Drug Development & Delivery

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CGT Manufacturing: A New Regulatory Era

The Science & Business of Pharmaceutical and Biological Drug Development

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LEW BENDER

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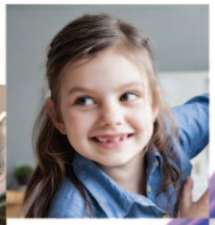

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CGT Manufacturing

"Despite today's uncertainty, advanced American manufacturing capabilities in CGT may see additional opportunity given tilt from ongoing tariff risks. Trade relationships that once looked predictable, when many manufacturing plants outside of the US were greenlit, now sit on shakier ground. If US lawmakers impose retaliatory duties on biologics, overseas production costs could spike overnight. Domestic capability would ultimately be faster and less expensive."

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"This past July, the World Health Organization and the United Nations Office on Drugs and Crime unveiled in a landmark report (Contaminated Medicines and Integrity of the Pharmaceuticals Excipients Supply Chain) that there are persistent and preventable threats of contaminated medicines with industrial-grade toxic chemicals, notably diethylene glycol and ethylene glycol. The result is lost lives and compromised patient health. The report claims that in the past 90 years, there have been 25 documented incidents of excipient contamination, resulting in more than 1,300 deaths worldwide."

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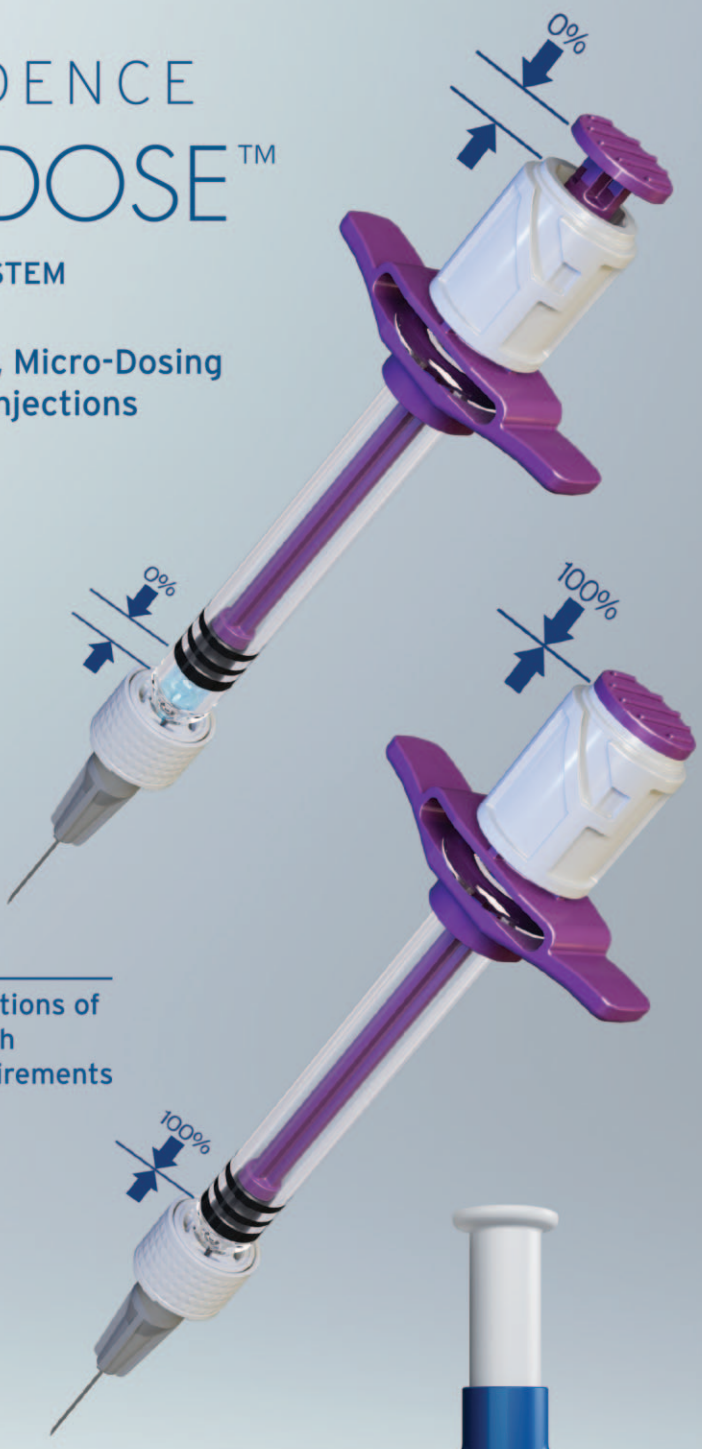

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Symbiosis Expands Sterile Manufacturing Capacity With Fill/Finish Line Qualification

Symbiosis Pharmaceutical Services has successfully completed qualification of its new FPD 50 Flexicon automated fill/finish line at its new commercial production facility in Stirling, Scotland.

The fully integrated sterile liquid fill/finish system operates under a Grade A Restricted Access Barrier System (RABS). Designed to deliver with both precision and efficiency, it incorporates rapid transfer ports for aseptic handling and high-accuracy vial filling with flexicon pump technology. The system also features a rotary crimp mechanism to ensure consistent overseal application and secure closure.

Colin MacKay, CEO of Symbiosis, said: "The qualification of our automated fill/finish line is a major step forward for Symbiosis. It enhances our technical capabilities and expands our capacity at a time when demand for high-quality sterile manufacturing continues to grow. Most importantly, it strengthens our ability to help clients bring vital therapies to patients quickly and to the highest regulatory standards."

Symbiosis will commence commercial production at their new facility in Q4 2025, manufacturing batches of up to 15,000 vials, and representing the latest in a series of recent milestones for the company.

In July 2025 Symbiosis manufactured its 1,000th sterile batch, marking over 14 years of support for biopharmaceutical clients across the globe. Earlier this year, the company was also honoured with the UK 2025 King's Award for Enterprise in International Trade from King Charles III, recognising the company's sustained growth and global business success.

Symbiosis has maintained a track record of successful GMP inspections with both the FDA and MHRA since it was founded. The company also played a pivotal role in supporting the clinical development of the Oxford University/AstraZeneca COVID-19 vaccine and has since expanded its global presence by consistently delivering sterile injectable products across a wide range of drug modalities and therapeutic areas.

Symbiosis Pharmaceutical Services (Symbiosis) is a world-class Contract Manufacturing Organisation (CMO) located in Stirling, UK, and is a specialist sterile GMP manufacturer of biopharmaceuticals for use in clinical trials and commercial sales globally. Symbiosis is MHRA-licensed and FDA-inspected and offers a range of services including the aseptic fill/finish of medicines into vials, analytical testing, QP release of product, inspection, labelling, packaging and GMP temperature-controlled storage and shipment of medicines.

The Symbiosis facilities in Stirling, Scotland, were designed for biologic and small molecule pharmaceutical production to support biotechnology and pharmaceutical companies worldwide requiring sterile injectable pharmaceutical products manufactured in short timeframes for clinical trial use and commercial supply.

Regulatory compliance, technical capability and operational flexibility are core to the Symbiosis value proposition along with direct access to a highly experienced team of life science experts. By adding value directly to the new drug development projects and the commercial manufacturing supply chain requirements of its clients, Symbiosis has demonstrated consistent annual growth and built long-term relationships with its client base globally.

Hovione & Microinnova Partner to Advance Modular Flow Chemistry for Multi-Purpose Manufacturing

Hovione recently announced a partnership to advance the development of multi-purpose, plug-and-play modular equipment for flow chemistry.

The companies will work together to test Microinnova's modular manufacturing equipment in an industrial setting. The Microinnova equipment is designed to offer greater flexibility, easier scalability, enhanced efficiency and sustainable practices in active ingredient production. Together, the companies are aiming at faster process development, simple transition from lab to large-scale manufacturing, and ultimately decreased time to market for pharmaceutical customers.

"This collaboration with Microinnova underscores Hovione's commitment to innovation in pharmaceutical manufacturing, with flow chemistry playing an important role in our long-term drug substance strategy," said Dr. Jean-Luc Herbeaux, CEO of Hovione. "This partnership will allow us to shape and validate emerging continuous manufacturing technologies, which can potentially accelerate drug development and production."

Dr. Dirk Kirschneck, Founder and Strategic Director at Microinnova. "This partnership reflects our shared vision to deliver modular manufacturing technologies that support pharmaceutical innovation and manufacturing excellence. We are proud to join forces with Hovione to showcase the capabilities of our next-generation modular equipment in a dynamic CDMO environment, demonstrating its versatility for multi-purpose manufacturing."

Hovione is an international company with over 60 years of experience in pharmaceutical development and manufacturing operations. As a Contract Development and Manufacturing Organization (CDMO) it has a fully integrated offering of services for drug substances, drug product intermediates and drug products. The company has four FDA inspected sites in the USA, Portugal, Ireland and China and development laboratories in Lisbon, Portugal and New Jersey, USA. Hovione provides pharmaceutical customers services for the development and compliant manufacture of innovative drugs, including highly potent compounds, and customized product solutions across the entire drug life cycle. In the inhalation area, Hovione offers a complete range of services, from API, formulation development and manufacturing, capsule filling and devices. Hovione's culture is based on innovation, quality and dependability. Hovione is a member of Rx-360, EFCG and participates actively in industry quality improvement initiatives to lead new global industry standards. For more information, please visit www.Hovione.com

Microinnova provides process development as well as successful pilot plant & manufacturing plant solutions. Based on more than 20 years of experience in flow chemistry & process intensification and 250+ successfully completed projects, Microinnova is the partner of choice for continuous manufacturing. Microinnova's team uses process intensification techniques and selects the most advantageous technology for each process, even in regulated environments. As an ISO 9001:2015-certified company, Microinnova designs plants that meet GMP and ATEX standards for quality and safety. Specializing in modular continuous plants, Microinnova scales processes from lab tests to tons-per-hour production, enabling rapid time-to-market and flexibility. For more information, please visit microinnova.com.

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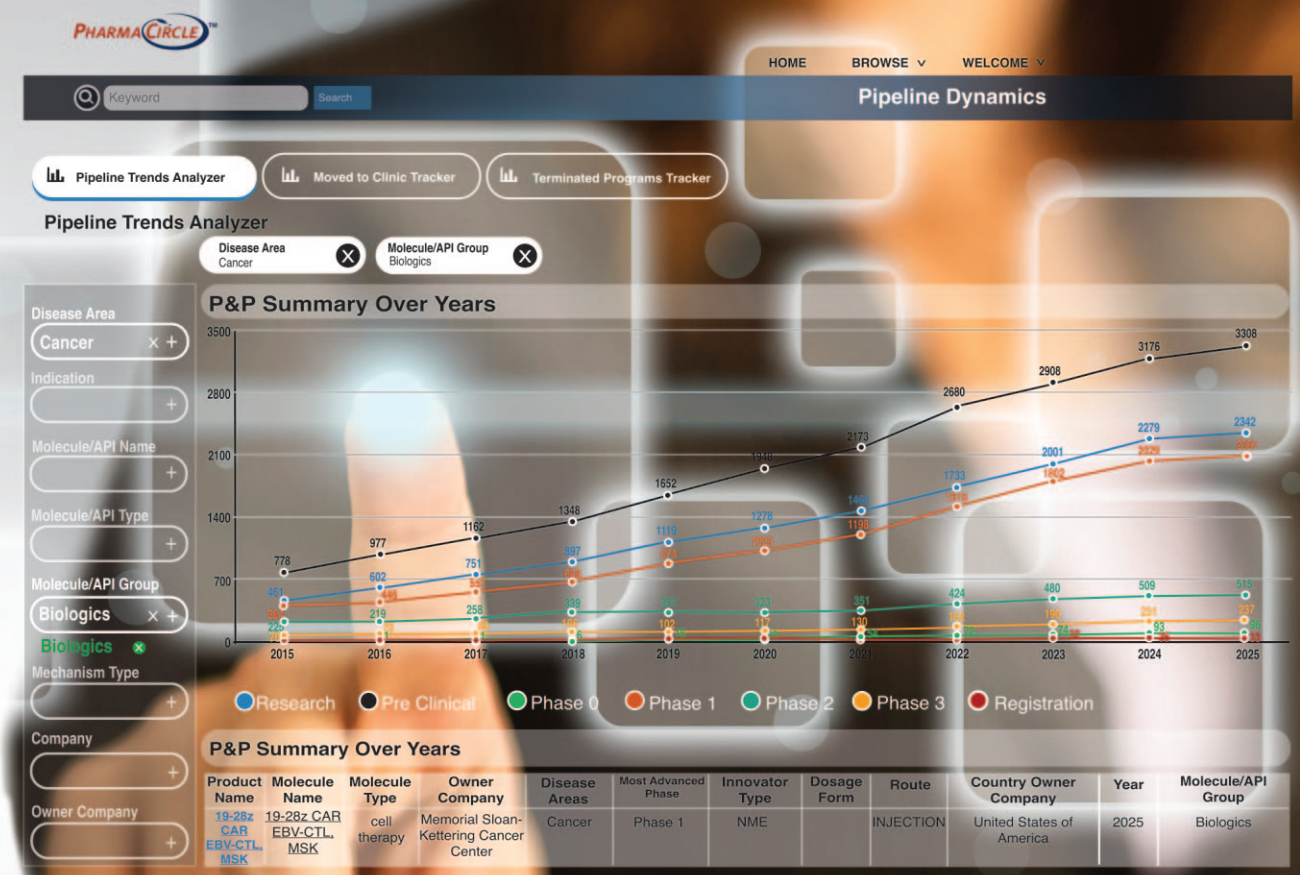

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Fortress Biotech & Urica Therapeutics Announce Crystalys Therapeutics' $205 Million Series A Financing

Urica Therapeutics, Inc., a Fortress Biotech, Inc. subsidiary, recently announced Crystalys Therapeutics, Inc., in which Urica maintains an equity position, closed a $205 million Series A financing to support the advancement of global Phase 3 clinical studies evaluating dotinurad for the treatment of gout. The financing round was co-led by Novo Holdings, SR One and Catalys Pacific with participation from a broad syndicate of investors including Perceptive Xontogeny Venture Funds, Lightstone Ventures, AN Venture Partners, funds managed by abrdn Inc., KB Investments, Pontifax, Longwood Fund, Alexandria Venture Investments, Wedbush Healthcare Partners and Prebys Ventures Fund.

Crystalys brings together a world-class team with a proven record in gout drug development and deep regulatory success with URAT1 inhibitors. Dotinurad is a next-generation URAT1 inhibitor with potential best-in-class safety and efficacy for the treatment of gout and has demonstrated robust efficacy and a well-defined safety profile across multiple clinical studies in Asia, supporting its approval in Japan, China, Philippines, and Thailand.

