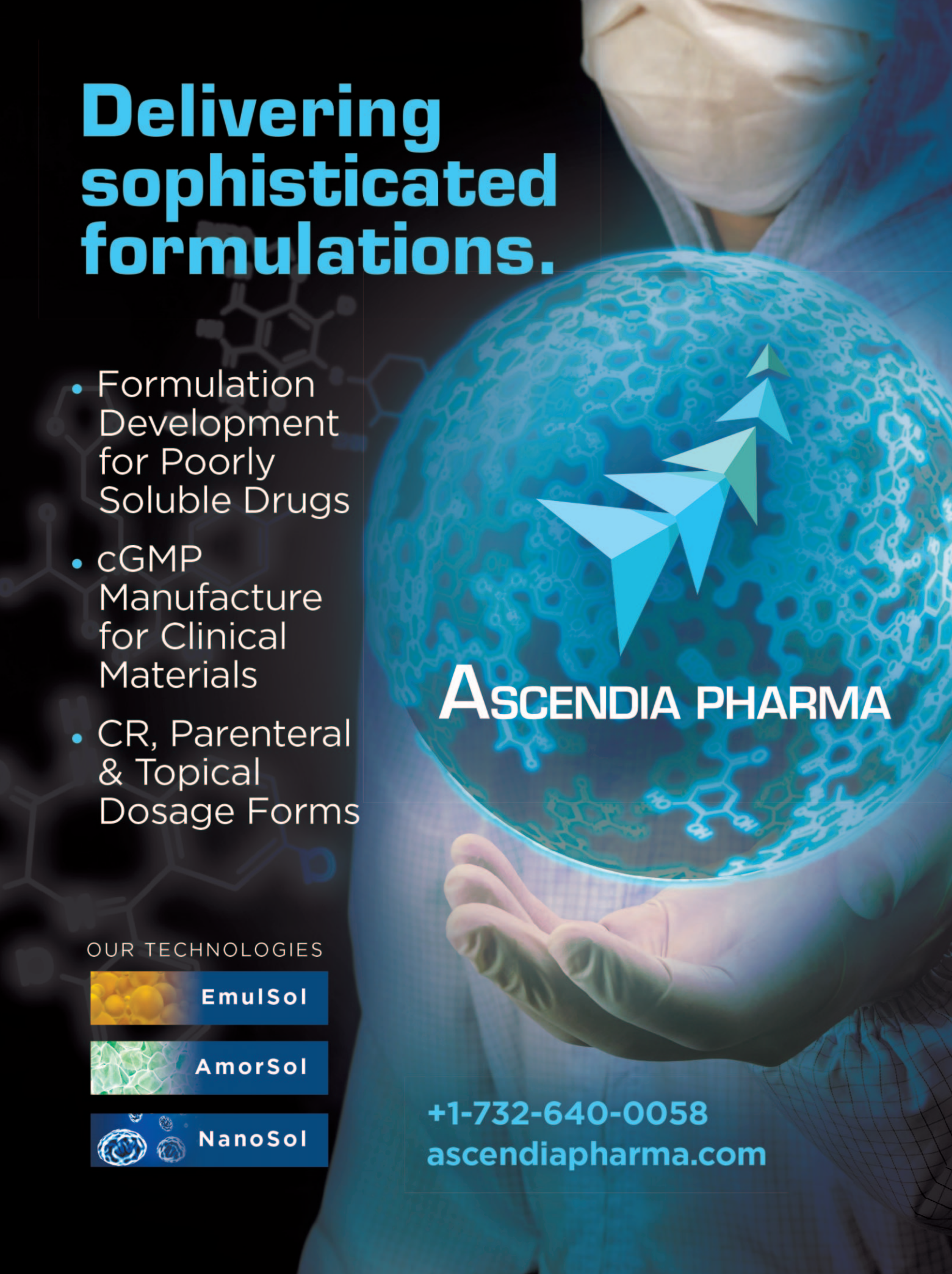
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Rani Therapeutics Unveils High-Capacity RaniPill Device for Oral Delivery of Biologics

Rani Therapeutics Holdings, Inc. recently announced the development of a high-capacity oral biologics device known as the RaniPill HC (High Capacity), capable of delivering up to a 500%-plus higher drug payload than Rani's existing oral biologics capsule. In preclinical testing, RaniPill HC demonstrated successful delivery of adalimumab and achieved high bioavailability.

"The RaniPill HC gives us the potential to deliver a much broader range of biologic drugs with its higher capacity of up to 20 mg of drug per capsule," said Mir Imran, Rani's Founder and Executive Chairman. "In addition, since the RaniPill HC shares many similarities with our existing RaniPill capsule, we are confident in our ability to achieve similar safety and performance metrics, and to leverage our existing investments in manufacturing and automation."

Today, biologics are predominantly delivered via injection or intravenous infusion, which limits long-term treatment adherence, often leading to suboptimal patient outcomes. An equally effective oral alternative could change the treatment paradigm for a number of patient populations, including those with autoimmune diseases, cancer, and diabetes.

"Therapeutic drug development has yielded a vast array of molecular entities, including peptides, antibodies and oligonucleotides. The new technology from Rani now allows for the potential oral administration of these drugs irrespective of their size or chemical nature," said Dr. Dennis Ausiello, a member of Rani's Board of Directors. Dr. Ausiello is the Director of the Center for Assessment Technology & Continuous Health (CATCH) and was previously Chief of Medicine at Massachusetts General Hospital.

Rani conducted a preclinical study of RaniPill HC, with each device containing an 18-mg dose of the biologic adalimumab, a tumor necrosis factor (TNF)-α inhibitor that is approved for multiple autoimmune conditions including rheumatoid arthritis and Crohn's disease. The unencapsulated RaniPill HC device was placed laparoscopically in the jejunum of each of three canine test subjects and allowed to self-deploy under observation. Successful delivery was achieved in all cases, and systemic serum drug concentration was detected and measured over 5 days. A copy of the data is available on the Presentations page of Rani Therapeutics' investor relations website: https://ir.ranitherapeutics.com/news-events/presentations.

"The RaniPill HC is a major milestone for our platform technology. It opens up a significant number of opportunities for new pipeline drugs and partnerships," said Talat Imran, Rani's CEO. "This sets the stage for the rest of the year, as we anticipate moving two programs into the clinic using our existing RaniPill capsule, while also advancing development of the RaniPill HC for high-dose biologics. We believe these technologies have the potential to improve the lives of millions of patients with chronic diseases who currently depend on frequent injections."

Rani Therapeutics is a clinical-stage biotherapeutics company focused on advancing technologies to enable the development of orally administered biologics. Rani has developed the RaniPill capsules, which are a novel, proprietary and patented platform technology, intended to replace subcutaneous injection or intravenous infusion of biologics with oral dosing.

Hovione & Zerion Pharma Announce Strategic Partnership

Hovione recently announced a strategic partnership with Zerion Pharma to market and commercialize Dispersome, Zerion's proprietary solubility enhancement technology platform.

Zerion´s innovative Dispersome technology builds on a new concept of increasing drug solubility by using natural protein-based excipients to formulate APIs into amorphous solid dispersions (ASDs) by spray drying. By combining Dispersome technology with Hovione's unique spray drying capabilities, experience in development, scale-up, and GMP manufacturing, Hovione further strengthens its leadership in amorphous solid dispersions and shows its commitment to innovative solutions to overcome one of the most prevalent challenges faced by the industry: low drug solubility.

"We are extremely pleased to have entered into this partnership with Zerion whom we recognize as a very innovative company in the field of oral drug formulations. By joining forces, Zerion and Hovione will be able to bring Dispersome to the market faster. We look forward to applying the technology in collaboration with our customers and partners in our effort to develop novel drugs with strong benefits to patients," said Jean-Luc Herbeaux, Hovione's Chief Operating Officer. "Hovione will continue to pursue opportunities to enhance its offering around core areas of expertise such as particle engineering and inhalation by partnering with companies and research institutions developing innovative drug formulation technologies, like Dispersome."

Zerion's CEO, Ole Wiborg, sees a strong synergy in the partnership and expects it to generate new pharma partnerships. "We consider Hovione the global leader in the field of producing amorphous solid dispersions by spray-drying. More importantly for us, this leadership has resulted in Hovione being, over the last 5 years, the main commercial manufacturer of novel FDA-approved drugs formulated as amorphous solid dispersions. Incorporating these competencies in our offering to the pharma industry both validates the strength of our Dispersome platform and provides us and our pharma partners immediate access to the highest quality in upscaling and commercial GMP manufacturing," says Ole Wiborg.

The announcement of this partnership follows Hovione's communication on a further expansion with an expected investment of $170 million in assets worldwide and shows the company's commitment to also expand its technology platforms. Hovione is investing both in new assets and innovative technologies to meet customer demand for integrated and differentiated services in drug substance manufacturing, particle engineering and most recently drug product manufacturing.

Hovione is an international company with over 60 years of experience as a Contract Development and Manufacturing Organization (CDMO) with a fully integrated offering of services for drug substance, drug product intermediate and drug product. The company has four FDA inspected sites in the USA, Portugal, Ireland and China and development laboratories in Lisbon, Portugal and New Jersey.

Zerion has pioneered the Dispersome technology that greatly enhances the solubility of poorly soluble, oral drugs and improves bioavailability and therapeutic outcomes for the patients.

Enteris BioPharma Highlights Progress in Oral Feasibility Program

Enteris BioPharma, Inc. recently provided an update on its oral feasibility programs involving the company's Peptelligence and ProPerma oral peptide and small molecule delivery technologies.

"During 2021, Enteris initiated six oral feasibility programs involving peptide and small molecule drugs targeting a variety of therapeutic indications that include cancer, women's health and disorders of the central nervous system. We anticipate some of these will transition to more extensive agreements in the near future," said Rajiv Khosla, PhD, Chief Executive of Enteris. "These partners range from emerging biotechnology firms to large, established pharmaceutical companies, illustrating the vast potential of Enteris' Peptelligence and ProPerma technology platforms and our ability to partner with companies that want to resolve the bioavailability constraints of their new chemical entity, extend a mature product's life cycle, or achieve better manufacturing and scale-up process by formulating those drugs for oral delivery."

Dr. Khosla continued "In a feasibility program, Enteris applies our Peptelligence platform to a client's peptide-based drug, or the ProPerma platform for a small molecule, to determine the potential of developing oral tablet formulations. We provide clients with optimized tablet prototypes, specifically tailored to the client's API, which are evaluated in preclinical PK studies. Once proof-of-concept is confirmed, we then advance the agreement to support the formulation, manufacturing, and clinical development of the solid oral tablet drug, from Phase 1 through to Phase 3 and potential commercialization."

Peptelligence is designed to enhance the oral delivery and bioavailability of peptide-based drugs by enhancing the permeability of such compounds and preventing their breakdown in the digestive tract. ProPerma improves the oral delivery of BCS class III and IV small molecules by improving the compounds' solubility and permeability. Enteris has demonstrated positive results in enhancing the oral bioavailability of BCS-III and BCS-IV small molecules, in some cases providing more than 20-fold improvement in oral bioavailability.

Enteris' oral delivery technologies have been the subject of numerous feasibility studies and active internal and external development programs. This includes Cara Therapeutics' ongoing development of CR845/difelikefalin (Oral KORSUVA), an oral formulation of Cara's first-in-class KOR agonist, which was initially developed via an oral feasibility program. Oral KORSUVA is currently the subject of four separate late-stage clinical trials for pruritus in patients with hepatic impairment due to primary biliary cholangitis (PBC), stage III-V non-dialysis dependent (NDD) chronic kidney disease (CKD), atopic dermatitis (AD) and notalgia paresthetica. In June and December 2021, Enteris announced the receipt of two separate milestone payments from Cara totaling $15 million per the definitive licensing agreement for Peptelligence. Since license inception Enteris has received $28 million in receipts from Cara. Enteris is eligible to receive additional potential milestone payments, subject to the achievement of certain development milestones for Oral KORSUVA, of which Enteris will retain half.

Recipharm Announces Acquisition of Vibalogics & Arranta Bio

Recipharm is continuing to build its service offerings in new biologic modalities through the acquisition of Vibalogics, a virotherapy CDMO and a portfolio company of Ampersand Capital Partners. Vibalogics holds a leading position in the manufacture of oncolytic viruses, viral vaccines and gene therapies, offering process and analytical development, manufacturing, testing and fill-finish services.

Vibalogics is responding to the rapidly growing biopharmaceutical industry demand for specialized CDMO capabilities for the manufacture of live viruses and viral vectors including Herpes Viruses, Pox Viruses, Adenoviruses, and other viral classes for cancer and other applications. The company has seen rapid growth of its global customer base comprised of Big Pharma, mid-sized biotechs and start-ups requiring its unusual process expertise, capabilities and capacity for virus production. Continued investment, including its recent expansion in Germany and the US, has positioned Vibalogics to support the full product lifecycle of its clients, including commercial supply.

The deal will provide Recipharm with capabilities in new biologics modalities, leveraging Vibalogics' expertise in oncolytic viruses, viral vaccines, and viral vector gene therapies to bring a high degree of diversification across multiple technologies and modalities. Vibalogics builds on the capabilities acquired through the recently announced GenIbet transaction and the acquisition of Arranta Bio, also announced today.

Recipharm also announced the acquisition of Arranta Bio, a prominent advanced therapy CDMO. Under the stewardship of Mark Bamforth and backed by Ampersand Capital Partners, the company has established a strong service portfolio as a leader in delivering microbiome therapeutic products and mRNA clinical production capabilities.

The acquisition forms a cornerstone of Recipharm's strategy to provide innovative drug developers in the Biologics market with scientifically differentiated contract development and manufacturing services for ATMPs and builds on the capabilities acquired through the recently announced GenIbet transaction and the acquisition of Vibalogics, also announced today.

Arranta Bio has established a strong microbiome platform with fermentation and purification expertise for naturally-derived and engineered bacteria consortia, complemented by services in analytics, proprietary media and cryopreservative formulations. These services maximize yields and enhance viability for live biotherapeutic products that clients are testing in the clinic against a range of infectious, inflammatory, neurological and oncological diseases.

In addition, Arranta Bio is progressing the supply of end-to-end mRNA capabilities across drug substance and drug product under one roof, providing its customers with substantial time savings in product manufacturing and a hedge against supply chain challenges.

The acquisition of Arranta establishes a robust US presence for Recipharm. It provides the company with a further platform from which to build its capabilities in new biologics modalities, leveraging Arranta's expertise in advanced therapies to bring a high degree of diversification across multiple technologies and modalities.

Celsion Reports Data Safety Monitoring Board Unanimous Recommendation to Continue Dosing Patients in the Phase 2 Portion of the OVATION 2 Study With GEN-1 in Advanced Ovarian Cancer

Celsion Corporation recently announced that following a pre-planned interim safety review of 81 as treated patients randomized in the Phase 1/2 OVATION 2 Study with GEN-1 in advanced (Stage III/IV) ovarian cancer, the Data Safety Monitoring Board (DSMB) has unanimously recommended that the OVATION 2 Study continue treating patients with the dose of 100 mg/m2. The DSMB also determined that safety is satisfactory with an acceptable risk/benefit, and that patients tolerate up to 17 doses of GEN-1 during a course of treatment that lasts up to 6 months. No dose-limiting toxicities were reported.

The OVATION 2 Study combines GEN-1, the company's IL-12 gene-mediated immunotherapy, with standard-of-care neoadjuvant chemotherapy (NACT) in patients newly diagnosed with Stage III/IV ovarian cancer. NACT is designed to shrink the cancer as much as possible for optimal surgical removal after three cycles of chemotherapy. Following NACT, patients undergo interval debulking surgery, followed by three additional cycles of chemotherapy to treat any residual tumor.

The OVATION 2 Study is designed with an 80% confidence interval for an observed Progression Free Survival (PFS) Hazard Ratio of 0.75, which would mean an approximate 33% improvement in risk for cancer progression when comparing the treatment arm (NACT + GEN-1) with the control arm (NACT only). GEN-1 is an immunotherapy that produces safe and durable local levels of IL-12, a pluripotent cytokine associated with the stimulation of innate and adaptive immune response against cancer. The GEN-1 nanoparticle comprises a DNA plasmid encoding IL-12 gene and a synthetic polymer facilitating plasmid delivery vector. Cell transfection is followed by persistent, local secretion of the IL-12 protein at therapeutic levels.

The company also announced that more than 75% of the projected 110 patients have been enrolled in the OVATION 2 Study. Interim clinical data from the first 39 patients who have undergone interval debulking surgery showed that the GEN-1 treatment arm is showing a 27% improvement in R0 surgical resection rate over the control arm. A complete tumor resection (R0) is a microscopically margin-negative resection in which no gross or microscopic tumor remains in the tumor bed.

In February 2021, the company announced that GEN-1 received FDA Fast Track Designation in advanced ovarian cancer. Celsion plans to request FDA Breakthrough Therapy Designation for GEN-1 based on the encouraging clinical data.

GEN-1, designed using Celsion's proprietary TheraPlas platform technology, is an IL-12 DNA plasmid vector encased in a nanoparticle delivery system, which enables cell transfection followed by persistent, local secretion of the IL-12 protein. IL-12 is one of the most active cytokines for the induction of potent anticancer immunity acting through the induction of T-lymphocyte and natural killer (NK) cell proliferation. The company previously reported positive safety and encouraging Phase I results with GEN-1 given as monotherapy or a combination therapy in patients with advanced peritoneally metastasized primary or recurrent ovarian cancer, and recently completed a Phase 1b dose-escalation trial (OVATION 1 Study) of GEN-1 in combination with carboplatin and paclitaxel in patients with newly diagnosed ovarian cancer.

Cyclerion Therapeutics & Ariana Pharma Announce Artificial Intelligence-Driven Precision Medicine Collaboration

Cyclerion Therapeutics, Inc. and Ariana Pharma recently announced an artificial intelligence-driven, precision medicine collaboration. This collaboration is expected to identify biomarkers of response to refine patient selection to guide and accelerate the clinical development of Cyclerion's investigational therapeutics for neurological and neuropsychiatric diseases associated with cognitive impairment.

Ariana Pharma's proprietary KEM (Knowledge Extraction and Management) eXplainable Artificial Intelligence (xAI) technology aims at significantly increasing success rates and accelerating clinical development timelines by fully evaluating complex clinical study data, including the discovery of hidden pharmacological and efficacy signals that may be beyond the reach of conventional statistical analyses. This approach enables identification of specific target patient populations, as well as biomarkers of therapeutic response for future clinical studies.

Ariana Pharma and Cyclerion will initially focus on supporting the development of CY6463, Cyclerion's lead clinical program. The collaboration will analyze data from completed Phase 1 clinical studies of CY6463, including a completed translational pharmacology study in healthy elderly subjects, as well as an ongoing study in Cognitive Impairment Associated with Schizophrenia (CIAS). Insights from these analyses are expected to accelerate and support further clinical development of CY6463.

CY6463 is an oral, first-in-class, central nervous system (CNS)-penetrant sGC stimulator that is being developed for neurological and neuropsychiatric diseases associated with cognitive impairment. CY6463 was designed to address multiple pathophysiological features of these disorders. Results from initial CY6463 clinical studies have demonstrated favorable safety and tolerability and pharmacologically relevant drug exposure in the cerebral spinal fluid. Furthermore, promising impacts on EEG measures, neuroinflammation, and other measures support the current clinical development of CY6463. In addition to the ongoing study in CIAS, studies to evaluate CY6463 safety and signals of clinical activity are also ongoing in participants with Alzheimer's Disease with vascular pathology (ADv) and Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes (MELAS). Cyclerion expects to obtain clinical results from the MELAS and CIAS studies in Q2 2022 and 2H 2022, respectively. The ADv study initiated patient dosing in January 2022 and enrollment is ongoing.

"Ariana integrates disease biology, mechanism information, and pre/clinical data in their AI platform. This multidimensional machine learning approach, based on Formal Concept Analysis, identifies all possible relationships, the strongest of which may form the basis of drug-specific patient selection and/or surrogate pharmacology/efficacy markers and identify additional indications. We believe that Ariana's extensive drug development experience in the CNS and the application of this technology to our innovative pipeline may be quite powerful in guiding efficient drug development, and we look forward to a productive collaboration focused on successfully advancing CY6463 for diseases associated with cognitive impairment," said Andy Busch Ph.D., Chief Scientific Officer of Cyclerion Therapeutics.

Moderna Initiates Phase 3 Portion of Pivotal Trial for mRNA Respiratory Syncytial Virus Vaccine Candidate

Moderna, Inc. recently announced the Data and Safety Monitoring Board (DSMB) for the RSV program has endorsed the start of the Phase 3 portion of the pivotal clinical study of mRNA-1345, the company's Respiratory Syncytial Virus (RSV) vaccine candidate, in adults 60 years and older. The DSMB's endorsement comes after independent review of preliminary Phase 2 data, which suggest that the vaccine has an acceptable safety profile in older adults at the selected dose. This study is known as ConquerRSV.

"RSV is one of the most widespread respiratory viruses, causing severe disease and hospitalization in older adults, and yet there is no vaccine available on the market," said Stéphane Bancel, Chief Executive Officer of Moderna. "We believe that our vaccine candidate against RSV has the potential to protect against over 1 million infections globally each year, improving quality of life for those at high-risk of becoming infected and reducing the burden on health care systems. An mRNA vaccine against RSV could have a positive impact on individuals, communities, and global public health. Our ultimate goal is to combine our RSV vaccine with our COVID-19 and flu boosters into a single dose booster."

RSV is a common respiratory virus that generally causes cold-like symptoms. While most people who contract RSV recover in approximately one to two weeks, the virus can be serious for young children and older adults. For these higher-risk groups, RSV is a leading cause of severe respiratory illness, including pneumonia and respiratory distress.

The burden of illness caused by RSV is substantial; each year in the US, RSV causes approximately 177,000 hospitalizations and 14,000 deaths in adults 65 and older, resulting in an estimated $3 billion in annual medical costs.

RSV tends to be a seasonal illness, with infections in the United States and countries with similar climates primarily occurring during fall, winter and spring. In the past year, however, the COVID-19 pandemic has impacted normal transmission patterns, leading to unusual levels of infection. In June 2021, the CDC issued a health alert flagging increased interseasonal RSV infection in certain parts of the US, and similar trends have been seen globally. There is currently no approved vaccine for RSV.

mRNA-1345 is a vaccine against RSV encoding for a prefusion F glycoprotein, which elicits a higher neutralizing antibody response compared to the postfusion state. mRNA-1345 uses the same lipid nanoparticle (LNP) as Moderna's COVID-19 vaccine and contains optimized protein and codon sequences. The FDA has granted Fast Track designation for mRNA-1345 in adults older than 60 years of age. The primary purpose of the Phase 3 segment of the study is to establish the safety and efficacy of mRNA-1345 vaccine in adults older than 60 years of age in support of licensure. Moderna expects to enroll approximately 34,000 participants.

Evelo Biosciences Announces Dosing of First Patient in Phase 2 Trial

Evelo Biosciences, Inc. recently announced the first patient has been dosed in EDP1815-207, its Phase 2 randomized clinical trial of EDP1815 for the treatment of patients with mild, moderate, and severe atopic dermatitis.

"We are pleased that dosing has begun in the Phase 2 trial to evaluate the potential of this novel product candidate to benefit people worldwide who are living with atopic dermatitis," said Jonathan Zung, PhD, Chief Development Officer of Evelo. "Our previously released Phase 1b data, together with the positive results we recently released from our Phase 2 trial in mild and moderate psoriasis, demonstrate that EDP1815 has the potential to be a safe, effective, well tolerated, oral, inflammation resolving therapy."

"Patients and prescribers are in need of a therapy that is safe and well tolerated, as well as orally delivered, for the treatment of atopic dermatitis," said Benjamin Ehst, MD, PhD, Board-certified Dermatologist, Investigator and Clinical Associate Professor with the Oregon Medical Research Center, and Chief Investigator of EDP1815-207. "The integrated safety, tolerability, and efficacy data seen in the Phase 2 trial of EDP1815 in psoriasis, along with its oral administration and potential to be affordably priced, could provide meaningful change to the treatment paradigm for patients living with atopic dermatitis."

Topline results from the Phase 2 clinical trial are expected in 1H 2023.

EDP1815-207 is a 16-week, multi-center, double-blind, placebo-controlled Phase 2 trial for the treatment of mild, moderate, and severe atopic dermatitis. Approximately 300 patients will be randomized, across approximately 60 sites globally, into one of three cohorts – each cohort has ~100 patients randomized in a 3:1 ratio (75 to EDP1815 and 25 to placebo). Cohort 1 will be administered a dose of 1.6 x 1011 total cells of EDP1815, or matching placebo administered as two capsules once daily. Cohorts 2 & 3 will be administered a dose of 6.4 x 1011 total cells of EDP1815, or matching placebo administered as two capsules once daily or one capsule twice daily, respectively. The primary endpoint is percentage of patients achieving an EASI-50 at week 16. Key physician-reported secondary endpoints are IGA (Investigator Global Assessment) and BSA (Body Surface Area). Key patient-reported secondary endpoints are DLQI (Dermatology Life Quality Index), POEM (Patient-Oriented Eczema Measure), and Pruritus-NRS (Numerical Rating Scale).

EDP1815 is an investigational oral medicine being developed for the treatment of inflammatory diseases. It is a non-live pharmaceutical preparation of a strain of Prevotella histicola, selected for its potential to provide systemic pharmacological effects after oral administration with gut-restricted distribution. Being non-live, it has not been observed to colonize the gut or modify the microbiome. Preclinically, EDP1815 had anti-inflammatory effects in models that cover multiple pathways of inflammation, Th1, Th2, and Th17. Clinical results from multiple independent cohorts provide evidence supporting EDP1815's potential to address Th1, Th2 and Th17-mediated inflammation.

Evelo Biosciences is a clinical stage biotechnology company developing orally delivered product candidates that are designed to act on the small intestinal axis, SINTAX, with systemic therapeutic effects. SINTAX plays a central role in governing the immune, metabolic, and neurological systems. The company's first product candidates are pharmaceutical preparations of single strains of microbes selected for their potential to offer defined pharmacological properties. Evelo's therapies have the potential to be effective, safe, and affordable medicines to improve the lives of people with inflammatory diseases.

