Drug Development & Delivery

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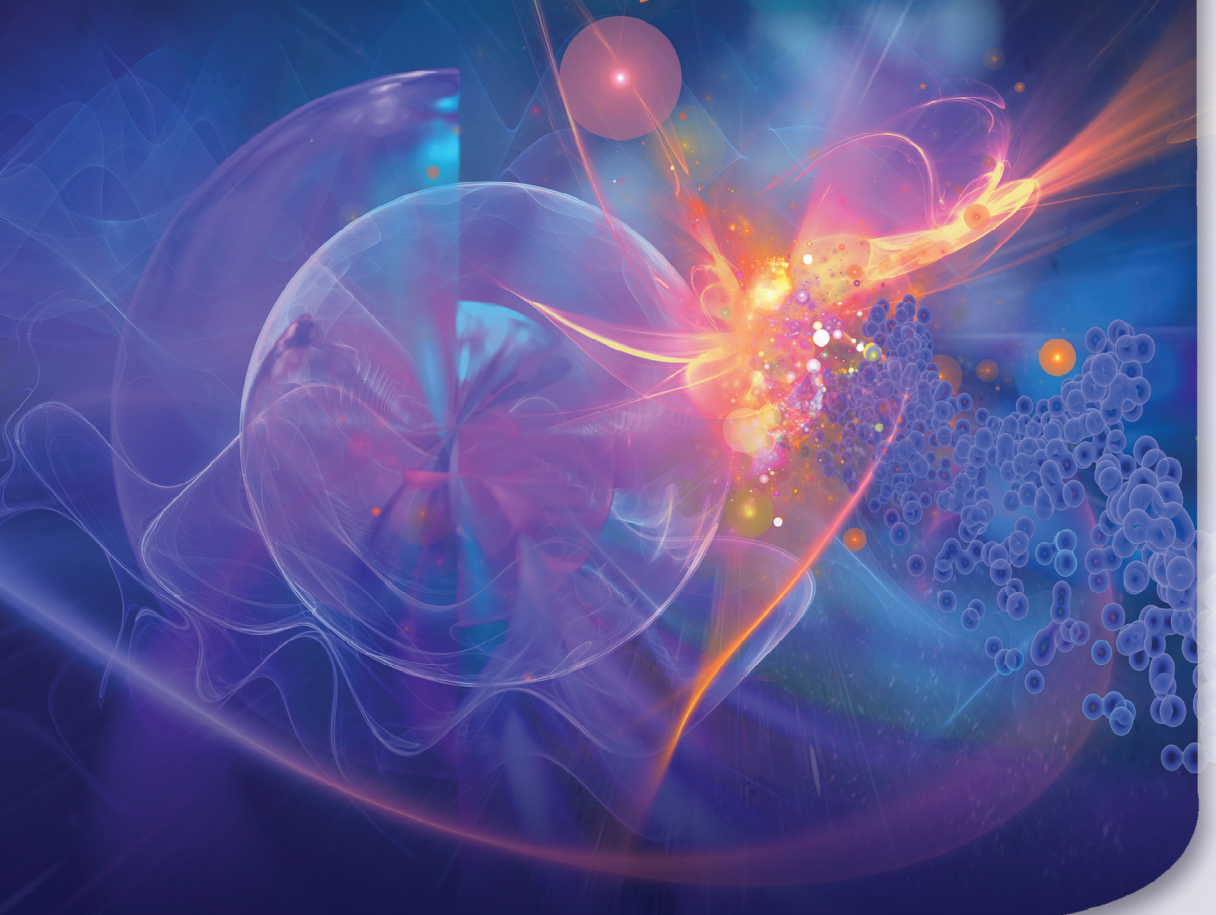

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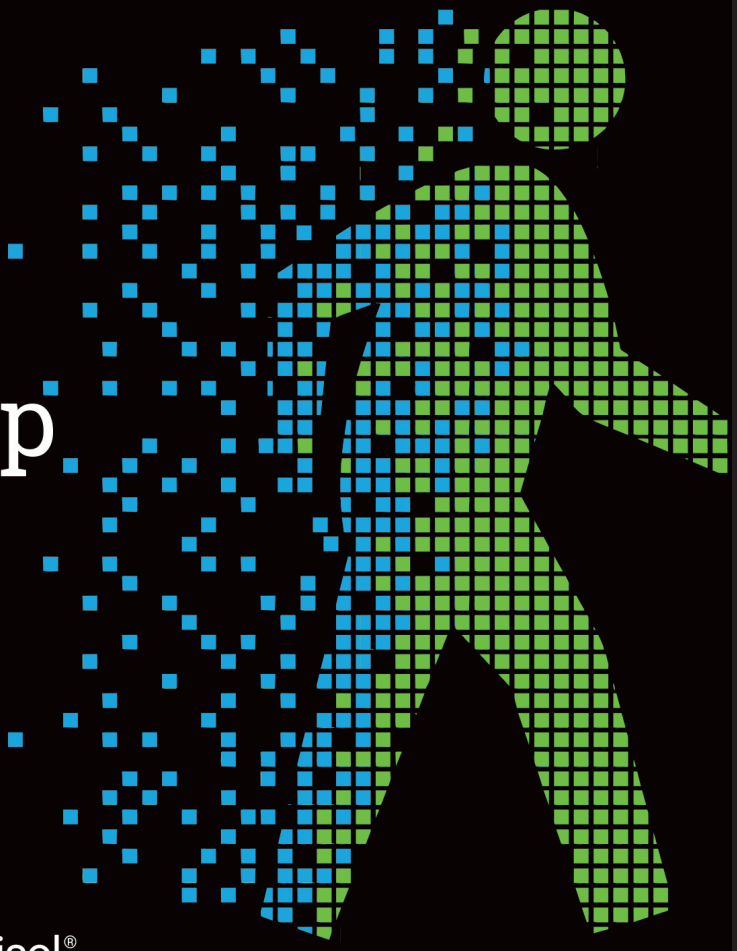

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Outsourcing Formulation Development & Manufacturing

"Sponsors increasingly want to run vial and device development in parallel, and often earlier in the life cycle than before, so they can move quickly into patient-centric presentations. Overlaying this are targeted therapies and pediatric indications, which further increase demand for ultra-high-potency handling, complex dosage forms and solubility-enhancing approaches that can be translated into robust, scalable products."

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Advancements in Respiratory Drug Delivery

"Success lies in the ability to manage risk, cost, and development timeline; understanding these new modalities, which may previously have been considered 'undruggable;' and combining the most appropriate formulation and device approach early enough in the development cycle to develop a product that is highly valued by the patient, healthcare provider, and payor."

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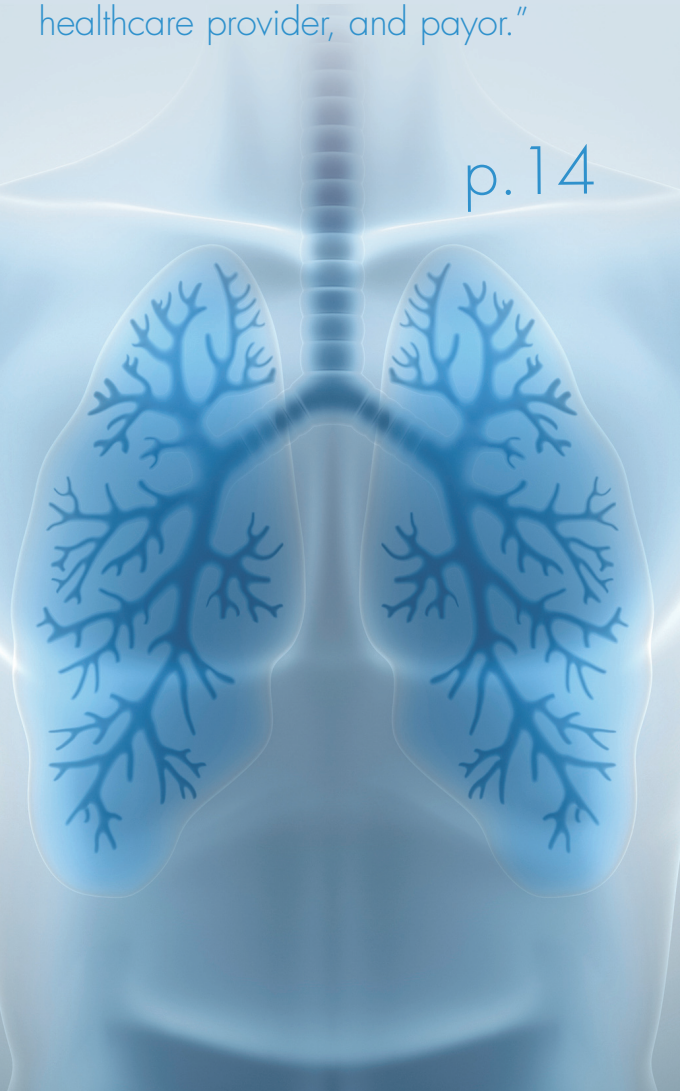

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ThermoFisher SCIENTIFIC

Successful scale-up requires more than just higher throughput

Controlling the pharmaceutical scale-up process requires factoring in the physics of twin-screw extrusion

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Market News and Trends

Plus Therapeutics Partners with Ephemeral Technologies to Deploy AI Execution Platform for CNS Oncology

Plus Therapeutics, Inc. (Nasdaq: PSTV) (the "Company"), a clinical-stage pharmaceutical company developing targeted radiotherapeutics for central nervous system (CNS) cancers, today announces that it has signed an agreement to enter into a strategic partnership with Ephemeral Technologies ("Ephemeral") to deliver a unique AI execution platform for CNS oncology. The AI execution platform is designed to integrate, organize, and derive actionable intelligence from longitudinal therapeutic, diagnostic and bioinformatic data sets generated across Plus' CNS oncology technology programs.

"Plus is building a CNS oncology platform to integrate across our therapeutics, diagnostics and bioinformatics data sets," said Marc Hedrick, M.D., Plus Therapeutics President and Chief Executive Officer. "Our partnership with Ephemeral and its expertise in deploying artificial intelligence brings industry-proven engineering and advanced AI capabilities to the most challenging area of oncology. This partnership is intended to help further position Plus as a leader in CNS oncology and accomplish our mission of improving survival for patients with the most devastating cancers."

Ephemeral was founded by the former co-heads of Palantir Technologies' U.S. healthcare business. Ephemeral was launched to bring AI solutions to life sciences to accelerate drug development.

Plus and Ephemeral believe the combination of multi-modal, longitudinal data with generative AI reasoning and agentic workflows will create both near- and long-term value for shareholders. Beginning in 2026, Plus anticipates tangible improvements in both laboratory and clinical operating efficiency and workflows. Beyond 2026, Plus intends to increasingly use artificial intelligence for fully integrated operational workflows, operational decision support, translational and treatment response analytics, patient stratification, precision oncology initiatives, pharmaceutical collaborations and real-world evidence initiatives.

"Ephemeral was founded to help companies like Plus align AI to real scientific and operational execution to more quickly deliver better medicines to patients," said Drew Goldstein, Ephemeral Co-Founder and Co-Chief Executive Officer. "Plus' unique positioning and data sets in CNS oncology represents an ideal opportunity for Ephemeral, and we are proud to leverage our technology to support Plus' mission to help patients with CNS cancers."

Under the agreement, Plus Therapeutics and Ephemeral will assess and implement AI-enabled data infrastructure to support the integration, organization, and analysis of complex CNS oncology data sets generated through the Company's therapeutic and diagnostic workflows. No financial terms of the agreement were disclosed.

Additional information is available at https://www.ephemeral.now.

Cereno Scientific Doses First Volunteer in CS014 PK-bridging Study

Cereno Scientific, an innovative biotech pioneering treatment to enhance and extend life for people with rare cardiovascular and pulmonary diseases, today announced that the first healthy volunteer has been dosed in the Phase I pharmacokinetic (PK) bridging study of the company's novel HDAC inhibitor CS014. The FDA-aligned study is designed to support the continued clinical development of CS014 and a streamlined pathway toward a Phase IIb trial in pulmonary hypertension associated with interstitial lung disease (PH-ILD) starting in Q1 2027.

The "PK bridging" study is a clinical Phase I, open-label, randomized, two-period crossover pharmacokinetic (PK) trial in 14 healthy adult volunteers. The study is conducted in Sweden. The study will evaluate steady-state pharmacokinetics following seven days of repeat oral dosing of CS014 compared to valproic acid (VPA), a well-established HDAC inhibitor. The primary objective is to characterize total and unbound plasma concentrations of CS014 at steady state compared to VPA.

"The study is intended to provide important comparative pharmacokinetic data and aim to significantly shorten the clinical development timeline and reduce development costs for CS014," said Rahul Agrawal, CMO and Head of R&D at Cereno Scientific.

CS014 is a proprietary deuterated HDAC inhibitor and a new chemical entity designed to optimize pharmacokinetic properties and metabolic stability while targeting disease-driving mechanisms relevant in rare cardiopulmonary diseases such as vascular remodeling, fibrosis, inflammation and thrombosis.

The PK-bridging study is designed based on feedback received in a pre-IND meeting with FDA and is expected to remove the need for additional non-clinical safety studies and a Phase IIa trial. This supports a streamlined and capital-efficient development pathway toward a planned Phase IIb trial in pulmonary hypertension associated with interstitial lung disease (PH-ILD) starting in Q1 2027.

"This marks an important operational and regulatory milestone for CS014 as we continue advancing the program toward Phase IIb development," said Sten R. Sörensen, CEO of Cereno Scientific. "Dosing of the first volunteer demonstrates the strong execution capabilities of our team and partners and reflects our focused strategy to efficiently advance innovative therapies with disease-modifying potential for patients with rare cardiopulmonary diseases with high unmet medical needs."

Results from the Phase I pharmacokinetic study are expected in mid-2026. For further information, please contact: Tove Bergenholt, Head of IR & Communications. Email: tove.bergenholt@cerenoscientific.com

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Asahi Kasei Life Science Acquires License for Novel Antibody-Drug Conjugate Technology from The Noguchi Institute

TOKYO – Asahi Kasei Life Science has acquired the license rights for a novel antibody-drug conjugate (ADC) technology from The Noguchi Institute. This modality enables precise control over the drug-to-antibody ratio and attachment site of single- and dual-payload ADCs, representing a breakthrough toward more effective and safer use in a broad range of therapies.

ADCs are an advanced form of targeted biologics treatment that combines the precision of an antibody with the potency of a cell-killing payload. Compared to conventional treatments, bioconjugation with ADCs more selectively targets cancer cells while minimizing damage to surrounding cells. Drawing from its longstanding research into carbohydrates and glycans, The Noguchi Institute has developed a novel ADC technology with a superior molecular structure conformity. This is expected to improve the predictability of drug efficacy and safety, enabling stable therapeutic effects.

Asahi Kasei Life Science continually explores opportunities for collaboration with external partners, seeking technologies that will lead to future drug development. The Noguchi Institute's ADC modality not only improves precision but can also combine dual payloads onto a single antibody. These characteristics offer the ability to add different payloads for targeting more diseases with better specificity and potentially less toxicity.

Under this agreement, the two partners will advance initiatives to commercialize ADC drug platforms, including possible future sub-licensing to biopharma companies and Contract Development and Manufacturing Organizations (CDMOs) such as Bionova Scientific, an Asahi Kasei company. In addition, both parties will engage in joint research to further refine the technology to solve medical challenges.

For more information, visit https://www.asahi-kasei.co.jp/lifescience/en/.

Recipharm Boosts BFS Capacity with Strategic Manufacturing Investment

Recipharm, a global contract development and manufacturing organization (CDMO), today announced a multi-million investment in a new Blow-Fill-Seal (BFS) manufacturing line, expanding capacity to support customer programs from development through commercial supply. The investment builds on 50 years of BFS expertise and further strengthens Recipharm's position in sterile drug product development and manufacturing.

The expanded capacity will support a broad range of ophthalmic product programs, backed by dedicated local execution teams and a global network of experts.

Greg Behar, CEO of Recipharm, said: "Customers need sterile manufacturing partners that can combine technical expertise, operational scale and reliable delivery. This investment expands Recipharm's BFS capacity, strengthens our technical offering and positions Recipharm to meet growing customer demand with the speed, scale and quality required for today's complex product programs."

Recipharm's BFS capabilities include pilot-scale manufacturing for feasibility studies and early-stage supply; clinical-scale manufacturing for small batches and stability studies; and proven high-volume commercial production. Together, these capabilities support customer programs as they progress toward commercial supply.

Recipharm provides BFS capabilities across biologics and small molecules, for ophthalmic application as well as vaccines. For products with more specific handling requirements, Recipharm offers specialized handling environments for oxygen- and temperature-sensitive formulations, including nitrogen atmosphere filling and temperature-controlled environments.

BFS technology delivers practical manufacturing and supply benefits. Its fully automated aseptic processing helps reduce contamination risk, while plastic containers simplify the supply chain through fewer components, no breakage risk and easier transport. Compared with traditional glass filling processes, BFS can also support lower cost of goods and a reduced carbon footprint.

For more information about Recipharm, please visit www.recipharm.com and www.recipharm-ab.com.

Orexo Announces PositiveOutcome from *In-vivo* Study of OX390

Uppsala, Sweden – Orexo AB, today announces positive data from a pre-clinical in-vivo study on the nasal absorption of atipamezole when delivered with Orexo's AmorphOX drug delivery technology. The study results mark an important milestone in the development of OX390, an emergency treatment to reverse overdoses involving xylazine and medetomidine, alpha-2 agonists often referred to as "Tranq" and "Rhino Tranq", respectively.

The study demonstrated rapid and substantial intranasal absorption of atipamezole, successfully establishing proof-of-concept across multiple formulations. The results support that a single nasal dose of OX390 achieves exposure within the targeted therapeutic range. The next milestone in the project is an upcoming type C meeting with the FDA to agree on the non-clinical development plan that will enable human clinical trials.

Ed Kim, Chief Medical Officer of Orexo, said: "OX390 is a potentially life-saving treatment and likely to be the world's first medical countermeasure (MCM) to the rising threat from xylazine and medetomidine. With the robust results from the in-vivo study we will proceed with the development of OX390 with strong confidence in OX390's viability for nasal delivery of atipamezole. Overdoses involving an alpha-2 agonist is on the rise in the US and is a rapidly evolving threat to public health in the United States. Orexo is leading the development of a highly needed treatment, and we look forward to the next milestone, the type C meeting with FDA."

Nikolaj Sorensen, CEO & President of Orexo, said: "I am very pleased with the in-vivo results, it clearly supports the continued development of OX390 and is another proof-of-concept not only for OX390, but also for Orexo's proprietary AmorphOX technology. Once again nasal delivery using the AmorphOX technology is confirmed to provide rapid absorption and high bioavailability."

This project has been supported in whole or in part with federal funds from the US Department of Health and Human Services; Administration for Strategic Preparedness and Response; Biomedical Advanced Research and Development Authority (BARDA), under contract number 75A50125C00010.

For more information, please visit www.orexo.com.

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SPECIAL REPORT

Advancements in Respiratory Drug Delivery

By: Kurt R. Sedo, Executive Editor, and Cindy H. Dubin, Senior Editor, PharmaCircle
Updated from article originally published in PharmaCircle *Weekly Intelligence* newsletter

INTRODUCTION

As of May 2026, chronic respiratory diseases affect more than 35 million Americans. Key, high-prevalence conditions include asthma, impacting 25 million people, and chronic obstructive pulmonary disease (COPD), affecting over 16 million. While acute respiratory virus (RSV, COVID-19, flu) levels are low as of May 8, 2026, the 2025–2026 season saw significant, high-level hospitalizations peaking in early January 2026.

Dan Morland, Head of Business Development at Nanopharm, an Aptar Company, says that some device and formulation innovations include: nebulizers with guided inhalation and haptic feedback to optimize breathing patterns and ensure precise deposition, and tunable frequencies and pore sizes to adapt to the needs of the biologics; Dry Powder Inhalers (DPIs) with the capacity for higher payloads for improved stability and room-temperature storage of biologics that may not be stable at high concentrations in solutions; and nanoparticles and lipid carriers to enhance epithelial transport and protect biologics, coupled with dry powder particle engineering technologies for the formulation approach to protect the biologic during storage and delivery via aerosolization.

BARRIERS TO DELIVERING BIOLOGICS TO THE LUNGS

Despite these advancements, targeted drug delivery remains challenging. "From vaccinations to gene therapies, delivering biologics to the lungs offers significant therapeutic potential," a spokesperson from Bespak says. "However, due to the large, fragile, and often costly nature of these molecules, their delivery presents unique challenges."

There are indeed product development (formulation, device) and physiological barriers, adds Morland. Regarding the former, the lung's highly branched structure makes it difficult to ensure uniform and deeper lung deposition. "Particle size is critical, and many traditional approaches to particle size control for inhaled drug products may be too aggressive for sensitive biologics molecules (micronization, spray drying)," he says.

In addition, biologics are large, fragile molecules prone to aggregation or denaturation during aerosolization and nebulization, so the devices used to deliver the drugs may also damage the integrity and bioactivity of the biologics. Therefore, he says, formulation development and device selection will be critical, and there will be fewer viable options.

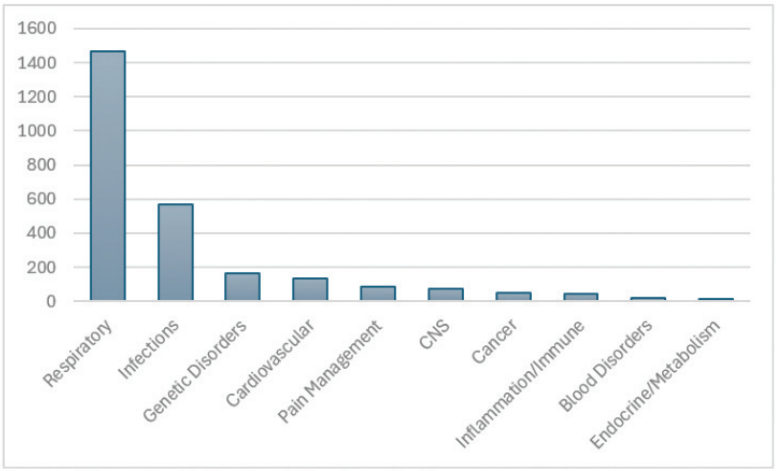
In terms of physiological barriers, the mucus layer and mucociliary clearance rapidly remove foreign particles, while proteases and peptidases degrade biologics, potentially damaging

FIGURE 1

Age	Prevalence % Male	Prevalence # Male	Prevalence % Female	Prevalence # Female	Prevalence % Total	Prevalence # Total
18+	6	7375	7.3	9455	6.6	16660
45+	9.5	6305	10.7	7960	10.2	14360

Incident Rates of COPD in the US
Source: *PharmaCircle Epidemiology Explorer*

FIGURE 2



Indications Being Treated By Respiratory Drug Delivery
Source: *PharmaCircle Pipeline & Products Intelligence*

or destroying the biologics before they have their therapeutic effect. "Overcoming this through structural alterations may then have the opposite effect, i.e. molecules stay around for too long leading to toxicity risks," says Morland. "Macrophage uptake and pulmonary surfactant interactions can alter drug stability and absorption, and the higher loads required for biologic activity may induce immune responses as a consequence of foreign material in the lungs, that might lead to safety concerns."

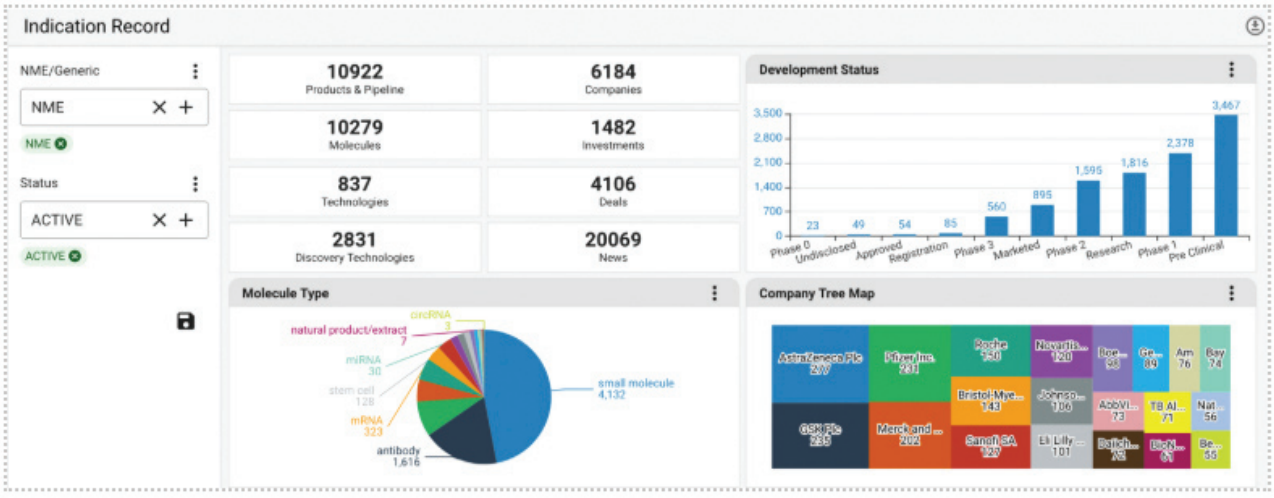
NANOPARTICLES ENSURE PRECISION TARGETING

One concern with biomolecules is the complexity in their structures, target engagement, as well as therapeutic and elimination pathways. They encompass a range of new therapeutic modalities: from engineered proteins and peptides, such as biospecific antibodies and peptidomimetics, oligonucleotides, viral vectors for gene therapy, RNA-based therapeutics, cell-based therapies such as exosomes, and other novel vaccines and immunotherapeutic approaches.

