Drug Development® & Delivery

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The Science & Business of Pharmaceutical and Biological Drug Development

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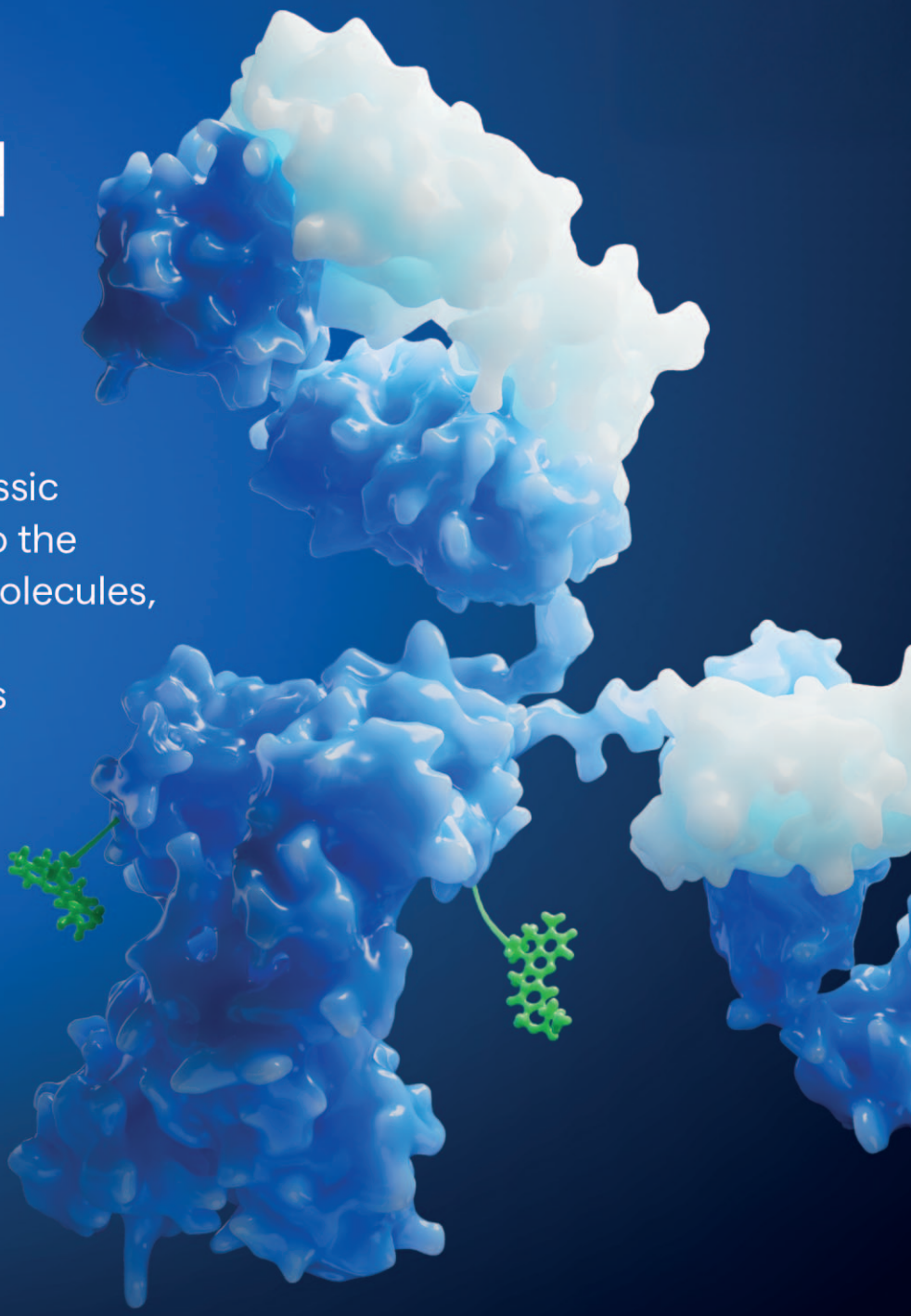

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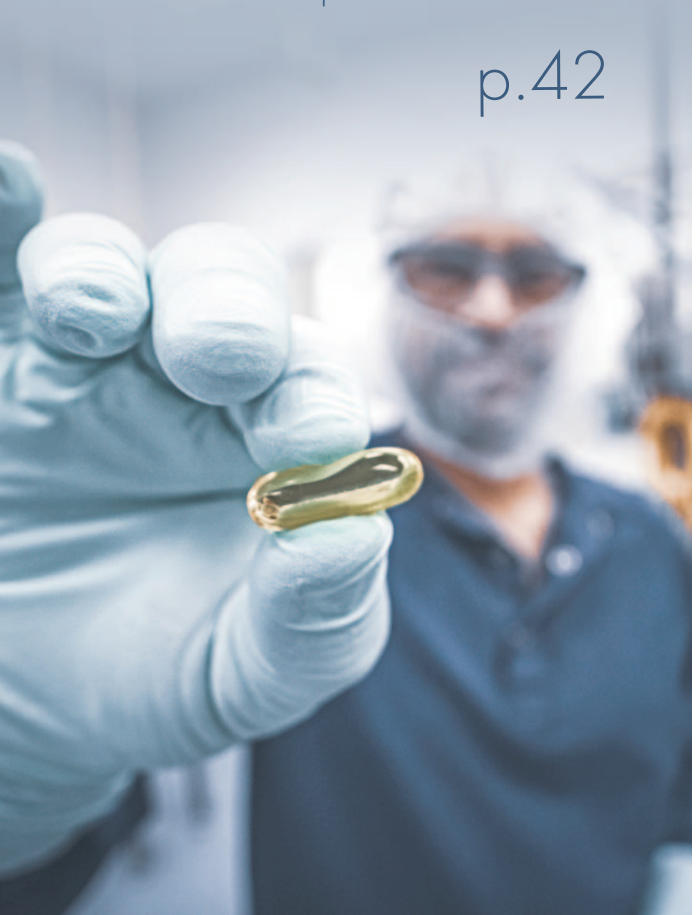
Bioavailability & Solubility

"There is somewhat of a consensus in life sciences that there have been significant advancements in improving bioavailability. Solubility, however, continues to elude formulators. Excipients are often lauded as a solution to tackling these challenges, but still do fall short. In a 2020 US Pharmacopeia (USP) survey of drug formulators, 84% said that the current roster of excipients present in approved drug products has imposed limitations on drug development, and as many as 28% experienced a discontinuation of drug development as a result of excipient limitations."

p.42



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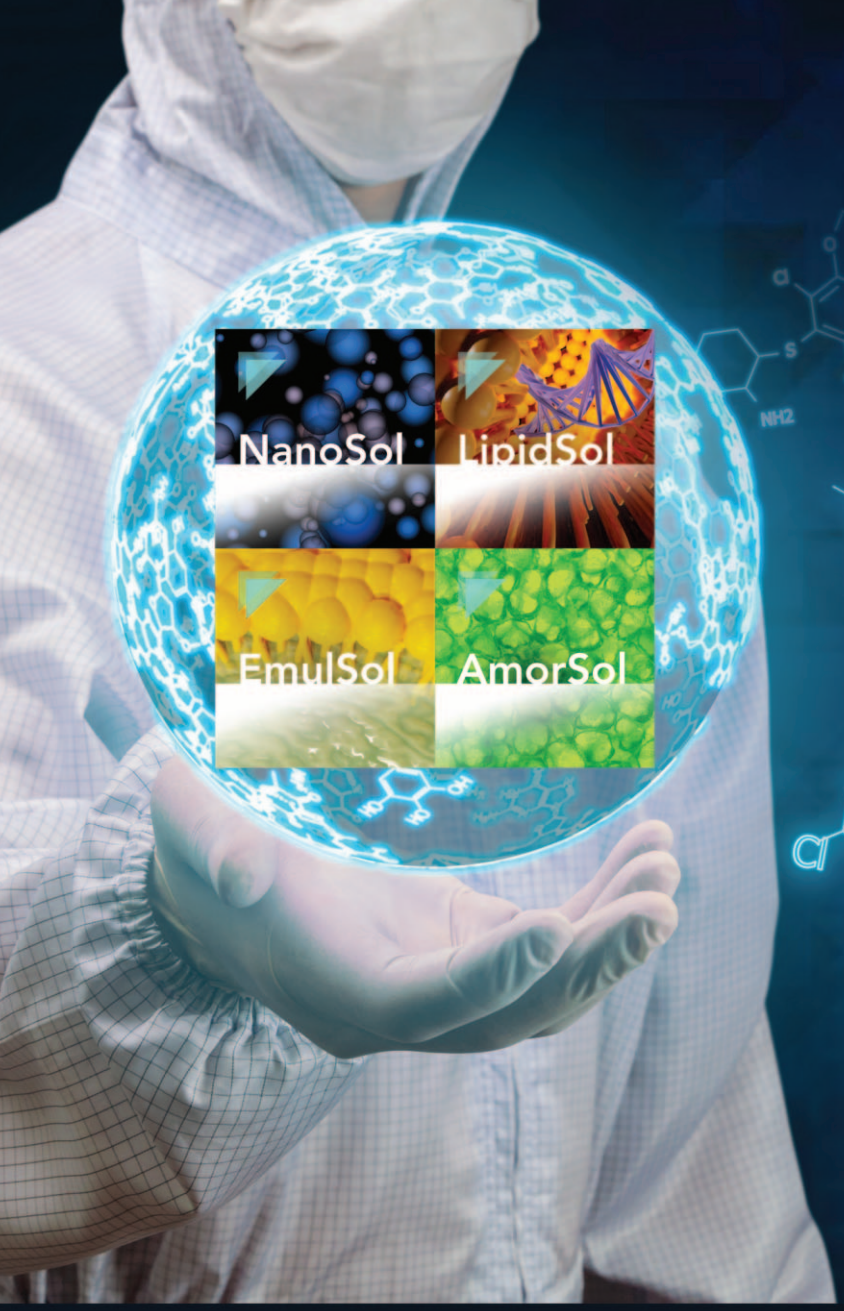

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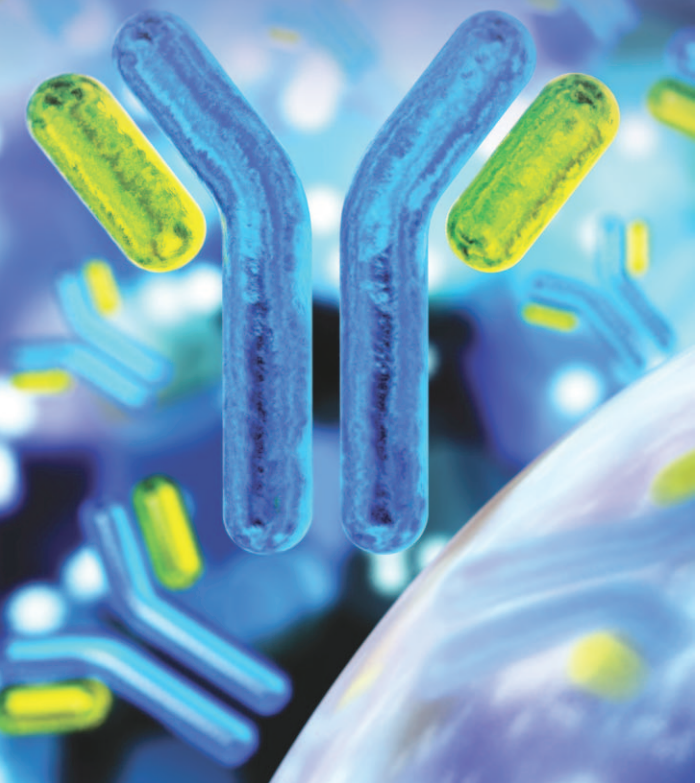
ADC Payloads

"The recent progress in research on novel camptothecin payloads highlights the potential for developing a new generation of ADCs that can overcome some of the limitations of first-generation therapies. As drug developers explore innovative technologies and strategies, interest in ADCs is poised to continually expand. Lessons learned from developing novel ADC payloads, including camptothecin analogs, suggest multiple opportunities exist to improve ADC design, despite the complexity of these molecules."

p.72



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Revive Therapeutics Announces Acquisition of Molecular Hydrogen Program

Revive Therapeutics Ltd. recently announce that further to its press release dated March 3, 2025, it has entered into an asset purchase agreement dated March 31, 2025 with DiagnaMed Holdings Corp. (CSE: DMED) (OTCQB: DGNMF) to acquire the full rights to DiagnaMed's intellectual property pertaining to molecular hydrogen as potential treatments for neurological and mental health disorders.

Pursuant to the Agreement, the consideration for the Acquired Assets will be satisfied through the issuance to DiagnaMed of one million common shares of Revive, at an issue price of $0.05 per share, representing a purchase price of $50,000. The issuance of the common shares is subject to regulatory approvals, including the CSE, and will be subject to restrictions on resale under applicable securities laws. There are no further financial terms, including milestones, royalties or other monetary obligation payments pursuant to the Agreement.

The Acquired Assets will include all of the following: (1) Provisional patent application with the U.S. Patent and Trademark Office outlining pharmaceutical-based methods and compositions for producing molecular hydrogen as potential treatments for neurological and mental health disorders. The patent application, entitled "Methods and Compositions for Producing Hydrogen for Treating Diseases and Disorders Affecting Brain Health," outlines novel combinations of certain pharmaceutical-grade hydrogen producing ingredients as a potential therapeutic option for a variety of neurological disorders such as, but not limited to, Dementia, Parkinson's disease, and Traumatic brain injury, and mental health disorders including, Depression, Anxiety, and Post-traumatic stress disorder (press release). (2) All intellectual and work property derived from DiagnaMed's research activities in amyotrophic lateral sclerosis (ALS) and its Orphan Drug Designation (ODD) for molecular hydrogen in the treatment of ALS by the U.S. Food and Drug Administration (FDA).

Michael Frank, CEO of Revive, commented: "This acquisition expands Revive's pipeline to brain disorders. Molecular hydrogen may offer a potential therapeutic option for neurological and mental health disorders. The orphan drug designation granted by the FDA for molecular hydrogen in ALS offers hope to patients and families impacted by this debilitating illness. We are committed to collaborating with leading ALS researchers, patient advocacy groups, and regulatory experts to ensure a rigorous and expedited path toward potential approval."

ALS is a progressive neuromuscular disease that attacks nerve cells responsible for controlling voluntary muscle movement, leading to paralysis and, ultimately, respiratory failure, and has a life expectancy of only two to six years after diagnosis. Currently, there is no known cure for ALS. ALS affects approximately 50,000 people in the U.S. and Europe, with over 5,000 new cases diagnosed annually. With limited treatment options available, the FDA's recognition of molecular hydrogen as an orphan drug offers hope to patients and families impacted by this debilitating illness.

Molecular hydrogen, a small molecule with antioxidant and anti-inflammatory properties, has shown early promise in preclinical studies for its ability to mitigate oxidative stress and inflammation – key factors implicated in ALS progression. The FDA's decision paves the way for Revive to accelerate its development programs with molecular hydrogen.

Gyre Therapeutics Announces NMPA Approval for Clinical Trial Evaluating Pirfenidone Capsules in Oncology-Related Pulmonary Complications

Gyre Therapeutics recently announced that the National Medical Products Administration (NMPA) of the People's Republic of China (PRC) has approved its clinical trial application for a potential new indication for pirfenidone in oncology-related pulmonary complications. The trial will evaluate pirfenidone capsules for the treatment of radiation-induced lung injury (RILI), with or without immune-related pneumonitis (CIP).

This regulatory milestone marks the expansion of pirfenidone beyond its established role in idiopathic pulmonary fibrosis (IPF) into the oncology supportive care space, offering a novel lung-protective strategy for cancer patients undergoing radiation therapy or immunotherapy.

In accordance with the NMPA approval, Gyre intends to pursue an adaptive Phase 2/3 clinical trial design, combining dose exploration with efficacy confirmation, to efficiently evaluate pirfenidone's potential in this new indication.

Radiation-Induced Lung Injury (RILI): Radiation therapy is a cornerstone of lung cancer treatment. However, 5%–25% of patients experience lung damage due to radiation exposure, limiting the ability to escalate doses and thereby compromising treatment efficacy.

Checkpoint Inhibitor Pneumonitis (CIP): Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment, but 13%–19% of patients develop CIP. This condition accounts for approximately 35% of immune-related adverse event (irAE) deaths and often necessitates treatment discontinuation.

Currently, no targeted therapies exist for lung injuries caused by radiation or immunotherapy. Distinguishing between RILI and CIP is challenging, particularly when both occur concurrently. Corticosteroids remain the standard of care despite significant long-term side effects. By targeting and inhibiting fibrotic pathways, pirfenidone may address the root cause of lung injury progression, offering a new treatment option for patients receiving radiation or immunotherapy.

Gyre anticipates initiating the trial in the second half of 2025 at leading academic and oncology centers across the PRC.

Pirfenidone is an orally administered small molecule approved for the treatment of IPF. It works by inhibiting TGF-β signaling and fibroblast proliferation. The drug has demonstrated clinical benefit in slowing lung function decline in IPF and is now being evaluated for oncology-related pulmonary complications. Gyre has held first-in-class status for pirfenidone in the PRC since its original approval in 2011, underscoring its pioneering role in treating fibrotic lung diseases.

Gyre Therapeutics is a biopharmaceutical company headquartered in San Diego, CA, primarily focused on the development and commercialization of F351 (Hydronidone) for MASH-associated fibrosis in the U.S. Gyre's strategy builds on its experience in mechanistic studies using MASH rodent models and clinical studies in CHB-induced liver fibrosis. In the PRC, Gyre is advancing a broad pipeline through its indirect controlling interest in Gyre Pharmaceuticals, including therapeutic expansions of ETUARY, and development programs for F573, F528, and F230.

DDL Launches New GMP Lab for Drug Delivery Testing

DDL, a leading provider of package, product, and material testing services, recently announce the opening of a new Good Manufacturing Practice (GMP) laboratory dedicated to drug-device combination product testing. This expansion enhances DDL's capacity to support the pharmaceutical, biotech and combination product industries with rigorous, regulatory-compliant testing solutions.

The new FDA registered 10,600-sq-ft GMP lab is located near DDL's Eden Prairie, MN headquarters. The lab will offer ICH stability testing, functional and mechanical performance testing (ISO 11040 & ISO 11608) and simulated distribution testing to meet the growing demand for high-quality GMP testing for devices such as auto injectors, pre-filled syringes, inhalers, and other combination products. With state-of-the-art equipment and an experienced team of engineers, DDL's new facility will provide comprehensive testing solutions in accordance with FDA, ISO, and other global regulatory standards.

"We are excited to expand our testing footprint with this new GMP laboratory, reinforcing our commitment to providing high-quality, reliable testing services to our medical device and pharmaceutical clients," said Aaron Liss, Director of Sales & Marketing, DDL, Inc. "This new GMP offering builds upon our 35 years of industry experience allowing DDL to collaborate with an entirely new host of healthcare providers."

"As the market for combination products continues to grow, our investment in this new facility will help ensure that manufacturers have access to the expertise and resources they need to bring safe and effective products to market," stated John Koch, General Manager, DDL, Inc. "DDL's investment in this GMP laboratory underscores its ongoing commitment to excellence in testing services for the life sciences industry. The company remains focused on delivering precise, reliable, and regulatory-compliant results to support clients in their product development and regulatory submission processes."

DDL will be highlighting its GMP testing capabilities, as well as its package, medical device and material testing service offerings in Booth #1143 at the INTERPHEX conference being held April 1-3, 2025 at the Javits Center in New York, NY. For more information on DDL's testing services, or to receive a quote, please contact DDL at DDLinfo@ddltesting.com or call us at 800-229-4235.

DDL is a third-party independent testing company that offers expertise in medical device, materials and package testing primarily serving the life sciences industry. DDL's testing laboratories are located in Eden Prairie, MN, Irvine, CA and Edison, NJ.

Apollomics & LaunXP Announce Development & Commercialization Agreement for Vebreltinib

Apollomics Inc. and LaunXP International Co., Ltd. recently announced the parties have entered into an agreement for the development and commercialization in Asia (excluding mainland China, Hong Kong and Macau) (the LaunXP Territory) of vebreltinib, Apollomics' proprietary c-Met inhibitor, in combination with an EGFR inhibitor (EGFRi) for the treatment of NSCLC. The EGFRi class of targeted kinase inhibitors is currently a foundational targeted therapy for the treatment of NSCLC and other tumor types.

"We are delighted to partner with LaunXP, who share our vision for the commercial opportunity for vebreltinib. EGFRi is currently the frontline treatment for many patients with NSCLC, and combining it with our c-Met inhibitor vebreltinib is expected to transform the standard of care," said Dr. Guo-Liang Yu, CEO of Apollomics. "We believe that LaunXP can advance this development program rapidly in this patient population, bringing us closer to potentially improving outcomes for many patients with NSCLC. We will continue to seek opportunities to maximize the global opportunity for vebreltinib, both as a single agent and in combination approaches for the treatment of cancers."

"We are thrilled to announce this collaboration with Apollomics. We believe the preclinical and clinical data supporting the combination of a c-Met inhibitor with an EGFRi is compelling," said Dr. Chiu-Heng Chen, Chairman and President of LaunXP. "By delaying the emergence of mutations which cause EGFRi resistance, we hope to demonstrate clinically that better patient outcomes can be achieved."

Under the terms of the agreement, Apollomics is to receive upfront payments totaling $10 million within 60 days of the date of the agreement. Apollomics is also eligible for regulatory and other pre-commercial milestones up to $50 million, and royalties on net product sales. LaunXP will be primarily responsible for the development of vebreltinib in combination with an EGFRi in the LaunXP territory for the treatment of NSCLC.

Vebreltinib is a potent, small molecule, orally bioavailable and highly selective c-MET inhibitor. It works by inhibiting the aberrant activation of the HGF/c-MET axis, a key pathway involved in tumor growth, proliferation, and the development of resistance to certain targeted therapies such as osimertinib. By targeting c-MET dysregulation, vebreltinib has demonstrated strong tumor inhibitory effect in a variety of preclinical c-MET dysregulated human gastric, hepatic, pancreatic and lung cancer xenograft animal models and patient-derived xenograft models (PDX).

Details on the Phase 1/2 SPARTA global clinical trial can be found on clinicaltrials.gov: NCT03175224. Apollomics is developing vebreltinib as single-agent cancer therapy in a variety of tumor types and actively assessing the potential of vebreltinib in combination with novel therapies. Avistone, Apollomics' partner in China, has received conditional approval from the National Medical Products Administration (NMPA) of China for vebreltinib for multiple indications. Vebreltinib is currently under clinical investigation and not approved for any use in any other regions in the world.

NeOnc Technologies Receives Rare Pediatric Disease Designation for NEO100 in Treatment of Pediatric-Type Diffuse High-Grade Gliomas

NeOnc Technologies Holdings, Inc. recently announced the US FDA has granted Rare Pediatric Disease Designation (RPDD) to perillyl alcohol (NEO100) for the treatment of pediatric-type diffuse high-grade gliomas, a serious and life-threatening condition affecting children and adolescents.

The designation, issued under Section 529(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), recognizes the urgent need for treatment options for pediatric-type diffuse high-grade gliomas. The FDA's decision is based on findings that the disease primarily affects individuals from birth to 18 years and meets the statutory definition of a "rare disease or condition."

"This designation marks a significant milestone in our efforts to develop innovative therapies for children battling this aggressive form of brain cancer," said Amir Heshmatpour, Executive Chairman, NeOnc Technologies Holdings, Inc. "We remain committed to advancing NEO100 through clinical development to bring new hope to patients and families facing this devastating disease."

"Receiving the Rare Pediatric Disease Designation for NEO100 is a crucial step forward in our mission to develop effective treatments for children facing diffuse high-grade gliomas," said Dr. Thomas Chen, CEO and Chief Science Officer of NeOnc Technologies Holdings, Inc. "This designation not only validates the potential of our research, but also strengthens our commitment to delivering innovative therapies that can make a real difference in children's lives."

The Rare Pediatric Disease Designation makes NeOnc Technologies eligible to receive a Rare Pediatric Disease Priority Review Voucher (PRV) upon approval of NEO100's marketing application. The PRV program is designed to encourage the development of new drugs and biologics for rare pediatric diseases by providing companies with an expedited regulatory review process. These vouchers, which are transferable and have been sold in recent years, have significant strategic and financial value, depending on market conditions and demand.

"Currently, there is a dynamic market for PRV's, which are quite valuable," added Heshmatpour. "This potential asset further underscores the value of our progress, especially for the patients and families we aim to serve."

As NeOnc Technologies continues to progress NEO100 through clinical trials, the company remains dedicated to working closely with the FDA and the broader medical community to bring this promising therapy to children in need. The company encourages collaboration with researchers, healthcare providers, and patient advocacy groups to further accelerate advancements in pediatric brain cancer treatment.

NeOnc Technologies Holdings, Inc. is a clinical-stage life sciences company focused on the development and commercialization of central nervous system therapeutics that are designed to address the persistent challenges in overcoming the blood-brain barrier. The company's NEO drug development platform has produced a portfolio of novel drug candidates and delivery methods with patent protections extending to 2038.

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CERo Therapeutics Holdings Receives FDA Clearance of Second Investigational NDA to Initiate Phase 1 Clinical Trial of Lead Compound CER-1236 in Solid Tumors

CERo Therapeutics Holdings, Inc. recently announced it has received clearance by the US FDA for a second Investigational New Drug (IND) application for lead compound CER-1236 for a Phase 1 clinical trial in advanced solid tumors, specifically non-small cell lung cancer and ovarian cancer.

CERo Chief Medical Officer Robert Sikorski, M.D., Ph.D. commented, "Following the launch of our AML trial, we are now starting a second clinical study of CER-1236 to evaluate its potential in solid tumors and bring new therapeutic options to patients with ovarian and lung cancer," said Robert Sikorski, M.D., Ph.D., Chief Medical Officer of CERo. "CER-1236 is novel: the first CAR-T cell therapy to target Tim-4L and the first with phagocytic activity programmed into a T cell. Preclinical data suggest that this dual mechanism may help overcome key resistance barriers that have hampered solid tumor CAR-T trials. The FDA's collaborative role has been critical to maintaining development velocity and enabling us to operate two open trials in both hematologic and solid tumors. Taken together, this expansion reflects our belief in the therapeutic breadth and the commercial and partnering potential of CER-1236."

The company recently announced data showing that CER-1236 treated ovarian cancer cells and did not generate toxicity in animal models (mice). Investigators found that following dosing, assessment of clinical and anatomic pathology after CER-1236 infusion showed T cell engraftment in lymphoid organs, but there were no in-life observations, clinical pathology, nor histopathological evaluations indicating toxicity caused by the compound.

"Of note, our team has been simultaneously progressing our Phase 1 AML trial in the US. Their incredible efforts cannot be under-emphasized, and I wish to convey my gratitude to our extremely competent and efficient team. We are looking forward to sharing progress on each of our two Phase 1 clinical trials in the near term," added CERo CEO Chris Ehrlich.

CERo is an innovative immunotherapy company advancing the development of next generation engineered T cell therapeutics for the treatment of cancer. Its proprietary approach to T cell engineering, which enables it to integrate certain desirable characteristics of both innate and adaptive immunity into a single therapeutic construct, is designed to engage the body's full immune repertoire to achieve optimized cancer therapy. This novel cellular immunotherapy platform is expected to redirect patient-derived T cells to eliminate tumors by building in engulfment pathways that employ phagocytic mechanisms to destroy cancer cells, creating what CERo refers to as Chimeric Engulfment Receptor T cells (CER-T). CERo believes the differentiated activity of CER-T cells will afford them greater therapeutic application than currently approved chimeric antigen receptor (CAR-T) cell therapy, as the use of CER-T may potentially span both hematological malignancies and solid tumors. CERo anticipates initiating clinical trials for its lead product candidate, CER-1236, in 2025 for hematological malignancies.