Quotient Sciences Completes Integration of Drug Substance Into Translational Pharmaceutics Platform

Quotient Sciences recently announced it has integrated drug substance into its flagship Translational Pharmaceutics platform. The newly integrated service unites drug substance, drug product, and clinical testing activities all within a unified organization and under a single project manager.

The full integration of drug substance R&D and manufacturing follows a year after the company's acquisition of its Alnwick, UK site and provides a more streamlined approach from candidate selection through to commercialization. Quotient Sciences Translational Pharmaceutics approach – combining manufacturing and clinical dosing at a single organization – enables innovators to adjust formulations and dosing in real time.

"Our Translational Pharmaceutics platform is now in its 15th year and has accelerated development timelines for more than 500 drug programs. We remain the only outsourcing partner able to offer innovators the ability to manufacture, release, and dose under one organization. This approach is proven to shave 12-months off timelines and, by adding drug substance synthesis, the timeline from candidate selection to clinic can be further accelerated by 2-4 months," said Mark Egerton, CEO of Quotient Sciences.

Translational Pharmaceutics was developed in consultation with the MHRA & FDA and employs a rapid "make-test" cycle, where drug products are manufactured, released, and dosed in a clinical study in days rather than months. This means biotechs and pharma companies can fast track molecules from First in Human (FIH) through Proof of Concept (POC).

"By fully integrating drug substance with drug product and clinical testing activities, Quotient Sciences can closely align manufacturing and dosing workflows, greatly improving R&D efficiencies, and increasing the potential for clinical and commercial success," said Peter Scholes, CSO of Quotient Sciences. "In fact, an independent study by the Tufts Center of the Study of Drug Development (CSDD) showed Translational Pharmaceutics delivered $200milllion in drug development cost saving per approved drug."

"Our purpose has always been to bring new medicines to patients faster, and our new capabilities in drug substance continue to break down traditional industry silos. As we look to the future, Quotient will continue to bring on new services that further integrate drug development and streamline the outsourcing needs of our customers," added Egerton.

Quotient Sciences is a drug development and manufacturing accelerator providing integrated programs and tailored services across the entire development pathway. Cutting through silos across a range of drug development capabilities, we save precious time and money in getting drugs to patients. Everything we do for our customers is driven by an unswerving belief that ideas need to become solutions, and molecules need to become cures, fast. Because humanity needs solutions, fast. For more information visit quotientsciences.com.

DRUG DEVELOPMENT

The Promise of Cutting-Edge Microbiome-Based Therapeutics

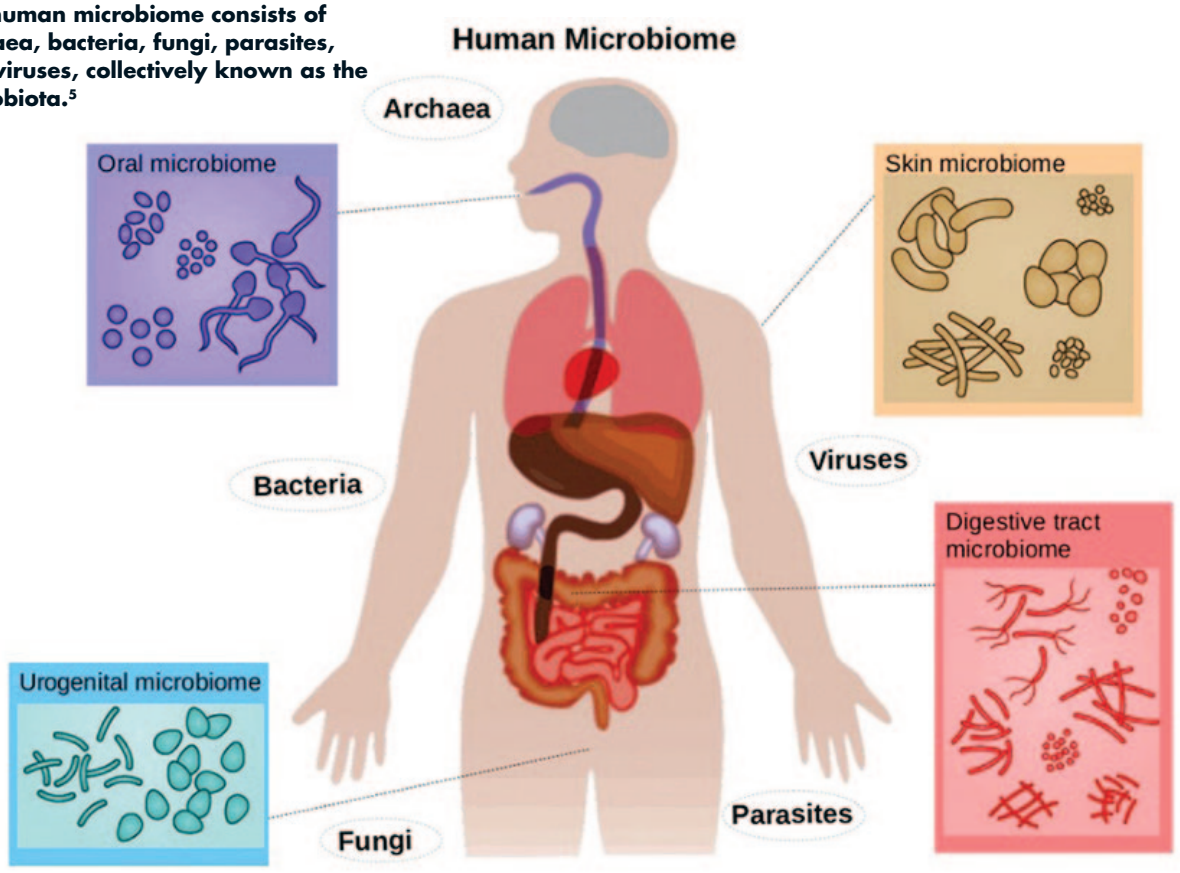
By: Andrew Thomson, Brian Carpenter, and Robert Broadnax

INTRODUCTION

In recent years, there has been increasing evidence that imbalances in bacteria living in the human microbiome (dysbiosis) contribute to a host of diseases that can be effectively treated by restoring harmonious bacterial populations (symbiosis).[1] This connection has established manipulation of the microbiome as a unique therapeutic approach and inspired research and development of microbiome-based therapies. Currently, there are several microbiome-based therapies progressing through various stages of clinical development and commercial readiness, with probiotic therapies being the most advanced. Several manufacturers of probiotic therapies recently announced positive topline results from pivotal trials assessing these therapeutics for treatment of C. difficile infection (CDI), and researchers from the University of Birmingham in the UK recently published results from a new study adding to a growing body of evidence showing that fecal microbiota transplantation (FMT) is highly successful in treat-

FIGURE 1

The human microbiome consists of archaea, bacteria, fungi, parasites, and viruses, collectively known as the microbiota.[5]



ing patients with CDI.[2]

As novel associations between the human microbiome, health, and disease continually emerge, and therapies including probiotics advance in clinical development, this progress shows the high growth potential of the microbiome therapeutics market.[3,4] Yet, barriers remain in development and commercialization, including (a) the inability to clearly demonstrate the clinical applications of microbiome-based therapies, (b) unclear guidelines for their use in physicians' treatment algorithms, and (c) the nascency of the field.[5,6] Developers must strategically address and overcome these challenges to successfully drive development and eventual adoption of microbiome-based therapies.

DISEASES ASSOCIATED WITH MICROBIOTA DYSBIOSIS

The microbiome is the diverse community of all microorganisms, helpful and harmful, in the human body. These communities of microorganisms exist in the skin, nasopharynx, oral cavity, respiratory tract, gastrointestinal tract (GI), and female reproduction tract.[1] Everyone's microbiome composition is different – genetics, environmental influences, diet, and health all subtly alter the composition of the microbiota. Clinical research around microbiome-based therapeutics focuses on manipulating bacteria in the gut, which is the most abundant and diverse microbial community in humans. Imbalances in the microbiota have recently been identified as the direct cause of more than 25 diseases and conditions, with significant alterations in the composition of gut microbiota shown to be the cause of neurodegenerative, inflammatory, and metabolic diseases.[6]

Neurodegenerative Diseases: The gut microbiome and brain communicate in a bi-directional manner via the gut-brain axis. The microbiome's modulation of the brain and spinal cord (central nervous system) is mediated by microbial chemical signals (called metabolites), which can influence neuroendocrine function, the level of circulating neurotransmitters in the body, and behavioral changes. In addition, psychiatric and neurologic disorders can lead to the reduction of microbiome diversity and GI-related symptoms. Studies have shown that dysbiosis is associated with some neurodegenerative diseases, such as Parkinson's disease, and a range of psychiatric and mood disorders.[6]

Inflammatory Diseases: Immune function is also influenced by the gut microbiome through interaction with the host's immuno-response system. Various species of gut bacteria have been shown to promote expression of regulatory T-cells, which are white blood cells that play a central role in the adaptive immune response. Changes in the interaction between the gut microbiome and the host's immune system have been shown to lead to inflammatory diseases, including inflammatory bowel disease (IBD). Gut bacteria can also indirectly modulate immune function through interaction with invading pathogens.[7]

Metabolic Diseases: Gut bacteria also play a role in metabolizing consumed food, metabolites, and foreign chemicals as well as harvesting energy by producing

FIGURE 2

Neurodegenerative Diseases	Inflammatory Diseases	Metabolic Diseases
Clostridia	Bacteriodetes	Clostridia
Bacteroides	ParaBacteroides	Bacteroides
Desulfovbrivio	Firmicutes	Prevetolla
Prevotellacae		Firmicutes
Lactobacillus		Lactobacillus

Correlations between key diseases and specific altered microbiota.[6]

vitamins. Metabolites are involved in regulation of glucose levels, and research has shown they are directly linked to metabolic disorders, such as obesity and diabetes.[8]

One well known therapeutic that focuses on manipulating gut bacteria is FMT for the treatment of recurrent CDI (rCDI), which involves extracting healthy bacteria from a donor's fecal matter and transferring the bacteria directly into the colon of an infected patient.[3] As the microbiome is directly related to the etiology of rCDI, FMT has been accepted by many clinicians, despite its lack of formal FDA approval, as the most effective treatment for patients with rCDI. Occasionally, FMT has been shown to negatively interact with a patient's existing microbiome, inadvertently introducing disease-causing bacteria.[9,10] The range of probiotic therapies advancing through clinical trials seeks to learn from the shortcomings of FMT and provide improved microbiome-based treatment options for rCDI and several other indications.

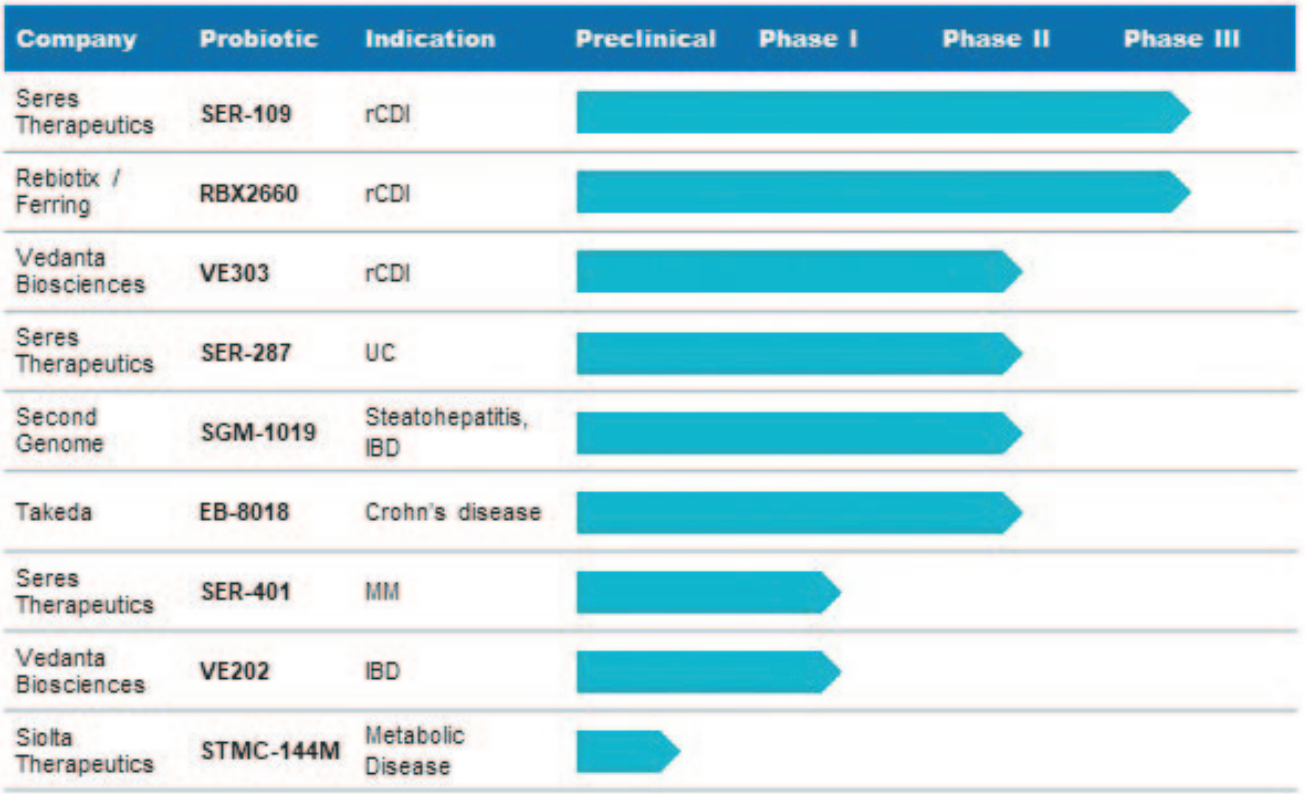
BARRIERS IN DEVELOPING MICRIOBOME-BASED THERAPEUTICS

Despite the range of promising microbiome-based therapies in development, there remain three key barriers that manufacturers must address to drive these therapeutics towards approval and eventual commercialization. These barriers include the following:

Unsubstantiated Body of Evidence: There is a lack of consensus among industry stakeholders, including physicians, around how altering aspects of the microbiome ultimately impacts human health, and many are calling for additional clinical data demonstrating the safety and efficacy of emerging microbiome-based therapies.[10] Some physicians are convinced the microbiome has significant influence on disease pathology and that microbiome manipulation will be critical in addressing a range of diseases, but others believe microbiome-based therapies should not be incorporated in treatment decisions due to the lack of empirical evidence supporting therapeutic use.[11] These physicians will have to be convinced of the real-world value microbiome-based therapies provide in order to adopt. Challenges in collecting real-world data also might deter other drug developers from entering the field.

Low Familiarity & Understanding: Currently, most patients and physicians have

FIGURE 3



Clinical timeline of leading microbiome-based therapies – January 2021 (rCDI: recurrent C. diff. infection, UC: ulcerative colitis, IBD: inflammatory bowel disease, MM: metastatic melanoma). (Source: CRA conducted analysis – 2021)

a limited understanding of these novel products and insight into differentiating factors due to the nascency of the field. Some also do not understand the complexity of the human microbiome or are skeptical of its role in human health. Pending approval, drug developers will need to effectively communicate a product's value proposition and mechanism of action in a way that resonates with target customers and aligns with their needs.

Undefined Commercial Opportunity: It is unclear exactly how these treatments will be adopted in clinical practice as clinical trials are showing that microbiome-based therapies can be used to address a range of unmet needs. It will be essential to identify the area of highest commercial opportunity in this untapped market where adopters have minimal reference points, but there may be a significant amount of risk for a first-to-market microbiome-based therapeutic.

OPPORTUNITIES TO OVERCOME CRITICAL BARRIERS TO ADOPTION

As shown in Figure 4, to successfully drive adoption, developers of microbiome-based therapies will need to overcome the barriers previously outlined and shape current stakeholder opinions by convincing physicians, patients, healthcare providers, payers, and others of the clinical benefits and value of these products. This will require drug developers seeking to enter the field to do so in a systematic manner, following these recommendations:

Assess the Commercial Opportunity: The first step for drug developers is to gain an in-depth understanding of the commercial potential of a product and identify the use that offers the highest commercial potential. This will require the development and application of an opportunity assessment framework, which should encompass defined metrics to assess factors, including (1) the strength of the product's value proposition; (2) clinical efficacy; (3) the size of the addressable patient population (based on target intervention points in the patient journey); (4) likelihood of physician and patient adoption; (5) level of current and future competitive intensity; and (6) likelihood of payers to cover the product.

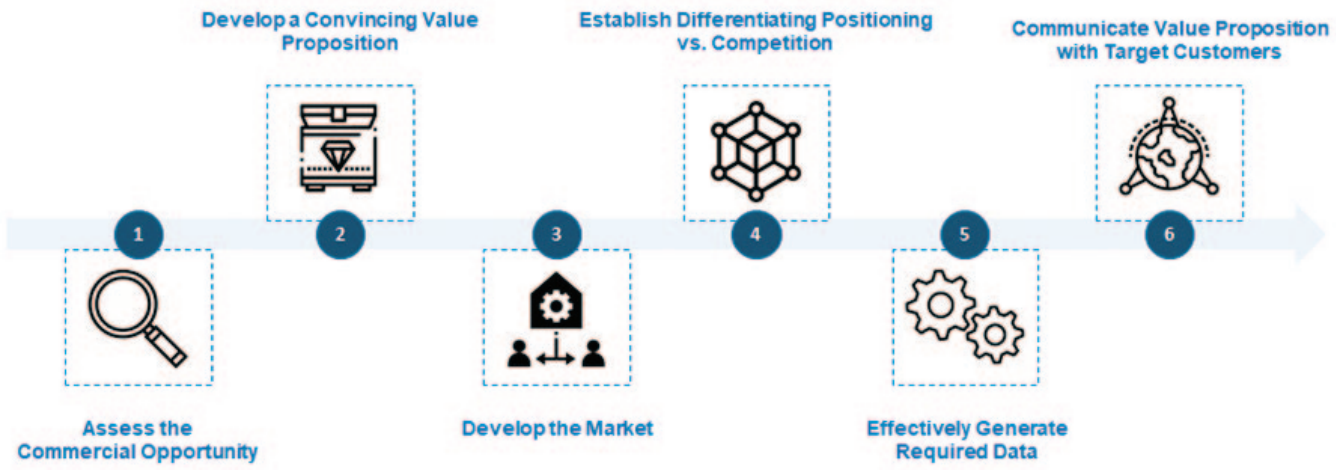
Develop a Convincing Value Proposition: Once the opportunity with the highest commercial potential has been identified, developers of microbiome-based therapies must take steps to crystallize the value proposition of their product to ensure it aligns with the unmet needs of target customers, can be sufficiently supported by available clinical data, and resonates with all stakeholders, including physicians, patients, and payers. It will be essential to develop a compelling value proposition in this emerging market to drive product uptake and effectively capitalize on the identified commercial opportunity.

Develop the Market: Another important step is developing the market, which includes building broader awareness and understanding of microbiome-based therapeutic approaches among target stakeholders to ensure potential adopters are willing to try these treatments once available. This may involve providing fundamental background information on what the human microbiome is and how research has shown its role in human health and causing disease. Establishing this baseline familiarity for microbiome-based therapeutics will require implementing a range of market-shaping techniques to convince stakeholders of their clinical value, including education strategy development and awareness campaign execution, to generate demand that supports successful market entry.

Establish Differentiating Positioning Versus Competition: As the microbiome sector gets increasingly crowded by more emerging innovative therapies, coupled with stakeholder skepticism about the clinical benefits they offer, it is essential that developers establish compelling positioning versus the competition. Strategies must differentiate their product from existing standard-of-care treatments and future market entrants. This well help build upon their product's unique value proposition to support uptake post-launch.

Effectively Generate Required Data: Lack of supporting clinical data is a primary challenge in the adoption of microbiome-based therapies, highlighting the need to build a comprehensive evidence generation strategy. Developers will need a guide for how to develop the level of clinical data required by regulators and preferred by customers, potentially going beyond data from ongoing clinical trials. An evidence generation plan should detail how to identify data gaps relevant to a product's value proposition (eg, patient outcomes, health economic and outcomes research data), prioritize these data gaps and generate the data needed to demonstrate a product's clinical benefits, value proposition, and positioning. Executing an evidence generation strategy will likely re-

FIGURE 4



Highlighted opportunities to overcome barriers in developing microbiome-based therapeutics. (Source: CRA conducted analysis – 2021)

quire developers to pursue a range of activities, such as conducting retrospective claims analyses, prospective chart studies, and additional clinical trials as efficiently as possible.

Communicate Value Proposition With Target Customers: When all required data are generated and collected, developers of microbiome-based therapies must then strategically communicate a product's value proposition with target customers using marketing and field efforts. This might include providing real-world payer or physician testimonials to customers, positioning sales teams to address physician concerns about a product's value and clinical benefits and developing patient FAQs and payer budget impact models. All activities should be tailored to each product and the needs of each customer to ensure they are targeted and cost-effective, and that the value proposition resonates with key stakeholders.

Coordination of successful development and commercialization for emerging microbiome-based therapies requires strategic execution of these tactics. Developers might consider partnering with experts who have experience in clinical development of innovative technologies and understand what it takes to successfully drive product uptake with customers post-launch. Developers in the microbiome sector should also observe their competitors' strategies, assess the benefits and risks of each and apply these learnings to their own operations.

SUMMARY

When identifying promising microbiome therapeutic approaches for any disease or condition, it is critical to understand the mechanism of disease and disease pathways as well as the role of the microbiome. While there has been increasing evidence that a healthy microbiome supports proper function of organs and metabolic systems, more research needs to be done to further establish the connection between the microbiome and human health. Advances in research will help drive a new focus on the treatment of diseases linked to the microbiome and the emergence of novel microbiome-based therapies, including probiotics, in the years ahead. Manufacturers must carefully consider any existing barriers and the optimal approach for entering the microbiome field to ensure success.

The views expressed herein are the authors' and not those of Charles River Associates (CRA) or any of the organizations with which the authors are affiliated. ◆

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BIOGRAPHIES

Andrew Thomson is a consulting associate within the Life Sciences Practice at CRA with 3+ years of experience in commercial strategy consulting with pharmaceutical and biotech clients alike, focused on microbiome-based healthcare solutions.

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NASAL DELIVERY

Improving Nasal Drug Delivery With Permeation Enhancing Technology

By: Stuart Madden, PhD, CCHEM, FRSC

BACKGROUND

Nasal sprays have a long history of use in medicine, but historically, this has been predominantly for their local effects on the mucosa. The treatment of nasal rhinitis (eg, sinusitis, nasal congestion, and /or a runny nose) that are brought about by infections, such as colds and flu, or allergens and irritants, that inflame the mucosa are traditionally treated by the application of a locally acting prescription or over-the-counter (OTC) nasal spray, such as a decongestant, saline rinse, or concomitant antihistamine. It is only recently that the nasal route of administration has come to prominence for the systemic delivery of therapeutics. At the end of the past century, there were relatively few approved nasal spray drug products commercially available in the US: nafarelin, nicotine, and sumatriptan are some early examples. Since that time, there has been a growing interest in nasal delivery for several reasons that cover a wide range of factors evidenced by the significant increase in approved nasal spray drug products for a wide range of therapeutic indications.

The nasal route is appealing for the following several reasons:

- Convenient, non-invasive, and easy to use, either by the patient or a caregiver, resulting in high patient compliance.
- Highly vascularized nasal epithelia that helps systemic absorption promoting rapid therapeutic blood levels that is an important aspect in the "rescue" setting, eg, the use of Narcan® (naloxone nasal spray) for drug overdose or Valtoco® (diazepam nasal spray) for acute repetitive seizures.
- The potential for direct nose to brain delivery. One of the limiting factors of drugs to treat neurological conditions is their inability to cross the Blood Brain Barrier (BBB). Nasal delivery provides a direct route to the CNS via the trigeminal nerve and olfactory lobe. This direct route may also contribute to the rapid onset aspect of nasal delivery.
- No first-pass metabolism, making it an attractive alternative to oral dosing where this is an issue.

The delivery of the dose is achieved by a nasal spray pump. This technology is well established, and there are numerous commercial manufacturers supplying nasal sprays in various configurations with respect to single or multi-dose units with an array of delivery volumes, typically in the range 25 μL to 100 μL.

Nasal delivery, however, does have challenges. The delivery volume limitation precludes high drug load products that may be solubility limited. At volumes more than 100 μL, there is the possibility of leakage through dripping back out the nostril or going past the upper reaches of the nasal passage to be swallowed via the esophagus, resulting in a sub-optimal dose. This constraint is compounded to some degree by the limited solvent systems that can be used due to the sensitive nature of the nasal mucosa and the need to limit any nasal irritation that may result from drug administration.

A final challenge is the need for rapid absorption. The nose has a mucocilliary clearance system that effectively replaces the mucosal film approximately every 15 to 20 minutes so rapid absorption is critical for achieving high bioavailability. It is this aspect of nasal delivery that can be significantly improved by the incorporation of a permeation enhancer into the drug product formulation.

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PERMEATION ENHANCERS

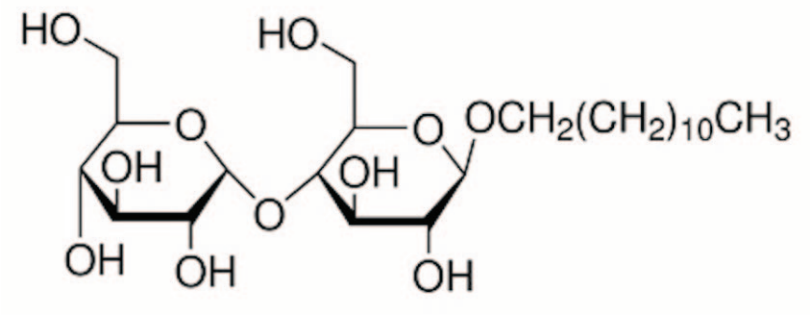
Although the main respiratory chamber of the nose has a large surface area (approximately 130-160 cm^2) and is highly vascular, the concentration of the drug is progressively reduced by the action of dilution from regenerating mucosal coating and by mucocilliary clearance that physically removes the drug. Absorption, therefore, must be rapid, ideally significantly less than 15 minutes. Because of these factors, improving the rate of absorption also increases the extent of absorption as more drug is absorbed before it gets diluted and washed away.