"Their precision targeting (including intracellular targets), personalization and long-lasting effects will transform how diseases are treated including the posology of dosing," Geraldine Venthoye, PhD, Chief Scientific Officer, Phillips Medisize, explains. "Products will become significantly less frequently dosed (from daily to monthly or even yearly dosing), which obviously will impact device and drug product presentation design."

Owen S. Fenton, PhD, who received the 2025 American Association of Pharmaceutical Scientists Emerging Leader Award for his work with nanoparticles, says that there are efforts in the mRNA medicine community to deliver mRNA to specific organs throughout the body, such as the lungs. mRNAs can be easily programmed to address a wide range of diseases – from infections and metabolic disorders to genetic conditions, including those originating in the lungs. Many mRNA therapeutics function in the liver, which limits their utility for non-liver diseases. Building on this challenge, Dr. Fen-

FIGURE 3



Overview of Respiratory Disease Sector
Source: *PharmaCircle Indication Record*

ton and his team developed a nanoparticle platform capable of delivering mRNA specifically to the lungs. The mechanism and efficacy of the platform have been studied under both low and normal oxygen conditions and is now being applied to treat several diseases that originate in the lungs.

mRNA is also playing a role in delivering antimicrobial peptides for resistant lung infection. An advanced platform utilizing lipid nanoparticles with anti-inflammatory properties transports mRNA constructs encoding the peptibodies into lung cells. By encoding the peptibody sequences as mRNA, researchers enable the patient's own lung cells to produce these antimicrobial agents internally. This cell-mediated production circumvents issues of protein stability and systemic degradation and aligns delivery with endogenous cellular machinery, facilitating more controlled and sustained therapeutic levels (Bioengineer.org).

Another innovative approach highlights the potential use of zinc oxide and berberine nanoparticles in addressing acute respiratory distress syndrome (ARDS). A study conducted by El-Salakawy et. al. explored novel therapeutic approach, focusing on the application of nanotechnology to combat the severe inflammatory condition. The study emphasizes the unique properties of zinc oxide and berberine when combined at a nanoscale level. Zinc oxide is known for its anti-inflammatory and antimicrobial characteristics, while berberine — a compound derived from plants — has demonstrated antioxidant and anti-inflammatory effects in previous research. By integrating these two substances into nanoparticles researchers aim to enhance their bioavailability and targeted delivery within the body. This approach seeks to mitigate lung inflammation more effectively while minimizing systemic side effects commonly associated with conventional treatments for ARDS. Further investigation is required to validate these findings and assess their clinical applicability (Gene Online).

INHALANT DELIVERY GOES BEYOND PARTICLE SIZE

Inhalation therapy remains the cornerstone of respiratory disease treatment, especially for obstructive pathologies as aerosolized particles under 5um reach the respiratory tract's terminal areas, ensuring targeted local effects with some systemic absorption (Science Direct). However, inhalation drug delivery is risky and expensive business as it combines a complex dosage form with a combination drug-device product development, says Dr. Venthoye.

"Success lies in the ability to manage risk, cost, and development timeline; understanding these new modalities, which may previously have been considered "undruggable," and combining the most appropriate formulation and device approach early enough in the development cycle to develop a product, which is highly valued by the patient, healthcare provider and payor," she says.

The Bespak spokesperson adds: "Many conventional aerosolization methods generate high shear forces that can lead to drug aggregation or reduced biological activity. On top of this, biologics require a sterile environment throughout their manufacture and use, and cannot tolerate the preservatives, additives or

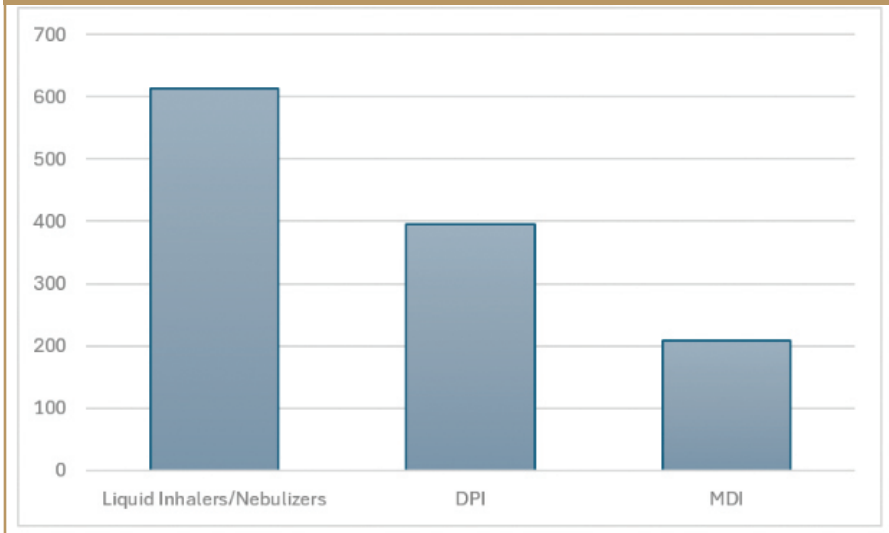
even propellants used in more traditional inhaler types."

Soft mist inhalers (SMIs) are designed to address many of these challenges. SMIs do not use propellants and instead generate a slow-moving aerosol cloud, enabling inhalation over several seconds of spray duration. "Not only does this support patient usability and consistent dosing of expensive therapies, the low shear forces and spray velocity have been demonstrated to protect fragile molecules," says the Bespak spokesperson.

Drug targeting requirements for inhaled biologics will not be just in terms of appropriate aerosol particle size for lung or nose delivery, but beyond deposition site, especially if the target is systemic or intracellular. Intracellular targeting may require targeting the cell's cytoplasm or nucleus, releasing the encapsulated genetic bioactive drug for transfection and therapeutic gene expression. Venthoye says: "Understanding this and enabling this precision in delivery is becoming essential for formulators working hand in hand with device developers."

She says there will be an emergence of new delivery devices – gentler in delivery of these labile molecules, efficient and less wasteful, with greater compatibility and delivery of higher payloads. Mesh nebulizers are already available as well as breath-actuated versions, such as the Phillips Medisize FOX™ Vibrating Mesh Nebulizer device, which ensure none of the "precious drug" is lost during a patient's exhalation cycle. New dry powder inhaler concepts are also emerging for the delivery of the much higher payloads. In fact, a Phillips Medisize O1 high payload device concept was presented for the first time at the 2025 Drug Delivery to the Lungs (DDL) Conference.

FIGURE 4



Inhalation Drug Delivery Programs by Device Type
Source: *PharmaCircle Pipeline & Products Intelligence*

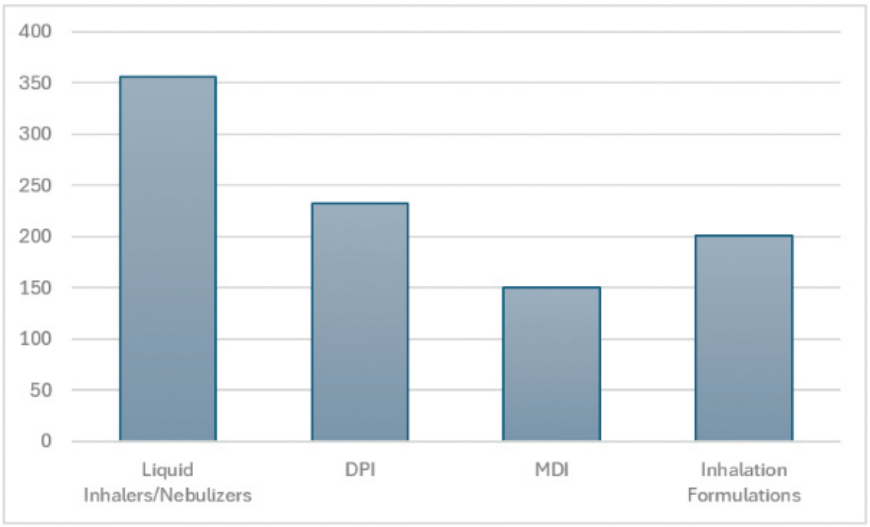
"Much is still to be learned, however, about the most appropriate delivery mechanisms for these sensitive molecules as well as their targeting requirements – we expect to see more data presented on this subject next year," she says.

Another device was introduced late last year. CorriXR Therapeutics, an oncology-focused biotherapeutics company developing a gene editing platform technology; InhaTarget Therapeutics, a company dedicated to the early development and clinical validation of innovative treatments of pulmonary diseases by inhalation; and Merxin Ltd., an inhaler device maker, have entered a strategic collaboration to develop an inhaled genetic therapy targeting lung cancer. The partnership draws upon CorriXR's CRISPR-based gene editing platform targeting NRF2, InhaTarget's proprietary formulation platform; and Merxin Ltd's inhalation device technology. Together, they will focus on treating squamous cell lung carcinoma (LUSC), which comprises 25 - 30% of worldwide cases, according to CorriXR.

Additionally, Amneal Pharmaceuticals, Inc. received FDA approval in 2025 for its albuterol sulfate inhalation aerosol (90mcg per actuation). The product is the generic equivalent of PROAIR® HFA (albuterol sulfate inhalation aerosol), a registered trademark of Teva Respiratory LLC. This approval follows the company's FDA approval of its beclomethasone dipropionate inhalation aerosol, a generic equivalent of QVAR® (beclomethasone dipropionate inhalation aerosol), advancing Amneal's entry into inhaled and respiratory drug delivery.

December 2025 continued to be a busy month for respiratory drug delivery. Savara Inc., a clinical-stage biopharma focused on rare respiratory diseases, announced that the European Patent Office issued a patent for the combination of Savara's investigational therapy Molbreevi and Pari's investigation eFlow® Nebulizer System for the treatment of autoimmune PAP, a disease where lung alveoli become filled with surfactant. Molbreevi, delivered via eFlow®, was granted Fast Track and Breakthrough Therapy Designations by the FDA, Orphan Drug Designation by the FDA and by the European Medicines Agency (EMA), and Innovation Passport

FIGURE 5



Inhalation Drug Delivery Technologies
Source: ***PharmaCircle Drug Delivery Technology Analyzer***

(IP) and Promising Innovative Medicine (PIM) designations by the UK's Medicines and Healthcare Products Regulatory Agency (MHRA). The plan is for eFlow® to be commercially marketed for use with Molbreevi under the name Vespera® Nebulizer System (Savara).

Startup Métopi, a company focused on making lifesaving medication easier and faster to access, has developed an inhaled drug delivery platform that turns a rescue inhaler into a compact wearable device.

"In general, greater engagement with the molecule originators, biotech or pharma companies on CMC development, platform devices, and enabling formulation approaches – at the early stages of development – will result in driving innovation and ultimately choosing the right device and formulation combination approach," says Dr. Venthoye. "Despite the cost and complexity of these products, inhaled biologics represent high commercial value and will bring valued products to patients."

MABS SHOW PROMISING COPD STUDY RESULTS

Also bringing value to patients are injectable monoclonal antibodies meant to treat respiratory illness. For example, AstraZeneca just released positive high-level results from Phase III OBERON and TITANIA trials in patients with chronic obstructive pulmonary disease (COPD). Results showed that tozorakimab reduced the annualized rate of moderate-to-severe COPD exacerbations, compared with placebo, in the primary population of former smokers. Tozorakimab is a potential first-in-class monoclonal antibody targeting interleukin-33 (IL-33) that uniquely inhibits the signaling of the reduced and oxidized forms of IL-33, offering the potential to both reduce inflammation and disrupt the cycle of mucus dysfunction that contribute to COPD worsening, according to an AstraZeneca press release.

Sharon Barr, Executive Vice President, BioPharmaceuticals R&D, AstraZeneca, says in a printed statement: "Today's tozorakimab results deliver the first two confirmatory Phase III trials for an IL-33 biologic, which is a major scientific advancement in COPD, the world's third leading cause of death. Tozorakimab works in a fundamentally different way from other biologics, inhibiting the signalling of the reduced and oxidized forms of IL-33 to both decrease inflammation and disrupt the cycle of mucus dysfunction that are key disease drivers in COPD."

Another mAb from Sanofi and Regeneron Pharmaceuticals is Dupixent (dupilumab), which is now reaching 1.4 million patients – a number is likely to grow as the FDA just approved the subcutaneous injectable monoclonal antibody for treating children (aged 2 to 11 years) with chronic spontaneous urticaria (CSU). This expands the previous approval for adults and adolescents ages 12 years and older with CSU who remain symptomatic despite histamine-1 antihistamine treatment. The fully human monoclonal antibody is administered as a subcutaneous injection. The drug is primarily used for moderate-to-severe eczema, asthma, chronic rhinosinusitis with nasal polyps, prurigo nodularis, certain types of COPD, and eosinophilic esophagitis.

AN EXCITING FUTURE FOR RESPIRATORY DRUG DELIVERY

Morland says he is excited about advancements in respiratory drug delivery and the value they can bring to patients. These include:

Smart Inhalation Devices: digitally enabled inhalers and nebulizers with feedback systems for personalized dosing and improved adherence.

Responsive Materials and Targeted Delivery: formulations that respond to pH,

enzymes, or oxidative stress in the lung microenvironment for controlled release.

***In-Silico* Modeling of Drug Delivery, Deposition and Bioavailability (Model Informed Drug Development):** computational simulations using patient-specific breathing data and lung physiology to predict drug deposition and dissolution, and ultimately optimize device/formulation design.

"Being able to perform modelling with disease/patient specific models allows drugs and products to be designed specifically with the patient in mind, e.g. mucus layer thickness, lung capacity, breathing capacity, etc.," says Morland.

He adds that this enables model informed drug development (MIDD) to accelerate and derisk product and clinical development. Already commonplace for other dosage forms, MIDD is now becoming possible for inhalation due to advances in the technologies and more realistic analytical methods to provide clinically relevant inputs into modelling.

"As the pipeline of respiratory biologics continues to expand, it is becoming increasingly vital that delivery platforms and administration routes are efficient, sustainable and easy to use," says the spokesperson from Bespak.

ABOUT PHARMACIRCLE

PharmaCircle is a thought leader in drug delivery and formulation development, publishing the *PharmaCircle Weekly Intelligence* newsletter, which has a worldwide readership, and in-depth reports in all areas of drug delivery, including new and novel technologies and devices. PharmaCircle is a leading information provider to the pharmaceutical and medical device industries, providing business prospecting and analysis tools, pipeline and products intelligence, regulatory data, and other information solutions to our clients. PharmaCircle's Premium database service delivers a comprehensive view into drug, biologics and combination product development and innovation, combining scientific, clinical, safety, regulatory, supply chain, and commercial data and insights into one solution. PharmaCircle recently launched MedTech Explorer, a hand curated database that assembles the latest intelligence on medical devices, diagnostic tests and drug delivery device technologies in development and on the market. For more information about the content of this analysis, contact PharmaCircle's Editorial Department at mailto: editorial@pharmacircle.com. For more information about PharmaCircle and our subscription database services, contact mailto: info@pharmacircle.com or visit our websites – http://www.pharmacircle.com and http://www.medtechexplorer.com. ◆

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CONTROLLED RELEASE

Precision in Every Dose: Advancing Controlled Release for Small Molecule Therapeutics

By: Manas Tilekar

INTRODUCTION

The evolution of controlled release drug delivery systems represents a transformative journey in pharmaceutical sciences, marked by decades of innovation, rigorous experimentation and the relentless pursuit of patient-centric therapies. As the pharmaceutical landscape becomes increasingly competitive and the regulatory environment more complex, the importance of precision in dosage, consistency in therapeutic effect and reliability in manufacturing has never been greater.

This article explores the scientific, technological and regulatory dimensions of controlled systems, with a focus on formulation strategies, excipient innovations, manufacturing challenges and future technologies such as 3D printing and smart polymers.

CONTROLLED RELEASE FORMULATIONS - AN OVERVIEW

Controlled release formulations are engineered to modulate the pharmacokinetics of small molecule drugs – altering their absorption, distribution, metabolism and excretion profiles to maximise therapeutic benefit and minimise risk. Unlike immediate release formulations, which may cause peaks and troughs in plasma drug concentration, controlled release systems aim to maintain levels within a defined therapeutic window over an extended period. This steady-state delivery reduces the frequency of dosing, mitigates the risk of adverse effects associated with high peak concentrations and ensures more predictable efficacy.

At the heart of controlled release system design lies a nuanced appreciation of the drug's properties – solubility, permeability, stability and half-life – as well as the physiological environment it will encounter. For example, a drug with a short half-life may benefit from a controlled release formulation to maintain efficacy without frequent administration. Similarly, compounds susceptible to degradation in the acidic gastric environment can be protected using enteric coatings or pH-sensitive excipients, allowing targeted release in the intestine.

Precision in controlled release formulations arise from the intricate interplay between drug properties, excipient selection and advanced manufacturing techniques. The journey towards an optimally designed system begins with a rigorous pre-formulation phase, in which the physicochemical characteristics of the active pharmaceutical ingredient (API) – including polymorphic form, particle size distribution and hygroscopicity – are meticulously evaluated. These factors significantly influence the selection of excipients and the choice of manufacturing process.

When developing controlled release formulations, a multidisciplinary approach is essential. Collaboration between chemists, material scientists, pharmacologists and engineers ensures that the final product not only meets therapeutic objectives but also adheres to practical constraints such as scalability and regulatory compliance. Computational modelling and simulation have become invaluable tools for predicting drug release kinetics and optimizing formulation parameters, reducing the reliance on trial-and-error experimentation and accelerating the path to market.

EXCIPIENTS

A critical decision in controlled release formulation development is the selection of appropriate excipients. Polymers – both natural and synthetic – serve as the foundational materials for creating matrices, coatings and membranes that govern the drug's release. These polymers must be carefully tailored to match the desired release profile, degrade at a controlled rate (if biodegradable) and maintain compatibility with the API. Additionally, the use of multifunctional excipients, which can simultaneously enhance drug solubility, stability and control release, has gained traction in recent years.

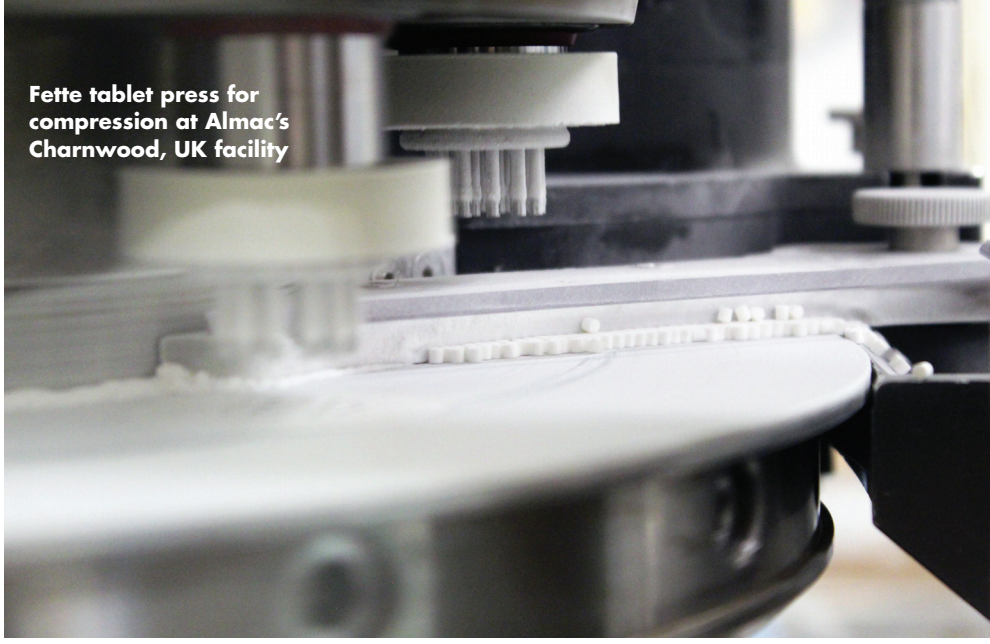
MECHANISMS OF CONTROLLED RELEASE

A plethora of mechanisms underpin the controlled release of small molecule therapeutics. Among the most prominent are:

Diffusion-Controlled Systems: Drug molecules diffuse through a polymer matrix or membrane. The release rate is governed by the properties of the polymer and the drug's molecular weight and solubility.

Dissolution-Controlled Systems: The drug is embedded in a matrix of a slowly dissolving carrier. The release rate is dictated by the dissolution rate of the carrier material.

Osmotically Controlled Systems: Here, osmotic pressure is harnessed to drive drug release at a constant rate, regardless of the pH or motility of the gastrointestinal (GI) tract.



Fette tablet press for compression at Almac's Charnwood, UK facility

Bioerodible and Biodegradable Systems: Polymers that degrade over time release the drug as they break down, a strategy often used for site-specific delivery, such as implants or injectable depots.

Stimuli-Responsive Systems: These advanced systems respond to environmental triggers (pH, temperature, enzymes) to release their payload at the desired site of action.

The versatility of these approaches enables formulation scientists to tailor drug release profiles according to the specific needs of the molecule, the indication and the patient population.

CURRENT ADVANCEMENTS IN MANUFACTURING, DESIGN & ENVIRONMENTAL IMPACT

Manufacturing techniques play a pivotal role in shaping the performance and reproducibility of controlled release systems. Traditional processes such as wet and dry granulation, direct compression and melt extrusion are being augmented by advanced methodologies like hot melt extrusion, spray drying and electrospinning.

Each technique offers unique advantages and imposes distinct challenges in terms of process parameters, scalability and cost. For example, spray drying facilitates the development of controlled release formulations by enabling the encapsulation of the API within polymer matrices, allowing for tailored release profiles through precise control of particle morphology and composition.

In the domain of small molecule therapeutics, controlled release systems unlock the potential for site-specific and stimuli-responsive delivery. For instance, targeting drug release to the colon can improve the management of inflammatory bowel diseases or deliver peptides and proteins that would otherwise degrade in the upper GI tract. Smart polymers, which respond to environmental triggers such as pH, temperature, or enzymatic activity, are at the forefront of this innovation. These materials enable "on-demand" release, opening avenues for personalized medicine and dynamic therapeutic regimens.

Patient-centric design is another emerging paradigm in controlled release development. Dosage forms are tailored not only to the pharmacological properties of the drug but also to the unique requirements of different patient populations.

Dissolution testing in progress at Almac's Charnwood, UK facility

Paediatric, geriatric and dysphagic patients, for example, benefit from orodispersible tablets, multiparticulate systems, or long-acting injectables that simplify dosing and improve adherence. Furthermore, 3D printing technology enables rapid prototyping and customization of dosage forms, allowing for the precise control of drug release kinetics and the incorporation of multiple APIs within a single unit.

The environmental impact of pharmaceutical manufacturing is gaining attention, prompting the development of "green" controlled release technologies. Biodegradable polymers, solvent-free processes and recyclable packaging are increasingly adopted to minimize the ecological footprint of drug production. Life cycle assessment and sustainability metrics are being integrated into formulation design, ensuring that therapeutic innovation is aligned with global environmental goals.

KEY OVERALL CONSIDERATIONS FOR DELIVERING A CONTROLLED RELEASE DRUG

One of the perennial challenges in controlled release drug development is the transition from laboratory scale to commercial manufacturing. Drugmakers must design scalable processes that ensure supply chain integrity. It is crucial to consider a flexible manufacturing infrastructure that can support both small clinical trial batches and large commercial campaigns. This will best accommodate a sponsor's evolving needs as products advance through the development pipeline.

REGULATORY AND QUALITY CONSIDERATIONS

Bringing a controlled release product from concept to commercial reality involves navigating a labyrinth of regulatory requirements. Agencies such as the US FDA and EMA demand robust evidence of safety, efficacy and quality, including detailed characterisations of release kinetics, stability profiles and manufacturing reproducibility.

In this regulatory landscape, it is crucial to anticipate potential pitfalls, assemble comprehensive CMC dossiers and manage complex interactions with health authorities worldwide. Expertise in Quality by Design (QbD) and risk-based approaches to process validation is invaluable, ensuring compliance and facilitating faster approvals.

QbD principles are increasingly embedded in the development of controlled release formulations. Systematic risk assessment, Design of Experiments (DoE) and continuous process verification help ensure that the final product consistently meets predefined quality attributes. In parallel, the adoption of Process Analytical Technology (PAT) allows for real-time monitoring of critical quality parameters during manufacturing, reducing batch-to-batch variability and enhancing regulatory confidence.

In-process controls and real-time release testing are increasingly utilized in controlled release manufacturing, supporting the principles of the aforementioned QbD and ensuring batch-to-batch consistency. Regulatory guidance documents, such as the FDA's "SUPAC-MR" (Scale-Up and Post-Approval Changes for Modified Release Solid Oral Dosage Forms), provide pathways but also underscore the technical rigor required for regulatory approval.

In analytical development, methods must be validated not only for the API but also for the wide range of excipients and intermediate products. This demands an advanced suite of techniques – such as dissolution testing, permeability assays, and imaging – to effectively characterise release profiles, drug-excipient interactions, and predicted *in vivo* performance. While one route to acceleration is the use of high-throughput automation and in sil-

ico modelling to increase data generation, another is to invest in strategic collaborations and tailored analytical approaches that support a robust understanding of formulation behavior and ensure regulatory alignment.