Lindsay A. Rosenwald, MD, Fortress' Executive Chairman, President and Chief Executive Officer, said "We are very pleased that our transaction with Crystalys could potentially expedite the development of dotinurad in the United States and Europe for millions of people suffering from gout, while simultaneously adding value to Fortress and subsidiary company, Urica, through our equity stake in Crystalys and future royalties from dotinurad once commercialized. This significant financing enables the advancement of global pivotal trials which could expeditiously lead to regulatory approval and commercialization of dotinurad in the United States and Europe."

Dr. Rosenwald continued "In addition to this transaction, Fortress has achieved several key milestones this year including the acquisition of our subsidiary Checkpoint Therapeutics by Sun Pharma, which was a notable validation of our business model, delivering approximately $28 million upfront, plus the potential for an additional contingent value right (CVR) payment and ongoing royalties on future sales of UNLOXCYT (cosibelimab-ipdl). Our goal is to continue to realize value from our extensive portfolio of commercial and clinical-stage assets, while also focusing on new business development opportunities."

Through the sale of dotinurad to Crystalys in 2024, Urica owns a minority equity position in Crystalys and holds the right to appoint a board member to the Board of Directors of Crystalys. In addition, Urica is eligible to receive a 3% royalty on future net sales of dotinurad. Urica is a majority-owned and controlled subsidiary of Fortress.

Fortress Biotech, Inc. is an innovative biopharmaceutical company focused on acquiring and advancing assets to enhance long-term value for shareholders through product revenue, equity holdings and dividend and royalty income. The company has eight marketed prescription pharmaceutical products and multiple programs in development at Fortress, at its majority-owned and majority-controlled partners and subsidiaries and at partners and subsidiaries it founded and in which it holds significant minority ownership positions.

Orexo US Awarded $8 Million by BARDA for OX390 Development Partnership

Orexo AB recently announced its wholly owned US subsidiary, Orexo US, Inc., has been awarded USD 8 million in funding by the Biomedical Advanced Research and Development Authority (BARDA), part of the Administration for Strategic Preparedness and Response in the US Department of Health and Human Services. The funding will support the development of OX390, an intranasal rescue medication for adulterated opioid overdoses.

The award is structured in five stages and is valued at up to USD 50.9 million that could be awarded if specific milestones and deliverables are achieved. It will contribute to the funding for Orexo to perform non-clinical toxicology, human clinical studies, drug and device manufacturing, and regulatory filing for a formulation of OX390 suitable for community use.

OX390 is a New Chemical Entity (NCE) with a novel formulation and route of administration for human use. OX390 is intended to reverse respiratory depression associated with adulterated illicit opioid overdoses, which is a rapidly increasing problem in the US. OX390 uses Orexo's proprietary AmorphOX® dry-powder drug delivery technology which has been validated in multiple clinical studies with other molecules and has demonstrated rapid and extensive drug exposure. The first stage of the contract provides approximately USD 8 million to support the completion of the agreed activities. Upon completion of the project and FDA approval of the product, Orexo will retain all commercial rights to OX390.

"We are excited to initiate our partnership with BARDA in the development of OX390. We aim to develop a rapidly deployable intranasal rescue medication using our proprietary AmorphOX technology for the emergency treatment of respiratory depression associated with adulterated illicit opioids. There is a crucial need for new treatment options that can complement opioid antagonists for the increasing number of patients exposed to adulteration of illicitly manufactured opioids. We look forward to continuing our collective efforts to develop medical countermeasures as the American opioid epidemic continues to evolve and expose the public in the US to new lethal adulterations of opioids," said Nikolaj Sørensen, President and CEO of Orexo AB.

This project has been funded 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, under contract number 75A50125C00010.

OX390 is a new chemical entity (NCE) designed to reverse respiratory depression associated with adulterated illicit opioid overdoses. Emerging evidence indicates that opioid-induced respiratory suppression (OIRD) may be greatly magnified in the presence of increasingly common adulterants, and that opioid antagonists such as naloxone and nalmefene may not be sufficient to revive victims of these overdoses. OX390 will be developed as a rapidly acting intranasal powder using Orexo's proprietary powder-based drug delivery technology AmorphOX® for community-based use by first responders and laypersons. OX390 is an investigational compound and is not approved for human use by the FDA.

Orexo's proprietary drug delivery platform, AmorphOX, is a powder made up of particles that are built using a unique combination of a drug, carrier materials and, optionally, other ingredients. The particles are presented as an amorphous composite of the various ingredients providing for excellent chemical and physical stability, as well as rapid dissolution. The technology works for a broad scope of active ingredients and has been validated in several human clinical studies showing rapid and extensive drug exposure.

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MarComm-2025-00277

Faeth Therapeutics' R&D Platform Delivers First Cross-Disease Validation Beyond Oncology

Faeth Therapeutics has launched a new R&D initiative aimed at preserving neurocognitive function in children with tyrosinemia type 1 (TT1), marking the expansion of its platform beyond oncology into inherited metabolic disorders.

Faeth R&D is supported by MetabOS, a computational model that integrates gene expression and tumor microenvironment data to pinpoint dependencies invisible to conventional approaches, simulating how drug combinations and nutrients interact to propose optimized therapeutic regimens.

While current TT1 therapy prevents liver failure, patients continue to face unmet needs, including neurocognitive impairment.

Untreated, TT1 can lead to fatal liver and kidney toxicity in infancy. Standard therapy dramatically improves survival but has on-label warnings of variable degrees of intellectual disability and developmental delay. Faeth's new program aims to change that trajectory.

Anand Parikh, Faeth CEO and co-founder, said "We have demonstrated that interrogating biology through a metabolic lens reveals insights not apparent in conventional drug development, and that these insights can be used not just in oncology, which is reflected in our lead clinical programs, but also in rare diseases."

Faeth expects to file an IND within a year to advance its TT1 program into the clinic. The company anticipates an initial study in older children or adults, followed by long-term cognition endpoints to measure the drug's ability to protect IQ and neurodevelopment.

"Cross-disease expansion of our discovery platform is very exciting," added Oliver Maddocks, PhD, Chief Scientific Officer of Faeth. "The fact that our R&D has yielded programs in oncology and now rare disease demonstrates its potential to systematically open up new categories of metabolism-driven therapies."

Faeth Therapeutics is a clinical-stage biotechnology company integrating targeted therapies with precision nutrition interventions to exploit metabolic vulnerabilities in cancer. Founded by renowned researchers from Cornell, Columbia, Cambridge, Memorial Sloan Kettering, and the Crick Institute – including Drs. Lewis Cantley, Siddhartha Mukherjee, Karen Vousden, Greg Hannon, and Scott Lowe – Faeth leverages its AI-driven MetabOS discovery platform to identify metabolic targets. Its lead clinical program, combining serabelisib and sapanisertib, is a multi-node approach to more completely inhibit the PI3K/AKT/mTOR pathway, demonstrating promising outcomes in cancers strongly associated with obesity and metabolic disorders. For more information, visit www.faeththerapeutics.com.

MetabOS is Faeth Therapeutics's machine learning-driven dynamic model of metabolism. The platform leverages AI and functional genomics to identify metabolic vulnerabilities as therapeutic targets. In cancer, Faeth is using MetabOS™ to uncover the precise metabolic vulnerabilities for a tumor based on genotype, organ of origin and therapy.

Credence MedSystems & SMC Ltd. Pharma Services Announce Collaboration to Advance Dual Chamber Fill-Finish Capabilities

Credence MedSystems, Inc. (Credence), an innovator in advanced injectable delivery systems that solve unmet market needs for the pharmaceutical industry, and SMC Ltd. Pharma Services (SMC), a leading UK-based contract development and manufacturing organization (CDMO), today announced the signing of a Memorandum of Understanding (MoU) to collaborate on clinical and commercial-scale fill-finish capabilities for combination drug-device Dual Chamber products.

Under the agreement, SMC and Credence will work together to implement and scale filling capabilities for the Credence Dual Chamber Syringe (DCS) platform, enabling pharmaceutical partners to advance innovative therapies from clinical development through commercial supply. This collaboration brings together SMC's proven expertise in aseptic drug product development, fill-finish operations, and regulatory support with Credence's proprietary Dual Chamber Syringe technology platform.

Together, SMC and Credence aim to provide biopharma partners with a robust, differentiated, and scalable solution to meet the growing demand for advanced Dual Chamber injectable therapies.

The phased approach will begin with the installation and qualification of clinical-scale GMP fill-finish equipment in SMC's Charlotte, NC based facility, with capabilities which will support both Credence's Sequential Liquid-Liquid DCS and Lyo-Liquid Reconstitution DCS products. The partners intend to expand towards commercial-scale manufacturing, creating an end-to-end pathway for dual chamber combination product development and supply.

"This collaboration with Credence strengthens our ability to support clients developing complex drug-device combination products," said Josh Gonzalez, VP of Marketing and Sales for SMC. "By integrating dual chamber fill-finish capabilities into our operations, we can help accelerate development timelines while ensuring the highest standards of quality and compliance."

"Partnering with SMC allows Credence to extend the value of our Dual Chamber Syringe platform to clients seeking both problem-solving device technology and trusted fill-finish expertise," said Laxman Halleppanavar, Head of Portfolio Strategy and Management for Credence. "Together we are building an offering that enables pharmaceutical innovators to bring important therapies to patients more efficiently."

SMC Ltd. is a global leader in pharmaceutical services and contract manufacturing for the pharmaceutical, medical device, and diagnostics industries. With over 35 years of experience, SMC has established itself as a trusted partner to pharmaceutical and medical device companies around the world, providing high-quality products and services that meet the strictest regulatory standards. Services include device design and development, engineering, molding, complete device assembly, testing and validation, sterile filling, supply chain management, packaging and labeling, and sterilization management.

Credence MedSystems is an innovator of drug delivery systems that solve unmet market needs for the pharmaceutical industry. Credence's philosophy of Innovation Without Change allows pharma manufacturers to solve challenges in injectable drug delivery while preserving their existing processes, sourcing strategies and preferred primary package components. This approach enhances patient safety, improves usability, and streamlines combination product development. Credence partners with leading pharmaceutical and biotechnology companies worldwide to advance injectable therapies from clinical to commercial stages.

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VERAXA Biotech & Secarna Pharmaceuticals Initiate Antibody Oligonucleotide Conjugate Alliance in Immunology

VERAXA Biotech, an emerging leader in designing novel cancer therapies and proposed de-SPAC acquisition target of Voyager Acquisition Corp. and Secarna Pharmaceuticals GmbH & Co. KG, a company redefining the discovery and development of best-in-class oligonucleotide therapeutics, today announced a strategic research collaboration to develop next-generation antibody oligonucleotide conjugates (AOCs). The combination of both technology platforms aims to unlock novel targeted therapies for the treatment of autoimmune and chronic immune diseases

AOCs combine the specificity of monoclonal antibodies with the functional versatility of oligonucleotides. One of the primary advantages of AOCs is their ability to deliver therapeutic oligonucleotides directly to disease-relevant cells, thereby enhancing treatment efficacy and minimizing off-target effects. This targeted delivery mechanism allows for precise modulation of gene expression, which is particularly beneficial in treating complex diseases including conditions involving the immune system.

As part of the collaboration, Secarna will leverage its proprietary, AI-empowered OligoCreator® discovery and development platform to identify promising oligonucleotide candidates, applying both antisense oligonucleotides (ASOs) and siRNA strategies. OligoCreator® has been shown to greatly expedite the drug discovery process, from target selection to therapeutic development, identifying and characterizing potentially safe and efficacious therapeutic candidates at unparalleled speed. VERAXA will use technology suite including its click chemistry conjugation platform to design and generate highly efficacious, uniform and safe AOCs.

"Today's alliance with Secarna highlights once more the versatility of our technology suite and the range of opportunities we can tackle with partners that are complementary to our R&D focus in oncology," commented Christoph Antz, Ph.D., CEO and Co-Founder of VERAXA. "AOCs represent a very attractive additional pocket in our industry where our expertise and antibody conjugation technology can enable unique therapeutic modalities. We are thrilled to partner with Secarna, a renowned expert in the field of developing oligonucleotide-based therapies."

"We are truly excited to collaborate with VERAXA on this new class of highly targeted therapeutics," said Konstantin Petropoulos, Ph.D., CEO of Secarna Pharmaceuticals. "The combination of our oligonucleotide platform with VERAXA's complementary ADC technologies, together with our mutual expertise in discovering and developing best-in-class therapeutics, will open up a wide range of potential therapeutic applications in the field of immunological diseases."

Mstack Launches Chemstack AI - A Revolutionary AI-led R&D Platform

As rising tariffs and shifting geopolitical dynamics drive unprecedented demand for domestic chemical supply chains, a fundamental bottleneck has emerged: the specialized process chemistry knowledge required for local manufacturing remains concentrated among a few global players. Mstack announced the commercial launch of Chemstack AI, the industry's first closed loop AI ecosystem to democratize this critical knowledge by reducing molecular synthesis and commercialization time from ~18 months to days. The platform launch coincides with exceptional business growth, with the company achieving a 10x revenue increase with operational profitability.

Mstack's rapid expansion reflects extraordinary market demand for supply chain diversification, scaling to over 100 enterprise customers across North America, India, China, and the Middle East, with over 100 employees spanning data science, artificial intelligence, technology development, R&D, operations, and sales. The company has successfully synthesized multiple key intermediates in strategic markets, with large agrochemical companies transitioning their procurement from Chinese suppliers to Mstack as their preferred partner.

This comes at a critical moment when escalating trade tensions have imposed tariffs of 10-50% on critical chemical intermediates in the USA, while traditional chemical companies struggle with decades of innovation stagnation that locks the industry into legacy synthesis routes requiring years for new route development. Mstack's differentiated approach addresses the fundamental knowledge bottleneck that has created a bifurcated industry structure dominated by large commodity companies and small specialty players, neither capable of rapidly scaling innovation across chemical domains.

Chemstack AI represents the industry's first closed-loop AI ecosystem specifically designed for molecular synthesis, fundamentally transforming development timelines. The platform features three capabilities: LiteratureIQ maps vast datasets of chemical literature into comprehensive knowledge graphs; MSTACK RetroRank generates and ranks viable synthetic routes with 98.6% exact match recall and 72.6% Top-1 accuracy, outperforming current industry standards; and Experimentation Assist uses Bayesian Optimization to intelligently navigate reaction configurations, creating closed-loop validation between AI insights and laboratory outcomes. The platform's vertically integrated architecture creates a powerful continuous feedback loop that distinguishes it from fragmented point solutions. This system-first approach architects specialized AI modules that work together to mimic chemist intuition and strategic thinking, turning traditionally linear manual R&D processes into self-correcting, autonomous discovery engines.