Understanding that there are significant constraints on the formulation itself, the incorporation of a permeation enhancer is an ideal solution to facilitate improved drug uptake into the systemic circulation. Throughout the past several decades, a range of compounds have been investigated as potential permeation enhancers. A comprehensive review of transmucosal absorption enhancers covering various routes has recently been published demonstrating the wide interest in this field.[1] This review focuses on the use of alkylsaccharides as absorption enhancers for nasal delivery of a wide range of drug types.

ALKYLSACCHARIDES

The alkylsaccharides are a family of non-ionic compounds consisting of a sugar moiety linked to an aliphatic carbon chain by a glycosidic or ester bond, and certain of these have shown to provide absorption enhancing properties. The sugar can be one of numerous oligosaccharides (typically a disaccharide) and the aliphatic chain is typically 8-18 carbons. An alkylsaccharide approved for use in commercial products in the US (Valtoco® and Tosymra®) is Intravail A3, n-dodecyl β-D-maltoside, shown in Figure 1.

FIGURE 1



n-Dodecyl β-D-maltoside

An important physicochemical property of Intravail A3 is its amphiphilicity. The hydrophilic-lipophilic balance (HLB) for Intravail A3 is approximately 14, giving it detergent-like properties. This versatility enables its use with a wide range of drugs across a broad spectrum of log P values in aqueous or non-aqueous solvent systems, enabling the formulator a wide choice of solvent systems.

SAFETY

Alkylsaccahrides are odorless, tasteless, and are essentially non-toxic and non- mutagenic (oral "no observable effect level" is ~20,000-30,000 mg/kg of body weight).[2] They are metabolized to their corresponding sugar and fatty acid following absorption.[3,4] Alkylsaccharides are used extensively in the food industry and are generally recognized as safe (GRAS) by regulatory authorities for food applications. Intravail A3 has been studied extensively in numerous animal models with a variety of drugs and delivery systems, and no toxicities have been observed. To date, there have been no data that indicate any issues with respect to damage to the epithelial cell membrane, and mechanistically, the permeation enhancement is transient, and once the Intravail has been removed by mucocilliary clearance, the epithelial morphology returns to its native state.

MECHANISM

To achieve systemic absorption, the drug must cross several barriers. First, there is a mucus layer that, as described earlier, is continually regenerating. Then, the drug must cross through the epithelial layer to the basement membrane before finally traversing into the capillary endothelium and thence to the systemic circulation. There are two primary mechanisms for absorption through the epithelial layer:

- Paracellular transport through opening of tight junctions between cells.
- Transcellular transport or transcytosis through cells through vesicle carriers.[5,6]

Facilitating transport across the epithelial layer is the key to improving drug absorption. The layer consists of columnar

cells interconnected via tight junctions. Small hydrophobic drugs can partition transcellularly via a concentration gradient, whilst small hydrophilic drugs benefit from an active transport mechanism (eg, vesicle formation). Larger drugs and hydrophilic drugs may also get absorbed via the paracellular pathway.

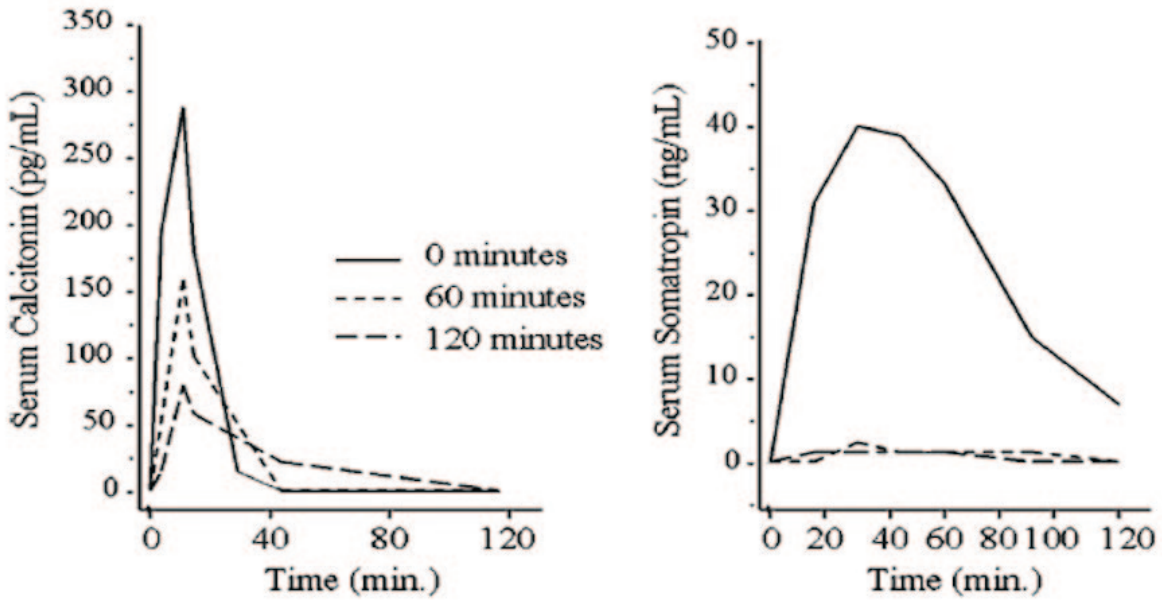
The addition of a non-ionic surfactant, such as Intravail A3, is believed to act via both mechanisms, although few definitive studies have been performed. In paracellular transport, it is likely the alkylsaccharide temporarily disrupts the interactions of the membrane proteins that maintain the tight junctions.[7] This loosening facilitates drug transport across the epithelia, allowing a drug to pass through more easily and quickly. Similarly, Intravail A3 may have a transient effect on the cell lipid membrane, disrupting it to allow a drug to pass into the cell or by active transport whereby a hydrophilic drug is encapsulated in an alkylsaccharide lipid vesicle and internalized into the epithelial cell.

The opening of tight junctions is particularly important for large molecules (proteins and peptides) that are typically poorly absorbed. Paracellular transport is typically restricted to molecules with radii of less than 1.1 nm.[8] The improvement in absorption of peptides and proteins is shown in the Examples section below (Figure 3). These data are taken from several publications using the same preclinical species, rat, and replotted on a single graph for comparative purposes.[5,16] In this instance, the alkylsaccharide is a C14 aliphatic chain maltoside. In each case, the authors are comparing nasal administration to subcutaneous injection at the same concentration except for calcitonin, which was compared to the corresponding intravenously administered dose of calcitonin, thus providing absolute bioavailabilities in this case.

There are two general trends that are observed. First, as the absorption enhancer concentration is increased from 0% to 0.5%, the bioavailability of each peptide or protein increases. Second, as the molecular weight increases from 4 kDa for calcitonin to 30 kDa for erythropoietin, the bioavailability at any given concentration of Intravail decreases. While the general trend of an inverse relationship between molecular weight and bioavailability is observed, there is also an indication of idiosyncratic differences between peptides. Specifically, while leptin is 16 kDa compared to insulin at 6 kDa, leptin has comparable bioavailability despite its higher molecular weight. It is worth noting that while rat data is generally accepted as indicative of general bioavailability trends in nasal delivery (with the reported exception of delivery of powders), inter-species differences in nasal morphology and physiology are known to exist, and the relative benefits and deficiencies of the variously employed animal models, which include rat, guinea pig, rabbit, dog, sheep, and various primates have been reviewed in detail with primates, not unexpectedly, generally considered the best nonhuman model species.[9]

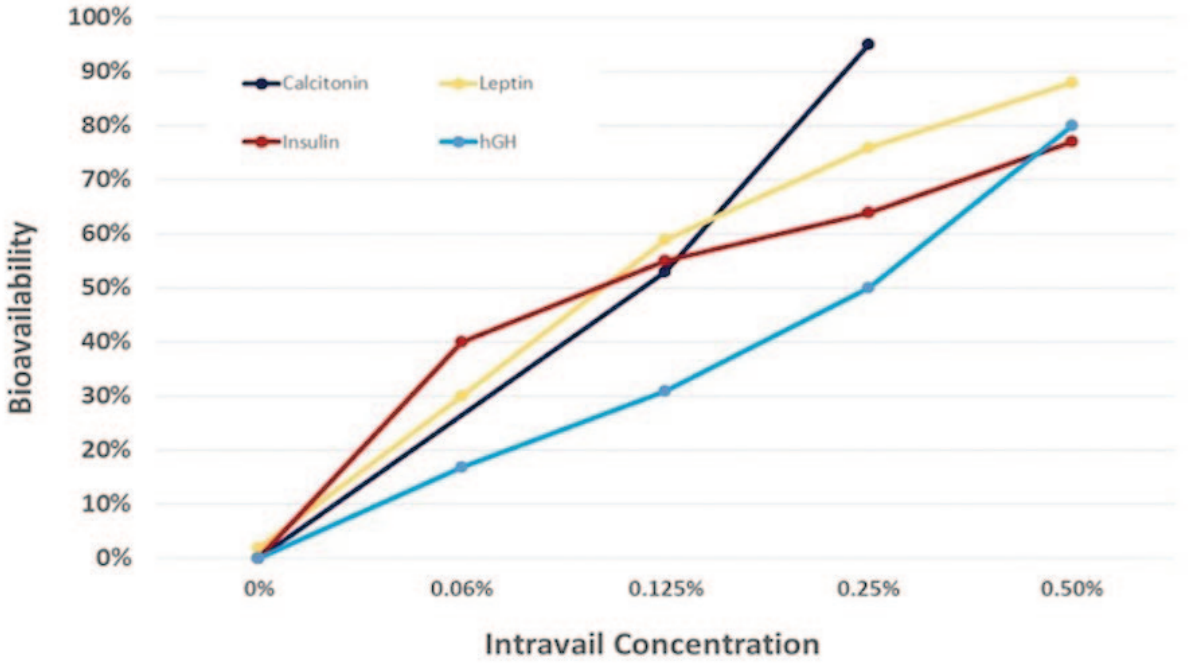
Studies have been done that look at

FIGURE 2



Reversibility of Intravail Action on Nasal Epithelia

FIGURE 3



Large Molecule Bioavailability With Intravail Observed in Calcitonin, Leptin, Insulin, and Hgh

changes in trans-epithelial electrical resistance (TEER).[10] In this type of study, human tracheal and broncoepithelial cells are grown to confluence in a microtiter well in a system that has been used as an in vitro screening model for nasal adsorption enhancement.[11,12] Tight junctions prevent ion flow when an electrical potential is applied thus reduction in TEER is a measure of tight junction opening. These experiments demonstrated Intravail A3 provided a significant reduction in TEER, which is indicative of loosening of tight junctions.

The transient effect of Intravail has been demonstrated in a PK study in rats administered calcitonin and somatotropin nasally under three sets of conditions.[13,14] Figure 2 summarizes the results. The uppermost curve for both proteins shows the pharmacokinetic profile when Intravail and drug are mixed and presented together (0 minutes). The next line shows the pharmacokinetic profile when Intravail is separately administered intranasally, followed 60 minutes later by a drug. Similarly, the lower line shows the pharmacokinetic profile when Intravail precedes drug administration by 120 minutes.

For the smaller molecule, calcitonin at 4 kDa, shown in the left panel, substantial absorption still takes place when the drug is administered 60 minutes after exposure to Intravail although the mucocilliary clearance half-time is approximately 15 minutes. Even 2 hours after Intravail administration, a small but significant amount of calcitonin is still able to enter systemic circulation, indicating the tight junctions are still partially open.

For the larger protein, somatotropin at 22 kDa, shown in the right panel, absorption takes place when the drug is administered in the presence of Intravail (0 minutes), but the tight junctions are already sufficiently closed at 60 minutes and 120 minutes to prevent essentially all passage of the protein. These results illustrate two important features of Intravail. First, the opening of tight junctions is a transient reversible phenomenon. Second, the excipient functions by acting on the mucosal membrane, not through direct interaction with these drugs, for example, by forming by drug-containing micellar inclusions, because the Intravail and drug can be administered separately physically and temporally.

Examples

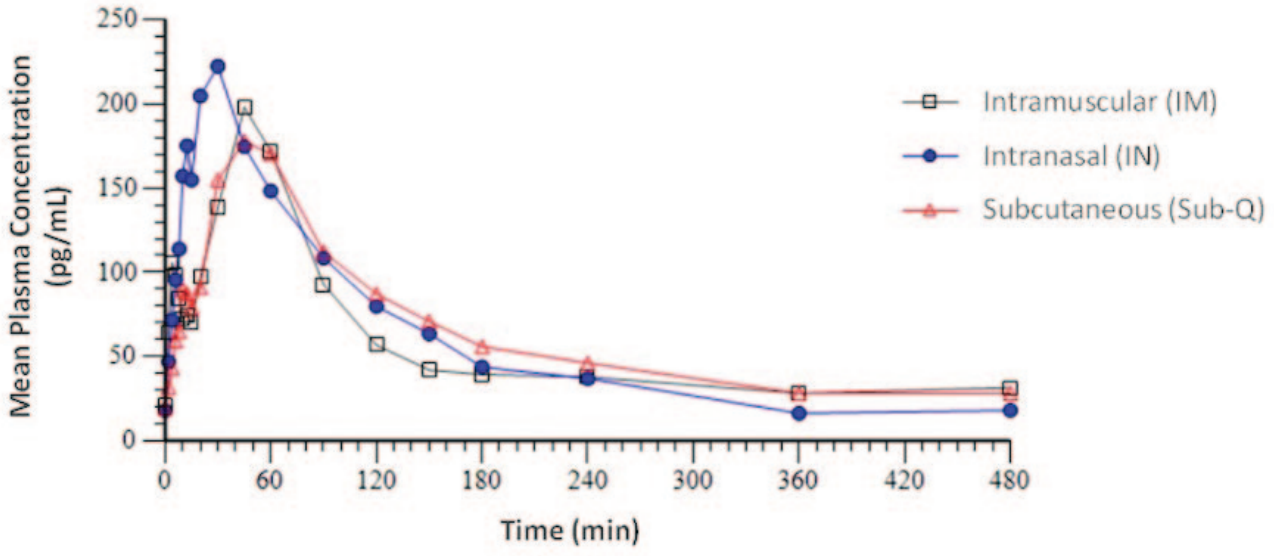
Figure 3 shows the relationship between Intravail concentration and bioavailability for a range of compounds of varying molecular weights: calcitonin (~3.4kDa), Insulin (~5.8kDa), Leptin (~16kDa), and human growth hormone, hGH (~22kDa) have been shown to increase bioavailability compared to intramuscular and subcutaneous injections. There is a significant improvement in bioavailability over the Intravail concentration range studied.

Figure 4 shows the plasma concentra-

tion-time profiles of a 1-mg intranasal dose of Neffy™ (an investigational formulation of epinephrine with Intravail) and 0.3-mg intramuscular (EpiPen®) and subcutaneous (Auvi-Q) injections of epinephrine. The data showed the intranasal spray absorption reaching 100 pg/mL within 9 minutes compared to 20 minutes for intramuscular and subcutaneous injections. Similarly, the maximum concentration (C_{max}), was achieved in 20 minutes with the intranasal dose compared to 45 minutes for intramuscular and subcutaneous injections.

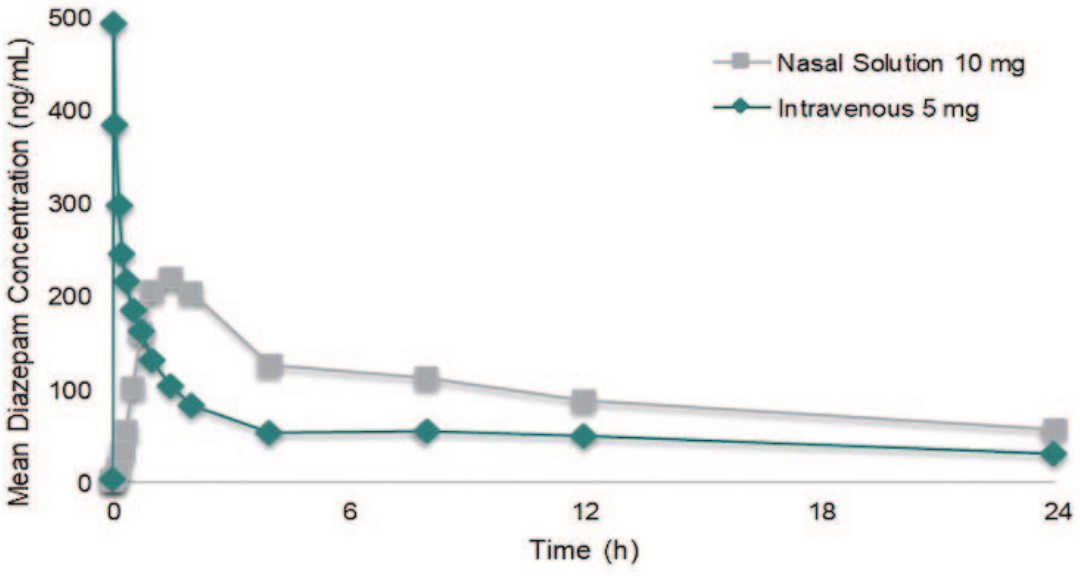
Figure 5 shows the plasma concentration-time profiles of a 10-mg intranasal dose Valtoco® (diazepam formulated with Intravail) and 5-mg intravenous injection of diazepam. The data showed the intranasal spray absorption, determined by the area under the curve (AUC), is comparable to the AUC for the injection and the absolute bioavailability of the intranasal spray is 97%.

FIGURE 4



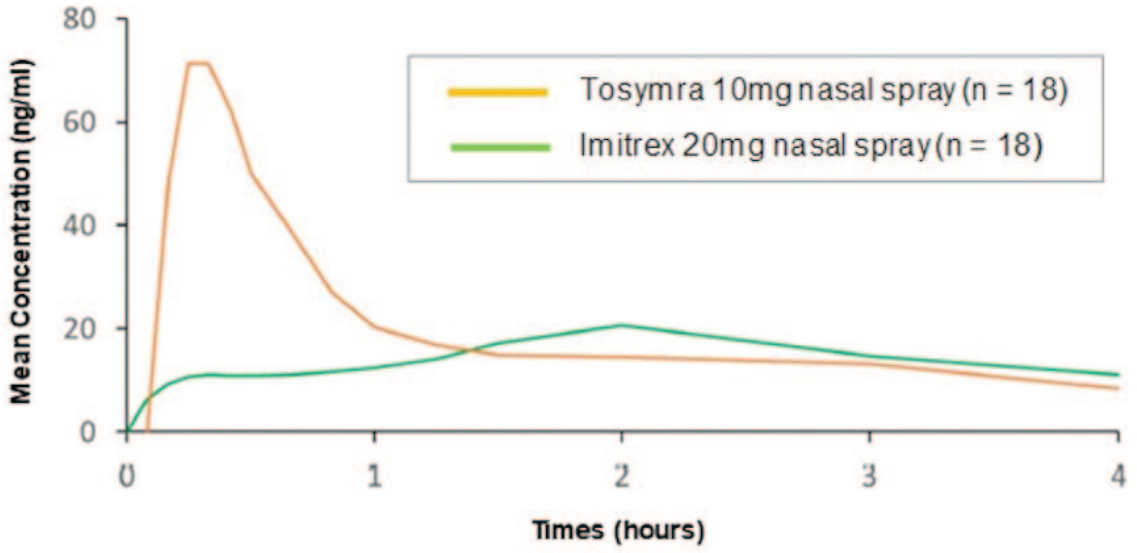
Neffy's Accelerated Absorption Relative to EpiPen & Auvi-Q

FIGURE 5



VALTOCO®: Plasma Concentration-Time Profiles of Diazepam

FIGURE 6



TOSYMRA®: Plasma Concentration-Time Profiles of Sumatriptan Versus Nasal Imitrex

Figure 6 shows the plasma concentration-time profiles of a 10-mg intranasal dose of Tosymra® (sumatriptan formulated with Intravail) and 20-mg intranasal dose of Imitrex (sumatriptan without Intravail). The data showed that Tosymra has a relative bioavailability of 200%, determined by the area under the curve (AUC), and Tmax is reduced from 120 minutes to 15 minutes. In addition, in a clinical study, Tosymra demonstrated 87% bioavailability to 4-mg subcutaneous injection of sumatriptan (data not shown).

As a further illustration of the broad applications of the Intravail technology, Neurelis has granted a license to DIODEM Therapeutics, a recently formed start-up company, for oral and nasal administration of a novel small peptide drug candidate developed at Albany Medical College in Albany, NY. This peptide addresses the major metabolic and neurologic dysfunctions associated with Down syndrome: weight gain, diabetes, peripheral and central insulin resistance, and Alzheimer's Disease-like disruption of cognitive function.

SUMMARY

The formulation of drugs to improve suboptimal pharmacokinetics or pharmacodynamics has been an ongoing challenge in pharmaceutical development. With the growing interest in nasal delivery for its inherent advantages over other routes of administration, improvements in rate and extent of absorption are critical components for this route of delivery. Equally fruitful and more challenging reformulation opportunities exist in the case of certain peptide and protein drugs. Intravail can be used to meet these challenges across a broad range of molecules in terms of molecular weight and lipophilicity.

The nasal route is an effective administration option for both local and systemic drugs, and significant advantages can come from delivering drugs through the nose. It is a relatively noninvasive approach with simple administration that offers the potential for patient self-medication. In addition to systemic and local access to the nose and sinuses, this can be a route of delivery for multiple target sites, including direct delivery of therapeutics to the brain bypassing the BBB. The anatomy of the nose presents unique challenges for drug delivery however, including dose-volume constraints, drug delivery and potential irritation concerns, and limited residence time requiring rapid and efficient absorption. The use of permeation enhancers offers an attractive option for improving absorption. ◆

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BIOGRAPHY

Dr. Stuart Madden is Chief Scientific Officer at Neurelis and has more than 30 years of experience in the pharmaceutical industry working on drug development programs, from proof of concept through to commercialization for New Chemical Entity (NCE) and 505(b)(2) products that have encompassed small molecules, biologics, and combination products. He has worked with Neurelis since 2008, supporting the development of VALTOCO®. Dr. Madden has previous experience in roles providing strategic consulting expertise to biotech and pharmaceutical clients, and in the development and commercialization of controlled-release oral dosage forms. He earned his BS in Chemistry and his PhD in Physical Chemistry from the University of Wales, Swansea, UK, and spent 2 years as a post-doctoral fellow at San Diego State University, CA. He is a Chartered Chemist and Fellow of the Royal Society of Chemistry and a past special government employee for the FDA's Advisory Committee for Pharmaceutical Science and Clinical Pharmacology.

FORMULATION DEVELOPMENT

Impact of Excipients & Manufacturing Process on Ritonavir Tablet Size & Weight Reduction

By: Gayatri Khanvilkar, MPharm, Ajit Bhagat, and Tejas Gunjikar, PhD

INTRODUCTION

Drug formulators and pharmaceutical manufacturers continue to experience and navigate low aqueous solubility challenges. With the human body made up of approximately 65% water, oral drugs must have certain water-solubility levels to fully dissolve into the bloodstream.[1] At the same time, low aqueous solubility limits new drugs' oral bioavailability and commercial viability significantly. In fact, studies suggest that 40% of drugs fail to reach pharmacy shelves due to this very issue.[2] Furthermore, drugs equipped with poor water solubility traits can present negative clinical effects and increased risks for patients.

Poor solubility typically results from stable crystalline forms that cannot fully absorb into fluids. Chemical and physical drug modification methods are evolving to optimize drug solubility and dissolution. For example, amorphous solid dispersions (ASDs) are a favored technique to increase solubility and bioavailability. ASDs can be used in a polymeric carrier to stabilize the active pharmaceutical ingredient (API) and bolster its solubility. This combination actively protects APIs against precipitation or re-crystallization upon contact with intestinal fluids.

As drug manufacturers battle with low solubility challenges, research has found that specific excipients – such as disintegrants and bulking agents – notably improve the biopharmaceutical performance of dosage forms. In this study, IFF researchers investigate bulking agents and disintegrants to develop efficacious Rotonavir tablets with improved *in vitro* release.

PROCESS OF PRODUCTION

Formulators are exploring and discovering new production processes for drugs with low solubility. Hot melt extrusion (HME) is a leading technology to produce ASDs. HME is a relatively straightforward, solvent-free process that transforms a powder blend of crystalline APIs and polymers into an extrudate for optimal solubilization. HME works by disrupting the crystal lattice of the API to promote its transition into an amorphous form. This unique, continuous manufacturing process is well-known for producing polymer products with a consistent shape and density. The API's amorphous properties allow for successful incorporation into the polymeric carrier for a homogenous dispersion. Homogenous dispersion refers to the finely dispersed API particles or solid API solution in a polymer, resulting from HME's thermal and mechanical energy.[3]

HME is commercially successful; however, the number of acceptable polymers suitable for the process is limited.[4] Hydroxypropyl methylcellulose (HPMC) is a favored water-soluble polymer for solid dispersion formation. HPMCs can help prevent API crystallization and maintain stable solid dispersions, promoting effective drug disintegration.[5-7]

Solid dispersions is a key technology for developing solid oral dosage forms containing APIs with bioavailability challenges. As such, researchers used a proprietary polymer tailored to address API's solubilization performance requirements. AFFINISOL™ HPMC HME 15 LV – an excipient specially designed for HME – can generate highly soluble ASDs from poorly soluble

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compounds within a broad processing window. Compared to marketed HPMCs, this excipient has a significantly lower glass transition temperature and melt viscosity, making it ideal for thermal processability.[8-10]

HPMCs act as binders in conventional tablets; however, they also promote gelling polymer network (GPN) formation. The GPN initiates a slower API release, hindering rapid tablet disintegration. Additional disintegrants or bulking agents may be required to maintain tablet performance.[10-12]

EXCIPIENTS & TABLET MASS FOR SOLUBILITY ENHANCEMENT

While solubility enhancement is critical, it is not enough to generate an efficacious drug product. Optimal downstream processing and tablet mass are essential considerations. Tablet mass plays a major role in the compressibility, hardness, friability, disintegration time, and release of the API. If overlooked, these elements can limit solubility-enhanced actives from converting into a tablet dosage form.