EMERGING TECHNOLOGIES IN CONTROLLED RELEASE

The field is seeing a surge of technological advancements aimed at enhancing both the sophistication and reliability of controlled release systems. 3D printing is enabling the on-demand fabrication of intricate dosage forms with complex internal geometries, which can be fine-tuned to deliver drugs at multiple rates or to distinct regions of the GI tract. Likewise, the development of "smart" polymers – materials that alter their properties in response to physiological cues – opens the door to responsive delivery systems capable of adjusting release rates in real time. While achieving a fully controlled release system through a simple dry blend technique remains challenging, smart polymers show promising potential to support such simplified approaches.

Another area of rapid progress is the use of nanotechnology in controlled release. Nano-carriers such as liposomes, dendrimers and polymeric nanoparticles can encapsulate small molecule drugs, improving their solubility, targeting and release kinetics. These systems offer opportunities for "stealth" delivery – evading immune recognition and enhancing tissue penetration – especially valuable for drugs with challenging pharmacokinetic profiles.

With this rise in progressing technology, access to specialised knowledge and technical infrastructure is more essential than ever in the development of robust controlled formulations. Product design will be most optimized when truly multidisciplinary teams – comprising formulation scientists, analytical chemists, process engineers and regulatory specialists – collaborate closely. Moreover, seeking and leveraging "platform technologies" – proprietary polymer blends, processing techniques and intellectual property that can be tailored to the unique needs of new drug candidates – can prove useful in accelerating the development timeline. This approach reduces the cost and uncertainty associated with "reinventing the wheel."

SUMMARY

Controlled release systems are transforming the landscape of small molecule therapeutics by offering precision, convenience and improved patient outcomes. Advancements in formulation science, excipient technology and manufacturing processes are enabling the development of increasingly sophisticated controlled products.

While challenges remain in terms of scale-up, regulatory compliance and technology adoption, the future holds immense promise. By leveraging emerging technologies and fostering cross-disciplinary collaboration, the pharmaceutical industry can continue to deliver on the promise of precision in every dose. ◆

BIOGRAPHY

Manas Tilekar leads Formulation and Process Development at Almac's Charnwood, UK campus. His responsibilities span early-stage development, clinical manufacturing, registration batches, and PPQ manufacturing. With over 13 years of experience in solid oral dosage form R&D, Manas brings specialized expertise in oral solid dosage forms, including various granulation technologies, tableting, encapsulation, and film coating. Today, he continues to drive innovation and quality through his technical insight and leadership.

Special Feature

Outsourcing Formulation Development & Manufacturing: Connecting Your Project to the Right Service Provider

By: Cindy H. Dubin, Managing Editor

The global contract development and manufacturing organization (CDMO) market size was valued at $255 billion in 2025 and is projected to grow from $273.40 billion this year to almost $581 billion by 2034.[1] Growing focus on precision medicine, the ability to handle more complex formulations, and a recent interest in highly potent active pharmaceutical ingredients is driving CDMO demand.

To be more efficient, CMDOs are turning to AI and data-driven tools. These technologies play a more practical role in formulation development and manufacturing, particularly in analyzing historical datasets and informing experimental design. While AI isn't replacing scientific expertise, it is helping teams review larger datasets faster and make more informed decisions.

Many of the leading CDMOs highlight their capabilities and share real-world examples of how they solved clients' formulation and manufacturing challenges in this exclusive *Drug Development & Delivery* annual report so that you can find the right provider for your own project.

Gattefossé offers tailored pre-clinical formulation development and in-depth customer training sessions at its TCE Lab in Paramus, NJ.

Abzena: Two Approaches to Formulation Studies

Abzena offers formulation development services that cover every stage of drug development, from early stages of candidate selection through first-in-human studies, commercialization, and any further life-cycle management as required.

Abzena applies two general approaches to formulation studies. Its "Fast-to-Clinic" approach is a streamlined methodology focused on enabling the customer to rapidly obtain FIH results in the shortest time possible. A "Best-in-Clinic" approach is focused on providing a superior product format often applied post-Phase 1.

"With the expansion of next-generation, highly complex biologic and bioconjugate drugs, we have seen an increasing demand for formulations aligned with maximizing stability and developing high-concentration forms," says Gary Watts, Head of Formulation, Abzena.

"Where developers are adding multiple functions through bi/multi-specific formats, or conjugating novel cargos to antibodies, there can be an inherent instability that requires a more considered formulation approach," he says. "We have also seen a requirement for high-concentration formulations for the rapidly growing area of antibody-oligonucleotide conjugates (AOCs), where a high frequency of high doses are often used to treat patients."

To illustrate these approaches in action, Mr. Watts points to a customer that went "Fast-to-Clinic" with an IV formulation for an antibody in early-stage first-in-human trials. Clinical and competitive data analysis highlighted the need for a high-concentration formulation for SC administration. While the target concentration of 150mg/mL was stable, it exhibited a high degree of viscosity, significantly exceeding the acceptable limit for standard SC injection devices, he says.

Abzena's formulation team undertook a systematic screening process to identify viscosity-reducing excipients to identify and test a selected panel of buffers and excipients to modulate protein-protein interactions without compromising stability. "A formulation was successfully developed that reduced the viscosity within the acceptable range for SC injection," he says. "Furthermore, stress testing confirmed that the selected composition did not introduce instability; in fact, it marginally improved the protein's resistance to aggregation under accelerated conditions, allowing the product to progress successfully to later clinical studies."

Adare Pharma Solutions: Tackling Complex Oral Solid Dose & Patient-Centric Formulations

Adare Pharma Solutions is a global, technology-driven CDMO offering integrated end-to-end services for oral solid dose: early formulation development through commercial manufacturing and packaging. The company specializes in tablets, capsules, multiparticulates, minitabs, orally disintegrating tablets with proprietary technology platforms supporting taste masking, customized release, and patient-centric dosing.

At Adare, demand continues to grow for complex oral solid dose and patient-centric formulation work. "Sponsors increasingly want partners who can bring solutions to challenging molecules, not just provide capacity," says Giuseppe De Franza, Director R&D, Adare, Italy. "Taste masking, solubility enhancement, controlled release, and dosage forms designed for specific patient populations have moved from differentiators to expectations, particularly for therapies serving pediatric, geriatric, and dysphagia-prone populations."

One mid-size pharma customer markets a drug treatment for patients with tremors and other persistent uncontrolled body movements caused by certain neurological conditions. The product works, but the capsule form was creating an adherence problem. An estimated 5% to 10% of patients in this population struggle with dysphagia, and many others face physical challenges handling a capsule due to severe tremors. The customer asked Adare to develop an alternative.

The Adare formulation team applied MMTS™ Minitabs technology to develop a sprinkle form: oral granules that can be sprinkled over soft food or mixed into a liquid, eliminating the need to swallow a capsule. "Getting there required a manufacturing innovation," says Mr. De Franza. "The taste-masking coating goes through a hardening process the standard compression was not built to withstand, so the team developed a novel method to increase the compression folds of the minitabs and keep them intact through production. That technique now applies to future microencapsulation projects as well."

The sprinkle form was approved by the FDA in spring 2024 and is now shipping to patients in North America, with clinical trials underway to expand availability to other regions. "Patients with dysphagia can take the medication without fear of choking," he says.

Alcami Corp.: Solving Technically Challenging Problems While Maintaining Timelines

Alcami Corporation supports clients from early formulation development through clinical and commercial manufacturing, primarily across sterile and oral solid dose products. Services include formulation and process development, analytical development, scale-up, manufacturing, packaging, serialization, and stability support. Alcami also supports a range of products, including potent compounds, modified-release formulations, and low-dose programs.

Saujanya Gosangari, PhD, Director, Technical Services, Alcami, says there is currently strong demand for formulation development, process optimization, analytical support, and late-phase manufacturing services. "A lot of clients are looking for partners that can help accelerate timelines while still maintaining quality and regulatory readiness," she says.

One project at Alcami involved the development of an ultra-low-dose orally disintegrating tablet for migraine treatment, where the API was dosed at the microgram level. The biggest challenge was achieving consistent content uniformity while also maintaining rapid disintegration and acceptable stability, explains Dr. Gosangari.

"Our team developed an integrated excipient strategy that used lipid excipients applied through a spray-on technique to improve API distribution within the blend," she says. "We also utilized high-shear wet granulation while avoiding fluid-bed drying to help reduce potential stability concerns. The result was a robust and reproducible manufacturing process capable of delivering precise microgram dosing with rapid ODT performance. The platform also supported the development of multiple dose strengths for clinical studies, which helped reduce overall development timelines and manufacturing risk for the client."

Alcami supports pharmaceutical programs from early formulation development through clinical and commercial manufacturing.

Almac Pharma Services: A Single Approach to Integrated Drug Development

Almac Pharma Services provides formulation development and manufacturing support across the product lifecycle, with strengths in oral dose development, process scale-up, clinical trial supply manufacture and commercial manufacture, supported by associated analytical and packaging capabilities.

"What differentiates us is the way we integrate drug substance and drug product development, manufacturing and supply chain execution for clinical trials or commercial supply under a single program approach," says Dr. Terry Ernest, Director, Manufacturing Science and Technology, Almac Pharma Services. "This reduces avoidable hand-offs between vendors, reduces 'white space' associated with moving materials from one CDMO to another, helps maintain continuity of product and process knowledge and allows project teams to make decisions with a clearer view of downstream manufacturing and distribution requirements. Almac selects formulation and process options that are aligned to a molecule's Quality Target Product Profile (QTPP) robust and at an appropriate at scale.

A recent example involved an oral solid dose product that showed variable dissolution performance during scale-up, despite meeting expectations at smaller scale. As indicated by the FMEA, the key risk was that dissolution variability could translate into inconsistent *in vivo* performance and consequently, delayed clinical timelines.

"We recommended a structured investigation designed using QbD tools that combined targeted formulation review with process evaluation, focusing on blend uniformity, granulation/end-point control (where applicable) and compression parameters that influence tablet porosity and disintegration," explains Dr. Ernest. "Rather than changing multiple variables at once, we applied a risk-based approach to identify the most likely drivers and ran a focused set of confirmatory trials. The re-

sult was a tightened control strategy and a more robust processing window that reduced batch-to-batch variability and delivered dissolution performance consistent with the target profile. This enabled the program to proceed with greater confidence into the next manufacturing campaign with a clearer understanding of critical parameters."

Ardena: In-House Drug Substance Development & Manufacturing

Ardena supports oral solid dosage form development from early pre-formulation through formulation development, analytical development, GMP clinical manufacturing, scale-up, validation, and commercial supply. This includes tablets and capsules for both conventional and complex small molecules, including poorly water-soluble compounds, modified-release products, and highly potent APIs that require specialist containment and handling. Formulation development and manufacturing are supported by in-house capabilities in drug substance development and manufacturing, solid-state research, bioanalysis, and CMC regulatory support. "This allows risks such as poor solubility, polymorphism, instability, manufacturability challenges, clinical performance, or regulatory requirements to be considered together rather than in isolation," says Iñaki Bueno, Formulation and Production Director, Ardena.

With formulation development and manufacturing sites in Europe and the US, Ardena can support projects close to where many customers run development, clinical, and supply activities, while maintaining technical continuity across programs.

"Our phase-appropriate approach helps clients generate the data needed at each stage without over-engineering early development or compromising later-stage manufacturability," says Mr. Bueno.

GMP spray drying manufacturing with a highly potent API at Ardena's site in Pamplona, Spain.

In a recent client project, Ardena helped address a scale-up risk during development of a solid oral dosage form. The client initially planned to use a direct blending process. During early scale-up assessment, Ardena's predictive tools, simulations, and stratified unit-dose uniformity testing indicated a risk of segregation at larger batch sizes, which could have affected content uniformity during clinical manufacturing, Mr. Bueno explains.

"Ardena recommended moving to a dry granulation process and assessed the impact on critical quality attributes, including dissolution, assay, and stability," he says. "The revised process mitigated the segregation risk while keeping product performance within specification, with no negative impact from the change in manufacturing technology. Because the issue was identified early, the change was implemented without affecting the client's clinical trial timeline."

Bend Bioscience: Breadth of Capabilities Enables Progression from TPP-Driven Design Through Scale-Up

CDMOs are increasingly expected to offer integrated solutions spanning early development through commercial manufacturing. At Bend Bioscience, services are structured around this continuum, including early formulation development, particle engineering, spray-dried dispersions, and solid oral dose manufacturing across clinical and commercial scales, explains David Vodak, PhD, Chief Scientific Officer, Bend Bioscience. Core capabilities include immediate-release (IR) liquids and solids, bioavailability enhancement (BAE), and modified-release (MR) systems such as monoliths and coated multi-particulates. "This breadth enables efficient progression from Target Product Profile (TPP)-driven design through scale-up and manufacturing, with vertical integration

GMP manufacturing operation featuring vacuum transfer of granulation at Bend Bioscience.

reducing handoffs and development risk," he says.

Industry demand continues to center on BAE, particularly for poorly soluble small molecules, increasingly combined with modified- or controlled-release strategies to optimize pharmacokinetics. There is also sustained pressure for rapid progression to Phase I for IR solid oral dosage forms. In parallel, multi-particulates and alternative formats such as sachets and sprinkle systems are gaining traction due to their flexibility, patient-centric dosing, and ease of administration.

Dr. Vodak illustrates how a recent case study illustrates how these capabilities come together. A client presented a poorly soluble molecule with a strong tendency to recrystallize and a narrow therapeutic window requiring control of peak exposure (C_{max}). The compound was formulated as a spray-dried amorphous solid dispersion to address solubility, with formulation strategies implemented to maintain physical stability. To meet pharmacokinetic targets, the ASD was incorporated into coated minitablets with a triggered release mechanism and erosion-based drug release. This approach enabled attenuation of C_{max} while maintaining overall exposure and was successfully demonstrated in human clinical studies.

"This example highlights the importance of integrating particle engineering, formulation design, and modified-release technologies to address complex and competing development challenges," he says.

Bespak: Outsourcing Formulation & Manufacturing in the Next Era of Inhaled & Nasal Drug Delivery

It has been a decade since the Kigali Amendment set in motion the global phasedown of hydrofluorocarbon (HFC) propellants. Since then, the inhalation industry has operated in a rapidly evolving regulatory environment, with increasing demand for low carbon pressurized Metered Dose Inhalers (pMDIs) using low Global Warming Potential (GWP) propellants. The transition to low GWP propellants requires much more than simple reformulation. As a result, pharmaceutical companies are partnering with specialist CDMOs ready to drive the transition.

Bespak®, a specialist inhalation CDMO, has invested significantly in the manufacturing capability for low carbon pMDIs and is a leader in commercial-scale readiness for the propellant shift. Alongside this, the CDMO has optimized its pMDI valves. However, the future of inhaled therapy is not limited to low carbon pMDIs, says Simon Gardner, Commercial Director, Bespak. The growing complexity of inhaled and systemic drug delivery is accelerating demand for broader platform expertise where multifaceted engineering challenges also exist.

"To meet these varied needs, Bespak provides formulation development, device design and contract manufacturing services across inhaled and nasal platforms, with the knowledge, flexibility and resources to take on projects of any shape or size," he says.

As the industry transitions to low carbon pMDIs and implements increasingly advanced analytics, success will depend on closer integration of formulation science, device engineering and manufacturing expertise, says Mr. Gardner. At the same time, growing regulatory, sustainability and performance demands are reshaping how inhaled and nasal therapies are developed. "In this context, specialist CDMOs are becoming increasingly central to enabling faster, more robust and scalable development of next-generation products.

BioDuro: Transforming Complex Oral Peptide Delivery Challenges Into Clinically Viable Assets

BioDuro offers integrated formulation development and cGMP manufacturing services spanning pre-formulation through to clinical supply manufacturing. Its capabilities begin with systematic pre-formulation characterization, leveraging scientific experience to evaluate physicochemical properties, identify drug delivery challenges early, and support informed candidate selection.


BioDuro's Jingsu site.

BioDuro's integrated DS-DP-DMPK model enables seamless collaboration across discovery, development, and manufacturing functions, explains Hong Li, PhD, Vice President, Formulation, BioDuro. "This integrated approach supports IND-ready formulations in as little as 8-12 weeks, helping accelerate development timelines," he says. "In particular, our solubility enhancement platform addresses challenges associated with poorly soluble compounds and has demonstrated strong success in improving oral bioavailability."

Oral peptide formulation services are seeing increased customer demand, driven largely by growing interest in GLP-1 therapeutics and the broader peptide pipeline. BioDuro has developed tailored formulation strategies based on the specific physicochemical and biopharmaceutical characteristics of each peptide candidate. Oral peptide delivery remains highly challenging due to poor gastrointestinal stability, rapid enzymatic degradation, and limited intestinal permeability, all of which contribute to extremely low oral bioavailability.

One program of BioDuro's involved the development of an oral GLP-1 formulation. Although the peptide demonstrated excellent aqueous solubility, intestinal permeability was negligible, explains Dr. Li. BioDuro designed a novel oral formulation utilizing a proprietary permeation enhancer and implemented a systematic development workflow spanning peptide characterization, preformulation assessment, and *in vitro/in vivo* proof-of-concept studies.

The program progressed successfully through IND submission and GMP manufacturing generating positive Phase I clinical results, ultimately supporting a significant out-licensing transaction for the client, he says. The candidate has since advanced into Phase II clinical studies.

CMC Pharma: Not Tied to Any Specific Facility, Equipment or Process

CMC Pharma is a drug development partner, specializing in the chemistry, manufacturing and controls of pharmaceutical products. The range of services provided include: pre-formulation and formulation development services; analytical method development and validation; stability testing (both routine ICH and custom testing); manufacturing site selection, qualification, and oversight; and regulatory support services for small molecule pharmaceutical products across a range of dosage forms. CMC Pharma supports programs from early feasibility and proof-of-concept through clinical manufacturing and commercialization with experience in oral solid and traditional and complex injectable products.

"CMC Pharma is not limited to specific technologies or dosage forms," says Mike Radomsky, President, CMC Pharma. "Our model ensures a seamless and efficient pharmaceutical scale-up process from lab bench to commercial GMP scale. You get one integrated partner with pharmaceutical lab capabilities, regulatory expertise, and CMO management built in, so that no value is lost in handoffs. The advantage is that we develop the formulation and process that is optimal for the program and then select the most appropriate CDMO for your project. We are not tied to any specific facility, equipment, or process."

One area seeing increased demand is integrated CMC support that combines the company's lab services, regulatory strategy, and manufacturing oversight into a coordinated development plan. One example of a successful client project involved a drug product that initially had a shelf life of only one to two months, creating significant challenges in executing clinical trials and advancing the product to commercialization. Mr. Radomsky explains that CMC Pharma rapidly evaluated multiple formulation parameters to identify factors that could improve product stability. Prototype formulations were then prepared and placed on stability to better understand the product's degradation pathways and long-term stability characteristics.

"Through iterative formulation optimization and stability testing, the development team was able to significantly improve the stability profile of the prod-

Manufacturing flexibility and a focus on early-stage CMC activities de-risks programs.

uct," he says. "Today, the formulation supports a multi-year shelf life and is suitable for long-term storage and distribution.

Codis: Supports a Complete Spray Drying Service Offering

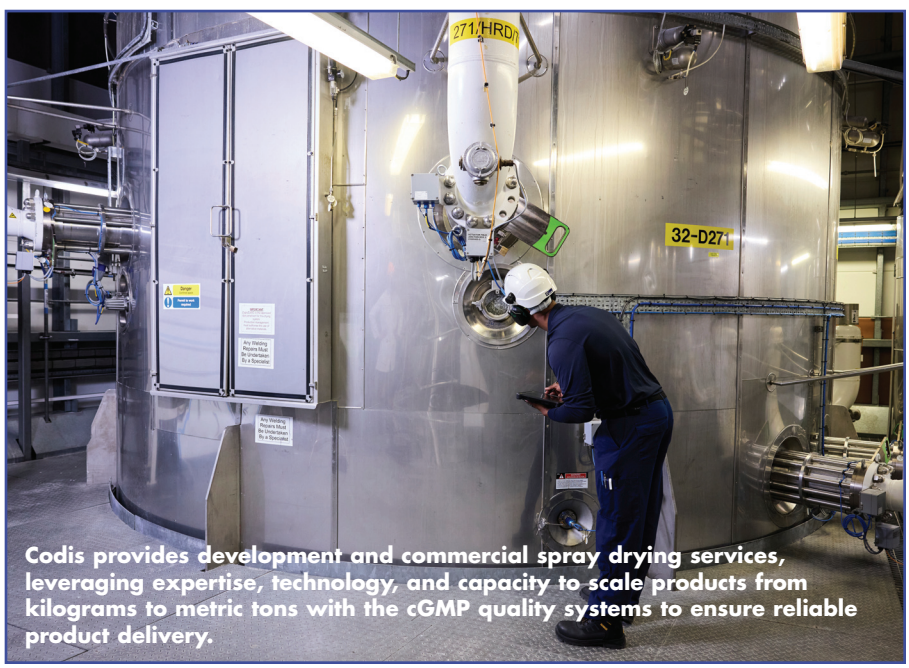
As Codis is predominantly a commercially oriented CDMO, formulation support activities are focused on the scale up and commercial operability of discovered formulations. The company builds on successful early-stage development work to deliver robust, sustainable, and commercially viable formulation solutions that enable the successful supply of innovative new drug therapies. In addition to spray drying as a core capability, Codis has experience in spray dryer feed preparation activities, including continuous chemistry, filtration, and purification processes, supported by at-line analytical measurements.

"Spray drying is a proven and robust technology for addressing poor solubility and bioavailability challenges and is therefore increasingly sought after by both emerging and established compound owners," says Mark Macdonald, Technical Sales Director, Codis. "It is used both to enable the commercialization of challenging new compounds and to unlock new IP opportunities for existing products through formulation enhancement."

To support spray dried compound onboarding and scale up, the Codis in-house data science team has established spray drying modelling tools that are physics based and mechanistic, built on established process understanding and experimental data. Artificial Intelligence is then applied in supporting roles to augment model performance through mechanism verification and by aiding interpretation and explanation of model outputs. Using limited datasets generated on R&D scale equipment, Codis can rapidly model processes and predict operating conditions on clinical and commercial scale units.

"This enables significantly accelerated onboarding of critical programs when required, and provides clients with flexibility in their route to registration and commercialisation, aligned with funding milestones," says Mr. Macdonald.

For one global client, rapid scale up and onboarding was required, involving progression from contract award to com-



Codis provides development and commercial spray drying services, leveraging expertise, technology, and capacity to scale products from kilograms to metric tons with the cGMP quality systems to ensure reliable product delivery.

mercial supply of tens of tons of spray-dried product within a six- to nine-month timeframe. "Leveraging our internal process modelling capabilities, we were able to accelerate onboarding and scale up activities and rapidly establish the process on commercial scale equipment," he says. "In parallel, variability in feed material from multiple manufacturing sites was incorporated into the process design, enabling the timely delivery of commercial material that met all specifications."

FUJIFILM Biotechnologies: The Power of Formulation Development On a Molecule's Developmental Journey

At FUJIFILM Biotechnologies, the goal is to be a partner and the formulation development team achieves this by onboarding and supporting partners at any stage of a molecule's development journey. FUJIFILM Biotechnologies offer an array of formulation development and supplementary packages to reach IND and, eventually, a BLA submission. This could include pre-clinical work (full formulation development, forced degradation, clinical in-use/compatibility studies, or downstream processing optimization support), or late-stage programs (formulation refinement and robustness).

Within formulation development, the need for high and ultra-high protein concentration (150+ mg/mL) therapies has skyrocketed, says Madison White, Senior Scientist, Formulation and Analytical Development, FUJIFILM Biotechnologies. The biotherapeutic industry is seeing a shift towards subcutaneous injections, as opposed to frequent and time-consuming infusions. This shift towards subcutaneous delivery often coincides with increasing the protein concentration to reduce the injection volume through auto-pens or prefilled syringes. However, increasing the protein concentration to high protein concentrations creates challenges with the product's manufacturability, viscosity, injectability, aggregative behavior, and overall stability.

To combat these added challenges, proper formulation development optimized for each individual molecule, while monitoring specific attributes related to high concentration production and stability, is imperative. In the case of one client, a fusion protein showed extremely high levels of aggregation coming out of the downstream development process. Optimization of various downstream process parameters were tested; however, there was little to no improvement in the aggregative behavior of this molecule. "As a solution, our team created a modified formulation development study to determine if there were any solution conditions that could reverse the level of aggregation that was coming out of the downstream process," she says.

Through this study, the primary chemical pathway of the aggregation was identified using core, biophysical techniques. With this information, FUJIFILM Biotechnologies created a broad excipient screen designed specifically to combat this primary mode of aggregation while remaining within the inactive ingredients found in regulatory-approved products. "With this, we were able to identify a single, rare excipient that comprehensively combatted the molecule's extreme propensity to aggregate on both the visible and sub-visible level," she explains.

This excipient was carried throughout the remainder of the formulation development studies, and a final, stabilizing formulation was identified. Also, the excipient was compatible with some of the downstream processes. Therefore, it was implemented into the process, which resulted in an increase in overall purity and stability. "With the completion of the downstream and formulation development, this molecule has gone on to DS and DP with three-plus years of stability, proving the power that formulation development can have across all aspects of a molecule's developmental journey," says Ms. White.

Gattefossé: Targeted Seminars & Training Guide Formulators

Lipid-based formulations offer key benefits across several routes of administration. These benefits include improved solubility and enhanced *in vivo* absorption via the oral route as well as penetration enhancement and effective, patient-friendly formats for topical/transdermal products. Gattefossé has four Technical Centers of Excellence (TCE Labs) in France, the US, India, and China to: aid in the selection and optimization of pre-clinical lipid-based formulations; provide tailored, hands-on customer support; and advance lipid knowledge through education and training.