Conduit Pharmaceuticals Receives US Patent Approval for Its Lead Asset Targeting Autoimmune Diseases

Conduit Pharmaceuticals Inc. recently announced that the United States Patent and Trademark Office (USPTO) has granted the composition of matter patent for its lead asset, AZD1656, a Glucokinase Activator targeting autoimmune diseases, including Lupus and ANCA Vasculitis. With this critical composition of matter patent protection now secured, the Company is strategically positioned to advance AZD1656 into clinical development, with clinical trial plans now in final stages of preparation.

The US autoimmune disease market is projected to reach $150 billion by 2030, with Lupus affecting approximately 1.5 million Americans and ANCA Vasculitis impacting 200,000 patients annually. This growing market reflects the increasing prevalence of autoimmune conditions and the demand for innovative treatments. Conduit's newly granted US composition of matter patent, complemented by existing approvals in Japan and Australia, provides partners with a dominant IP position in three major pharmaceutical markets, with pending applications in Europe and other regions expected to further expand this footprint. Through this approval, Conduit has secured up to 20 years of composition of matter patent protection in the US, reinforcing its competitive positioning and opening the door to commercial and strategic licensing and partnership opportunities.

Composition of matter patents, classified as "drug substance" patents in the US FDA's Orange Book, represent the gold standard in pharmaceutical intellectual property, providing strong market exclusivity and robust protection against generic competition.

"Securing USPTO approval for AZD1656's composition of matter patent is a major milestone, further solidifying our intellectual property portfolio and strategic value," said Dr. David Tapolczay, Chief Executive Officer of Conduit Pharmaceuticals. "With the composition of matter patent now in place in this critical market, this also indicates an increased likelihood of patent success in the outstanding additional geographies worldwide."

Conduit is a dynamic, multi-asset clinical stage, life science company delivering an efficient model for compound development. Conduit both acquires and funds the development of Phase 2-ready assets, building an integrated and advanced platform-driven approach powered by artificial intelligence (AI) and cybernetics, and seeking an exit through third-party license deals following successful clinical trials. Led by a highly experienced team of pharmaceutical executives including Dr. David Tapolczay and Dr. Freda Lewis-Hall, this novel approach is a departure from the traditional pharma/biotech business model of taking assets through regulatory approval.

LIXTE Launches New Study to Determine if Certain Pre-Cancerous Cells Found in an Aging Population Can Be Eliminated by LB-100

LIXTE Biotechnology Holdings, Inc recently announced it will conduct a new pre-clinical study in collaboration with Netherlands Cancer Institute (NKI) to test whether "initiated" cells that carry mutations found in cancer cells can be eliminated by treatment with LIXTE's proprietary compound LB-100.

"In addition to our ongoing clinical trials in ovarian and colorectal cancer, this study represents a new opportunity in cancer prevention," said Bas van der Baan, LIXTE's Chief Executive Officer. "Thus far in our Phase 1 clinical trials, LB-100 has shown patient tolerance, with little toxicity, making it a promising candidate as a broad and effective cancer prevention modality."

Increasing evidence indicates that as individuals age, certain mutations accumulate that are found in cancer cells. While these "initiated" cells behave essentially normally, they can propagate to form reservoirs of pre-malignant cells from which malignant cells may eventually emerge. Recent data from LIXTE's ongoing clinical collaboration with NKI shows that LB-100 activates oncogenic signaling and that this is detrimental to cancer cells.

The new study in animal models will investigate whether "initiated" cells, harboring a mutant RAS oncogene, can be eliminated with LB-100. If successful, LB-100 could have a significant role in the elimination of initiated cells in aged individuals and could reduce the risk of developing a wide range of cancers as a person ages.

The study will be led by René Bernards, Ph.D., a global leader in the field of molecular carcinogenesis and Senior Staff Scientist at NKI, one of the world's leading comprehensive cancer centers. Dr. Bernards also is a member of LIXTE's Board of Directors.

LIXTE Biotechnology Holdings, Inc. is a clinical-stage pharmaceutical company focused on new targets for cancer drug development and developing and commercializing cancer therapies. LIXTE has demonstrated that its first-in-class lead clinical PP2A inhibitor, LB-100, is well-tolerated in cancer patients at doses associated with anti-cancer activity. Based on extensive published preclinical data LB-100 has the potential to significantly enhance chemotherapies and immunotherapies and improve outcomes for patients with cancer.

LIXTE's lead compound, LB-100, is part of a pioneering effort in an entirely new field of cancer biology – activation lethality – that is advancing a new treatment paradigm. LIXTE's new approach is covered by a comprehensive patent portfolio. Proof-of-concept clinical trials are currently in progress for colon, small cell lung and sarcoma cancers.

Lexicon Pharmaceuticals Announces Exclusive License Agreement With Novo Nordisk

Lexicon Pharmaceuticals, Inc. recently announced it has entered into an exclusive license agreement with Novo Nordisk A/S for LX9851, a first-in-class, oral non-incretin development candidate in obesity and associated metabolic disorders. Under the terms of the agreement, Novo Nordisk obtains an exclusive, worldwide license to develop, manufacture and commercialize LX9851 in all indications. Lexicon will be responsible for completing agreed upon Investigational New Drug (IND) application-enabling activities for LX9851. Novo Nordisk will be responsible for filing the IND, all further development, manufacturing and commercialization of LX9851.

Lexicon is eligible to receive upfront and near-term milestone payments of up to $75 million. In total, Lexicon will be eligible to receive $1 billion in upfront and potential development, regulatory and sales milestone payments. Lexicon is also entitled to tiered royalties on net sales of LX9851.

LX9851, discovered and developed by Lexicon, is a potent and selective oral small molecule inhibitor of Acyl-CoA Synthetase 5 (ACSL5). ACSL5 plays a key role in the metabolic pathway which regulates fat accumulation and energy balance. Additionally, LX9851 may activate the ileal brake mechanism leading to increased satiety by delaying gastric emptying and suppressing appetite. Preclinical in vivo efficacy data presented at Obesity Week 2024 show that LX9851, when combined with semaglutide, significantly reduced weight, food intake and fat mass compared to semaglutide alone. Separately, LX9851 mitigated weight regain and had positive effects on liver steatosis when introduced after semaglutide discontinuation.

"We are thrilled that Novo Nordisk, a global leader in diabetes care and obesity management, has recognized the potential of LX9851," said Mike Exton, Ph.D., chief executive officer and director of Lexicon. "This arrangement decisively strengthens our financial position, providing optionality as we further invest and accelerate our R&D portfolio."

"Novo Nordisk is committed to serving the diverse needs of people living with obesity and other metabolic diseases and to build a pipeline of differentiated drug candidates in this space," Jacob Sten Petersen, Senior Vice President, Diabetes, Obesity and MASH therapeutic area at Novo Nordisk. "We are pleased to enter this agreement with Lexicon as it will allow us to explore a novel biology and potential treatment paradigm further, and we look forward to building on the great work Lexicon has already done with the development of LX9851."

LX9851 is an orally delivered small molecule drug candidate for the treatment of obesity and associated cardiometabolic disorders. Lexicon is investigating the pharmacology of LX9851 as a stand-alone therapy and in combination with GLP-1 agonists such as semaglutide. Lexicon scientists identified the function of ACSL5, the target of LX9851, based on their discovery that knockout mice lacking the target enzyme exhibited favorable phenotypes across multiple measures of metabolic syndrome in preclinical models, including resistance to diet-induced obesity and improved body composition.

Lexicon is a biopharmaceutical company with a mission of pioneering medicines that transform patients' lives. Through the Genome5000 program, Lexicon's unique genomics target discovery platform, Lexicon scientists studied the role and function of nearly 5,000 genes and identified more than 100 protein targets with significant therapeutic potential in a range of diseases. Through the precise targeting of these proteins, Lexicon is pioneering the discovery and development of innovative medicines to treat disease safely and effectively. Lexicon has a pipeline of promising drug candidates in discovery and clinical and preclinical development in cardiology, neuropathic pain, metabolism and other indications.

Formulation Forum

Lymphatic versus Portal Drug Delivery: An Understanding of Drug Oral Absorption & Food Effect

By: Shaukat Ali, PhD, Sr. Director, Scientific Affairs & Technical Marketing, and Jim Huang, PhD, Founder & CEO, Ascendia Pharmaceutical Solutions

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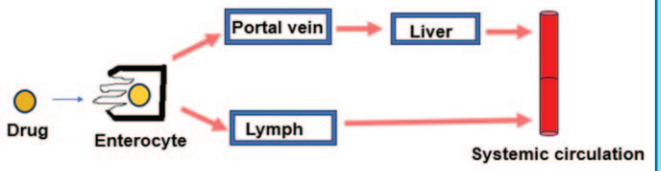
KEYWORDS: Lipid nanoparticles, SEDDS, lymphatic absorption, portal absorption, drug transport pathways, poorly soluble drugs, oral bioavailability, solubilization technologies, food effects, GMP manufacturing.

INTRODUCTION

As the industry facing challenges with new chemical entities due to their poor solubility and bioavailability, the applications of novel excipients and delivery technologies and their mechanisms by which the drug molecules get absorbed into systemic circulation via oral drug delivery, are still subject of continued interest.[1] Oral low bioavailability of drugs stems from low solubility, poor permeability, enzymatic degradation in the stomach and gastrointestinal (GI) tract, and the hepatic first-pass metabolism.[2] The first-pass metabolism remains one of the main impediments for enhancing absorption and bioavailability of many drugs. Even though there is a lot known about first-pass (pre-systemic) metabolism, there are still reasons not clearly understood, especially how the lymphatic pathway absorption impacts oral bioavailability. Other barriers also include P_{gp} transport pumps and limited permeability across intestinal lumen in the GI tract. To by-pass first-pass metabolism for enhancing the absorption of lipophilic drugs, lipids have been used to increase the oral bioavailability via intestinal lymphatic system as shown in Figure 1.[3]

These two pathways, upon molecules transit across the enterocytes in epithelial cells, play an important role for drug absorption; one in which the molecules enter blood capillaries through the portal vein, and the other one by lymph capillaries through the lymphatic system. Soluble, small molecules preferably transported through the portal vein get metabolized, leading to lower concentrations in the plasma. Lipophilic drugs with logP >5, on the other hand, are preferentially transported through the intestinal lymphatic system that leads to greater

FIGURE 1



Pathways for Drug Transport via Portal Vein & Lymphatic System

absorption and bioavailability. The greater association with lipoproteins and chylomicrons assemblies due to inherent lipophilicity of molecules gets into enterocytes and then transported to plasma through the intestinal lymphatic system. Less lipophilic molecules with logP <5 get transported via the portal system. For example, macromolecules like insulin and GLP-1 are preferably transported through the portal vein (Figure 1).

The lymphatic system is a network of capillaries and small vessels, nodes, and organs, that is filled with fluids that play an important role in modulating immune functions as well as also help facilitate the lipid absorption, a key mechanism to overcome the portal absorption and by-pass the first metabolism in liver. This distinctive route is essential for drug transport and delivery of large and lipophilic molecules by alleviating the challenges in penetrating blood capillaries. Composed of a single layer of epithelial cells, filled with interstitial fluids, these capillaries are distributed throughout the body and allow the entry of dissolved substance into the lymphatic system that enter the bloodstream via drainage and filtration of lymphatic fluid into lymph nodes. The filtration of lymphatic fluid eliminates bacteria, viruses, or any other foreign particles. Lymph nodes are important in fighting invasion of foreign particulates and help protect the immune response by triggering the lymphocytes to produce antibodies to fight infections.

LIPID NANOPARTICLES

Lipid-based formulations, composed of lipid aggregates with varied structure and compositions, are one of the important routes for delivery of drugs though lymphatic systems to by-pass the liver metabolism. Designed to enhance solubility and stability, the lipid assemblies protect drug from degradation as they transit through GI tract. These lipid aggregates are further categorized as liposomes, solid nanoparticles, nanostructured lipid carriers, cubosomes, self-emulsifying nano- and microemulsions (SNEDDS/SMEDDS). Drugs with higher logP have shown higher solubilization than those with lower logP by this formulation approach.[4] Lipophilic drugs dissolved in SNEDDS does not necessarily improve the absorption. In fact, lipid suspensions have also shown the improvement of bioavailability of drugs like griseofulvin, and others.[5] Like lipids, proteins also play an important role in enhancing oral bioavailability by lymphatic pathway. Proteins engineered with certain receptors can target lymphatic endothelial cells, and hence, allowing more uptake by the lymphatic system. For instance, albumin and immunoglobin G (IgG)-based nanoparticles can lead to improved stability and controlled systemic release due to lymphatic absorption as well. Conjugation of drug with proteins can lead to improved pharmacokinetic properties by facilitating the interactions with lymphatic transporters and receptors and enhancing the drug accumulation in the lymphatic tissues.

There are several approaches to increase drug transport to lymphatic system.[3]

1. Postprandial state – a diet-based inclusion of drug with food
2. Lipid prodrug- drug is covalently linked with lipid moieties like long chain fatty acids, glyceride and phospholipids making drugs to be more lipophilic
3. Lipid nanoparticles (LNPs) – administration of drug with lipid-based assemblies comprised of lipids, solubilizers and/or surfactants can lead to significant lymphatic transport of drugs

In postprandial state, the chylomicrons level increases after consuming fatty foods with increased lipoproteins synthesis in the lymphatics. For example, halofantrine, an antimalarial drug, when administered with food in postprandial state, increased the lymphatic uptake in dog by 54% as opposed to only 1.3% increase in fasted state.[6] Like postprandial, lipid conjugates with covalently liked drugs, making the drug more lipophilic, results in association with lipoproteins/chylomicrons that leads to faster uptake by lymphatics and greater bioavailability. For example, valproic acid conjugated with phospholipids, especially with longer fatty acid lipids, shows greater association with chylomicrons and absorption in enterocytes leading to higher bioavailability compared with short chain lipids.[7] Mefenamic acid modified with glycerides as a prodrug also shows higher plasma concentration compared to free drug, suggesting that lipid prodrugs increase bioavailability and reduce the adverse effect in the GI tract.[8]

ROLE OF LIPIDS IN LYMPHATIC DRUG TRANSPORT

Lipid nanoparticles (LNPs) improve the stability of drugs by encapsulating into interior aqueous and hydrophobic bilayers. Composed of a different class of lipids, short- and long-chain phospholipids, the liposomes or different lipid assemblies protect drugs from harsh conditions in the GI tract and minimize the degradation by enzymes. Phospholipids (and cholesterol) are digested in the intestine. Once the bile salt is released into the small intestine, phosphocholines are hydrolyzed to lyso-phospholipid and fatty acids by Phospholipase A_2. Thus, drugs like cefotaxime incorporated in liposomes are stable and showed higher concentrations in lymph and plasma as compared to solution state, further supporting the fact that lymphatic transport plays an important role in increasing the oral bioavailability of this drug.[9] Surface-modified liposomes containing cyclosporine A with a

TABLE 1

Model Drug	Technology	Results	Reference
Testosterone	Conjugation with C-9 fatty acid	Ab. oral bioavailability >3% with >90% lymphatic transport	12
Docetaxel	Conjugation with oleic acid	Over 2-fold higher BA than unconjugated drug in SNEDDS	13
Nitrendipine	SLN	BA >3-fold higher than suspension	14
Carvedilol	Microemulsions	BA >3% higher than solution	15
Olanzapine	NLC	BA >5% vs suspension	16
Lopinavir	Mesoporous silica	Cmax 1.69-fold and AUC 5.97fold increase vs free drug	17
Probucol	SNEDDS	BA >10-fold improvement	18
Baicalin	Nanoemulsions	BA >26% and AUC 14.6-fold increase	19
Lutein	SMEDDS	Enhance lymphatic transport efficiency	20
Hepatitis B surface antigen (HBsAg)	PLGA coated with lectin	Higher anti-HbsAb antibody levels and enhanced mucosal immunity	21
Hepatitis B surface antigen (HBsAg)	Liposomes	Comparable IgG level with IM following immunization for 3 consecutive days	22

The contribution of intestinal lymphatic transport in improving the bioavailability of a few representative drugs.[11]

positive charged stearyl amine showed better muco-adhesion than chitosan and much higher lymphatic absorption.[10]

As previously shown in Figure 1, the first-pass metabolism is the result of efficient uptake and hepatic metabolism of drugs by liver. The blood filters through the GI tract and is collected in the portal vein and then passes through liver where all substances get absorbed with blood and distributed to other organs. To circumvent the passage through port vein and divert to lymphatic system, structural modifications are commonly practiced for improving the oral bioavailability. As shown in Table 1, testosterone's oral bioavailability is low, but on modification as prodrug with a fatty acid (undecanoic acid), oral bioavailability improved about 3% resulting from >95% contribution from lymphatic transport.[12] Docetaxel modified with an oleic acid also showed about 2-fold increase in oral bioavailability in SNEDDS formulation as compared to unconjugated drug.[13]

FOOD EFFECT ON DRUG TRANSPORT

Food effect also known as food-drug interaction, plays an important role in determining efficacy and bioavailability of drugs. This is clinically relevant, specifically in cases to prevent the undesired adverse effect and reduce drug overdosing. A majority of compounds are prone to food effects belong to BCS class II and/or Class IV, especially the positive food effect. Only a few have shown the negative food effect. A typical dosage is susceptible to fed and fasted state. Increasing plasma concentration of a drug with food (low or high fat diets) is referred to as positive food effect, while lowering plasma concentration of a drug with food referred to as negative food effect, as shown in Figure 2.[23]

After consuming food, the gastric pH is raised from about 2 to 4 and remains elevated about 4.5 hours. As the food travels in duodenum and small intestine, the pH does not fluctuate as much as stomach and remains around 6-8. Fluid volumes could elevate in stomach to 500 ml or higher and in small intestine may increase from 200 ml to 1000 ml. The solubility of drugs is increased by bile salts secreted from gall bladder. In addition, increasing in viscosity could hamper the release of drugs, making them less available for systemic absorption. Drug absorption is also affected by inhibition of transporters. For example, grapefruit juice when co-administered with drug leads to higher bioavailability due to inhibition of cytochrome P450 $3A_4$. On the other hand, with lipophilic molecules, the lymphatic uptake route leads to increasing the bioavailability with fatty food diet.

Many drugs are food dependent, and a majority belong to Class II with some Class IV, and also Class I, and Class III. They are also recommended to be taken with and without food and/or in an empty stomach before the meal. Taken collectively, the food effects on drug absorption can be neither be avoided nor exploited. Undesirable food effects can lead to exposure and increased toxicity or reduced therapeutic efficacy. Hydrocortisone, for example, when taken with food leads to delayed release by reducing C_{max} and prolonged T_{max} as opposed to fasted state. Therefore, hydrocortisone should be taken with empty stomach before breakfast and to be more clinically relevant.[24] On the exploitation, co-administration with food is required to increase solubility and absorption of drugs and to achieve the desired bioavailability. For example, rivastigmine when taken with food, led to 30% AUC and 30% decrease in C_{max} with 1.5 h delay in T_{max} to achieve the desired bioavailability.[25] In many cases, the food intake is required and recommended to prevent the adverse effects, such as gastric irritation, bleeding, nausea among others, which are all clinically relevant.

CONCLUSION & FUTURE PERSPECTIVES

Lymphatic absorption remains as an alternative and an ideal approach to enhance the oral bioavailability of poorly soluble molecules, especially those belonging to BCS II and IV. We expect more molecules being

FIGURE 2

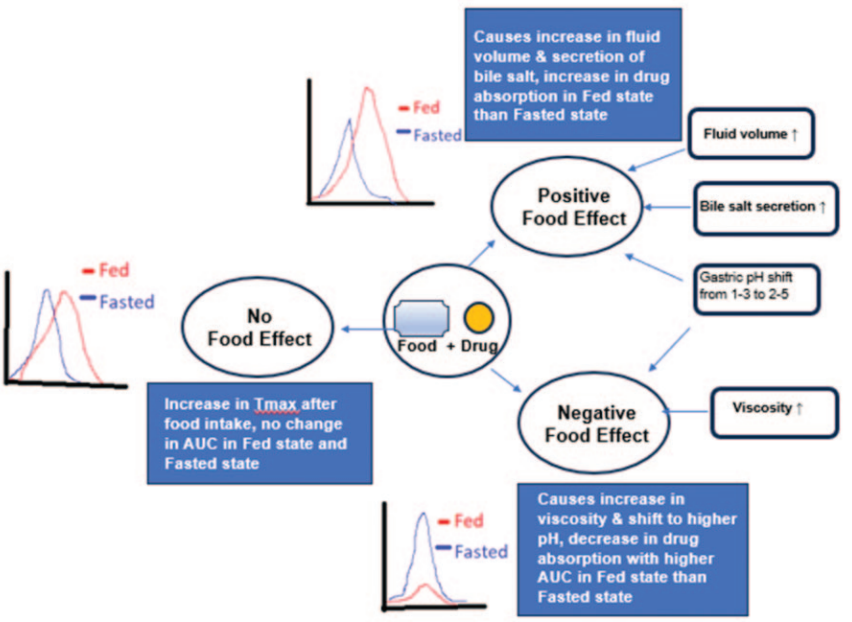


Illustration of Food Effects on Absorption of Drugs

discovered will be utilizing the lymphatic system versus portal system for delivery of poorly soluble and permeable drugs to target sites.

Food intake can impact drug transport and may divert the transport via lymphatic or portal vein or could be preferential favoring one over other. There are no obvious reasons to believe which of the 2 transport routes will be preferred and to what extent it will be impacted. There are pharmacokinetic models to evaluate the food effect on bioavailability of drugs. Lower absorption and bioavailability are taken as markers for hepatic first metabolism.

Ascendia's enabling technologies (LipidSol™, EmulSol®, NanoSol®, and AmorSol®) offer a range of formulation choices to design better and smarter dosages, oral liquids, and solids to mitigate the food effect and improve the oral bioavailability by finding the appropriate class of lipids and surfactants, and oils to achieve the desired outcomes. This is essential and required for new chemical entities with solubility challenges and for improving their bioavailability by directing them to lymphatic pathways.◆

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TREND SCOUTING

Anticipating the Future of Pharma

By: Gregor Deutschle

INTRODUCTION

Innovation in today's world moves at a fast pace. Various industries are experiencing unprecedented growth, and pharma and biotech are no exception. The global pharmaceutical contract development and manufacturing organization (CDMO) market is expected to grow from $161 billion US to $322 billion US from 2023 to 2033.[1] Total reported R&D spend has increased from $139 billion in 2022 to $145 billion in 2023, an increase of 4.5%.[2] This immense growth across the industry indicates a need for CDMOs to proactively invest in the tools, technologies and process optimization which will shape pharmaceutical manufacturing in the coming years.

With the constant evolution of the biopharmaceutical industry, companies need to maintain their competitive edge to succeed in the market. Outsourcing partners in particular need to make sure their service portfolios address shifting customer needs and remain at the forefront of the industry. A large part of this is adapting a forward-thinking mindset to consistently innovate and predict potential solutions in time before customers want to address new challenges.

By implementing a strategic, considerate, and proactive approach to trend forecasting, pharmaceutical service providers can effectively weigh the benefits and challenges of potential trends, invest in those most aligned with customer needs, and avoid the allocation of time and resources in trends that will not provide meaningful return on investment (ROI). Let's explore the development of reliable trend scouting processes through tried-and-true methods.

INFORMATION-DRIVEN PREDICTIONS

Service providers can sustain a holistic view of emerging trends by scouting ahead. This is an important approach for surveying, analyzing, and implementing the latest in components, technologies, and methodology to meet future and evolving customer needs. As, for example, new devices or substance classes, to name a few, emerge and gain popularity, the needs of the market will change. This makes trend scouting a critical skill to acquire the foresight to proactively innovate and maintain relevance and resilience in today's market.

Globally operating CDMOs have large customer bases of biopharma companies that have nuanced requirements and products. Scouting and tracking industry trends allows outsourcing partners to collect valuable information from drug owners that can inform decision-making to implement the required infrastructure, devices, substances and more.

That said, trend scouting can be a cumbersome process. The life science industry has innately special requirements for the implementation of new methods due to regulations and required risk management. With patient safety the top priority for manufacturing partners, trends don't emerge and permeate as quickly as they do in other industries. Substantial time and resources are required to implement the most relevant trends. Comprehensive practices help prevent a service partner from missing any crucial topic and allow the focus to remain on getting ahead of lengthy implementation timelines.

UNDERSTANDING THE VALUE OF TREND SCOUTING

Trend scouting highlights the importance of evaluating comprehensive market needs, rather than single customer needs, to make careful use of available resources, and is a key element of a holistic risk management system. Today, how trends evolve can somewhat be unpredictable and may change frequently. For example, as biopharma companies plan to introduce drug products to market in novel devices like wearable on-body-injectors, they

might find a lack of adequate reimbursement for drug delivery systems. While the tried-and-true system of drug delivery has established proper reimbursement practices, new system products are more likely to be reimbursed if they offer a significant improvement in patient treatment outcomes.

Emerging topics may rise and fall, sometimes disappearing for a while only to re-emerge later with fresh enthusiasm. CDMOs understand the importance of dedicating significant time and resources to monitoring trends to create solutions that address future customer needs yet avoid straining resources prematurely. However, because it can take years for fill and finish partners to address new ideas in the industry, it's essential to look beyond the short term and focus on long-term trends when evaluating trend risk management.

By conducting a comprehensive trend tracking, the companies can benefit from becoming early adopters of emerging trends by integrating new technologies and methods into their supply chain long before they become the industry standard. Implementing new and trending practices to address future customer needs can lead to marketability in a competitive industry. Staying on trend can entice new customers to partner with you. The ability to strategically adopt elements of a new trend allows a biopharma service provider to become a leading voice in the market and cultivate trust in their expertise from customers. However, when a company is slow to adapt to a new trend or misses a potential trend in their scouting that ends up panning out, they can fall behind in the market and lose out on customer relationships.

HOW TO IDENTIFY POTENTIAL PROMISING TRENDS

CDMOs are well advised to keep an eye on the biopharma industry. Monitoring for potential trends can be crucial as the first step in the trend tracking process to enhance operations and offer valuable capabilities to customers.

Before investing in a technology or method in response to a potential trend, it may be beneficial to conduct thorough assessment of its potential value and risks. Adoption of any new trend or technology needs to support existing quality standards and current Good Manufacturing Practices (cGMP). The key to successful trend scouting can be optimizing the flow of information from every channel and outlet. The trend scouting team can absorb information from sessions and discussions at conferences and trade shows, as well as from academic journals, new datasets and studies, evaluations of new technologies, and conversations with customers.

By systematically comparing trends against one another and in the context of their area of focus, they can create a truly comprehensive trend radar to predict the future of the market and derive the required action from the most relevant trends. This tool, which is used across different departments and overseen by management to identify, monitor and evaluate potential trends, involves grouping potential trends into distinct categories. Experts in different departments look at various areas in the industry to monitor trends on several topics and make thoughtful recommendations for a path forward.

The potential trends are then ranked by experts based on their current relevance and predicted applicability for the future. Often, experts try to find topics that might become the new industry standard. For example, large volume autoinjectors have become a competing trend for on-body wearable injectors as the call for solutions

to meet the rising customer need for self-administered injectables at a higher dosage increases.

Throughout the trend evaluation process, it may be helpful to maintain a balance of qualitative and quantitative research. We employ various methods to obtain and confirm information about emerging trends. For example, desk research with market reports from respected sources and new regulation and authority feedback provide valuable quantitative research. On the other hand, customer and partner interviews as well as conferences and trade shows offer important qualitative findings. Together, the various sources of qualitative and quantitative research contribute to trend tracking efforts.

The trend tracking process should be ongoing and consistent to account for any shifts and changes in the market. Outsourcing partners can then use these insights to inform customers of the latest and most promising trends to help them make crucial implementation decisions regarding their devices and substances.