A polymer's content can range from 50%-90% of the ASD, directly influencing tablet weight and size.[10-12] Irrespective of ASD bulking agents and disintegrants play a dominant role in tableting and disintegration when evaluated *in vitro* or *in vivo*.

Tablet mass can determine esophageal transit ease and timing, regardless of patient factors or administration technique (patient position, use of fluids, etc). In this respect, smaller tablets have generally displayed faster transit times among patients.

Researchers attempted to formulate a smaller Ritonavir tablet with improved bioavailability through HME. The effects of formulating with different bulking agents and disintegrant concentrations were investigated.

Ritonavir is a poorly soluble drug used for HIV-infection treatment.[13] Previous studies have confirmed that when Ritonavir is formulated into an ASD, the drug's solubility and commercial viability can significantly improve. However, Ritonavir exhibits thermal instability above its melt temperature, which presents challenges for the HME process.

To promote process temperature reduction, additional excipients may be required to ensure stability of each component through HME. With that said, drug manufacturers should be cautious as additives can create undesired formulation complexity. Close collaboration with a reliable supplier partner – equipped with formulation and process expertise – is recommended.

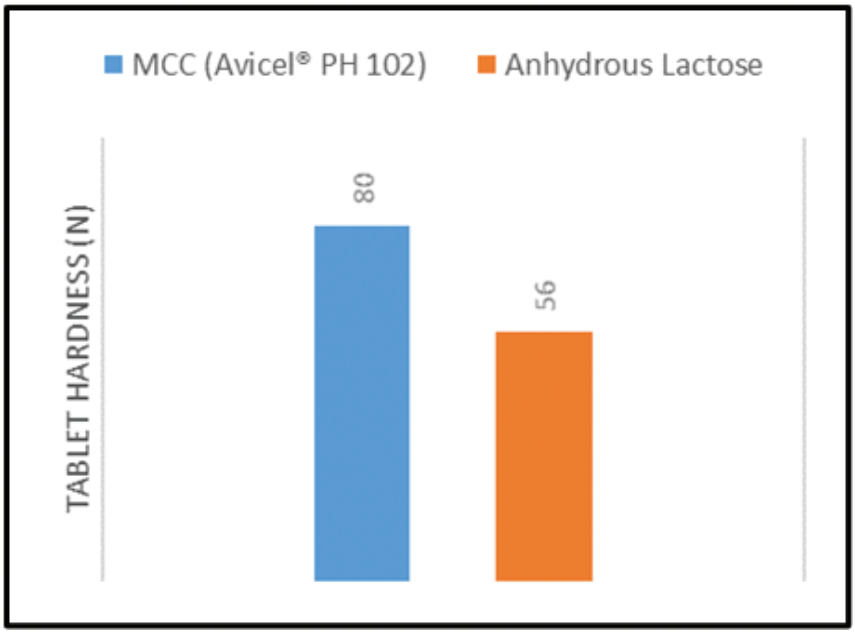
METHODOLOGY

Researchers used a mixture with a 1:2 ratio of Ritonavir and HPMC, based on previous screening trials. The API and polymer were blended for 10 minutes. The blend was then passed through a 30# mesh sieve and fed through a Thermo Fisher Pharma 11 twin-screw extruder at 120°C to obtain extrudates.

The extrudates were cut into pellets (1-2 mm) using a Varicut Pelletizer, and further milled using a Retsch Ultra-Centrifugal Mill ZM 200 to achieve extrudates with a particle size of < 250 µm. The milled extrudates were blended with various bulking agents (Avicel® PH 102 or Directly Compressible Anhydrous Lactose) and tablet disintegrants (Ac-Di-Sol® SD-711).

The various blends were then compressed on an 8 Station Kambert tablet compression machine (KMP-D-8) using standard concave 12-mm round punches. Upon the tablets' completion, they were evaluated for hardness, disintegration time, and *in vitro* drug release.

FIGURE 1



Tablet Hardness

RESULTS & DISCUSSION

Applied compression force can significantly influence tablet hardness and disintegration timing. While a stronger compression force increases the chance of a GPN forming, a compression force that is too low results in physically weak tablets with increased friability, which can be a major limiting factor for manufacturers.[11,12]

The application of correct excipients can help optimize tablet properties eg. tablet weight and drug release. Bulking agents or fillers are utilized as spacers among ASD particles to prevent a GPN from forming. For example, microcrystalline cellulose (MCC), an insoluble filler, is widely used in DC.

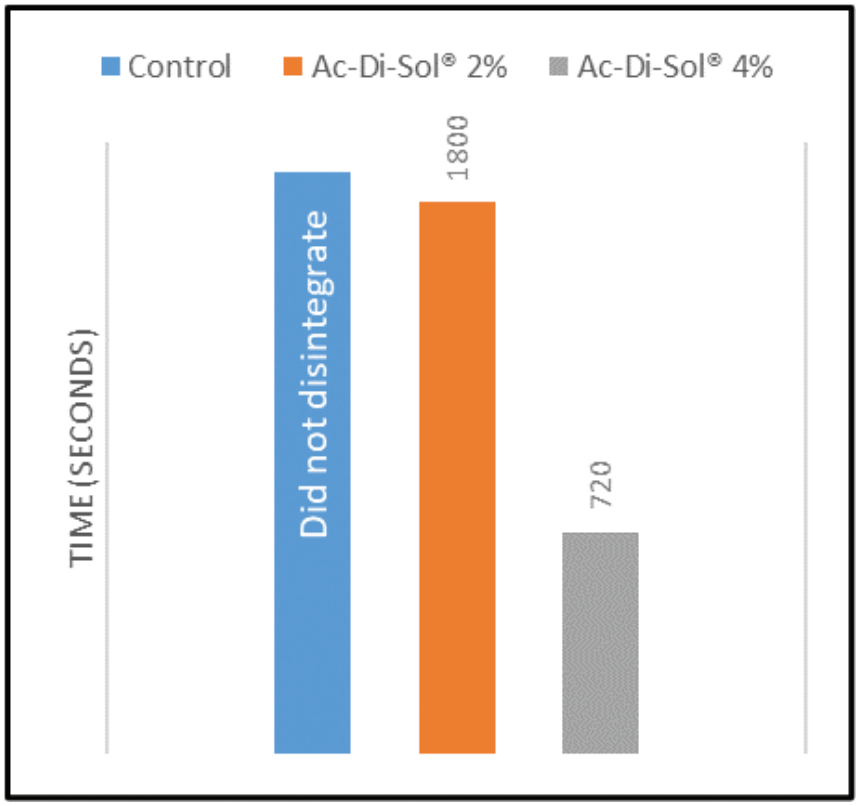
MCC can increase tablet strength and decrease porosity after atmospheric moisture exposure. Avicel® PH 102 – a purified, partially depolymerized alphacellulose excipient – is obtained by the acid hydrolysis of specialty wood pulp. This MCC is most often used in tableting as a compression aid, flow aid, and filler for directly compressed tablets.

Researchers developed round-shaped Ritonavir tablets with 12-mm diameters and thickness varying from 5.6 mm to 6 mm, based on composition and weight. The performance of MCC and Anhydrous Lactose (AL) was then evaluated as water-insoluble and water-soluble fillers, respectively.

The drug release from tablets formulated with bulking agents – MCC or AL – was not complete as the tablets disintegrated after 20 minutes. The tablets' initial water uptake indicated immediate GPN formation. GPNs can hinder rapid tablet disintegration; therefore, additional disintegrants were needed to achieve a faster disintegration time.[13,14]

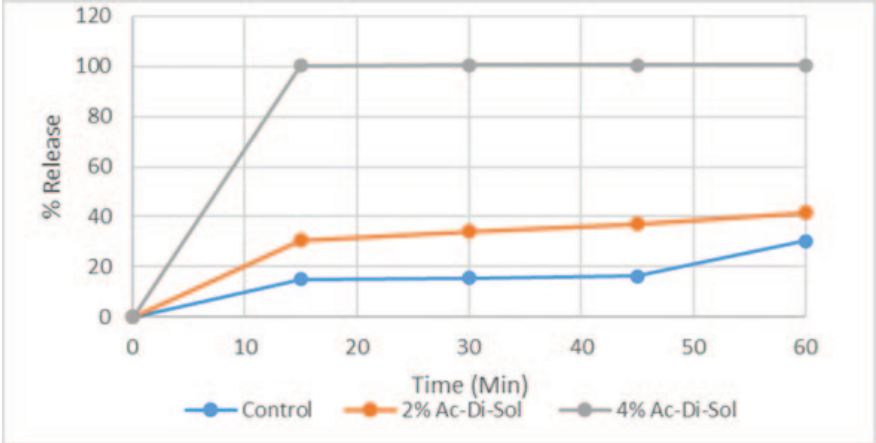
In the case of AL, atmospheric water was absorbed by the hygroscopic amorphous lactose fraction. There was an initial increase in tablet hardness, but water content negatively impacted AL's glass transition temperature (Tg). At a critical value, AL's Tg dropped below ambient temperature. When this transaction occurs, the amorphous material morphs into a crystalline state. Crystallization occurring at the surface of AL promotes GPN formation, which further hinders tablet disintegration.

FIGURE 2



Effect of Ac-Di-Sol® SD-711 concentration on tablet disintegration time.

FIGURE 3



Effect of Ac-Di-Sol® SD-711 concentration on in vitro drug release.

MCC can undergo plastic deformation at a relatively low yield pressure, which helps prepare dense compacts at low compression forces.[15,16] By incorporating this filler, researchers saw a significant increase in tablet hardness, compared to those formulated with AL.

As observed in Figure 1, MCC yielded stronger tablets. This formulation was further evaluated to study the effects of varying disintegrant concentrations (Ac-Di-Sol® SD-711 from 2%-4% w/w).

Researchers also observed the impact of Ac-Di-Sol® – an internally cross-linked sodium carboxymethyl cellulose (NaCMC) that aids in tablet disintegration and dissolution – on tablet disintegration time.

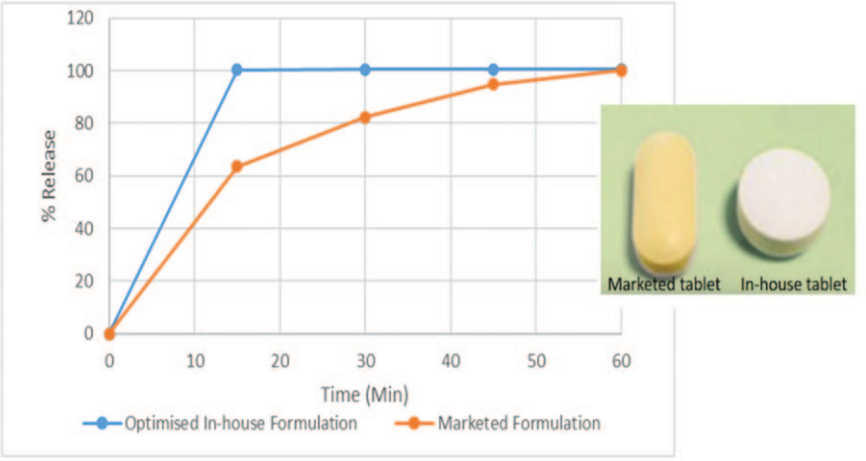
Results showed that increasing the concentration of NaCMC enhanced tablet disintegration time. Therefore, the rate and extent of liquid uptake and water penetration into the tablets was improved. Disintegrant particles in such powder mixtures likely make up a continuous network or skeleton, which helps facilitate plastic deformation and disintegration processes.[16,17]

NaCMC has consistent disintegrative functionality due to its efficient water uptake and rapid swelling properties. Exposure to water causes this excipient to swell and exert pressure against surrounding tablet ingredients. The increased swelling prompts existing bonds between particles to break. The tablet's quick disintegration time exposes drug particles to the dissolution medium, resulting in rapid drug release.[16,17]

The formulation with 4% NaCMC showed a faster and complete drug release, compared to the control and 2% NaCMC.

As a final test, researchers developed a round-shaped in-house formulation with MCC and 4% NaCMC. As shown in Figure 4, this tablet provided a complete drug release within 15 minutes. The tablet weighed 525 mg – 20% lower than the marketed formulation (675 mg).

FIGURE 4



Drug release profile from in-house formulation versus marketed formulation.

The smaller, round-shaped in-house tablet exhibited a faster disintegration rate compared to the marketed formulation. The results showed that tablets with 20% lower weight than typical marketed formulations deliver a superior *in vitro* dissolution performance.

These results present ample opportunities for drug manufacturers seeking to overcome low solubility challenges. Based on the in-house tablet's release profile, excipients can heavily influence tablet mass for drug bioavailability, solubility, and patient compliance.

CONCLUSION

Formulation and process designs are both critical to consider when manufacturing efficacious tablets. By utilizing bulking agents and tablet disintegrants, researchers successfully developed a Ritonavir ASD tablet through HME with optimal physical and drug-release properties.

Excipients can significantly impact the bioavailability of dosage forms. The research team's combination of a bulking agent and disintegrant (MCC and NaCMC) helped improve tablet strength and disintegration timing. These results suggest a bright future for the manufacturing and processing of previously unviable APIs. With the appropriate formulation methods, physical properties and excipients, improved drug performance, and commercial viability may be achieved.

While study results are promising, developers should remain cautious when looking to incorporate excipients for increased drug bioavailability. Regulatory standards and risk assessment protocols for new delivery methods continue to evolve. Close collaboration between drug manufacturers and reliable suppliers is recommended to not only improve formulations, design, and cost, but further propel the commercial availability of new, innovative pharmaceutical products. ◆

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BIOGRAPHIES

Gayatri Khanvilkar, as a Application and Innovation Specialist at IFF Pharma Solutions, has focused her career at the intersection of pharmaceutics, Good Laboratory Practice, JMP, R&D, and regulatory affairs. She earned her Master's degree in Pharmacy with a focus in Pharmacology and her Bachelor's degree in Pharmacy from Mumbai University.

Ajit Bhagat is a Senior Technologist at IFF Pharma Solutions, based in Hyderabad, India. He earned his Bachelor's degree from Mumbai University and is well-trained in equipment operations and experimental design for formulation development.

Dr. Tejas Gunjikar is the pharma application and innovation leader at IFF Pharma Solutions, focused on oral fast-dissolving technologies, biopharmaceutical formulations, solid oral dosage forms, and more. He earned his PhD in Pharmaceutics from University of Mumbai, and his Bachelor's degree in Pharmacy from Savitribai Phule Pune University.

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Excipient vs Strength	375 mg telaprevir
HYPROMELLOSE ACETATE SUCCINATE 12070923 (3 MM2/S) **(Core/Content)**	375 mg
SODIUM LAURYL SULPHATE (Core/Content)	7.58 mg
DIBASIC CALCIUM PHOSPHATE ANHYDROUS **(Core/Content)**	75.76 mg
CROSCARMELLOSE SODIUM **(Core/Content)**	30.3 mg
MICROCRYSTALLINE CELLULOSE **(Core/Content)**	75.76 mg
SODIUM STEARYL FUMARATE **(Core/Content)**	29.29 mg
COLLOIDAL SILICON DIOXIDE **(Core/Content)**	7.58 mg
POLYVINYL ALCOHOL, UNSPECIFIED **(Tablet/Capsule coat)**	11.72 mg
POLYETHYLENE GLYCOL **(Tablet/Capsule coat)**	5.92 mg
TALC **(Tablet/Capsule coat)**	4.33 mg
FERRIC OXIDE YELLOW **(Tablet/Capsule coat)**	0.32 mg
TITANIUM DIOXIDE **(Tablet/Capsule coat)**	7 mg
FD&C RED NO. 40 **(Tablet/Capsule coat)**	
FD&C BLUE NO. 2 **(Tablet/Capsule coat)**	

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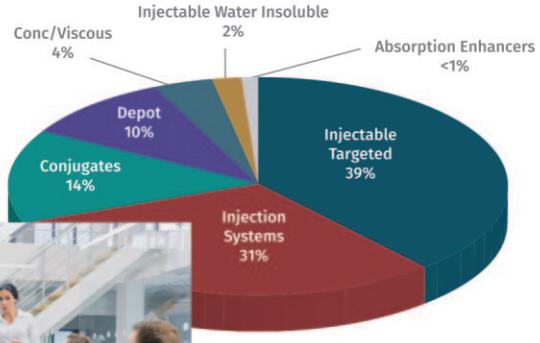


Injectable Drug Delivery Technologies

Screen Potential Partnering and Investment Opportunities

Select Companies

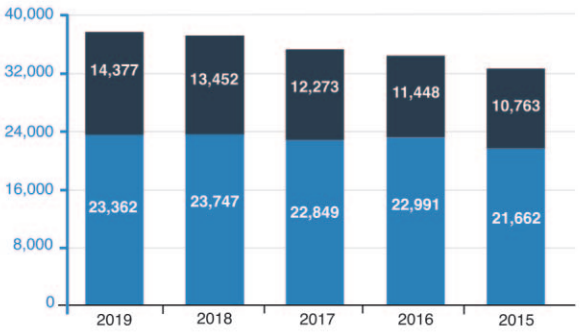
Amgen Inc. x

Biogen, Inc. x

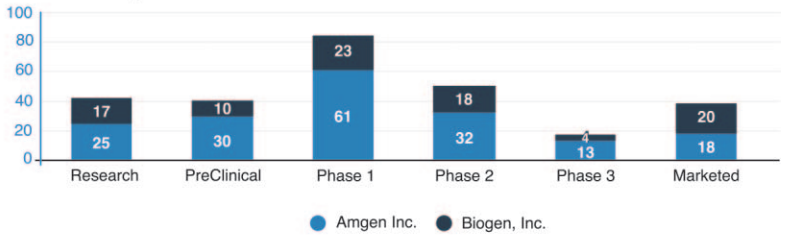
Attribute Type

- Gross Profit
- Net Income
- Number of Employees
- Operating Income
- Research and Development Expenses
- Sales, General and Admin. Expenses
- Total Assets
- Total Current Assets
- Total Current Liabilities
- Total Equity
- Total Liabilities
- Total Revenue

Annual Data



Product & Pipeline Count



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CDMO INNOVATION

How a Global CDMO Puts Innovation at the Forefront of its Business Strategy

By: Kai Vogt,
Senior Vice President
Corporate Development/Legal/Corporate Compliance/IT, Vetter

INTRODUCTION

By its very nature, the healthcare industry is subject to continuous change. The need to adapt to customer and patient requirements, ever-more complex and sensitive drug substances, and steadily increasing regulatory requirements in the pharmaceutical environment poses numerous challenges. And, while the dominance of the blockbuster drugs is no longer the status quo, COVID-19 and its variants have also demanded significant time and energy from pharmaceutical/biotech companies. To keep pace with future challenges in this rapidly changing market, innovation is essential.

In the pharma/biotech market the term "innovation" refers to developments that open up new markets, processes and/or technologies. It also means pioneering ways of putting existing technologies to the test, rethinking, and utilizing them to the best of their advantage. Innovation begins with an idea or an invention, which is then subject to research, creativity, discipline, and consistent ongoing development before being market ready.

At Vetter, a leading Contract Development and Manufacturing Organization (CDMO), progress has always been an element of its identity. As a family business, we drive innovation, so that we can continue playing a leading role in the global markets and improve the quality of life for patients worldwide. We also recog-

Innovation begins with an idea or an invention.

nize that an innovative corporate culture forms the basis for motivated and committed employees.

THE FUTURE IS NOW

As part of a wide-ranging digitization strategy, our focus areas include projects in the areas of production, quality, and industry 4.0. Innovative technologies, such as the Internet of Things (IoT), augmented reality (AR), and autonomous, cooperative robots, are firmly anchored in the company's strategy. Digitization always plays a role where it clearly and comprehensibly leads to quality or process improvements.

The factory processes of the future also have high priority. Artificial intelligence methods are key to tomorrow's smart factory with topics such as predictive maintenance, data analysis, or intelligent worker-assistance systems. In addition, robotic process automation is planned to be used for suitable processes in the future. Recurring, clearly definable, or time-intensive activities can be carried out by digital software robots.

EFFICIENCY INCREASES & AUTOMATION

Our continuous, company-wide pursuit of excellence in production, aptly named Production Excellence (Prodex), leads to sustainable results. By creating an internal team of experts, "solutions from production for production" are designed and implemented with internal resources. This enables a holistic approach for all production sites as well as for cooperation with other departments. Through ProdEx, we strive to meet high flexibility and efficiency in production while exceeding the increased quality requirements of customers and regulatory authorities.

Recurring, clearly definable or time-intensive activities can be carried out by digital software robots.

Quite a few of the systems we are using were developed completely in-house. In this manner, our company is building up internal competencies that will become increasingly important in the future. The holistic cleanroom concept V-CRT® (Vetter Cleanroom Technology) is based on the idea of a fully automated decontamination of the entire cleanroom. Our company was awarded the Fraunhofer CLEAN! award for this in-house-developed system which honors groundbreaking developments in cleanroom technology.

Collaborative work with so-called YuMi® robots (short for you and me) is already taking place within our company. After a successful pilot phase with the two-arm robot in secondary packaging, we have now increased the use of this technology. The close cooperation between man and machine makes it possible to design manufacturing processes more flexibly and thus be able to respond even better to customer requirements.

PARTNERSHIP AS A SUCCESS FACTOR

Developments in the pharmaceutical world are multifaceted. As a future-oriented service provider, we continuously monitor market trends and customer requirements. To achieve a new industry standard for small batch production, our company has partnered with Syntegon Technology to develop a fully automated, highly flexible production cell that sets new standards in the fill/finish industry. For this successful partnership, the industry association Parenteral Drug Association (PDA) awarded both companies with the Drug Delivery Innovation Award 2021 – Partnership Category.

Partnerships can be an important basis for innovative strength and future-oriented processes. The strategic alliance with Rentschler Biopharma SE, initiated in 2020, is intended to create added value for customers and their patients through the active exchange of know-how and best-practice experience. Our two companies expand their service portfolio by providing complementary services and

With the ideas, visions, and passion, the 5,700 employees lay the foundation for successful innovations.

expertise along the value chain. This way, promising new therapies are intended to reach patients with severe and rare diseases even faster.

BUSINESS COURAGE

Innovations are advanced at all corporate levels, both across the business divisions as well as within the individual departments. A well interlocked and open organization focusing on resources and goals forms the foundation of an innovative company culture. Innovative strength goes hand-in-hand with reliable, efficient, and safe processes. A continuous, close dialogue with customers about product, service, and process requirements is also crucial.

In addition to a good organizational structure and close orientation toward the markets, it is important to have a feel for emerging trends among our staff members and throughout the company. Innovative action also requires business acumen because innovation requires investment in the idea as well as effort in its implementation. There is no doubt, however, that there is no alternative to this courage. As the development and manufacturing of medications becomes increasingly complex and competition more intense, future-oriented companies must work on innovative solutions to keep pace.

SUCCESS FACTOR STAFF MEMBER

Innovation is diverse. Therefore, we have in place a variety of methods in order to promote innovation. One of them is managing innovation processes. This is realized in many of our business areas dealing with trends, new developments, or technology ideas in terms of filling processes as well as injection systems and packaging solutions. In addition, all staff members can submit ideas via an internal platform that are then reviewed by a multiprofessional committee of experts. If proposals are successfully implemented, the innovators receive a bonus.

In addition to cooperation and intensive exchange across all levels, willingness to innovate is of fundamental importance. The decisive factor is to be passionate about what you do, finding the topics exciting and meaningful. The focus is always on people – on the patients whose quality of life we improve with the drugs we produce and on all the staff members who have shaped and developed the company for more than 70 years. Today, there are around 5,700 of them on three continents. With their ideas, visions, and passion, they lay the foundation for successful innovations.

Developing and producing drugs for our international customers and ultimately for patients around the globe is our world, but it is innovation that keeps it going and continues to move us forward. ◆

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DATA STRATEGIES

As We Shift Toward Biologics, We Also Need to Shift Toward Smarter Data Management

By: Christian Marcazzo

INTRODUCTION

Despite the curveball the pandemic threw us, 2020 was a year for the books in the way of FDA approvals — 53 new medicines were approved, second only to the all-time high of 59 in 2018.[1] Throughout the past few years, there's been a clear trend in the makeup of approvals, with biologics representing a growing percentage.[2] But even within biologics, newer technologies like mRNA, cell, and gene therapies are gaining ground. The approvals are not one-off events, but evidence of an exciting long-term trend — these technologies will have massive impacts on human health throughout the next decades, and we should expect to see innovative biologics accounting for more and more of the drug landscape in the coming years.

The trend is also reflected in many of the individual portfolios of biopharmaceutical organizations: biologics may make up 50% to 60% of a company's new products. Among the top 20 pharmaceutical companies, almost all are making monoclonal antibodies. For cell and gene therapies, at least two dozen companies are now well established in the area, and more small companies are moving in that direction. And whereas about 12 companies were researching mRNA therapies before the pandemic, this number has now increased significantly.

These trends should make it clear to organizations that we're at an inflection point — this is truly the century of biology, and biology is much richer and more varied than it was just years ago. Investors have certainly pricked their ears and are putting more money into the area.

We should therefore expect to see increased competition between the players who are developing these therapies. Biologics have quickly become billion-dollar revenue streams that need to be moved out of R&D and into the market and patients. Speed is important, not just for patients, but also for the organization — the first monoclonal antibody to serve unmet need X has a much greater competitive advantage over the second monoclonal antibody to do so. It's clear that companies large and small need to start building capacity for the future and prepare to get new therapies faster to market.

A key consideration in this competition is that lifecycle development is much more complicated for biologics than for small molecule drugs. Whereas the chemical compound itself is what's patented in small molecules, for a biologic, much of the IP is in the know-how associated with the process to produce a biologic. "The process is the product" is a phrase often used in the industry, meaning the value has shifted from the therapy to the process that can repeatedly produce that therapy safely and at scale. This highlights the importance of data and a company's ability to capture it across the entire development lifecycle.