Technical capabilities range from screening/compatibility studies for liquid and semi-solid excipients to the development of binary and ternary systems that utilize multiple lipids to optimize drug loading, maximize drug exposure, and improve product performance. Gattefossé also performs *in vitro* lipolysis and Franz cell diffusion testing to simulate *in vivo* conditions and guide both oral and topical formulation selection.

Formulators are increasingly seeking permeation enhancers that offer performance, regulatory confidence, and scalability. Gattefossé offers several medium chain

fatty acid esters that act as safe, reversible tight junction modulators, such Labrasol® ALF, Capryol® 90, and Labrafac™ MC60.

"Through targeted customer seminars and in-depth training sessions at our Paramus, NJ lab, Gattefossé is guiding formulators on the keys for handling lipids, maximizing performance, and avoiding common pitfalls in stability and pre-clinical dosing," says Nick DiFranco, Senior Marketing Manager – Pharmaceuticals, Gattefossé USA.

While lipid excipients offer tremendous benefits for bioavailability enhancement, they have traditionally been limited to liquid and semi-solid dosage forms, such as soft gelatin capsules. However, permeability-limited compounds have driven increased interest in incorporating lipid excipients into oral solid dosage forms. To meet this demand, Gattefossé has invested in oral solid dosage form capabilities at its New Jersey TCE Lab. Additions for 2026 include a hot melt extruder and tablet press, which allow Gattefossé to evaluate lipid excipients as plasticizers, permeation enhancers, and recrystallization inhibitors in amorphous solid dispersions. Gattefossé is also partnering with companies in the spray drying field, such as GEA, to investigate the use of lipids in solvent-based techniques.

"These added capabilities allow us to address the growing interest in combining lipid and polymer excipients to improve in vivo translation for new drug modalities," he says.

Hovione: Seamless One-Site Stop Integration from ASD Development to Drug Product Manufacturing

Hovione is a CDMO provider of Amorphous Solid Dispersions (ASDs) formulations manufactured by spray drying to address solubility and bioavailability challenges. This formulation strategy is integrated with downstream manufacturing of the final dosage form, such as tablets or capsules or nasal drug delivery.

Hovione manufacturing operator in company production area.

"Hovione's spray drying expertise is unique thanks to our regulatory track record, a large GMP spray drying capacity, and our ability to offer seamless "one-site stop" integration from ASD development to drug product manufacturing, for both batch and continuous tableting," says João Ventura, PhD, Senior Director, Strategic Business Management – Pharma, Hovione. ASDs by spray drying has become a leading formulation strategy. This demand has also triggered growth in integrated and specialized offerings from CDMOs that integrate ASD formulation manufacturing with downstream manufacturing services into final dosage forms.

In formulation development, artificial intelligence (AI) tools enable faster, data-driven process and approaches with minimal experimental work and material consumption. Application examples include integrated formulation development and screening tools, such as Hovione's ASD-HIPROS, capable of rapidly screening for the best combination of drug loads, excipients, and surfactants using advanced formulation models and high-throughput screening methods supported by AI tools. At Hovione, these tools are based on hybrid mathematical models that combine mechanistic understanding with machine learning methods, enabling scientists to predict drug-polymer behavior and optimize formulation composition in a fraction of the time, Dr. Ventura says.

In manufacturing, AI tools are being used to support increased digitalization and automation of manufacturing processes, informing greater understanding and insights from data-rich manufacturing process execution that support continuous improvements. In continuous tableting, advanced control strategies (PAT and real-time quality control) are being deployed to enhance process robustness and scalability.

"In early development stages, we use ASD-HIPROS, our data-driven high-throughput screening tool, to rapidly characterize the challenge and select the most appropriate strategy, screening for the best combination of drug loads, excipients, and surfactants to create a robust, scalable spray drying process from the outset," he

explains. "We then apply Quality-by-Design principles and standardized tech transfer methodologies to ensure scalability and de-risk the transition to GMP manufacturing."

LATITUDE Pharmaceuticals: Transforming Difficult-to-Deliver APIs into Efficacious Drug Products

LATITUDE Pharmaceuticals positions itself as a specialized formulation CDMO, distinguishing itself from the high-volume one-stop-shop large CDMOs by focusing on the "D" instead of just the "M," explains Matthew Singer, PhD, Vice President, Business Development, LATITUDE Pharmaceuticals.

LATITUDE's service suite revolves around complex formulation development and clinical trial manufacturing. The CDMO specializes in transforming difficult-to-deliver APIs into stable, efficacious drug products. Capabilities span a wide array of dosage forms, including complex injectables, oral liquids and solids, ophthalmics and topicals.

LATITUDE also offers an integrated development-to-manufacturing model, which allows clients to move seamlessly from formulation design to clinical trial material production under cGMP, accelerating timelines and reducing technical risk.

Dr. Singer says that LATITUDE's most in-demand services currently center on biologics and injectable and oral drugs, including the formulation of peptides for both of these delivery formats. Other in-demand services include aseptic fill-finish and ophthalmic manufacturing.

"There is also strong demand for LATITUDE's end-to-end services that combine formulation development and clinical trial supply," he says. "LATITUDE's flexible manufacturing capacity and advanced analytical testing are especially valued as clients seek faster scaling and more resilient global supply chains."

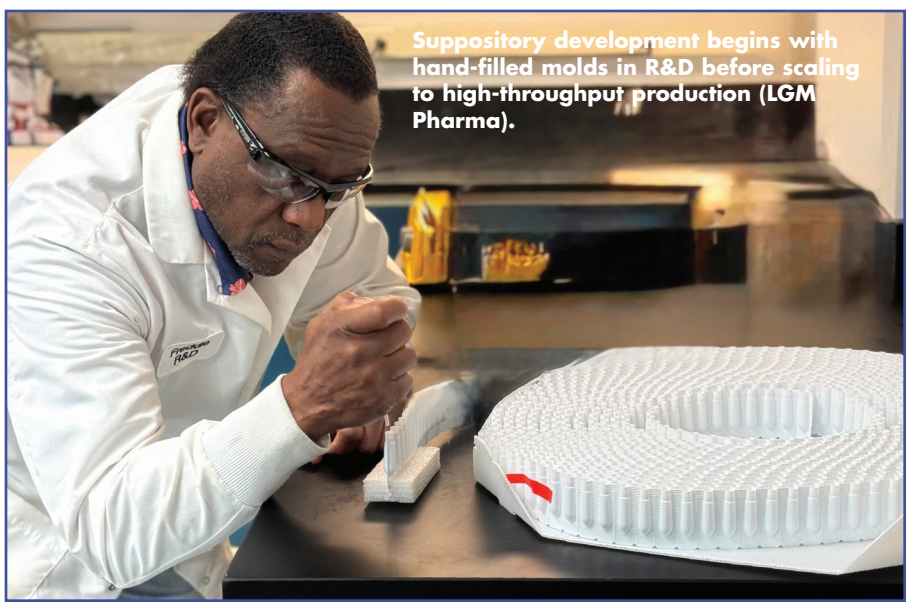
LGM Pharma: A Faster, Smoother Route From Bench to Commercial Suppository Production

LGM Pharma, a US-based CDMO specializing in API sourcing, contract analytical testing, and drug product services, offers specialized formulation development and manufacturing services with expertise in complex dosage forms, including suppositories. The company supports clients through the full product lifecycle – from sourcing high-quality active pharmaceutical ingredients (APIs) to commercial-scale manufacturing of finished drug products.

Suppository development presents unique challenges, particularly around solubility and stability. Unlike most oral formulations, suppositories rely on bases such as hard fats, polyethylene glycols, or cocoa butter. The drug's solubility in the base affects its release rate. These formulations are highly sensitive to temperature, both during manufacturing – where precise control during mixing, filling, and cooling directly affects drug distribution and product uniformity – and throughout transport and storage, where fluctuations risk melting or deformation.

"We address these complexities with customized formulation strategies and robust analytical capabilities," says Mike Stenberg, Vice President of Business Development, LGM Pharma. "Scaling from R&D to commercial manufacturing typically requires transitioning from small batches and hand-filled molds to commercial-scale filling equipment and container closure systems. The capital investment and technical expertise required to manufacture suppositories at commercial scale limits the number of CDMOs capable of offering this service, particularly in the domestic market."

A common challenge LGM Pharma addresses is scaling suppository formulations from development to commercial production. One client needed to transition from hand-filled R&D batches to consistent, high-quality commercial output, where differences in equipment, process parameters, and temperature sensitivity introduced added complexity. Through early technical evaluation and close collaboration, LGM Pharma identified scale-up risks and addressed formulation and process considerations. The result was improved



Suppository development begins with hand-filled molds in R&D before scaling to high-throughput production (LGM Pharma).

batch consistency and a smoother path to commercial manufacturing, says Mr. Stenberg.

"To further streamline the transition from R&D to commercial scale, we recently expanded capabilities at our Texas facility to include both R&D and commercial-scale suppository production," he says. "By bringing development and manufacturing under the same roof, we give our clients a faster, smoother route from bench to commercial production – with fewer tech transfer requirements and less risk with scale up."

Lifecore Injectables CDMO: Early Phase Design for Manufacturability Informed by Successful Late Phase Scale Ups

As drug pipelines move toward more complex therapies, injectables development and manufacturing are becoming less linear and more connected. Biologics, long-acting injectables, highly viscous formulations, suspensions, advanced delivery systems, and other complex products benefit from greater and earlier collaboration between formulation process development and manufacturing teams.

Lifecore Injectables CDMO specializes in aseptic process development and fill/finish for complex injectable drug products and devices from early clinical stages through commercial launch. With experience that spans the full product lifecycle, Lifecore incorporates commercial scale formulation, filling, and quality testing into early phase development. Lifecore embeds manufacturing personnel directly into pilot scale development work to ensures that process decisions made early are grounded in practical considerations for future manufacturing.

For example, while a process development engineer may define an optimal filtration strategy from a theoretical standpoint, direct input from formulation scientists and manufacturing staff responsible for filter setup, execution, and testing provides critical insight into feasibility, robustness, and operational complexity at scale. Manufacturing operators contribute to the development and refinement of SOPs and supporting documentation that they will use in routine production. "Their involvement helps ensure that procedures reflect real-world manufacturing practices, use standardized and familiar terminology, and accurately capture how processes are executed on the manufacturing floor," says Jackie Klecker, Executive Vice President, Quality & Development Services, Lifecore Injectables CDMO.

A similar integration is applied across Analytical Development and QA/QC functions. Analytical scientists and QC testing teams work in parallel during late-stage method development and validation activities to verify that analytical methods are not only scientifically sound, but also clear, reproducible, and readily executable in a quality control environment. By validating methods with end users involved early, potential gaps in clarity, training, or execution are identified and resolved before formal transfer.

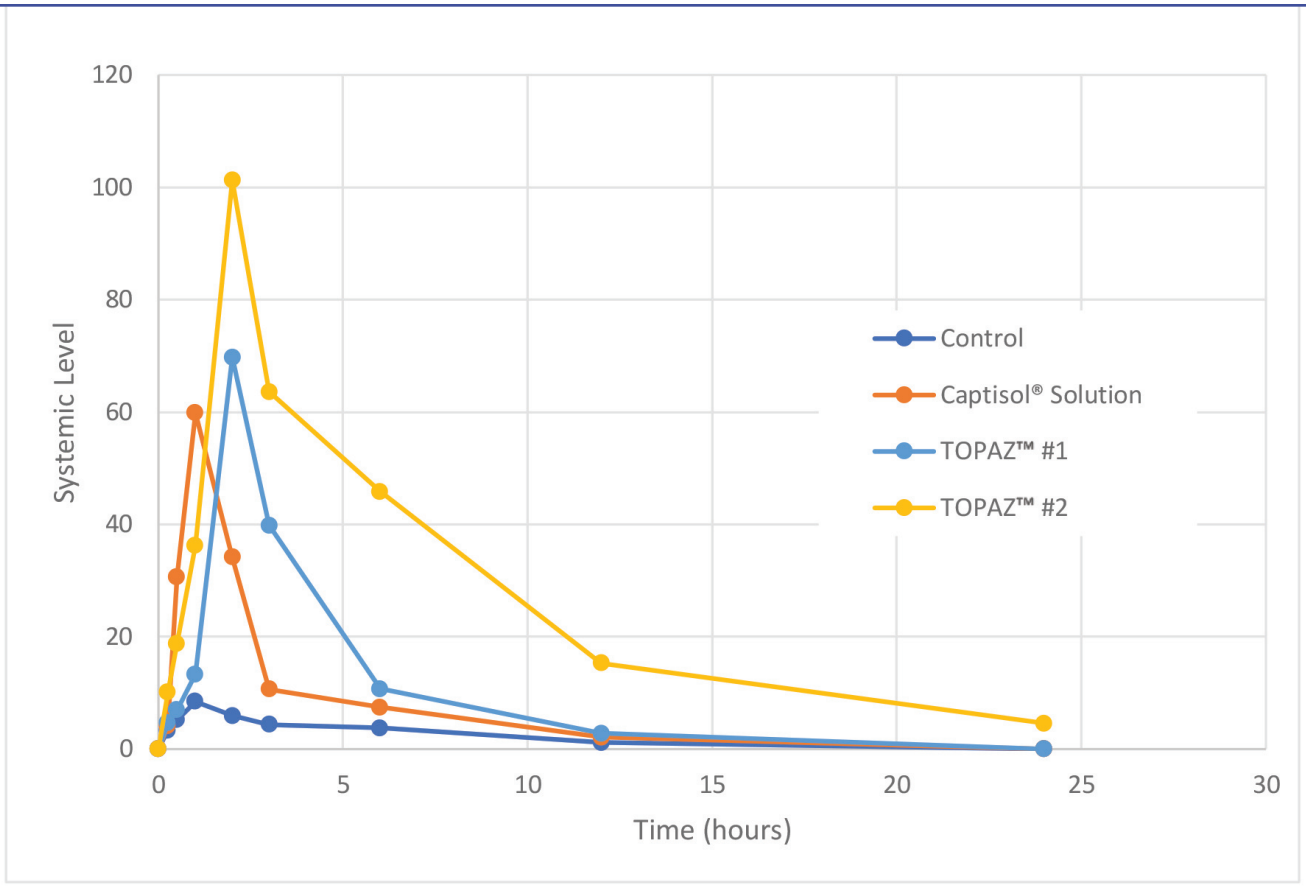
Complex injectables benefit from early collaboration between formulation process development and manufacturing teams at Lifecore.

Ligand: From Rapid Feasibility to Clinical Success

A central element of Ligand's offering is a rapid early-stage formulation service known as FAST (Feasibility Assessment/Solubility Testing). The FAST program is designed to quickly assess the interaction between an active pharmaceutical ingredient (API) and cyclodextrins, enabling informed go/no-go decisions at the preclinical or early development stage. Rather than relying on empirical screening alone, these studies are conducted by cyclodextrin experts who understand complex host-guest chemistry, competitive binding, and the impact of formulation conditions on solubility and stability.

"FAST studies typically provide an early read on solubility enhancement, excipient compatibility, and manufacturability," says Lian Rajewski, PhD, Sr. Director Formulation Development, Ligand. "This rapid insight reduces development risk, shortens timelines, and often informs the selection of a path forward for prototype and final formulation development."

One illustration is of a poorly soluble compound given by ocular route that also required a systemic formulation for safety studies. Through rapid cyclodextrin-based screening, interaction between the API and Captisol® was identified and characterized as Type AP (Positive Deviation) from linear-



Enhanced solubility translated into improved oral bioavailability for a complex oral formulation (Ligand).

ity. Based on the results of the FAST studies and taking into consideration the non-linear interaction, further development studies were warranted that lead to a viable prototype formulation. Stability studies supported by qualified analytical methods were performed, followed by successful transfer to a CDMO, allowing the program to advance without delay.

A more complex example involved an oral formulation of a poorly soluble, intensely bitter natural alkaloid supplement. While conventional cyclodextrin approaches achieved approximately a ten-fold increase in solubility, the client's target product profile required at least a 100–fold improvement. To meet this goal, a novel Captisol-enabled formulation platform, TOPAZ™, was used. "This approach achieved the desired solubility enhancement and addressed palatability by delivering the formulation in a liquid-filled capsule," says Ms. Rajewski.

Pharmacokinetic evaluation in animal studies demonstrated a marked increase in systemic exposure compared with earlier cyclodextrin and control formulations, confirming that the enhanced solubility translated into improved oral bioavailability.

MedPharm: Specializing in Topical & Transepithelial Drug Delivery

MedPharm is a CDMO that specializes in topical and transepithelial drug delivery including skin, nasal, pulmonary, ocular, nail, and mucosal, across a broad range of formulation types from simple liquids, through to complex semi-solids, foams and aerosols. Drugs in development span small molecules and larger molecules that present physicochemical challenges for topical/transepithelial. In support of product development activities, MedPharm has developed a suite of proprietary *in vitro* and *in silico* tools designed to generate physiologically relevant data earlier in development, mitigating the risk of failure and reducing reliance on less predictive legacy models, explains Charles Evans, PhD, Senior Vice President of Pharmaceutical Development, MedPharm.

Two areas of work have seen particularly consistent demand in recent years. The first is formulation troubleshooting and rescue programs where stability failures, thermodynamic and solubility problems, or regulatory concerns stall development, often after work with an earlier partner. These projects typically require root-cause analysis before an optimized formulation strategy. The second is in intellectual property, where sponsors seek to expand patent coverage beyond drug composition of matter and initial formulation type or for lifecycle management, extending protection from a single dosage

form to a broader range of formulations to reduce competitive risk and support long-term commercial value. "Both reflect a broader climate with early-stage investment harder to secure, and sponsors needing credible data/IP early and a plan for extended protection to support funding," he says.

The growth of precision medicine is changing what sponsors expect from *in vitro* data during product development. As therapies become more targeted, demonstrating that a drug reaches a target tissue is no longer sufficient on its own and there is growing expectation to understand biological activity. MedPharm has been developing living human tissue *in vitro/ex vivo* pharmacodynamic models to understand this ahead of costly clinical studies. Dr. Evans says that using a combination of pharmacokinetic/pharmacodynamic readouts give sponsors more translatable evidence of whether a formulation is performing as intended, critical when seeking investment or planning clinical studies.

The importance of applying the right scientific framework from the outset is well illustrated by recent development work. A sponsor arrived at MedPharm with a previously developed biologic formulation intended for nail delivery, which was exhibiting 30% impurity growth over its intended shelf-life. The root cause was a fundamental misclassification; the drug had been treated as a small molecule rather than a biologic, leading to a flawed formulation strategy. Following biologic-appropriate forced degradation and compatibility studies, incompatible excipients were removed and biologic stabilizers introduced, improving stability by approximately 70% and allowing the program to advance to IND-enabling studies.

PCI: Integrated Services for Oral & Sterile Drug Products

PCI offers integrated end-to-end formulation, analytical development, manufacturing and packaging across both oral and sterile drug products to support programs from early phase through commercialization. Oral D&M capabilities span oral solid dose and liquids, including high potency, ultra-high potency compounds and pediatric solutions and suspensions. Sterile D&M capabilities support a range of biologics and small molecule modalities in solution, suspension, lyophilized forms in vials, Ophthalmic bottles, prefilled syringes, and cartridges.

"What makes PCI's D&M capabilities distinct is this combination of breadth and integration: fully integrated services for drug product for both orals and sterile within one network, while tailoring phase–appropriate solutions and avoiding "black box" technologies," says Anshul Gupte, PhD, RAC Drugs, Vice President, Pharmaceutical Development, PCI.

The CDMO is seeing particularly strong demand for sterile development and for drug-device combination products, especially prefilled syringes and cartridges. High dose coupled with solubility limitation and constrained by injectable volumes is pushing sponsors towards complex formulations, such as suspensions that are technically challenging to formulate and characterize, he explains. At the same time, accelerated by the success of GLP-1 therapies and autoinjectors, patient expectations are driving the switch from vial to drug-device combination products. "Sponsors increasingly want to run vial and device development in parallel, and often earlier in the lifecycle than before, so they can move quickly into patient–centric presentations," says Dr. Gupte. "Overlaying this are targeted therapies and pediatric indications, which further increase demand for ultra-high-potency handling, complex dosage forms and solubility-enhancing approaches that can be translated into robust, scalable products."

A recent client approached PCI with a biologic platform and needed a Phase I formulation for IV administration, ideally one that could be employed across multiple related molecules, with a clinical batch required within three to four months. PCI recommended a phase-appropriate, platform-oriented development approach that allowed for an early switch to lyophilization if stability in solution proved inade-

Manned isolator for ultra-high potent API at PCI.

quate, explains Dr. Gupte. For one molecule, this contingency was triggered, so PCI rapidly developed a conservative lyophilization cycle focused on robustness rather than commercial efficiency.

"By keeping specialized analytics with the drug substance manufacturer and concentrating on in-process controls, sterility and standard release tests at our site, we avoided time-consuming method transfers," he says. "The result was a small GMP batch of lyophilized product, delivered within the aggressive timeline, enabling a first-in-human study and demonstrating that a platform formulation strategy could be applied across the client's biologic series."

Quotient Sciences: Integrated CRDMO Supports Development & Supply for Phase I Studies

Quotient Sciences' Translational Pharmaceutics® platform was introduced nearly two decades ago to innovate the way formulation development and supply for early clinical trials are designed, supported and managed. In a traditional drug development model, formulation development and drug product manufacturing (CDMO) and clinical testing (CRO) are separate activities, often handled by different vendors and conducted on different timelines. If not managed well, siloed activities performed by each vendor can cause inefficiencies that increase timelines and risk, says Dr. Vanessa Zann, Vice President, Scientific Consulting, Translational Pharmaceutics & Clinical Pharmacology – USA, Quotient Sciences.

"Translational Pharmaceutics® eliminates these burdens, allowing sponsors to mitigate risks by integrating drug product formulation development, cGMP manufacturing, and clinical testing into a single, adaptive workflow," she says. "Quotient Sciences performs all activities within its facilities under the oversight of a single project/program manager."

Quotient Sciences has partnered with CROs, including Biorasi and Lindus, enabling seamless transition to proof-of-concept clinical studies with patients and special populations, explains Dr. Zann. Quotient Sciences' partnership with Intrepid Labs is integrating the ANDROMEDA™ Machine Learning platform into formulation development. This AI-guided approach rapidly explores formulation options, predicts clinical performance, reduces experimental burden and drug substance requirements, and supports more informed, data-driven decisions. "Leveraging this platform, clients will be able to move optimized drug products into clinical development faster and with greater confidence," she says. "A pilot program is ongoing, with notable milestones ahead."

A notable project Quotient Sciences recently tackled was to advance YourChoice Therapeutics' YCT-529, the first non–hormonal oral male contraceptive, into human clinical testing, says Dr. Zann. While preclinical data showed strong efficacy, reversibility, and a favorable safety profile, the company needed to focus on scaling API, designing a flexible oral dosage form capable of supporting dose escalation with limited drug substance, and executing a first-in-human program that balanced volunteer safety with rapid data generation.

The team based in Alnwick, UK (Arcinova, a Quotient Sciences Company) developed scalable API manufacturing for YCT-529. This was followed by a flexible capsule formulation and matching placebo using manual capsule filling, and Translational Pharmaceutics was applied to deliver the first-in-human program. Formulation development, GMP manufacturing, clinical supply, and Phase 1a clinical testing were integrated at Quotient Sciences – Nottingham. UK, enabling real-time dose adjustment and efficient decision-making.

The Phase 1a study was completed successfully, demonstrating YCT-529 was well tolerated with no hormonal side effects or food effect. "The data validated its safety profile and enabled progression into multiple-ascending-dose studies, marking a major milestone in non-hormonal male contraception development," says Dr. Zann.

Recipharm: Specializing in HPAPIs

Recipharm offers a full range of formulation services for multiple dosage forms, including oral solids, sterile injectables, and biologics. To ensure reliable outcomes, the CDMO combines these services with ReciPredict®, a statistical modelling and simulation platform.

"This ensures we understand right away how formulations are likely to behave during scale-up and technology transfer," explains Lidia Garcia Martin, MSAT & News Productions Head, Recipharm. "This foresight allows us to identify and address potential issues much earlier, reducing unwanted surprises for our partners across development and manufacturing."

The pharmaceutical landscape has been reshaped by the recent interest in highly potent active pharmaceutical ingredients (HPAPIs). These compounds are increasingly in demand due to their applications in oncology and immunotherapy, but their production requires added sophistication in handling, containment, and process control. However, she says,

not every drug developer has this expertise in-house; some CDMOs lack the infrastructure needed to handle HPAPIs safely.

Recipharm is also integrating digitalized monitoring systems into its HPAPI workflows to enable real-time in-process controls, assuring containment environments, ensuring all our advancements work together to elevate our high-potency operations.

One global pharmaceutical company was looking for a manufacturing site able to produce an HPAPI to supply to the US and Japan markets. Recipharm was chosen for its HPAPI expertise and tailored facilities. The project's success relied on adapting the client's process to the chosen site's HPAPI-primed equipment. "Our team worked closely with the client to understand the design of their experiments and with several suppliers to address technical issues," she explains. "Thanks to this collaboration and our team's firm knowledge of HPAPI handling, the workflow was quickly streamlined, and the product was successfully brought to market within a tight time frame."