THE IMPACT OF SUCCESSFUL TREND FORECASTING

Trend scouting enables manufacturing partners to adjust practices and processes to relevant trends in a timely manner. By implementing new methods to adapt to the right trends, CDMOs can maintain their competitive edge against other pharmaceutical service providers in the long run. In our experience, trend forecasting throughout the company's history has proven valuable in contributing to long-term success.

When prefilled syringes first entered the market in the mid-20th century, it marked a significant advancement in global injectable technology. Vetter recognized early on that patient-friendliness would be the trend of the future, which is why the company focused on prefilled syringes as early as the 1970s. Vetter was well prepared when prefilled syringes became the new standard. The company led the emergence and growth of this trend by introducing the original idea of a prefilled syringe, which became a core element in drug production during that decade. In 1984, Vetter sought to get ahead of the industry trend and introduced the first dual-chamber syringe. Today, advanced prefilled syringes remain a market standard.

Vetter is continuing to lead the injectable market with its early investment in a new trend: ready-to-use vials and cartridges. The company is tracking the trend closely and dedicating a new clean room for the prefilled syringe-equivalent of vials. By installing an increasing amount of flexible equipment, CDMOs can process primary packaging types in various shapes, sizes and yearly volumes consistent with how the industry evolves. Remaining flexible can be important as trend scouting can sometimes lack precision in its predictions.

Trend scouting and tracking is necessary to monitor trends constantly and with proper care. Using the right resources and employing appropriate time management may be beneficial in trend forecasting to help companies know which trends are the most critical to implement. As CDMOs' ability to first meet future customer needs becomes more competitive, the capacity to perform extensive trend scouting will be instrumental in anticipating evolving market needs. A holistic approach is needed to provide the best possible trend forecasting that spans the entire industry, engaging in interdepartmental conversations and monitoring to create a comprehensive picture of the market.

The future of the biopharmaceutical industry is bright, as the global market continues to grow and evolve. By leveraging all available sources of information, understanding the value of trend scouting, and developing a comprehensive trend radar system, CDMOs can be prepared for industry shifts far enough in advance to adapt accordingly. ◆

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BIOGRAPHY

Gregor Deutschle serves as the Director Product and Service Management at Vetter since 2021. In this role, he leads a team responsible for matching Vetter's product and service offering with the demand of the biopharmaceutical market and evolving the portfolio according to the latest industry trends. Prior to joining the independent CDMO, he worked in several roles over the past 16 years, most of them in the biopharma industry. He started his career by earning a degree in mechanical engineering from RWTH Aachen University in 2008.

ECO-DESIGN TOOL

How Life Cycle Assessment is Transforming Drug Delivery Device Sustainability

By: Alex Fong, MBA

INTRODUCTION

Sustainability is now a key concern for all actors in the pharmaceutical industry, including drug delivery device manufacturers. And while good progress has been made in addressing scope 1 (direct, in-house) and scope 2 (purchased energy) emissions, indirect emissions occurring in the supply chain (scope 3) continue to pose a challenge.[1]

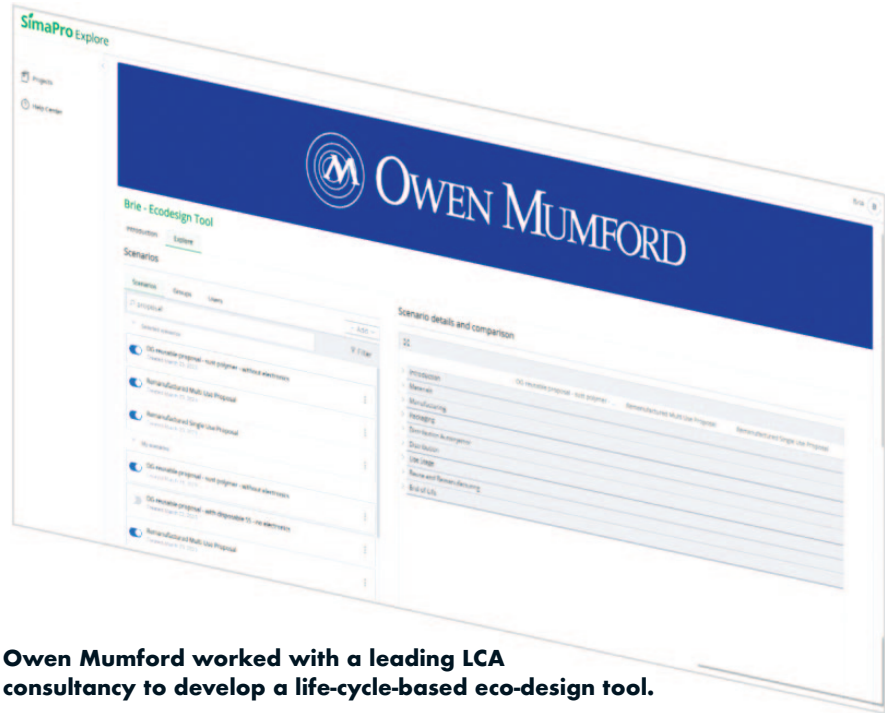
Given the complexity of the device development process, it is crucial that manufacturers take a holistic, "cradle-to-grave" approach to sustainability, based on an understanding of the multiple complex factors that contribute to the environmental impact of drug delivery devices. This is where methodologies such as life-cycle assessment (LCA) can provide valuable, data-driven insight into opportunities for reducing environmental impact across the global value chain and, as per ISO14040, "throughout a product's life cycle from raw material acquisition through production, use, end-of-life treatment, recycling and final disposal."[2]

FROM FRAMEWORK TO PRACTICAL TOOL

To harness the value of this comprehensive yet notoriously complex methodology, Owen Mumford worked with a leading LCA consultancy to develop a life-cycle-based eco-design tool detailed enough to provide meaningful analysis yet simple enough to be used by personnel who are not Lifecycle Assessment experts.

Using this tool, it is possible to autonomously model the environmental impact of products across seventeen categories, including water and land use, climate change, and fossil and mineral resources, taking into account potential damage to ecosystems, human health, or resource availability.

Product manufacturing, supply chain and distribution characteristics including component weights, material choice and supply, manufacturing location, transportation, and end-of-life scenarios, are entered into the tool, which then calculates an estimated impact score for each category. This score can then be easily communicated across departments to improve understanding and ensure that product design prioritizes sustainability at every level.



Owen Mumford worked with a leading LCA consultancy to develop a life-cycle-based eco-design tool.

AVOIDING SUSTAINABILITY PITFALLS

Scenarios comparing different product concepts and configurations can then be produced to evaluate the impact of each change, maximizing sustainability whilst preventing unintended negative consequences at other points of the supply chain. It is then possible to assess whether or not changing specific product characteristics ultimately improves or worsens the overall LCA score, allowing informed decision making early in the development process.

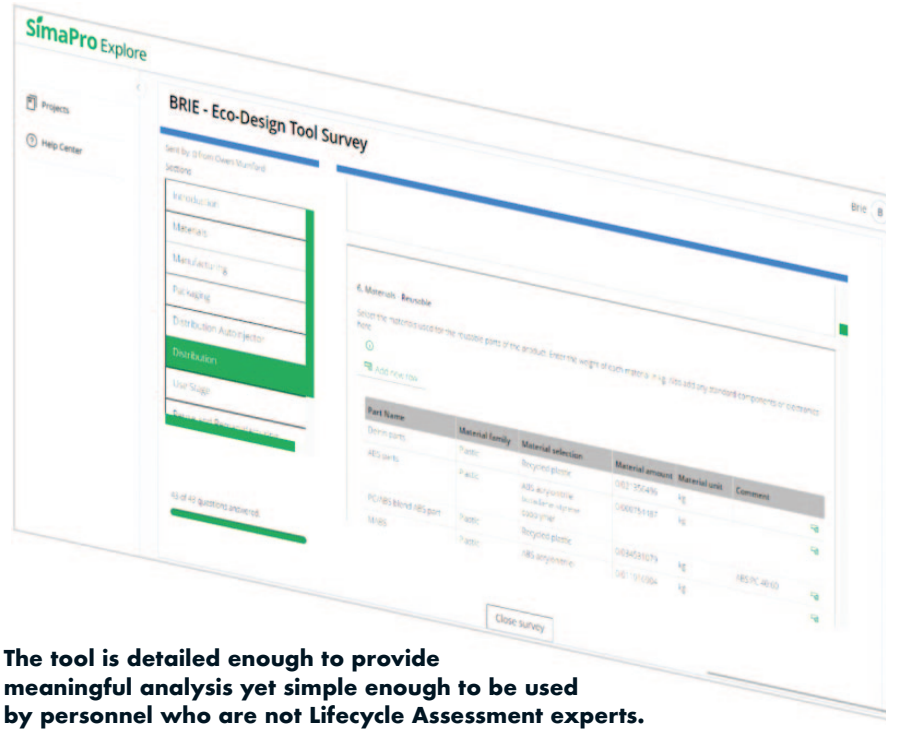
In concrete terms, sustainable drug delivery device development means striking a balance between product longevity and the manufacturing and distribution footprint. Whilst the use of more robust materials to ensure a longer product life and better reusability may seem the obvious choice, in reality, the increased weight, manufacturing energy and material use involved may outweigh the environmental benefits.

Similarly, moving away from traditional medical polymers in favor of renewable raw materials like bioplastics may not be the straightforward sustainable choice it seems. A recent analysis highlighted the importance of taking into consideration factors such as the choice of feedstock, land use, energy consumption, and waste management practices when assessing the benefits of these alternatives to fossil-based feedstocks.[3]

Using renewable energy is another key strategy for sustainable design. But it is not as simple as whether a supplier reports using renewable energy – the financial mechanism underlying how the energy is obtained can also be taken into account to evaluate whether purchasing from the supplier will result in further investment in renewable energy generation. In terms of sustainability, on-site renewable energy generation and direct power purchase agreements (PPAs) are preferable to sleeved or virtual PPAs, supported by renewable energy certificates.

CHALLENGING THE STATUS QUO

The highly regulated nature of the medical device industry has traditionally been an obstacle to more obvious routes to sustainability. Safety and reliability are paramount, and any modifications to im-



The tool is detailed enough to provide meaningful analysis yet simple enough to be used by personnel who are not Lifecycle Assessment experts.

Using this tool, it is possible to autonomously model the environmental impact of products across seventeen categories.

prove sustainability must not negatively impact these parameters. Manufacturers are limited, for example, in the materials they may use, which must be rigorously tested 'medical grade' options and often prohibited from incorporating recycled materials into new devices at the point of manufacture.

Nevertheless, disruptive thinking and innovative new approaches can reveal opportunities to reduce environmental impacts at every phase of the product life cycle. And this can mean working with pharmaceutical companies to adapt the delivery device design brief, for example to change the intended drug formulation to a lyophilized drug product that can be recombined through the device at the point of administration. The potential environmental benefits of the resulting increase in shelf life and stability extend throughout the supply chain.[4]

Comparing the environmental impact of different end-of-life scenarios with LCA can also provide the data needed to back up early decision-making on recycling methods, and encourage fresh thinking on how products can best be cycled. While highest-value recycling (ie, the product is re-used in the same or similar applications) is usually the aim, the processing involved may mean this is not the most sustainable option overall. If this is the case, reviewing the LCA results may prompt the product design to be simplified, making the product cheaper and easier to recycle as components ("next best" point of value) or raw materials ("least best").

BENEFITS FROM CRADLE TO GRAVE

In many cases, design changes made as a result of LCA yield additional benefits. Optimizing size and weight not only downsizes the carbon impact of packaging and distribution, but can also reduce manufacturing emissions related to mass and processes. Simplifying product design streamlines manufacturing and encourage users to dispose of the product correctly instead of simply throwing it away – not to mention the potential improvements to user experience.

In an era where sustainability is not just a goal but a necessity, LCA has the potential to reshape how the pharmaceutical industry approaches this multifaceted issue. By embracing this holistic approach, the industry can address complex challenges, reduce its ecological footprint, and align with global sustainability goals. Ultimately, LCA is not just a tool for compliance or cost-saving; it is a pathway to a more sustainable future in healthcare, benefitting not only the environment but also manufacturers, healthcare systems, and patients alike. ◆

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BIOGRAPHY

Alex Fong, MBA, is an experienced senior manager in the Insight, Analytics and Strategy fields. He has applied these skills in a broad range of Industries including the FMCG/CPG, tourism, Investment banking, telecoms and management consulting sectors. For the last 8 years Alex has been leading the market research drive at Owen Mumford, with an ever-increasing focus on sustainability.

Drug Development
EXECUTIVE

Sebastian Stenderup

Executive Director, Head of Commercial EMEA

Lonza

Lonza

Driving Innovation & Sustainability: CDMO Trends & the Future of ADCs

As the pharmaceutical industry evolves, Contract Development and Manufacturing Organizations (CDMOs) like Lonza are at the forefront of addressing complex challenges and driving innovation. From advancing antibody-drug conjugates (ADCs) to embedding sustainability into manufacturing practices, Lonza continues to set benchmarks in delivering solutions that meet the needs of today's healthcare landscape.

Drug Development & Delivery recently interviewed Lonza's Sebastian Stenderup, Executive Director, Head of Commercial EMEA, about some of the trends CDMOs are currently facing, from the growth of ADCs to the importance of sustainability, and how his company is responding to them.

Q: What do you think will be next in the world of ADCs?

A: One aspect that is coming into sharp focus right now is the payload. About half of the antibody-drug conjugates (ADCs) that are already on the market use one or other of two payloads – and most target microtubules or inhibit DNA-acting enzymes. What might be next?

A good deal of research effort is being put into the next generation of payload-linker combinations. For example, there is significant interest in looking again at older and less potent payloads for traditional ADCs.

Two of the ADCs that have gained significant market penetration target topoisomerase 1, both of which use derivatives of camptothecin. What about payloads targeting topoisomerase 2 instead? While earlier attempts to create them proved unsuccessful, there may be potential, and multiple other payloads with diverse mechanisms of action are also being investigated. It is going to be interesting to see what the next big thing will be.

Away from the payload itself, modified linker technologies could improve the therapeutic index by targeting different lysosomal enzyme triggers that avoid payload release in healthy tissues. There should be plenty of mileage in developing modified payload-linker combinations, including finding ways to improve their release from the ADC once they reach the target, or even incorporating two different payloads in the same ADC. And if the drug-antibody ratio can be better controlled, and the conjugation made at a more stable site on the antibody, this could also lead to more effective ADCs.

What about ADCs that include bispecific antibodies? These could be designed to allow the antibody to give more specific targeting of tumour cells that co-express two cancer associated antigens that are not present in non-tumour tissues. And, of course, smaller peptides might be able to have a similar targeting effect to antibodies. Peptide-drug conjugates are still in their infancy, but the potential is clear.

Q: What about alternative mechanisms of action?

A: It's true that the lion's share of ADC effort has been focussed on traditional cytotoxic payloads, but there are certainly indicators that alternative mechanism of action payloads could have utility in the fields of cancer-immunology and also targeted protein degradation, too. It's early days, of course, but there is considerable interest in the potential of immunostimulatory ADCs. STING – stimulator of interferon genes – is a great example as it is involved in the tumour-dependent activation of the immune system's quiescent myeloid cells that can then attack the tumour directly. And while there have been some early setbacks in the clinic, it may be that toll-like receptor agonists (TLRs) could ultimately prove effective as ADC payloads, too.

It could even be that targeted protein degrader molecules such as PROTACs could be conjugated to target-directing antibodies. There is growing preclinical interest here, and as the molecules tend to be fairly complex, experienced CDMOs like Lonza are well placed to contribute in this space. While they are complex molecules, in practice the E3 ligase targeting units they contain are fairly modular, lending themselves to libraries.

Q: I guess the complexity poses additional challenges for GMP manufacture?

A: Definitely. One is obvious – the different volumes that are required depending on the application and the nature of the components. Some ADCs are being developed to treat solid tumours with high prevalence, where the quantities needed will be much greater than for those designed to treat rare haematological cancers. Volumes are also affected by the potency of the payload – there can be a 2-log difference between the potency of different payloads, and the more potent it is, the less will be required. The drug-antibody ratio can also significantly impact volumes, too.

In order to cover the entire space for ADC manufacture, a range of GMP capacities will be required, from a few tens of grams for niche products in the early stages of clinical development through to hundreds of kilograms for the commercial manufacture of ADCs targeting more common tumour types where the market is, naturally, larger.

Containment requirements pose a significant challenge because of the high potency of the molecules. A CDMO looking to work across the range of ADC types and from preclinical through to commercial will have to have capacities at multiple scales. With the requirement for OEB5 containment, this represents a significant investment, and one that Lonza has made to ensure we can support customer projects across the board.

Q: What about the physical nature of the molecules? Can you give me examples of challenges there?

A: A good example is the crystallinity of payload-linkers, which is often problematic. Many contain solubilising or hydrophobic-masking chains such as polyethylene glycol (PEG) or polysarcosine. These impact the crystallinity of the payload-linker combination, making them more complicated to purify. We often find that large-scale preparative HPLC is required, followed by lyophilisation. And, of course, both of these will need to be carried out under OEB5 containment. This has a significant effect on productivity, and unless those time-consuming purification and isolation steps are taken offline, they can seriously impede the overall productivity of an asset by reducing its availability for other projects.

Q: Aggressive development timelines are becoming increasingly common, so presumably this is also the case for ADCs?

A: Absolutely. The industry is increasingly promoting DNA to IND times of 13 to 15 months, and this includes Lonza. In reality,

for ADCs to achieve these timelines would require a GMP payload-linker to be fully developed in eight to 10 months. And, of course, there's far more to a payload-linker structure than simply the small molecule API component. The growing complexity of ADC payload-linkers means they typically include a solubilising linker, a protease trigger, a self-immolation motif and a conjugation handle in addition to the small molecule payload itself.

This timescale can only be achieved if a well-defined supply chain is in place for all the building blocks. Otherwise, developing, scaling up and manufacturing the payload-linker in fewer than 10 months would be extremely unlikely. An additional layer of complexity comes with the decision on which building blocks will need to be sourced as GMP starting materials.

Q: How can high-throughput experiments help?

A: High-throughput experimentation is an essential tool in finding the optimal process as quickly as possible, whether the project involves ADC payload-linkers or more traditional small molecule drugs. By carrying out test reactions on a small scale and in parallel, we can get pointers towards the conditions that might be successful far more rapidly. For early phase projects, these are invaluable – whether working on route selection, or screening catalysts, ligands and solvents.

A robotic system can carry out far more experiments in parallel than a human chemist could ever hope to, and with a broader range of conditions that could be used in large-scale manufacture, such as high temperature or pressure. It allows us to narrow down the options for solvents, reagents and reaction conditions far more quickly by screening all the many different options in parallel. The human chemists can then get to work refining the conditions, and carrying out scale-up experiments that are less amenable to automation.

Importantly, our high-throughput robot in Visp is supported by a dedicated team and includes UPLC analytics capabilities. Analytics can frequently become a substantial bottleneck in high-throughput operations, and we are keen to prevent this from slowing our development projects down.

Q: This leads us nicely on to route scouting. Can you tell me more about Lonza's new AI-enabled route scouting service?

A: Sure. Route scouting is all about designing the optimal way to make a target molecule. It builds on the decades-old technique of retrosynthetic analysis, where a chemist looks at a complex organic molecule and works out how it might be put together from smaller pieces, a bit like a jigsaw. They work backwards until all the pieces needed to assemble the molecule are commercially available.

The potential drugs entering the development pipeline are getting increasingly complicated, and it's not unusual for a synthetic route coming from medchem to have 20 or more steps. This is slow, resource-intensive, and costly. Artificial intelligence and machine learning are proving a real godsend in trying to find shorter routes that are synthetically feasible, suggesting multiple options for process chemists to triage.

Here at Lonza, we are working with a computer-assisted retrosynthesis tool, which includes a huge database of reactions. We have combined this with our own supply chain database to give commercially relevant insights into the relative costs of different routes, and the real-world availability of the intermediates and reagents. It helps customers to identify and prioritise the best route for manufacturing their molecule right from the outset, building on advice provided by computer tools and the decades of experience of process chemistry that has been built up by our subject matter experts.

Q: With sustainability now such an important topic for all aspects of business, can you give me an example of how Lonza is putting sustainability at the heart of its operations?

A: Sustainability is a broad concept, of course, but looking at the environmental aspects, we are committed to cutting our emissions, reducing our water and energy use, and improving our material intensity. Obviously, this covers a huge number of activities, but one concrete example from our manufacturing operations involves wastewater.

As we must not discharge any traces of API in our wastewater, traditionally it has been incinerated to ensure no API ends up in the local water treatment facility. But this uses a huge amount of energy, so our team in Visp looked at alternative ways that would remove all traces of API while also having a much smaller carbon footprint.

This involves looking closely at the precise contents of the waste stream so we can decide how best to clean it up. It might involve adsorption or extraction, stripping and distillation, thermal hydrolysis, or even membrane technology. And we may need to use more than one technique – perhaps first evaporating any traces of low-boiling solvents, and then adsorbing any API that remains. We've also been working with external partners on alternative techniques such as an advanced oxidation process and enzymatic decomposition.

We've also been looking to reduce our solvent use. Organic solvents are used in significant volumes in pharmaceutical manufacturing, and represent a substantial waste stream. But the volumes also mean that if they can be recycled rather than disposed of, it will significantly improve the overall sustainability of the process. We have invested in multiple technologies to clean up and recycle our waste solvents, such as distillation, membrane technologies and rectification systems in our sites in Visp and Nansha. There is also a dedicated solvent recovery plant in Visp and, of course, we re-use high-grade recycled solvents within our processes, or sell them on for reuse elsewhere.

These two activities are already making a huge impact on the sustainability of Lonza's manufacturing activities. In 2023 in Visp alone, we treated more than 2,000 tons of wastewater to avoid incineration, and regenerated more than 10,000 tons of solvent. This is a concrete example of how Lonza has made significant investments to make our manufacturing activities more sustainable. ◆

DRUG DEVELOPMENT

Improving Bioavailability & Solubility in OSDs

By: Hibreniguss Terefe, PhD

INTRODUCTION

The majority of drug candidates emerging from contemporary drug discovery pipelines exhibit too low aqueous solubility to allow for adequate absorption after oral intake. Over 90% of drug substances have bioavailability limitations, of which 70% are related to solubility challenges.

Formulators have multiple technologies available to enhance solubility or dissolution rate for drug products including oral solid dosage (OSD) forms, but there is no such thing as a one-size-fits-all solution. Selection of a formulation approach must be done in light of the physicochemical profile of the drug candidate, its permeability and its dose. In the early stages of drug development, selection is biased towards technologies that enable high drugloads, have low manufacturing complexity and high administration flexibility.

In this article, Hibreniguss Terefe (Ph.D.), Director of Product Development, Ardena, explores the options available to improve bioavailability and solubility and provides guidance to support decision-making when designing oral formulations for poorly soluble drug candidates in early development.

FORMULATION APPROACHES TO ADDRESS SOLUBILITY CHALLENGES

Particle size reduction for crystalline active pharmaceutical ingredients (APIs) can improve rate of dissolution by increasing the surface area available to come into contact with the solvent. This requires specialized technologies such as nanomilling, careful formulation development and multiple process steps to reduce the particles to the precise and uniform size needed for controlled dissolution.

Alternatively, amorphous solid dispersions (ASDs) can be used. An ASD is a solid material that lacks the organized atomic structure typically found in crystalline solids. ASDs exhibit a single glass transition temperature. These materials possess higher energy states, leading to faster dissolution rates and increased solubility.

The process of creating an ASD involves converting a crystalline API into an amorphous form and then embedding it within a polymer carrier. Spray drying, a solvent based method or hot melt extrusion, a fusion based method could be used to make amorphous solid dispersions. Lipid formulation approaches, such as lipid-based drug delivery systems (LBDDS) is another approached used to improve bioavailability.

Hot melt extrusion (HME) is a particularly effective technology to manufacture ASDs. HME has many benefits, including:

- **Fewer processing steps:** Compared to other ASD manufacturing methods, which can shorten production time and cost of goods (COGS).
- **No solvents:** This can reduce patient safety concerns and development costs.
- **Continuous process:** minimizes scaleup efforts by increasing batch size as a scale of time instead of equipment size.
- **Versatile:** HME can be used to make many types of OSD forms, including tablets, minitablets, pellets, capsules, and sachets.

The choice of method – whether HME is chosen, or another method entirely – depends on specific formulation considerations.

PRE-FORMULATION DEVELOPMENT: PHYSICOCHEMICAL EVALUATION

At the pre-formulation development stage, physicochemical evaluation plays a crucial role in understanding the materials involved and ensuring appropriateness for HME formulation in terms of thermal stability, processibility as well as physical and chemical stability up on storage. The objective of this evaluation is to gather comprehensive information about the drug substance, polymer, and other additives to lay the foundation for successful product development.

When considering the potential suitability of a drug substance for HME, a number of factors should be explored.

For the drug substance, various properties are assessed, including the melting temperature (Tm), glass transition temperature (Tg), thermal degradation temperature (Tdeg), molecular weight (MW), pH solubility profile, solvent solubility, pKa, logP, logC, as well as the presence of hydrogen bonding acceptor/donor groups. Additionally, the degradation pathway and chemical stability of the drug substance are investigated.

Similarly, the polymer used in the formulation undergoes evaluation, considering its MW, Tm, Tg, Tdeg, and the presence of hydrogen bonding donor/acceptor groups. Viscosity, an important property for processing, is also considered.

Other additives such as plasticizers, surfactants, and process aids are assessed for their properties and compatibility with the formulation.

To conduct these evaluations, various tools are utilized, including differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), hot stage microscopy (HSM), and x-ray powder diffraction (XRPD). These tools provide valuable insights into the thermal behavior, stability, and crystallinity of the materials.

Approximately 100mg of the drug substance is typically required for these characterization tests. The physicochemical properties of the drug substance are thoroughly reviewed by examining technical data, development reports, and relevant literature to gather available information. In cases where information gaps exist, API characterization tests are conducted to fill in the missing details.

Understanding the physicochemical properties of the drug substance and having knowledge of the potential excipient properties are crucial for successful formulation development. This pre-formulation evaluation sets the stage for further formulation optimization and ensures the quality and effectiveness of the final product.

PRE-FORMULATION DEVELOPMENT: THERMODYNAMIC ASSESSMENT

At the pre-formulation development stage for HME ASDs, a thermodynamic assessment is conducted to select the appropriate carrier polymer and evaluate the drug load (DL) for the formulation. Additionally, the interaction between the drug substance and the polymer is thoroughly evaluated.

Miscibility studies are conducted between the drug substance and four to five polymers, considering two to four different drug loadings. The assessment includes the evaluation of melting point depression, the Tg of the ASD, polymorphism, and the propensity of the amorphous drug substance to recrystallize within the polymeric matrix.

A phase diagram is constructed to illustrate the impact of drug loading on critical factors such as processing temperature, degradation temperature limit, solubility of the drug substance in the molten polymer, as well as the recrystallization curve. This diagram provides valuable insights into the formulation process and helps optimize the drug-polymer system.

To conduct these assessments, various tools are utilized, including DSC, thermal rheometer, HSM, XRPD, and the construction of a phase diagram.

Approximately 1g of the drug substance is typically required for these assessments. The thermodynamic assessment focuses on understanding the interaction between the drug substance and the polymer, ensuring compatibility and optimizing the formulation for the HME process.

FORMULATION DEVELOPMENT: API SPARING HME FEASIBILITY

At the formulation development stage, the primary objective is to assess the feasibility of HME and identify potential formulations that ensure compatibility, performance, and stability upon storage.