Since raising funding from Lightspeed and Alphawave, Mstack has executed on several transformative initiatives: launching Chemstack AI, establishing robust R&D laboratories in Hyderabad with over 25 scientists who have successfully developed and commercialized custom molecules, driving growth across new geographies and categories including CASE (Coatings, Adhesives, Sealants, and Elastomers), agrochemicals, oil and gas, home and personal care and construction chemicals, and creating flexible supply chains to navigate macroeconomic volatility. The company's success in the Indian agrochemicals market exemplifies this impact, where enhanced supply predictability through local manufacturing eliminates cross-border logistics uncertainties, superior product quality through AI-optimized synthesis routes delivers more consistent specifications, and competitive pricing through novel synthesis pathways reduces production costs while improving yields.

The company's success reflects broader market dynamics reshaping the chemical industry, where dangerous supply concentration has made entire product categories vulnerable to capacity constraints or geopolitical restrictions, regulatory divergence across major markets creates new barriers to cross-border commerce, and conventional solutions requiring massive capital investments and multi-year timelines fail to address concentrated chemical knowledge. Mstack's asset-light manufacturing model has proven particularly valuable in navigating current macro-economic conditions, with the platform's ability to seamlessly onboard suppliers from the USA, Middle East, Asia, and South Korea providing customers cost-effective alternatives while maintaining quality standards.

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Abzena Enhances AbZelectPRO Cell Line Offering With New GS Knockout Platforms

Abzena recently announced the expansion of its AbZelectPRO cell line development (CLD) platform with the launch of two next-generation Glutamine Synthetase (GS) knockout CHO-K1 expression systems, including a double knockout ADCC+ platform for afucosylated proteins. The addition of the new GS knockout cell lines will further enhance speed, scalability, and flexibility for biopharma customers.

Named AbZelectPRO-KO and AbZelectPRO-KO+, the new GS knockout platforms are available as a standalone CLD offering or as a fully integrated GMP program, with fully transparent pricing to IND with no royalty fees. This flexible offering will enable customers to select a CLD strategy that aligns with their project-specific goals, timeline, and budget.

Licensed from Revvity, both GS knockout CHOSOURCE expression systems have been integrated into the AbZelectPRO CLD workflow and paired with ProteoNic Bioscience's 2G UNic next-generation vector technology. This unified approach has been proven to significantly enhance productivity and flexibility, enabling biopharma customers to quickly transition from DNA to research cell banks (RCB) in 10 weeks, with high-performing titers of up to 10g/L.

"We are proud that our 2G UNic vector technology continues to deliver premium performance within Abzena's AbZelectPRO platform. ProteoNic's technology boosts productivity in CHOSOURCE and other cell lines and strengthens the value of this offering for biopharma customers," said Frank Pieper, CEO of ProteoNic.

Bryan Kipp, SVP Technology & Licensing, Revvity said "At Revvity, we tell customers that when they work with us, they should expect more — more collaboration, more breakthroughs, and more impact. What excites me most about Abzena's new expanded cell line development platform, inclusive of Revvity's well-established CHOSOURCE cell lines, is that it directly targets ongoing major challenges for customers, enhancing productivity and flexibility. Ultimately, Abzena's approach will lead to a greater impact for customers, which is a common passion we share and support."

Revvity's proprietary CHOSOURCE Glutamine Synthetase (GS) knockout cell line is an industry standard, cGMP-manufactured CHO-K1-derived suspension cell line. It has been referenced in over 90 IND filings and is currently featured in four approved drugs on the market. Revvity's CHOSOURCE ADCC+ (Antibody Dependent Cellular Cytotoxicity) cell line is a double knockout of both the glutamine synthetase (GS) & fucosyltransferase genes.

Abzena is the leading end-to-end bioconjugate and complex biologics CDMO + CRO. From discovery through commercial launch, we support customers with fully integrated programs or individual services designed to de-risk and streamline the development of new treatments for patients in need. With the ability to tailor its strategy and customer experience to each project, Abzena develops and implements innovative solutions that enable biotech and biopharma companies to realize the full potential of their molecule and move medicines forward faster. The company has research, development, and cGMP facilities across locations in San Diego, CA, Bristol, PA, and Cambridge, UK. Abzena is owned by Welsh, Carson, Anderson & Stowe, one of the world's leading private equity investors. Learn more at abzena.com.

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Formulation Forum

Orally Disintegrating Tablets

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

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KEYWORDS: Orally dispersive tablets, ODT, granulation, direct compression, taste-masking, disintegration time, stability, storage

INTRODUCTION

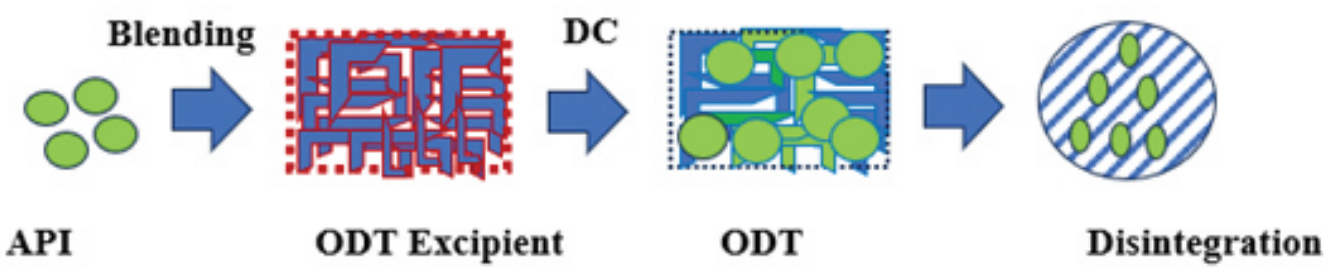
ODT formulations are referred to as quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, rapid dissolving tablets, rapid melts among others.[1] United States Pharmacopoeia (USP) monographed these dosages as fast "Orally Disintegrating Tablet" or ODT that disintegrates within 30 seconds or less. European Pharmacopoeia also published a similar monograph on "Orodispersible Tablet" "for solid oral dosage that disperse inside the mouth readily and within 180 seconds or less. The FDA's Guidance for Industry: Orally Disintegrating Tablet, was issued in 2008.[2]

Orally disintegrating tablets (ODTs) have drawn attraction in the recent past in certain patient population and expect that market will continue to grow in the future. A survey conducted in 2017 predicts that ODT market will grow from 11 billion to over 27 billion.[3] This upward trend is due, in part, to demands, in pediatric, geriatric population, and also in those who suffer from ailments like dysphagia.[4] A typical ODT solid dosage form is aimed at improving the disintegrating and dissolution rate of drug in a short time, leading to faster absorption and onset as opposed to conventional swallowed pills. The rapid disintegration time, requiring 30 sec or less, results from enabling excipients possessing high porosity and low density with high compressibility at low compaction force.[5] The ingredients used in an ODT should meet certain criteria like hydrophilic in nature and quickly dissolves and possesses good mouthfeel and taste-masking effect. Finding all these criteria in an ODT excipient might be challenging, especially when addressing poor solubility, taste masking of bitter drugs, higher drug loading among others.[6]

Figure 1 illustrates the disintegration of an ODT tablet prepared by blending and direct compression of an API with an ODT excipient. The resulting tablet is subjected to disintegration and dissolution to achieve the desired dosages.

Other processing methods are also used to prepare ODT dosages and those include spray drying, extrusion, lyophilization, molding, among other patented technologies.[5] These technologies, however, require expensive equipment as compared with the standard direct compression manufacturing process and with some requiring special packaging.

FIGURE 1



Preparation & Disintegration of an Orally Dispersible Tablet

TABLE 1

ODT Platform	Manufacturer	Composition
Ludiflash®	BASF	Mannitol, crospovidone, polyvinyl acetate, povidone
Pearlitol® Flash	Roquette	Mannitol, starch
F-Melt® - Type C and Type M	Fuji Chemical	Mannitol, xylitol, dibasic calcium phosphate, crospovidone, magnesium aluminometasilicate
Partek® ODT	Merck	Mannitol, croscarmellose sodium
Prosolv® ODT G2	JRS Pharma	Mannitol, fructose, crospovidone, MCC, colloidal silica
Pharmaburst®	SPI Pharma	Mannitol, starch, crospovidone, croscarmellose sodium, colloidal silica
StarLac®	Meggle	Lactose, starch
Granfiller®-D	Daicel	Mannitol, crospovidone, carmellose, MCC
PanExcea® ODT	Avantor	Mannitol, silicate salt

Mannitol Based ODT Excipient Platform

ODT offers several advantages including the patient compliance, faster dissolution in saliva, rapid onset, to avoid hepatic metabolism, greater stability, accurate dosing, easy manufacturing, small packaging size, and easy transportation.[7,8] A SeDeM-ODT expert system tool is also used to predict the powder blending to produce conventional tablets by direct compression.[9] This predictive tool provides information about the powder or mixture of different excipients, which could help in optimization of ingredients in direct compression (DC) to avoid granulation in the initial formulation.[10]

ODT EXCIPIENTS

There are several co-processed excipients commercially available for orally dispersive tablets. Table 1 lists several ODT excipients commercially available by different manufacturers.[11]

Many of them contain mannitol with disintegrants to yield rapid disintegration within the desired time to meet an ODT requirement. Mannitol is used as non-cariogenic excipient as sweetener and good mouth feel and crospovidone with smaller particles provides creamy palatability.[6]

This article sheds light on the composition and utilities of a few selected ODT excipients.

LUDIFLASH®

Ludiflash, a co-processed excipient is comprised of 90% mannitol, 5% crospovidone and polyvinyl acetate 30% dispersion with 5% povidone. It is highly compressible and at compression force as low as 4.8 kN with 98% Ludiflash and 2% sodium stearyl fumarate, it yields placebo tablets (each weighing 300 mg and 10 mm diameter in size) with hardness of 44 N and < 0.2% friability. These placebo tablets showed the disintegration time of < 20 seconds in water and as well as in mouth saliva of healthy volunteers.[12]

On loading with drugs, Ludiflash maintains the ODT properties, meaning the disintegration time is still within 30 seconds. For example, cetirizine dihydrochloride ODT prepared by direct compression of granulated API with 6.5% PVP K30 and magnesium stearate as lubricant, showed the disintegration of 25 seconds in water for the tablet with hardness of 34 N, each weighing 200 mg with 8 mm flat surface and with < 0.4% friability.

PEARLITOL® FLASH

A co-processed ODT excipient is comprised of 80% mannitol and 20% starch with <3% moisture content. It is widely used for different active ingredients.[13] Kollmer et al. (2013) investigated benzocaine in ODT formulations comprised of different orally dispersive excipients. Oral palatability, good mouth feel, disintegration time, and stability of drug was investigated in the mannitol based, a less hygroscopic filler in combination with a disintegrant and a lubricant. Since many ODT excipients are ready to use, benzocaine was directly compressed in tablets.[13]

PROSOLV® ODT G2

A highly functional ODT excipient is comprised of mannitol, fructose, MCC, and crospovidone as disintegrant. Ondansetran containing 5 mg and 10 mg in ODT dosages prepared by compression with hardness of 50 N containing 0.7 mg and 1.4 mg sodium stearyl fumarate (Pruv), respectively, showed the disintegration time < 30 seconds, which is comparable to the reference drug. If required, the additional disintegrant could be added to meet the criteria for a quick dissolving tablet to 30 sec or less, especially, those requiring higher drug loading.[14]

F-MELT®

F- Melt is commercially available in Type C and Type M. Type C and Type M are comprised of dibasic calcium phosphate anhydrous (Fujicalin®) and magnesium aluminometasilicate (Neusilin®), respectively. Both are commonly used depending on the compatibility and performance with active

ingredients. Type C leads to faster disintegration needs, whereas, Type M offers better flowability and improves tablet quality. In acetaminophen ODT formulations comprised of 10%, 20% and 40% drug, the disintegration times of tablets, with each 8 mm in diameter and hardness of 30 N, were within 20 seconds.[15]

PHARMABURST® 500

Comprised of mannitol, crospovidone, croscarmellose sodium, starch and colloidal silica, it has been used in several marketed ODT drugs. It is designed to improve patient compliance, rapid disintegration, and to yield robust tablets with higher drug loading coupled with good mouth feel with disintegration time of < 30 seconds. For example, with 25% and 50% loading of a highly crystalline drug, the hardness varied within 50 N - 100 N but the disintegration (Dt) was within the monograph range of 30 seconds or less.[16]

STARLAC® ODT

A lactose based co-processed excipient contains 15% corn starch as functional binder and disintegrant, and 85% lactose monohydrate as filler, diluent and binder. With its exceptional flowability and binding properties, it can be compressed with a lubricant at lower compression force to yield desired hardness and disintegration time. For example, when compressed to tablet hardnesses of 40 N to 120 N, the disintegration time remains within 30 seconds. On compression with 30% highly crystalline vitamin C. it achieved the fastest disintegration and a complete dissolution within 10 min.[17]

GRANFILLER- D™

Comprised of mannitol, MCC, carmellose and crospovidone, it is highly compressible at low compression force due to its higher porosity. When compressed with higher drug loadings as high as 50% of acetaminophen or ibuprofen or 70% ethenzamide, each tablet containing 250 mg of drug, the disintegration time was within 30 sec regardless of tablets hardness which varied between 30 N and 60 N. It also yielded an excellent content uniformity throughout the tableting.[18]

Kollmer et al., (2013) evaluated a range of selected ODT excipients including Pearlitol Flash, Ludiflash, Prosolv and F- Melt in tablets comprised of 6% benzocaine and 1.5% magnesium stearate and compressed at 20kN with hardness of 100N. The friability test passed for each tablet, and disintegration times were 68 sec for Pearlitol, 150 sec each for Ludiflash and F-Melt and was 600 sec for Prosolv ODT.[19] On stability at 25°C/60% RH and under the accelerated conditions (40°C/75%RH), Perlitol Flash, Ludiflash, and F-Melt ODT tablets were shiny, and showed no degradation of drug as N-formylbenzocaine but Prosolv ODT showed a significant degradation over 6 months, especially at the accelerated conditions, suggesting the fructose in ODT was susceptible to humidity and higher temperature. The critical relative humidity (CRH) of fructose was 64% when stored at 40°C.