To support biologics development and speed it along, a new strategy to collect, manage, store, and draw insight from data is required: a biopharmaceutical lifecycle management (BPLM) system.[3] This type of system captures data at the point of execution across the entire development lifecycle and creates a contextualized data backbone, which deepens the insights that are drawn from the data and makes them easier to interpret. This is a fundamentally different way of thinking about data, and one that involves bringing tech transfer into the equation right from the beginning.

Unfortunately, a startling number of organizations still rely on antiquated methods of data collection. In a recent survey, 50% of participants were using legacy applications such as electronic lab notebooks (ELN) to record process development work; the other 50% were using a mix of paper and Excel spreadsheets and standalone instrument software.[4] In addition, 62% of participants reported spending at least 5 hours a week on data administration, and in some cases, more than 20 hours a week. Too often, there is an attempt to make one process or one lab more productive with an ELN or laboratory information management system (LIMS) — but sets of data still become siloed and difficult to integrate.

In contrast, collecting data across the entire development lifecycle has several advantages: one is that collection occurs not only from beginning to end, but also across researchers and departments. Having data all gathered and available in one place is ex-

tremely helpful, particularly as early data are important later on, as in regulatory filing. Additionally, a serious problem in R&D is data that are lost due to the use of disparate systems. With BPLM, the rework needed to replace lost data is greatly reduced, which saves an organization both time and money, particularly in biologics, where development and scaling are inherently more complex. Saving time is incredibly important in this field because delays put IP exclusivity at risk.

While these benefits are clear, BPLM can also help set the stage for even more exciting ventures like the generation of digital twins. The ability to interlink variables at multiple time points and structure data allows an organization to develop increasingly complex algorithms, which in turn, can lead to the creation of full digital twins of instruments, assets, and processes. Biopharma is catching up to other industries that have been using digital twins for some time to create in silico representations that provide powerful predictive capabilities. In biopharma, we want to move increasingly toward a place where phases of drug development are predictive, which cuts down on time to market. The older, siloed methods of data collection are not conducive to movement in this direction and into biopharma 4.0.

The pandemic has accelerated trends already underway, and the digital divide was clear: digitally savvy companies hardly missed a beat, while those still using paper fell behind. There's been a rise in mid-size and small biotechs coming to market that are primed to grow and are looking for digital solutions that support the cutting edge; they often have the advantage of not being handcuffed by legacy systems that older companies are using. Big investments are going into mRNA and cell therapies, so it's especially beneficial for these organizations to think differently about their data. Each new generation of these therapies can move faster if learnings from the first ones are captured. This is the digital mindset that must be adopted — thinking about software and data as central, in a way that older companies may still be trying to retrofit.

Finally, CMOs and CDMOs are also transforming fast — from service organizations to major drivers of innovation and process development. They're becoming more strategic in how they serve customers and how they can help accelerate the critical business milestones like regulatory filing and tech transfer that are so crucial to their customers. The volume of the work they do and the nature of the IP they work on for their customers creates unique requirements for workflow support and data management.

It's time for organizations of any size and type to think differently about their data, and how to accrue it and structure it across time and different entities in the lab. The competition that comes with the move toward biologics will require companies to move faster. Lifecycle data management won't change the probability of success, but it will make a difference in whether you're first or second to market. Adopting a new kind of data strategy might be disruptive to the expectation of how biologics development is carried out — but it may also be transformational. ◆

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BIOGRAPHY

Christian Marcazzo is the General Manager of IDBS. He earned his BA in Molecular and Cell Biology from the University of California, Berkeley. He is based at the IDBS headquarters in Guildford, UK, and has spent 25 years at the interface of biology and software, leading organizations like Spotfire and LION bioscience through the genomics revolution and the digitization of R&D.

Drug Development
EXECUTIVE

Joseph F. Bristow, PhD

Chief Technology Officer

Kytosan USA

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A lift from nature

Kytosan USA, Inc.: Blazing a Trail in Chitosan Manufacturing in the United States

Kytosan USA, Inc., a subsidiary of AgraTech International Holding, Inc., is planning to construct a manufacturing facility in the Beaumont, TX, area to produce the biomaterial chitosan. Included in its plans is a medical-grade production facility intended to address the rising demand for chitosan in medical and pharmaceutical applications in the United States. Kytosan USA is currently engaged in a private securities offering to raise a minimum of $9 million up to a maximum of $14 million to fund the construction and operation of their facility. *Drug Development & Delivery* recently interviewed Dr. Joseph F. Bristow, Chief Technology Officer for Kytosan USA, to discuss chitosan and its impact on the pharmaceutical industry, as well as Kytosan USA's production plans.

Q: What is chitosan and how is it used in the medical and pharmaceutical industry?

A: Chitosan is a polysaccharide derived from chitin, a naturally occurring linear polymer of *N*-acetylglucosamine found in the exoskeletons of crustaceans and insects as well as the cell wall of fungi. Chitin is a linear polymer made up of *N*-acetylglucosamine monomers and is considered the second most abundant natural polymer, with cellulose being the most abundant. Chitosan is produced by extracting chitin from the source material and removing the acetyl group from the *N*-acetylglucosamine monomer to create *d*-glucosamine monomers. Typically, the deacetylation process does not convert every *N*-acetylglucosamine monomer, so chitosan is a linear random copolymer of *N*-acetylglucosamine and *d*-glucosamine. The degree of deacetylation characterizes the extent to which the chitin monomers have been deacetylated.

Chitosan is a cationic polymer due to the amine groups along the polymer chain. It is soluble in acidic solutions (pKa = 6.3) with 1% (v/v) acetic acid being the most common

solvent. Chitosan is biodegradable, biocompatible with humans (non-allergenic and non-toxic), and has antimicrobial properties. Through chemical or enzymatic modification of the amine groups or the hydroxyl groups along the polymer chain, chitosan's properties can be tailored to suit the needs of applications that unmodified chitosan would otherwise not satisfy.

Medical applications of chitosan include wound healing, burn treatment, resorbable sutures, and membranes. Chitosan has been used in tissue regeneration and as a component in a hydrogel tissue adhesive. Other applications take advantage of chitosan's polycationic nature as well as its antimicrobial properties.

In the pharmaceutical industry, chitosan is used in drug delivery systems, such as slow-release capsules, and as a carrier agent, particularly for cancer treatments. A significant amount of research is being done with chitosan and chitosan nanoparticles to achieve greater control in delivering drugs to target sites.

Q: What are Kytosan USA's plans for producing chitosan?

A: Kytosan USA plans to construct a chitosan manufacturing facility in the Beaumont, TX, area to produce industrial-grade chitosan from chitin imported from overseas. Using imported chitin will allow us to reduce the initial capital expense and minimize operating costs. Kytosan USA will target lower-value, higher-volume markets, such as water treatment, agriculture, and cosmetics/personal care products, to establish a solid financial base from which to grow the company.

Imported chitin may run into problems with international shipping, such as delays or disruptions that could interfere with our production schedule. Therefore, it is important to have another chitin source. Because there is potentially more than 100 million pounds of crustacean shell waste produced along the Gulf Coast from seafood processors, Kytosan USA has prepared a plan and compiled data for the collection and processing of that waste into chitosan. The ability to have both sources of chitin available will ensure stable production.

Kytosan USA will also be developing a medical-grade chitosan production facility to address the growing use of chitosan in medical and pharmaceutical applications. Because of the FDA rules and regulations governing medical and pharmaceutical materials, we believe producing medical-grade chitosan directly from crustacean shell waste is the best way to ensure compliance. There are two shrimp processors in the Beaumont-Port Arthur area, so a local source of shell waste is available. We anticipate it will take approximately 2 years to design and construct the medical-grade chitosan facility.

Q: Why is now a good time to begin?

A: The chitosan market, both globally and in the US, has been growing throughout the past several years. Marketing reports suggest the chitosan market in North America is projected to grow by as much as 24% over the next 5 years with a global Total Addressable Market of USD 28.93 billion by 2027. Yet less than 1% of the North American chitosan market is produced domestically. There is a clear opportunity for domestically producing chitosan for the US market, especially with the plethora of chitin-containing raw materials available.

The medical and pharmaceutical markets for chitosan are also projected to grow significantly, particularly with chitosan featured in numerous medical and pharmaceutical research projects. Market reports suggest the medical market for chitosan should grow by about 8% over the next 5 years. Kytosan USA could become a driver for the US medical market by providing a domestic source for medical-grade chitosan, and through collaboration with researchers developing new chitosan-based medical and pharmaceutical applications.

Q: Can you discuss the offering and what you expect to achieve with the funding?

A: Kytosan USA is engaged in a private securities offering to raise a minimum of $9 million up to a maximum of $14 million to fund our chitosan manufacturing project. These securities are being offered under an exemption provided by SEC Regulation D Rule 506(c). Only accredited investors who meet the SEC Regulation D 501 "accredited investor" accreditation standards and who provide suitable verification of accredited status may invest in this offering. Our investment portal (https://invest.kytosanusa.com) has more information about the offering.

Once the minimum amount is obtained, Kytosan USA will begin construction of the industrial-grade chitosan manufacturing facility. If the maximum amount is obtained, we will begin development of the medical-grade facility shortly after construction of the industrial-grade facility has begun. If we are not able to raise the maximum amount, Kytosan USA will reinvest profits from the industrial-grade facility toward the development of the medical-grade facility. ◆

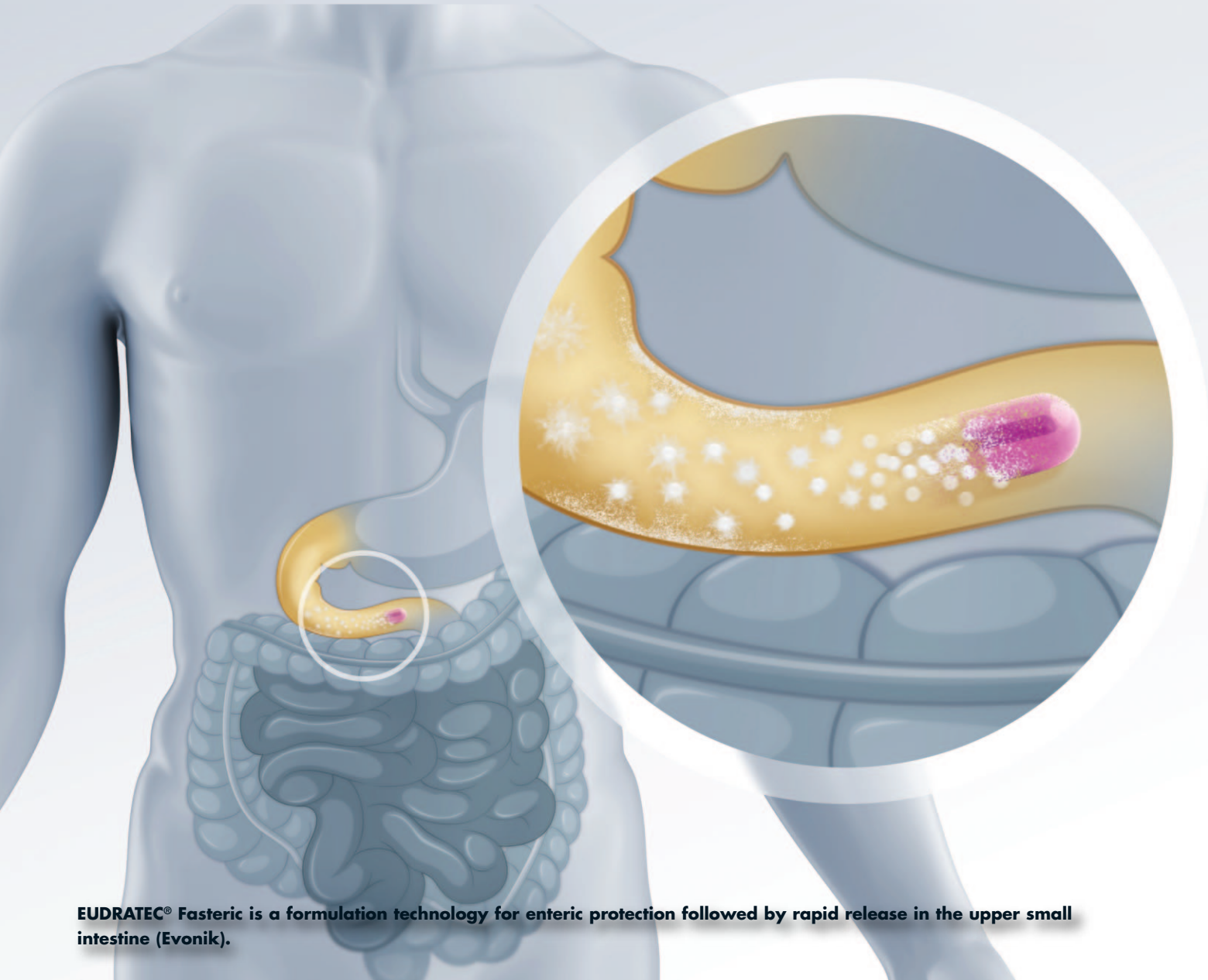
Special Feature

Solubility & Bioavailability: Familiarize Yourself with Enabling Technologies

By: Cindy H. Dubin, Contributor

"The biggest impediment in addressing bioavailability issues likely lies with a lack of deep familiarity with enabling technologies," says Dr. Masumi Dave, Application Laboratory Manager, Pharmaceutical Division, Gattefossé USA. "Improving drug bioavailability begins with a thorough evaluation of the API's physical and chemical properties in relation to solubilization in the dose, but more importantly its dissolution *in vivo* at the site of absorption."

These technologies, such as nanoparticles, cocrystals, computer-aided prodrug design, and electrospinning, represent innovations aimed at enhancing the solubility of a candidate molecule, particularly in the gastrointestinal tract. "Technologies such as electrospinning, deep eutectic solvents, and ionic liquids are upcoming formulation approaches



EUDRATEC® Fasteric is a formulation technology for enteric protection followed by rapid release in the upper small intestine (Evonik).

to enhance drug solubility, and as the science matures, and the relative strengths and weaknesses are better understood, we expect to see further application of these innovative approaches," says Nathan Bennette, Director, Scientific Advisory, Catalent. "They have shown to be successful for some compounds, and have a place alongside other bioavailability enhancement technologies, where each strategy has its benefits and corresponding liabilities. For them to be successful and widely adopted however, they will also have to provide a compelling benefit compared with other well-understood, and commercially precedented technologies, such as amorphous solid dispersions and lipid-based formulations."

In fact, according to Dr. Jessica Mueller-Albers, Strategic Marketing Director Oral Drug Delivery Solutions, Evonik Health Care, extreme compounds require either significant amounts of stabilizers to maintain the amorphous state or they are not amenable to common manufacturing technologies with reasonable cost of goods due to their low solubility in organic solvents. These include amorphous solid dispersions using polymethacrylate, cellulose, or povidone-based polymeric carriers, she says. In addition, thermostability of new molecular entities becomes an issue as most new molecules have melting points well above 400°F. Alternative production methods for amorphous solid dispersions can address these issues.

In this annual *Drug Development & Delivery* report, interviewees describe how they are using technologies such as lipid nanoparticles to achieve a high drug loading, combining anti-solvent continuous crystallization with micro-mixing technology to control crystallization and reduce crystal size, and robotic capsules to improve bioavailability in the range of 47% to 78%.

Ascendia Pharmaceuticals, Inc.: A Tailored Approach to Nanotechnologies

It is very challenging to improve solubility and bioavailability of a BCS II or IV API with a high melting point and a low solubility in a broad range of solvents. A high melting point makes it unfeasible to use hot melt extrusion to prepare amorphous solid dispersion, whereas low solvent solubility makes it challenging to spray dry or solubilize the compound in carriers. In some cases, these types of compounds can be nanosized by nanomilling, micro-fluidization or formulated into nano-emulsion or nanoparticles with an aid of a cocktail solubilizer combinations.

"Nanosuspension prepared by a top-down process such as nanomilling or high-pressure homogenization, amorphous nanoparticles by a bottom-up process or a combination of bottom-up and top-down process, and lipid nanoparticles utilizing lipid carrier, have been routinely used in Ascendia's labs, attaining good results in achieving formulation with high drug loading and good bioavailability," says Jim Huang, PhD, Founder and CEO of Ascendia Pharmaceuticals, Inc. "A tailored approach based on compound properties will always increase the chance of success using available nanotechnologies."

For example, a BCS II compound (a high melting point and poor solubility in a range of solvents) was presented to Ascendia with a request to formulate and manufacture cGMP CTM for a Phase I study in a six-month window. Dr. Huang explains that Ascendia was able to formulate the compound with lipid nanoparticle technology for an oral route of administration, utilizing a combination of lipid and solubilizer to achieve a synergetic effect in solubilizing the compound. On the other hand, for an IV dosage form, by leveraging Ascendia's in-house capability in aseptic nano-milling and microfluidization technologies, a sterile nanosuspension formulation was developed to achieve a high drug loading that enabled toxicology and Phase I dose range studies.

Catalent: The Root Cause of Bioavailability

Solubility-limited absorption remains a key challenge in terms of bioavailability for a large number of compounds looking to progress from the discovery phase towards the clinic. Increasingly, these molecules also exhibit high melting points and poor organic solubility, making these so-called "brick dust" compounds extremely difficult to process using conventional solubility-enhancing methods such as hot melt extrusion (HME) or spray drying. Alternative solubility-enhancing technologies, alongside innovations in the HME and spray drying processes, may be

Analytical scientists working at Catalent's early-phase development center in Nottingham, United Kingdom.

required to enable the development of such challenging solubility-limited compounds.

"Additionally, we are seeing a significant increase in the number of compounds that are beyond Lipinski's rule of five (bRo5) where bioavailability is limited by permeability through the intestinal epithelium," says Nathan Bennette, Director, Scientific Advisory, Catalent. There are presently very few options for formulating and delivering permeation-limited molecules, and the success of programs for drugs with these properties will depend upon the development of new tools and approaches for enabling their bioavailability."

To successfully address a bioavailability issue, it is critical to first understand the pharmacokinetics of a molecule and evaluate whether bioavailability is limited by poor absorption, a physiological process (e.g., efflux or metabolism), or a combination of the two. If poor absorption is the root cause, it is important to distinguish between an inadequate dissolution rate, low aqueous solubility, and poor permeability, and each of these physiological and physicochemical conditions will require a different formulation approach. For example, where metabolism is the key issue, it is sometimes possible to design formulations that target pre-gastric absorption or enhance lymphatic absorption, both of which bypass first-pass metabolism by the liver. Particle size reduction and amorphous dispersions are well-precedented strategies for addressing slow dissolution or poor aqueous solubility, respectively.

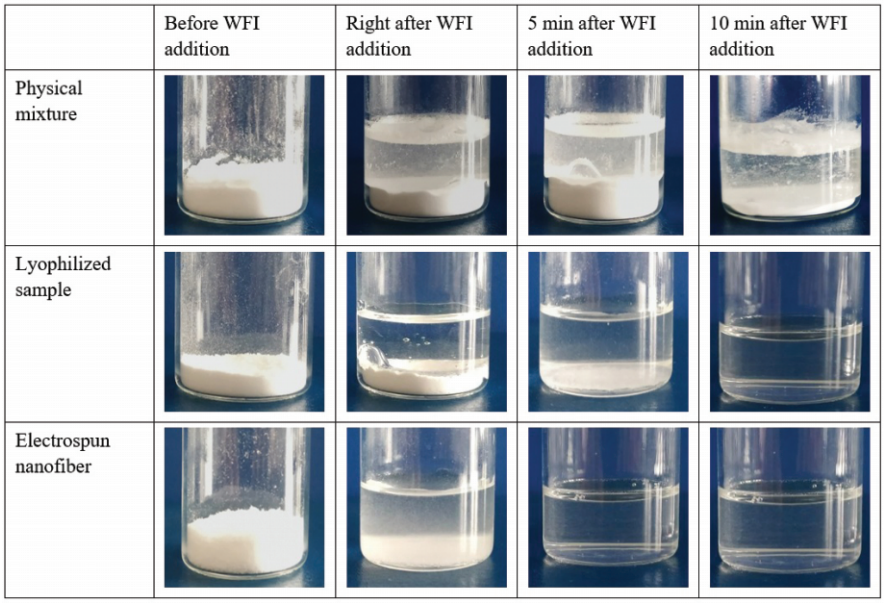
"Early application of physiologically-based pharmacokinetic modeling can provide significant insight and guidance, so that formulation strategies can be focused on developing solutions to the actual challenges of bioavailability enhancement," says Mr. Bennette.

CycloLab Ltd.: Electrospun Nanofiber Form vs. Lyopholized Remdesivir

Remdesivir, a monophosphoramidate prodrug, was discovered and developed by Gilead Sciences, Inc. It has been introduced as a promising new antiviral agent for the therapy against SARS-CoV-2 in the form of an intravenous product marketed under tradename Veklury®. Due to the poor aqueous solubility of remdesivir (0.028 mg/mL at room temperature), a need arose for solubility enhancement. CycloLab performed research to explore possibilities for electrostatic fiber drawing.

Dr. István Puskás, principal scientist with CycloLab, explains that this was attempted by employing different solubilizer excipients, such as surfactants, polymers, co-solvents and sulfobutylether-beta-cyclodextrin (SBECD). Twenty percent (w/w) aqueous solutions of Tween-80 provided 3.9 mg/mL dissolved remdesivir, PEG-400, dissolved 3.3 mg/mL, while SBECD at this concentration resulted in 8.5 mg/mL dissolved remdesivir.

The application of surfactants and polymers – despite their solubility-enhancing effect – was found inadequate for solubilizing enough active ingredient for a preferred formulation; the only satisfactory solubility enhancement was achieved by using SBECD. Currently, 13 FDA-approved injectable products are on the market that contain SBECD-solubilizing excipient and numerous clinical candidates are under development. Isolation of solid drug/SBECD complexes from common solution might be performed by various solvent removal techniques.



CycloLab studied the differences of wettability, dissolution rate, and water solubility of the physical mixture of remdesivir and SBECD compared with those of the two complex formulations (lyophilized and electrospun samples).

To compare the performance of solid complexes prepared by two methods suitable for manufacturing injectable products, two types of formulations with identical composition were prepared and investigated by lyophilization and electrospinning, respectively. Common aqueous solutions of remdesivir and SBECD were prepared and filtered at room temperature. The resulting clear filtrates were processed by lyophilization and electrospinning into solid binary formulations. This study aimed at the comparison of wettability and dissolution properties of freeze-dried and electrospun nanofiber formulations of SBECD-enabled remdesivir compared to a mere physical mixture of the constituent powders (non-complexed form).

The CycloLab image demonstrates the differences of wettability, dissolution rate, and water solubility of the physical mixture of remdesivir and SBECD compared with those of the two complex formulations (lyophilized and electrospun samples). Dr. Puskás says the physical mixture did not dissolve completely, the partial dissolution of the composite powder could be attributed to the hydrophilic SBECD matrix. After 10 minutes measured from the addition of water (WFI), the lyophilized sample spontaneously dissolved. Full dissolution of the electrospun nanofibers was observed notably faster. The dissolution was completed in 5 minutes after contact with the dissolution medium. Significant differences were found in wettability and dissolution rates of formulations with identical average composition, indicating that solid-phase engineering and complexation with SBECD do matter.

"In conclusion, reconstitution and dissolution properties of an electrospun nanofiber form of remdesivir were found to outdo those of the lyophilized formulation having identical composition," he says. "These superior wetting and dissolution properties of electrospun nanofiber offer the possibility to develop non-invasive, quickly absorbable dosage forms of a drug. Further studies are in progress to prove the feasibility of electrospun nanofiber made from SBECD-enabled remdesivir as a non-invasive therapeutic option."

Enteris BioPharma: A Game Changer Transforms Treatments

With an increased number of "beyond rule of 5" (bRo5) compounds in clinical trials and some recent drug approvals by FDA in the oncology space, there is heightened interest among pharmaceutical companies to pursue drug development of these compounds. bRo5 compounds, such as peptides, peptidomimetics, and a growing number of intermediate-sized molecules, are traditionally considered undruggable for oral delivery due to low aqueous solubility, or poor permeability, and other challenges. The use of an external enabling technology for oral delivery of these compounds combined with a scalable manufacturing process can present a win-win situation for drug makers and patients by reducing time to drug launch, speeding up market entry, and improving patient compliance.

While most enabling technologies can improve solubility, the ability to develop oral tablet formulations that address both the permeation and solubility challenges represents a game changer for drug makers to enhance multiple drug products and transform entire treatment paradigms. Enteris' ProPerma® and Peptelligence® platforms tackles both issues of solubilization and permeation using solubilizing agents that are also permeation en-

hancers, explains Dr. Rajiv Khosla, CEO of Enteris BioPharma. The ProPerma approach utilizes an enteric coating surrounding a tablet core containing the API, along with the enhancing excipients. By delivering the formulation directly to the highly absorptive area of the small intestine, such permeation enhancers enable the transport across the epithelium via diffusion through the tight junctions, or by the transcellular route, crossing the cell membrane. The technology employs granulated citric acid, which acts as a permeation enhancer that makes the tight junctions more porous and removes diffusion barriers. It also protonates basic drugs, adding positive charge, which increases water solubility. In addition, the formulation contains a surfactant, suitable for tablet manufacturing, to further increase solubility and permeation.

"The Enteris platform improves oral bioavailability through a combination of the pH-lowering and solubilizing effects of the formulation in a highly-scalable solid oral dosage form, without making modifications to the API," he says.

The process for testing oral feasibility using the Enteris platform involves a transparent review of the physicochemical properties of the partner's API to determine fit and compatibility with the technology, using a developability assessment. Given an appropriate fit and alignment with the partner's goals, Enteris will then provide a plan to develop customized formulations containing enterically-coated tablet prototypes with the API to demonstrate proof-of-concept of oral bioavailability enhancement in nonclinical pharmacokinetic studies and ultimately human clinical trials.