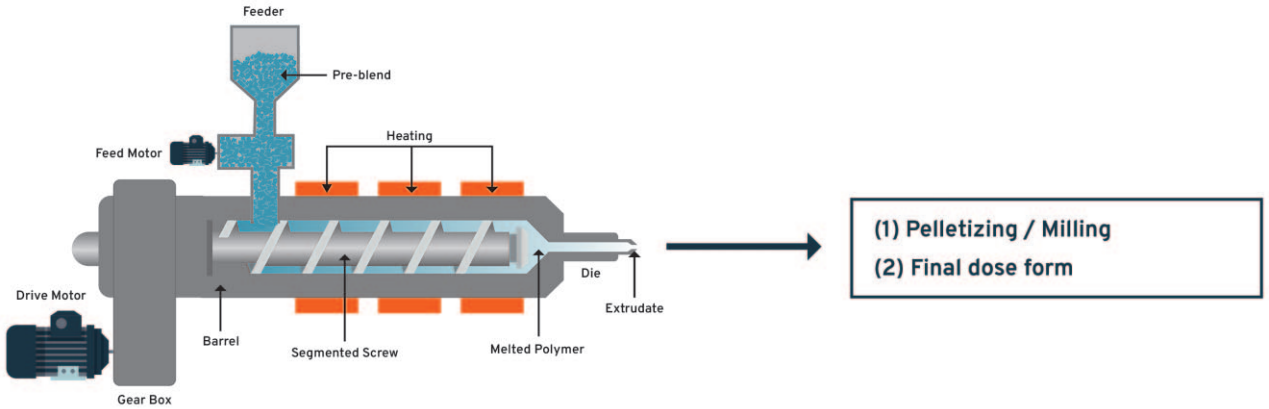
The process begins with a screening phase, where two to three polymers are carefully evaluated along with three different DL values. Consideration is given to the impact of processing temperature range and time, and additives such as plasticizers and surfactants are incorporated as needed.

Comprehensive characterization of the formulations must then take place. This involves assessing various aspects including amorphicity, related substances, super saturated kinetic dissolution (SSKD), physical stability, chemical stability, and bioavailability, using a range of techniques.

A notable approach is vacuum compression moulding (VCM) combined with prior cryomilling, which optimizes the success probability while minimizing API usage. With this method, it becomes possible to evaluate up to 12 experimental conditions using less than 100mg of API, resulting in significant API savings compared to using an 11mm extruder where at least 20g of API would be required to perform the same number of experiments.

Additionally, if force degradation data is not available for the API, the VCM technique can be used to quickly assess accelerated API degradation and study excipient compatibility, which would otherwise take 4 weeks using conventional stability studies. Other tools utilized in the formulation development process include: polarized light microscopy (PLM); DSC; XRPD; dissolution testing; high-performance liquid chromatography (HPLC), and animal pharmacokinetic (PK) studies.

In terms of batch size, the API sparing feasibility studies typically involve working with 100-200mg of the formulation, while the API requirement can vary depending on the drug loading. As a result, approximately 5g of API would be needed, which could include a series of experimental



Hot Melt Extrusion

Downstream Processes

batches and some material for preliminary animal PK study. Alternatively, utilizing a 11mm extruder, one to two batches only at a 20% DL would require 10-15g of API.

The formulation development stage focuses on sparing the API while thoroughly assessing the feasibility of HME and optimizing the formulation for compatibility, performance, and stability during storage. This approach allows for efficient pre-clinical supply with minimal API usage and aids in determining whether HME is the ideal technology for the specific molecule under development.

FORMULATION DEVELOPMENT: PROTOTYPING

A viable formulation must be established for further optimization and evaluation through prototyping.

Prototyping involves assessing the impact of critical material attributes (CMA), both qualitatively and quantitatively, on critical quality attributes (CQA) such as amorphosity, related substances, physical stability, and chemical stability.

The extrusion process evaluation aims to assess the impact of critical process parameters (CPP) on CQA. This includes evaluating factors such as screw design, processing temperature profile, feed rate, and screw speed. An 11mm extruder is typically used along with various tools including DSC, XRPD, dissolution testing, and HPLC.

The batch size for prototyping typically ranges from 20-50g. The API requirement for this stage is approximately 50 - 100 g depending on the drug loading.

By carefully assessing the impact of formulation components and process parameters on critical attributes, the goal is to develop a robust formulation that meets the desired quality and performance criteria.

PROCESS DEVELOPMENT: ESTABLISHING A ROBUST & SCALABLE PROCESS FOR CONSISTENT PRODUCT QUALITY

At the process development stage, the primary objective is to establish a robust and scalable HME process that ensures consistent product quality. This involves conducting an extrusion process design of experiments (DOE) to determine the design space, identify failure points, and define scale-up factors. Additionally, optimization of upstream and downstream processes, as well as manufacturing of clinical trial material (CTM) and conducting stability studies per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), are key objectives.

The DOE factors considered in the process development include independent variables such as screw design, process temperature profile, feed rate, and screw speed. These variables are carefully evaluated to understand their impact on the extrusion process and product quality.

Dependent variables, including melt temperature, percent load (%torque), residence time distribution, and specific mechanical energy, are measured to assess the performance and characteristics of the extruded product.

To conduct these evaluations, an 18mm extruder is typically used along with the same analytical tools from previous stages. The batch size for process development typically ranges from 5-25kg, depending on the scale of production. The API requirement for this stage is approximately 0.5-2kg depending on the drug loading. For early phase clinical studies with smaller clinical material requirement smaller batch sizes could be considered.

The process development stage focuses on establishing a robust and scalable process that can consistently produce high-quality products. By conducting DOE experiments and analyzing various process variables, the goal is to optimize the extrusion process, ensure product quality, and prepare for scale-up manufacturing. Additionally, stability studies following ICH guidelines are conducted to assess the long-term stability and shelf-life of the manufactured product.

SCALE-UP AND PROCESS OPTIMIZATION: FINE-TUNING PROCESS PARAMETERS, OPTIMIZING EQUIPMENT CONFIGURATIONS & STREAMLINING WORKFLOW

At the scale-up and process optimization stage, the focus is on fine-tuning the process parameters, optimizing equipment configurations, and streamlining the workflow to ensure successful commercial-scale manufacturing.

The objective is to scale up the HME manufacturing process and optimize it for commercial production. This includes specifying manufacturing process parameter targets and ranges, as well as defining process control strategies to ensure consistent product quality.

The DOE factors considered in this stage include independent variables such as screw design, process temperature profile, feed rate, and screw speed. These variables are carefully adjusted and optimized to achieve the desired product characteristics and performance.

Dependent variables, including melt temperature, % torque, residence time distribution, and specific mechanical energy, are monitored and controlled to ensure the process operates within the desired parameters and produces consistent results.

To conduct these evaluations, a 27mm extruder is typically used along with the previously mentioned analytical tools. These provide valuable insights into the physical and chemical properties of the product and help optimize the process.

The batch size for scale-up and process optimization typically ranges from 50-100kg, depending on the desired production scale. The API requirement for this stage is approximately 10-20kg depending on the drug loading.

The scale-up and process optimization stage focuses on fine-tuning the manufacturing process, optimizing equipment configurations, and streamlining the workflow for efficient commercial-scale production. By carefully adjusting process parameters, controlling variables, and utilizing advanced analytical tools, the goal is to achieve consistent product quality and ensure a smooth transition from lab-scale to commercial-scale manufacturing.

BIOGRAPHY

Dr. Hibreniguss Terefe is the Director of Product Development at Ardena US in Somerset, New Jersey, a leading contract development and manufacturing organization (CDMO). He is responsible for the development of preclinical and clinical solid oral dosage forms, overseeing their transition to commercial manufacturing through both conventional and specialized pharmaceutical manufacturing processes. Prior to this role, Dr. Terefe served as Director of Research and Development at Catalent Pharma Solutions in Somerset from April 2021 to January 2024, where he led the product development department. Following Ardena's acquisition of the Somerset site in February 2024, he transitioned to his current position. Dr. Terefe brings over 27 years of experience in pharmaceutical research, development, and manufacturing. He previously spent 14 years as Vice President of Research and Development at ExxPharma Therapeutics and nine years as Head of the Department of Pharmacy at the University of Asmara, Eritrea. A recognized expert in pharmaceutical research and development, Dr. Terefe has extensive expertise in drug product development, commercial manufacturing, and Chemistry, Manufacturing, and Controls (CMC). His core competencies include solubility enhancement, modified-release solid oral dosage forms, drug delivery system development, and twin-screw extrusion processes. With more than 18 years of experience in Hot Melt Extrusion, he has led product development efforts for new chemical entities (NCEs) from preclinical stages through Phase III clinical development, utilizing advanced drug delivery technologies and specialized pharmaceutical manufacturing techniques. Dr. Terefe holds a PhD in Pharmaceutical Chemistry and a Pharmacy degree from Westfälische Wilhelms-Universität Münster, Germany. He was also a Fulbright Visiting Scholar at the University of California, Berkeley.

STRATEGIES FOR SUCCESS

Keeping all of this guidance in mind, and by harnessing HME, organizations can enhance the drug development process, reduce costs, and expedite the journey from early development to clinical studies. These strategies contribute to overall success and enable timely delivery of safe and effective formulations to patients in need. ◆

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CELL-FREE GENE SYNTHESIS

Eliminating Critical Bottlenecks in Genetic Medicine Development

By: Marc Unger

INTRODUCTION

The rising tide of genetic medicines is shifting the role of synthetic DNA in pharmaceutical development. Custom DNA constructs have been used in research since the inception of advanced molecular biology techniques, but with the clinical success of genetic medicines, DNA is now often a critical precursor to the active pharmaceutical ingredient (API), or part of the pharmacologic substance itself. This article explores the market trends, challenges, and opportunities new DNA production technologies provide to accelerate genetic advances in healthcare.

GROWING DEMAND FOR DNA

The recent growth in the biopharmaceutical arena can be described as nothing short of explosive. In 2022 alone, the industry witnessed a phenomenal acceleration, surging to 333.09 billion USD with a trajectory to reach 856.1 billion USD by 2030.[1]

Traditionally propelled by monoclonal antibodies and other biologics, the market dynamics are undergoing a major shift. Genetic medicines, comprising cell and gene therapies as well as RNA-based vaccines and therapies, have emerged as major actors poised to claim a substantial share of the market. This shift, likely intensified by the growing demand for personalized medicine and precision therapies as well as the global impact of the COVID-19 pandemic, has put an even bigger spotlight on the need to accelerate the pace of discovery and scale-up for clinical testing. In response to this demand, cell-free DNA synthesis and cloning technologies have stepped into the limelight.

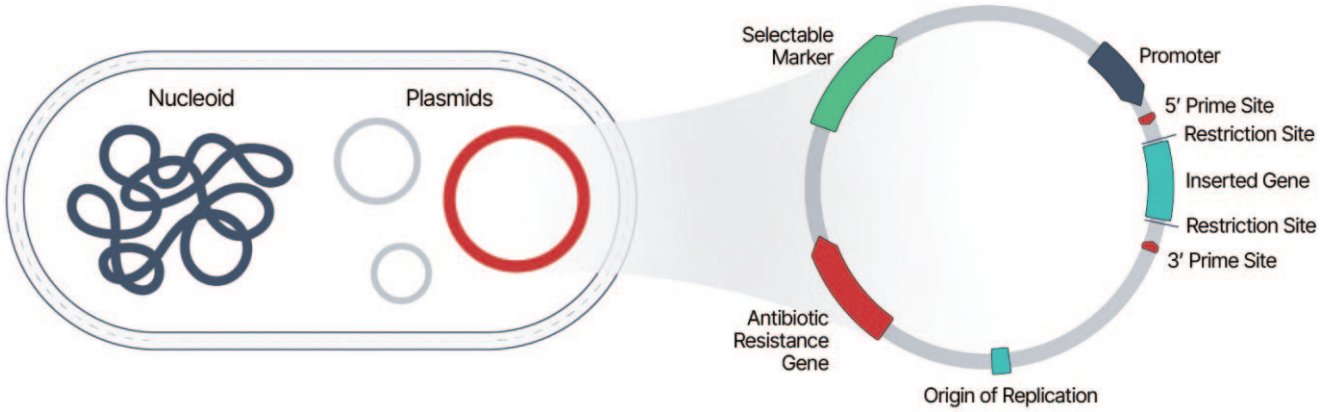
GENETIC MEDICINES: KEEN CLINICAL INTEREST BUT AN APPROVALS BOTTLENECK

Despite the ambitious growth predictions, the number of genetic medicines approved by the Food and Drug Administration (FDA) remains relatively low. The number of FDA-approved cell and gene therapies increased from five in 2022 to just seven in 2023. RNA therapy approvals increased from five in 2022 to eight in 2023. Many candidates continue to fail clinical trials due to low efficacy or adverse effects.

Regardless of the low FDA approval rates observed thus far for genetic medicines, the entire field is expanding rapidly as technologies like AAV, lentiviral, and other vector platforms for both in vivo and ex vivo genetic modification of target cells are translated into therapies. Applications for chimeric antigen receptor-modified T-cells (CAR-T) are also growing quickly, primarily in oncology but also targeting autoimmune and other diseases. A search of the NIH clinical trials database yields almost 2,500 studies that are currently recruiting participants for gene therapy and over 700 currently recruiting for CAR-T trials.[2]

The transition of DNA to a biopharmaceutical construct is leading to increasing scrutiny and guidance from the FDA[3] and EMA,[4] with efforts to harmonize the regulatory frameworks for the manufacture of genetic medicines. DNA constructs intended to be used *in vivo* in human beings require GMP manufacture.[5] However, DNA utilized as a template for RNA (or mRNA) transcription may be defined as a starting material rather than API.[6] In contrast, DNA used to modify cells *ex vivo*, with the cells delivered as the therapy, might be considered as a precursor or an API.

FIGURE 1



Cell-based Cloning Risk Factors.
Cloning plasmids using traditional cell-based methods carries inherent risks that can complicate workflows. Residual DNA from vector backbones or bacterial origins often creates challenges in downstream processes and regulatory approvals. Additionally, cellular contaminants (i.e. endotoxins) introduced during the process increase the testing burden, driving up costs and extending timelines. In contrast, cell-free technologies eliminate these risks, offering streamlined workflows that bypass bacterial hosts, reduce contamination concerns, and enable faster, more reliable and efficient production.

INHERENT RISKS OF CELL-BASED DNA APPROACHES

Cell-based cloning is currently the industry-standard method to isolate, purify, and scale the production of custom DNA for the development of most genetic medicines. However, using this decades-old method to assemble, identify, and amplify sequence-perfect DNA constructs has significant drawbacks:

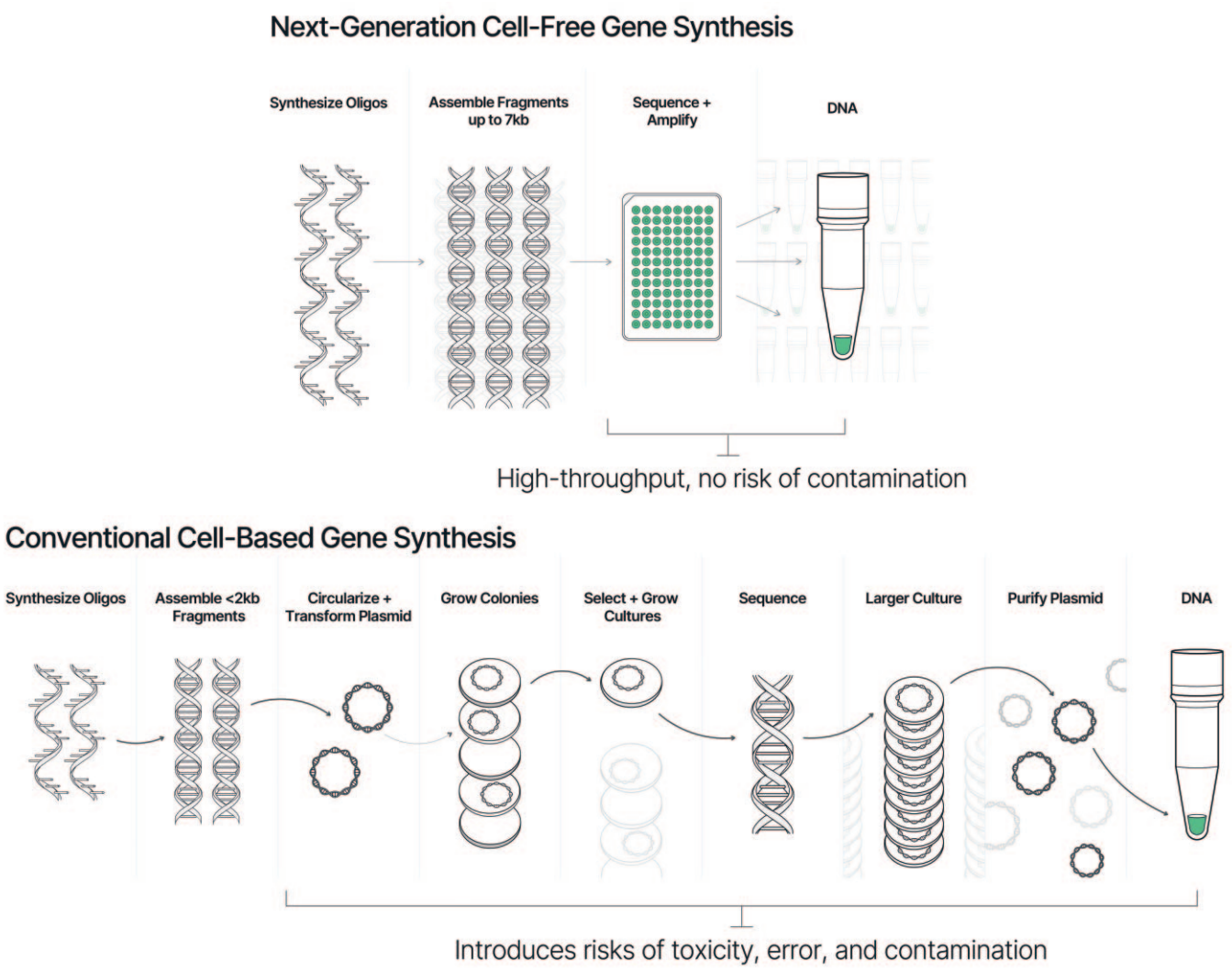
Time & Cost: Time and cost are always primary considerations and drivers at the center of drug development, and genetic medicines are no exception. From ordering oligos to sequence assembly, cloning, and purification, the hierarchical build cycle to attain long, sequence-perfect DNA takes ample time as well as dedicated equipment and highly-trained personnel — all costs that significantly add to the overall expense of development. These costs may manifest as dedicated internally resourced biofoundry labs or outsourced CROs/CDMOs.

Additionally, promising DNA candidates can have highly complex sequences that take longer to produce and thus bear a cost in go/no-go decisions of moving a nucleic acid-based drug forward. Viable candidates and targets can be abandoned prematurely due to time and cost considerations.

Failures in Scaleup: There are instances where DNA assemblies are toxic to the host cell or are structurally challenging to assemble, resulting in cloning failure or mutations in the intended assembly. These kinds of failures are why GMP production of plasmid DNA requires a master cell bank: both the plasmid and host strain may require significant engineering to result in a construct that will amplify the DNA stably. Such genetic engineering often costs several hundred thousand dollars and takes several months. In contrast, cell-free DNA production approaches do not rely on host cell-mediated replication and therefore do not exhibit these kinds of failures.

Risks of Vector and Bacterial Origin DNA: For plasmid-based approaches, bacterially derived selectable marker and replication of origin DNA sequences are part of the isolated plasmid DNA and can pose downstream risks for both horizontal gene transfer and virus-mediated gene therapy approaches.[7] For example, AAV-mediated gene therapy approaches that relied on plasmid constructs produced between 3-26% viral particles containing an antibiotic resistance gene of plasmid backbone origin. The percentage of AAV particles that contain incorrect sequences can vary significantly depending on the production method; in fact 10-90% of AAV particles may be "empty" or incorrectly filled, the exact proportion dependent on the efficiency of the packaging process and the QC measures implemented during production.[8] Obviously, the integration of plasmid-originating DNA into the genome of transduced cells is a serious safety concern for AAV gene therapy.[9] These risks can be reduced using small backbone and antibiotic-free selection methods such as minicircle and Nanoplasmid (Aldevron) approaches, which reduce

FIGURE 2



Conventional Cell-Based vs. Cell-Free Gene Synthesis.
Cell-based gene synthesis requires a more complicated, time- and resource-intensive workflow to assemble, sequence, amplify, and purify a single DNA sequence. In contrast, new cell-free gene synthesis technologies produce long, complex, high-accuracy DNA fast and with high-throughput, enabling researchers to shift the effort normally spent building DNA to analyzing downstream results, improving designs, and exploring a broader sequence space instead.

the size and nature of the DNA elements required for DNA amplification. However, the safest approach is to eliminate bacterially derived sequences entirely.

Contaminants & Testing Burden: Cell-based DNAs typically contain contaminants including bacterial genomic DNA, RNA, protein, and endotoxin (e.g. LPS) and require additional time and costs for ensuring complete removal. Endotoxin is the most critical risk factor, since contamination levels can confound downstream cell-based assays, and removal of endotoxin must be confirmed prior to clinical use. The most widely accepted and sensitive assay used for endotoxin testing, the limulus amebocyte lysate (LAL) assay, represents yet additional cost and instrumentation. The removal of contaminating RNA, DNA, protein, and endotoxin from cell-based DNAs adds significantly to production cost and time and increases the risks associated with a failure of any one of these purification steps.

Supply Chain Risk: Many small- and mid-sized biotech and biopharmaceutical companies outsource the scaleup and production of complex therapies like gene therapies. These third-party organizations offer specialized expertise, advanced manufacturing capabilities, and scalability, allowing companies to focus on core research. However, using a CMO or CDMO for cell and gene therapy development and/or manufacturing introduces several supply chain risks. These risks include potential delays in production due

to the availability of an external CMO/CDMO, their capacity constraints, and obligations or prioritization of other clients' projects. Outsourcing to external partners also could expose intellectual property and complicate regulatory compliance. Furthermore, any disruption in the CMO/CDMO's operations can lead to delays in clinical trials or product launches, ultimately affecting patient access and market competitiveness.

CELL-FREE CLONING: A DE-RISKED PATH TO DNA PRODUCTION

Forward-thinking biopharma companies seeking ways to produce high-quality therapies with greater speed and efficiency are already exploring the use of new DNA production methods including cell-free DNA cloning to accelerate pipelines, improve the purity and fidelity of DNA constructs, and make their overall DNA-based drug development operations less costly, error-prone, and brittle.

Cell-free DNA cloning is advancing rapidly. Rather than performing laborious cloning of imperfect DNA fragments in bacteria, cell-free cloning enables researchers to shift the effort normally spent building DNA to analyzing downstream results, improving designs, and exploring a broader sequence space instead. Today, researchers can receive 1-60 μg of sequence-perfect, high-complexity, NGS-verified dsDNA molecules up to 7,000 bases long within 6-8 business days — manufactured cell-free. Such cell-free DNA production technologies are just starting to gain a foothold, and the speed, quality, and length of the DNA produced are improving. For example, cell-free DNA manufacturing companies like Elegen are already delivering high-complexity, clonal-quality DNA at lengths up to 15 kb in as fast as 10 days to early access program customers.

The benefits of cell-free cloning extend well beyond speed. Cell-free cloning can handle a wider range of complexity more reliably than plasmids, thus improving the chances of success. Furthermore, since the DNA produced never touches a bacterial cell, the risk of endotoxin contamination (and other bacterially derived contamination) is eliminated. Finally, cell-free cloning successfully enables the synthesis of sequences that fail to propagate through conventional methods using bacterial cell cloning.

NOT ALL "CELL-FREE" APPROACHES INVOLVE CELL-FREE CLONING

In recent years, emerging DNA suppliers have featured technologies that enable the production of large quantities of DNA without using bacterial cells. Since these technologies avoid the time and high costs of growing and maintaining bacterial colonies in large fermentation tanks, they present an attractive option for biopharma.

These "cell-free" technologies use isothermal enzymatic amplification techniques such as rolling circle amplification (RCA) to produce amplified copies of a circular DNA template. While promising as a replacement for the conventional replication of DNA through the propagation of bacteria, the circular template is typically produced by cell-based cloning, bringing all the baggage associated with cell-based cloning into the production workflow.

To avoid generating replicates of an imperfect sequence with RCA, weeks of time and effort are required to produce a sequence-perfect template for amplification. This template also needs to be purified of contaminants, adding more time and expense to the overall process.

NEXT-GEN DNA: CLINICAL-GRADE, CELL-FREE DNA PRODUCTION IS THE FUTURE

With new technologies emerging to offer cell-free cloning and cell-free amplification of synthetic DNA, it's easy to envision a state where genetic medicines are more efficiently developed and produced. By eliminating the drawbacks of cell-based approaches, cell-free DNA production saves several weeks in the discovery phase and many months in the scale-up phase for clinical testing.

For personalized genetic medicines, the cost of growing and maintaining a master cell bank to produce DNA for each patient is prohibitive. With personalized RNA neoantigen vaccines entering clinical testing, it's only a matter of time before personalized genetic medicine makes the transition from clinical investigation to routine therapeutic – provided the method of DNA production is sequence-perfect, scalable, and cost-effective.

Thanks to a handful of innovative DNA manufacturers, the era of next-gen DNA manufacturing, produced entirely cell-free from digital design to end product, at any length and complexity, and ready for use without further manipulation, is very near. In the race to produce the next wave of advanced genetic vaccines, cancer therapeutics, and personalized therapies, cell-free DNA production is the one asset biopharma cannot afford to overlook.◆

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BIOGRAPHY

Marc Unger is the Chief Scientific Officer at Elegen, with more than 20 years of expertise bringing pioneering technology and products to the biotechnology and life sciences industries. After a successful career as CSO of Fluidigm, whose products and technology were based on the Multilayer Soft Lithography technology he invented, Marc took on the challenge of transforming the DNA supply market, using a combination of microfluidics and advanced molecular biology to deliver high-throughput, NGS-verified, cell-free gene synthesis at industry-leading length, complexity, and speed. At Elegen, Marc is responsible for overseeing research and product development. He is driven by Elegen's mission to solve the DNA Write challenge, enabling programmable biology to drive advancements in genetic medicine, agriculture, and synthetic biology.

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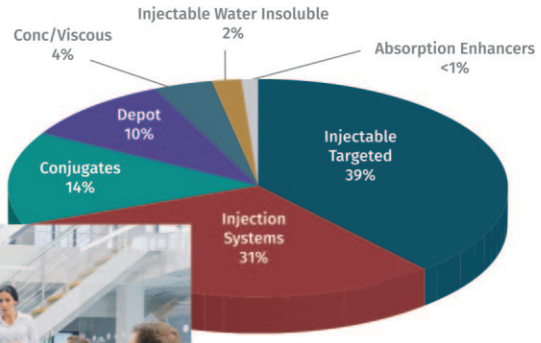
Excipient vs Strength	375 mg telaprevir
HYPROMELLOSE ACETATE SUCCINATE 12070923 (3 MM2/S) **(Core/Content)**	375 mg
SODIUM LAURYL SULPHATE (Core/Content)	7.58 mg
DIBASIC CALCIUM PHOSPHATE ANHYDROUS **(Core/Content)**	75.76 mg
CROSCARMELLOSE SODIUM **(Core/Content)**	30.3 mg
MICROCRYSTALLINE CELLULOSE **(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)**	

Evaluate New and Promising Technologies



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Special Feature

Bioavailability & Solubility: The Promise of Novel Ingredients

By: Cindy H. Dubin, Contributor

There is somewhat of a consensus in life sciences that there have been significant advancements in improving bioavailability. Solubility, however, continues to elude formulators. Excipients are often lauded as a solution to tackling these challenges, but still do fall short. In a 2020 US Pharmacopeia (USP) survey of drug formulators, 84% said that the current roster of excipients present in approved drug products has imposed limitations on drug development, and as many as 28% experienced a discontinuation of drug development as a result of excipient limitations.