Tayel et al. (2017) evaluated sumatriptan succinate in an ODT formulation comprised of Pharmaburst, Ludiflash, Pearlitol, Prosol ODT, StarLac as sublingual ODTs.[20] Other mucoadhesive polymers like HPMC K4M, Carbopol, chitosan, and Polyox were used with aims at improving the residence time in the sublingual area. Pharmaburst showed the disintegration time of <30 seconds with over 83% release in 5 min, the relative bioavailability as compared with marketed Imitrex® tablet was over 132%, and HPMC was able to prolong the disintegration time to 184 sec and was considered the optimal best optimal for sublingual formulation. This data can be taken to suggest that Pharmaburst can be used for increasing the residence time while maintaining the lower disintegration time. With the understanding that Ludiflash and Prosolv ODT all contain mannitol and crospovidone as compared to Pharmaburst, their rate of hydration was different due to lack of sorbitol, suggesting a rapid hydration for Pharmaburst, caused by equatorial position of hydroxyl groups. *In vitro* disintegration times of Pharmaburst, Pearlitol Flash and StarLac excipients showed the following order: Pharmaburst < Perlitol Flash < StarLac, meaning the wetting was significantly much greater in Pharmaburst due to higher water absorption uptake of crospovidone.[21] In a comparative study with carvedilol in Pharmaburst and Ludiflash, the latter did not yield the desired disintegration time of drug in Soluplus® amorphous dispersion when compressed with ODT excipients, which could be attributed to particle size differences of two crospovidone grades (Kollidon® CL vs Polyplasdone® XL) used in the tablets.[22]

FDA APPROVED ODT DRUGS

ODT products have been marketed for different indications ranging from migraine to anti-emetic agents, antihistamine and to most serious chronic diseases such as depression and schizophrenia. Table 2 list the ODT drugs approved by FDA.[6]

Although these drugs have tendencies to quickly disintegrate in mouth with saliva, their good creamy mouth feel and physical attributes vary considerably from one to other as some require special packaging in blisters and others as lyophilized powder.[23]

TABLE 2

API	Company	Key Inactive Ingredient *
Acetaminophen	H.E.B.	Mannitol, povidone, ethylcellulose, dextrose
Adzenyz - XR (amphetamine)	Neos Therapeutics	Mannitol, crospovidone, microcrystalline cellulose, colloidal silicon dioxide,
Alprazolam	Jazz Pharma	Mannitol, corn starch, crospovidone, methacrylic acid copolymer, MCC
Carbidopa and Levodopa	Mylan	Mannitol, sorbitol, aspartame, crospovidone, MCC
Clonazepam	Par Pharma	Mannitol, sorbitol, crospovidone, aspartame,
Dartisla® (glycopyrrolate)	Edenbridge	Mannitol, gelatin, poloxamer 188,
Diphenhydramine	Pfizer	Mannitol, aspartame, citric acid, ethylcellulose, lactitol monohydrate
Donepezil	Eisai	Mannitol, carrageenan, polyvinyl alcohol
Hyoscyamine	Alaven Pharma	Mannitol, lactose monohydrate, starch
Lamotrigine	GSK	Mannitol, crospovidone, ethylcellulose, polyethylene
Lansoprazole	Takeda	Mannitol, crospovidone, citric acid, magnesium carbonate, MCC, HPC
Loratadine	Merck	Mannitol, gelatin, aspartame
Loratidine	Pfizer	Mannitol, crospovidone, MCC, citric acid, starch, sodium bicarbonate, aspartame
Metoclopramide	Salix Pharma	Mannitol, gelatin, acesulfame potassium
Mirtazapine	Merck	Mannitol, crospovidone, hypromellose, aspartame, citric acid, sodium bicarbonate, MCC, povidone, starch
Olanzapine	Eli Lilly	Mannitol, gelatin, aspartame
Ondansetron	GSK	Mannitol, gelatin, aspartame
Ondansetron	Ranbaxy	Mannitol, croscarmellose sodium, aspartame
Piroxicam	Pfizer	Mannitol, gelatin
Prednisolone	Shionogi	Mannitol, citric acid, crospovidone, HPMC, MCC, methacrylate copolymer, sodium bicarbonate
Resperidone	Janssen	Mannitol, ion exchange resin, gelatin, glycine, simethicone, carbomer, aspartame
Rizatriptan benzoate	Merck	Mannitol, gelatin, glycine, aspartame
Selegiline	Valeant	Mannitol, gelatin, glycine, aspartame, citric acid
Tascenso® (fingolimod)	Pfizer	Mannitol, medium-chain triglycerides, and sodium lauryl sulfate.
Tramadol	Shionogi	Mannitol, aspartame, copovidone, crospovidone, ethylcellulose
Zolmitriptan	Astra Zeneca	Microcrystalline cellulose, crospovidone, colloidal silicon dioxide

ODT Approved Drugs (*http://dailymed.nlm.nih.gov/dailymed/about.cfm)

STORAGE OF ODT DOSAGES

Storage of the ODTs is important to meet the critical quality attributes of drug products. Moisture protection is required to protect the excipients and API to prolong the shelf life and to maintain the integrity of tablets and/or to avoid unpleasant mouth feel. Excipient manufacturers typically provide guidance for stability and packaging of ODTs. Since the ODTs are not coated, the protection from humidity, atmosphere and heat makes it highly inevitable. For example, mannitol based Ludiflash ODT requires storage at ambient condition at 25°C or less with dense packaging material to control the humidity and moisture permeation. In a study, stability data showed that disintegration of Ludiflash placebo ODT dosage remains unchanged (< 30 seconds) even on exposure to higher humidity at ambient temperature.[6] In another study with Ludiflash, containing 2 mg loperamide in an ODT, when stored in closed polyethylene bottle for 12 month under relevant ICH climate conditions, the disintegration time remained constant (< 30 seconds), and was found to be independent of the storage conditions.

CONCLUSION & FUTURE PERSPECTIVES

As more new chemical entities (NCEs) being discovered, the industry is weighing all options for evaluating those molecules in different dosages to improve solubility and oral bioavailability. With requirement for taste-masking of bitter drugs with commercially available ODT excipients, it poses additional challenges for improving taste-masking and performance of molecules for the intended usages. A recent market trend suggests that half of the patient population prefers ODTs over other dosages like regular pills or liquids. Faster absorption in the mucous civility makes ODTs better choice for children and geriatric patients. ODTs offer clinical advantages with reference to safety and improved efficacy for broad range of therapeutic indications. For those advantages, coupled with regulatory and patient compliances, the excipient manufacturers have developed their ODT platforms to serve the industry by expanding the products to formulate the drugs for life cycle management and extend the patent protection.

As more repurpose drugs and new molecules become part of the life cycle management, the regulatory requirements for ODTs could play an important role in drug development with respect to appropriate tablet size and weight, ingredients/components, drug solubility, taste-masking for an intended use to satisfy the patient compliance. For instance, a tablet weight of 300 mg -500 mg is generally recommended but higher weight ODT dosages can also be justified based on the product performance such as ingredient solubility and stability, and packaging conditions.

Ascendia, with its expertise in cGMP manufacturing of oral and injectable drug products, can help clients interested in solid oral dosage forms (SODFs), and ODTs as well. With its four enabling platform technologies

including LipidSol®, EmulSol®, NanoSol® and AmorSol®, Ascendia can handle the challenging molecules across all modalities in oral tablets and liquids and injectables. ◆

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CGT MANUFACTURING

Scaling CGT Manufacturing Inside the US: The New Regulatory Paradigm

By: John Tomtishen

INTRODUCTION

Cell and gene therapies (CGTs) represent one of the most transformative advances in modern medicine. These living drugs offer the potential for one-time cures for conditions previously considered incurable. But traditional biologics manufacturing systems were never designed to handle the complexity, variability, and patient-specific nature of CGTs, meaning an entire new paradigm was needed.

Unlike conventional pharmaceuticals, autologous CGTs – particularly approved cell therapies, which are primarily chimeric antigen receptor (CAR) T-cell therapies – require personalized processing, where a patient's own cells are collected, modified and returned, all under strict timelines and sterile conditions. This creates immense pressure on manufacturing facilities, which still rely heavily on manual labor, open systems, and fragmented workflows.

Now, amid shifting Food and Drug Administration (FDA) priorities as well as developing geopolitical considerations, US companies are entering a new regulatory era, one that will define how CGTs are scaled, distributed, and delivered domestically. Despite the uncertainty of this moment, three major trends are unchanged and continue to shape this new era: a mandate for domestic manufacturing, an emphasis on novel platform technologies, and a push toward automation and standardization to meet total patient demand.

WHY THE US IS REASSERTING MANUFACTURING CONTROL

Lawmakers have shown increasing urgency to source life sciences manufacturing within the US. This largely reflects both domestic political realities and security concerns. In June, the FDA invoked a Biden–era data–security rule to pause new clinical trials that ship American patients' living cells to China and certain other countries for processing. The rules were designed to safeguard American health and genomic data from being accessed or processed in "high-risk" countries.[1] In parallel, the Department of Defense and an allied bipartisan coalition in Congress continues to advance the BIOSECURE Act, which would bar federal agencies from funding therapies, or even contracting for disposable gloves, if any tier of the supply chain relies on biotech "companies of concern" headquartered overseas.

Both the BIOSECURE Act and the data security rules reflect a coordinated policy shift aiming to restrict the offshoring of clinical-grade materials and genomic data to certain nations, including China. They are also accelerating the push for domestic CGT manufacturing.

The practical implications become vivid when we revisit the early days of CAR T development. Before US manufacturing networks were established for certain cell therapies, such as Carvykti (ciltacabtagene autoleucel), there were cases of US patients traveling to China when they ran out of options.[2] Back then, the inconvenience was framed as an unavoidable cost of innovation. Today, the same design would be unacceptable – in fact, even the transport of patient-derived materials would be a no-go for trial participants, payers, investigators, and regulators worried

IMAGE 1

First cGMP Cell Shuttle

that genomic data collected from immune cells could be siphoned off into foreign databases.

REEVALUATING CAPACITY IN A SHIFTING LANDSCAPE

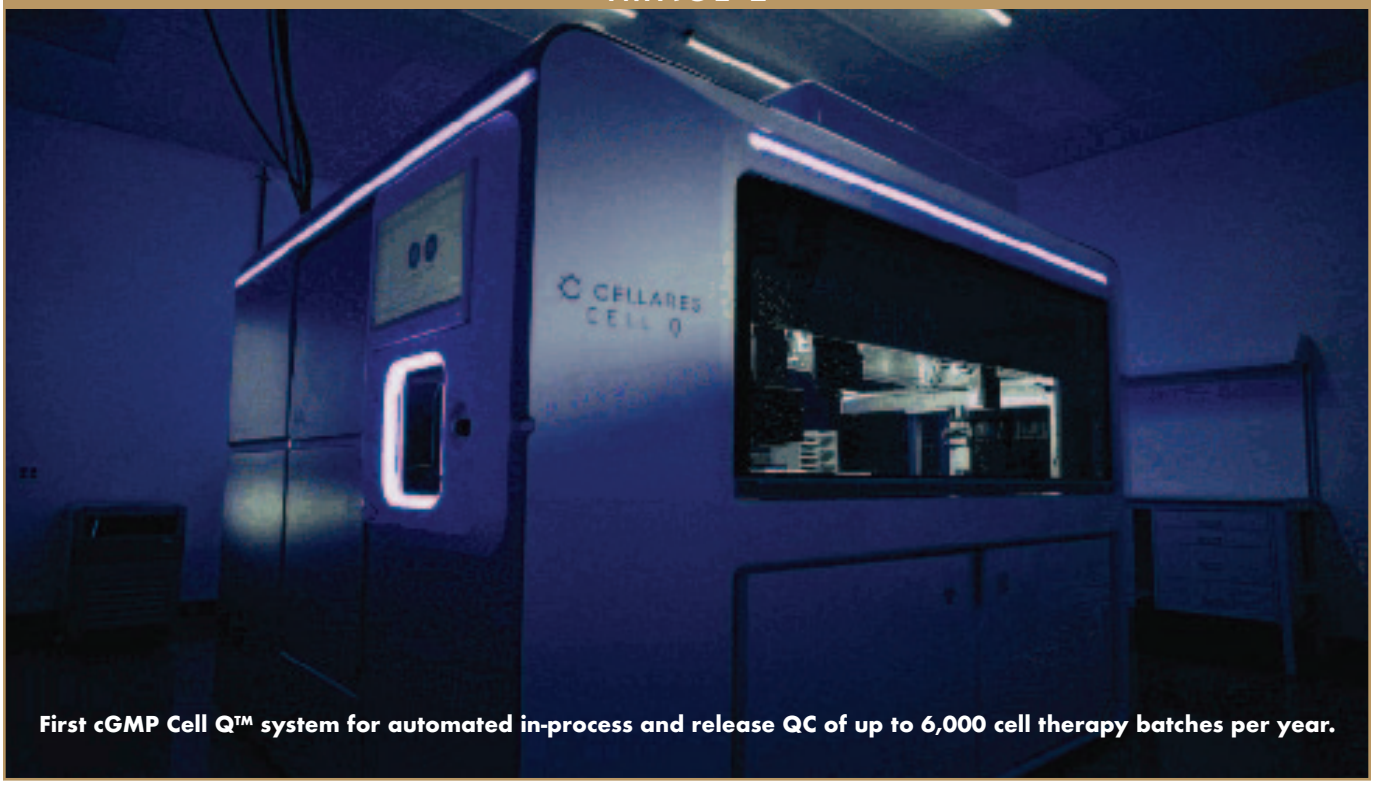
If a CAR T manufacturing process begins in America, having it end in America simplifies the issue. Resolving it means addressing the disconnect between therapeutic innovation in CGT and the infrastructure required to deliver it at scale. There have been multiple efforts around the world to address this friction between cutting-edge science and capacity-limited manufacturing systems. Between 2018 and 2022, every major pharmaceutical company in the space, as well as multiple CDMOs and a herd of venture–backed start–ups, announced brand-new CGT facilities.

Some of that momentum has reversed. A few examples: over the past 2 years, AGC Biologics mothballed its CGT plant in Colorado, citing under–utilization; Rentschler Biopharma decided to retool its Stevenage asset for conventional biologics; and AmplifyBio filed for bankruptcy after macro–volatility throttled early–phase demand.[3,4] These announcements might appear as evidence that we've over–built – and yet, CAR T demand today is both drastically unmet and poised for rapid expansion.

A closer look reveals a mismatch between square footage and utility. For one, much of the capacity was constructed overseas, of decreasing value in the current climate. Even in the US, CGT manufacturers built capacity with largely legacy technologies for yesterday's way of working, then realized too late that the goalposts had moved. Many of those new suites were engineered around open, manual workflows that top out at a few hundred batches per year. They may sit thousands of miles from the patients they intend to serve and depend on long lead–time technology transfers that make next–generation upgrades painfully slow.

The incrementalism these facilities relied on is insufficient because their existing systems have proven unscalable. Meanwhile, the appeal of CAR T-cell technology is growing. Autologous CAR T therapy was once reserved for adults whose blood cancers had resisted every other modality. Less than ten years later the evidence is building toward frontline use, and coming approvals for therapies in larger indications like autoimmune disease are expected to dwarf the addressable market for current approved drugs.[5] Layer on other cell-based therapies like *ex vivo* gene–edited therapies and novel cell therapy technologies on the horizon, and the mismatch grows wider. Older multiproduct suites cannot efficiently flex to sufficient volume.