As an example, Enteris recently worked with a partner to improve the bioavailability of a bRo5 compound with poor solubility and permeability. This compound had a molecular weight greater than 600 Da, with multiple H-bond acceptors, poor solubility at neutral pH, and poor permeation. Enteris' proprietary oral solid dose formulation technology improved bioavailability of the API, showing pharmacokinetics similar to a lipid-based formulation but with the convenience of a solid oral dosage form."Enteris' technology provides a unique approach to addressing both solubility and permeation in a tablet formulation," says Dr. Khosla.

Evonik Health Care: Optimized Compound Outcomes

Over the past few years, Dr. Jessica Mueller-Albers, Strategic Marketing Director Oral Drug Delivery Solutions, Evonik Health Care, has observed that one of the most common customer challenges is creating a development strategy for preclinical toxicology and first-in-human studies for poorly soluble drugs. "Small molecules are continuing to become more complex so that more sophisticated formulation strategies are required," she says. "Usually, the major challenges, however, revolve around limited budget and limited amounts of API. At the same time, the number of accelerated approvals from the FDA with Fast Track and Breakthrough designations on low solubility compounds is increasing. This is especially true for oncology programs that show promising early-stage results and may have reduced clinical study requirements."

Miniaturized screening tools have been developed to support the design of the best formulation. But it is not only the formulation that has a strong influence on the pharmacokinetic profile and later performance of the drug product, she notes. The choice of the process technology is also key and can change during the development program when transitioning from early to later stages. Therefore, a seamless transition from drug discovery to preclinical toxicology to clinics and commercial manufacturing is still a hurdle for many programs. "All formulation and process development activities must have a strong sense of scalability early on to ensure this seamless transition and realize right-first-time formulation," she says.

Pharmaceutical companies are looking for partnerships during the early phase of development to gain access to the newest and most innovative solutions and technologies. These are not limited to solubility-increasing solutions, but also focus on optimized targeting and delivery outcomes for the compound. One example of these new technologies is EUDRATEC® Fasteric, a bilayer formulation technology for enteric protection followed by rapid release in the proximal region of the small intestine, the duodenum. Several drugs require the release in the duodenum to avoid exposure to P-glycoprotein transporter, which increases towards the distal region of the intestine. EUDRATEC Fasteric can rapidly release 90% of the

drug within 30 minutes of arrival at a specific, pre-defined pH level between 3.0 and 5.5 to precisely match the release profile requirements of APIs, which have a narrow absorption window. The formulation technology is suitable for use with a range of oral dosage forms, including multiparticulates, tablets, and capsules.

Gattefossé USA: Lipid-Based Excipients in Your Toolbox

Every formulation technology has its unique set of advantages and shortcomings. Salt formation or prodrug design approaches, for example, necessitate medicinal chemists to go back to the drawing board, starting anew. Nanoparticles offer some interesting advantages that may address some but not all the challenges presented by any given API. Solid dispersions have their own limitations in terms of drug stabilization and development time. Most importantly many of these techniques are appropriate for late-stage formulation optimization and are inadequate for early preclinical handling of the API.

"However, lipid-based formulation technologies, notably SEDDS/SMEDDS for oral delivery or microemulsions for dermal/transdermal delivery, can be used as early as preclinical phases and carried throughout the development process," says Dr. Masumi Dave, Application Laboratory Manager, Pharmaceutical Division, Gattefossé USA. "The lipid approach can help solubilization, dissolution *in vivo*, and improve absorption, notably by mitigation of the food effect. Our extensive work confirms that lipid-based excipients should be in the formulation toolbox to be considered from early- to late-stage formulation with no hiccups in the process."

For a customer project, Gattefossé worked on a BCS Class II API that was initially developed as an injectable formulation. However, due to complications involving sterilization of the API, the customer wanted to target an oral solid dosage form. After solubility screening studies, Gelucire® 48/16, Labrasol® ALF, and Transcutol® HP were selected given their ability to solubilize the active at desired dosage levels, explains Dr. Dave. Gelucire 48/16 and Labrasol ALF are polyoxylglycerides with a high hydrophilic lipophilic balance (HLB) value and are widely used as solubilizers and bioavailability enhancers. Transcutol HP is the highest purity grade of diethylene glycol monoethyl ether used as a solubilizer and topical permeation enhancer.

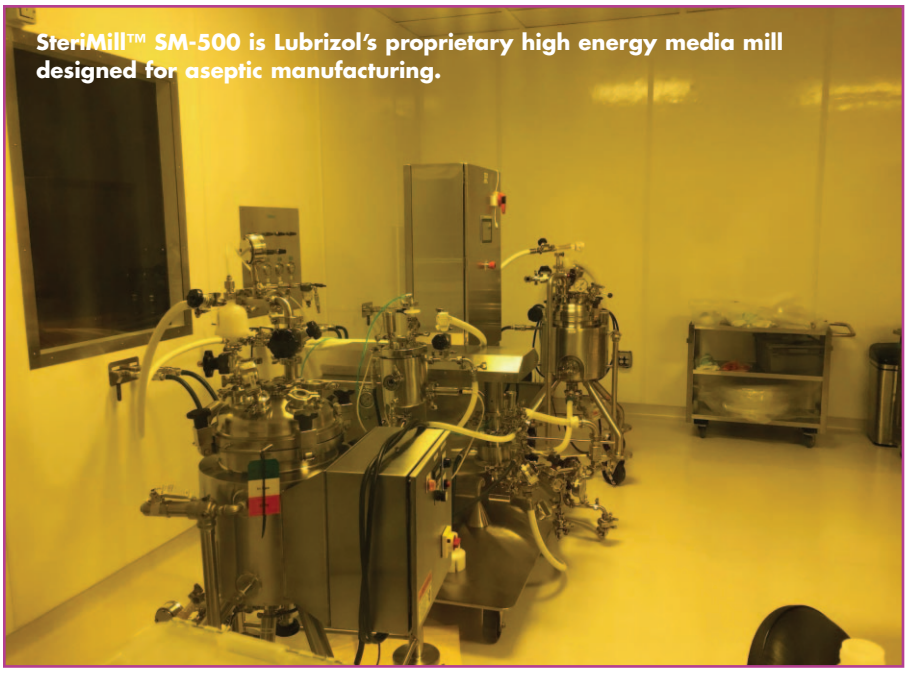
The performance of the formulation was assessed by checking its dispersibility in aqueous media and its ability to maintain the API in solubilized form *in vitro* lipolysis testing. "This test is a great predictive tool to aid in screening formulations to be selected for clinical study," she explains. "The formulation(s) with the ability to maintain the active in solubilized form throughout the test is selected for further evaluation in animal models. In the end, we were able to recommend formulations to the customer that should be selected for evaluation in animal models."

Lubrizol Life Science Health: Polymers for IP-Protection & Lifecycle Management

While there are excipients and techniques available to address bioavailability and solubility, they often have low efficiency and lead to complex manufacturing processes or undesired side effects for patients, says Robert W. Lee, PhD, President of the CDMO Division of Lubrizol Life Science (LLS) Health. Additionally, a lack of patented excipient options makes it difficult to formulate viable 505(b)(2) products.

"IP-protected polymers and technologies not only solve difficult technical challenges, but they also incentivize companies to pursue reformulation of existing APIs and bring new/improved options to patients," he says. "There are many polymer chemistries being explored for solubility enhancement, but only a limited number have advanced beyond lab-scale into GMP manufacturing. To be a truly viable commercial option, excipients require investment in process scale-up as well as regulatory and quality oversight."

LLS Health's oral-grade Apinovex™ and injectable-grade Apisolex™ polymers were designed to overcome poor solubility using simple, scalable manufacturing techniques. Apinovex and Apisolex are excipient-grade polymers that offer IP-protection and lifecycle management for BCS Class II and IV APIs. Apinovex polymers are GMP-validated, high molecular weight polyacrylic acid excipients designed to provide both processing and formulation benefits for spray-dried amorphous solid dispersions (ASDs).



SteriMill™ SM-500 is Lubrizol's proprietary high energy media mill designed for aseptic manufacturing.

Apinovex polymers enable formulators to achieve stable, high drug loading (up to 80%), and up to 10 times improvement in drug release for crystalline APIs. "With Apinovex, formulators can develop efficient, IP-protected oral solid dosage forms for a range of poorly soluble APIs," says Dr. Lee.

The Apisolex polymer is an injectable-grade poly(amino acid)-based co-polymer that has been shown to increase the solubility of hydrophobic APIs by up to 50,000 times where other commonly-use excipients fail, he says. "Robustly patented, safe, efficient, and scalable, Apisolex formulations can achieve drug loading up to 40%, dramatically increase the achievable concentration of API in water, and reconstitute in saline in less than 30 seconds."

In addition to these polymers, LLS Health routinely uses a variety of nanotechnology-based drug delivery technologies, including polymeric nanoparticles, solid lipid nanoparticles, nanoemulsions, and nanoparticulate suspensions (i.e., nanocrystals). "We frequently evaluate nanocrystals produced using a high energy media milling process (i.e., nanomilling) for water-insoluble APIs," explains Dr. Lee. "We believe that Lubrizol does more nanomilling than most other CDMOs and since most of our programs are intended for parenteral administration, we would consider this to be a trend and a go-to technology for sterile products."

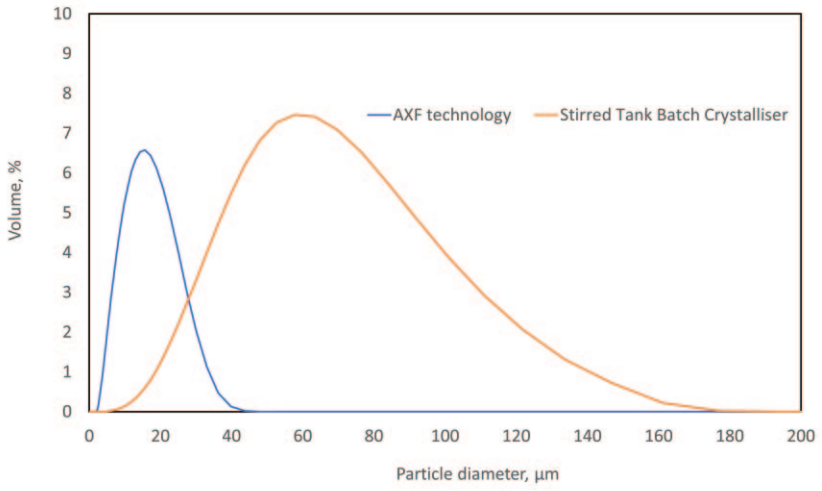
When it comes to sterile products, most nanocrystal formulations are not amenable to terminal sterilization, so LLS Health offers aseptic nanomilling to its clients. Using its proprietary SteriMill™ Technology, Lubrizol can scale aseptic nanosuspensions up to and including commercial batches.

"Nanomilling is a scalable, proven technology and we can achieve concentrations up to 50% API," Dr. Lee says. "This leads to a more efficient process requiring fewer unit operations to produce the final drug product. Nanomilling ultimately facilitates scale up and eventual commercialization for our clients."

Micropore Technologies Inc.: Controlled Crystallization

One way to improve solubility is through the control of the crystallization process of APIs. During a recrystallization process, control over the size, size distribution, morphology, and crystallinity of the crystals can be difficult. API crystallization is directed by supersaturation and can result in size growth as the driving force, resulting in the formation of larger crystals. The rate of crystallization throughout the entire system can also be uneven and uncontrolled. This leads to a wide distribution of crystals of various sizes and morphologies. Crystallization also favors the formation of API crystals that are in a more structurally ordered crystalline state. Ordered crystalline API crystals (unlike amorphous particles) tend to have poor solubility, which can also lead to poor bioavailability during medical use.

Micropore has combined reverse anti-solvent continuous crystallization with its micro-mixing technology, giving a highly (or exquisitely) controlled crystallization process and environment. "Through understanding the solubility of an API, we have found its controlled introduction to an anti-solvent can dictate the size, size distribution of the crystals, their morphology, and, critically for bioavailability, we could dial in the degree of crystallinity," says Dr. Matthew Bennett, Crystallization Scientist, Micropore Technologies Inc. "We have worked with drugs of low solubility and bioavailability and have succeeded in obtaining small particle sizes in amorphous states. This breakthrough work will result in increased API solubility



Comparison of size distribution of an API using batch and AXF technology for crystallization (Micropore Technologies Inc.).

and bioavailability."

One leading biopharmaceutical company approached Micropore for methods that reduced the size of crystals for one of its major APIs. Dr. Bennett explains that initial work involved replicating the company's crystallization methods using Micropore's advanced crossflow (AXF) technology. Further worked involved changing the overall formulation while also carrying out the crystallization through AXF technology. The results showed the crystal's average size was reduced from 240µm to that of almost a tenth of the size at 26µm along with a smaller size distribution.

Quotient Sciences: Integrated Development Strategies Overcome Solubility Challenges

There is no one-size-fits-all solution for improving bioavailability and solubility, and what is correct for one molecule could be over-engineering, or worse, limiting the potential of another drug. It is therefore crucial for development teams to understand the drivers of a given molecule's solubility and its permeability properties to select the correct technologies for assessment, and then back up that selection with data. "One of the biggest challenges we see is the expectation of an *in vitro/in vivo* correlation in developing these technologies, which is not realized when clinical data is obtained," says John McDermott, Executive Drug Development Consultant, Quotient Sciences. "Having access to human data to assess formulation technologies for poorly soluble drugs is therefore crucial in guiding formulation selection and optimization."

Quotient has had the opportunity to work on several programs that have assessed the clinical performance of some of these novel and emerging technologies to enhance drug bioavailability. "We have seen some great successes for some drugs, and we have also had experiences where performance observed in preclinical and *in vitro* studies have not translated into humans," he says.

Quotient Sciences delivers fully integrated programs incorporating formulation development with clinical manufacturing, regulatory support, and clinical testing. This platform, termed Translational Pharmaceutics™, can be applied to accelerate the progression of prototype formulations to clinical assessment and onward, to efficiently and accurately assess candidate formulations, and to improve the likelihood of clinical and commercial success, explains Mr. McDermott.

In one recent case study, a customer with a BCS II molecule had completed its first-in-human study, which demonstrated inadequate exposure and a significant food effect.

Quotient Sciences possesses a broad suite of technologies to address solubility challenges.

These issues were stalling the project from advancing into proof-of-concept patient studies. To respond to this, the client needed to rapidly evaluate solubility enhancement technologies and demonstrate its utility to enable efficacy assessments in order to proceed to the next project milestone.

In this program, Quotient Sciences developed three different solubility-enhancing formulations: a micronized form of API; a self-emulsified lipid delivery system; and a spray-dried dispersion. A Translational Pharmaceutics study was performed to achieve a quick proof-of-concept assessment, removing the need to conduct larger scale, cost-prohibitive process development and lengthy stability programs for multiple technologies. The human pharmacokinetic (PK) study used a 5 period cross-over design in 16 healthy volunteers with the micronized formulation delivering the best outcome.

"By applying our Translational Pharmaceutics approach, the overall timeline – from initiating formulation lab work to having clinical PK data to select the optimal formulation – was just six months," says Mr. McDermott. "While it's exciting to be involved at the forefront of research in drug delivery technologies, it's important to remain focused on the patient – and the best model for assessing humans is a human."

Pii: Creating Amorphous Material for Improved Bioavailability

The majority of new APIs are still poorly soluble in aqueous media and fall either under the BCS Class II or IV category. A drug molecule needs to be in a solution state to get across the intestinal membrane at enough concentration and rate to elicit the desired pharmacological effect. Hence, solubilization and permeability are prerequisites for good bioavailability. For a very poorly soluble drug with a limited option of formation of salts, co-crystals or prodrug, finding GRAS solvent/excipient combination that can solubilize the drug at sufficient concentration and prevent precipitation in the G.I. tract is a major hurdle to improving bioavailability, says Sundeep Sethia, PhD, Senior Director, Pharmaceutical R&D at Pharmaceutics International, Inc. (Pii).

Dr. Sethia describes how Pii helped improve bioavailability of a poorly soluble drug, in combination with solubilizer/excipients. This drug showed an incomplete and very slow release profile. The product needed to be developed as a tablet dosage form. As a result, the combination of drug and excipients were dissolved in a solvent and spray dried to provide amorphous material. Soluble drug material was hygroscopic and static with poor flow. The material was roller compacted with a binder and glidant to achieve compacted material milled to get acceptable flow properties. The milled material was then final blended with lubricant and compressed in the tablet dosage form. Precaution was taken to ensure humidity controls during processing, and desiccants were used for storage of finished product. "The amorphous API in the tablets showed faster and complete release that yielded desired PK profile and much improved bioavailability compared to the micronized API tablets," said Dr. Sethia.

Rani Therapeutics: Robotic Capsules Enhance Injectables Bioavailability

The vast majority of biologic drugs have to be delivered through an injection or infusion. The main impediment to oral delivery of biologics has been the catabolic nature of enzymes in the gut, which are extremely efficient at digesting biological matter and absorbing it as nutrients. Biologics are also much larger in size and weight than small-molecule drugs,

The RaniPill capsule is an orally ingestible robotic pill intended to replace subcutaneous or IV injection of biologics, designed to automatically administer a precise therapeutic dose of medication upon deployment in the small intestine (Rani Therapeutics).

making permeation across the gut epithelium a challenge. Thus, when taken orally, most biologics have extremely poor absorption and low bioavailability.

Many attempts have been made to deliver biologics orally, most of which have taken a chemistry-based approach involving permeation enhancers, protease inhibitors, or enteric-coated capsules, explains Talat Imran, CEO of Rani Therapeutics. These mechanisms are used to encapsulate or shield biologic drugs from the digestive action of gut enzymes and increase systemic uptake. However, even the successful attempts have shown bioavailability no greater than ~1%, he says. Robotic pills are another approach, which may combine several features for targeted delivery to the gut.

One example of a robotic pill having a successful outcome is in the case of octreotide, a synthetic hormone for the symptomatic treatment of acromegaly and carcinoid syndrome. Acromegaly in particular impacts 25,000 patients in the US each year, who require ongoing treatment for chronic symptoms. However, current treatment using octreotide involves painful subcutaneous injections administered three to four times daily or an extended-release formulation via painful, deep intramuscular injections every four weeks, and as many as 13% of patients cannot adhere to long-term therapy.

The majority of previous attempts to develop oral versions of biologics like octreotide were chemistry-based, and the best attempts have resulted in low bioavailability of certain peptides up to 1%. "Instead, we developed a robotic pill to deliver octreotide directly to the jejunum," says Mr. Imran. The capsule has a protective enteric coating designed to withstand stomach acid and only dissolve in the small intestine. Once dissolved, intestinal fluids activate a self-inflating balloon, which deploys a microneedle containing octreotide to deliver the biologic into the highly vascularized wall of the small intestine, where it easily enters the bloodstream. "Bioavailability for our robotic capsule has been in the range of 47% to 78%."

In a Phase I clinical trial of 62 healthy patients, bioavailability of octreotide delivered by oral robotic capsule was 65% relative to the IV group, confirmed in one or more hourly blood samples.

Seqens: A Toolbox of Strategies

Fine-tuning the molecular design of APIs is required to enhance binding selectivity for a biological target. It is now common to observe new drugs weighting more than 800 Da, with multiple stereocenters. Among other consequences, the drug solubility or permeability is often reduced, resulting in absorption issues, first pass metabolism, and elimination by the kidneys.

"Within the BCS classification, more than two-thirds of APIs present a bioavailability challenge –10% to 20% of them being classified as Class IV – suffering from both low solubility and permeability," says Frédéric Schab, PhD, Drug Delivery Solutions Managing Director, Seqens. "Several strategies can be deployed to improve bioavailability, leveraging a wide range of scientific competencies."

Reducing the particle size of APIs is one method to increase the surface area and improve the dissolution kinetics. Physical post-treatments, like milling or micronization, are commonly used tools, but more advanced technologies, such as cryomilling and nanomilling are deployed to treat more reluctant APIs, he says. One way to monitor the particle size is to control the granulometry during the crystal formation step. For instance, continuous crystallization (through plug flow tubular systems or continuous stirred-tank reactors) requires high process engineering know-how and can help to reach fine and tight particle size distribution, avoiding an extra production step.

A second approach consists of altering the API's solid state form to improve the physico-chemical properties. "Pharmaceutical crystal engineering, with high-class analytical and screening tools, allows us to investigate alternative salt forms with various counter-ions, perform polymorph screening (metastable form, hydrates), or develop co-crystals to enhance the absorption performances," explains Dr. Schab.

A third strategy consists of formulating drug with carefully selected excipients, such as polymers and lipids. These ingredients offer a level of customization potential, and open up enormous application potential, not limited to improving solubility. "Lipids recently marked a milestone in the medical field," he says. "Due to their high biocompatibility and low immunogenicity, lipids are the most com-

monly used non-viral vectors for nucleic acid delivery required for gene therapy and DNA/mRNA vaccines."

Bioresorbable polymers, such as PLA/PLGA or polycaprolactone, are used in controlled-release drug formulations for their ability to protect APIs from degradation, reduce the number of intakes, and liberate the drug over a long period of time. Other hydrosoluble polymers (polyethyleneglycol, polyethyleneimine, polyoxazoline, copolymers) are widely studied to encapsulate APIs or design API-polymer conjugate prodrugs.

"Remarkably, hybrid polymers and lipids excipients also constitute major research tracks for the development of new improved delivery systems," says Dr. Schab.

Serán BioScience, LLC: Turning Technologies into Dosage Forms

Advances in human biology continues to identify novel druggable targets. These new targets create fundamental challenges for medicinal chemists. Many of these targets require novel drug properties, such as hydrophobicity in order to achieve sufficient binding efficiency and to avoid off-target interactions. Many of these new molecules are insoluble in water and have limited permeability in the small intestine. These new molecules can therefore exhibit very low bioavailability in both preclinical species and humans. This is a daunting problem to overcome for drug development.

New technologies enable sufficient bioavailability of these compounds; many of these technologies have been demonstrated at commercial scale. Examples include spray dried dispersions, nanomilling, and melt extrusion. Other approaches, such as salt forms and co-crystals are also applicable in many cases. With appropriate know-how and expertise, these technologies can be developed into various dosage forms, such as suspensions, capsules, and tablets.

Serán BioScience, LLC is a science-based CDMO that specializes in a variety of drug delivery and formulation approaches suited to optimizing bioavailability. Serán's approach begins with a comprehensive review of the molecular properties of the drug and the client's development goals to identify the preferred technical and development approach that can dramatically reduce time to the clinic and launch. Often, the development path begins with preclinical studies that require very high drug exposure (often 10-100 times greater than desired clinical exposure), explains Dan Smithey, PhD, CEO, Serán BioScience, LLC. This is a common challenge that requires engineered formulations to achieve consistent results in dose-escalation and toxicology studies. These formulations (suspensions) ideally consist of particles specifically engineered for these studies. Amorphous particles in suspension can provide exposure at high doses, but stabilizing these suspensions is critical to maintaining exposure. "Serán has unique approaches that enable stable suspensions of amorphous particles," he says.

Serán has developed a multitude of spray dryers that are capable of manufacturing formulations that enhance bioavailability across a wide range of scales, from 100mg to 100kg. "All of our spray dryers have the ability to produce engineered particles using virtually any type of nozzle system, including pressure nozzles, 2-fluid nozzles, and ultra-sonic nozzles," says Dr. Smithey. "This capability provides ultimate flexibility in formulation design to optimize exposure and downstream processability."

In addition to particle engineering, the development of a solid dosage form is key to successfully improving bioavailability. Due to the unique nature of engineered particles that are developed to enable bioavailable formulations, solid dosage forms also need to be engineered to ensure the physical properties, performance, and stability of these particles is acceptable. Typically, dry granulation using roller compaction is required to achieve acceptable dissolution. Granulations can then be used to produce a final dosage form, such as a capsule or a tablet. Dr. Smithey says: "Serán's approach to development of solid dosage forms enables the manufacture of clinical trial materials at virtually any scale, from first-in-human clinical studies through commercial manufacturing." ◆

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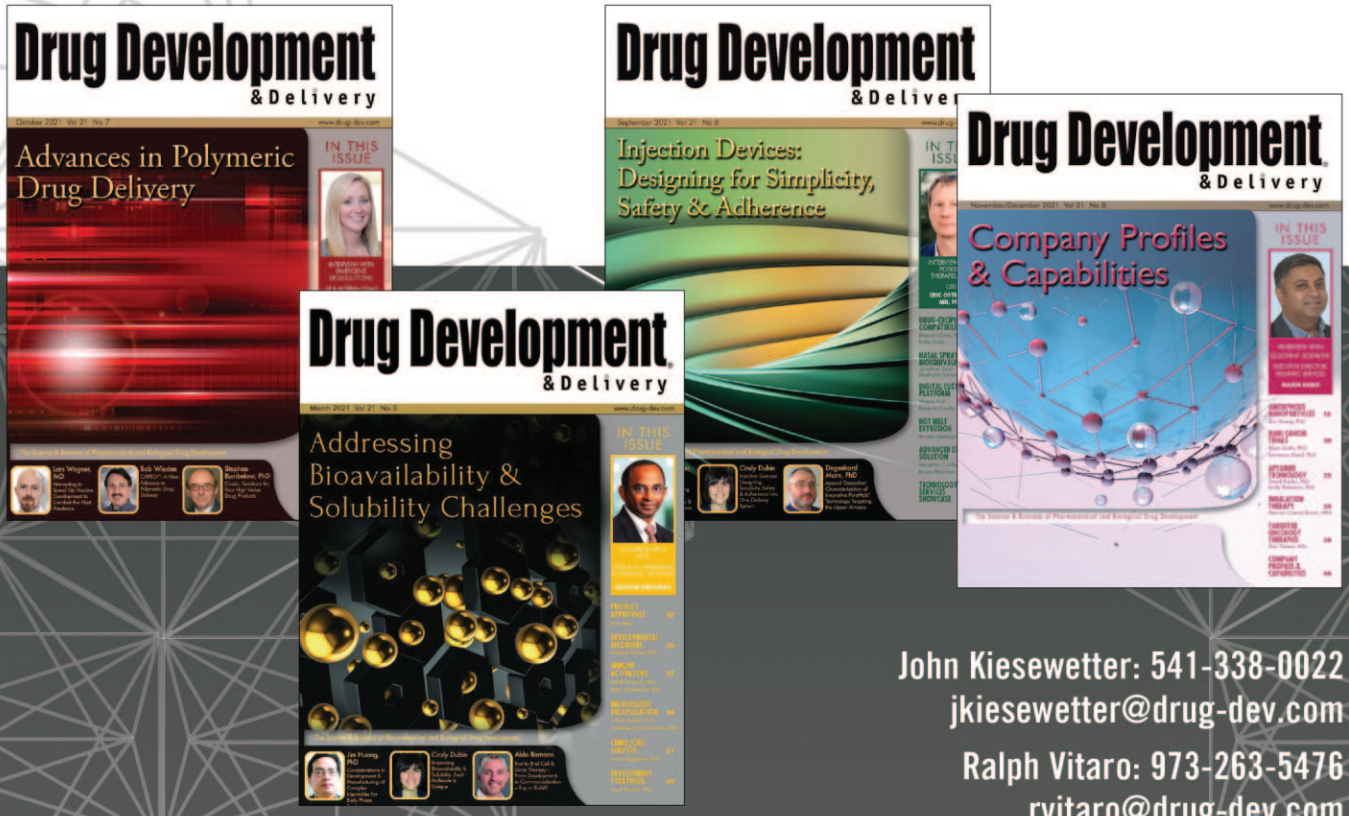

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MARKET LANDSCAPE

The Future of Cancer Care Post-Pandemic: What Doctors, Patients, and the Healthcare Industry at Large Should Expect

By: Angelos Stergiou, MD, ScD hc

INTRODUCTION

The future of the healthcare ecosystem for cancer patients from a post-pandemic perspective is complex. The COVID-19 pandemic saw failures in the healthcare delivery system not only in general medicine, but also specifically in oncology. At the same time, several opportunities came to light during such a difficult, frightening moment, bringing a number of large- and small-scale innovations forth.