Resilience Biotechnologies Inc.: Upstream & Downstream Process Development

Resilience's Toronto team offers biologics development and manufacturing services spanning early-stage clinical to commercial scale processes. This includes upstream and downstream process development and scale-up for monoclonal antibodies (mAbs) and mAb-like proteins. The company's Toronto site also specializes in protein chemistry development and scale-up for complex bioconjugates, such as metal chelator-modified mAbs for radiopharmaceutical therapies and protein-nanoparticles for drug delivery or immune therapies. The Manufacturing Science and Technology (MSAT) team, which is made up of scientists, engineers, and analysts, spearheads technology transfer and carries out all process and analytical development activities, including early bench scale studies through to manufacturing supportive studies.

Steve Brookes, PhD, Director, MSAT and Process Development, Resilience Biotechnologies Inc., explains how Resilience Toronto developed and scaled up a client mAb conjugate process. The engineering run gave a broader conjugate-to-antibody ratio compared to development lots, which required quick resolution to meet the GMP manufacturing schedule. The conjugation process consisted of a pre-mix step of the reactants prior to distribution across multiple reaction vessels containing the protein. Distribution of the difficult-to-mix non-uniform pre-mix among the units was identified as the cause that resulted in variation in reactant loads on the protein in the separate reactors. The Resilience MSAT team conducted mixing studies with surrogate solutions and optimized parameters to be used with the equipment and setup that was designed in time for the cGMP mAb conjugation run. Average load and distribution specifications were met and matched prior development lots, allowing the client to proceed with their program. This example highlights the value of at-scale engineering runs to truly de-risk clinical cGMP batches, especially for non-standard unit operations being conducted for the first time.

In another process, Dr. Brookes says that for a particular conjugate product, the conjugation process involved derivatizing one macromolecular construct with a linker and chemically reducing a second mAb-like protein of interest to combine with the first construct in the conjugation reaction; however, the reduced protein had to undergo removal of the reducing agent as quickly as possible as it was prone to re-oxidation and loss of reactivity resulting in the resultant construct being underloaded with the protein. The MSAT team designed the manufacturing process such that the reaction and subsequent ultrafiltration/diafiltration (UF/DF) process steps were kept in a closed system under nitrogen to minimize oxidation; all associated buffers used in the reaction and UF/DF steps were deoxygenated by nitrogen purging.

"Most critical was that the team worked out a schedule for the various required parallel activities that was tightly choreographed to avoid delays once the protein reduction step was begun and which avoided time-consuming in-process gating analytics," he says. "These steps were implemented into the at-scale manufacturing process where the conjugate was shown to have the desired protein load and the process performance matched earlier development scale runs in terms of yield and quality attributes."

Samsung Biologics: Developing High-Concentration Biologics

Samsung Biologics offers clients a broad range of development services, spanning cell line development, upstream development, downstream development, pilot production, formulation development, and analytical development. The CDMO offers comprehensive formulation development services, including late discovery, as exemplified in DEVELOPICK™, which is an in-house developability assessment that supports molecular selection as well as the identification of development risks. The formulation team also launched a high-concentration formulation develop-

ment platform, S-HiCon™, to help clients achieve product concentrations for their desired route of delivery (e.g. subcutaneous delivery for later phase development).

Samsung Biologics is witnessing high demand from clients for high-concentration formulation development, driven by the need to deliver relatively high doses to the patient, sometimes in the range of hundreds of milligrams. Additionally, a frequently preferred route of delivery is subcutaneous injection, which requires delivery in volumes less than 1.5mL. Therefore, delivering subcutaneous doses in the range of hundreds of milligrams requires that product concentrations be at least 100mg/mL, says Derrick Katayama, Associate Director of Formulation Development at Samsung Biologics. "The Samsung Biologics formulation team has experience with developing high-concentration biologics, which led to the launch of the S-HiCon™ platform," he explains.

A client came to Samsung Biologics with a challenging molecule that, at a previous site, had experienced solubility and physical stability issues during process development, he explains. "Therefore, we had the opportunity to re-formulate the molecule, but at the request of the client, at a higher concentration than previously developed," he says.

Leveraging the target molecule's existing development and stability data, the team performed extensive screening of multiple excipient types and buffer conditions. In short, the team successfully identified an optimal set of pH, buffer, and excipient conditions that led to a higher formulation concentration. This was achieved through a step-by-step approach that narrowed down the promising compositions to finally identify an optimal formulation specific for the given molecule.

Serán BioScience: Minimizing Downstream Reformulation Risks

Serán BioScience is a CDMO specializing in vertically integrated drug product development, formulation, and cGMP manufacturing services. The company supports pharmaceutical and biotechnology clients from early discovery through commercial support focusing on complex small molecules, bioavailability enhancement, and advanced delivery systems. Core services include: formulation and dosage development; amorphous solid dispersions; spray-dried dispersions; HME; lipid formulations; particle size reduction (including nanomilling); analytical services; quality control; and scalable cGMP manufacturing of spray drying, HME, tablets, capsules, and powders for oral and inhalation.

"What sets Serán apart is its "Right-From-the-Start" philosophy," says Dan Smithey, PhD, President & CEO, Serán BioScience. "By strategically selecting and optimizing commercially viable formulation technologies and scalable processes early in development, Serán minimizes downstream reformulation risks, accelerates progression to the clinic, and builds a clear line of sight to robust commercial manufacturing."

Many of Serán's clients look to resolve formulation challenges preventing them from moving their molecule forward. One leading biopharma focused on innovative therapies for rare diseases came to Serán during Phase II trials with a significant challenge: their existing amorphous solid dispersion formulation as well as the nature of and number of excipients caused significant concerns over formulation as well as process robustness and scalability. In addition to filler and flow aids, the 50mg dose required a 950mg tablet, and full dissolution under sink conditions required 240 minutes. With projections of a high dose for clinical efficacy, the highest priority for optimization was to develop a scalable tablet formulation with a reduced pill burden to be introduced to clinic for Phase III, explains Dr. Smithey.

Serán's team developed an optimized formulation for Phase III, cutting excipients in half and reducing tablet weight by 28%. The team identified the tablet excipients critical to performance and robust manufacturing and were able to achieve an increased drug loading in the tablet and improvement in tablet dissolution. Additionally, by pivoting to an alternative polymer in the SDD formulation, the resulting SDD sustained supersaturation and over a 30% increase in bioavailability. Serán's formulation optimization addressed the client's scale-up needs, while also increasing drug load, lowering pill burden and positioning them for commercial success with a marketable product and improved patient outcomes.

Shilpa Medicare Ltd.: Hybrid CDMO Model Derisks & Saves Time

Shilpa Medicare Ltd. operates as a fully integrated pharmaceutical company spanning APIs, biologics, and finished formulations. Formulation development and manufacturing services cover oncology oral solids, complex injectables, transdermal patches, oral thin films, peptides, and novel drug delivery systems. In addition to offering comprehensive discovery, clinical, and commercial outsourcing services across small and large molecules, its 'hybrid CDMO model' includes commercially ready 'off-the-shelf' novel formulations for exclusive b2b licensing.

"This dual approach enables pharmaceutical companies to leverage our expertise in oncology without the direct risks

Shilpa Medicare facility in Raichur, India.

and lengthy timelines associated with development," says Abhay Sapre, PhD, Senior Vice president R&D-Formulations and Site head at Shilpa Medicare Ltd.

Oncology continues to be the strongest area of demand for Shilpa, with the company supplying more than 30 oncology APIs and corresponding finished formulations into the US, EU, and other regulated markets. One challenge involved oncology products that required complex reconstitution steps in hospitals before administration. This created preparation delays, dosing variability, and handling risks for pharmacists working with cytotoxic compounds. Shilpa's formulation team redesigned the products into stable ready-to-use liquid presentations, eliminating the need for reconstitution while maintaining stability and sterility requirements. The products later secured FDA approvals and helped hospitals reduce preparation time, improve handling safety, and simplify administration workflows, particularly in high-volume oncology settings.

Dr. Sapre also shares that another sponsor had a product facing multiple innovator patents covering polymorphs, release profiles, and manufacturing processes. Instead of following the originator pathway directly, the team developed a non-infringing formulation approach using alternative polymorph selection and modified-release technology designed to achieve bioequivalence without infringing core patents. Regulatory, formulation, and Paragraph IV strategy were developed in parallel throughout the program. The result was a differentiated product pathway that supported successful filings in regulated markets and helped position the client for earlier market entry opportunities, says Dr. Sapre.

Simtra BioPharma Solutions: Advancing Efficiency Through Expertise

Simtra BioPharma Solutions offers comprehensive formulation and process development services for large and small molecules, using a data-driven, statistical design of experiments (DoE) approach.

"This methodology reduces the number of formulation iterations required, minimizing material use while accelerating timelines and managing costs," says Greg Sacha, Global Senior Scientist, Simtra BioPharma Solutions.

Simtra develops solution formulations suitable for vials and prefilled syringes (PFS), as well as lyophilized products. Simtra's lyophilization processes employ a design space strategy, enabling efficient development while facilitating smooth technical transfer and scale-up, he explains.

Among the services Simtra provides, lyophilization expertise remains one of the most sought-after. Many clients specifically engage Simtra for its depth of experience in freeze-drying. Additionally, demand for PFS filling continues to rise, driven by patient-centric considerations such as ease of use, dosing accuracy, and improved compliance. "These trends underscore the importance of CDMOs with specialized capabilities and the ability to support multiple delivery formats," says Mr. Sacha.

A recent example highlights the value of Simtra's collaborative and methodical approach. A client faced challenges with the reconstitution of a difficult-to-dissolve molecule following lyophilization. Simtra systematically evaluated formulation excipients in a structured sequence to determine which adjustments most effectively improved reconstitution performance. Data from each iteration were carefully analyzed and shared with the client, enabling a transparent, evidence-based selection of the optimal formulation candidate. Mr. Sacha says the result was a successful resolution that improved product usability while maintaining stability and quality.

Greg Sacha, Global Senior Scientist, Simtra BioPharma Solutions, loading vials into a laboratory-scale lyophilizer, illustrating data-driven formulation development and the precision processes required to ensure successful freeze-drying, scale-up, and manufacturing in outsourced CDMO partnerships.

Symeres: A Predictable Path from Molecule to Clinic

Symeres offers an integrated chemistry, manufacturing and controls (CMC) model. This brings drug substance (DS) development, DS manufacturing, drug product (DP), formulation development, analytical testing, stability and drug product (DP) good manufacturing practice (GMP) manufacturing together at a single site. "Co-location enables real-time collaboration between chemists, formulators and manufacturing teams, eliminating delays and data gaps common with multi-vendor approaches," says Paul O'Shea, Managing Director, Symeres. The company's formulation services span preclinical developability, toxicology formulation development, pre-formulation screening, solid-state and salt/polymorph selection, solubility and bioavailability enhancement, excipient compatibility and development, and manufacturing of oral dosage forms.

"With DS and DP operations tightly integrated, we can iterate quickly, accelerate tech transfer and move programs efficiently into GMP manufacturing," he says. "This model provides biotechs with a faster, more predictable path from molecule to clinic."

In the case of one small-molecule solution formulation, Dr. O'Shea explains that it rapidly degraded and became discolored at room temperature, requiring storage at -20°C. An assessment of degradation pathways indicated that pH-dependent hydrolysis and oxidation were the primary mechanisms underlying this instability.

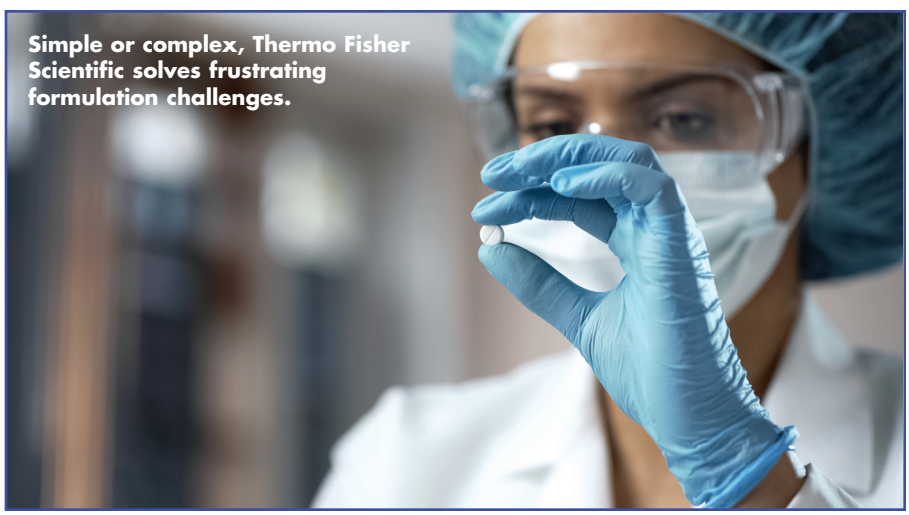
"By identifying an optimal pH range that balanced chemical stability and solubility, adding an antioxidant to limit oxidative reactions, and adjusting the co-solvent system to reduce hydrolytic stress, we improved the formulation's stability," he explains. "Formation of an inclusion complex with a suitable excipient further enhanced stability. These combined modifications enabled the formulation to maintain potency and appearance for six months at room temperature, supporting ambient storage and eliminating the need for cold-chain distribution."

Symeres is building a focused AI strategy centered on improving early development decisions, strengthening process understanding and enabling more predictive manufacturing. Priority areas include evaluating AI models that forecast solubility, stability and solid-state risks to guide salt and polymorph selection with fewer experiments.

Thermo Fisher Scientific: Saving API, Time & Money

The Pharma Services Group of Thermo Fisher Scientific through its Drug Substance and Drug Product Divisions offers a full range of pre-formulation drug substance characterization, salt and polymorph screening, preclinical candidate and technology selection using its AI/ML based OSDPredict® digital toolbox for poorly soluble and bioavailable new molecular entities.

Formulating poorly soluble drug candidates, developing complex APIs in once a day orally delivered patient-centric dosage forms is in high demand. Thermo Fisher Scientific has implemented AI/ML-based tools into predictive modeling and



Simple or complex, Thermo Fisher Scientific solves frustrating formulation challenges.

technology selection of poorly soluble candidates in the early IND stage of development, bringing high probability of success and saving API, time and cost in early development.

One Thermo Fisher Scientific customer faced the challenge of validating a dual API sourcing strategy for a late-phase commercial drug product while minimizing material use, timelines, and risk of scale-up failure. The recommended approach was a data-driven, risk-based validation using R&D compaction simulation and QbD studies to understand mechanical properties and predict scale-up performance, supported by targeted lab testing and regulatory guidance. As a result, they spared 144 kg of API (significant cost savings), accelerated time to market by ~3 months, and de-risked validation by confirming the design space and enabling right-first-time batches, explains Anil Kane, Senior Director, Global Technical and Scientific Affairs, Thermo Fisher Scientific.

In another example, a customer faced poor solubility and bioavailability of a DCS Class II compound with very limited API available and tight timelines for clinical trial material. The recommendation was to use a data-driven ASD strategy combining in-silico modeling (Quadrant 2®) to select a spray-dried intermediate (SDI) approach, followed by targeted prototyping, stability/PK evaluation, and scale-up to clinical manufacturing. As a result, development was streamlined with reduced experimentation and API use, SDI formulations significantly improved exposure versus crystalline API, stability was confirmed, and a lead formulation was successfully selected and scaled up for clinical trials.

UPM Pharmaceuticals: Supports Formulation Development & Manufacturing for Oral Solid & Semi-Solid Drugs

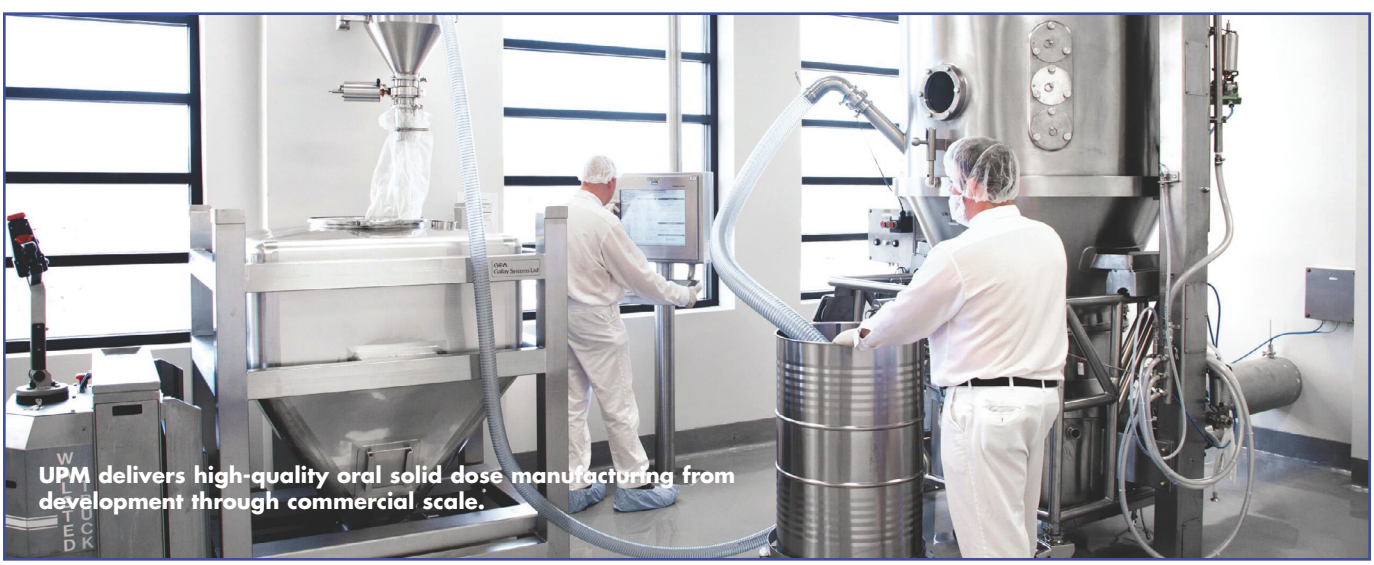
In the competitive CDMO market, one of the more important differentiators is continuity, ensuring that development decisions are made with commercial manufacturability in mind. In practice, that means placing a strong emphasis on process understanding and scalability early, particularly for modified-release and more complex formulations.

UPM Pharmaceuticals supports formulation development and manufacturing for oral solid dose and semi-solid drug products from early development through commercialization. This includes formulation and process development, analytical method development and transfer, scale-up, validation, and commercial supply.

Narayan (Kani) Kanikkannan, Vice President, Product Development & Technincal Operations, UPM Pharmaceuticals, explains how one client encountered dissolution variability during scale-up of a modified-release oral solid product, which introduced uncertainty ahead of late-stage development. A focused evaluation of formulation and process parameters suggested that coating uniformity and process controls were contributing factors. Adjustments were made to both the formulation and the coating process, with an emphasis on improving consistency and robustness. "The outcome was a more reproducible dissolution profile and a process that could be advanced into validation with greater confidence," he says.

Veranova: Enabling Formulation Strategies for Improved Drug Candidate Performance in Preclinical Studies

Under the Pharmorphix offering, Veranova designs and evaluates early preclinical formulations. The Enabling Formulation service explores non-GMP formulation strategies, including prototype formulations suitable for toxicology studies. These strategies include simple screening approaches, for example, co-solvents and liquid formulation vehicles, inclusion



UPM delivers high-quality oral solid dose manufacturing from development through commercial scale.

Veranova solid form and particle engineering scientists.

complexes, and the formation of salts or cocrystals. More complex approaches, such as nanosuspensions, lipid-based formulations, and amorphous solid dispersions (ASDs), can also be explored.

"Our strategy, guided by the initial physicochemical and solid form characterization data collected in-house, selects the most viable formulation development routes for exploration," explains Olana Couzins, Associate Director, Analytical Services, Veranova.

Veranova has witnessed a growing use of nanotechnology in recent years, particularly driven by the increasing prevalence of larger and more complex molecules. Nanoparticles play a key role in the delivery of injectable formulations, including long-lasting injectables. Other solubilizing approaches such as ASDs are being widely employed to increase the solubility of poorly oral-soluble APIs. Together, these strategies can address most of the bioavailability issues associated with insoluble drugs, particularly in the BCS Class II range. "Our solid form selection and enabling formulation services are delivered under one roof and with minimal material requirements, enabling faster project progression," she says.

One client was developing a non-ionizable compound with poor aqueous solubility, and was interested in identifying a solution to improve exposure of the compound in animal studies. Ms. Couzins explains that Veranova characterized the API to determine the most appropriate formulation routes. The API was first evaluated in key excipients and surfactants, showing limited enhancement of aqueous solubility using simple solution-based screening approaches. Then, nanomilling was evaluated to reduce particle size and increase dissolution rate. A nanosuspension formulation was identified with a suitable stability confirmed through determination of the zeta potential. The nanosuspension formulation was rechecked after 1 week by HPLC for purity and by XRPD for form change. After additional work, a lyophilized formulation (a few hundred mg) was shipped to the client, and the nanosuspension was reconstituted for their pharmacokinetic study.

"The API nanosuspension demonstrated greatly enhanced dissolution properties, to such an extent that our traditional online UV dissolution platforms were unable to capture it, and also generated new IP for the client," she says. ◆

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

CHEMOENZYMATIC LIGATION

Enabling Scalable, Sustainable Oligonucleotide Manufacturing

By: David Butler, PhD

INTRODUCTION

Nucleic acid technologies (NAT) are now a central focus of modern drug development. The success of mRNA vaccines and the growing number of small interfering RNA (siRNA) and single guide RNA (sgRNA) drugs in clinical pipelines are reshaping how the industry targets disease. siRNA and sgRNA are oligonucleotide modalities that allow the selective silencing or editing of disease-associated genes, opening new therapeutic avenues across cardiovascular, metabolic and genetic disorders.

This momentum, however, brings new manufacturing challenges. Achieving the required levels of purity, consistency and cost-efficiency at a commercial scale is increasingly difficult using conventional methods. Solid-phase oligonucleotide synthesis (SPOS), long the industry standard, now faces limits in scalability, sustainability and yield.

To meet future demand, developers are turning to next-generation approaches. Among these, chemoenzymatic ligation offers a practical and scalable bridge between traditional chemical synthesis and fully enzymatic methods. By combining the precision of enzymatic assembly with the flexibility of SPOS fragment production, this hybrid process enables high-purity oligonucleotide manufacturing at scale, while eliminating many of the inefficiencies of full-length chemical synthesis. In this article, David Butler, Chief Technical Officer at Hongene Biotech, explains how chemoenzymatic ligation can be implemented at an industrial scale and what it means for the future of oligonucleotide manufacturing.

WHY TRADITIONAL SPOS STRUGGLES TO MEET FUTURE DEMAND

The phosphoramidite-based SPOS method has been the foundation of oligonucleotide synthesis for nearly four decades. It remains highly effective for short, chemically modified sequences, but as the length and volume of oligonucleotides increase, its limitations become evident.[1]

SPOS is a batch-based process, typically yielding up to 10 kg per run and consuming large volumes of organic solvents and reagents. Scaling up requires multiple synthesis campaigns and batch pooling, driving up cost, complexity and environmental burden. As production scales, so too do sustainability and regulatory concerns.

Issues with SPOS are often most keenly felt when synthesizing long single-stranded oligonucleotides such as sgRNA and pegRNA. Each nucleotide addition during chain elongation introduces the risk of incomplete coupling and side reactions, leading to the formation of truncated sequences (shortmers) and other impurities that can accumulate through the synthesis cycle. These byproducts are difficult to remove during chromatographic purification, resulting in poor yield and issues with batch-to-batch consistency.

Market demand adds urgency. siRNA drugs targeting genes associated with cardiometabolic disease, such as PCSK9, AGT, LPA, HSD, APOC3 and INHBE, are advancing toward large patient populations, with projected global needs in the multi-ton range. SPOS, in its current form, is unlikely to support this level of commercial-scale output efficiently.

To meet this challenge, the industry needs platforms that pre-

serve the flexibility of chemical synthesis while enabling scalable, cost-effective and environmentally sustainable production.

THE EVOLUTION OF OLIGONUCLEOTIDE MANUFACTURING

Oligonucleotide manufacturing can be described in terms of three generations of technology.

Generation 1: Chemical synthesis. Traditional SPOS remains the industry standard for short chemically modified sequences. However, its limitations in scalability, yield and environmental impact become increasingly apparent as demand grows.

Generation 2: Chemoenzymatic ligation. A hybrid approach that begins with the synthesis of short oligonucleotide fragments using SPOS. These fragments are then enzymatically ligated to produce full-length sequences, delivering improved yield, reduced impurities and better process efficiency than full-length SPOS.

Generation 3: Enzymatic synthesis. A next-generation strategy that uses modified nucleoside triphosphates (NTPs) and engineered enzymes to build oligonucleotides, emulating cellular processes of DNA and RNA polymerization. Whilst not ready for industrial use, recent reports have demonstrated the potential of the technology to synthesize DNA2 and chemically modified RNA.[3,4]

Chemoenzymatic ligation stands out because it can be implemented today using established SPOS infrastructure to synthesize high-purity fragments with fewer chances for impurity formation. These fragments are then joined enzymatically, creating complete oligonucleotide products without the inefficiencies of full-length SPOS. The result is a scalable, modular and environmentally responsible process that fits seamlessly into current manufacturing environments.