IMAGE 2



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REGULATORY ALIGNMENT

This is one aspect of what FDA's evolving regulatory stance now seeks to address. FDA has introduced a number of programs to lower the barriers to innovation, reduce time to market, and increase patient access to CGTs. Programs like Support for clinical Trials Advancing Rare disease Therapeutics (START) offer early and frequent engagement with FDA reviewers, reducing uncertainty, avoiding costly protocol revisions, and accelerating trial readiness.[6] Another is Regenerative Medicine Advanced Therapy (RMAT) designation, which reduces the time between clinical milestones and commercial approval, critical for companies investing heavily in infrastructure for one or more high-risk CGT assets.[7]

The agency also recognizes that to meet growing demand, CGT manufacturers need to adopt novel technologies that are scalable, efficient, and regulatory-ready. In 2024, FDA finalized its Advanced Manufacturing Technologies (AMT) designation program aimed at reducing manufacturing bottlenecks by encouraging early adoption of platforms that can improve product consistency, reduce costs, and increase scalability. The AMT program's first disclosed designation was in cell therapy, for Cellares' Cell Shuttle, a fully closed, automated, end-to-end manufacturing platform purpose-built for the modality.8 Under the AMT designation, companies utilizing the Cell Shuttle access expedited FDA review, shorter IND/BLA timelines, and a streamlined regulatory path for additional therapies built on the same technology. The shortened regulatory timeline is especially attractive in competitive spaces such as BCMA and GPC3. As such, we expect other CGT manufacturing technology companies in the space to similarly pursue their own AMT designations.

ADVANCED TECH MEETING US MANUFACTURING NEED

The US has an opportunity to lead by embracing an increasingly automated, standardized CGT manufacturing model designed for the realities of 2025 and beyond.

FDA support for AMT is far from the only reason to embrace next-generation manufacturing for CGTs. Domestic cell therapy developers are also attracted to advanced manufacturing technology benefits like the ability to lower costs, a major existing limitation to cell therapy accessibility. A number of elements related to novel manufacturing approaches can reduce batch manufacturing costs, including streamlining facility designs to support multi-product manufacturing based on the capabilities of these novel platform technologies. These novel and fully closed technologies like the Cellares Cell Shuttle can also be deployed in controlled non-classified environments instead of the

more stringent ISO 7 suites that have dominated legacy autologous manufacturing sites, which can significantly lower facility buildout costs.

Unlike traditional approaches, standardization through next-generation manufacturing has the potential for quick implementation and rapid scale-up acceleration. By integrating with software-driven automation, transferring and replicating manufacturing onto additional devices – in any location – is much more straightforward than traditional requirements.

While accelerated manufacturing platforms have streamlined upstream processes, downstream bottlenecks, particularly in quality control (QC), remain a hurdle. As the volume and complexity of CGT products increase, the demand on QC infrastructure ramps up, often leading to release delays and added variability.

To meet this challenge, interest is growing in fully automated QC systems that can integrate directly into the production workflow. Like manufacturing systems, these platforms aim to reduce manual interventions, enable real-time data capture and support continuous release models, all while maintaining compliance with evolving FDA standards.

Cellares' automated QC platform is called the Cell Q. These stations bring rapid sterility, identity, and viability measurements in line. This creates a real-time feedback loop that immediately improves process control. That transformation is exactly what FDA's Center for Biologics Evaluation and Research (CBER) envisioned when it asked industry to align around quality–by–design principles rather than rely on end–product testing alone.

This evolution aligns with the principles of Industry 4.0, where manufacturing systems are digitally connected, self-monitoring, and adaptive. In the context of CGT, it means creating fully integrated, intelligent facilities that can scale flexibly, respond to demand signals and ensure consistent quality, without duplicating infrastructure across geographies. The emergence of the integrated development and manufacturing organization model, which brings together process development, manufacturing, automation, and quality within a unified, software-integrated platform, is helping to make this vision a reality. Rather than building more brick-and-mortar capacity, CGT companies can now access the benefits of modular, cross-functional units that deliver global scalability through digital replication.

By embedding quality into every layer of production, these next-gen systems offer more than operational speed; they enable resilience, precision, and readiness for the next phase of CGT expansion.

BUILDING A CROSS-FUNCTIONAL CGT MANUFACTURING ECOSPHERE

Despite today's uncertainty, advanced American manufacturing capabilities in CGT may see additional opportunity given tilt from ongoing tariff risks. Trade relationships that once looked predictable, when many manufacturing plants outside of the US were greenlit, now sit on shakier ground. If US lawmakers impose retaliatory duties on biologics, overseas production costs could spike overnight. Domestic capability would ultimately be faster and less expensive.

The industry is facing a decision point. The existing trajectory is widely acknowledged as unsustainable, putting at risk the future of the CGT industry and the fate of patients awaiting potential cures. To bridge the gap between innovation and infrastructure, CGT companies must take proactive steps now. This includes leveraging platform technologies that align with FDA incentives and enable scalable, repeatable manufacturing. Standardization through automation can strengthen both upstream and downstream workflows to ensure end-to-end readiness for clinical and commercial demands.

With strategic investment and thoughtful adoption of next-generation manufacturing systems, US-based CGT developers are uniquely positioned to lead the next wave of innovation, reducing cost, accelerating time to market, and staying ahead of evolving regulatory expectations.

None of this is an abstract policy debate. The children with relapsed neuroblastoma, the adults battling refractory multiple myeloma, and the families confronting rare genetic disorders care only that a curative therapy is available when they need it. Meeting that expectation is more than a commercial opportunity; it is a moral obligation.

In 2024, I lost my father to erythroblastic acute myeloid leukemia. While there were limited treatment options available for him, science has given us the tools to re–engineer living cells into medicines and transform patient treatment. Continued innovation and investment within the space to find potential cures in the future will largely depend on our ability to transform the manufacturing paradigm and ensure these therapeutics can reach every eligible patient in a timely, affordable, and secure manner and help patients similar to my father. In the process, there are worthwhile opportunities to strengthen domestic man-

ufacturing and ensure another generation of American biopharma leadership. But success in CGT manufacturing will belong to those who scale smartly, adapt fast, and stay aligned with a shifting regulatory landscape. ◆

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BIOGRAPHY

John Tomtishen is a former Senior Vice President & General Manager, IDMO Business, at Cellares. He is a proven, results driven Business Operations and CMC strategic leader with broad experience in organizational and operational planning, technical development, and business transformation. He has extensive career experience within cell and gene therapies (Kymriah - tisagenlecleucel and Carvykti - ciltacabtagene autoleucel), biologics (Herceptin - trastuzumab), and vaccines (M-M-R II and ProQuad). A recognized expert and leader within the Biopharmaceutical and Cell and Gene Therapy Industry serving as the CMC Committee Chair with the American Society of Gene and Cell Therapy (ASGCT), the Manufacturing Advisory Committee Co-Chair with BioNJ, a member of the Cell Therapy Advisory Committee with the Alliance for Regenerative Medicine (ARM), and a member of the Advisory Board for the New Jersey Aseptic Process and Biomanufacturing Coalition. The views expressed in this op-ed are solely those of the author and do not necessarily reflect the views or positions of Cellares.

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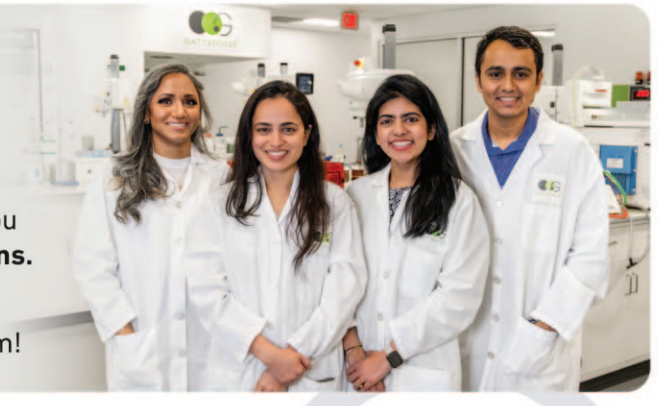

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PRECLINICAL SCREENING PLATFORM

From Preclinical Screening to Clinical Optimization: Accelerating Poorly Soluble Drug Development

By: Andrew Parker, PhD, John McDermott, and Sandeep Kumar, PhD

ABSTRACT

It's well understood most drugs emerging from discovery pipelines possess poor aqueous solubility and/or low permeability, providing barriers to absorption and bioavailability. Enhancing absorption is therefore a cornerstone of formulation science, directly impacting oral bioavailability and therapeutic index.

When choosing a CDMO partner, finding one with experience in the development of enabled formulation systems, such as amorphous solid dispersions and lipidic systems, is critical to advancing molecules that have poor solubility. Additionally, an "end-to-end" integrated service philosophy, in which all elements of drug development can be procured through a single vendor with capabilities and experience to pivot to the respective needs of a drug's biopharmaceutic properties, can further accelerate development at all stages.

In the preclinical phase, establishing formulations capable of achieving sufficient drug solubility to probe toxicology is key. Here, Quotient Sciences, applies a systematic, data-driven screening platform evaluating solubility-enhancement approaches to direct the toxicology formulation. As a drug approaches a first-in-human (FIH) trial, the Quotient Sciences Translational Pharmaceutics® platform enables development teams to minimize investment in GMP drug product manufacturing by making drug products on-demand. This allows the development team to reduce supply chain complexity and rapidly apply enabled formulations in the trial to ensure drug exposure. Finally, the Translational Pharmaceutics platform can be applied to further optimize drug product formulations using clinical data following Phase 1 studies.

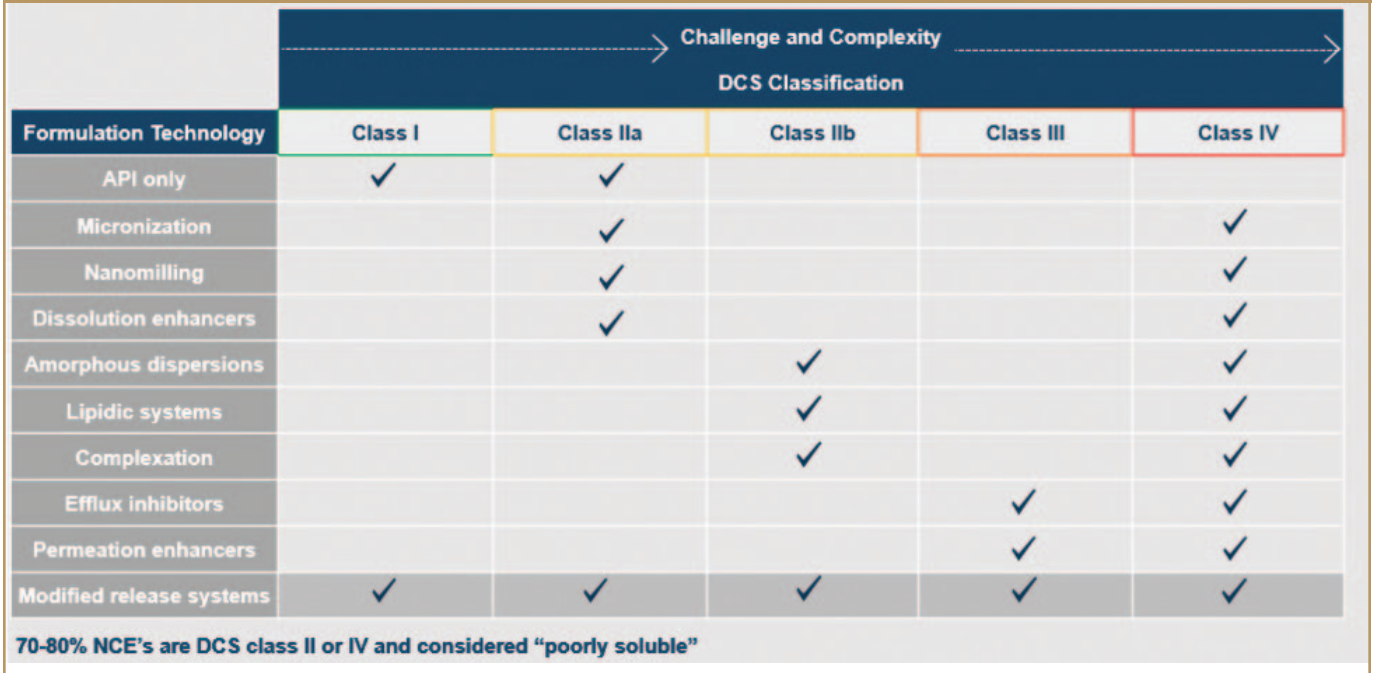
In one case, Quotient Sciences successfully developed an amorphous solid dispersion of a poorly soluble molecule using spray drying. The drug product was used in the first-in-human study of an oral therapy intended for the treatment of amyotrophic lateral sclerosis (ALS). The randomized, placebo-controlled Phase 1 trial evaluated safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and impact of food in healthy volunteers. Among the three formulations tested in this trial, the spray-dried version showed superior performance and was selected for further development. This study highlights how an integrated approach and adaptive design accelerates early phase development and de-risks formulation decisions using real-time clinical data.

INTRODUCTION

The pharmaceutical industry continues to face a critical formulation barrier: the intrinsically low aqueous solubility of numerous new chemical entities (NCEs), which adversely affect bioavailability and therapeutic performance. It is estimated that approximately 40% of marketed pharmaceuticals and nearly 90% of investigational compounds in the discovery pipeline exhibit poor water solubility, creating significant challenges for oral drug delivery and consistent pharmacokinetic profiles.[1]

Retrospective analyses of clinical trial outcomes from 2010 to 2017 indicate a drug development failure rate approaching 90%.[2] Clinical efficacy has been attributed to upward of 50% of

FIGURE 1



The developability classification system (DCS) is a framework incorporating dose, biorelevant solubility, and permeability to better predict in vivo performance. These technologies are evaluated in animal pharmacokinetic (PK) non-GLP studies within a 3-to-4-month timeline, allowing for rapid selection of the most promising formulation for toxicology purposes and achieving high dose targets that can often exceed 1000 mg/kg. This early screening is essential for de-risking clinical development and ensuring that viable candidates move forward to complete GLP toxicology studies and advance into the clinic.

failures, while other factors included dose-limiting toxicities (30%), suboptimal physicochemical and biopharmaceutical properties (10%-15%), and deficiencies in commercial strategy or portfolio alignment (10%).[2] These trends have continued in recent years.

Among the physicochemical limitations, poor solubility and membrane permeability are predominant contributors to clinical attrition, often resulting in inadequate plasma exposure, high inter-individual variability, and therapeutic failure. These limitations, however, can be mitigated through formulation strategy and an integrated approach to formulation and clinical testing. Quotient Sciences has established this through the Translational Pharmaceutics platform, which enables rapid optimization of formulation and clinical performance by aligning drug product development with real-time clinical data.