While some areas of medicine will remain unaltered post-COVID, the unique nature of cancer research and cancer care delivery has ultimately been changed forever. As a result, here's what doctors, patients, and the entire healthcare industry as a whole can and should expect for cancer care in the very near future:

THE REGULATORY ENVIRONMENT FOR APPROVING & AUTHORIZING NOVEL MEDICINES FOR THE MARKET WILL BE AFFECTED

From a regulatory perspective, it is becoming more apparent that a dichotomy is evolving between the liberalism of health authorities, such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), to provide emergency use authorizations for a number of anti-infective agents (specifically those having to do with COVID-19, including vaccines) and the reticence over the past year by the FDA to approve oncology agents.

This may be a temporary effect due to the recent change in the US administration, but there are already signs the regulatory environment for oncology agents may be stricter in the near future, with several recent agents under review at the FDA receiving seemingly unexpected Complete Response Letters (CRLs) that indicate the FDA has conducted a complete review but cannot approve the application. We need to be vigilant as to whether this trend will continue.

Additionally, although the FDA is not able to regulate prices for drugs in the US, the overall pressure in the federal budget by various relief plans during the COVID-19 pandemic may be reflected in some regulatory hesitancy in providing a torrent of new approvals. There may be a tendency for requesting more analysis of data and/or real-world evidence for not only the efficacy but also the real-world "effectiveness" of new anti-cancer therapies, especially in niche indications that are typically managed with very pricey novel therapies.

CANCER PATIENT "FLOW" & IMPLEMENTING CANCER SCREENINGS, DIAGNOSES & MANAGEMENT PLANS ARE STILL BEING IMPACTED BY COVID

The COVID-19 pandemic has slowed, or even temporarily stopped, access to standard, routine cancer screenings (eg, skin exams for melanoma, mammography for breast cancer, Pap smears for cervical cancer, etc) and raised barriers for patients who need to make initial visits for suspected cancer diagnostic

"There is no doubt that both the public and other stakeholders in the healthcare ecosystem, have been exposed to the potential of novel technologies that are RNA-based, considering the rapid and successful clinical development of mRNA-based anti-SARS-CoV-2 vaccines (eg, Pfizer/BioNTech, Moderna). This enthusiasm is certainly shared by the investor community and, therefore, access to healthcare public and private investment capital for RNA-based technologies will increase."

work-ups, follow-ups, and monitoring for those who have a known cancer diagnosis. This has led to delays in applying standard therapies, especially when it comes to surgical oncology.

Therefore, there is a broad belief among the medical community that significant underdiagnoses, misdiagnoses, or delayed diagnoses of cancer cases have occurred since March 2020. Consequently, post-COVID-19 – after most of society has been vaccinated and a satisfactory level of herd immunity has been reached – there is the possibility of seeing a marked increase in the volume of patients who are seen in cancer practices, especially in the community setting.

This will have a significant impact on hospital budgets, as well as general care expenses that will be submitted for reimbursement at insurance carriers (Centers for Medicare and Medicaid Services and private insurers). It is possible we may see a period sometime in mid-2022, whereby there have been "unspent funds" in major insurance carriers' budgets, which were specifically allocated for cancer care expenditures for several millions of "covered" lives in the US. Thus, the reimbursement environment may be paradoxically positive or elastic during this particular period.

However, once large volumes of patients return and, furthermore, the percentage of patients presenting for care ends up coming in with more advanced stages of malignancies (which are much more expensive to manage), we may see intense efforts for cost containment and retrenchment from the insurers' standpoint, with increases in demands for prior authorizations, more restricted drug formularies, and more stringent pathways of clinical care in oncology. Hence, access to novel agents and "expensive" cancer care (extensive and complex cancer surgeries, stem cell transplants, etc) may lessen after mid-2022.

THERE IS INCREASED AWARENESS & RECEPTIVITY OF MRNA-BASED NOVEL TECHNOLOGIES/DRUGS

There is no doubt that both the public and other stakeholders in the healthcare ecosystem have been exposed to the potential of novel technologies that are RNA-based, considering the rapid and successful clinical development of mRNA-based anti-SARS-CoV-2 vaccines (eg, Pfizer/BioNTech, Moderna). This enthusiasm is certainly shared by the investor community and, therefore, access to healthcare public and private investment capital for RNA-based technologies will increase.

The potential for growth in genomic and proteomic platforms for individualized patient care in cancer is clear. There may be a very specific halo effect regarding the development of RNA-based cancer vaccines.

TRUE INNOVATION & ENTREPRENEURSHIP IN THE PHARMACEUTICAL & BIOTECH SECTORS ARE HERE TO STAY

From an innovation perspective, there has been an unprecedented speed of progression in the anti-infective drug/vaccines arena with the Operation Warp Speed initiative and the mobilization of huge resources at a global level, both from the government and private sectors.

However, the general environment of innovation support, both by governmental funding sources and the broader capital markets, remains uncertain for therapeutic areas other than anti-infectives/vaccines and antivirals. This uncertainty cuts across the board for smaller pharmaceutical and biotech companies, as well as the oncology portfolios of Big Pharma.

To some degree, the capital markets have been stronger than anyone would have anticipated, with the exception of the 2020 spring dip in the indices globally, but there is currently an overall cautious optimism in the general market. Whether this will continue unabated specifically in the healthcare sector remains to be seen.

TELEHEALTH IS AN ESTABLISHED TOOL FOR CANCER CARE & ADVANCED PRACTICE PROVIDERS ARE EVEN MORE CRITICAL

While telemedicine was introduced at least a decade ago, until the advent of the pandemic, its uptake had been slow and incremental. The pandemic turned that notion around rapidly, and now telemedicine is here to stay.

There is a broad belief that perhaps 40% to 50% of all office visits, even after the COVID-19 pandemic, will be done virtually through telemedicine. This brings into the foray the enhanced and crucial role of mid-level providers, or Advanced Practice Providers (APPs) in oncology, including Advanced Practice Registered Nurses (APRNs), Nurse Practitioners (NPs), Clinical Nurse Specialists (CNSs), Physician Assistants (PAs), and Nurse Navigators (NNs). The role of these professionals as "extenders" of surgical, radiation, and medical oncologists will become even more valuable and visible in the post-COVID-19 era across the entire cancer care ecosystem.

Along these lines, COVID-19 brought forth the need for patients to think about more self-care options. The pandemic forced patients to take more individual responsibility for their care by being more inventive and solution-seeking (along with their caregivers) regarding how to best manage their disease.

PUBLIC DEMAND FOR TRANSPARENCY IN CANCER RESEARCH HAS INCREASED

During the pandemic, there has been a clarion call by the public – at a global scale – demanding more transparency and accountability among major organizations, such as the World Health Organization's (WHO) research in infectious diseases in general and clinical virology. This will create a halo effect in the cancer healthcare ecosystem as well, especially for organizations with increased global remit and influence – eg, the International Agency for Research on Cancer (IARC), an agency that is part of the WHO, as its proclamations and guidelines affect cancer care at a global level.

There will also be a need for transparency at the regional and national level organizations with guidelines or policy-making authorities, along with governmental agencies, regulatory bodies, and state-level Medicaid.

This need for more transparency in many ways will affect perception of credibility and level of reputation and public trust of all the various innovation incubators, both in academia and Big Pharma. On a global scale, there will be heightened sensitivity in the way that certain avenues of research, as well as key clinical and translational data, will be communicated to the public through all available channels, including FDA guidance documents, presentations, and FDA advisory committee meetings.

This may also affect the way that industry (both at the level of individual manufacturers and Pharmaceutical Research and Manufacturers of America as an organization) and academic centers issue press releases in the media in their effort to communicate key findings and corporate leadership decisions to investors, analysts, payers, patients, caregivers, and the public at large.

Post-COVID-19, the public will expect some degree of audacity from this long and diverse list of organizations to "tell the truth." This may be a welcome change, as there are already indications that the acceptability, popularity, and credibility of the pharmaceutical/biotech industry have already modestly increased.

Further enhancement of transparency, especially by the drug manufacturers that are involved in developing novel medicines for cancer and publicly traded healthcare companies (eg, manufacturers of medical devices, various lab diagnos-

tics, and imaging agents, including radionuclides, manufacturers of generics and biosimilars, as well as hospital systems and healthcare insurance carriers) will help to translate innovation into long-term trust by the public, which can only be a positive outcome for the shareholders of these companies.

THE INDUSTRY IS BOTH ACCEPTING & EMBRACING NEW TECHNOLOGIES IN CANCER MEDICINE POST-COVID

There is no doubt the pandemic exposed decision-makers within the entire healthcare ecosystem to unprecedented levels of uncertainty, anxiety, false hope (eg, early data with hydroxychloroquine) or even desperation and decision-paralysis. On the other hand, one of the attitudes of these key decision-makers that was profoundly affected by COVID is the level of readiness to use novel tools and solutions – from telehealth to the rapid deployment of special equipment, to novel patterns of healthcare delivery, to the development and successful market entry of vaccines based on the highly innovative mRNA technology.

Along these lines, 2020 was not only the year of COVID-19, but it was also the year of the Nobel Prize in Chemistry given to the discoverers of the CRISPR/Cas9 gene editing technologies and the spawning of several companies and academic groups that are currently working on the use of CRISPR/Cas9-based therapeutics for several diseases, including cancer.

This past year, we also witnessed a true explosion in molecular novel biomarkers of tumors and progressively broader applicability of next-generation sequencing (NGS) technologies. Several of these innovations will pass regulatory barriers and translate into commercially available companion diagnostics. This trend will continue; however, how it will evolve exactly in the post-COVID-19 era remains unknown. We must wait and see how the entire cancer care ecosystem will transform itself in the near future.

In summary, in the post-COVID era, key aspects of healthcare far beyond infectious disease will change – in many cases significantly and permanently. Subtle or not so subtle changes in attitudes, degree of knowledge, and understanding of the pandemic across all stakeholders (physicians, patients, payers, guideline- and policy-issuing bodies, pharmaceutical manufacturers, regulatory authorities, various governmental organizations and NGOs, as well as the sentiment of the healthcare investor community) will continue to evolve.

Perhaps what looked familiar and ordinary in the pre-COVID-19 era will become only a memory, while some completely novel and emerging patterns of societal and healthcare ecosystem stakeholder behaviors change across the board. We are already living during an era of transformation, which will lead to an altered environment. All of us involved in cancer research and oncology care will be witnessing and feeling these shifts.

This is a time of meta-stable milieu – an environment in transition – and we all have to be sensitive and vigilant during these shifts to ensure we avoid undesirable or unpredictable effects from these changes. In other words, we don't want to go down the wrong path. We need to have the courage and aptitude, especially in the pharmaceutical and biotech industry, to steer the ship back to the right direction. This can only be done by continuous optimization, identification, and immediate correction of errors of judgment, omission, and commission during these years of change. ◆

BIOGRAPHY

Dr. Angelos Stergiou is the Founder, President, and Chief Executive Officer of SELLAS Life Sciences Group, Inc., a late-stage clinical biopharmaceutical company focused on developing novel cancer immunotherapies for a broad range of indications. Prior to founding SELLAS in 2012, he co-founded Genesis Life Sciences, Ltd., a boutique health economics and pricing-reimbursement and health access company, where he served as President and Chief Operating Officer from 2009 to 2011. Dr. Stergiou has also previously held various leadership roles at a number of pharmaceutical and biotechnology companies, including PAION AG, Accentia Biopharmaceuticals, BioVest International, Analytica International, and Anavex Life Sciences, ranging from Head of Clinical Research and Vice President of Product Development to Chief Medical Officer and Chief Operations Officer.

GENE EDITING TECHNOLOGY

Harnessing a Cell's Natural DNA Repair Process to Develop Medicines With Higher Levels of Precision & Durability

By: Mariana Nacht, PhD

INTRODUCTION

The ability to target and modify the human genome, or alter its functionality, has transformed molecular biology-based research and opened up the possibility of treating a wide range of genetic diseases. Recent progress in the development of gene editing technologies, including those based on zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and most notably CRISPR-Cas9-associated nucleases, has taken gene editing from concept and discovery stage to clinical use in human trials.

While gene editing technologies have significant potential, many of the current gene therapies offer limited benefit due to lack of durability and the inability to target pediatric indications. But a new nuclease-free approach to gene editing is emerging and advancing through clinical development, raising the prospect of revolutionizing the treatment of many rare and devastating diseases that represent significant areas of unmet need in global health. Researchers at LogicBio Therapeutics are working to develop next-generation gene delivery and genome editing technologies with the goal of addressing limitations and supporting treatment of diseases that affect patients at any age, from infancy throughout adulthood.

In many rare genetic diseases, such as inborn errors of metabolism, symptoms present in the first year of life and progress rapidly, often leading to significant and potentially irreversible consequences and even death. Early intervention is critical.

A major challenge in applying traditional gene therapy approaches in the pediatric population is the proliferation of cells in the growing tissues of a child, which dilutes the therapeutic benefit. With existing gene therapy technologies, the corrective genes do not integrate into a patient's chromosomes but remain floating inside the nucleus. This means that the corrective gene is not carried through to successive generations when cells divide and, as a result, the therapeutic effect is diluted over time, especially in children, or in cases when the tissue is regenerating, such as in a damaged liver.

Gene editing technologies including CRISPR-Cas9, TALENs, and zinc fingers use engineered nucleases to cut a patient's DNA and remove or insert a corrective gene. But this process is often not precise and has been shown to lead to off-target effects and uncontrolled deletions or insertions in a patient's chromosomes. These unintended changes to a patient's DNA can increase the risk of genomic instability, cancer, and other genotoxicities. The use of nucleases, which are typically derived from bacteria, can also raise the risk of provoking a strong immune response in patients.[1]

THE POWER OF GENERIDE™

LogicBio's proprietary GeneRide™ technology is a new genome editing approach that harnesses a cell's natural DNA repair process, known as homologous recombination, to insert a corrective copy of the gene (or transgene) at a precise spot in a patient's genome. If successful, the gene then persists as an inte-

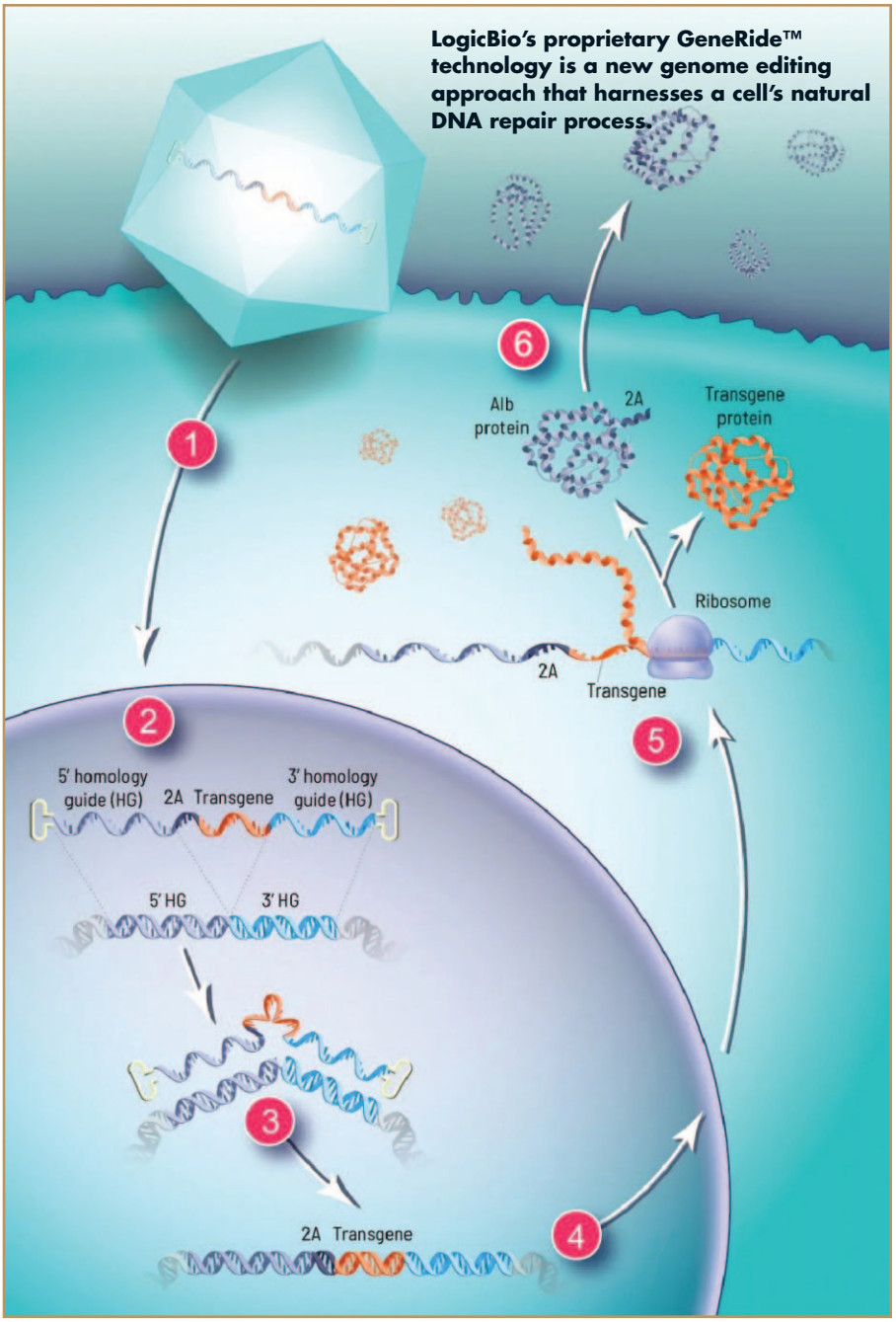
gral part of a patient's DNA as cells divide. GeneRide is nuclease-free, site-specific genome editing technology with the potential to enable durable expression and lower risk of harmful off target integration. The GeneRide technology was born out of the Kay Lab at Stanford University by LogicBio's co-founders Mark Kay, MD, PhD, Adi Barzel, PhD, and Leszek Lisowski, PhD, MBA, whose goal was to create an approach for precise and durable genome editing that could provide safety and efficacy benefits.

GeneRide is designed to work in a six-step process:

1. A synthetic, non-pathogenic adeno-associated viral (AAV) vector is used to deliver the corrective transgene to the nuclei of a patient's cells via an infusion.

2. Two homology guides – strands of DNA several hundred base pairs long that are designed to precisely match a specific stretch of a patient's genome – flank the corrective transgene.

3. Upon sensing the therapeutic DNA in the nucleus, the cell's natural DNA repair machinery responds and integrates the corrective transgene at a specific site in the patient's genome. The transgene is inserted in the same place every time – in the chromosome and at the gene that corresponds to the DNA sequence encoded in the homology guides. For LogicBio's liver-targeted therapies, this specific location for integration is within the albumin locus. Albumin is the most abundant protein in circulation and the most highly expressed gene in the liver. This high expression level is driven by the endogenous albumin promoter, which is very robust and tissue specific.



LogicBio's proprietary GeneRide™ technology is a new genome editing approach that harnesses a cell's natural DNA repair process.

4. When the therapeutic transgene is integrated into the albumin locus, downstream of the albumin coding region, it can hitch a ride on the endogenous albumin promoter to drive expression of the corrective transgene a patient has been lacking, without disrupting albumin production.

5. By using a 2A peptide – which is a short chain of amino acids that induces ribosomal skipping during translation of a protein in a cell – the cell produces albumin and the transgene as two separate proteins and modifies albumin with a small "tag." This tag enables LogicBio to monitor GeneRide activity in a patient's body in a non-invasive way. The tagged albumin protein can be easily detected in the circulation as a surrogate for site-specific integration and protein expression.[2]

6. Shortly after treatment, the modified

"While gene editing technologies have significant potential, many of the current gene therapies offer limited benefit due to lack of durability and the inability to target pediatric indications. But a new nuclease-free approach to gene editing is emerging and advancing through clinical development, raising the prospect of revolutionizing the treatment of many rare and devastating diseases that represent significant areas of unmet need in global health."

cells begin producing the therapeutic protein to combat the target disease.

The GeneRide platform is being leveraged to develop therapies that target diseases that cannot be treated by current genetic medicines, including rare genetic diseases such as methylmalonic acidemia (MMA) and Crigler-Najjar syndrome. To target different genetic diseases, the goal is for a different corrective gene to be substituted within the GeneRide construct while largely maintaining all other components of the system.

LB-001: *IN VIVO* GENE INSERTION FOR EARLY INTERVENTION IN MMA

LogicBio chose to first focus on MMA, a rare autosomal recessive disease, because of the potential benefits that GeneRide can provide by treating patients very early in the course of the disease. MMA affects approximately one in 50,000 newborns in the US.[3] It can be caused by mutations in several genes, but a mutation in the mitochondrial enzyme methylmalonyl-CoA mutase (MMUT) gene is the most common.[4] Mutations in this gene, which provides instructions for making the MMUT enzyme, prevent the body from properly processing certain fats and proteins and can lead to the toxic buildup of methylmalonic acid and other disease-causing metabolites. Patients with severe MMA may present with symptoms at birth including poor feeding, vomiting, hypotonia, respiratory distress and progressive encephalopathy.[3-5] They are also at increased risk of neurological symptoms, failure to thrive, intellectual disability, severe infections, and progressive renal insufficiency.

To manage symptoms, patients must adopt a severely restrictive, low-protein, high-calorie diet, often through a feeding tube.[4,5] Even with aggressive management, these patients often experience life-threatening metabolic crises that can cause permanent neurocognitive damage. In some cases, patients may need to undergo liver transplantation, an invasive and high-risk procedure that is not widely available and that presents lifelong health ramifications. Due to the need for early intervention, newborns are screened for MMA in every state in the US.[5,6]

Although newborns are screened for MMA and diagnosed early in life, unfortunately, there are currently no approved treatments that can target the root cause of the disease. Patients can only try to manage symptoms, leaving them and their families with an enormous burden and no medications to help.

LB-001 is an investigational, first-in-class, single-administration, in vivo genome editing therapy in development for early intervention in MMA, leveraging the GeneRide platform. LB-001 is designed to non-disruptively insert a corrective copy of the MMUT gene into the albumin locus to drive lifelong therapeutic levels of MMUT expression in the liver, the main site of MMUT expression and activity. The investigational therapy is delivered to hepatocytes via a liver-targeted, engineered recombinant AAV vector (rAAV-LK03).

In preclinical studies, LB-001 was shown to be safe and demonstrated transduction of hepatocytes, site-specific genomic integration, and transgene expression. LB-001-corrected hepatocytes in a mouse model of MMA demonstrated preferential survival and expansion (selective advantage), thus contributing to a progressive increase in hepatic MMUT

expression over time. In MMA mice, treatment with LB-001 resulted in improved growth, metabolic stability and survival.[7,8]

LB-001 is now being evaluated in MMA patients in a Phase 1/2 clinical trial, called the SUNRISE trial, an open-label, multi-center study designed to assess the safety and tolerability of a single intravenous infusion of LB-001 in pediatric patients with MMA characterized by MMUT mutations. With the aim of evaluating LB-001 at an early age, before irreversible damage has occurred, the SUNRISE trial is designed to enroll up to eight patients with ages ranging from six months to 12 years and evaluate a single administration of LB-001 at two dose levels (5×10^{13} vg/kg and 1×10^{14} vg/kg). This is believed to be the first in vivo genome editing therapy delivered systematically to pediatric patients and represents a key step in the effort to treat children suffering from early onset genetic diseases such as MMA.

BROAD POTENTIAL OF GENERIDE IN OTHER GENETIC DISEASES

The GeneRide technology platform is modular in nature, meaning it has the potential to be used to develop multiple genome editing therapies generally using similar principal components. At the European Society of Gene & Cell Therapy, or ESGCT, conference in October 2021, LogicBio presented preclinical data that validates previous research in MMA and highlights selective advantage in two additional indications that are also characterized by intrinsic liver damage: hereditary tyrosinemia type 1 (HT1) and Wilson disease.

Selective advantage enables healthy, edited hepatocytes carrying a corrective gene to survive and reproduce better than the endogenous mutated hepatocytes and to ultimately repopulate a part or whole of a diseased liver. In all three of the disease mouse models, expansion of the corrected healthy hepatocytes correlated with improved diseased markers.