Novel excipients may be the answer. In September 2023, the Office of New Drugs and the Center for Drug Evaluation and Research (CDER) launched a voluntary Pilot Program for the Review of Innovation and Modernization of Excipients (PRIME). This program is intended to allow biopharmaceutical manufacturers to obtain FDA review of novel excipients. The development of novel excipients is gaining momentum as pharmaceutical companies seek improved performance and versatility in drug formulations. Novel substances support nanoparticle drug delivery for oncological medications to provide better stability and adoption of medicines.

"The invention of novel excipients bearing the amphiphilic and solubilization characteristics in the recent past has helped excipient and drug manufacturers alike to overcome the regulatory barriers for expediting the new drug candidates to market," says Shaukat Ali, PhD, Senior Director of Scientific Affairs and Technical Marketing at Ascendia Pharmaceutical Solutions.

A Thermo Fisher employee holds up a softgel capsule from the manufacturing line in High Point, NC.

According to a May 2024 USP white paper: "While the FDA PRIME program represents a step in a new regulatory direction for excipients, drug developers are currently reluctant to use novel excipients as there is no independent FDA regulatory pathway outside of its drug application and approval process to review and evaluate the safety and toxicity of an excipient for introduction into a new drug, abbreviated new drug, or non-prescription drug. FDA may determine that novel excipients are not fully supported by the submitted safety data such as for the proposed level of exposure, route of administration, duration of exposure, and patient population. An entire drug application using a novel excipient could be rejected due to uncertainty surrounding acceptance of the excipient by FDA. Considering the barriers to using novel excipients that exist in the normal application process for drug products, USP supports the development of a transparent, independent approval pathway for novel excipients."

This exclusive *Drug Development & Delivery* annual report explores the use of novel excipients as well as other methods and technologies for tackling bioavailability and solubility once and for all.

Abzena: Formulation Stability Study Increased Concentration

Formulating complex biologics, such as monoclonal antibodies (mAbs), fusion proteins, and bispecifics, require robust development strategies that are flexible and phase-appropriate in order to optimize them for solubility, delivery, safety, and sustained stability. Utilizing preformulation assessments to establish and characterize the physiochemical characteristics of the biologic can dictate which approaches are taken during formulation development and allow developers to rapidly identify and solve any complex problems earlier on in the process, avoiding costly downstream issues.

In a recent case study, a customer of Abzena's had acquired a novel mAb that had been formulated by another CDMO. However, there was an issue with the selected formulation due to the fundamental properties of the mAb not being assessed during preformulation. During refrigerated storage, the formulation exhibited signs of phase separation and gelation that were resolved by warming to room temperature, without any apparent impact on quality, explains Dr. Gary Watts, Head of Formulation, Abzena.

"This was not ideal from a regulatory perspective or for patient administration," he says. "A study was designed to evaluate the fundamental factors crucial to formulation stability, such as the optimum pH, and stability at high or low ionic strength."

Dr. Watts says an optimal formulation was identified that showed the desired physical and chemical stability, and was clear, colorless and free of visible particles after >6 months storage at 2-8°C. Furthermore, solubility was sufficiently improved to allow the concentration to be increased to 100mg/mL from 50mg/mL, in line with the customer's requirements.

Ardena: Exploring the Dual Role of 2-(Hydroxypropyl)-Beta-Cyclodextrin in Parenterals

Cyclodextrins (CDs) have been widely used in the pharmaceutical industry to improve aqueous solubility, bioavailability, and physicochemical stability of active pharmaceutical ingredients. Two CD derivatives are 2-(hydroxypropyl)-beta-cyclodextrin (HP-β-CD) and Sulfobutylether-Beta-Cyclodextrin (SBE-β-CD) utilized as excipients in marketed drug products. Over the past decade, CDs, especially 2-(hydroxypropyl)-beta cyclodextrin (HP-β-CD), have emerged as increasingly significant therapeutic agents mainly due to their ability to sequester and mobilize cellular lipids. Trappsol®, a proprietary intravenous formulation of HP-β-CD, is designated an orphan drug in both the US and Europe. It is currently in a Phase III clinical trial for treating Niemann-Pick Disease Type C1 and a Phase 2b study for Alzheimer's disease. Intravenous HP-β-CD is also being studied for the treatment of diabetic kidney disease. The FDA has approved a modified gamma cyclodextrin (sugammadex®) for the reversal of neuromuscular blockade induced rocuronium and vecuronium in general anesthesia.

"These emerging applications of cyclodextrins raise an important question," says Oluwatomide Adeoye, Formulation Development Scientist, at Ardena. "If these 'excipients' exhibit therapeutic activity, is their continued classification as pharmaceutical excipient justifiable, given that they are traditionally expected to be inert? Our experience as a CDMO developing New Chemical Entities (NCEs) for various pharmaceutical and biopharmaceutical companies indicates a growing industry concern regarding the use of cyclodextrins as solubilizers in new parenteral drug products."

Timothy Pas, Director, Formulation Development & Production at Ardena, adds that these concerns primarily stem from the risk of ototoxicity associated with high concentrations of HP-β-CD observed

Sterile production in an isolator (grade A in C) for small sterile GMP batches (Ardena).

in clinical studies for Niemann-Pick Disease Type C1. "While the causative mechanism of HP-β-CD induced ototoxicity has not been perfectly elucidated, the consensus is that it is related to altered lipid trafficking in the cochlear structures," says Mr. Adeoye.

The long history of use in parenteral formulations suggests that the risk of HP-β-CD induced ototoxicity is minimal at typical concentrations and parenteral use cases, Mr. Pas says. However, formulation scientists must carefully assess the clinical requirements of a drug before selecting HP-β-CD as solubilizer. "For instance, it is reasonable to avoid its use in drug formulations intended for prolonged administration, where a regular maintenance dose is required, or those that may lead to high cumulative concentrations of HP-β-CD," says Mr. Adeoye. "Alternatively, SBE-β-CD should be the preferred choice for drug formulations when it can form non-inclusion complexes with the same drug, as its reduced interaction with cell membranes minimizes the risk of cholesterol sequestration."

Ascendia Pharmaceutical Solutions: Solubilization Technologies Tackle Challenging Molecules

As more molecules coming out of discovery possess poor solubility, industry is relying on more innovative approaches to enhance the permeability and bioavailability of those molecules. Excipients are crucial to help design better and smarter formulations to achieve the desired solubility to overcome the bioavailability challenges. Compounded with stability challenges, the industry is looking for the ingredients, solubilizers, and polymers to maximize the drug-polymer intermolecular interactions in the formulation matrices.

"Ascendia's enabling solubilization technologies, especially EmulSol®, address the challenging molecules for enhancing the solubility and oral bioavailability of drugs formulated in microemulsions and nanoemulsions comprised of lipid-based solubilizers and surfactants, and oils as well," says Shaukat Ali, PhD, Senior Director of Scientific Affairs and Technical Marketing at Ascendia Pharmaceutical Solutions.

Lipophilic drug molecules (BCS II and IV) require the most advanced technologies to improve their solubility and bring them to the clinic. For instance, the molecules having higher melting and log P due to their inherent high lattice energy and lipophilicity with log P (4-8), require solid amorphous dispersion and/or microemulsion technologies.

"Ascendia's enabling solubilization technologies AmorSol® for oral solids and EmulSol and NanoSol® for oral liquids can help engineer better and smarter formulations for tablets and liquid capsules using generally regarded safe (GRAS) excipients approved by FDA," he says. "These technologies are aimed at improving solubility of lipophilic and hydrophobic molecules bearing higher melting and logP. Designed with a carefully selected class of excipients and lipids/surfactants/solubilizer, and coupled with our expertise in the enabling technologies, we can expedite the formulation and development of molecules and bring them to clinic faster."

Excipient/surfactant composition and particle size also have a great impact on formulation composition and the desired outcomes. For instance, cyclosporine A available as Sandimmune® (comprised of corn oil, linoleoyl macrogolglycerides) is prone to much greater food effect than Neoral® formulation (comprised of corn oil, polyoxyl 40 hydrogenated castor oil) with much smaller particle size. Dr. Ali says that Ascendia's Emulsol technology can be used for drugs like cyclosporine and peptides to achieve faster absorption and permeation, thus higher oral bioavailability.

BioDuro: Exploring Cutting-Edge Tech for More Reliable Formulations

The development of enhanced drug formulations requires an in-depth, data-driven understanding of Active Pharmaceutical Ingredients' (APIs) physicochemical properties and their behavior *in vivo*. At BioDuro, formulation challenges such as poor solubility, stability, and bioavailability are addressed by systematically analyzing key characteristics of the API and the target patient population, explains Dr. Yuan Yang, Senior Scientist III, Formulation Development, BioDuro. A scientific approach that balances the inherent risk of formulation complexity with the practical needs of the drug product is critical for success.

For APIs with poor solubility, several formulation strategies are employed, each with specific advantages and challenges depending on the solubility profile and therapeutic window. Nanoparticles, nanocrystals, lipid-based formulations, cyclodextrin incorporation, and Amorphous Solid Dispersions (ASD) have proven to be essential tools for solubility enhancement. "BioDuro specializes in employing these strategies, selecting the most suitable formulation based on factors such as API stability, solubility, partition coefficient, and the required dose strength," he says.

By transforming the API into an amorphous state and dispersing it in a polymer matrix, ASDs improve dissolution rates while maintaining stability. This strategy is particularly beneficial for drugs with poor solubility, as it enhances dissolution rates and improves the drug's absorption, leading to more consistent and predictable bioavailability. By leveraging precise modeling and predictive tools, formulation scientists can mitigate risks while maximizing therapeutic performance.

The core of formulation enhancement often lies in the ability to manipulate the physical form of the API. Spray drying and hot melt extrusion (HME) are widely used, proven techniques that provide effective solutions for API solubility challenges. Conventional spray drying has been the standard for producing amorphous dispersions and enhancing the bioavailability of poorly soluble drugs. Dr. Yang says: "With a success rate of over 90% in scale-up from lab to commercial manufacturing, spray drying is a reliable method for formulating high-quality solid dispersions." HME, similarly, is recognized for its capacity to produce stable, uniform formulations and is integral to the development of immediate-release and controlled-release dosage forms, with more than 50% of commercial products utilizing this technique. However, the increasing complexity of drug candidates has led to the exploration of newer technologies to address evolving challenges. "Electrospray, a cutting-edge technique, has gained significant attention in producing ASDs," he says. "Electrospray offers several advantages, such as highly repeatable and reproducible processes and the ability to produce fine, uniform particles with a narrow size distribution. Studies show that electrospray-generated formulations exhibit improved stability and dissolution rates compared to conventional methods, making them particularly beneficial for high-potency, low-dose drugs."

In addition to electrospray, other emerging technologies are being explored to enhance solubility and bioavailability. Techniques, such as formulating with solubility-enhancing excipient, amorphous dispersion granulation and coating fluid bed, co-precipitation, and electrospinning are being evaluated for their potential to improve the solubility of challenging APIs. These approaches, alongside spray drying, HME, and electrospray demonstrate the pharmaceutical industry's ongoing commitment to innovation. "BioDuro continues to explore and implement these cutting-edge techniques to develop more efficient and reliable drug formulations," says Dr. Yang.

Bend Bioscience: Spray Drying Is Best in Early-Phase Design

As a CDMO specializing in bioavailability, particle engineering, and solubility enhancement via spray drying, Bend Bioscience has tackled complex formulations for decades. "We find that the spray drying process is best for early phase design work in terms of material sparing, speed, and efficiency," says David Vodak, PhD, Chief Scientific Officer, Bend Bioscience, Oregon. "We are, however, still observing that amorphous solid dispersion (ASD) technology is the most applicable to a broad range of solubilization problem statements. Certain combinations of ASD technology with other functional architectures, like controlled release, seem to be trending with respect to dialing in specific release and extent profiles for challenging molecules and target product profiles."

Understanding the relative release rates of functional excipients and active molecule are important features to achieve optimal performance, and designing a particle architecture through spray drying can be enabling, he says. "All molecules are unique and have specific challenges to deliver a successful commercial dosage form. Our science-based approach to design – incorporating a deep understanding of material science, rigorous experimenta-

Bend Bioscience analysts observe solution behavior of samples during dissolution testing.

tion and analysis, and emphasis on process optimization and scalability – translates to efficient and effective progressable solutions in drug development."

Lipophilic (LogP>2) compounds remain prevalent in Bend's portfolio. Many compounds in the kinase inhibitor class tend to be more polar with high melting points (i.e., 'brick dust'). The company is seeing high logP compounds in trends toward PROTACs and other TPD programs. Although these compounds are lipophilic, Dr. Vodak says they are often ionic and higher molecular weight moving them into the BCS IV regime.

"At Bend Bioscience, we are still working to discover a 'magic bullet' in terms of the technology to delivery these types of molecules," he says. "In the meantime, we are able to efficiently apply our experience and acumen to design formulations that solve the challenge of delivery in a commercializable manner, whether a spray dried amorphous dispersion or lipid-based formulation is optimal."

Artificial Intelligence (AI) is also helping Bend formulate those challenging molecules. AI is helping Bend organize data sets and look for patterns in compound properties and successful formulations. "We have evaluated 'black box' modeling and deep learning algorithm techniques, but have not yet found a satisfactory data set with appropriate truth metrics to ensure anything predictable from the data," says Dr. Vodak. "However, it is early days for AI, and we fully expect to stay on the cutting edge in this area and use the data that we have from a diverse set of pipelines to continue to challenge what AI can do to improve our efficiency in formulation and process design."

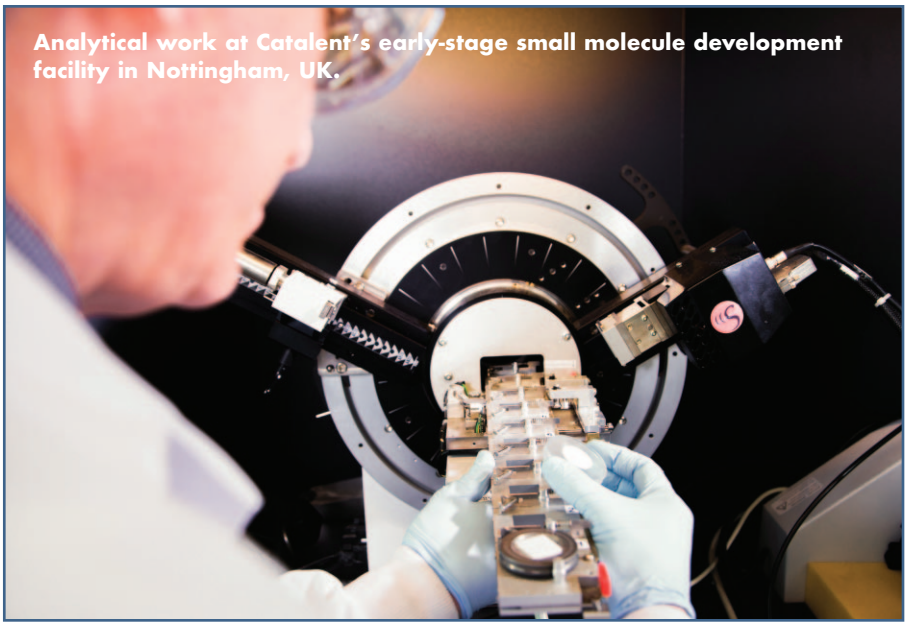
Catalent: PBPK Modeling Identifies Root Causes

Developability assessment with physiologically-based pharmacokinetic (PBPK) modeling has transformed Catalent's early development service. "The use of PBPK modelling replaces simplistic tools like BCS/DCS classification, that oversimplify the challenges in bringing a molecule to the clinic for simple small molecules as well as those in the Beyond Rule-of-5 space," says Stephen Tindal, Director, Scientific Advisory, Oral Small Molecules, Catalent.

As an example, a small biotech faced bioavailability and dose escalation failures with a Beyond Rule-of-5 molecule, leading them to consider shelving the project. Instead of trial-and-error formulation, Catalent applied its Developability Assessment, integrating PBPK modeling and early development screening to identify the root cause.

"Oral delivery proved unviable, so we recommended a sublingual formulation that significantly improved systemic exposure," he explains. "We also optimized their preclinical study design by identifying species-specific absorption issues and developed a modified-release strategy to manage dose escalation. This structured approach saved the molecule from termination, accelerating its path back to the clinic and reducing development costs."

He adds that Catalent's expertise in technology selection, route evaluation,



Analytical work at Catalent's early-stage small molecule development facility in Nottingham, UK.

and formulation design empowers biotech teams to make data-driven decisions, salvaging high-risk molecules and optimizing early development.

Croda Pharma: Enhancing Drug Formulation with Machine Learning

Drug formulation that exhibits enhanced solubility, stability, and bioavailability is a challenging craftsmanship. In recent years, many have tried resorting to Artificial Intelligence (AI) and Machine Learning (ML) to streamline this process. "Unfortunately, developing digital solutions for drug formulation is difficult by itself, with challenges such as low amounts of (relevant) data points, the need to model complex systems, and frequently changing objectives that require practitioners to shoot at moving targets," says Claas Strecker, Lead Technical Data Scientist, Croda Pharma.

Croda aims to empower the drug formulation process with smart digital approaches that can support drug developers in navigating complex systems, focusing on three key pillars:

1) Automatization: Automating tedious lab experiments is of core importance. "It is not only improving the productivity of our scientists and allowing us to respond to our customers faster, but also opening access to vaster amounts of data that can fuel more complex predictive models downstream," explains Mr. Strecker.

2) Predictive Modelling: Croda has built a model that predicts if combinations of excipients will form stable self-(micro)emulsifying drug delivery systems (S(M)EEDS). "These systems have emerged as a powerful tool in pharmaceutical formulation and enhance the solubility and bioavailability of poorly water-soluble drugs by spontaneously forming fine oil-in-water emulsions in the gastrointestinal tract under mild agitation, thereby improving drug dissolution and absorption," says Veronica Blanco, Lead Applications Scientist, Croda Pharma.

Despite their potential, optimizing S(M)EDDS formulations is a complex, iterative, and time-intensive process. Key variables, such as the selection and ratio of excipients, drug characteristics, and system stability, require extensive experimentation. Ms. Blanco says: "Thus, we challenged ourselves to accelerate this experimentation by using ML, but quickly faced a major challenge: How could we inform our model to learn the underlying physics of such complex systems?"

Excipients such as polysorbate 80 are not one well-defined compound, but constitute structurally diverse mixtures. Moreover, Croda's series of super-refined (SR) excipients only deviate from their regular counterparts at the trace component level, but exhibit significantly improved formulations properties, says Mr. Claas. "During

Veronica Blanco, Lead Applications Scientist, Croda Pharma.

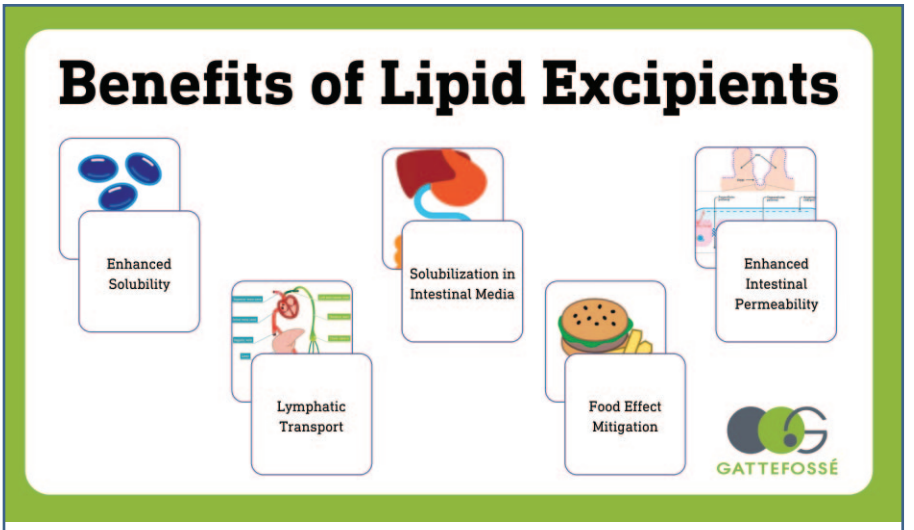
our work, we found that NMR (nuclear magnetic resonance) spectra can serve as a good feature source to inform our predictive model."

3) Optimization: Drug formulation predictive modelling frequently falls short either simply due to lack of relevant data to tackle the problem at hand or because, for complex systems, no informative descriptors are found that could inform a predictive model sufficiently enough, explains Mr. Claas. In such scenarios, optimization techniques such as Bayesian optimization (a method for finding the best solution to a problem without in-depth understanding of how it works internally) can be used. Different options are evaluated, results are presented, and well-calibrated probabilities of expected improvements are used to make smarter choices. "This can help us to iterate fast and achieve our objectives without wasting vast amounts of resources and time," says Mr. Claas.

Ms. Blanco adds: "As formulations continue to become more complex, automation improves efficiency and data collection, while predictive models help design stable drug delivery systems."

Gattefossé: Lipid Excipients Enhance Drug Absorption

Lipophilic drug compounds are a major component of the pre-clinical pipeline, and formulators are increasingly seeking approaches to enhance absorption and drug permeability. A PharmaCircle analysis performed by Gattefossé showed that approximately 70% of NCEs in the preclinical pipeline today are poorly soluble. However, only 55% of FDA-approved NCEs from 2019-2023 are considered poorly soluble compounds. "This 15% gap shows that traditional solubility enhancement techniques are not sufficient to bring all these challenging new molecules to market," says Nick DiFranco, Senior Marketing Manager – Pharmaceuticals, Gattefossé USA. "There is significant untapped potential for lipid-based drug delivery systems, which not only address poor solubility but also enhance permeability and absorption of challenging compounds."



Lipid excipients enhance drug absorption and bioavailability by leveraging the body's natural digestion and transport pathways (Gattefossé).

An area of growing interest is utilizing combinations of excipients to access new "synergies" and overcome common formulation challenges. "For example, an amorphous solid dispersion (ASD) may solubilize a high dose of API, but these formulations often face *in vivo* performance and stability challenges," says Mr. DiFranco. "In contrast, lipid-based formulations (LBFs) improve drug permeation and absorption through mechanisms such as tight junction modulation and lymphatic uptake. LBFs may also reduce dosing variability associated with the food effect."

Lipid excipients significantly improve drug delivery by enhancing the permeation and absorption of drugs. Their similarity to dietary lipids allows them to be processed through the digestive system, increasing the solubility and supersaturation of lipophilic drugs, especially for BCS Class II and IV compounds. The lipid digestion process, involving gastric lipase, bile salts, and pancreatic enzymes, also creates colloidal carriers and mixed micelles that prevent drug precipitation. These colloidal structures maintain drug solubility and can penetrate the mucus layer, releasing the drug and creating a supersaturated environment for passive diffusion.

"By combining LBFs and polymeric formulations, scientists can achieve the high drug loading of an ASD with the benefits of lipids, such as improved *in vivo* permeability and prevention of recrystallization, resulting in boosted bioavailability," he says. "Utilizing IID-listed polymers and lipids in these ternary systems ensures innovation without additional regulatory risk, and these systems can often be manufactured with existing equipment, ensuring a clear path to scale-up and commercialization."

Excipients with high medium-chain fatty acid ester content, such as Gattefossé's Labrasol® ALF, Capryol® 90, and Labrafac™ MC60, are especially good at modulating tight junctions, enhancing

paracellular permeation for Class III and IV compounds and helping drugs bypass P-glycoprotein (PgP) inhibition, says Mr. DiFranco.

As an example, alendronate sodium, a BCS Class III drug, has very low bioavailability due to its polar, hydrophilic nature and susceptibility to pH and enzymatic degradation. In an *in vivo* rat study using a closed-loop small intestinal administration, vehicles with a high medium-chain fatty acid ester content, namely Capryol 90, Labrasol ALF, and Capryol PGMC, were the most effective permeation enhancers (Ukai et al. 2020). Capryol 90 generated 9.8-fold increase in AUC, which was attributed to an increase in both transcellular and paracellular uptake facilitated by intestinal membrane fluidization and safe, reversible modulation of tight junction proteins.

Additionally, a human clinical study on enlicitide chloride, a macrocyclic peptide developed by Merck & Co., demonstrated the ability of Labrasol ALF to improve solubility and modulate tight junctions, generating a 2- to 3-fold increase in plasma concentration (Johns et al. 2023).

"These studies show how lipid excipients with high medium-chain fatty acid ester content, such as Capryol 90 and Labrasol ALF, can greatly enhance drug absorption *in vivo*, especially for BCS Class III and IV compounds," says Mr. DiFranco.

Hovione: Early-Stage ASDs by Spray Drying Result in Viable Oral Dosage Form

Amorphous solids dispersions (ASDs) remain the most used enabling platform for solubility enhancement. There are a variety of molecule structures in the pipeline that require tailored bioenhancement, including the common greaseballs as well as chameleonic and brick-dust APIs. "ASDs by spray drying are a versatile platform to formulate across the board," says Inês Ramos, R&D Manager (Formulation Development, Oral Drug Product) at Hovione.

For BCS II and IV compounds, bioavailability enhancement is driven by absorption enhancement needs, target product profile, and drug molecular features. "To maintain a strong focus on manufacturability since early-stage, the delivery of a viable ASD oral dosage form follows an integrated approach involving ASD formulation screening, particle engineering, drug product formulation and process development using data-driven tools to expedite development," says Dr. Ramos.

Hovione's approach relies on a streamlined workflow supported by computational tools that starts with a "technology fitting" to assess the suitability of using ASDs by spray drying. ASD development includes a comprehensive high-throughput formulation screening (ASD-HIPROS™ proprietary platform that includes common polymers and alternative excipients such as the Dispersome® technology), designed to fast-track first-in-human (FiH) formulations that are scalable and provide adequate performance. The ASD-HIPROS platform requires a few grams of API and less than eight weeks to narrow down thousands of possible formulations to the most viable candidates. The drug product intermediate is then formulated into a tablet, capsule, or pellets/granules for oral delivery. "This methodology was designed to expedite the delivery of an enabling formulation and an industrially viable manufacturing process," says Dr. Ramos. "The goal is to maintain performance and ensure patience compliance."

LATITUDE Pharmaceuticals: Formulating the Most Insoluble Compounds

LATITUDE Pharmaceuticals takes a pragmatic approach to identify the most effective solubilization technologies for each client's individual desired drug profile. For more potent compounds with an estimated human dose under 200mg, the company utilizes amorphous solid dispersions and self-emulsifying formulations, which are free from synthetic lipids, detergents, and organic solvents – ensuring improved safety profiles and compatibility with capsule shells, says Andrew X. Chen, President and Founder of LATITUDE Pharmaceuticals. For drug substances with an estimated human oral dose exceeding 200mg, the company typically develops nanoparticle suspensions or tablet formulations containing API nanoparticles, which significantly enhance the dissolution of insoluble compounds.

"For injectable formulations, we have successfully formulated even the most insoluble compounds using one of our three preferred solubilization technologies: nanosuspensions, nanoemulsions, and LATITUDE's own ClearSol™, all of which are free from toxic or allergenic ingredients, and only contain components approved by the FDA for injection," he says. "Any of these formulations are readily scalable and can be manufactured under GLP or GMP conditions for human use."

Over the past 12-18 months, Dr. Chen says roughly 50% of the projects that LATITUDE developed were for compounds that were lipophilic, insoluble, and required increased bioavailability. LATITUDE often relies on a combination of a bile acid with triglycerides and lecithin (as in its patented ClearSol solubilization platform) for significantly enhanced solubility and

safety. "ClearSol is a highly effective, broad-spectrum solubilizer with a systemic and local safety profile that is comparable to, and often better than, cyclodextrins," he says.