PRECLINICAL SCREENING STRATEGIES LEVERAGING BCS & DCS

A foundational framework published over 20 years ago for understanding developability is Lipinski's Rule of Five, which outlines molecular properties that influence drug-likeness.[3] Compounds that violate these rules are more likely to suffer from poor absorption or permeation, making them less viable as oral drugs.

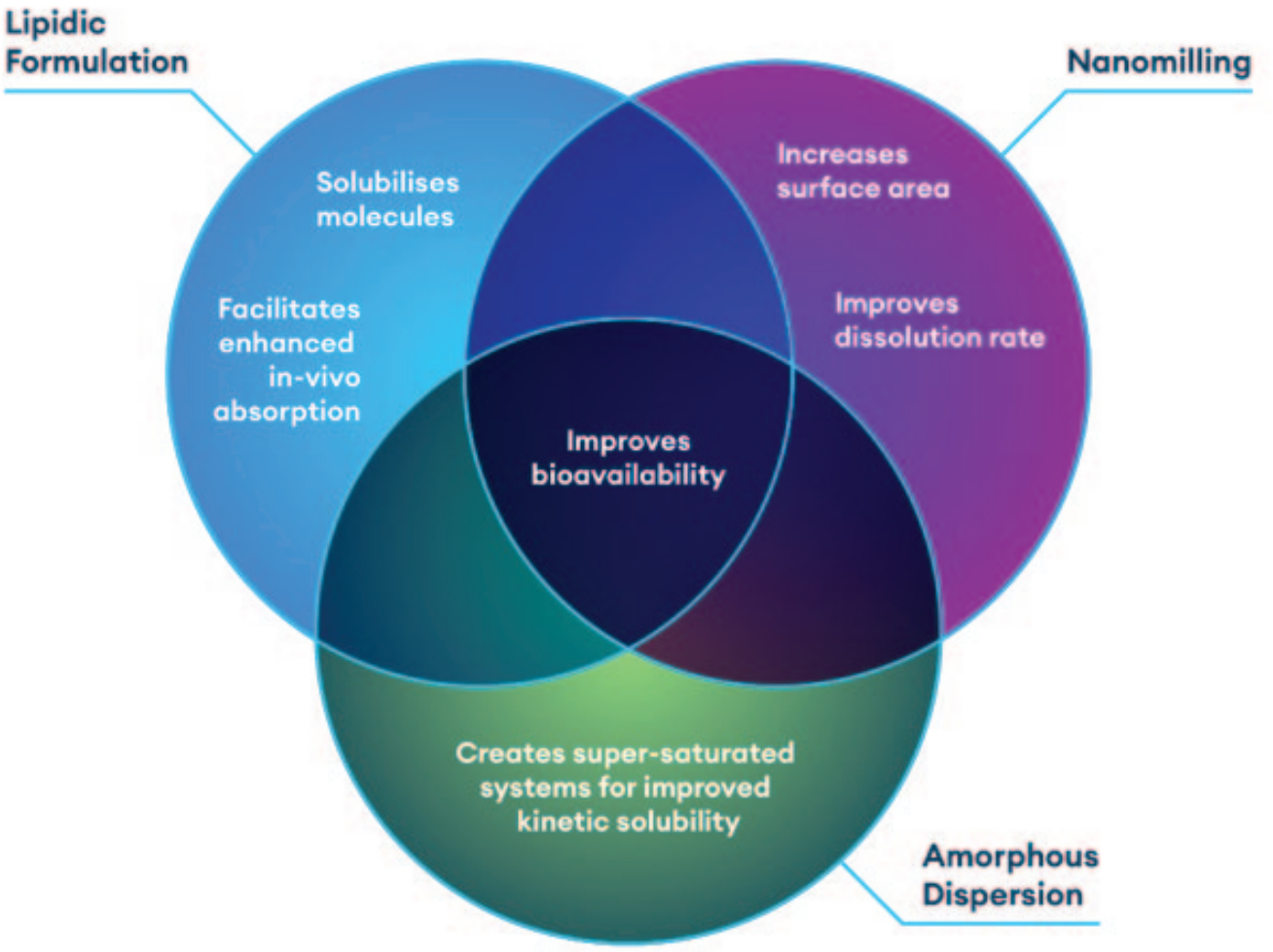
As small molecule therapeutic design has evolved against more challenging targets and binding sites, Lipinski's rules have needed to be significantly bent — and broken — over the past 2 decades.

As the industry has embraced more innovative and integrated ways to progress drug candidates, developers have seen that early identification of solubility issues is critical to avoid costly delays later in development. Traditional high-throughput screening (HTS) methods are used to assess solubility, permeability, and stability. However, these methods often fall short in predicting human pharmacokinetics, especially for Biopharmaceutics Classification System (BCS) Class II and IV compounds.

To address this, the Developability Classification System (DCS) emerged as a more nuanced framework (Figure 1).[4] Unlike the BCS, which focuses on solubility and permeability, the DCS incorporates dose, biorelevant solubility, and permeability to better predict *in vivo* performance. This system also guides formulation strategy by identifying whether a compound is dissolution-rate limited or solubility-limited.

A preclinical screening platform that integrates DCS principles with advanced formulation technologies, like the one de-

FIGURE 2



Quotient Sciences preclinical screening platform includes enabling formulation technologies that can help improve the chances of downstream success.

veloped by Quotient Sciences, can be used to accelerate preclinical pathways. Quotient Sciences' approach includes nanomilling for particle size reduction, amorphous solid dispersions to enhance dissolution, and lipidic formulation screening for compounds with high lipophilicity (Figure 2).

THE TRANSITION TO FIRST-IN-HUMAN WITH INTEGRATED FORMULATION STRATEGY & CLINICAL TESTING

For first-in-human (FIH) studies, a phase-appropriate clinical formulation, which has scientific justification related to the toxicology-based formulation presentation, is prepared for dosing the drug substance of interest. Typically, these are formulations that enable dose titration in response to emerging clinical data. This approach offers flexibility in dosing for healthy volunteers during single and multiple ascending dose (SAD/MAD) phases.

Using the Translational Pharmaceutics platform, dose escalation decisions can be made in real time based upon emerging clinical data. This adaptive approach supports informed decision-making, enabling the selection of the optimal formulation and dosage strength based on actual clinical outcomes.

A recent study published in the American Society for Clinical Pharmacology and Therapeutics' Clinical and Translational Science (2024) Journal highlights how the Translational Pharmaceutics platform supported a client in conducting a healthy volunteer study for a promising new treatment for ALS.[5] The study featured a flexible design that enabled the team to develop and test three different formulations of the drug within the same clinical trial, saving months of time from the clinical program:

- A crystalline methylcellulose (MC) suspension
- A spray-dried dispersion (SDD)

- A hot-melt extrusion (HME) suspension

The HME and SDD formulations showed two- and four-fold higher exposure than the MC suspension, respectively. The SDD formulation was selected for progression to subsequent SAD and MAD cohorts.

Combining formulation development and clinical testing into one streamlined process, the program saved time, improved drug performance, and helped move the treatment forward more efficiently.

ADVANCING INTO PHASE 2 WITH A FOCUS ON COMMERCIALLY READY FORMULATIONS

Advancing solubility-enhanced formulations (such as nano-milled suspensions, lipid-based systems, and amorphous spray-dried dispersions) into solid oral dosage forms requires carefully designed strategies to maintain bioavailability and support scalable manufacturing.

Nano-milled APIs, typically stabilized in aqueous media, can be converted into solid intermediates through spray drying or lyophilization, followed by granulation and compression or encapsulation. Lipid-based systems, including SEDDS, may be adsorbed onto porous carriers to create free-flowing powders suitable for encapsulation, or directly filled into hard or soft gelatin capsules to retain their liquid characteristics and self-emulsifying behavior. Amorphous solid dispersions produced via spray drying are generally blended with functional excipients to improve flow and compressibility, roller compacted into granules to enable final blending for tableting direct compression or capsule filling.

Each formulation pathway must be optimized to maintain enhanced dissolution performance and desired PK profile while ensuring physical and chemical stability throughout processing and shelf life. Quotient Sciences' RapidFACT® programs, enabled through the application of the Translational Pharmaceutics platform, approach allows for a more advanced strategy to ensure that a drug product can be a commercially-ready formulation.

PHASE 3 ONWARDS COMMERCIAL FORMULATION LIFECYCLE MANAGEMENT & IP MAXIMIZATION

As drug candidates progress into Phase 3 and approach commercialization, transitioning from immediate-release (IR) solubility-enhanced formulations to modified-release (MR) formats can serve as a strategic lever for lifecycle management and intellectual property (IP) optimization. For example, IR tablets developed using spray-dried dispersion (SDD) technology during Phase 2 can be reformulated into MR dosage forms, offering valuable line extension opportunities.

Leveraging the Translational Pharmaceutics platform enables rapid prototyping, clinical evaluation, and real-time optimization of MR formulations. This integrated platform facilitates adaptive formulation development, allowing release profiles to be fine-tuned based on emerging pharmacokinetic (PK) and pharmacodynamic (PD) data. Converting an IR SDD into a once-daily matrix tablet or a sustained-release coated system can help reduce peak plasma concentrations (Cmax), mitigate side effects, and maintain therapeutic levels over an extended duration. These enhancements not only improve clinical outcomes but also support differentiated product positioning in a competitive market.

From a commercial and regulatory standpoint, MR formulations derived from SDDs can underpin new patent filings based on novel composition, process, or therapeutic use claims. This approach offers a strategic pathway to extend market exclusivity beyond the original compound patent, particularly when aligned with the expiration of the primary patent. Additionally, such line extensions can be tailored to address new patient populations, enhance adherence in chronic conditions, or introduce alternative dosing regimens — each contributing to sustained product value and long-term competitive advantage.

SUMMARY

The development of poorly soluble drugs remains a significant challenge in pharmaceutical R&D. However, by adopting an adaptive approach that integrates services from preclinical screening to clinical optimization, developers can achieve significant time- and cost-saving benefits.

The Quotient Sciences Translational Pharmaceutics platform can be applied to optimize drug product formulations using clinical data following Phase 1 studies, a RapidFACT program. This enables real-time formulation adjustments and seamless transitions between development phases to reduce timelines, lower costs, and improve clinical outcomes. ◆

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BIOGRAPHIES

Dr. Andrew Parker has over two decades of experience in the pharmaceutical industry, spanning from preclinical development, through early clinical formulation development into late-stage development, scale-up, and commercialization. At Quotient Sciences, his focus is on Translational Pharmaceutics® and the acceleration of drug candidate progression provided through the integration of formulation development, clinical drug product manufacture, and clinical dosing activities. He has an interest in enabling technologies for bioavailability enhancement, characterization of all delivery formats, innovative technologies, and understanding drug product structure and function relationships. Additionally, he has advised clients in all types of clinical pharmacology study objectives, including first-in-human, drug-drug interaction studies, relative bioavailability, bioequivalence, TQT, and studies where various types of PD biomarkers and PD bio-responses (such as EEG) are part of exploratory endpoints in healthy volunteer studies. Before joining Quotient Sciences, he worked at Cooper Surgical and Healthcare as a Program Director and at Catalent as an Open Innovation Director covering two business units. He also spent 15 years at Juniper Pharma Services and Molecular Profiles CDMOs in a variety of roles combining technical and commercial knowledge, sitting at the operational and business interfaces with external clients.

John McDermott has over 25 years of experience in pharmaceutical sciences with prior roles at companies including Rhone Poulenc Rorer and Covance (later acquired by LabCorp). He joined Pharmaceutical Profiles in 2001, which, following a series of M&A and organic growth, was rebranded as Quotient Sciences in 2017. He has been central to the development of Quotient Sciences Translational Pharmaceutics®, the company's flagship drug development platform. This platform integrates formulation development, on-demand GMP drug product manufacturing, and healthy volunteer clinical testing to deliver time and cost efficiencies in small molecule and oral peptide drug programs and applications. He has significant experience in scintigraphy imaging studies for oral and inhaled dosage forms, including the development and validation of radiolabeling methods.

Dr. Sandeep Kumar is a Drug Development Consultant at Quotient Sciences, with a PhD in Pharmacy and experience across the CDMO and excipient industries. He specializes in formulation development and early phase clinical strategy, supporting programs from candidate nomination through first-in-human trials. He is passionate about working closely with clients to shape scientifically grounded study designs that reflect the unique needs of each molecule. He uses a practical and strategic approach to help teams solve development challenges clearly and effectively. Prior to joining Quotient, he held roles in formulation and technical consulting, contributing to preclinical service innovation and client engagement.

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Special Feature

Excipients: Innovation in a Shifting Pharma Landscape

By: Cindy H. Dubin, Contributor

This past July, the World Health Organization and the United Nations Office on Drugs and Crime unveiled in a landmark report (Contaminated Medicines and Integrity of the Pharmaceuticals Excipients Supply Chain) that there are persistent and preventable threats of contaminated medicines with industrial-grade toxic chemicals, notably diethylene glycol and ethylene glycol. The result is lost lives and compromised patient health. The report claims that in the past 90 years, there have been 25 documented incidents of excipient contamination, resulting in more than 1,300 deaths worldwide. The agencies point to systemic vulnerabilities in the gobal supply chain of pharmaceutical excipients as the culprit. WHO and UNODC are urging global action to close regulatory gaps and strengthen oversight of excipient supply chains.