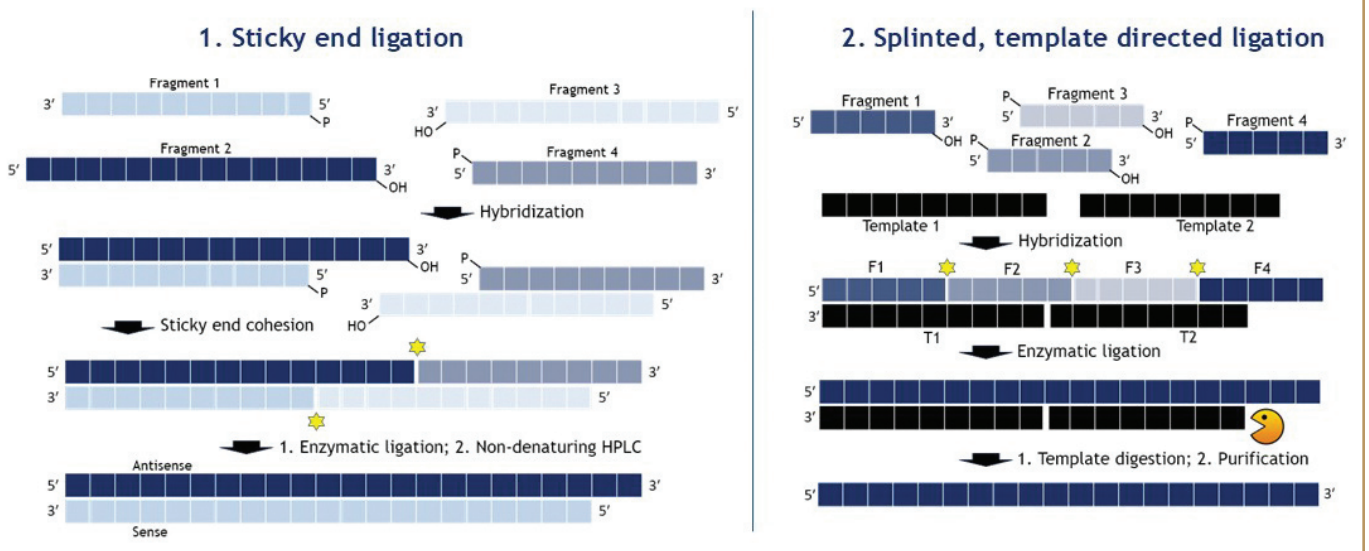
HOW CHEMOENZYMATIC LIGATION WORKS

Chemoenzymatic ligation combines the flexibility of chemical synthesis with the precision of enzymatic assembly. Short oligonucleotide fragments, also called blockmers, are synthesized by SPOS, purified, then joined in solution by ligase enzyme,[5] which catalyzes the formation of phosphodiester bonds between the terminal 3′-hydroxyl and 5′-phosphate groups of adjacent fragments.

A key strength of this approach lies in its selectivity. Only fragments with correctly positioned terminal groups serve as substrates, meaning that many of the truncated impurities that are common in SPOS are excluded from the final product, reducing the purification burden and improving final purity.

The ligation reactions are carried out in aqueous solution at concentrations up to 120 g/L, with parameters such as pH and temperature finely tuned to optimize efficiency and fidelity. Single-use bioreactors and batch reactors enable scalability within standard GMP manufacturing suites.

FIGURE 1



Ligation Strategies Employed at Hongene

Two chemoenzymatic ligation strategies have been the focus of development at Hongene (figure 1):

Sticky end ligation – Generally used for double-stranded oligonucleotides such as siRNA, this method uses complementary overhangs to align fragments before ligation.[6-8]

Splinted ligation – Applied to single-stranded molecules such as sgRNA and pegRNA, this approach uses short complementary DNA "splints" to align fragments and guide enzymatic assembly.[9,10]

Both processes are compatible with the chemical modifications widely used in therapeutic oligonucleotide production, including backbone modifications (phosphodiester, phosphorothioate, mesylphosphoramidate), ribose modifications (2′-O-methyl, 2′-fluoro) and conjugates such as GalNAc. As a result, chemoenzymatic ligation maintains compatibility with current drug designs while enabling the efficient manufacture of longer, more complex oligonucleotide molecules.

Both sticky-end and splinted ligation processes are also highly scalable. Because ligation occurs in solution, the process can be run in stainless steel or single-use bioreactors, enabling straightforward scale-up using equipment common to manufacturers. Yields are typically higher than full-length SPOS, as shorter fragments are easier to synthesize and purify and the enzymatic ligation step proceeds with near-quantitative conversion under mild, aqueous conditions. This results in higher purity, reduced solvent usage and a smaller environmental footprint, supporting more sustainable and cost-effective oligonucleotide manufacturing.

INNOVATION DRIVING THE NEXT PHASE OF MANUFACTURING

Chemoenzymatic ligation is a continuously evolving platform. Ongoing research is focused on enhancing scalability, reducing environmental impact and driving down cost. Current efforts target three core innovation levers:

Scalable fragment synthesis: Transitioning from flow-through synthesizers to batch or liquid-phase synthesis methods will increase capacity and reduce solvent use, making the system more compatible with large-scale manufacturing.

Elimination of chromatography: New workflows are being developed to bypass purification column chromatography. Early results suggest that "crude-to-purified" and even "crude-to-crude" ligation strategies can maintain product quality while significantly reducing material use and cost.

Engineered ligases: Thermostable ligases are being developed to operate efficiently at elevated temperatures. Conducting the reaction at higher temperatures reduces RNA secondary structure formation, which is hypothesized to improve ligation efficiency by enhancing the enzyme's ability to recognize and join fragments that are correctly aligned.

These innovations are not only advancing chemoenzymatic ligation but also laying the foundation for next-generation fully enzymatic RNA synthesis. As the field progresses, hybrid platforms will serve as a critical bridge between today's manufacturing needs and tomorrow's biologically inspired production systems.

REGULATORY READINESS & CMC ALIGNMENT

As manufacturing technologies for oligonucleotides change, regulatory expectations are also advancing in parallel. With chemoenzymatic ligation approaching wider clinical and eventually commercial application, clear global guidance is needed to define acceptable CMC practices.

One important regulatory consideration is how oligonucleotide fragments are classified within the manufacturing process, either as starting materials or GMP intermediates. This designation defines the level of GMP oversight and documentation required and is made in accordance with the principles outlined in ICH Q11.

Analytical comparability is another priority. Developers must demonstrate that the quality of ligation-derived oligonucleotides is well-controlled and comparable to those produced via traditional SPOS. Comprehensive analytical characterization, including impurity profiling and stereochemical analysis, supports this and helps de-risk regulatory submissions.

Analytical testing strategies must evolve to accommodate the chemoenzymatic manufacturing approach. For siRNA products, the sense and antisense strands are no longer synthesized separately, making individual-strand testing unfeasible. Instead, quality is assessed at the fragment level, with denaturing HPLC/MS methods used to identify and quantify single-strand components and their associated impurities within the duplex context.

Phosphorothioate stereochemistry is an increasingly scrutinized quality attribute in therapeutic oligonucleotide manufacturing. Differences in reaction conditions between SPOS and ligation-based processes

can influence the stereochemical distribution of the final product. HPLC and nuclear magnetic resonance (NMR) methods are used for demonstrating batch-to-batch consistency and establishing comparability between synthetic approaches.

The enzyme-based nature of chemoenzymatic ligation introduces a new critical quality attribute: residual enzyme content. Ensuring that enzymes used during ligation are of acceptable quality and effectively removed is essential. Trace enzyme levels can be detected and quantified using methods such as ELISA and MS to confirm compliance with established specifications.

TOWARD A SCALABLE & SUSTAINABLE OLIGONUCLEOTIDE MANUFACTURING ECOSYSTEM

Chemoenzymatic ligation represents a shift toward sustainable and scalable oligonucleotide manufacturing. By combining the precision of enzymatic ligation with the versatility of SPOS, this hybrid approach offers a practical path to consistent, cost-effective and environmentally responsible manufacturing. It enables developers to meet rising global demand without compromising on quality, control or speed.

A vertically integrated model, like that at Hongene, linking raw material production, ligation platform technology and CDMO services for both drug substance and drug product, addresses the growing need for supply chain cohesion and resilience. This approach can be a key competitive advantage.

Looking ahead, continued innovation in chemoenzymatic manufacturing is expected to strengthen process robustness and scalability, shaping how broadly chemoenzymatic assembly can be applied across different NAT applications. The focus now is on translating this manufacturing technology to support global therapeutic development and ensure patients have access to the life-changing medicines they need. ◆

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BIOGRAPHY

Dr. David Butler, Chief Technology Officer, has nearly two decades of experience in the oligonucleotide field. Prior to joining Hongene in 2023, he led organizations driving drug discovery and development of oligonucleotide therapeutics, most recently as Head of Chemistry at Korro Bio, Head of Therapeutics Development at Alltrna, and Head of Medicinal Chemistry at Wave Life Sciences. He began his career in oligonucleotides as a Principal Scientist at Alnylam Pharmaceuticals in 2007 developing early LNP technologies for siRNA delivery that were the progenitors of those used for mRNA related products today. He holds a PhD in Chemistry from the University of St Andrews, and is passionate about working with individuals and companies to help them succeed.

Drug Development
EXECUTIVE

Dr. Michalis Papadakis
Founder & CEO
Brainomix

Brainomix: AI Imaging Analysis in Drug Development

Dr. Michalis Papadakis, founder and CEO of AI Imaging company Brainomix shares how the company's AI Imaging software is supporting drug development in both retrospective analysis of trial data to more precisely identify clinical meaningful impact, and in prospective trials as AI biomarker endpoints.

Key Points - Brainomix has expanded its AI imaging services to support the clinical development of numerous novel therapies; both in stroke as well as lung fibrosis

Brainomix, a company founded in Oxford over 15 years ago as a spin-out from the University, began its journey by developing AI-powered imaging solutions for acute stroke assessment. By now, the Brainomix 360 Stroke platform boasts an extensive clinical footprint, supporting physicians in more than 350 hospitals across 20+ countries to detect and characterise stroke faster and more reliably, thereby significantly improving patient outcomes.

Since its inception, Brainomix has expanded its services to support the clinical development of numerous novel therapies; both in stroke as well as lung fibrosis, which are diseases with high mortality and significant unmet medical needs, with an opportunity for improved diagnosis and management through accurate imaging.

With data-trained and robustly validated biomarkers, a flexible service offering, strategic partnerships with leading pharmaceutical and device companies as well as imaging CROs, Brainomix has positioned itself as a leader at the forefront of digital innovation in the drug development sphere.

Q: Brainomix originally focussed on clinical adoption of AI imaging software in stroke. For the past few years, you have steadily increased your presence in the clinical development space. How would you say your clinical success has translated to clinical trials?

A: Yes – our foundation was always focussed on optimised care and outcomes for patients through improved medical imaging analysis. This remains our overall purpose, but this is clearly aligned with Life Sciences organizations, and working more closely with these partners through their entire development lifecycle has allowed us to realize our vision more effectively.

Our Life Science partners can also benefit from the data and evidence we have built over the years in the real-world clinical setting using our software.

For example, the success of our clinically implemented stroke software was recently highlighted by a study published in the Lancet Digital Health, which showed that Brainomix Stroke AI technology enabled more patients to access life-saving stroke treatments, much earlier.

Use of our stroke AI tool recently yielded successful results through our analysis of data from Argenica's Phase II trial of a neuroprotective agent in acute ischemic stroke: our digital biomarkers were able to confirm a significant treatment effect in severe stroke patients, supporting Argenica's continuation of its development program, and providing the opportunity for optimised future trial design in regards to specific patient selection, characterisation and efficacy determination.

We recently also announced two additional partnerships with Boehringer Ingelheim: a prospective multicenter study (*PROGRESS-PPF*) to enable earlier diagnosis of progressive pulmonary fibrosis; and another on their DROP-FPF study, a Phase III trial investigating the efficacy of Jascayd® in people with a family background of pulmonary fibrosis. This is a pivotal moment for the field as this study marks the first time a quantitative, digital HRCT biomarker is used as a co-primary endpoint in a Phase III pulmonary fibrosis trial, highlighting our partners' confidence in our imaging biomarkers, and the impact AI imaging can have for under-served therapeutic areas.

Q: Where do you see the greatest value of AI imaging analytics in guiding clinical development?

A: Many trials rely on accurate detection of clinically meaningful changes in relevant tissue – but studies show that even highly trained specialists struggle to recognize subtle signals of disease in CT images, and opinions often vary, making clear diagnosis very challenging. Our software, which has been trained on thousands of diverse real-world cases, provides quantitative assessment of even subtle changes, and at much earlier timepoints than the human eye. This reduces inter-physician variability, and through its reliable, highly sensitive biomarkers provides greater statistical power than traditional methods. For instance, our Brainomix 360 Stroke platform is able to make quantitative assessments of net water uptake as a characteristic of the severity of stroke damage, and the complex blood flow analysis we are able to do with perfusion imaging in stroke is not possible by radiologist visual assessment alone.

Q: One of your services includes retrospective analysis of historical data from completed clinical trials. How do you provide value in this area?

A: In clinical trials for example, for partners such as AstraZeneca, we performed a post-hoc analysis of their previously completed clinical trial in IPF; demonstrating our ability to extract new insights from existing data. The ability to almost go back in time with more advanced modern approaches is something that is very exciting now we have these types of AI technologies.

Any post-hoc findings of course need to be translated into prospective pre-specified analyses, which makes our work with companies like Argenica more impactful, where our blinded analysis and imaging quantification of their stroke study allowed them to make critical decisions regarding the viability of their asset.

Q: What are your other services, particularly for prospective trials?

A: We have a comprehensive suite of capabilities to support a long-term partnership for sponsors across all stages of drug development, and also in the delivery of treatments to patients in the real-world.

Where we can provide significant value for drug development is in the preparation and design of studies, using inputs into statistical design, selection of endpoints and thresholds for enrollment criteria. The high repeatability and sensitivity of our biomarkers also allows for reduced cohort sizes, which is particularly relevant for rare disease indications, and together this approach allows us to position our sponsor

partners to have confidence and clarity in their results.

In prospective studies, we can unlock unique opportunities through the use of our regulatory cleared software and biomarkers for clinical use, allowing us to provide relevant sites with the required software directly to inform enrollment decisions, including with automated flagging of eligible cases to investigators.

The use of clinical-grade software distinguishes Brainomix from other AI-imaging tools in the field, and the availability of Brainomix software in routine clinical practice also offers the unique opportunity to connect clinical trial findings with market access strategies for new and existing treatments in the real-world setting.

Q: How does Brainomix ensure its analyses are aligned with regulatory standards?

A: Given our deep roots in clinical practice, we are well-used to working in a secure and heavily regulated environment. For real-world clinical use, regulatory agencies consider our AI software as a medical device, and as such, we have an extensive Quality Management System (QMS) framework which is needed for us to achieve and maintain authorisation for provision of our software. To that end, our software and biomarkers are FDA cleared, and CE marked for clinical use.

In the context of clinical trials, these clearances by regulatory agencies have allowed us to give our partners confidence in our biomarkers, and we are seeing increased adoption in clinical trials, and the agencies appear to be open to further inclusion of these types of assessments to support clinical development.

In order to continue to make progress, we are partnering with like-minded clinical trial sponsors which are incorporating imaging endpoints into their trials. In this way we are working together to support their clinical development, but also to generate data which can support improved design for future trials across the field.

Q: What are Brainomix' strategic priorities over the next few years?

A: Ultimately, our vision will always have patients at the heart. Everything we do strives to improve patient outcomes, whether it be through adoption of our software in a clinical setting, or by supporting the development of treatments that address unmet medical needs. To this end, we are aiming to deliver value in existing and new partnerships with pharmaceutical companies developing novel treatments, and to provide them with tailored support for their clinical development.

We'll also be extending our current partnerships with clinical trial sponsors and CROs into new disease areas, and we are always open to working with new partners which are looking to integrate smart AI imaging into their development and service strategy.

We see the value we add in clinical trials as a continuum to what translates into clinical practice. The imaging criteria used in clinical trials define the guideline criteria when these new treatments translated into clinical adoption.

In the future, we aim to focus even more on clinical data integration for our biomarker development; this will boost the refinement of prediction and composite markers and it will expand our role in the digital innovation of the clinical trial sphere, for example through integration of digital control arms for trials.

Q: What should clinical trial sponsors consider when integrating AI imaging into clinical development programmes?

A: While we can help at all stages of clinical trials, early integration yields the greatest value. This allows imaging biomarkers and decision-support tools to be aligned with desired trial objectives, endpoints, and patient stratification strategies from the outset. Sponsors should also consider AI solutions that are thoroughly clinically validated, transparent, and developed under appropriate QMS processes.

To optimize the use of quantitative AI imaging tools, sponsors should also consider longitudinal imaging, with baseline, early, and late-time follow-up timepoints. This allows ideal tracking of disease progression, and highly sensitive AI-biomarkers can detect changes even at early timepoints, giving an indication of treatment trends throughout study duration.

The other consideration is that AI is a tool which at this stage should still sit within a human-reviewed environment and as one component of an overall development strategy. Sponsors should ensure that they work with a partner that understands the strengths and limitations of any algorithms, biomarkers or software that is incorporated into drug development strategies.

Finally, sponsors should consider scalability of AI solutions, including whether they have sufficient evidence, readiness and regulatory status for adoption and translation into clinical use.◆

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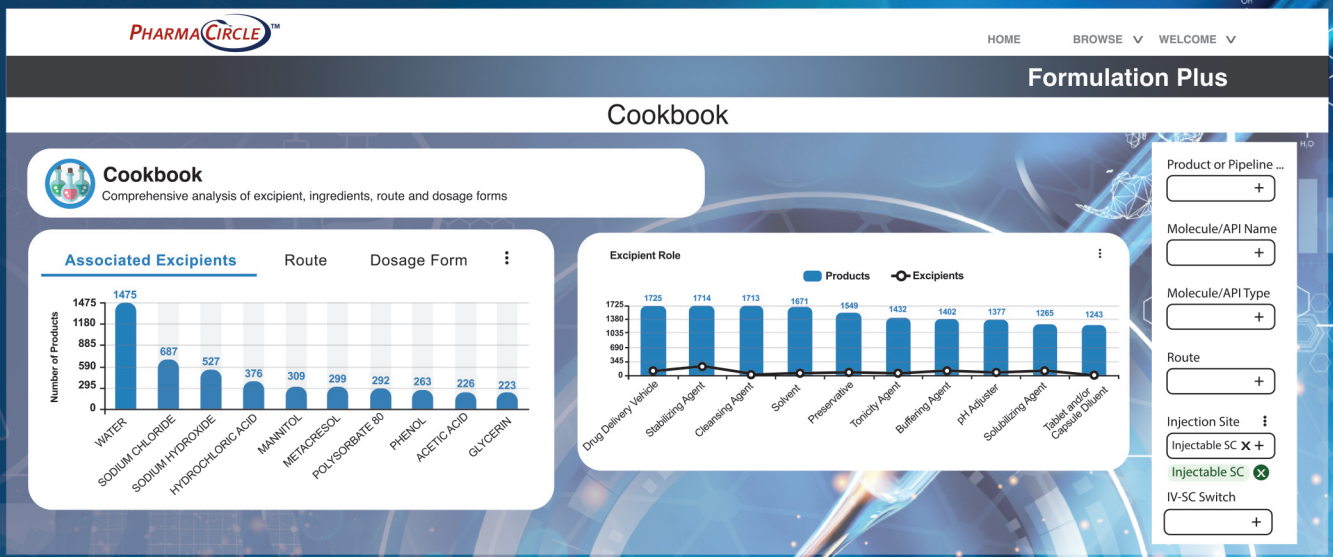

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DRUG DEVELOPMENT

Drug Combination Screening in Oncology: Advancing Predictive Strategies for Precision Drug Development

By: Jinying Ning, PhD

INTRODUCTION

Combination therapy has become a defining strategy in modern oncology drug development. Many cancers rely on redundant signaling pathways, adaptive resistance mechanisms, and dynamic tumor microenvironment interactions that limit the durability of single-agent therapies.[1] While targeted agents and immunotherapies have improved outcomes in specific patient populations, monotherapy responses often decline due to pathway compensation or acquired resistance.[2]

As a result, combination regimens now represent a substantial proportion of oncology clinical trials. However, empirical selection of drug pairs based on limited mechanistic assumptions has frequently led to additive toxicity without meaningful efficacy gains. Identifying synergistic interactions that translate into durable clinical benefit requires more systematic and predictive approaches.

Drug combination screening platforms aim to address this challenge by enabling high-throughput evaluation of compound pairs across biologically relevant models. When integrated with genomic annotation and mechanistic analysis, these systems support rational prioritization of therapeutic combinations and reduce translational uncertainty.

WHY SINGLE-AGENT PARADIGMS OFTEN FALL SHORT

Cancer biology rarely depends on a single dominant signaling pathway. Oncogenic drivers frequently coexist with compensatory networks that sustain proliferation and survival.[3] Inhibiting one node in a signaling cascade may temporarily suppress tumor growth, but adaptive responses can restore pathway output through alternative routes.

For example, inhibition of the MAPK pathway can trigger feedback activation of PI3K-AKT signaling, allowing tumor cells to maintain viability.[4] Similarly, blockade of immune checkpoints may be insufficient when tumors exploit additional immunosuppressive mechanisms within the microenvironment.

Single-agent screening strategies may identify potent inhibitors of isolated targets, yet they provide limited insight into combinatorial vulnerabilities. Consequently, development programs increasingly incorporate combination hypotheses early in preclinical evaluation.

PRINCIPLES OF DRUG COMBINATION SCREENING

Drug combination screening extends conventional high-throughput screening by testing compound pairs across defined concentration matrices. Rather than evaluating compounds individually, investigators assess interaction effects using dose–response surfaces and synergy models.[5] Key elements include:

- Matrix-based experimental design
- Multi-dose testing of each agent
- Quantitative synergy modeling
- Statistical validation of interaction effects

Common analytical frameworks, such as Bliss independence and Loewe additivity, quantify whether observed combination effects exceed predicted additive responses.[6] These models help distinguish true biological synergy from simple dose accumulation.

HIGH-THROUGHPUT PLATFORMS & MULTIPARAMETRIC READOUTS

Advances in automation, liquid handling robotics, and assay miniaturization have enabled large-scale combination screening with improved reproducibility.[7] Modern platforms evaluate hundreds to thousands of drug pairs across multiple cell models, generating high-dimensional datasets.

Beyond simple viability measurements, multiparametric readouts may include the following:

- Apoptosis markers
- Cell cycle distribution
- Pathway activation status
- Cytokine secretion
- Immune cell engagement

These layered datasets allow investigators to distinguish cytotoxic effects from mechanism-specific interactions. For example, a combination that enhances apoptosis without excessive off-target toxicity may represent a more promising candidate than one that reduces viability through nonspecific stress responses.

INTEGRATION OF GENOMIC & MOLECULAR ANNOTATION

Precision oncology increasingly depends on linking therapeutic response to tumor genotype.[8] Drug combination screening becomes more informative when integrated with genomic annotation of cell models.

By correlating synergy patterns with specific mutations, copy number variations, or pathway activation signatures, researchers can identify patient subpopulations most likely to benefit from a given combination.[9] This approach supports biomarker-guided trial design and reduces exposure of unresponsive patients to ineffective regimens.

For instance, tumors harboring KRAS mutations may exhibit enhanced sensitivity to specific MEK inhibitor combinations compared with wild-type counterparts.[10] Integrating molecular context strengthens translational relevance.

TRANSLATIONAL IMPLICATIONS FOR CLINICAL DEVELOPMENT

Many oncology trials fail due to insufficient efficacy despite strong preclinical rationale.[11] One contributing factor is inadequate modeling of tumor complexity during early screening.

Combination screening platforms can improve translational alignment by:

- Testing across diverse tumor subtypes
- Incorporating patient-derived models
- Evaluating immune cell interactions
- Identifying resistance pathways

When screening data inform early clinical hypotheses, trial design can incorporate rational dose selection and biomarker-driven stratification.

Furthermore, quantitative synergy metrics may guide regulatory discussions by providing mechanistic justification for combination strategies.[12]

ADDRESSING TOXICITY & THERAPEUTIC WINDOW

A frequent limitation of combination therapy is increased toxicity. Effective screening must therefore consider not only synergy but therapeutic window. Parallel testing in nonmalignant cell lines or organotypic systems helps evaluate differential sensitivity.[13]

Combinations demonstrating tumor-selective synergy with limited toxicity signals are more likely to advance successfully. Incorporating toxicity assessment during preclinical screening reduces late-stage safety surprises.

RESISTANCE MODELING & ADAPTIVE PATHWAY ANALYSIS

Drug resistance remains a primary obstacle in oncology. Screening platforms that incorporate longitudinal exposure models can identify combinations that delay or prevent resistance emergence.[14]

Mechanistic profiling of resistant clones may reveal secondary pathway activation that can be targeted through rational triple combinations or sequential regimens. This dynamic approach extends beyond static synergy analysis and better reflects clinical reality.

INTEGRATION WITH PREDICTIVE MODELING & DATA ANALYTICS

Large-scale combination datasets require advanced analytical frameworks. Machine learning approaches can identify interaction patterns not readily apparent through conventional statistical methods.[15] Predictive algorithms trained on synergy datasets may prioritize promising drug pairs for further validation.

However, computational modeling must remain grounded in biological interpretation. Data-driven predictions require experimental validation to confirm mechanism-of-action and therapeutic relevance.

Integrating high-throughput screening with structured analytics enhances decision-making efficiency while maintaining scientific rigor.

STRATEGIC VALUE IN COMPETITIVE ONCOLOGY LANDSCAPES

As oncology pipelines become more crowded, differentiation often depends on demonstrating superior combination efficacy or targeting resistant populations.[16] Systematic screening enables exploration of novel pairings beyond established standards of care.