Nanoform: Reduce Pill Regimens with Nanoforming

While numerous biologics have been approved in the last decade, small molecules still dominate development pipelines. As the complexity and lipophilicity of new APIs steadily increase, the challenges associated with poor solubility, leading to incomplete absorption and suboptimal pharmacokinetics, persist.

Established technologies such as ASD, nanomilling, cyclodextrins, and lipid formulations have been extensively reviewed. Of the emerging technologies, Tamas Solymosi, PhD, Lead Scientist and Technical Sales Manager, Nanoform, says it is worth mentioning deep eutectic solvents capable of solubilizing poorly soluble compounds, drug-drug co-amorphous systems improving both the solubility and stability of APIs even compared to individual amorphous states, and nanoforming, which is a green, 'bottom-up' particle engineering process to produce nanocrystalline or nanoamorphous particles.

Nanoforming technology can decrease the particle size of APIs to the 10nm range. The process works by the controlled precipitation of APIs from supercritical CO_2 ($scCO_2$) solution. "As nanoforming is relatively new, it is necessary to establish whether a compound is suitable for the nanoforming process," says Dr. Solymosi. "Nanoform uses its sparse data AI tool, STARMAP®, to predict the solubility of an API in $scCO_2$. This enables formulators to select the best suited APIs before committing to experimental work."

Nanoforming can also be used to enable single pill-per-day regimens for numerous poorly soluble drugs. Consider that early formulations sometimes sacrifice patient-centric perspectives with large pill burdens and strict food restrictions. He says: "Reformulations and optimized compositions can help improve patient centricity and adherence to therapy."

Dr. Solymosi adds that initial lipid-based capsules are typically phased out by ASDs. "We have seen that for enzalutamide, decreasing pill size and pill burden."

Nanoform successfully nanoformed the prostate cancer drug enzalutamide, already marketed as an ASD. The marketed treatment has a regimen of 4x40mg pills per day. By formulating the treatment in a nanocrystalline form, a single 160mg pill regimen was developed that matched the exposure of the supersaturating ASD formulation. Production was scaled up to several tons/year and the nanoformed tablet showed promising results in clinical evaluation and is set to enter the market in 2027.

Pharmaceutics International Inc.: Physical Property Evaluations Predict Solubility

In recent years, there has been a lot of focus on biologics and personalized medicine that are mostly delivered via parenteral routes, but oral medication is still the most convenient route of administration accounting for more than 80% of approved drugs. Use of combinatorial chemistry and high throughput screening in pharmaceutical discovery for the next drug candidate has kept funneling on molecules with poor aqueous solubility. Ninety percent of the new chemical entities and 75% of the compounds under development have inadequate water solubility. Biopharmaceutical Classification System Class II and IV compounds fall into this category. Bioavailability of an active moiety, among other factors, is predominantly affected by its solubility and permeability. Adequate aqueous solubility at absorption site is necessary for sufficient permeation and pharmacological action translating to desired clinical outcome.

To achieve optimal bioavailability, scientists have used various physical and chemical approaches to modify the rate of dissolution and solubility. Prodrug, salt formation, and cocrystals are the main chemical approaches that are used in early development to enhance solubility. Physical approaches to improve solubility have been mainly focused on solid dispersion, lipid-based drug delivery systems using oils, lipids, surfactants and/or cosolvents, particle size reduction and Cyclodextrin inclusion complex. Primary technologies that were used to improve solubility in FDA-approved products since 2000 are hot melt extrusion and spray drying to form solid dispersion; self-emulsifying -emulsion, -microemulsion, and -nanoemulsion systems (SEDDS, SMEDDS, SNEDDS) for lipid-based delivery; micronization and nanoparticles using dry or wet milling processes; and Cyclodextrin inclusion complexes. Among these, 30% of products were based on a solid dispersion platform.

At Pharmaceutics International Inc., a Jabil Company, initial evaluation of physical properties of insoluble drug molecules is done utilizing Hansen Solubility Parameters in Practice (HSPiP) software to predict the solubility in various solvent or solvent combinations, explains Sundeep Sethia, Vice President of R&D at Pharmaceutics International.

"Here, the API and solvent are characterized by just three parameters δD for

Dispersion (van der Waals), δP for Polarity (related to dipole moment) and δH for hydrogen bonding and represented as points in three dimensional HSP space," he says. "API and solvents sharing similar HSP space shows favorable solubility. Solubility is subsequently verified by experimental data. Based on the output, a typical formulation approach may be development of a SEDDS or SMEDDS using lipidic excipients and delivered as an oral liquid or soft gelatin capsule dosage form. Softgel capsules mask the oily taste and provide ease of unit dosing."

For compounds with poor solvent solubility, wet milling to nano size to increase the diffusional surface area is one option. Here, the API is milled along with stabilizers (surfactants/co-surfactants) using mills, such as agitator bead mill (Dyno®Mill), high pressure homogenizer, etc. Mr. Sethia says that increased surface area improves *in vivo* dissolution, thereby improving bioavailability.

Quotient Sciences: SDD Suspension Enhances Absorption

Dr. Vanessa Zann, Vice President, Scientific Consulting, Quotient Sciences, says she has seen positive results with spray dried dispersion (SDD) formulations to help enhance fraction absorbed, which in turn increases exposure. Quotient Sciences uses biorelevant dissolution to rank solubility-enhanced technology platforms and then selects the most promising for clinical assessment.

"Note there is often a disconnect between preclinical *in vivo* data and clinical outcomes," she says. "We recommend assessing the SDD platform initially as a suspension formulation, which provides gold standard data for what is likely to be achieved with a good performing SDD tablet."

For example, Tranquis approached Quotient Sciences in the preclinical stage to help develop clinical formulations for first in human (FIH). The compound in question was a BCS II compound (poor solubility and high solubility) and had shown solubility limited exposure preclinically, hence an enhanced formulation was anticipated to be required to achieve efficacious clinical exposures, explains Ms. Zann. Quotient Sciences used an integrated approach for drug product development, manufacturing, and clinical testing (this is the Translational Pharmaceutics® platform) to rapidly identify and overcome solubility and bioavailability challenges for this compound.

Three suspension formulations were developed for assessment in the FIH: a methylcellulose crystalline (MC) suspension; a spray-dried dispersion (SDD) suspension; and a hot melt extrusion (HME) suspension. The regulatory package was filed with 90 days stability for the SDD and HME GMP intermediates and seven days for the powder in bottle (PiB). The suspension had four hours in use stability and a rinsing trial performed on each to allow total dosing volume to be 240mL. She explains that the SDD and HME both showed superior dissolution to the crystalline API in a biorelevant dissolution assessment, demonstrating a spring and parachute effect with reduced precipitation in the intestinal phase. A number of SDD suspensions were also assessed in the rat prior to the FIH but didn't show any improvement over the MC suspension.

The FIH study started dosing SAD cohort 1 (60mg) and 2 (180mg) with a methylcellulose crystalline suspension, which gave three-fold higher exposure than anticipated from the preclinical species. At SAD cohort 3 (540mg), the subjects were initially dosed with the MC suspension, but then returned to the clinic for dosing with the SDD and HME suspensions. The dose of the SDD and HME suspension was reduced to 180mg to ensure that the exposure caps were not exceeded due to the already higher exposure in the clinic than originally predicted. The SDD had the highest exposure showing a four-fold increase compared to the MC suspension. This formulation was selected for dosing the remainder SAD and MAD cohorts.

"The Translational Pharmaceutics platform allowed the study not only to deliver safety, tolerability, and pharmacokinetic data, but also formulation selection assessment ahead of Phase II patient trials," says Ms. Zann.

Serán Bioscience: A Scientific Approach to Understanding a Molecule's Barriers

The landscape for oral delivery of novel new chemical entities (NCEs) is rapidly evolving as we leave the "rule of five" era, says Rod Ketner, PhD, Vice President of Business Operations at Serán Bioscience. Increasingly large and complex "small" molecules with poor solubility and permeability present unique challenges to drug delivery. Successful formulation strategies must meet the target product profile with a robust and scalable manufacturing process, often on accelerated development and approval timelines.

Serán's team takes a hypothesis-driven scientific approach to understanding the physical, chemical, and biological barriers to absorption. "Avoiding a shotgun approach to formulation design, we characterize an NCE and its performance in biorelevant media and dissolution conditions," he says. "An understanding of a

molecule's performance in these media can set the foundation for formulation approaches and dosage form architecture."

Conventional formulation strategies – such as leveraging the low-pH environment of the stomach to solubilize weak bases – increasingly prove insufficient and more advanced techniques are necessary, he says. Converting crystalline APIs into amorphous solid dispersions (ASDs) can substantially increase solubility, but require excipients that sustain supersaturation through GI transit. "ASDs, manufactured through methods like spray drying, melt extrusion, or precipitation, yield a higher free energy state and, consequently, greater solubility in the small intestine," says Dr. Ketner. "Amorphous forms have been demonstrated to lead to a tenfold or greater enhancement in solubility."

Spray dried dispersions (SDDs) stand out as a preferred method for enhancing solubility in the gastrointestinal (GI) tract. These stable, amorphous formulations combine an API and a polymer in an organic solvent, followed by spray drying to create particles ranging from 5-50um. The resulting particles exhibit physical stability and dissolution properties that significantly boost bioavailability compared to crystalline API alone. "The scalability and well-established nature of spray drying technology are notable, with over 50 approved SDDs on the market currently," he says. "However, developing and scaling SDDs effectively requires specialized experience, not just an off-the-shelf dryer."

Beyond solubility, permeability-limited absorption is an increasing obstacle, especially for complex molecules like protein degraders and peptides. Their larger size (800-1500 MW) reduces their passive permeability across the epithelium in the small intestine, and complex self-assembly can lower the driving force for permeation. Multiple approaches have been screened to address these issues, including lipid systems, and additional permeability enhancers. Permeation enhancers that modify the lipid bilayer or tight junctions between epithelial cells remain controversial and require further research.

"Given these challenges, outside-the-box approaches to addressing permeability challenges are essential for achieving acceptable pharmacokinetics," says Dr. Ketner. Nanoparticles, for instance, can maximize drug concentration at the surface of the epithelium. For peptides, protecting them from enzymatic degradation in the GI tract and designing dosage forms that transit, protect, and dissolve at the right location is critical. Patient-friendly injectable options, such as subcutaneous and intramuscular formulations, also merit consideration for drugs facing significant permeability issues.

Serán applies materials science principles to develop formulations, including enabled approaches like ASDs, along with scalable processes designed for sustained progress. He says: "This allows Serán's team to offer flexible formulations and processes that support evolving clinical study needs and ensures R&D resources are effectively focused on the assets most likely to be successful."

Spokes Sciences: Highlighting the Utility of SNAC with Lipophilic Compounds

In both the development of drug products for new chemical entities (NCEs) and within product life cycle management of existing drug products (such as developing oral dosage forms out of known actives currently administered by injection), major hurdles to the use of new pharmaceutical excipients are the time, cost, and uncertainty associated with obtaining FDA approval. Despite lipophilic drug compounds remaining a driving force behind the development of bioavailability enhancement technologies, these regulatory approval challenges can hamper or delay the adoption of novel functional excipients for that purpose, explains Kimberly Zubris, PhD, Chief Science Officer, Spokes Sciences.

Originally developed to improve the oral bioavailability of water-soluble active ingredients, salcaprozate sodium or SNAC, is an absorption-enhancing excipient already approved by the FDA and used in a blockbuster diabetes drug with the active ingredient semaglutide (Rybelsus®). SNAC's generally recognized as safe (GRAS) status means it could immediately be used in over-the-counter supplements, says Dr. Zubris.

Spoke Sciences creates innovative proprietary technologies through the delivery of highly lipophilic/poorly water-soluble active pharmaceutical and plant-derived functional ingredients. Previously, Spoke and its predecessor discovered that SNAC could be combined with some lipophilic functional ingredients to make new proprietary oral dosage forms with significantly improved bioavailability. Striking among these data are a human clinical study showing that SNAC increases cannabidiol (CBD) oral bioavailability by 6-fold compared to standard solid-filled capsules without SNAC, and another clinical study showing that SNAC increases oral tetrahydrocannabinol (THC) exposure by 2.3-fold compared to THC in ethanol.

Highlighting the utility of SNAC as a blockbuster absorption enhancing ingredient, Dr. Zubris says that Spoke has re-

cently undertaken studies to show that a broad range of hydrophobic actives can be combined with SNAC to significantly improve both their aqueous solubility and their rate of dissolution. This SNAC-driven solubility enhancing effect applies to molecules that span the range of the lipophilic spectrum, including: melatonin (Log P ≅ 1.6), resveratrol (Log P ≅ 3.09), pterostilbene (Log P ≅ 3.54), ibuprofen (Log P ≅ 3.8), curcumin (Log P ≅ 4.28) and coenzyme Q10 (Log P ≅ 10). With a stoichiometric optimum ratio of SNAC:active, solubility was seen to increase by up to 350 times in the presence of SNAC relative to that of water alone.

"SNAC enhances the oral bioavailability of lipophilic drugs, not just hydrophilic drug substances as previously assumed," she says.

Ongoing studies at Spoke continue to develop data validating SNAC's mechanism of action with these lipophilic active ingredients. But given these results, Dr. Zubris says that SNAC is well poised to become a key tool for the use in formulating poorly absorbed drugs.

Thermo Fisher Scientific: Molecule-Centric Approach to Amorphous Drug Development

When asked how Thermo Fisher Scientific solved a bioavailability issue for a client, Sanjay Konagurthu, PhD, Senior Director, Science and Innovation, Pharma Services, at Thermo Fisher Scientific, shares the design of a solubilized amorphous spray dried dispersion (SDD) that enhanced oral bioavailability of a poorly water-soluble drug. To support this partner, Thermo Fisher used a molecule-centric approach to amorphous drug development that, instead of empirical or 'shotgun' approaches to accelerate formulation screening, is routinely performed leveraging Thermo Fisher's Quadrant 2® approach. Quadrant 2 is an artificial intelligence (AI) and machine learning (ML)-based predictive modeling platform, designed for solubility and bioavailability enhancement.

"Lead formulations were identified with a combination of *in silico* modeling and *in vitro* solubility-supersaturation measurements to predict drug-excipient interactions," he explains. "The combination of computational and experimental tools provides a cost- and time-efficient strategy to select drug-excipient combinations, prior to embarking on more time-consuming formulation and process development."

Thermo Fisher performed molecular modelling to characterize interactions of pure drug, excipients, and drug-excipient systems via molecular dynamic (MD) and quantum mechanical (QM) simulations using a suite of programs assembled by the team. The goal of this work was to examine the drug-drug and drug-excipient molecular level interactions between a BCS Class II molecule and compendial/GRAS polymers, in order to provide a rational basis for the selection of appropriate polymers for inclusion in a solubilized drug product intermediate.

"This rationale is based on molecular descriptors and specific drug-polymer interaction energies. *In silico* modelling results were corroborated by an *in vitro* solvent spike assay," Dr. Konagurthu says.

Lead drug loading and polymer systems were characterized by *in vitro* tests and confirmed by *in vivo* animal studies. In agreement with the *in silico* predictions, SDDs demonstrated substantial improvement of bioavailability in both *in vitro* and animal pharmacokinetic studies compared to the crystalline drug. Solvent spike assay analysis demonstrated that the addition of polymer excipients improved the sustainment of supersaturation in FaSSIF (Fasted State Simulated Intestinal Fluid). Non-sink dissolution results agreed with predictive *in silico* modelling and solvent spike analysis that HPMCP HP-55, Eudragit L-100 and CAP provided the greatest synergistic effects and provided improved sustainment of supersaturation.

He says: "The *in vivo* data demonstrated that the SDDs resulted in significant enhancement of oral bioavailability. SDDs with a ranging polymer composition and drug loading provided up to an approximately three-fold increase in maximum drug plasma concentration and an approximately seven-fold increase in total AUC (Area Under the Curve). *In silico* modeling accurately predicted that HPMCP HP-55, CAP and Eudragit L-100 based SDDs would provide miscible drug-polymer systems with significantly enhanced performance."

In summary, Dr. Konagurthu says that a combination of experimental and computational modeling approaches allows for predictive drug-polymer miscibility and supersaturation sustainment. "Utilization of Quadrant 2 modeling allows for rapid screening with zero Active Pharmaceutical Ingredient (API) usage and a significant reduction in benchtop manufacturing/analysis," he says. "This led to the successful development of an enabling formulation for a BCS Class II drug that demonstrated superior oral bioavailability by leveraging our Quadrant 2 platform." ◆

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CLINICAL TRIALS

Need for Accessibility to Meet FDA Guidance for Decentralized Trials

By: Neil Vivian, MSc

ABSTRACT

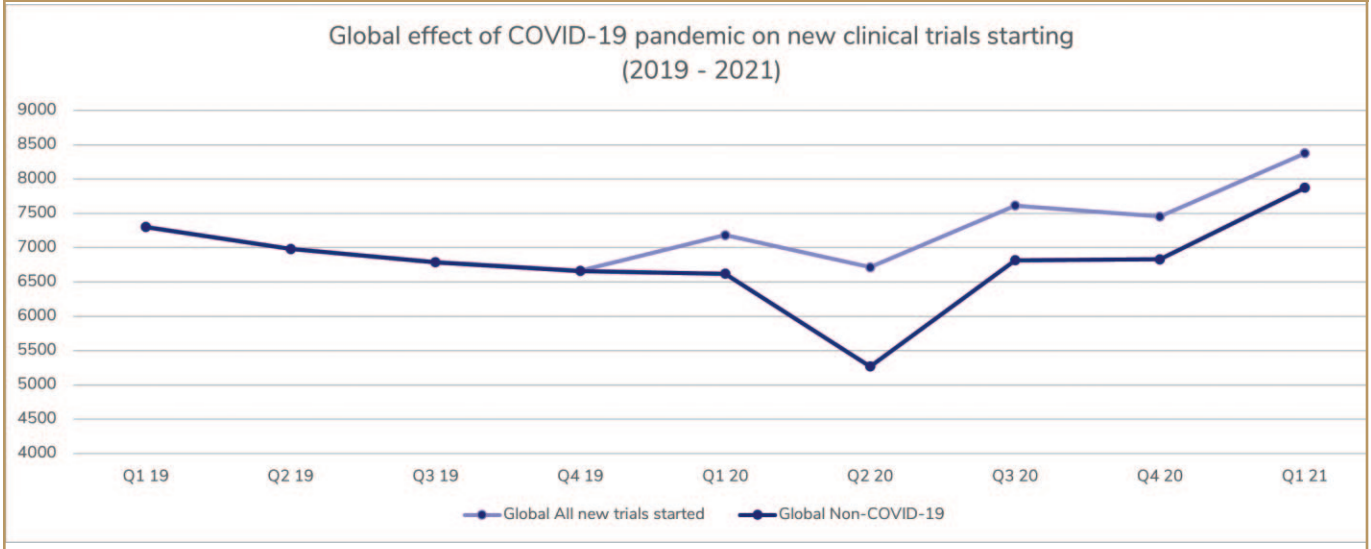
As decentralized clinical trials (DCTs) gain in popularity, regulators are pushing sponsors to make trial populations more diverse. Progress toward greater diversity has been uneven, largely due to factors such as the COVID-19 pandemic and the limited manageability of voluminous data generated via wearable devices. Nevertheless, advances in electronic data collection and analysis are helping to make DCTs more accessible to broader and more diverse patient populations. Further innovations, particularly in artificial intelligence technology, are expected to accelerate these trends.

The decentralized clinical trial (DCT) model received a significant boost in May 2023, when the U.S. Food and Drug Administration (FDA) issued a draft guidance encouraging the design and implementation of clinical trials conducted at the point of care, facilitated by the use of wearables and other technologies. The guidance positioned technology-enabled DCTs as a means to help researchers become "more agile and efficient" , emphasizing the following potential benefits:[1]

- Improved recruitment, enrollment, and retention: The DCT model enables recruitment of more diverse patient populations, and avoids having to focus recruitment efforts around trial sites.
- Collection of patient data in real time: This capability is a vast improvement over traditional trials' 7-14-day timeframe for entering patient data into a trial database.
- Reduced drug development costs and administrative burden on investigators and sponsors: The DCT approach eliminates the need for 100% source data verification (SDV).

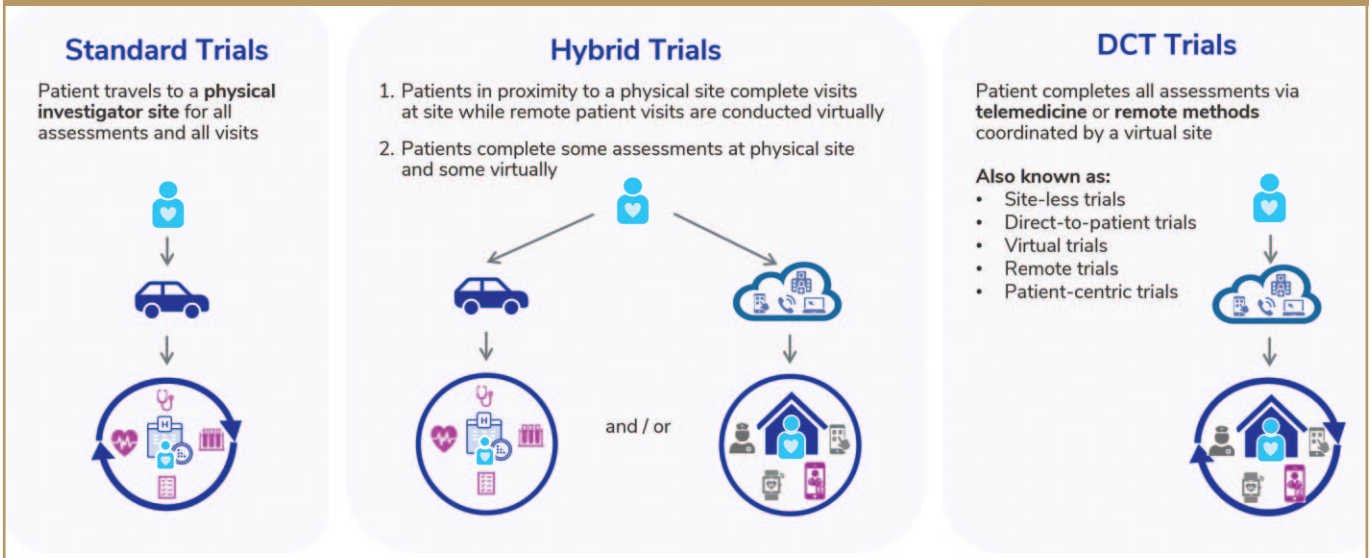
The basic rationale for DCTs is that they can "bring clinical trials to the patient." This approach enables the movement of

FIGURE 1



Effect of COVID-19 pandemic on new clinical trial starts (2019-2021, global)

FIGURE 2



Standard vs. hybrid vs. decentralized trials: Typical patient experience

prospective data collection away from the "brick and mortar" of the investigator site. By integrating data collected via digital technology (e.g., wearables, telehealth visits, online patient diaries, electronic informed consent [eConsent] programs, patient apps), DCTs allow sponsors to:[2]

- Gain access to expanded source evidence (e.g., labs, insurance claims, media reports)
- Encourage enrollment of more diverse patient populations within community settings
- Obtain data more representative of a "real-world" population to support more informed treatment decisions

DCT POLICY & PLANNING CONSIDERATIONS

As further evidence of its advocacy of the DCT model, the FDA, as outlined in its May 2023 draft guidance, aims to operationalize goals to reduce on-site monitoring, maintain data integrity, and oversee patient safety and product efficacy using remote monitoring technologies.[1],

The FDA's DCT-related policies are informed by the following planning considerations:

- 15% to 20% of trials never enroll a single patient
- Two-thirds of sites fail to reach enrollment goals[4],
- 70% of potential trial participants in the U.S. live more than two hours away from the nearest study center
- More than half of patients surveyed say they are more likely to participate in a clinical trial if home care is offered
- Employing virtual/direct-to-patient services helps maintain patient retention rates above 95%[5]

THE DEPICT ACT: A PUSH FOR GREATER DIVERSITY

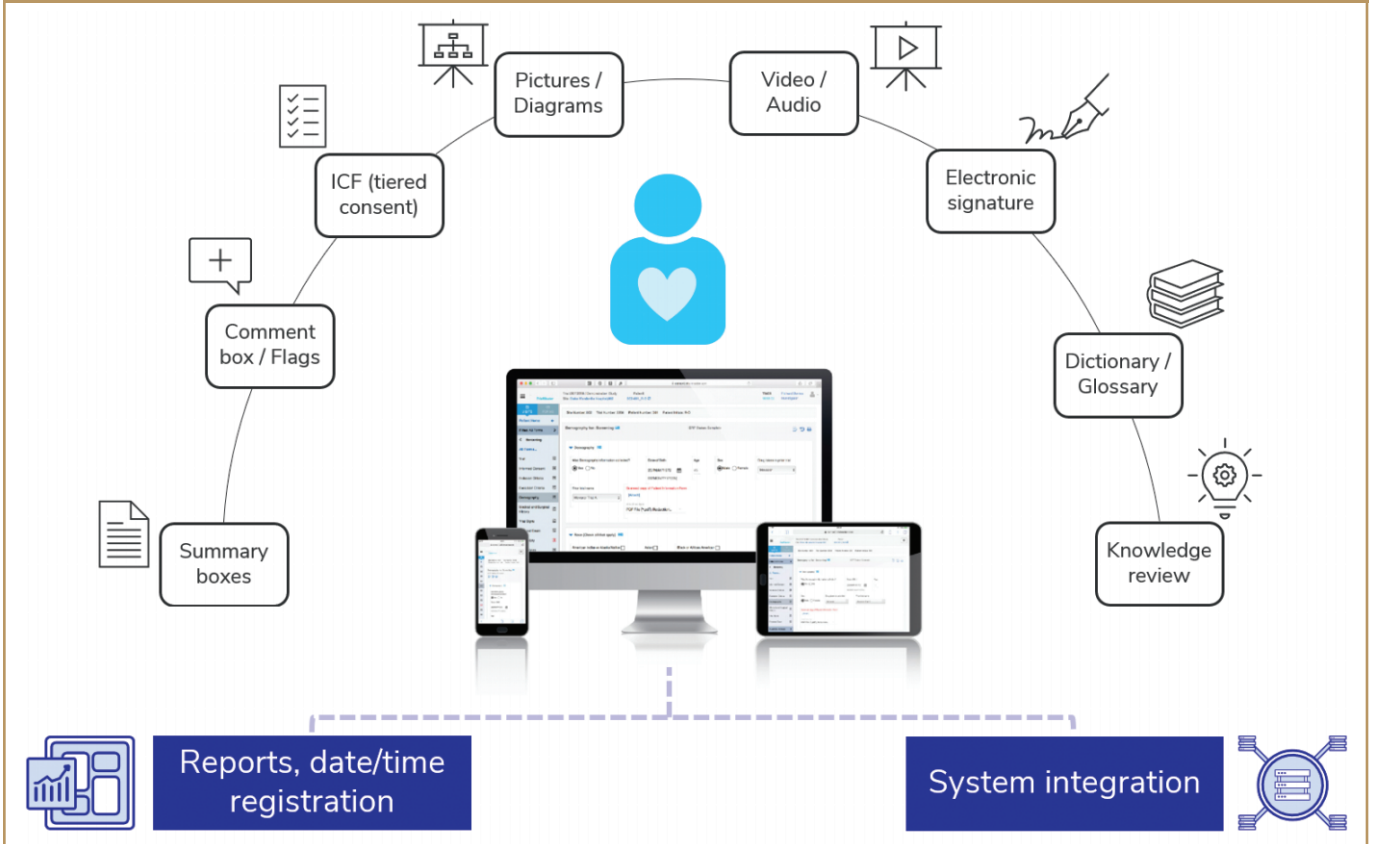
Meanwhile, the DEPICT Act (H.R.6584), introduced in February 2022, has sharpened regulators' focus on increasing diversity in clinical trials. This piece of legislation aims to strengthen diversity through enhanced data reporting and increased resources for underrepresented communities. It requires Investigational New Drug (IND) and Investigational Device Exemption (IDE) applicants to report trial enrollment targets by demographic subgroup (e.g., age, race, ethnicity, sex). Those targets should be accompanied by a Diversity Action Plan outlining strategies for reaching enrollment goals and improving diversity.