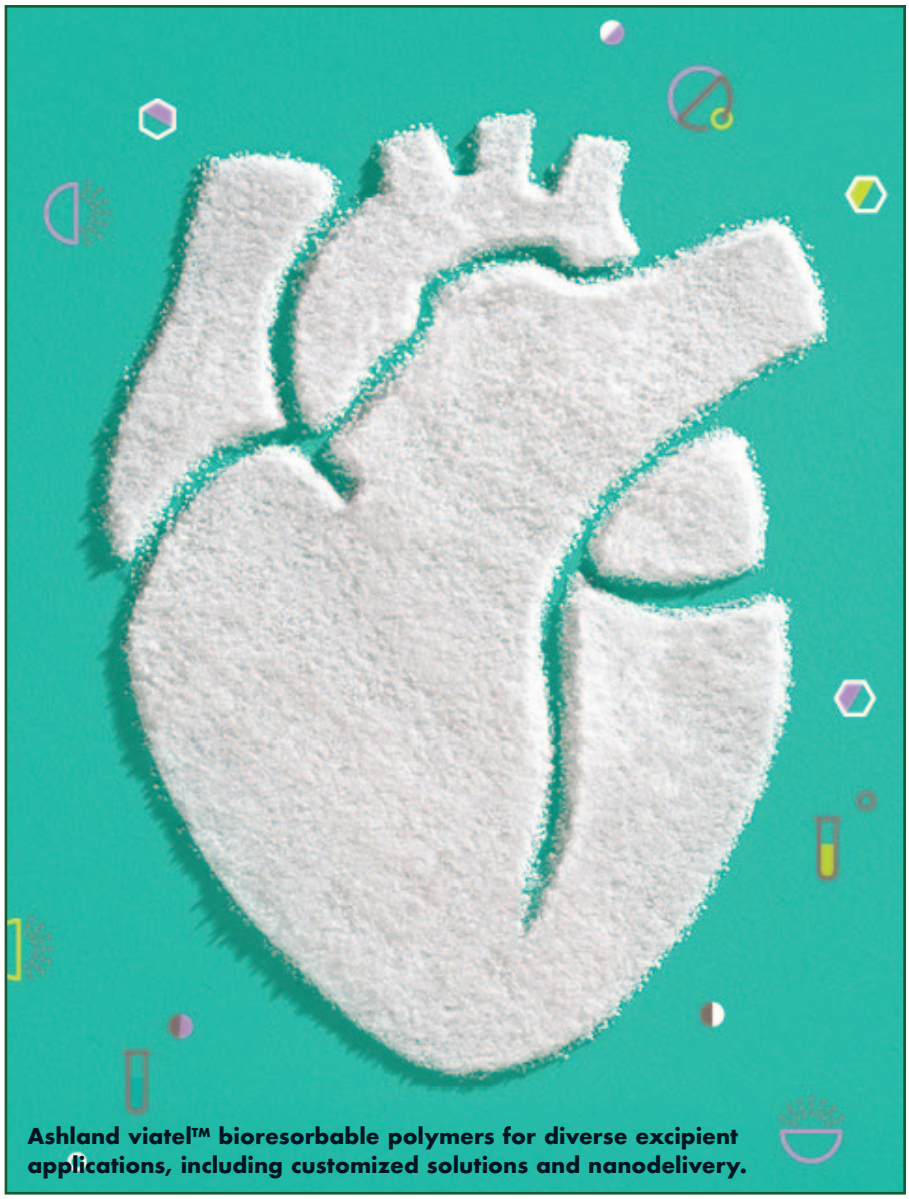
Additional challenges include geopolitical instability, raw material shortages, economic uncertainty, and manufacturing bottlenecks, all of which can disrupt the pharmaceutical excipients market (BCC Research). While working to overcome these disruptions, excipient suppliers are focused on a shifting pharma landscape that is calling for multifunctional excipients for more

A scientist showcases oral solid dose capabilities at Thermo Fisher Scientific's site in Bend, Oregon.

personalized medicine, natural and plant-based excipients for fewer side effects, and nanoexcipients for more targeted drug delivery.

"By ensuring reliable supply, advancing sustainability, and supporting the precision demands of personalized medicine, excipients are helping shape the future of drug development," says Dr. Sreejit Menon, Head of Life Sciences R&D, North America – Croda. "Excipients are no longer passive ingredients; they are strategic enablers of therapeutic innovation."

Drug Development & Delivery's annual excipient report highlights this innovation and reveals how excipient suppliers are doing their part to ensure a reliable, resilient, and compliance-driven supply chain.



Ashland viatel™ bioresorbable polymers for diverse excipient applications, including customized solutions and nanodelivery.

Ashland: Collaborative Customer-Centric Approach

The pharmaceutical industry is witnessing a surge in interest around novel chemistries that enable nanoparticle drug delivery — particularly those that offer biocompatibility, tunable release profiles, and scalability for complex formulations. Among these, bioresorbable polymers, such as Poly D,L-lactide-co-Glycolide (PLGA), Poly D,L-Lactide (PDLLA), customized variants, and cationic chemistries, have emerged as frontrunners due to their proven safety, versatility, and regulatory acceptance.

The ability to modulate degradation rates through compositional changes, as well as the flexibility to functionalize with tailored end groups, offers versatility for precision medicine and personalized therapies. "Ashland has responded to this growing demand by expanding our viatel™ bioresorbable polymer platform, which now supports a broad range of nanomedicine and parenteral applications — including cationic variants for nucleic acid delivery," says Sean McMahon, PhD, Director of Pharmaceutical Business Development and Strategic Marketing, Injectables, Ashland.

The vitatel scalable technology platform enables the creation of advanced drug delivery systems, including injectable hydrogels, nanoparticle carriers, drug depots, implants, stents, device coatings, and tissue regeneration scaffolds and wound closure devices.

Dr. McMahon explains: "These polymers are metabolized into non-toxic byproducts and are compatible with modern processing techniques like solvent-based processing, 3D printing, hot melt extrusion, and injection molding — making them ideal for both clinical and commercial scale-up."

Customized polymer solutions are developed at Ashland through a collaborative engagement, enabling the company to tailor excipients to meet drug compound needs in terms of stability, as well as drug delivery needs related to tissue targeting or processing requirements. He adds: "The recent completion of a $15 million facility expansion in Mullingar, Ireland, sig-

nificantly enhances Ashland's capacity to accelerate drug development programs. This means we can help our customers bring more life-changing medicines to patients, reinforcing our position as a leader in polymer innovation and R&D."

BASF Pharma Solutions: Virtual Guidance Empowers Formulators

Formulators are increasingly encountering challenges with poor drug solubility, as many new drug candidates are difficult to solubilize. This can lead to suboptimal dissolution profiles and reduced bioavailability. To address these issues, solubilizers like BASF's Kolliphor® HS 15 or Soluplus® can be used in various formulations. "To assist formulators in identifying suitable solubilizer options, BASF developed ZoomLab®, a virtual formulation assistant that applies algorithm-based analysis to offer science-backed formulation guidance," says Gloria Ho, PharmD RPh, Global Technical Marketing Manager, BASF Pharma Solutions.

Formulation guidance is also needed in the regulatory landscape, particularly as nitrosamines have emerged in the last year as a major concern for authorities worldwide. In response, BASF proactively developed nitrite-tested grades of povidone, copovidone, and crospovidone, which are supported by validated nitrite testing protocols. Additionally, to help customers navigate the nitrosamine risk, a "Nitrosamine Risk Assessment and Mitigation" app is available for users of ZoomLab®. "The app offers structure-based prediction tools and formulation guidance, empowering formulators to assess nitrosamine formation risks and select appropriate excipients with confidence," says Claudia Scholten, Strategic Marketing & Innovation Manager Excipients, BASF Pharma Solutions.

BASF's GMP Solution Center in Wyandotte, Michigan, provides reliable supply of bioprocessing ingredients and excipients for biopharma applications and molecules.

Aligning with regulatory expectations are customer sustainability goals, particularly in Europe where demand for traceable supply chains is accelerating. To that end, a shift toward sustainable and traceable sourcing in the future will be shaped by a balanced portfolio that includes RSPO-certified, SuCCESS-certified, and reduced product carbon footprint (rPCF) excipients, says Ms. Scholten. "Today, we are focusing on our lipids portfolio, which is 100% RSPO-certified, ensuring responsible palm sourcing."

There is also a trend towards more personalized therapies, which is directly influencing the demand for tailored excipient solutions (e.g., for targeted delivery, controlled release, bioavailability enhancement). At BASF's new GMP Solution Center in Wyandotte, Michigan, the focus is on high-performance poloxamers and other surfactants that are uniquely suited to the needs of precision therapies by, for example, allowing specific gelling behavior or meeting a very narrow specification range, she says.

Croda: Vast Surfactant Toolkit for Advanced Drug Delivery

The pharmaceutical excipients market faces multiple pressures, including geopolitical instability, raw material shortages, and stringent regulatory oversight. These challenges have highlighted the importance of supply chain resilience and compliance-driven innovation. To mitigate disruptions, Croda has strengthened regional partnerships and implemented multi-source procurement strategies, ensuring reliable access to high-quality materials. "Embedding compliance into development workflows has accelerated robust excipient advancements," says Dr. Sreejit Menon, Head of Life Sciences R&D, North America – Croda.

Innovation remains central to Croda's business, he says, helping customers meet strict regulatory standards while also providing them with a wide surfactant toolbox. For example, Super Refined™ Poloxamer 188 and Tween™ 20 HP LSA were developed to enhance cell viability in upstream bioprocessing and improve biologic formulation stability, respectively. "Super Refined Poloxamer 188 acts as a reliable

shear protectant and protein stabilizer, while Tween 20 HP LSA features ultra-low peroxide and aldehyde levels and a controlled fatty acid profile, ideal for enzymatically sensitive formulations," he explains. "Together, these excipients support customers in achieving high-performance, regulatory-compliant formulations in a geopolitically charged environment."

Looking ahead, organic excipients are expected to dominate the sector within the next four years (The Business Research Company). As sustainability and biocompatibility become central to formulation strategies, organic excipients, particularly those from renewable, non-animal sources, are gaining traction due to their favorable safety profiles and reduced environmental impact. Their adoption, however, will depend on overcoming variability and ensuring scalability.

"Our high-purity lipid technologies for mRNA delivery illustrate how organic materials can meet the stringent demands of advanced therapeutics, undergoing rigorous purification for consistency and performance," says Dr. Menon. "Refined synthetic excipients, such as Super Refined Poloxamer 188 and Tween 20 HP LSA, remain indispensable in biologic formulations where ultra-low impurity levels are critical. The future will likely be a hybrid landscape, with organic excipients leading in some areas and refined synthetics supporting others."

Personalized medicine is further shaping excipient innovation. Tailored therapies demand excipient systems that are equally precise, supporting route-specific delivery, enhanced bioavailability, and patient-specific therapeutic goals. High-purity lipid platforms for nucleic acid delivery are optimized for encapsulation efficiency, cellular uptake, and endosomal escape – all critical for personalized therapies. He says: "Similarly, excipients such as Tween 20 HP LSA or Super Refined Poloxamer 188, with ultra-low impurity profiles, stabilize protein-based therapies, ensuring each formulation meets its intended patient population's needs."

At Croda, excipients are no longer passive ingredients; they are strategic enablers of therapeutic innovation.

As nanoparticle delivery systems gain prominence, interest is rising in novel substances that can enhance their performance. Lipid carriers, surface modifiers, and polymeric stabilizers are increasingly designed to preserve nanoparticle integrity and improve intracellular delivery. "Our high-purity lipids for mRNA and siRNA therapeutics support stability and consistency in lipid nanoparticle systems while boosting delivery efficiency, critical for next-generation vaccines and gene therapies," says Dr. Menon. "At the same time, our work with novel surfactants and polymers focuses on modulating immune response and optimizing biodistribution, expanding the toolkit for advanced drug delivery."

A practical example of excipient impact is seen with customers developing monoclonal antibody injectables. Protein aggregation and oxidative degradation present significant challenges, and conventional surfactants can increase instability, compromising both shelf life and efficacy, he describes. Pointing to real-world scenarios, he says: "Super Refined Poloxamer 188 reduced oxidative stress in a high-concentration protein formulation, enhancing stability and supporting lower immunogenicity risk, while Tween 20 HP LSA stabilized a formulation requiring a non-ionic surfactant, supporting successful scale-up and regulatory submission. These cases demonstrate how carefully designed excipients, aligned with therapeutic needs, can transform an unstable formulation into a commercially viable biologic."

Evonik Health Care: Excipients for Difficult-to-Formulate Substances

Evonik is involved in the development of excipients and solutions for poorly soluble APIs and biologics, offering polymeric carriers as well as functional capsules that enable the delivery of difficult-to-formulate drug substances. The company develops formulations and supplies excipients for lipid nanoparticles and polymeric nanoparticles.

Evonik takes a proactive approach to current supply chain disruptions and regulatory hurdles by diversifying suppliers. Dr. Tom Tice, Senior Director Global Strategies & Technical Marketing Parenteral Drug Delivery, Evonik Health Care, says the company has a robust global network to avoid dependence on single regions for raw materials. As part of its global network, Evonik supplies excipients locally around the world via regional warehouses, and bioresorbable excipients for long-acting injectables are manufactured in Europe and the US. When it comes to sustainability, Evonik's excipients are manufactured under stringent quality systems, and the company actively engages with regulators to stay ahead of evolving compliance standards.

"We are implementing digital tools for supply chain visibility and predictive analytics, which enables us to anticipate and respond to disruptions more effectively," says Dr. Tice.

Thomas Froehlich, Global Product Manager Oral Drug Delivery Solutions, Evonik Health Care, adds that an additional challenge is increasing complexity of oral drug formulations. "Evonik is meeting this challenge by investing in, and building up, a robust body of knowledge on advanced polymer technologies. We use this to create the customized excipient solutions that are needed to support these complex formulations and meet the needs of both immediate- and controlled-release profiles," he says.

Evonik is also evaluating its portfolio of functional organic excipients due to an increasing regulatory preference for natural and organic excipients that are favored in regulatory submissions because of their safety profiles. "Biocompatibility and biodegradability are becoming increasingly important for drug developers because these properties enable formulations to be more sustainable and patient friendly," says Mr. Froehlich. "As the number of biologics and sensitive APIs being developed increases, there is also a greater need for organic excipients. This is because these materials often exhibit better stability and performance in complex formulations."

Personalized medicine is also transforming the way excipients are developed. "One major trend is the growing need for tailored release profiles — precision therapeutics often require drugs to be released at specific sites or times within the body," says Mr. Froehlich. "EUDRAGIT® and EUDRACAP® platforms are designed to meet these demands, offering flexible solutions for controlled and targeted drug delivery."

For parenteral applications, Evonik's RESOMER® and LACTEL® bioabsorbable polymers are tunable to meet the needs of precision therapeutics. RESOMER and LACTEL polymers have been used in commercial long-acting injectable products since 1986. These polymers enable the release of the active ingredients over a desired period of weeks or months for many classes of drugs and continue to be an excipient for development of new long-acting injectables and polymeric nanoparticles. Moreover, RESOMER and LACTEL are being tested in multiple immunotherapy applications, including treatments for various cancers, allergies and other autoimmune diseases.

The rise of individualized therapies also calls for excipients that can scale efficiently from small clinical batches to full commercial production. Evonik has engineered its excipients to support this scalability. The company also works closely with pharmaceutical partners to adapt excipient properties such as solubility, permeability, and stability, ensuring they align with the needs of specific patient populations for customized therapies.

A recent project involved EUDRACAP, a customizable enteric capsule system. One of Evonik's pharmaceutical partners was developing an oral biologic drug, but faced significant hurdles — namely, degradation in the stomach and poor absorption in the intestine. "By leveraging EUDRACAP, we were able to enable targeted release in the intestinal tract, effectively shielding the active ingredient from gastric acid and enhancing its bioavailability," says Mr. Froehlich. "What made this solution particularly impactful was the capsule's modular design, which allowed for rapid prototyping and seamless scale-up. This not only resolved the formulation issue, but also supported the client's goal of accelerating development timelines and reducing costs."