In highly competitive therapeutic areas, combination strategies that demonstrate mechanistic rationale and biomarker linkage can provide strategic advantage. Early identification of synergistic interactions reduces dependence on empirical clinical experimentation.

RISK REDUCTION IN DRUG DEVELOPMENT

Bringing a new oncology therapy to market requires substantial financial and operational investment.[17] Attrition during Phase II or III trials significantly impacts portfolio performance.

Drug combination screening contributes to risk mitigation by:

- Improving hypothesis generation
- Supporting biomarker-informed stratification
- Reducing reliance on empirical pairing
- Strengthening preclinical rationale

When combination selection is supported by systematic screening and mechanistic validation, development decisions are more defensible, and data driven.

FUTURE DIRECTIONS

Emerging advances include incorporation of 3D tumor models, organoids, and co-culture systems that better reflect tumor microenvironment complexity.[18] Integration with immune-competent systems will further improve predictive accuracy.

As oncology shifts toward increasingly personalized treatment strategies, combination screening platforms that integrate molecular annotation, toxicity profiling, and predictive analytics will become central to development workflows.

SUMMARY

Combination therapy is no longer an optional strategy in oncology drug development. The biological complexity of cancer demands approaches that account for pathway redundancy, adaptive resistance, and tumor heterogeneity.

Drug combination screening provides a systematic framework for identifying synergistic interactions, linking response to molecular context, and reducing translational uncertainty. When integrated with mechanistic analysis and predictive modeling, these platforms support more informed therapeutic prioritization and improve the probability that preclinical findings translate into meaningful clinical outcomes. ◆

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BIOGRAPHY

Jinying Ning, PhD, is a biotechnology expert with a background in Environmental Science and Structural Biology. As an Executive at KYinno, she specializes in oncology drug discovery, focusing on immune treatments against cancer and next-generation kinase inhibitor design. With a passion for scientific innovation, Jinying is dedicated to advancing personalized oncology therapies and pushing the boundaries of cancer research.

SINGLE B CELL ANTIBODY DISCOVERY

Improving Therapeutic Candidate Selection in Drug Development

By: Changchun Zha

INTRODUCTION

Therapeutic antibodies now represent one of the fastest-growing classes of biologic drugs, with more than 100 monoclonal antibodies approved globally and hundreds more in clinical development.[1] Despite this success, early stage antibody discovery remains critical in drug development. Programs frequently advance candidates that later fail due to insufficient specificity, suboptimal developability, or incomplete characterization of binding properties.[2]

Traditional antibody discovery methods, including hybridoma technology and display-based libraries, have contributed substantially to therapeutic innovation. However, these approaches often involve artificial heavy- and light-chain pairing, multi-step screening funnels, and extended timelines that can delay candidate optimization.

As competitive therapeutic landscapes intensify, discovery platforms must do more than generate binders. They must enable early, sequence-defined, functionally relevant candidate selection that reduces downstream attrition.

Single B cell antibody discovery technologies address this challenge by directly isolating antigen-specific B cells and preserving their native heavy- and light-chain pairing. By capturing immune-selected clones at the single-cell level, these platforms improve molecular fidelity, accelerate recombinant expression, and strengthen confidence in early candidate selection.

LIMITATIONS OF CONVENTIONAL ANTIBODY DISCOVERY APPROACHES

Although hybridoma and phage display platforms remain widely used, they introduce structural and operational constraints that can affect translational predictability.

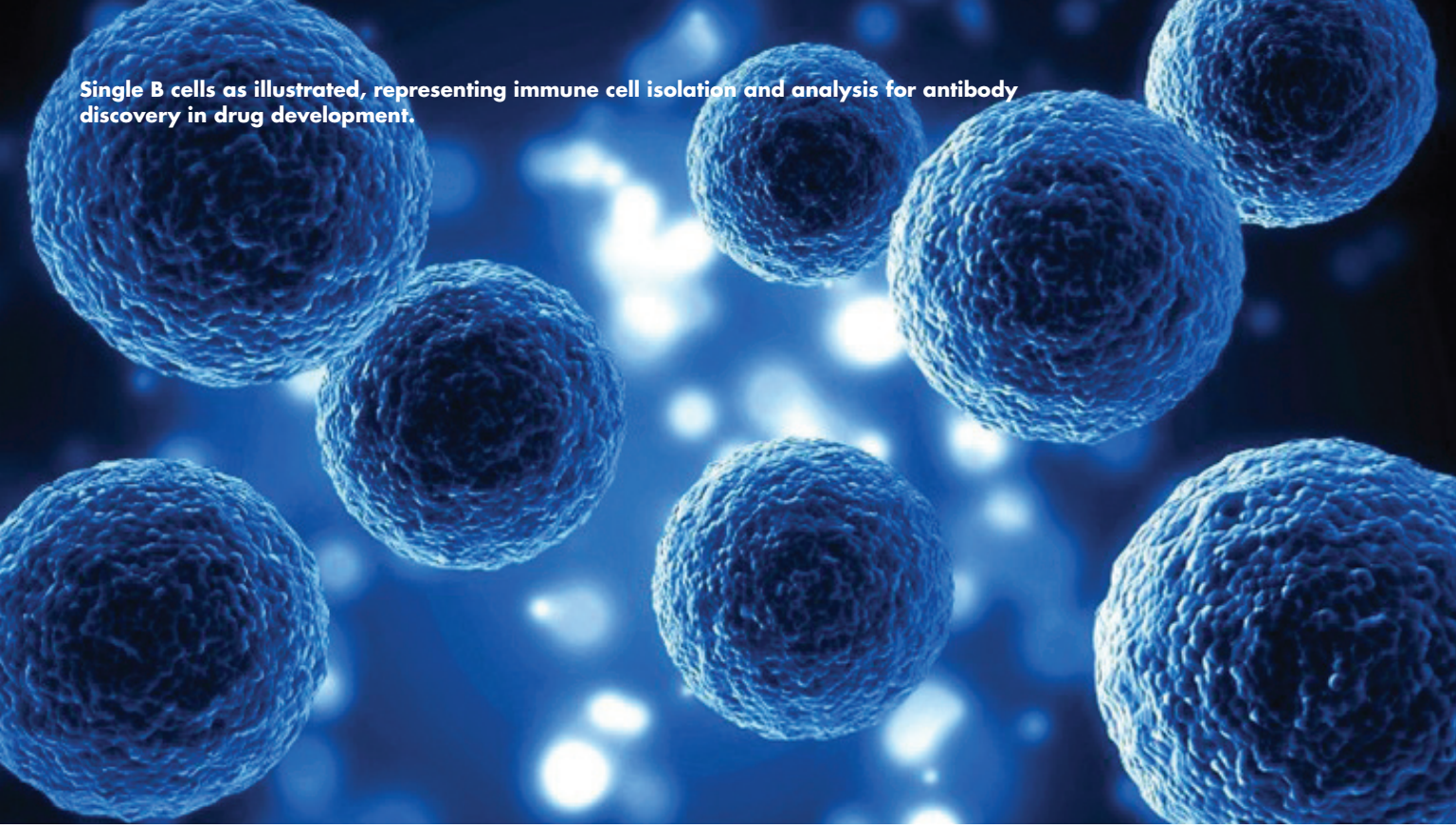
Hybridoma Technology

Hybridoma-based discovery relies on fusion between antigen-immunized B cells and immortalized myeloma cells, followed by clonal selection and expansion.[3] While robust, this method may result in clonal loss during fusion and screening. In addition, hybridoma-derived antibodies are not inherently sequence-defined unless subsequent sequencing is performed, introducing risk of lot variability or long-term reproducibility challenges.

Display-Based Libraries

Phage, yeast, and ribosome display technologies allow screening of large combinatorial libraries *in vitro*.[4] However, heavy and light chains are often paired artificially rather than reflecting natural immune selection. Artificial pairing can generate antibodies that bind *in vitro* but lack functional stability or developability in therapeutic contexts.

Moreover, multi-stage panning and enrichment steps may introduce bias toward high-affinity binders that are not necessarily optimal for *in vivo* performance. These factors can increase downstream engineering requirements and delay clinical advancement.



Single B cells as illustrated, representing immune cell isolation and analysis for antibody discovery in drug development.

DIRECT CLONAL CAPTURE: THE PRINCIPLE OF SINGLE B CELL TECHNOLOGIES

Single B cell antibody discovery platforms isolate individual antigen-specific B cells using fluorescence-activated cell sorting (FACS), microfluidics, or droplet-based systems.[5] Once isolated, paired heavy- and light-chain genes are amplified directly from each cell and cloned into recombinant expression vectors. This approach preserves the following:

- Native heavy/light chain pairing
- *In vivo* affinity maturation signatures
- Natural immune selection pressure
- Sequence traceability

Eliminating artificial pairing and hybridoma fusion steps, single-cell methods streamline discovery and reduce clonal ambiguity.

IMPACT ON EARLY THERAPEUTIC CANDIDATE SELECTION

Early candidate selection strongly influences downstream drug development success rates. Studies suggest that a significant proportion of biologic attrition occurs due to target biology uncertainty and molecular developability liabilities.[6] Single B cell platforms strengthen early-stage confidence in several ways.

Sequence Definition From the Outset

Each recovered antibody sequence is defined at the genetic level before large-scale expansion. This reduces batch-to-batch variability and supports intellectual property positioning, regulatory documentation, and long-term reproducibility.[7]

Improved Developability Profiling

Because recombinant antibodies can be expressed rapidly after sequence recovery, early stage profiling can include:

- Aggregation propensity
- Thermal stability
- Expression yield
- Liabilities such as deamidation or oxidation

Early integration of developability assessment reduces the risk of advancing unstable candidates into costly preclinical programs.[8]

Functional Screening at the Single-Cell Level

Some Single B cell platforms allow secretion-based screening prior to gene recovery. This enables selection of clones based not only on binding, but on functional attributes such as blocking activity or receptor modulation.[9]

APPLICATIONS IN ONCOLOGY & IMMUNE-MEDIATED DISEASES

Single B cell discovery is particularly relevant in oncology and autoimmune disease programs, where antigen specificity and functional precision are critical.

Tumor-Associated Antigens

In cancer research, identifying antibodies that distinguish tumor tissue from healthy tissue is essential for minimizing off-target toxicity.[10] Single B cell methods allow screening against complex antigens, including membrane proteins and conformational epitopes that are challenging for display systems.

Rapid Response to Emerging Targets

For emerging disease targets or rapidly evolving antigens, speed is a competitive advantage. Direct clonal capture shortens discovery timelines, enabling faster progression from immunization to recombinant candidate evaluation.[11]

Autoimmune & Inflammatory Targets

High-specificity antibodies are necessary to avoid cross-reactivity with structurally related proteins in immune-mediated disorders. Native pairing preservation increases the likelihood of physiologically relevant binding profiles.[12]

INTEGRATION WITH DEVELOPABILITY & CMC CONSIDERATIONS

Drug Development & Delivery audiences are increasingly focused on reducing Chemistry, Manufacturing, and Controls (CMC)-related risk early in development. Antibody discovery cannot be isolated from manufacturing considerations. Single B cell discovery supports:

- Early sequence analysis for manufacturability
- Humanization strategy planning
- Framework liability identification
- Reduced re-engineering cycles

Sequence-defined antibodies facilitate smoother transition into cell line development, process optimization, and scale-up.[13] When discovery and developability assessment are integrated rather than sequential, the probability of late-stage failure decreases.

COMPETITIVE ADVANTAGE IN CROWDED THERAPEUTIC LANDSCAPES

In highly competitive areas, such as PD-1/PD-L1 targeting or HER2-directed therapies, differentiation often depends on subtle differences in epitope binding or functional modulation.[14] Single B cell discovery can:

- Enable epitope diversity
- Capture rare clones
- Reduce screening bias
- Improve functional candidate diversity

Preserving immune-driven clonal selection, these platforms may uncover unique binders that are missed in artificial library systems.

TRANSLATIONAL IMPACT & RISK REDUCTION

Biologic development carries substantial financial risk. Industry analyses estimate that bringing a new biologic to market can exceed $1 billion in total investment.[15] Reducing early stage molecular uncertainty is therefore a strategic priority. Single B cell antibody discovery contributes to risk reduction by:

- Improving molecular traceability
- Reducing re-engineering cycles
- Enabling earlier functional validation
- Supporting regulatory documentation with sequence clarity

These advantages align with increasing regulatory expectations for transparency and reproducibility in biologics development.[16]

ACCELERATING THE PATH FROM DISCOVERY TO CLINICAL SUCCESS

Advances in microfluidics, single-cell sequencing, and high-throughput screening are making antibody discovery faster and more precise. When paired with AI-supported sequence analysis, these tools help researchers identify promising candidates earlier, assess their potential with greater confidence, and reduce costly setbacks later in development.

As therapeutic pipelines become more complex, technologies that combine biological relevance with molecular accuracy are shifting from helpful additions to essential capabilities. Single B cell antibody discovery supports this transition by capturing naturally occurring antibodies, preserving native chain pairing, and producing sequence-defined candidates from the beginning.

Stronger clinical outcomes start with better discovery decisions. By enabling direct clonal recovery and early insight into developability, Single B cell platforms help teams focus on candidates with a higher likelihood of success. The result is a more efficient development process, reduced risk across programs, and a clearer path toward clinical advancement. ◆

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BIOGRAPHY

Changchun Zha is the Founder and CEO of Biointron, specializing in antibody discovery technologies, including Single B cell screening, hybridoma sequencing, and recombinant antibody production. With experience supporting therapeutic antibody programs across oncology and immune-mediated diseases, he focuses on improving molecular traceability and discovery efficiency in biologics development.

DRUG DELIVERY

Improved Prediction of Food Effect on Oral Absorption

By: Balint Sinko, PhD

INTRODUCTION

Oral administration is the most common route of drug delivery due to the convenience, relative cost-effectiveness, and ease of administration. Whether an oral drug is taken in a fed or fasted state can markedly affect bioavailability and how much of the drug reaches the systemic circulation. The "food effect" describes the extent to which food influences drug absorption and can be positive, negative, or zero.[1] Properties of the active pharmaceutical ingredient (API) and its formulation can also contribute to the food effect.

Dosage instructions regarding food intake in conjunction with orally administered drugs are determined through clinical studies, which assess the impact of food on drug absorption.

A variety of theoretical and empirical prediction schemes for food effects based on the physicochemical properties of drugs have been reported. In addition, various *in vitro* dissolution-permeation experiments have been applied to predict food effects.

This article describes methods for predicting food effects using *in vitro* dissolution-permeation devices, as reported in peer-reviewed publications. Unlike the use of dissolution data alone, the addition of permeation data can accurately predict positive and negative food effects.

THE BILE-RELATED FOOD EFFECT

Gastrointestinal conditions in the fed state differ from those in the fasted state.[2] For example, the concentration of bile micelles is about 5-fold higher in the fed state compared to the fasted state.[3] Bile micelles are tiny, water-soluble aggregates of digested lipids and bile salts that transport fat-soluble nutrients to the intestinal wall for absorption. They affect the dissolution, supersaturation, and precipitation profiles of drugs[4] and impact their effective intestinal permeation.[5]

The higher concentration of bile salts in the fed state aids the solubilization of poorly water-soluble drugs through micelle formation.[6] This solubilization, however, may not always increase oral absorption. Bile micelles may entrap and reduce the free drug concentration available at the epithelial membrane (EPM) surface. Micelle formation may also reduce the diffusion coefficient of the drug in the unstirred water layer (UWL) adjacent to the epithelial membrane, leading to a decrease in effective permeability.

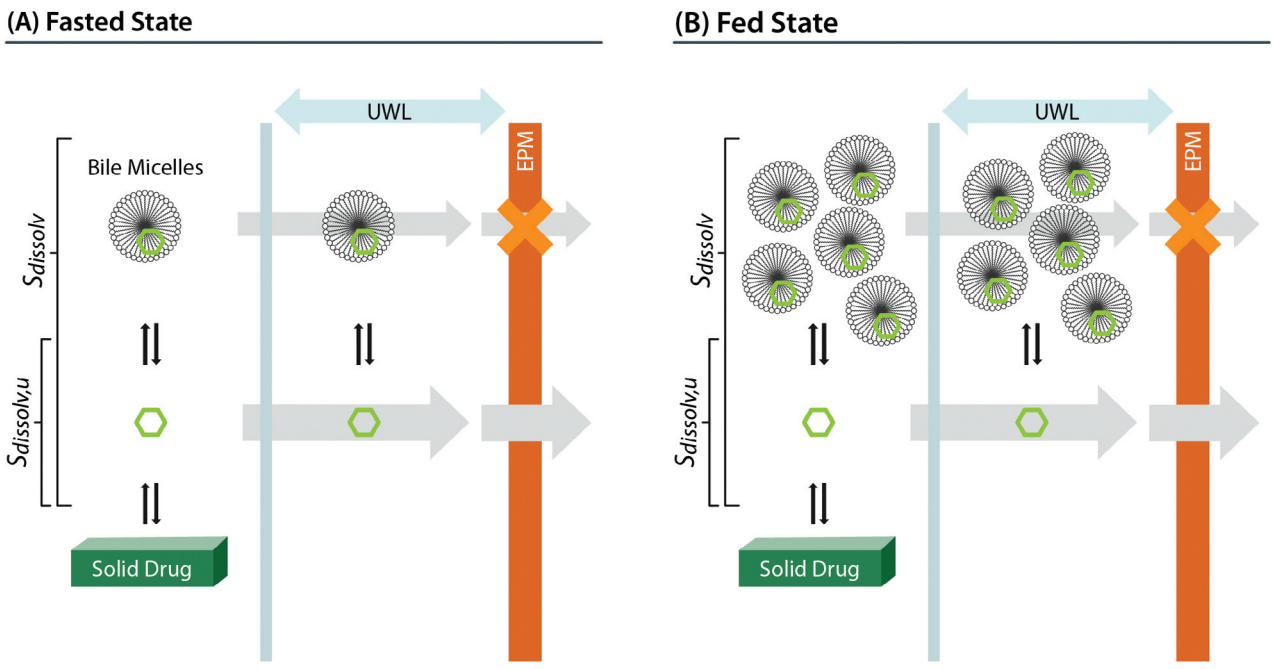
The food effect depends on the rate-limiting step for absorption. The Fraction absorbed Rate Limiting Step (FaRLS) classification categorizes oral drug absorption into five classes: dissolution rate limited (DRL), epithelial membrane permeation limited (PL-E), unstirred water layer permeation limited (PL-U), solubility – epithelial membrane permeation limited (SL-E), and solubility – unstirred water layer permeation limited (SL-U).

In a bile micelle-containing environment, drug molecules exist as bile micelle-bound and unbound species in rapid equilibrium (Figure 1). The solubility of a drug ($S_{dissolv}$) is the sum of the concentrations of these species ($S_{dissolv,u}$ and $S_{dissolv,b}$) in equilibrium with a solid-state drug. An increase in bile micelles increases $S_{dissolv,b}$ and $S_{dissolv}$. However, the concentration of unbound (free) drug remains the same ($S_{dissolv,u}$).

Both bile micelle-bound and unbound drug molecules can permeate the UWL adjacent to the EPM, whereas only unbound (free) drug molecules can permeate the EPM (according to free drug theory).

In the case of SL-E drugs, the permeation is not increased even when $S_{dissolv}$ is increased by bile micelles because the free

FIGURE 1



Bile micelle solubilization and permeation in a fasted state (A) and a fed state (B). The width of the grey arrows indicates the permeation coefficient of a drug across the unstirred water layer (UWL) and epithelial membrane (EPM) (dimension: length/time). For SL-U cases, the overall absorption will increase in Fed State due to the permeation of bile micelles through UWL, while the absorption will remain the same for SL-E cases as the process is rate limited by EPM permeation.

drug concentration remains the same (= $S_{dissolv,u}$). In other words, an increase in $S_{dissolv}$ by bile micelles is cancelled out by a decrease in the "effective" permeation coefficient (P_{eff}), which is defined based on the total drug concentration dissolved in the intestinal fluid. Fraction absorbed (*Fa*) and flux value (*J*) are proportional to $S_{dissolv}P_{eff}$.

Various *in vitro* dissolution-permeation experiments have been investigated for food effect prediction. While SL-U drugs were mainly used as model drugs in these studies, little is known about the applicability of these systems for SL-E drugs. One study[7] showed that the food effect on *Fa* of pranlukast can be appropriately predicted by the dissolution/permeation system; no other studies of SL-E have been reported.

OVERVIEW OF EXPERIMENTAL DESIGN

A complete description of the materials and methods used in this study, as well as the physicochemical properties of the model drugs, can be found in Higashiguchi, et al.[8]

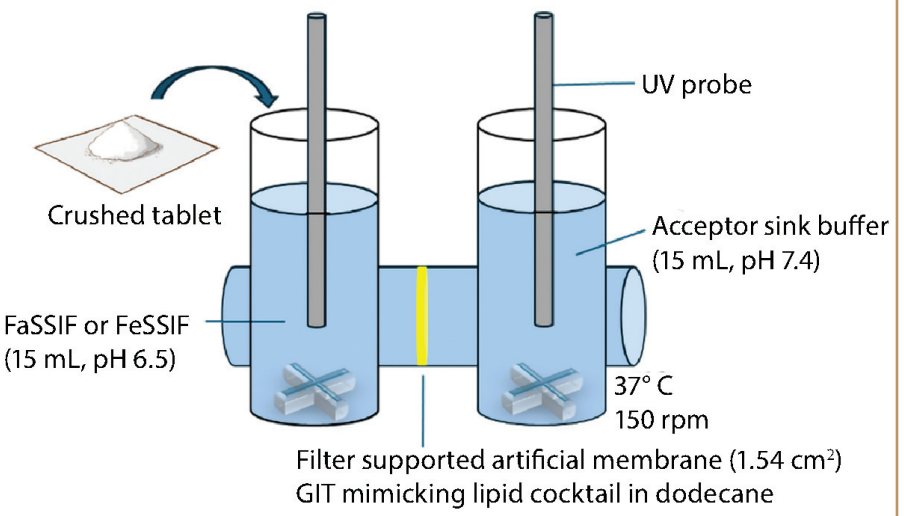
Bosentan, fidaxomicin, pranlukast, and rifaximin were employed as model SL-E drugs while celecoxib and danazol served as model SL-U drugs. Bosentan, fidaxomicin, and rifaximin are beyond-rule-of-five (bRo5) drugs. An increasing number of bRo5 drugs, including over 30% of approved kinase inhibitors, are reaching clinical trials and FDA approval and about half of small molecules targeting protein-protein interactions fall into the bRo5 category.[9]

The food effect for SL-E drugs was predicted based on FaRLS. Dissolution-permeation experiments performed in a MicroFLUX device were then used to further understand the mechanism of the food effect by bile micelles (Figure 2).

The Pion MicroFLUX is a small-volume, *in vitro* dissolution-permeation apparatus designed to simulate drug absorption by measuring the movement of compounds across a biomimetic lipid-coated artificial membrane, which separates a donor chamber (containing the sample) and an acceptor chamber (representing the blood). It allows for continuous, real-time measurement of drug concentration in both chambers, enabling detailed assessment of drug dissolution, permeation, and the effects of different formulation strategies and excipients

Fasted and fed state simulated intestinal fluids (FaSSIF and FeSSIF, respectively) were used as the donor solution in the device. Each drug formulation in a biorelevant dose to volume ratio was added after

FIGURE 2



MicroFLUX device used to perform dissolution-permeation experiments

the tablets were gently crushed using a mortar and pestle. The drug concentrations in the donor (C_D) and acceptor (C_A) solutions were monitored using a UV probe for 2 h, except for pranlukast, which was monitored for 4 h. The flux value (*J*) was calculated from the slope of the drug concentration-time curve in the acceptor solution in the last 30 min.

RESULTS & DISCUSSION

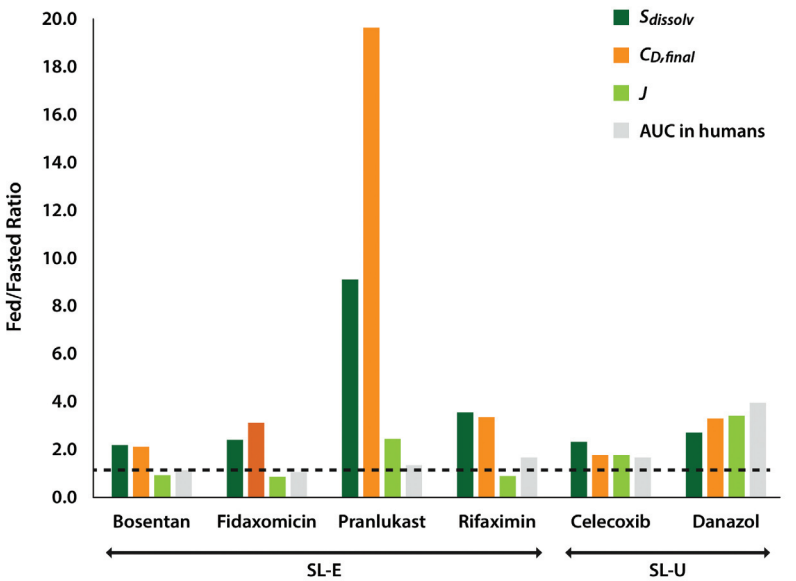
Food effect prediction by solubility ratio, dissolution ratio, and dissolution-permeation results.