In the HT1 models with acute liver damage, the data showed that GeneRide-corrected hepatocytes repopulated the entire liver within four weeks post-administration, replacing the diseased hepatocytes with corrected hepatocytes. HT1 mice are deficient in the gene encoding fumarylacetoacetate hydrolase (FAH), which is required to metabolize the amino acid tyrosine, resulting in the accumulation of toxic metabolites. HT1 mice that received the GeneRide-FAH vector were no longer reliant on the current standard of care for the disease, and demonstrated restored normal body growth, liver function, and undetectable succinylacetone levels, one of the toxic metabolites that accumulates in patients with HT1. Compared to the current standard of care, treatment with the GeneRide vector resulted in superior succinylacetone reduction and lower alfa-fetoprotein levels, a clinically validated biomarker for hepatocellular carcinoma and another risk factor for untreated HT1 patients.

Wilson disease results from a defect in copper transport, leading to toxic accumulation of copper and damage to tissues. In a Wilson disease mouse model, GeneRide-corrected hepatocytes repopulated the liver over time, and treated mice showed improvements in liver function, hepatomegaly, and urinary copper excretion.

Selective advantage and expansion of corrected hepatocytes was observed in these preclinical models, demonstrated by detection of increasing levels of a tagged albumin protein, albumin-2A, a technology-related biomarker indicating site-specific gene insertion and protein expression, as well as immunohistochemistry for the corrective protein in liver sections. Results presented at ESGCT also showed increasing levels of albumin-2A correlated with increased expression of the corrective gene and improved disease burden. LogicBio believes that these data support the development of GeneRide vectors to durably treat multiple genetic diseases with liver dysfunction.

EXPANSION OF GENERIDE PLATFORM AND CAPSID DEVELOPMENT

The unique potential of the GeneRide platform to support development of therapies like LB-001 that can target pediatric indications, where other genetic medicines cannot, has been recognized by others in the industry. In January 2020, LogicBio announced a research collaboration with Takeda to further develop LB-301, an investigational therapy for Crigler-Najjar syndrome based on the GeneRide platform. In April 2021, LogicBio entered into a research collaboration with Daiichi Sankyo for the development of treatments for two indications based on GeneRide. The agreement also grants Daiichi Sankyo an exclusive option to negotiate to enter into a worldwide license to develop and commercialize LogicBio's treatments in these two indications. In the same month, LogicBio also entered into a strategic collaboration with CANbridge Pharmaceuticals for an exclusive option to obtain an exclusive license to develop and commer-

cialize LB-001 in Greater China.

As part of this agreement, CANbridge was also granted a worldwide license for certain intellectual property rights, including those relating to AAV sL65, the first capsid produced based on LogicBio's sAAVy™ platform, to develop, manufacture and commercialize gene therapy candidates for the treatment of Fabry and Pompe disease. LogicBio also granted CANbridge options to license sL65 and certain other intellectual property rights for the development and commercialization of two additional gene therapy candidates for the treatment of two additional indications. Similar to the GeneRide platform, sAAVy is uniquely designed to overcome limitations with older-generation AAV technologies by bringing enhanced functionality with the potential for increased safety. To design these next-generation AAV capsids, LogicBio, together with the Translational Vectorology Research Team at Children's Medical Research Institute (CMRI), apply innovative genetic and cell and molecular biology techniques, including bioinformatics, machine learning, and other advanced computational methods.

Based on recent preclinical data, the sAAVy platform shows high potency in a humanized mouse model and in non-human primates compared to widely used benchmark capsids. The sL65 capsid also shows high production yields in suspension HEK293 cells and in bioreactors, meaning it can potentially overcome the current limitations of traditional AAV vectors, including high dosage-related toxicity, high manufacturing costs, and low translatability from mouse studies to human trials. These data were presented at the American Society of Gene and Cell Therapy (ASGCT) meeting in May 2021.[9]

SUMMARY

In developing promising genome editing therapies for any disease or condition, including rare diseases such as MMA, Crigler-Najjar syndrome, HT1, Wilson disease, Fabry and Pompe disease, it is essential to work to understand the mechanism of disease and disease pathways as well as the unmet need and patient experience. Of the 7,000 rare diseases, about 80% have genetic origins, with some caused by mutations in multiple genes (polygenic).[10] Treating these diseases is often very complex and presents important considerations regarding vector delivery, manufacturing, and regulatory requirements. Genome editing will be an important technique for treating both monogenic and polygenic diseases and potentially non-genetic diseases in the future. With the advancement of novel technologies such as GeneRide, there is the promise of developing genome editing therapies that will make a life changing difference for people, at any age, who have few or no treatment options. ◆

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BIOGRAPHY

Dr. Mariana Nacht is Chief Scientific Officer at LogicBio Therapeutics. She previously served as Chief Scientific Officer and was a founding executive team member of Cereius, where she led a small internal research team and a group of collaborators to develop radiolabeled proteins for the treatment of brain metastases. She has also served in key scientific roles at Vivid Biosciences, Padlock Therapeutics (acquired by Bristol Myers Squibb in 2014), and Avila Therapeutics (acquired by Celgene in 2012). Earlier in her career, she spent a decade working at Genzyme (now Sanofi Genzyme), where she led anti-angiogenesis and oncology target discovery efforts. She earned her BS in Biology from Tufts University and her PhD from the University of Pennsylvania.

INJECTION TECHNOLOGY

Patient Centricity in Insulin Injection: Using Technology to Improve Self-Administration

By: David T. Novotny

INTRODUCTION

For the past century, insulin injection has been used to treat diabetes mellitus, which is caused by the body not being able to produce enough of, or properly utilize, its own insulin. While there have been a number of methods of insulin delivery developed throughout the years, such as insulin pumps or even inhalers, the most common method remains daily self-administered injection through the use of syringes or insulin pens.

There are many reasons why people with diabetes might choose injections over a pump. Pumps are significantly more expensive, and insurance coverage concerns are a deterrent. Alternately, some people choose not to continuously wear a device due to lifestyle preferences. A pump can only be removed for short periods of time, which is undesirable for some prospective users. Adding to the perceived inconvenience, certain activities, such as those involving water or contact sports, require extra consideration to protect an insulin pump. Another factor is ease of use; a pump is a complex device that can be difficult to learn to use and maintain — and errors in usage can lead to serious complications, such as severe hypoglycemia.

However, there remain a number of challenges to those who

self-administer their insulin injections. For some, particularly older people, diminished manual dexterity and eyesight can make it physically difficult to carry out their own injections. Additionally, multiple daily injections (MDIs) can be painful and cause scarring. Other challenges are less physical, such as fear of needles, or difficulty determining how much insulin to use and remembering doses.

Advances in injection technology that make insulin self-administration easier are growing ever more important in patient-centric diabetes care. For a long time, this primarily meant the development of injection aids. Now, advances in smart technology have opened up new options for people with diabetes. The following will explore how injection technology has made self-administration of insulin easier, and how it will continue to develop into the future.

OVERCOMING CHALLENGES WITH INJECTION AIDS

For some time, people with diabetes who use MDIs had to rely on injection aids to assist with any difficulty in self-administration. There are many kinds of injection aids, including modifications or attachments to traditional syringes or insulin pens. These aids typically help with physical challenges — such as by adding magnification to better read the numbers on a syringe. Several of these can meaningfully assist insulin users with the act of injection.

One example is the automatic insulin injector, which allows patients to insert a needle at the push of a button. A spring-loaded mechanism that actuates the needle behind a shield offers users control over drug delivery by manually pressing the syringe's plunger. Models, such as the Inject-Ease® from AmbiMedinc, are compatible with multiple syringe sizes and use spacer rings to control injection depth. Automatic injectors offer assistance to those with limited dexterity who might otherwise have difficulty properly inserting a needle or reaching the insertion point. Additionally, they provide an easier means of delivery for those who fear needles.

A different kind of aid is the temporary injection port, which is a short-term cannula that allows for multiple injections with just one skin puncture. A needle introduces a soft cannula that will remain in the patient's skin for several days, allowing the patient to use the same site to inject insulin with either a syringe or pen. For those who need as many as four injections a day, this significantly reduces the number of needle punctures: one 3-day port can eliminate the need for 11 additional injection sites. This can reduce pain, bruising, and scarring sometimes caused by MDIs, removing a deterrent to self-administration.

Another meaningful modification of injection devices has been to allow users to inject with just one hand. Often, patients use one hand to pinch tissue at the injection site to ensure the needle enters fatty tissue rather than muscle, while the other hand injects the insulin. Aids such as the TickleFLEX Insulin Injection Aid, are extensions that can be added to an insulin pen to increase the available area for injection by using arms to gather tissue on their own. This means insulin users are no longer limited to areas that can be reached by both hands, and reduces the scarring and the risk of lipohypertrophy caused by repeated injection in the same site.

These injection aids have, for the most part, been in use for several years. Though they do not significantly alter the basic function of syringes and insulin pens, they do provide solutions to material problems that many people with diabetes face in administering their own injections. Still, there are difficulties — particularly related to the cognitive strain presented by tracking, remembering, and calculating insulin doses — that these aids cannot solve, which require new and innovative approaches.

THE RISE OF SMART INJECTION TECHNOLOGY

Currently, advances in technology are taking insulin injection one step further. As more and more everyday items, from refrigerators to thermostats, are gaining smart connectivity for user convenience, so too are insulin delivery devices. Data connection and compatibility with devices, such as phones, are enabling people with diabetes to have more information at their disposal about their health and are helping them make decisions regarding insulin dosing.

For people using MDIs, smart insulin pens represent new possibilities for making their administration routine easier. One of the key advantages of these devices is the ability to sync up with, and process data from, a continuous glucose monitor (CGM). Rather than requiring as many as 10 finger pricks a day to check blood glucose levels, a CGM is a tiny sensor that is inserted beneath the skin to measure blood glucose every few minutes on an ongoing basis. These readings can then be sent to a smart pen, which processes the information and uses it to provide dosing recommendations that help users decide the right amount to take based on current data. Because calculat-

"Smart pens are only the beginning for people with diabetes looking for an improved experience with self-administration. As developers set their sights on more ambitious goals for insulin injection systems, and as technology advances, the options for insulin users will grow. Ultimately, one of the major goals of injection technology going forward is to create a fully closed loop system, also referred to as an artificial pancreas, which calculates and measures the appropriate dosing to manage the user's blood glucose levels without any outside intervention."

ing the correct dosage with every injection can be mentally taxing for people with diabetes, having a recommendation based on their current levels removes a huge burden.

Smart pens can also help users by tracking doses. Insulin injections can become so routine that people with diabetes sometimes have trouble remembering when they have last administered a dose, or what that dose was. With smart pens, insulin users no longer need to rely on memory or on keeping their own log. Instead, dose history is automatically recorded and stored for easy reference. More importantly, the pen can provide reminders when it is time for another injection.

Another function of smart pens is to provide notifications for a variety of user concerns. For example, if the insulin is exposed to high temperatures that might render it unusable, or if it is set to expire soon, the pen can let the user know so that the cartridge can be replaced.

All of this is made even easier for smart pen users by the fact that most smart pens work with an associated mobile app. The smart pens automatically upload information, such as dose history or blood glucose levels, to the app for easy access, in addition to including helpful tools, such as dose calculators. As the use of smartphones has become the norm in countries around the world, this creates an easy integration of the smartpen and the advantages it offers into everyday life.

A number of developers are seeing the potential offered by smart insulin pens. A recently released study showed that the Medtronic InPen™, the first smart pen to be approved by the FDA, increased the amount of time that patients spent in their desired blood glucose range, among other positive results.[1]

Other smart insulin pens are entering the market as well. The Bigfoot Unity™ Diabetes Management System was approved by the FDA in May, offering greater levels of decision support, including a connected insulin pen cap that tracks long- and short-term insulin doses. Other pharmaceutical companies, such as Lilly and Novo Nordisk, currently have smart insulin pens in development.

Smart patches may soon provide another option for patients who cannot or do not want to use pumps. Transdermal insulin patches, which use preloaded microneedles to deliver insulin subcutaneously, have been available for some time. However, researchers have been working to develop patches made with a glucose-responsive polymeric matrix that can respond to blood glucose and release insulin accordingly.[2] While these patches are still early in testing, they may someday present a less invasive and less painful choice that requires little daily intervention on the part of the user.

THE PURSUIT OF A CLOSED LOOP

Smart pens are only the beginning for people with diabetes looking for an improved experience with self-administration. As developers set their sights on more ambitious goals for insulin injection systems, and as technology advances, the options for insulin users will grow.

Ultimately, one of the major goals of injection technology going forward is to create a fully closed loop system, also referred to as an artificial pancreas, which calculates and measures the appropriate

dosing to manage the user's blood glucose levels without any outside intervention. While there is some level of automation in insulin delivery, the technology currently approved for use is only a hybrid closed loop, which means that the user must intervene to compensate for mealtime spikes in blood glucose levels. In many cases, a fully closed-loop system refers to an insulin pump — but not always.

Even for people who use MDIs, automated insulin delivery is on the horizon. Though these individuals will still need to administer the physical injections, advances in monitoring and the algorithms used to calculate correct dosing will mean it will take progressively less decision-making or input on the part of the user. The goal is to someday make the process so fully automated that the user will only have to perform the injection, and the smart pen and related technology will do the rest.

Advances in artificial intelligence (AI) may have a large role to play in achieving that closed loop. AI is being integrated with injection devices to better assess fluctuations in blood glucose levels and to determine whether they are being caused by meals, allowing for faster and more appropriate insulin response.[3] As better AI further develops, users will need to do less, and eventually, little to no mental work to ensure they are taking the right dose at the right time, making self-administration progressively easier.

KEEPING PATIENT NEEDS IN MIND

Though injection devices, such as syringes and insulin pens, have remained the standard for people with diabetes for a long time, there is still a great deal of room to grow in making those devices easier to use. While injection technology is making great strides in its ability to maintain users' health, it remains just as important to continue to find ways to minimize the everyday challenges they face in administering their own insulin injections. Advances, such as smart pens and closed loop systems, offer the opportunity for insulin users to reduce some of the mental burden that comes with MDIs and make injection a smoother part of their routine. And after all, technology can only help if people are able to use it. ◆

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BIOGRAPHY

David T. Novotny is the General Manager & Global Head of ICON's Medical Device and Diagnostic Research business unit. He has more than 18 years of experience within the medical device, diagnostic, biotech, and clinical industries. He has held leadership roles in Sponsor and CROs companies as well as in-clinic appointments. He is also an industry consultant and author to the life-science industry for the past 10 years across the product development lifecycle and clinical research field. His working experience includes strategic business development, quality systems, technology integration, business optimization, clinical operations including program management and market access. His global expertise in operations and market intelligence enables him to support clients in key markets like North America, EMEA, and Asia.

Technology & Services Showcase

Specialty CDMO

Adare Pharma Solutions is a global technology-driven CDMO providing end-to-end integrated services, from product development through commercial manufacturing and packaging, with expertise focusing on oral dosage forms for the pharmaceutical industry. Our specialized technology platforms provide taste masking, controlled release, solubility enhancement, and patient-centric dosing solutions. We have developed and manufacture more than 45 products sold by customers worldwide. We have the expertise and proven track record to guide projects from clinical research stages through optimization, validation, and approval. We operate seven facilities in the US and Europe, equipped to facilitate efficient drug product development and manufacturing, maintaining excellent environmental conditions compliant with US and EU cGMP regulations. Our in-house regulatory and quality teams have a proven global track record, assuring that products we manufacture are provided with the highest relevant standards for patient care. For more information, visit Adare Pharmaceuticals at **www.Adarepharmasolutions.com.**

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

Platform Technology

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

OptiDose® Design Solution

Catalent's OptiDose Design Solution integrates pharmaceutics, critical CMC and DMPK parameters, and dose form design target patient characteristics to create differentiated treatments that are successful for innovators, patients and healthcare professionals. The methodology combines data-driven scientific tools with Catalent's extensive development expertise. Patient needs and market realities are considered upfront in the process, to guide development decisions and ensure a product with the optimal combination of patient acceptance and adherence, as well as differentiation from existing standards of care. By taking an agnostic evaluation of a molecule against potential dose form technologies, products can be designed to maximize their potential using Catalent's broad technology toolkit, which includes advanced softgel solutions, as well as Zydis® orally dissolving tablets, and FlexDose℠ stick pack solutions. For more information, contact Catalent Pharma Solutions at (888) SOLUTION or visit **www.catalent.com.**

Technology & Services Showcase

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Celanese Corporation is a global chemical leader in the production of differentiated chemistry solutions and specialty materials used in most major industries and consumer applications. Our VitalDose® EVA drug delivery platform offers the flexibility for formulators to design patient-centric dosage forms for effective long-acting, controlled release of both small and macro molecules. We work closely with you as a strategic partner from concept to commercialization providing development services, material supply aligned with GMP principles, and regulatory support. For more information, visit **healthcare.celanese.com/.**

Formulation Technology

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

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With application and R&D Centers in the United States, France, India, and China, the **Gattefossé** group is providing formulation support for oral, topical, transdermal, and other routes of administration. Equipped with state-of-the-art analytical and processing instruments, we stand to assist with your projects at all stages of development, from solubility screening to late-stage formulation and "proof-of-concept" studies. Moreover, we provide extensive regulatory support, sharing toxicological and safety data, and analytical/characterization methods. For more information, visit Gattefossé at **www.gattefosse.com.**

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Jubilant Pharma Limited (JPL), a company incorporated under the laws of Singapore and a wholly owned subsidiary of Jubilant Pharmova Limited, is an integrated global pharmaceutical company engaged in manufacturing and supply of Radiopharmaceuticals, Allergy Therapy Products, Contract Manufacturing of Sterile Injectables and Non Sterile products, APIs, and Generics, through six US FDA- approved manufacturing facilities in the US, Canada, and India and a network of 49 radiopharmacies in the US. The company has a team of around 5,200 multicultural people across the globe. It is well recognized as a Partner of Choice by leading pharmaceutical companies globally. For more information, visit Jubilant Pharma at **www.jubilantpharma.com.**

Technology & Services
SHOWCASE

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MITSUBISHI GAS CHEMICAL

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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PharmaCircle is a leading provider of global data and analysis on the pharmaceutical, biotechnology, and drug delivery industries. PharmaCircle's premier database delivers an integrated scientific, regulatory, and commercial landscape view with unprecedented access to hundreds of company, product, and technology attributes. PharmaCircle connects product and pipeline information for drugs and biologics with formulation and component details, and provides due diligence level data on nearly 6,000 drug delivery technologies and devices. Drug label comparison tools and full-text document search capabilities help to further streamline research. No other industry database matches PharmaCircle's breadth of content and multi-parameter search, filtering, and visualization capabilities. To learn more, email contact@pharmacircle.com, call (800) 439-5130, or visit **www.pharmacircle.com.**

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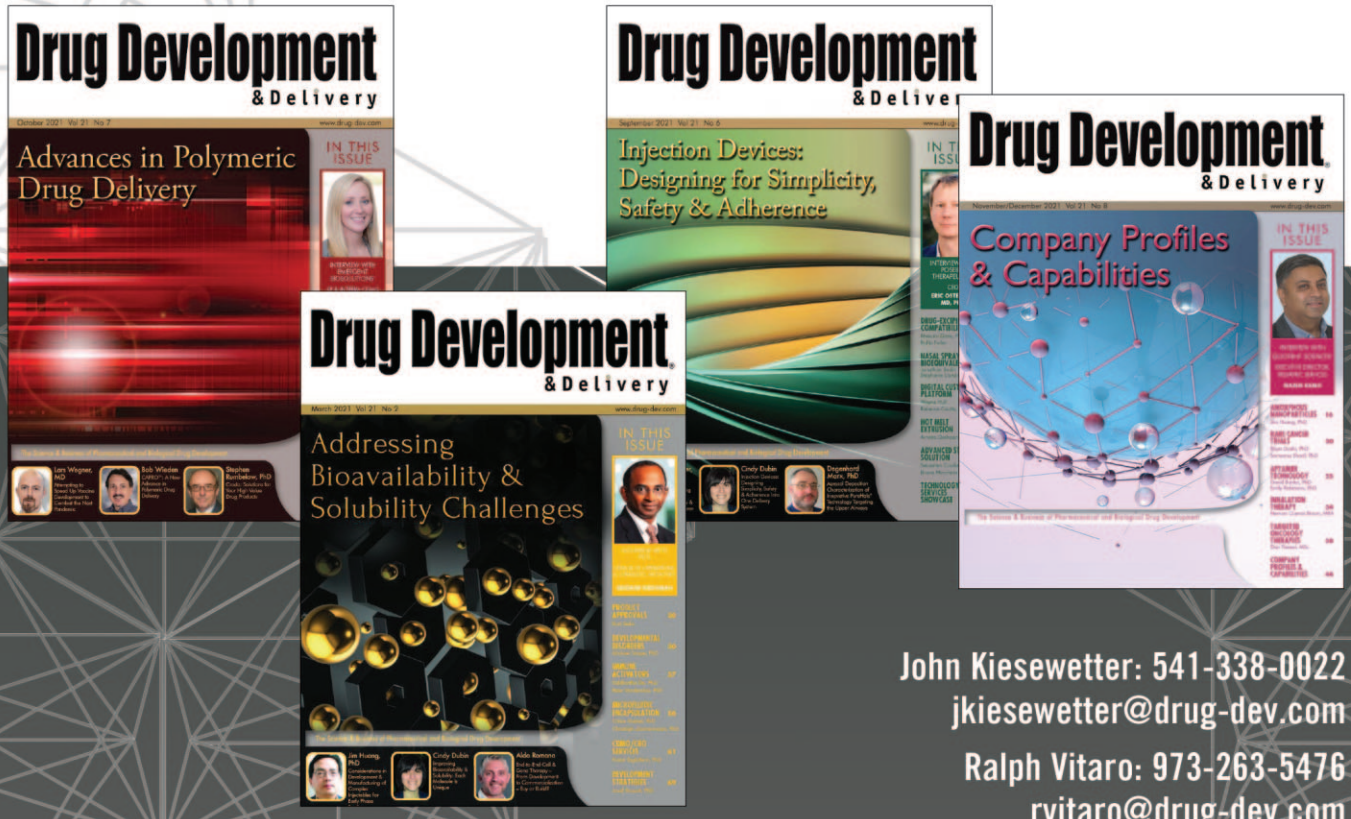

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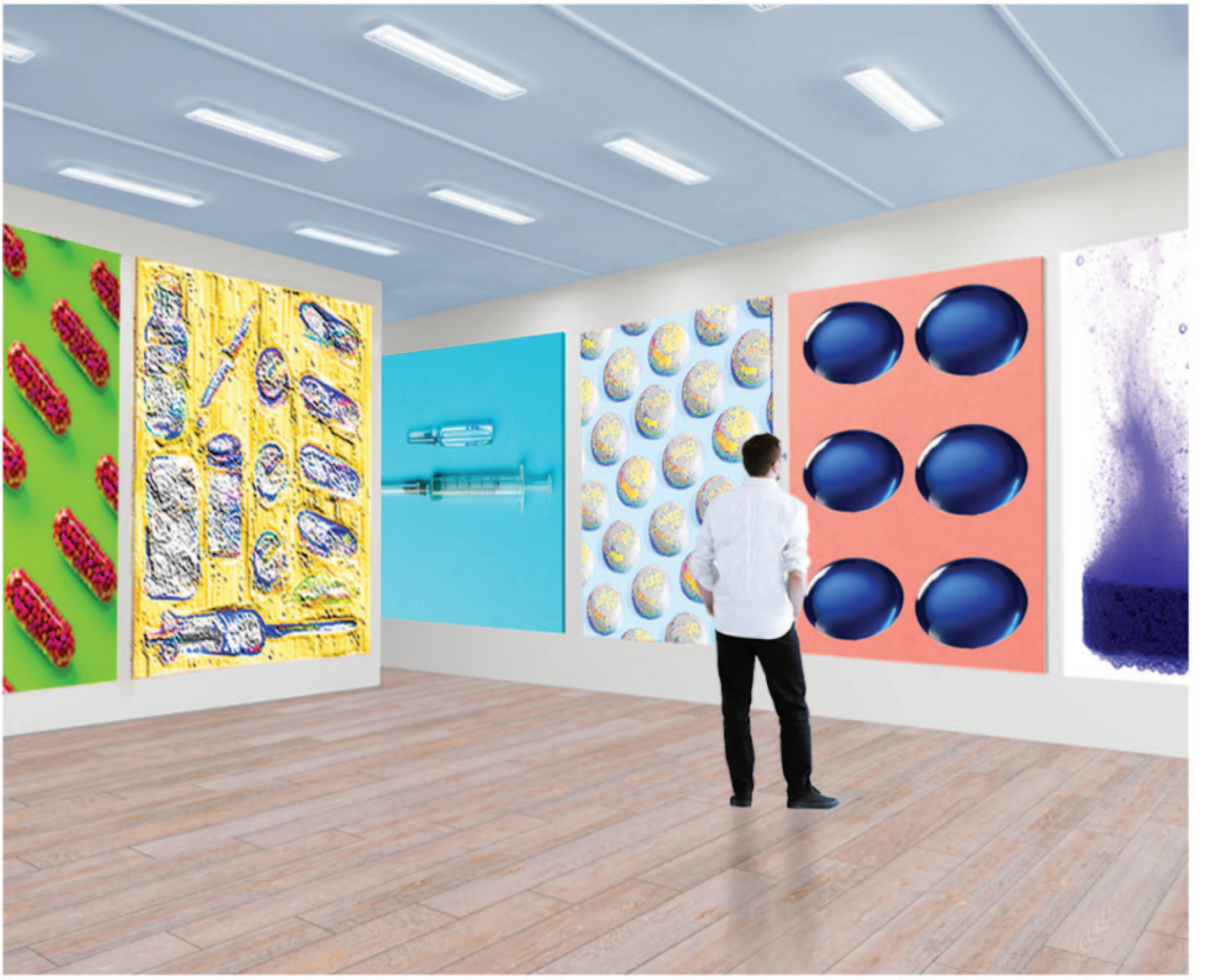

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