The DEPICT Act also grants the FDA authority to mandate post-market studies when sponsors fail to meet diversity enrollment targets without sufficient justification. Additionally, it requires the FDA to publish an annual report analyzing data provided by sponsors on their progress toward improving diversity.[8]

UNEVEN PROGRESS TOWARD GREATER ACCESS & DIVERSITY

So, how successful have the FDA draft guidance and the DEPICT Act been in increasing access to and diversity in clinical

FIGURE 3



eConsent (Adapted from: TransCelerate eConsent Assets http://www.transceleratebiopharmainc.com/econsent/)

trials? The answer thus far: not so much. To be fair, the uneven success of these regulatory and legislative initiatives is largely due to the COVID-19 pandemic, which had a major impact on new clinical trial starts, as vividly illustrated by a sharp downturn in the second quarter of 2020 (Figure 1). The pandemic left patients unable to travel to trial sites, resulting in delays or cancellation of new trials and suspension of ongoing trials. Presumably, earlier and more widespread adoption of the DCT model would have been far less disruptive to clinical research programs.

Additionally, the DCT model has run into an unforeseen obstacle: wearables generate more data than is needed for sponsors to enter into electronic data collection (EDC) systems. A potential solution to this logjam is to apply filters to wearables-generated data to limit the volume of returned data. The filters can be customized to focus on key values such as those that are out of a specified range, or those that reflect rapid changes in a patient's condition.

Digital data collection also raises privacy concerns. These can be addressed by de-identifying data presented to an EDC platform to safeguard patient privacy.

ENHANCING PATIENT ACCESS

Facilitating patient access is crucial to promoting and increasing diversity in trial populations. DCTs and hybrid trials enable patients to be more involved as trial participants, as they allow direct entry of patient-reported data (e.g., via wearables) without having to travel to the trial site (Figure 2).

DCT and hybrid models also provide advantages to sponsors and sites, particularly in terms of better and earlier identification of at-risk patients, compared to traditional data-gathering methods. Other key advantages include enhanced patient safety and access to patient data in real time.

Achieving diversity in clinical trials is not easy and requires continuous collaboration between medical affairs teams and clinical research teams. These teams must avoid bias and improve clinical care quality for marginalized populations, and reduce barriers to trial access.

Anju's clinical intelligence solution, TA Scan, enables sites to visualize global ethnicity data, socio-economic data, and site/principal investigator (PI) experience on a single map. It also filters data by age, gender, racial distribution, and average income. Perhaps the most unique feature of TA Scan is its capacity to visualize and analyze newly integrated European diversity data in addition to US diversity data.

FACILITATING INFORMED CONSENT

Informed consent issues were the number 3 reason for FDA Form 483 findings in 2017 and 2022. However, total informed consent issues declined from 10.7% of 483 findings in 2017 to 5% in 2022.[6] The decline appears to reflect more widespread adoption of eConsent, a technology-enabled patient engagement tool that can improve site/patient discussions and clinical trial efficacy.

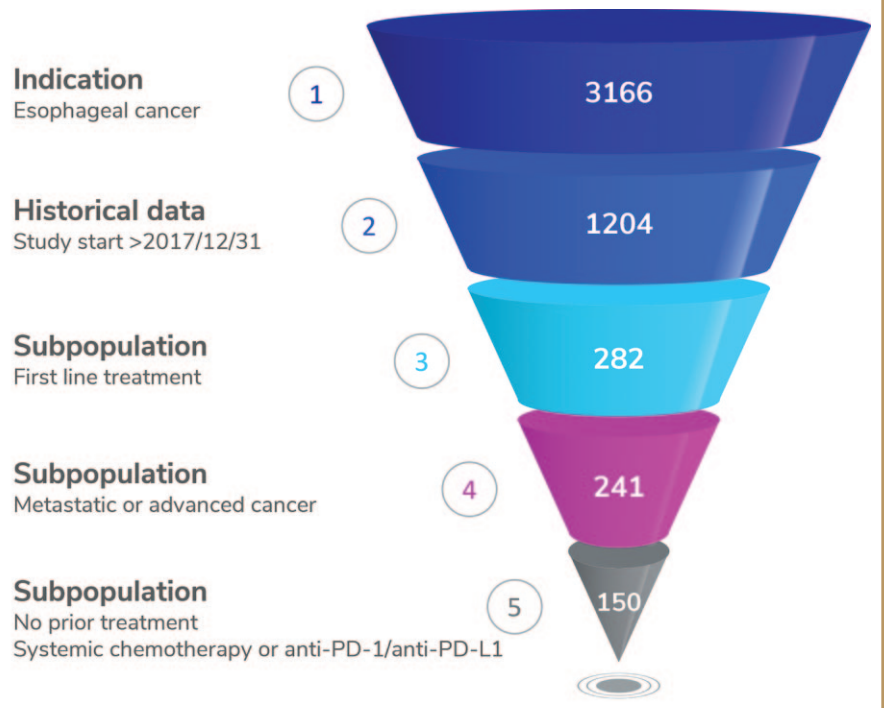
An FDA Form 483 is issued when an inspector(s) has observed any conditions in possible violation of the Food Drug and Cosmetic (FD&C) Act and related Acts.

A key advantage of eConsent is that it leverages advanced technologies (e.g., video/audio, pictures/diagrams, electronic signature, materials in different languages) to facilitate provision of consent (Figure 3).

eConsent also allows for greater consistency and regular updating of materials to ensure use of the most recent versions. Moreover, eConsent is extremely convenient; it can be deployed remotely, allowing patients to access consent materials from home via portals; eConsent also allows patients to review eligibility criteria earlier in the screening process, potentially facilitating more informed decision-making.

The pandemic encouraged more widespread use of eConsent, and adoption of this tool continues to increase, but the adoption rate is slow, reflecting the conservatism of the industry. Institutional review boards (IRBs) have been a major stumbling block, particularly when a trial involves multiple IRBs. Nevertheless, guidance from the FDA and other authorities has eased some IRB-related roadblocks. As a result, IRBs are now generally more open to eConsent.

FIGURE 4



Sample historical data: Estimated number of esophageal cancer trials in the past five years (Source: TA Scan, April 2023)

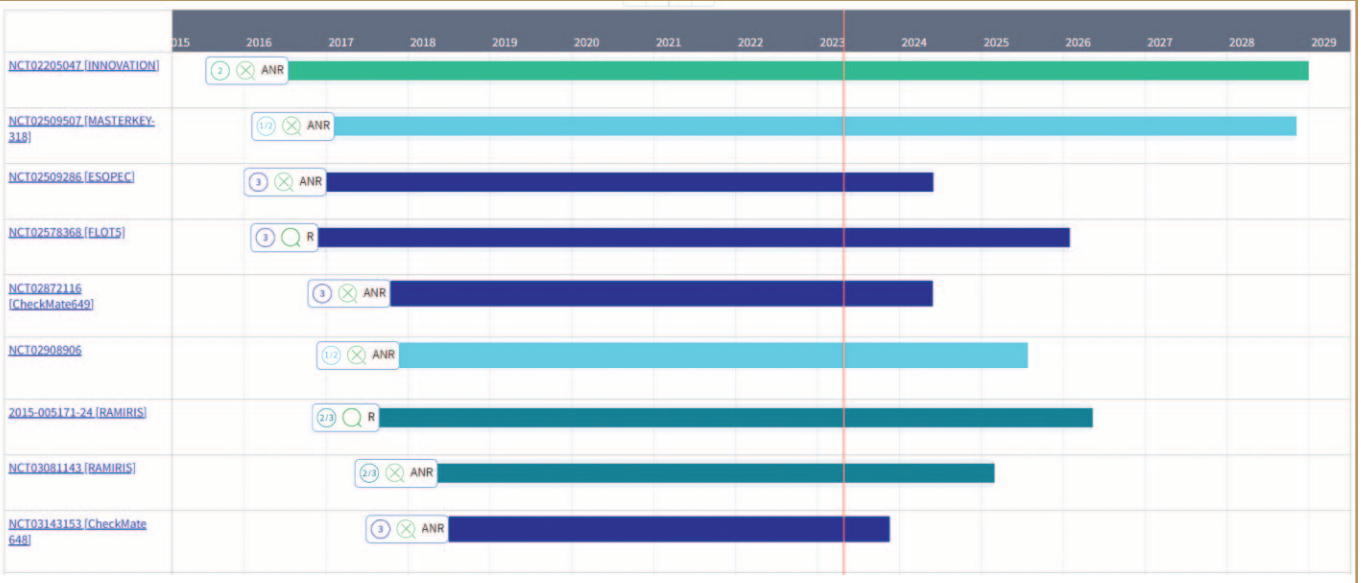
Another key advantage of eConsent is that it can help to accelerate trial activation. Speed is vital in all clinical trials. Many trials require rapid turnaround due to disease severity, a factor that can make data management needs more complex and slow to implement. The best EDC systems deliver flexibility and adaptability in the design from the beginning. For example, Anju Software was recently involved in a trial in which its EDC system, TrialMaster, was activated in two weeks, compared to the industry standard of approximately 4-12 weeks.

STREAMLINING ELECTRONIC DATA COLLECTION & ANALYSIS

Recognizing the need to speed up efforts to enhance patient access, numerous vendors have developed intuitive EDC suites with built-in eConsent, electronic patient-reported outcomes (ePROs), and electronic clinical outcome assessment (eCOA) software. These offerings enable collection of medical histories and medication information from patient diaries, surveys, and validated questionnaires. They empower patients to enter data directly into the system in real time, using their own devices, yet do not require source data verification. Additionally, these tools allow real-time evaluation of compliance and outcomes, and enable flagging of patients who may benefit from a check-in call, follow-up visit, or other timely intervention.

One notable trend is the development of intuitive, web-based, clinical business intelligence platforms that apply rules to large volumes of data to analyze trends of interest. Such platforms can be used to mine data from extensive global databases of clinical trials, investigators, publications, and other sources and variables. These platforms thus enable the analysis,

FIGURE 5



Sample Gantt chart (Source: TA Scan, April 2023)

measurement, and ranking of trial and site data, including key opinion leader and principal investigator experience and involvement.

Notably, some of the newer business intelligence platforms can help sponsors find sites that can meet enrollment needs by recruiting participants from a trial's target population. This feature can help sponsors meet diversity goals, and can also provide justification for DEPICT Act exemption from the FDA.

Some of the more advanced platforms include a feasibility module, whereby the sponsor enters trial parameters, target countries, the desired number of patients, and other key variables over a defined period of time. The module thus facilitates identification of countries and/or regions to consider or avoid, based on competitive trial activity (or lack thereof) in those geographic areas. Incorporation of Monte Carlo simulation can enable modification of parameters to help determine whether a study is feasible in a specific location. In case of underperforming sites in an ongoing trial, the module can identify alternate/backup sites.

FUTURE DIRECTIONS: LEVERAGING AI TO FACILITATE DCTS

As in many fields, artificial intelligence (AI) is increasingly used in medical research, particularly in the development of new antibiotics targeting drug-resistant bacteria. The utility of AI and machine learning in drug discovery and development lies in their ability to screen thousands of potential compounds to isolate a handful that may be druggable.

Similarly, AI/machine learning has great potential in the clinical trial setting, although their use in DCTs is still in its infancy. Sponsors are exploring the use of AI to streamline various aspects of DCTs including identifying eligible patients. AI can also be useful in reviewing and analyzing voluminous data that are currently stored in data warehouses; the technology can be deployed to detect trends in ePROs, medication/protocol adherence, and other drug-related data.

Additionally, as sponsors respond to intensifying demands to make trial populations more diverse and reflective of the general population, AI may prove valuable in identifying medications and other interventions that are effective in specific patient populations, whether stratified by age, sex, ethnicity, geography, disease variant, or molecular makeup.

The nascent field of AI is just one example of technological advances that are expected to make DCTs more accessible to broader and more diverse patient populations. The next few years will be a crucial time to observe how quickly and thoroughly such advances are adopted in the DCT setting.

SIDEBAR: TA SCAN

TA Scan is Anju's web-based clinical intelligence platform that analyzes, measures, and ranks trial and site data, including key opinion leader (KOL) and investigator experience and involvement. Designed to support the entire clinical study workflow, TA Scan can facilitate trial planning and benchmarking by helping sponsors:

- Understand the competitive landscape
- Estimate patient enrollment benchmarks
- Identify sites with capacity to recruit and that support diversity strategies

TA Scan can pinpoint specific patient populations on a global or local scale by browsing the literature to identify relevant publications, producing a citation list with PubMed links to each article, along with semantic linking of data types to enable assessment of trial results. It can also quantify the number of trials in a specific disease subtype over a defined time period, sorted by phase and geographic area (Figure 4). TA Scan yields intelligence on currently recruiting trials, regulatory lag, and number and experience of sites and investigators, with built-in Gantt charts to facilitate comparison of competitive trial timelines (Figure 5).

TA Scan's site inference algorithm unlocks undisclosed site data, with an unbiased investigator scoring system based on clinical or scientific footprint. The platform's site capacity calculator enables assessment of a site's ability to accommodate additional trials; sites with sufficient capacity can be layered on a diversity distribution map to streamline site selection and diversity strategy.

In summary, TA Scan is an all-in-one tool that collects, aggregates, and analyzes clinical, publication, and congress data, with integrated analytics modules for quick and easy analysis. Its features include weekly data updates, exportable graphical outputs and reports, a self-driven and intuitive user interface, and dedicated customer support covering all time zones. ◆

BIOGRAPHY

Neil Vivian is Senior Director of Business Solutions, Anju Software. He provides technical support to the Business Development group and positions Anju Solutions and Services to potential and existing clients. His Product Manager responsibilities include providing guidance and high-level business requirements for new product features based on his industry experience and understanding of new emerging Regulatory Guidance. He has over 43 years' experience in the software industry built from a solid foundation in the Defense Industry, 29 of those focused on Life Sciences. He has a BSc in Physics and Engineering Science and MSc in Information Technology.

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Drug Development
EXECUTIVE

How Vetter's Expansion of its Senior Management Team Aligns with Prioritization of Strategic Growth

The European Commission released its reform of the EU pharmaceutical legislation, which prioritizes several key objectives. This includes enhancing the delivery of safe medicines to all patients and security of supply. It also consists of advancing innovation-friendly environments for drug development and production as well as making medicines more environmentally sustainable. To effectively contribute to these targets while emphasizing the strategic and sustainable growth of the company, Vetter announced the expansion of its senior management team. This crucial step positions the Contract Development and Manufacturing Organization (CDMO) to consistently act as a dependable and forward-thinking member of the larger pharma and biotech value chain. The change adds three leaders to its executive C-suite, resulting in a total of five managing directors with a varied breadth of experience.

As of January 1, 2025, Henryk Badack, Titus Ottinger and Carsten Press became managing directors alongside Thomas Otto and Peter Soelkner.

Drug Delivery and Development recently interviewed Vetter's leadership to discuss the company's vision for strategic restructuring, their insights on Contract Development and Manufacturing trends in 2025, and what this strategic change means for the sustainable growth of the company and its global expansion.

This restructure illustrates the company's commitment to address the increasingly complex needs and expectations of its customers and their patients worldwide by creating a viable framework of leadership to guide its 7,000 employees worldwide in their day-to-day activities and future planning.

Q: Tell me about your specific responsibilities in your role as managing director.

Henryk Badack: In my role, I am responsible for the development service and quality division. In my charge of managing quality and development, I am focused on

compliance with regulatory standards in our quality departments as well as management for clinical manufacturing initiatives. Our comprehensive fill and finish services offer customers analytical studies, support in achieving regulatory approvals and supply for clinical trials. In addition, we offer personalized clinical production with intent to deliver drug products to market at an accelerated rate and optimized scale-up services based on decades of experience.

Titus Ottinger: I am now leading the charge of the company's finance and controlling departments. My 20 years of experience at Vetter position me to responsibly manage its finances and external accounting. I plan to place a heavy prioritization on planning and managing our strategic company growth and on risk management as we invest approximately 1.5 billion Euros in our strategic expansion until 2029 to make sure our investments most effectively support our customers and advance our success as a company.

Carsten Press: I now have the responsibility for leading human resources and supply chain management across our globally operating organization. My role consists of supporting employees and their professional development and getting new talented people on board. In addition, I plan to oversee the supply chain with a focus on the security of supply, resilience, efficiency and protecting the safety of patient care with medicines for patients and customers. While I was deeply invested in our supply chain management in my previous role, the HR facet of my position is an exciting new endeavor for me.

Thomas Otto: I am continuing to lead our production and engineering departments as well as the technical service and internal project management. I joined Vetter 35 years ago, and I have served in my current role for the past 22 years. With the expansion of our senior management, my role has become more targeted to allow me to better focus on our core business of manufacturing customer drug products to ultimately get them to the patients who rely on them in a timely and efficient manner.

Peter Soelkner: I have been managing director at Vetter since 2008, and I will continue to be responsible for global sales and corporate development. I am focused on expanding our global market reach by optimizing our corporate strategy and building meaningful, long-term relationships. Through this, I aim to establish mutually beneficial partnerships with customers. My ultimate goal is to continue to make Vetter a trusted global leader and reliable partner in the industry.

Q: What excites you the most about taking on this new leadership position? What are your primary goals in your new role as managing director, and how do you plan to achieve them?

Henryk Badack: As I navigate my new responsibilities, I am most excited to contribute to enhancing quality and development practices and to continue writing the Vetter success story together with my colleagues. It has been a pleasure getting to know my colleagues in these particular departments, who can now help me perform better in this new role. My responsibilities are now shifting, and I am looking at the big picture to focus on where the company is now and where it is heading.

Titus Ottinger: I am looking forward to continuing my management of finance and controlling. With my years of experience in strategic planning and controlling of financial managements as well as risk assessment, I hope to contribute to the company's intent to further improve as a reliable partner and conduct our business processes in a sustainable manner.

Carsten Press: I've been in supply chain management for years, and I am really looking forward to extending my skills to human resources in my new position. With my extensive management experience, I hope to foster professional development and an optimal work environment for my colleagues. Vetter prides itself on operating as a reliable employer for its 7,000 employees and I am looking forward to finding the right balance to provide my teams with a framework that equips them to do their job in the best way possible.

Thomas Otto: My expertise lies in a variety of departments, including pharmaceutical production, technology, technical service and internal project management. The expansion of the senior management team allows me to bring heightened focus to my responsibilities. My primary goal is tied to implementing more automation and additional advanced technologies in our cleanrooms to achieve the highest possible level of quality and efficiency in every batch we manufacture. I look forward to helping my peers adapt to their new responsibilities and offering them the tools and counsel to succeed.

Peter Soelkner: I am excited to see the company benefit from the leadership of this senior management team. I am looking forward to becoming more focused on global sales and corporate development, particularly as the company navigates several capacity expansion opportunities in the coming years.

My hope is that our management team can foster synergy across our various focus areas and work together to seamlessly continue bringing Vetter toward a future of sustainable growth.

Q: How do you envision contributing to Vetter's sustainable growth and the needs of your global customers through this restructuring?

Henryk Badack: My dedication to enhance quality and development services will support Vetter's commitment to producing high quality injectable medicines. I will focus on improving efficiency in our quality assurance processes to further advance the company's reputation as a premier quality CDMO in our sector. As quality regulations evolve and customer expectations increase, so will our business practices to prioritize compliance and protect the effectiveness and safety of our customers' drug products.

Titus Ottinger: With the new structure, I want to encourage mutual respect and understanding among the five managing directors. Transparency and clarity on our end can lead to increased reliability and result in finding good solutions, which can encourage trust among employees and foster a healthy work environment. Each of us brings our own individual expertise and years of experience in Vetter leadership, allowing the opportunity for productive collaboration that will drive the company's growth globally.

Carsten Press: I have always believed in trusting our teams and letting them do their work autonomously. Often, I feel more like a coach for my employees. It's important to provide a good framework and direction for staff and trust them to do their job. I strive to embolden our employees to embrace authenticity and reliability. It's important to me that my colleagues and I are very open and direct with each other to establish an equal footing, and I find that is often the best way to discover the most creative solutions. It is critical that we honor our responsibilities towards our customers and their patients but also towards our employees to create a harmonious work environment that promotes innovation.

Q: What are the trends and technological developments that you expect to define the CDMO landscape in 2025 and beyond and how is Vetter adjusting?

Thomas Otto: CDMOs, including Vetter, are focusing on sustainability and altering operations to act in line with global climate goals. In addition to our own sustainable and ethical practices, our company is part of the UN Global Compact and recognizes its ten principles on human rights, labor standards, the environment, and anticorruption to pursue sustainability on a global scale. Vetter is continuing to invest in new capacities and capabilities to incorporate sustainable practices for customers and track progress.

Carsten Press: CDMOs play critical roles in the pharmaceutical supply chain. Vetter constantly considers the state of the industry, including the impact of evolving industry demands, technological advancements, and regulatory requirements on the supply chain. The company shifts its strategy in response to current trends to adapt to the needs of both small and large biopharma companies and invests in automation and advanced digital tracking systems to enhance supply chain security and traceability.

Peter Soelkner: To anticipate and proactively prepare for the future needs of our customers, Vetter is investing in more filling lines and expanding capacity today. In addition to expanding our Ravensburg and Des Plaines facilities, the company also has plans for a new commercial plant. This capacity expansion allows Vetter to become more efficient and flexible so it can meet increasingly complex customer needs.

Q: How does an expansion of the management structure support investment and expansion of the company, particularly, as CDMOs are increasingly viewed as collaborative rather than transactional partners to drug developers?

Thomas Otto: With the expansion of senior management, investment in the future is the priority. As a strategic partner, CDMOs are expected to be leaders in ethical and sustainable business practices to maintain reliability as a partner for our customers. Sustainability has been an anchor in our corporate strategy for decades. Our accountability programs support our strategies to reduce waste and conserve resources, which then enables our customers to achieve their own sustainability goals.

Our role in the larger value chain makes it critical that we embody an environmentally sound operation that aligns with those of our customers. With more leadership, we are able to more closely prioritize driving meaningful results that benefit our customers.

Peter Soelkner: The growth of Vetter globally to foster these evolving customer relationships is more important than ever. Mutual trust is very important to me, in all dimensions. Expanding the management structure brings together vast experience from individualized areas of expertise to create an all-encompassing outlook to improve customer partnerships. It further allows us to dedicate even more time to developing long-term partnerships with our clients and provide a heightened level of leadership presence in customer engagements. ◆

ORAL DOSAGE FORMS

The Future of Oral Dosage: Innovations, Challenges & the Path Forward in 2025

By: Sébastien Croquet

INTRODUCTION

Oral dosage forms have long been the backbone of pharmaceutical development, past, present and fast-approaching future. The category has come a long way since the introduction of the first aspirin tablets in 1897, with sales of orally administered drugs now accounting for more than 80% of the total pharmaceutical market.[1,2] Just as the size and shape of the oral dosage segment has evolved over the intervening century, so too have the drugs themselves. Where once there was relatively little choice over medication form and function – beyond perhaps selecting either tablet or capsule – today, scientific and technological advances have opened up the potential for a myriad of highly targeted or even fully personalized drugs.

With viable alternatives to the traditional one-size-fits-all approach continuing to emerge, the time is ripe to pause, take stock of the current oral dosage market – and consider where it could shift next.

Read on as we explore the latest industry challenges, cutting-edge manufacturing techniques and patient needs defining today's oral delivery methods, and break down some of the ways drug producers can ride, or even define, the next wave of oral drug delivery.

THE VIEW FROM THE TOP: INDUSTRY CHANGE & CHALLENGES

At the quarter mark of the twenty-first century, the oral dosage market finds itself in a place of contrast. On the one hand, a wave of patent expirations looms on the horizon, with potential to remove $200 billion in annual revenue from top players over the next five years.The introduction of Medicare-controlled price limits for the US' best-selling drugs is also squeezing margins for manufacturers – big names and generics producers alike[4,5] Conversely, the advent of artificial intelligence (AI), continued digitalization and the increasing viability of practices, such as continuous manufacturing and 3D printing (3DP), have the potential to smooth the path to launching profit-earning pharma products.[6]

This contradiction in trends has prompted various responses, one of the most interesting being the rise of drug premiumization and hyper-personalization – whether in the form of individualized dosing, custom delivery methods or even bespoke manufacture-to-order medications. For the top brands in particular, the potential to produce fully customized medicines on-demand via 3DP presents a more attractive opportunity than competing with contract development and manufacturing organizations (CDMOs) on the price of out-of-patent, mass-produced generic drugs. Indeed, commentators surveying the potential of the technology in pharmaceuticals, as well as other fields, such as biomechanics and surgery, point to an eye-opening future market value of 1.9 billion USD.[7] Although, as with most advancements, accessing this is all dependent on the turning of the regulatory tide.

Concerns surrounding safety, quality and consistency have so far barred 3DP from mainstream acceptance, with bodies like the US Food and Drug Administration (FDA) unable to establish broadly applicable guidelines for approved 3DP drug formulations or their AI support systems.[8,9]The immediate outlook is complex yet promising, with proponents of these technologies, such

as China-based pharma manufacturers, Triastek Inc., pushing regulators to approve 3DP Investigational New Drugs (INDs), like their ulcerative colitis medication T21.[10] In the near future, therefore, we could see the revolutionary potential of 3D drug printing fully unleashed.

Then, there are the perennial challenges facing oral drug producers – principally sustainability and patient compliance. These topics simmer beneath the surface as newer concerns capture the headlines, only to occasionally burst through when their scale and severity become impossible to overlook. Impact assessments on the environmental cost of drug manufacturing are fairly sparse in comparison to other major industrial fields, but it has been estimated that pharma's emission intensity is 55% higher than that of the automotive sector – raising thorny questions with regard to net positives and the trade-off between human health and that of the planet.[11]

Figures relating to rates of medication adherence are equally concerning, with as many as 50% of patients not taking their medicines as prescribed, costing health authorities across Europe and North America 415 billion US dollars annually.[13,14] As pill fatigue is commonly cited among the key causes of medication non-compliance, designing new, more convenient and appealing oral dosage formats takes on a whole new level of importance for global health outcomes.[15]

The current picture is mixed but packed with truly electrifying advancements. The question therefore becomes, what can oral dosage do to turn up the voltage and turn possible into probable?

ON THE (PRODUCTION) LINE: ORAL DOSAGE MANUFACTURING TRENDS

First, there is the matter of physically producing orally administered drugs, and technologies' capacity to enhance it. While the theory behind continuous manufacturing (CM) is far from new, its increased adoption, particularly among CDMOs, is a more recent development.[16]

Promoting a constant flow of raw materials in at the top of the line to finished drugs at the end, the main advantages of CM are improved production efficiency through the use of real-time release testing (RTRT) and tools such as Process Analytical Technology (PAT), smaller space, equipment and staffing requirements, and greater supply chain resilience.[17-19] Despite the clear benefits of CM, however, many larger or more traditionally minded producers are not yet comfortable with its implementation.[20] Most, if not all, of the training given to current manufacturing line workers, drug developers and testers alike was based on the assumption of batch-processing, meaning each and every CM project presents a steep learning curve.[21] This uncertainty has created a self-perpetuating cycle; a limited portfolio of approved CM drugs leaves producers unclear on regulatory expectations, discouraging development and compounding authorities' lack of experience with the medium.[22] As a result, regulators have been slow to co-sign the use of CM, with only seven continuously produced drugs approved by major international bodies between 2015-2021.[23] The other major barriers to CM adoption – set-up cost and complexity –are starting to erode, though, thanks to the accelerating adoption of AI technologies.