Figure 3 compares the fed/fasted ratios of $S_{dissolv}$, $C_{D,final}$, *J*, and the clinical area under the plasma concentration-time curve (AUC). $S_{dissolv}$ data (dark green) represents the ratio of the solubility measured in fed and fasted conditions. The $C_{D,final}$ (orange) is the ratio of the donor concentration in the dissolution-permeation assay measured in fed and fasted conditions. *J* (light green) is the flux through the membrane of the MicroFLUX. The dissolved drug concentration in the donor fluid (C_D) was significantly increased in FeSSIF compared to FaSSIF in all cases. In the case of SL-E drugs, absorption was lower or less affected.

In the case of rifaximin, significant supersaturation was observed in the dissolution data in the early time points. However, there was little difference in absorption between FaSSIF and FeSSIF, suggesting that the unbound drug concentrations in FaSSIF and FeSSIF were the same in the supersaturated state. In the case of SL-U, the increase in C_D in the fed state condition translated to an increase in absorption, in good agreement with previous findings.

Overall, these findings highlight that reliance solely on solubility data can overpredict the food effect, while predictions based on dissolution-permeation data are more closely aligned with the *in vivo* results (AUC).

FIGURE 3



Comparison of the fed/fasted ratios of $S_{dissolv}$, $C_{D,final}$, *J*, and clinical area under the plasma concentration–time curve (AUC). The dotted line is the predicted *Fa* ratio for SL-E (ratio = 1.2). All data are ratios of a particular parameter measured under a fed versus fasted condition. $S_{dissolv}$ data (dark green) represents the ratio of the solubility measured in fed and fasted conditions. The $C_{D,final}$ (orange) is the ratio of the donor concentration in the dissolution-permeation assay measured in fed and fasted conditions. *J* (light green) is the flux through the membrane of the MicroFLUX. The ratio of $C_{D,final}$ can therefore be higher than the $S_{dissolv}$ value.

LARGE-SCALE DISSOLUTION/PERMEATION STUDIES

In addition to the smaller volume MicroFLUX and MiniFLUX devices, which are typically used in earlier development, large volume dissolution-permeation devices such as the BioFLUX and MacroFLUX are well-suited for later-stage development where full tablets or capsules can be used in the assay without having to be crushed.

A combined dissolution-permeation evaluation using the full-scale MacroFLUX device to estimate the direction and extent of food effects observed in the clinical setting for several BCS Class II and Class IV drugs with different underlying food effect mechanisms was published by Novartis in 2025.[10]

BCS Class II drugs, typically falling into the SL-U class, have high intestinal permeability, meaning they can easily pass through cell membranes, but low aqueous solubility, meaning they do not dissolve readily in water. Class IV drugs, typically falling into the SL-E class, have low aqueous solubility and low intestinal permeability, making oral delivery relatively challenging.

In the published study, food effects were accurately predicted for 60% of drugs within 1.25-fold based on dissolution-permeation analysis, compared to 30% when only dissolution analysis was used, as summarized in Table 1. Of the ten compounds evaluated, only five displayed the same direction of food effect compared to clinical studies based on dissolution results alone, while nine compounds aligned with the direction based on dissolution-permeation data analysis. Use of dissolution alone did not identify any of the negative food effects. The study also showed that the assumption that compounds exhibiting a positive food effect due to increased dissolution/solubility from fasted to fed state does not always hold.

Upon further analysis of the Remibrutinib data, it was found that there was no clinically relevant food effect observed for

TABLE 1

Compound	In vivo food effect		Prediction accuracy	
API	C_{max} ratio	AUC ratio	$C_{dissolution}$ ratio	Flux Ratio
Asciminib	Negative	Negative	✗	✓
Dabrafenib	Negative	Negative	✗	✓
Eltrombopag	Negative	Negative	✗	✓
Iptacopan	None	None	✓	✓
Lapatinib	Positive	Positive	✓	✓
Nilotinib	Positive	Positive	✓	✓
Palbociclib	Positive	Positive	✓	✓
Remibrutinib*	Positive	None	✓	✗
Ribociclib	None	Positive	✓	✓
Trametinib	Negative	Negative	✗	✓

Positive: Fed to Fasted ratio more than 1.25, None: Fed to Fasted ratio between 0.08 and 1.25, Negative: Fed to Fasted ratio less than 0.08.

Assessment of the direction of the food effect for the ten drugs evaluated in the study. *Dissolution testing of Remibrutinib predicted a strong positive food effect, while dissolution-permeation analysis revealed a negative effect that aligned much more closely with clinical results showing no clinically meaningful food effect.

Remibrutinib due to a marginal fed/fasted ratio. Dissolution-permeation results predicted a negative food effect with a fasted/fed ratio of 0.53, while the dissolution results predicted a significant positive effect (4.08). Based on this finding, the study authors conclude that the predictions from dissolution-permeation studies were closer to clinical data compared to dissolution results. Overall, the MacroFLUX device was confirmed to be a valuable tool that can predict clinical food effects, support formulation development, and guide the design of clinical pharmacology studies.

CONCLUSION

The data described above demonstrate that evaluating both dissolution and permeation is essential for accurately predicting food effects, particularly for SL-E and SL-U drugs. FaRLS theory provides the mechanistic basis for understanding why increased solubility in the fed state does not always result in increased absorption because, although bile micelles can enhance total solubility, they often reduce the free drug fraction available to cross the epithelial membrane. This balance explains why dissolution data alone may suggest a positive food effect, while dissolution-permeation measurements more closely reflect clinical outcomes.

The Remibrutinib case clearly illustrates this distinction. Dissolution testing predicted a strong positive food effect, yet dissolution-permeation analysis revealed a marginal negative effect that aligned much more closely with clinical results showing no clinically meaningful food effect. This example underscores the limitations of relying solely on dissolution data and highlights the value of incorporating permeation into predictive models.

By coupling mechanistic theory with experimental systems such as Pion's MicroFLUX, MiniFLUX, BioFLUX and MacroFLUX devices, drug developers can gain a more accurate, clinically relevant understanding of food effects. This integrated approach not only reduces the risk of an incorrect prediction but also supports formulation optimization, improves the design of clinical pharmacology studies, and ultimately helps accelerate the development of orally administered therapies, including challenging bRo5 compounds. As demonstrated here, dissolution-permeation analysis is a powerful complement to dissolution testing, providing a predictive framework that bridges *in vitro* studies with *in vivo* outcomes and strengthens decision-making throughout the drug development process. ◆

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BIOGRAPHY

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DRUG-DEVICE COMBINATION PRODUCTS

Incorporating Self-Administered Drug-Device Combination Products Into Clinical Trials Can Bring Outsized Challenges & Outstanding Rewards

By: Laura Zurlinden

INTRODUCTION

The self-administered injectable drug-device combination (DDC) product market finds itself in the beginning stages of unprecedented therapeutic advancements. And all easy pharma buzzwords aside – "revolutionary," "breakthrough," "dedicated expertise" – the overarching reason for this paradigm shift boils down to one word: Necessity.

This new dawn for DDCs is addressing healthcare's horizon. And while it certainly may be revolutionary, first and foremost it is preparatory.

In the US alone, the number of people over 50 with at least one chronic disease is expected to nearly double over the next three decades, increasing from 71.5 million in 2020 to 142.7 million by 2050. Much of this is inevitable, as Baby Boomers and Gen Xers first enter their golden years, then live deeper into them.

Rarely is the economic principle of supply and demand so predictable. With demand for streamlined therapeutic solutions all but guaranteed to increase for the foreseeable future, it's little wonder why those designing and supplying DDCs are responding with improvements in usability, convenience and safety. Fortunately, these advancements have guideposts, as established self-administration treatments for prevalent conditions such as diabetes inform therapies for more varied illnesses across smaller patient populations.

The current and projected market figures back this up – and then some. In 2023, the global drug-device combination products market was valued at approximately USD $138 billion; by 2030, the market is expected to nearly double to $252 billion, reflecting a 9.0% compound annual growth rate (CAGR). Considering this, self-administered injectable DDCs have emerged as a keystone technology toward upgrading drug delivery, enhancing patient compliance, and optimizing health outcomes.

Unsurprisingly, part of this effort involves incorporating DDCs into medication regimens right from the outset: during clinical trials. However, leveraging self-administered parenteral applications in clinical studies requires a strategic approach to address various design, regulatory, user-centric and scalability challenges.

TOGETHER FROM THE START: CLINICAL TRIAL BENEFITS OF DDCS

Traditionally, single- or multi-use vials have been the primary container of choice for subcutaneous drug administration during preclinical and early-phase clinical trials. These vials offer significant flexibility in terms of fill volume and dosage, aligning with the primary objectives of early trials: establishing proof of concept, ensuring safety, and determining tolerated doses.

However, with growing emphasis on patient-centricity and the increasing prevalence of self-administration devices in treating chronic diseases, the industry is shifting toward less skill-de-

pendent subcutaneous dosage forms. In this environment, prefilled syringes, passive safety needle devices and autoinjector delivery systems are becoming integral aspects of product portfolios. Promisingly, several prominent biopharmaceutical companies are actively investing in research and development to enhance device functionality, ensure compatibility with a wide range of drug molecules, and incorporate these devices into clinical trials earlier in the development process.

Of the myriad benefits to utilizing DDCs in clinical trials, improved patient compliance and retention may be the most substantial. Self-administration simultaneously reduces dependency on healthcare professionals and empowers patients to literally take matters into their own hands. Such convenience can increase adherence to trial protocols, particularly in long-term studies where frequent clinic visits might otherwise lead to elevated dropout rates.

Dosage standardization is another significant plus. Prefilled injectables deliver precise and consistent doses, minimizing human error associated with traditional syringe-based methods. Such commonality is crucial for ensuring accurate pharmacokinetic and pharmacodynamic data. And to offset any potential verification shortcomings stemming from unmonitored administration, many DDCs can be equipped with technology that captures dosing events, up to and including exacting timestamps.

Finally, DDCs uplift the overall clinical trial experience – for both patients and trial sponsors. For the former, user-friendly designs, minimal pain and reduced injection-related anxiety contribute to more positive experiences, fostering greater engagement throughout the trial. For sponsors, injectable DDCs provide real-world insights

by mimicking post-market applications. Whereas conventional clinical trials offer a controlled environment for the drug, clinical trials incorporating DDCs do so for both the drug and its usage scenarios, providing real world data and evidence supporting regulatory decisions and improving patient care.

However, these advantages are earned rather than bestowed. Incorporating injectable DDCs into clinical trials requires meticulous, multifactor planning and evaluation. Implementing any sophisticated process brings a checklist of challenges, and clinical trials utilizing DDCs are certainly no exception.

DDCS FOR CLINICAL TRIALS: A CHALLENGES CHECKLIST

Any drug-device combination product intended for self-administration must be designed with laypersons in mind. This holds especially true for clinical trials, since participants often comprise varying levels of dexterity and familiarity with drug-device combination products.

For the sake of streamlining, let's focus on autoinjectors for the moment. Concerning ergonomics, autoinjectors must be easy to handle and operate for diverse populations, including those with limited dexterity and vision impairments. Ideally, clinical trial participation should be seen as a subset of the ever-broadening push for inclusivity in medication accessibility.

Notably, ergonomics best practices should extend to the mind: intuitive operation is vital, with elements like two-step or three-step usage, audible clicks and visual and tactile feedback serving situation-specific roles. The simpler the self-administration, the more exacting the trial results.

A suitable device/drug pairing also is key. Devices should align with a drug product's particular requirements regarding viscosity, dose volume and injection speed. For example, high-viscosity biologics require autoinjectors with sufficient force for effective drug delivery. And with any self-injecting device, stability testing must prove that its materials do not interact with the formulation, and work to maintain the drug's stability throughout its intended shelf life.

Regarding delivery speed, assessments beyond overall drug-device compatibility should extend to more nuanced considerations, such as striking an ideal balance between patient comfort and optimized drug delivery. Crucially, in line with ISO 11608-5 standards the device also must consistently deliver the intended dose, especially for biologics where dosing precision is critical.

All totalled, such painstaking match-

making exercises are reminders that the "C" in DDC stands for "combination." Indeed, a drug and its vehicle must be viewed as inextricably intertwined, for the sake of both medication efficacy generally and reliable trial results specifically.

Of course, this commonsense approach to device selection should also extend to those using them – and often, considerations involving trial participants may differ from those concerning patients in commercial settings. Not only must trial sponsors account for demographic diversity, but also varying experience with (and psychological barriers to) self-injection. Optimizing DDCs in clinical trials means accounting for all of this, and all without sacrificing priority #1: safety.

Though addressed last in this section's checklist, safety must always come first. Both in clinical trial settings and beyond, DDCs are sophisticated instruments frequently used by novices, exponentially increasing the importance of safety. To varying degrees, needle shields, automatic retraction elements and lock mechanisms all play uncompromising roles toward preventing accidental activation and needlestick injuries. Always, pharma companies and trial organizers must recognize the reality that participants are not trained healthcare personnel.

REGULATORY COMPLIANCE

From a regulatory standpoint, incorporating self-injectable drug-device combinations often involves a more complicated approval process that, refreshingly, clears the way for streamlined commercialization.

The first step is device classification, which requires an understanding of a self-administered injectable device's categorization within its specific regulatory jurisdiction. Most commonly, such solutions are designated combination products mandating integrated regulatory submissions covering both device and drug. Here, proof of compatibility between device materials and formulation is essential.

Human factors studies also come into play. To pass regulatory muster, detailed usability tests must convincingly and consistently demonstrate that a formulation can be self-administered safely and effectively in real-world conditions. This places a premium on holistic patient-centric design encompassing the entire DDC-related experience, including packaging, instructions for use and, of course, the physical self-administration process.

All this entails a convergence of corresponding, often cascading factors, so establishing robust mediation and risk management plans are critical for identifying and mitigating potential issues. This includes satisfying concerns related to drug product stability, device functionality, and potential adverse component interactions.

In many cases, conducting usability studies and integrating human factors considerations early in the design process can help identify potential issues and, from there, guide necessary design modifications. In all cases, human factors and usability engineering are integral components of regulatory submissions, essential for demonstrating a DDC's short- and long-term viability and usability.

ENVISIONING SUCCESS: MANUFACTURABILITY & SCALABILITY

A sound, savvy plan for transitioning from clinical trials to commercial triumphs is a must-have with any drug; with drug-device combination products, such here-to-there roadmaps must be especially detailed.

Among other considerations, effective autoinjector development requires reliable sourcing, cost-benefit analyses, and strategic decisions that weigh differentiating exclusivity and customization against tried-and-true standardization. The interconnected nature of DDCs can make such manufacturing and sourcing concerns seem daunting compared to conventional scale-up scenarios.

First, the supply chain must never be scalability's weakest link. Reliable sourcing of self-administered injectable device components is as vital post-approval as it is to avoid delays in clinical trial timelines. Sponsors should establish strong relationships with suppliers and CDMOs to implement risk mitigation strategies and have

contingency plans in place to address potential disruptions.

Squaring best-possible solutions with cost considerations also should occur during trials. Here as with supply chain factors, a comprehensive plan accounts not only for unforeseen failures but entirely intended successes. The question then becomes: "What if I need to make millions – or even tens of millions – of these?"

As volumes increase, so does the need for marrying efficacy, functionality and cost-effectiveness. Among other factors, deciding between bespoke autoinjectors tailored to the trial drug or off-the-shelf devices, often with a limited set of available options, can impact both cost and speed of development. And on the production line floor, defining a low-volume starting point and expected commercial volume destination enables development of a cost-effective scaling strategy, eliminating excess costs for equipment, tooling and validations.

SUMMARY

In the end, pharma companies deciding whether to incorporate self-administered injectable drug-device combination products into their clinical trials would be well-advised to heed this article's lone italicized word: Necessity. Even if current projections fall short, the number of Americans with chronic diseases will soon climb precipitously – and with it, the need to treat such illnesses with streamlined therapies.

These mounting needs will not be met without complications. Injecting DDCs more broadly into clinical trial settings will require comparably high front-end resources, including device manufacturing costs, documentation efforts, and training for both trial sponsors and patients. But even if such investments weren't in the name of necessity, the long-term value DDCs bring to clinical trials and eventual commercialization make the outsized challenges pale in comparison to the outstanding rewards. ◆

BIOGRAPHY

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CAR T CELL THERAPY

The Rise of Scalable Allogeneic CAR T: Shaping a New Era in Oncology

By: Zachary Roberts, M.D., Ph.D

INTRODUCTION

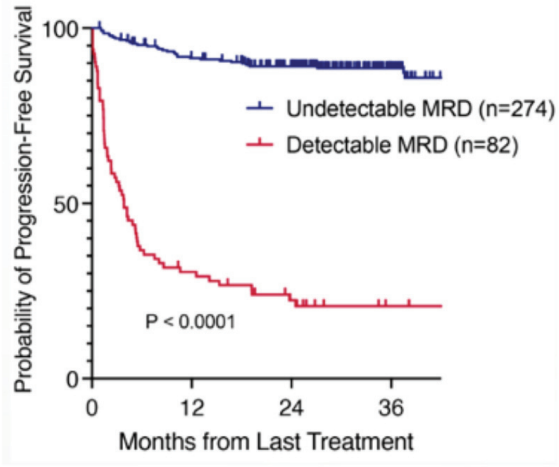
CAR T cell therapy has revolutionized cancer care by harnessing the patient's immune system to deliver highly personalized and often durable responses in hematologic malignancies once deemed incurable. Despite these outcomes, the widespread adoption of autologous CAR T therapies remains constrained by well-documented barriers – including referral patterns, infrastructure requirements, adverse event management, and manufacturing complexity – underscoring the need for a more accessible, scalable approach.

Between 2017 and 2021, three autologous CAR T therapies have been approved for relapsed/refractory large B-cell lymphoma (LBCL). However, fewer than 15% of eligible patients receive treatment[1] due to a complex manufacturing process and the challenging referral pathway to one of the limited number of centers qualified to deliver treatment.

Next-generation allogeneic, also known as off-the-shelf, CAR T products aim to transform CAR T from a bespoke procedure limited to a small number of academic centers into a scalable therapy that can be offered in community cancer settings, where most patients receive care. With scalable manufacturing, on-demand availability via next-day shipping, and a generally well-tolerated safety profile, off-the-shelf CAR T expands where and how these therapies can be delivered – and when they can be used. This creates the potential to treat patients earlier in the disease course, before the cancer returns and becomes more difficult to treat, and in care settings closer to where they live.

This shift in timing is particularly meaningful as CAR T therapy has historically been reserved for later lines of treatment. However, a growing body of evidence supports its use earlier in the disease course and, ideally, when the disease burden is lower. Findings from studies of cemacabtagene ansegedleucel (cema-cel), an investigational off-the-shelf anti-CD19 CAR T product for

FIGURE 1



Nearly all patients with undetectable MRD at the end of 1L treatment maintained remission

Detectable MRD identified patients at high risk of relapse

MRD is emerging as a reliable predictor of relapse in LBCL.

LBCL, are consistent with observations across other CAR T therapies: patients with lower disease burden tend to respond better to treatment than those with more advanced disease.[2]

CHANGING THE CURRENT WATCH-AND-WAIT STANDARD OF CARE

The hypothesis that earlier intervention can improve outcomes is currently being tested in the ALPHA3 clinical trial (Allogene Therapeutics). ALPHA3 is the first pivotal, randomized trial to study the use of a CAR T as first-line consolidation in patients with LBCL who have evidence of remaining disease in the form of minimal residual disease (MRD). The trial will assess whether MRD-guided intervention with a one-time dose of cema-cel before clinical relapse can potentially prevent recurrence.

MRD status post 1L treatment has emerged as a strong predictor of relapse in LBCL, creating an opportunity to intervene earlier in the course of disease, when disease burden is low, but risk of progression is high.[3,4] Patients with LBCL who have completed curative-intent treatment in both front-line and later-line settings, including autologous CAR T therapy, and who achieve MRD-negative status have demonstrated improved progression-free survival (PFS) and event-free survival (EFS) compared with those who do not[5] (Figure 1).

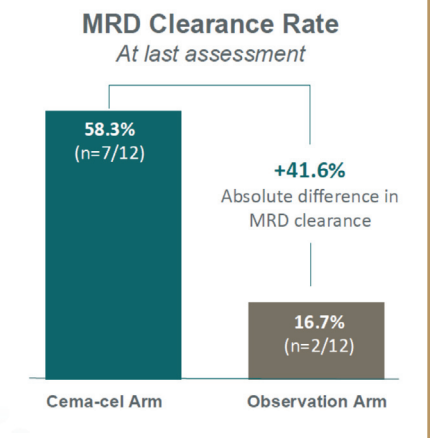
The ALPHA3 trial challenges the standard of care – observation – by introducing a more proactive approach: identifying high-risk patients using Natera's CLARITY™ MRD assay and treating them before clinical relapse.

The study leverages cema-cel as a one-time, off-the-shelf treatment that can be administered immediately upon discovery of MRD following six cycles of R-CHOP or other chemoimmunotherapy regimen, positioning it as the "7th cycle" of frontline treatment for eligible LBCL patients who remain MRD positive.

In April 2026, data from a planned interim futility analysis showed early evidence for the potential of cema-cel in 1L consolidation with MRD clearance of 58.3% in the cema-cel arm versus 16.7% in the observation arm as of the data cutoff – a 41.6 percentage-point absolute difference. Earlier studies have found that as little as a 24% differential in treatment arms led to statistically longer event free survival (EFS).[6] Together, these data highlight the potential for a one-time dose of cema-cel to prevent relapse and improve cure rates (Figure 2).[7]

Importantly in this analysis, cema-cel was well-tolerated as of the data cutoff with no treatment-related serious adverse events. There were no cases of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) or graft-versus-host disease (GvHD), and there were no treatment-related hospitalizations (Figure 3). This profile compares favorably with the broader CAR T experience, where hospitalization for toxicity management remains common.

FIGURE 2



Absolute difference in cema-cel arm over observation arm exceeded clinically meaningful benchmark.

BROADENING ACCESS TO COMMUNITY CANCER CENTERS

CAR T therapy has largely been confined to specialized centers, even as most patients are treated in the community setting. Off-the-shelf CAR T potentially changes that by enabling on-demand use and removing key logistical barriers to access.

At the time of the interim analysis, community cancer centers accounted for approximately one-third of screening ac-

FIGURE 3

TEAEs of Special Interest	Cema-cel Arm (N=12) n (%)	Observation Arm (N=12) n (%)
CRS (Any Grade)[1]	0	-
ICANS (Any Grade)[1]	0	-
GvHD (Any Grade)	0	-
Infection[2]	2 (16.7%)	2 (16.7%)
Infection (Grade ≥ 3)	0	0
Other Neurologic Events[3]	6 (50%)	1 (8.3%)
Other Neurologic Events (Grade ≥3)	0	0

1. No reported use of tocilizumab or steroids
2. Infection events were low grade and limited to urinary tract infection, subcutaneous abscess, COVID19, and skin infection
3. Other neurologic events were low grade and limited to headache, dizziness, numbness or tingling in the hands or feet, and altered taste

Well-tolerated interim safety results support use in outpatient and community settings.

tivity and cema-cel infusions, including sites with limited or even no prior CAR T experience. This shift is further supported by the feasibility of outpatient administration: in the interim futility analysis, 10 of 12 patients treated with cema-cel were managed entirely outpatient post-infusion. This contrasts sharply with the broader CAR T experience, where hospitalization remains common: approximately 70-90% of patients require admission, and about 75% are hospitalized for adverse events within 30 days.[8]

CAR T ON DEMAND

Allogeneic CAR T cells are derived from healthy donors which means that these products are available on demand, allowing patients to begin treatment faster. This also transforms how CAR T therapies are made, using a more advanced, scalable process that allows them to be produced in larger quantities, more like traditional medicines.

At Allogene's 136,000 square-foot manufacturing facility in Newark, California, the company is able to manufacture upwards of 60,000 doses per year (depending on the product and dose), which is nearly three times more than all CAR T infusions provided to all U.S. cancer patients between 2017 and 2024.[9] In fact, a single manufacturing run has the potential to yield treatment for more than 100 patients, compared to one patient with an autologous CAR T.

THE FUTURE OF CAR T

CAR T is on the cusp of a fundamental evolution – from a highly personalized, resource-intensive therapy to a scalable, off-the-shelf platform with the potential to deliver curative outcomes in blood cancer. As MRD becomes an established standard for guiding treatment decisions, it creates a powerful opportunity to intervene earlier – treating patients at highest risk of relapse before clinical progression.

A single, well-tolerated infusion of cema-cel as part of first line treatment has the potential to shift blood cancer care from reactive to preventative. Allogeneic CAR T is poised to become the new foundation of cell therapy – enabling earlier MRD-guided intervention, expanding access, and redefining how these therapies are delivered at scale. ◆

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BIOGRAPHY

Zachary Roberts, M.D., PhD, is the Executive Vice President, Research & Development, and Chief Medical Officer of Allogene. Dr. Roberts is a trained immunologist and board-certified oncologist with extensive experience in clinical oncology, including the development of cell therapies. Before joining Allogene, Dr. Roberts was Chief Medical Officer of Instil Bio, where he led development of both clinical and preclinical programs. Prior to that, Dr. Roberts held various roles of increasing responsibility at Kite Pharma (acquired by Gilead in 2017), where he was instrumental in the development and execution of the ZUMA trials across multiple indications for YESCARTA®, the first autologous CAR T therapy approved for non-Hodgkin lymphoma. Before joining Kite, Dr. Roberts led several solid tumor studies at Amgen. He holds an M.D. and Ph.D. in immunology from the University of Maryland, Baltimore and completed clinical and post-graduate training at Massachusetts General Hospital and the Dana-Farber Cancer Institute.

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