Slotting neatly into the well-established industrial digitalization movement, AI-enabled machine learning, smart integrated machinery and predictive monitoring software allow site managers to design, integrate and run highly sophisticated RTRT and PAT systems, which in the past may have taken months to install. The value of such technologies also extends well beyond the set-up phase. Equipped with comprehensive data from every stage of the integrated CM production line, AI

models can make real-time adjustments to optimize quality, throughput and equipment performance, and afford producers the vital opportunity to spot issues early, and avoid costly recalls.[24] Taken together, CM and AI could be the perfect combination to help generics producers protect and even boost their margins in 2025 and beyond.

A NEW DIMENSION: ADVANCEMENTS IN 3D-PRINTED PHARMACEUTICALS

While the mass-market segment stands to profit through an update to existing manufacturing practices, the more premium end of the sector is exploring a whole new perspective on orally delivered drugs. As previously alluded, the potential of 3DP pharmaceuticals is vast, if a little uncertain. To make the vision of precisely tailored, low waste, print-on-demand oral dosage forms a reality, what producers need most is concrete formulation guidance – for their own peace of mind, as well as that of regulators.

Fortunately, such protocols are slowly starting to emerge. Focusing on the most commonly used pharmaceutical printing method, fused deposition modeling (FDM), successful drug production rests on selecting the right excipient – in this case a thermoplastic polymer.[25] The ideal candidate is a safe, pharmacopeia-compliant material with the correct thermophysical properties to be melted, extruded according to the pre-programmed design, fused and finally solidified – quickly – before the next layer is added.[26] Over the short history of modern drug printing, oil-based polymers like polyvinylpyrrolidone, polyvinyl alcohol, and polylactic acid have typically won the draft.[27] That said however, their synthetic status has hindered regulators' and patients' acceptance of 3DP as a safe, scalable and environmentally sound production method.[28]

Enter a newcomer to 3D drug manufacturing: modified starches (MS). Already widely pharmacopeia-compliant and plant based, MS, like hydroxypropyl methylcellulose (HPMC), present a safer and more sustainable alternative to existing 3DP excipients. To confirm the suitability of MS for FDM production models, the authors of a recent study devised two model formulations. The first featured pregelatinized hydroxypropyl pea starch as its excipient, the other a combination of pregelatinized potato starch and hydroxypropyl methylcellulose (HPMC). In both models, the selected polymers were combined with mannitol and sorbitol to act as plasticizers, while stearic acid was added as a lubricant. Upon testing, both preparations were able to yield extrudable filaments with good printability, capable of achieving immediate and controlled API release for BCS Class 1 drugs.[29]

Results like these are incredibly significant for the future of 3DP technology in pharmaceuticals. Not only do they suggest a more sustainable formulation route without the need for synthetic polymers, but mainstream acceptance of FDM could also drastically cut time to prototype for new oral dosage designs. What's more, faster routes to market for rare disease medications could revolutionize the care of underserved or overlooked patient groups.[30] But before producers invest too heavily in a continuously manufactured, AI-driven and 3D-printed future, they must spare serious attention for the biggest and most enduring challenge that will inevitably follow in the new year.

WINNING HEARTS, MINDS & MOUTHS: PATIENT-CENTRICITY IN 2025

More than any other area of drug development, oral dosage is defined in conversation with patient needs – making it one of the most dynamic, and at times, difficult segments to navigate. In 2025, the themes shaping user experience are trust,

transparency and tackling inequalities. Between essential medicine shortages, price spikes, access issues and the increasing politicization of healthcare topics since the pandemic, the last three years have seen US consumers' opinion of the pharmaceutical sector sour significantly.[31,32] Indeed, a 2023 Gallup poll reporting that 60% viewed the industry negatively, versus just 18% who expressed positive associations.[33,34] Many of the factors underpinning this dip are partly or sometimes wholly out of the industry's control, but regardless of their cause, drug manufacturers can play a significant part in turning the tide of negative feeling.

One route to reputational rehabilitation could be to focus on meeting previously un- or under-met patient needs. The recent expansion of health consciousness across North America and around the world has laid bare the challenges faced by groups including women, the elderly, children and those diagnosed with psychiatric disorders when trying to secure orally administered drugs tailored to their needs. Indeed, there was no congressionally mandated requirement to include people assigned female at birth in clinical drug trials until as late as 1993, and even today, clinicians are forced to prescribe off-label adult medications in the absence of drugs approved for use in pediatrics.[35,36] At best, these blind spots contribute to issues such as swallowing difficulties, dosing confusion and pill fatigue, all of which worsen patient compliance and leave users feeling left behind by healthcare systems. Beyond ethical considerations, manufacturers have a strong business case for designing patient-friendly drug delivery methods, particularly as the lines between patient and consumer subtly begin to blur.

Bringing our discussion back to the potential of 3D printing, the promise of

build-your-own medications, such as the bespoke, multi-action and staggered-release pills printed in layers by researchers at the UK's University of Nottingham, could allow patients with specialized needs full control over the format, delivery profile, color, size and shape of their medications – with radical results for acceptability and compliance.[37-39] To further ameliorate user experiences, drug developers can combine the freedom of personalization with the convenience of alternative dosage forms, such as orally dispersible tablets and films (ODT/Fs), both of which are highly suited to 3D-printed production methods.[40] For a real-world example of the impact such interventions can have, a recent study found that more than half of 3-5-year-old children stated they liked their personalized, 3D-printed orodispersible films "very much."

Amid the excitement of new possibilities, however, manufacturers must still pay close attention to fundamentals, such as the choice of excipient. For tablets and films designed to dissolve in the mouth, excellent dispersibility upon contact with saliva is key, as well as good mechanical strength to keep doses stable and effective prior to administration. Achieving a pleasant taste and mouthfeel is so important it feels obvious. But selecting fillers, binders or coatings with an effective masking element becomes especially critical for unlocking more convenient delivery options for the most unpleasant-tasting APIs. The optimal approach to improving patient compliance in 2025 therefore appears to be one of cutting-edge technologies paired with tried and tested truths about patients and their needs.

RISING TO THE OCCASION

Let's end as we began – with an acknowledgement of just how central oral dosage is to the global population's health and well-being. Already the most widely used delivery format, breakthroughs in the development of 3D-printed drugs, innovative dosage forms and radically efficient manufacturing methods are only bolstering the category's significance. Oral drug manufacturers therefore have a duty and responsibility to relentlessly pursue emerging opportunities, while maintaining an unwavering focus on their fundamental mission: improving and safeguarding human health. ◆

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BIOGRAPHY

Sébastien Croquet has over 16 years of experience in pharmaceutical technology, specializing in the development of highly functional excipients. After earning his bachelor's degree in Pharmaceutical Technology from IMT Paris and a master's in Business Development Management from EDHEC Business School, he joined Roquette Pharma Solutions. Throughout his career, he has held various roles in Customer Technical Service, contributing to innovation, research, and digital transformation. Now, as a Global Technical Developer - Pharma, he leads customer technical relationships and pharmaceutical development projects, supporting product development and technical studies to drive innovative solutions.

DAIKYO PLASCAP READY TO USE VALIDATED (RUV) CLOSURES

Securing Annex 1 Compliance Through Contamination-Control Closure Innovation

By: Jim Thompson, MBA

For the intended patient, any injectable therapy can be regarded as precious, given its potential for enhancing, maintaining, or even prolonging life itself.

There are, however, some types of therapy that might be described as more precious than others from the point of view of their inherent sensitivity to degradation, the challenging nature of their manufacture at low volumes, and their comparatively high costs.

Advanced therapy medicinal products (ATMPs), such as cell and gene therapies, are examples of drug products that fit this definition, along with various emerging biologics and vaccines. Over many years, continued research and development efforts have resulted in a strengthened pipeline of promising treatments for a range of inherited and acquired disorders in oncology, cardiovascular disease, ophthalmology, neurological disorders and infectious disease. Indeed, the American Society of Gene and Cell Therapy (ASGCT) reported more than 4,000 gene, cell and RNA-based therapies in development in the third quarter of 2024, with momentum building around the targeting of more common diseases such as diabetes.[1]

In many cases, these therapies show great potential in terms of patient outcomes, yet their delicate nature necessitates extremely precise containment and storage conditions to ensure they retain physico-chemical integrity and deliver efficacy while closely controlling any possible contamination risk to patients.

From primary packaging specification to manufacturing processes, this translates into a series of important and interlinked decisions, which are further complicated by the need to demonstrate compliance with the revised Annex 1 of the European Union's Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use (EU GMP Annex 1).[2] These globally accepted rules set forth a number of stringent requirements, making drug product manufacturers responsible for taking "all steps and precautions necessary to assure the sterility of the products manufactured within its facilities."

A key priority introduced by Annex 1 is the need for facilities to implement a detailed Contamination Control Strategy (CCS) to define, monitor and manage any risk to product quality that might arise from microbial, endotoxin/pyrogen contamination and particulates (both visible and sub-visible). The scope of the guidelines extends to primary packaging components from a contamination perspective, and there is also additional focus on assurance of Container Closure Integrity (CCI) and an expectation for in-depth understanding of the container closure system employed.

Under the requirements set out by Annex 1, the stoppering and capping process takes on particular significance since it crosses into all these areas of concern. Here, the use of more traditional metal-based crimp seals presents potential for contamination of the drug product with metallic foreign matter, while there is also a challenge to reduce process steps to a minimum and to incorporate the use of pre-sterilized ready-to-use components in alignment with the demands of a cleanroom environment.

In addition, when it comes to high-value drug products produced in lower volumes, there are further important considerations around the need for components to integrate with more compact and flexible automated filling lines, which have become increasingly prevalent over the last decade. These fill-finish systems are designed to accommodate a range of container formats on a single line, in batch sizes spanning 20,000 units down to as few as 500, with rapid changeover between batches. As such, they are predicated on the use of nested vials and ready-to-use components that not only conform to standard dimensions but also perform the critical function of assuring sterility, maintaining CCI and supporting the integrity of the drug product throughout its lifecycle.

Through its long-standing partnership with Daikyo, a market-leading provider of proven quality containment solutions, West can answer this multi-faceted vial stoppering and capping challenge with both Crystal Zenith® (CZ) polymer nested vials and PLASCAP® Ready-to-Use Validated (RUV) press-fit closures.

Available in 13mm and 20mm vial crowns compliant with ISO standards, PLASCAP closures combine both stopper and polypropylene cap into a single integrated component providing one-step vial stoppering and sealing for serum applications. In the context of Annex 1 and the requirement for close control over contamination risks, PLASCAP closures replace the traditional metal crimp closures that had the potential of shedding metal particles. With PLASCAP, the elastomer stopper is combined with a polypropylene cap and the entire assembly is subject to 100% vision inspection before being supplied ready-to-use after E-beam sterilization.

Appropriately for a closure assembly intended for applications involving sensitive therapies, PLASCAP closures feature a stopper that is engineered from high-performance D777-1 elastomer and the drug contact surface is coated with Flurotec™ barrier film, which is a highly protective barrier between the drug product and the closure. The Flurotec barrier film reduces extractables and leachables while restricting absorption and adsorption, mitigating the risk of impurities and drug-product degradation and, therefore, protecting the contained therapy and supporting an extended shelf-life. Moreover, Flurotec is naturally lubricious, limiting the potential for abrasion that may result in the generation of fewer particles.

The integration of two parts into one assembly means PLASCAP closures have the advantage of reducing what were traditionally two steps in fill-finish down to a single step, enhancing convenience and introducing production efficiencies through time savings. PLASCAP closures also add a valuable layer of tamper-evident security due to the inability to re-attach the flip off cap once it is removed. This design feature consists of four clips that engage with the vial crown when seated to close the system. Once these clips are engaged, they cannot be removed. Furthermore, the distinctive translucent plastic cap facilitates improvements in vision inspection, supporting end-of-line analysis and allowing customers to confirm the closure is properly seated.

An additional benefit of the PLASCAP closures is the numerous options available. Multiple nested packaging configurations are offered including 10 x 10 for 13mm vial crowns and 8 x 6, 5 x 5, 4 x 6, 6 x 4 and 4 x 4 for 20mm vial crowns. There is a new 6x8 nested configuration of PLASCAP closures for 20mm vial crowns (which can be supplied as three nests per tub, four tubs per carton) which is compatible with the nested CZ 10mL vials for a complete containment solution for ATMPs and Cytiva flexible robotic filler systems.

For Cell and Gene Therapy (C&GT) applications in particular, selecting the appropriate packaging is crucial for manufacturers of these treatments. CZ vials have a proven track record in this area, with many FDA-approved gene therapies utilizing these polymer vials as their primary packaging. It is essential to ensure that the press-fit closures function seamlessly in tandem with the vial to ensure the components can demonstrate container closure integrity. As such, PLASCAP closures are

meticulously designed to integrate flawlessly with CZ polymer nested vials. The 6x8 nest configuration is the latest product offering example of this integration providing a comprehensive packaging solution for C&GT applications.

As with other West products, our established supply chain has been structured to provide manufacturing partners with guaranteed continuity of PLASCAP closures. Components are originated, and all units are assembled and sterilized in Japan under the guidance of Daikyo Seiko to the internationally recognised quality standards of ISO 9001, ISO 13485 and ISO 11137-1. West then supplies from stock to local markets in small quantities with reduced lead-times.

For product quality and continuity of supply, PLASCAP closures are complemented by robust documentation and technical support. This includes critical component specifications and formulation characteristics as well as regulatory support documentation. Indeed, the area of regulatory support is a particular strength at West considering our long-standing commitment to ensure activities are aligned with Annex 1. We are prepared for the impact of the revised regulations and work closely with our pharmaceutical partners to ensure optimal containment of valuable drug products with low contamination risk.

A crucial part of our approach has been the establishment of a company-wide master CCS framework to define our objectives in relation to the requirements of Annex 1. This has subsequently become established as a Standard Operating Procedure (SOP) across West guiding the consistent manufacture and supply of high-quality packaging components for contamination-controlled sterile drug-production environments.

For our partners, this contamination-control mindset is evident in all aspects of our business, from our products and processes to our people. Moreover, our efforts in this area are designed to complement pharmaceutical companies' individual approaches to CCS, creating a truly holistic end-to-end model for compliance. Key facets of this approach are the guidance of our skilled and knowledgeable team, who can support practical considerations around CCI and contamination control, and our forward-looking investment plans to continually evolve West facilities in pursuit of the very highest standards in sterile component manufacture.

PLASCAP closures can be seen as a manifestation of this thinking as a one-step stoppering/sealing component, simplifying process steps and offering ease of inspection by way of the translucent cap which allows inspectors to see the cap is correctly seated around the vial crown. Combined with the availability of multiple nest configurations, PLASCAP closures provide manufacturers of small-batch drug products – and particularly those using robotic aseptic filling machines – with a convenient and efficient closure option that complies with the contamination-control guidance dictated by Annex 1.

Failure to support these therapies with an appropriate packaging solution brings enhanced risk of degraded efficacy or contamination, which can in turn carry uncomfortable financial implications for supply-chain stakeholders. Such complications represent avoidable barriers to improved patient health outcomes.

At West, our aim is to help ensure that drug products are contained in an optimal manner befitting of their sensitivity and value. Through a commitment to innovation and continuous improvement, both for products and manufacturing processes, our ambition is to enhance the manufacturing supply chain and advance the availability of precious therapies to healthcare providers and patients in need.◆

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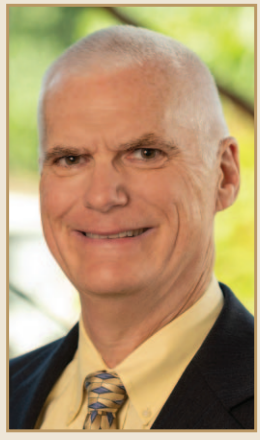
BIOGRAPHY



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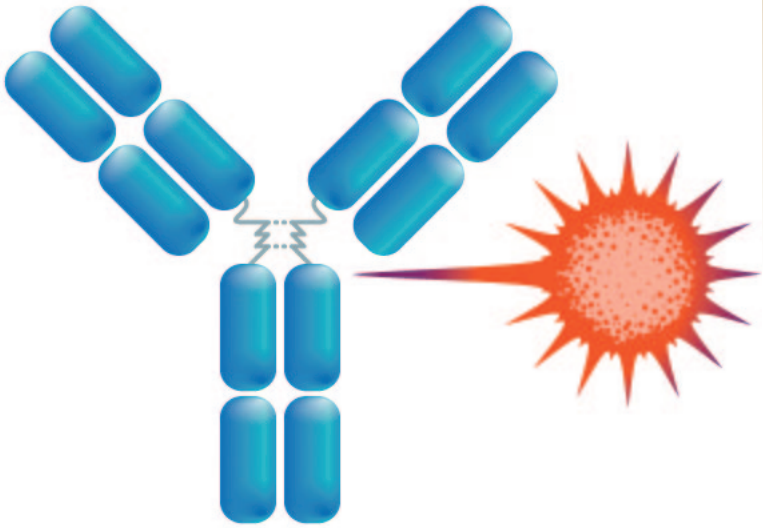
ADC PAYLOADS

Progress in Development of Camptothecin-Based ADC Therapeutics

By: Paul Moore, PhD, Raffaele Colombo, PhD, and Jamie Rich, PhD

INTRODUCTION

Antibody-drug conjugates (ADCs) first arose as an area of interest in oncology drug development in the early 1980s, when researchers started to conjugate cytotoxic drugs (such as DNA-alkylating agents and Vinca alkaloids) via linkers to polyclonal antibodies targeting antigens found on cancer cells. Early ADC clinical trials didn't show any benefit, with only one patient showing a partial response out of 10 different Phase I studies. Gemtuzumab ozogamicin (GO), an ADC targeting CD33 and bearing a calicheamicin payload, was the first ADC to show benefits for patients with relapsed acute myelogenous leukemia (AML). GO received initial approval from the US FDA in 2000, although with a black box warning due to the increased risk of veno-occlusive disease. In 2010, GO was withdrawn from the US market after a subsequent confirmatory trial failed to verify clinical benefit and demonstrated safety concerns. GO was later re-approved in 2017 with a different dosing schedule to improve the safety profile. ADC research continued steadily in the 2000s-2010s, focusing mainly on microtubule inhibitors (MTIs) as ADC payloads (maytansinoids and auristatins). In 2011, brentuximab vedotin was approved for patients with non-Hodgkin lymphoma, followed by the first approval of an ADC to treat solid tumors, trastuzumab emtansine, in 2013. Other classes of payloads have been investigated, including more potent DNA-damaging agents such as pyrrolobenzodiazepine (PBD) dimers and duocarmycins. Between 2017 and 2022, eight other ADCs were approved by the U.S. FDA, most bearing MTI payloads. Notably, the exceptional clinical successes of trastuzumab deruxtecan (approved in 2019) has recently sparked a renewed focus on ADCs. Currently, there are more than 280 ADCs at different stages of clinical development, including datopotamab deruxtecan and patritumab deruxtecan, which are currently under regulatory review. Collectively, these



therapies represent a generational advance in therapies for a wide variety of liquid and solid tumors, many of which are considered difficult to treat.

CHALLENGES IN ADCS

Despite groundbreaking progress in research, ADCs present several challenges that can limit their applications in cancer treatment. In particular, ADCs with more established payload classes, such as maytansinoids, auristatins, and PBD dimers, are associated with high clinical failure rates. In fact, more than 150 ADCs have been discontinued in clinical trials due to limited efficacy at tolerated doses. Given the significant unmet needs in cancer treatment, improving efficacy while reducing treatment-related toxicities is an increasingly important issue.

In recent years, researchers have worked to identify new approaches in ADC therapeutic structures to circumvent these limitations. One focus has been the use of camptothecin payloads. Camptothecin ADCs, and in particular trastuzumab deruxtecan,

have shown significant benefits for patients across several types of cancer. In 2024 the FDA granted accelerated approval to trastuzumab deruxtecan for patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors, regardless of type or location.[1] This represents the first tumor-agnostic approval of an ADC. While ADCs bearing campothecin payloads can deliver significant therapeutic benefit for patients, they are also associated with potentially severe payload-related toxicities, including nausea, neutropenia, anemia, gastrointestinal toxicities, and interstitial lung disease (among others, and payload dependent).

Emerging clinical data suggest the efficacy of ADC-based treatments, especially for solid tumors, is likely driven by a complex combination of targeted payload delivery, free payload exposure, and tumor sensitivity to the molecule's components. ADC features (including conjugation and drug-linker designs) and target expression may influence sites and rates of ADC disposition, and thus tumor, tissue, and systemic exposure to the payload. In addition, treatment-related toxicities and maximum tolerated doses (MTDs) in patients are primarily related to the ADC payloads. Based on these insights, researchers are now developing new strategies to maximize clinical efficacy and reduce the risk of toxicities. A key area of intensive research involves optimizing payload properties along with the overall properties of ADCs, including the target, antibody, linker, and payload itself.[2]

RECENT ADVANCES IN CAMPTOTHECIN-BASED ADC RESEARCH

Camptothecin is a natural product topoisomerase I inhibitor that acts by binding to DNA-topoisomerase I complexes to inhibit DNA cutting, relaxing, and reannealing processes, which are essential for cell survival and reproduction. Camptothecin was first isolated in 1966, but clinical progress involving synthetic camptothecin small molecules has been hampered by challenges such as low solubility, rapid *in vivo* clearance, limited oral bioavailability, and severe hematologic and gastrointestinal toxicities. Additionally, camptothecins are susceptible to a reversible hydrolysis of the camptothecin lactone form at physiological pH to a less active carboxylate form.[3,4] Thus, when a camptothecin small molecule is injected intravenously, it rapidly establishes an equilibrium in plasma favoring the less active form. Despite these challenges, the FDA has approved two camptothecin small molecules, topotecan and irinotecan, for the treatment of colon, ovarian, cervical, and small cell lung cancers, and the Korean Ministry of Food and Drug Safety (MFDS) has approved another, belotecan, for the treatment of ovarian cancers.

ADCs address many of the major challenges associated with camptothecin small molecules. When conjugated to an antibody, the solubility of camptothecin small molecules can be enhanced, and their exposure in patients can be improved due to the prolonged half-life inherent to antibody therapeutics. Furthermore, through trafficking of the ADC into endosomal and lysosomal compartments after cellular uptake, the camptothecin payload is exposed to a low-pH environment, which shifts the equilibrium toward the more active lactone form.[5,6]

In a promising advance in ADC development using camptothecin as a payload, researchers at the life sciences company Zymeworks prepared and assessed a panel of camptothecin analogs. Leveraging insights gained from over 60 years of camptothecin SAR data, they produced a library of approximately 100 compounds featuring different substituents

at the C-7 and C-10 positions of the camptothecin core scaffold.[7] They then advanced research to screen these novel camptothecin small molecules in a cytotoxicity assay against a panel of cell lines. The selected analogs spanned a range of potency and hydrophilicity profiles and were evaluated as ADC payloads using different linker strategies. Ultimately, the ZD06519 payload was selected based on a favorable in vitro ADME/DMPK profile, and *in vivo* efficacy in multiple *in vivo* CDX and PDX models and superior tolerability observed in rats and non-human primates (NHPs) when conjugated to different antibodies. Importantly, ZD06519 also has a unique structure and properties compared to other camptothecin payloads currently in development. Findings from this research effort were published recently in Molecular Cancer Therapeutics.[7] The design of the novel camptothecin analog supported a range of advantageous properties for ADCs, including moderate payload potency, low hydrophobicity, strong bystander activity, robust plasma stability, and high monomeric ADC content.

DELIVERING BETTER ADCS TO PATIENTS

The recent progress in research on novel camptothecin payloads highlights the potential for developing a new generation of ADCs that can overcome some of the limitations of first-generation therapies. As drug developers explore innovative technologies and strategies, interest in ADCs is poised to continually expand. Lessons learned from developing novel ADC payloads, including camptothecin analogs, suggest multiple opportunities exist to improve ADC design, despite the complexity of these molecules. To advance these efforts, researchers must assess the antibody, linker, and payload together, using a range of technologies to carefully select and refine each ADC design feature. By better understanding the role and potential of each component and how they can work together in an integrated design, we have the opportunity to bring forward a new generation of ADCs to benefit patients.

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BIOGRAPHIES

Dr. Paul Moore is Chief Scientific Officer at Zymeworks, Inc. He has more than 25 years of US-based experience in biologics drug discovery and development in biotechnology research. His career efforts have led to the discovery and development of a range of FDA-approved and clinical-stage biologics for patients with difficult-to-treat cancers and autoimmune conditions. He earned a PhD in Molecular Genetics from the University of Glasgow. He has an extensive research record co-authoring more than 75 peer-reviewed manuscripts and is a named co-inventor on over 50 issued US patents.

Dr. Raffaele Colombo is Associate Director, Medicinal Chemistry at Zymeworks Inc. He has more than 14 years of experience in studying the design and synthesis of new payloads and drug-linkers for antibodies, small molecules, and nanoparticles. He has a strong research background co-authoring 23 publications and is a named co-inventor on 10 patents. He earned a PhD in Organic and Medicinal Chemistry from Università degli Studi di Milano.

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Ascendia® Pharma's expanded state-of-the-art 60,000 sq./ft. R&D and manufac-turing facility provides cGMP manufacturing formulation development, pro-cessing and scale-up along with toxicity and clinical trial materials with com-mercial supply for sterile and non-sterile dosage forms, including ophthalmic, parenteral, topical, and oral. Its facility includes the Netzsch Vakumix for state-of-the-art aseptic processing, and a complete suite of Precision NanoSystems equipment to provide comprehensive lipid nanoparticle manufacturing. For more information, visit Ascendia at **www.ascendiapharma.com**.

Formulation Technology

The scientists at **Ligand Pharmaceuticals** have developed in-house and aided clients in developing parenteral, oral, ophthalmic, nasal, and inhalation formulations with Captisol and other cyclodextrins. With the recent addition of internal resources and analytical tools, we can provide greater responsiveness for collaborative feasibility and development programs. In addition, the Captisol team have successfully completed or assisted with orphan designations and approvals, preclinical, CMC, and clinical development for ANDA, 505b2, and traditional NDA programs. Our Team is Ready. Are you? Contact us Today! **www.captisol.com**.

Global Development Partner

Lonza is a preferred global partner to the pharmaceutical, biotech and nutrition markets. We work to enable a healthier world by supporting our customers to deliver new and innovative medicines that help treat a wide range of diseases. We achieve this by combining technological insight with world-class manufacturing, scientific expertise and process excellence. Our business is structured to meet our customers' complex needs across four divisions: Biologics, Small Molecules, Cell & Gene and Capsules & Health Ingredients. Our unparalleled breadth of offerings across divisions enables our customers to commercialize their discoveries and innovations in the healthcare industry. For more information, visit Lonza at **www.lonza.com**.

CDMO Services

Pace® Life Sciences provides a full suite of contract CMC development, CTM manufacturing, regulatory compliance, consulting, and facility support services to the pharmaceutical, biopharmaceutical, and gene therapy industries. Pace® Life Sciences operates from a network of CDMO sites, GMP analytical testing laboratories, and manufacturing support service centers across the United States. Our experienced, highly trained industry experts, and our investment in state-of-the-art development and manufacturing facilities emphasize our commitment to efficiently advancing client programs through the clinic to commercialization. We are dedicated to delivering the best and most reliable services with positive customer experiences across all channels of our business. For more information, visit Pace® Life Sciences at **www.pacelifesciences.com**.

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Adare Pharma Solutions is a global technology-driven CDMO providing end-to-end integrated services, from product development through commercial manufacturing and packaging, with small molecule expertise focusing on oral dosage forms. Adare's specialized technology platforms provide taste masking, customized release, solubility enhancement, and patient-centric dosing solutions. With a proven history in drug delivery, Adare's seven facilities in the US and Europe have developed and manufactured more than 65 products sold by customers worldwide.

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