Gattefossé: Lipid Excipients Are A Readily Accessible Source of Innovation

With ongoing supply chain uncertainty and increasingly complex APIs in development, it is critical that US innovators have access to a reliable supply of functional excipients. Gattefossé partners with customers to de-risk both formulation development and commercialization. To better serve its customers worldwide, Gattefossé has invested in the construction of a third manufacturing facility (in addition to France and Singapore), strategically located in Lufkin, Texas.

"The Lufkin facility specializes in lipid-based excipients to serve both the human and animal health markets, providing dedicated manufacturing capacity for

Gattefossé's EXCiPACT-certified manufacturing plant for lipid excipients (Lufkin, Texas).

North American customers," says Nick DiFranco, MEM – Senior Marketing Manager, Pharmaceutical Division, Gattefossé USA. "This expansion enables Gattefossé to provide faster delivery, greater production flexibility, and a more resilient supply chain, even amid market uncertainty."

The Lufkin facility achieved EXCiPACT certification in early 2025 and will soon supply lipid excipients to the North American market. This facility, together with a Technical Center of Excellence in Paramus, NJ, offers an end-to-end solution for North American customers – from excipient selection and screening to large-scale supply.

"Gattefossé's Lufkin plant arrives at a pivotal moment for the North American market," says Mr. DiFranco. "The pharmaceutical industry is at an inflection point, with modalities such as PROTACs and molecular glues advancing into clinical trials, and the rise of GLP-1 receptor agonists fueling new interest in oral peptide delivery. These molecules face significant permeability challenges that traditional formulation approaches may not adequately address. If formulators wish to succeed in these promising segments, they must be willing to change their perspective and work with the body to enhance drug exposure."

Lipid excipients, which rely on fatty acid chains derived from plants, can leverage the body's natural processes to overcome *in vivo* obstacles and access alternative absorption pathways. When ingested, lipid excipients trigger the digestion process, forming colloidal structures that fight recrystallization and maintain the drug in a supersaturated state, he explains. This process can also mitigate food effect to minimize dosing variability.

For poorly permeable compounds, lipid excipients containing medium-chain fatty acid esters (e.g., Labrasol® ALF) enhance both transcellular and paracellular absorption through supersaturation and tight junction modulation. This is a useful formulation tool for BCS Class III/IV compounds as well as oral peptides, says Mr. DiFranco. Highly lipophilic compounds can also utilize long-chain fatty acids (e.g., Maisine® CC) to access lymphatic uptake and bypass first pass metabolism.

"By harnessing the body's natural processes, lipid excipients provide distinct advantages for both emerging small molecule modalities and orally administered peptides, serving as a readily accessible source of innovation," he says.

Lubrizol: Building Formulator Confidence in Novel Excipients

Excipient suppliers face a regulatory Catch-22 that is stifling innovation on all sides. As drug molecules become more complex, the need for novel excipient technologies to overcome their formulation challenges has snowballed. This is particularly the case with the growing number of insoluble and poorly bioavailable active pharmaceutical ingredients (APIs).

"Many excipients with precedence of use are decades old and suboptimal for transforming today's challenging APIs into effective therapeutics," says Meera Raghuram, Director of Regulatory and Sustainability Strategy, Lubrizol. "However, regulatory approval ambiguity for novel excipients means formulators are risk-averse, preferring to use familiar ingredients even when better novel options exist. In turn, excipient manufacturers are reluctant to develop new excipients whose market success is essentially dependent on their assessment as part of a complete drug product submission package."

Thus, she says Lubrizol believes early collaboration between excipient suppliers and pharmaceutical manufacturers is the solution for building formulator confidence in novel excipients and supporting the development of promising brick-dust APIs. It can enable inclusion of the excipient in an API's non-clinical toxicology studies, for example, helping to demonstrate safety and highlight any data gaps. Lubrizol supports this model by partnering with formulators to co-develop data and regulatory submissions, using Drug Master Files (DMFs) and data-sharing agreements in regions where DMFs are not used. She adds that

Early collaboration between excipient suppliers and formulators enables the development of promising APIs (Lubrizol).

bridging arguments – using an approved excipient's safety data to support a novel excipient where the two have similar chemistry – is also an effective strategy.

Regulatory bodies are increasingly focusing on the patient experience, so selecting a novel excipient that enables more patient-centric drug delivery is highly desirable, she says. Lubrizol's Apinovex™, for example, is a high molecular weight polyacrylic acid excipient designed to provide processing and formulation benefits for spray-dried amorphous solid dispersions (ASDs).

"Apinovex enables formulators to enhance the solubility of brick-dust APIs and develop more efficient oral dosage forms with high, stable drug loading," says Ms. Raghuram. "This maximizes the API's benefits and allows a customized, consistent extended-release profile."

API particle size reduction is an effective way to combat solubility issues by creating nanoparticles of crystalline API that can be used for virtually any route of administration. Polymeric micelles are another proven method to create stable nanoparticles. Lubrizol's Apisolex polymer for parenteral and injectable formulations, for example, utilizes micellar technology to encapsulate molecules of hydrophobic API. This enhances solubility by up to 50,000-fold, with minimal API loss and more than 90% API recovery.

Additionally, the high drug-loading capabilities of novel excipients such as Lubrizol's Carbopol® polymer can allow for smaller, easier-to-swallow tablets – key considerations for pediatric and geriatric populations – and reduced dosing frequency. Carbopol BioSense Polymer is a naturally derived rheology modifier and sensory enhancer for use in topical applications, including serums, lotions, and creams. "Responsibly sourced from sustainable eucalyptus plantations under certified forest management practices in Brazil, it is biodegradable, non-GMO, Cosmos-approved, and addresses the 12 principles of green chemistry," says Ms. Raghuram.

In one example, Carbopol enabled an ophthalmic solutions manufacturer to create a market-leading, easy-to-use eyedrop that enables clearer vision. Key benefits included superior water-binding capabilities, improved wetting properties, and greater dwell time on the eye's surface, she explains.

Thermo Fisher Scientific: Tailoring Excipients for Precision Medicine

The global precision medicine market is experiencing robust growth, accounting for at least a quarter of all new drug approvals annually. In 2024, the FDA approved numerous personalized medicines, with reports suggesting 18 to 38 new drugs classified as precision medicine. "The rise of precision medicine is altering how formulators approach new product development and patient care," says Anil Kane, Executive Director, PhD, Global Head of Technical & Scientific Affairs at Thermo Fisher Scientific. "Instead of looking to treat a large population with one blanket therapy, pharmaceutical companies are shifting to a more patient-centric approach that considers factors unique to an individual."

Precision therapies typically have patient populations of around 200,000, indicating a small market requirement. APIs and formulations designed for precision drug products are often highly complex, requiring specialized handling and solutions to challenges such as stability, absorption, and processing. Similarly, they often utilize specialized manufacturing procedures. Throughout this process, selecting the right amount of the appropriate functional excipients is critical in overcoming complex formulation challenges.

Excipients play an important role in the oral solid drug product performance with respect to manufacturability and stability. This is in addition to its release profile's ability to deliver the drug at the right concentration to the appropriate site for

the optimum outcome. "Excipients take on a similar role for sterile injectable products in regard to solubilization, by maintaining pH, osmolality, preservation, lyophilized cake formation/stability and other aspects," says Dr. Kane. "In this way, excipients can solve formulation issues for many biotech and biopharma clients."

For example, Thermo Fisher Scientific leveraged excipient selection to improve the solubility and bioavailability of a poorly soluble and permeable BCS Class IV drug candidate. He explains that Thermo Fisher's computer-based modelling (AI) tool – Quadrant 2® – and simulation played a critical role in both excipient and technology selection for solubility enhancement. Modelling predicted any interaction of functional groups of excipients and APIs, as well as the technology selection predicting "spray drying as a method of creating amorphous dispersions," with a high probability of success for solubility enhancement. Among the various polymers evaluated from vinyl polymers (including polyvinyl pyrrolidone (PVP), cellulosic polymers and acrylic polymers), only a specific grade of cellulosic polymer showed promise both in prediction as well as confirmed with an in-vivo animal pharmacokinetic (pK) study.

In another example, polymer and technology selection played a role in Thermo Fisher's development of a patient-centric once-a-day (QD) formulation of a drug candidate for a neurological condition. A robust formulation design and process for a controlled release drug product was required to meet the following criteria:

- Release in a reliable and consistent manner at a predefined release rate and at the site of release/activity;
- Demonstrate High Quality Attributes, consistently meeting the critical quality specifications and providing the pharmacodynamic and PK response after the drug product is administered;
- Manufacturable, including ease of manufacture with a robust manufacturing process;
- Stable throughout the shelf life with respect to degradation products and consistent, predictable drug release; and
- Consistent in performance in patient population, meeting the release rates and thereby efficacy in a variety of patient populations across the globe, disease states, age groups, etc.

After successful utilization of a physiological-based pharmacokinetic (PBPK) modelling and determining the release rates at specific target sites in the gastro-intestinal tract, polymers such as hypromellose acetate succinate (HPMCAS) of a specific grade and viscosity for the membrane coating on an osmotic delivery system followed by a laser-drilled orifice of a specific diameter helped in meeting the release specifications and confirming the efficacy of the drug candidate, explains Dr. Kane.

"While these examples demonstrate a few solutions in action, it's clear that, as precision medicine and therapeutic approvals continue to increase and expand into broader markets like Alzheimer's and autoimmune diseases, precision medicine and tailored excipient solutions are moving from niche applications to the mainstream," he says. ◆

LIPID FORMULATION DEVELOPMENT

Why Softgels Are the Technology of Choice

By: Dipanwita De, PhD, and Kaspar van den Dries, PhD

INTRODUCTION

As biotech and pharmaceutical organizations focus on bringing life-changing therapies to patients as quickly as possible, they must also determine the needs of their proprietary molecules and the market. Today, many companies are prioritizing patient-friendly drug formats, such as oral solid dose (OSD) drugs or sterile injectables, in order to deliver safe and efficacious therapies to patients in need.

However, within the pharmaceutical industry, the development of new OSD drugs is fraught with challenges, one of the most significant being the issue of low bioavailability. This problem is particularly prevalent during the early stages of drug development and is a recognized reason why many drugs fail to progress beyond preclinical stages.[1]

Despite the risks that stem from low bioavailability, many pharma and biotech organizations continue to opt for standard OSD forms, such as tablets and capsules. In fact, there are several factors in choosing a final formulation that will offer precise control of the drug release rate, content uniformity and site of absorption. Lipid formulations, particularly softgels, offer a compelling solution to the bioavailability challenge and present several key advantages that make them worth considering from the outset.

WHY COMPANIES OPT FOR STANDARD ORAL SOLID DOSAGE FORMS

Despite the known risks associated with low bioavailability, many pharmaceutical companies continue to choose standard OSD forms for several different reasons. The first stems from the familiarity of traditional dosage forms. Companies are often more comfortable with conventional formulations like tablets and capsules, since these are well-known dosage forms as companies typical have internal capabilities and knowlegde. To replace have well established manufacturing process and regulatory pathways.

Additionally, during the early stages of development, the primary goal is to demonstrate that the drug is effective. At this point in the timeline, formulation scientists are often more focused on clinical proof of concept, rather than formulation optimization.

Finally, developing alternative dosage forms, such as lipid formulations, can be perceived as more costly and time-consuming. Companies may be concerned about the potential impact on development timelines and budgets.

Of course, bioavailability challenges can be overcome by developing formulations for intravenious administration such as sterile injections. However, in general, this route of administration is less patient-friendly and more expensive. Because of these considerations, OSD drug formulations are widely accessible, making up for 84% of drugs on the current market.[2]

THE CHALLENGE OF LOW BIOAVAILABILITY

Bioavailability refers to the proportion of a drug that enters the systemic circulation and is available to exert its therapeutic effect. Solubility plays a critical role in influencing a drug's bioavailability. Poorly soluble compounds often demonstrate lower bioavailability, which can reduce drug efficacy.[3] This is a prevalent concern affecting around 80% of active pharmaceutical ingredients (APIs).

For many drugs, particularly those that have poor water solubility, achieving adequate bioavailability can be a significant

hurdle. Poor bioavailability can lead to suboptimal therapeutic outcomes, necessitating higher and/or multiple unit doses to achieve the desired exposure, which in turn can increase the risk of side effects and toxicity. However, without addressing bioavailability issues early on, promising drug candidates may fail to progress, resulting in wasted resources and lost opportunities.[4]

Recent innovation has enabled scientists to develop a toolbox of technologies to help overcome solubility issues. Some of these technologies include:

- Particles size reduction, which reduces the particle size to a micronized form, helps the molecules to dissolve more rapidly, resulting in quicker absorption into the bloodstream compared to larger particles.[5]
- Solid dispersion – when a drug is dissolved into a solvent and then sprayed or melted with excipients that stabilizes the amorphous drug which is obtained – creating a formulation which ultimately leads to a higher absolute bioavailability.
- Complexation of drugs with excipients like cyclodextrins/mesoporous silica, which can wrap around drug molecules to make them more water-soluble and stable, improving how well the body absorbs them.

While largely effective, these approaches can be limited by stability concerns, material requirements or cost. This is where lipid formulations, and specifically softgels, come into play.

THE CASE FOR LIPID FORMULATIONS

Lipid formulations have been well-established and proven to overcome bioavailability challenges.[6] In fact, there is growing evidence that suggests this process is predictive, effective and offers several key advantages.

First, as mentioned, lipid formulations can enhance the solubility and absorption of poorly water-soluble drugs, leading to improved bioavailability. Lipid formulations have the advantage of leveraging the body's natural digestive processes. By utilizing the digestive tract's mechanisms for lipid digestion and absorption, these formulations can enhance the solubility and bioavailability of poorly soluble drugs. This approach allows for more efficient drug delivery and improves therapeutic outcomes. This can result in more consistent therapeutic outcomes and potentially lower required doses. At the same time, initial formulations can be screened using very limited amounts of API, typically between 10 to 40 grams. This is particularly preferable during the early stages of development when API availability may be limited.

It is necessary to also note that the benefit of lipid formulations is advantageous throughout the entirety of the drug development cycle, from pre-clinical studies and clinical Phase 1 trials to subsequent clinical stages and commercialization. This continuity can simplify the development process and reduce the need for formulation changes. In fact, the manufacturing process for lipid formulations, particularly softgels, is semi-continuous, making it relatively straightforward to scale up from small-scale laboratory batches to commercial production. This can help streamline the development process and reduce time to market.

SOFTGELS: THE TECHNOLOGY OF CHOICE

Softgels offer a particularly attractive option for addressing bioavailability challenges. These drug formats consist of a gelatin-based shell filled with a liquid or semi-solid formulation, which can include lipids, surfactants and other excipients designed to enhance drug solubility and absorption.

Softgels offer several key features like enhanced solubility and absorption, meaning the lipid-based fill material in softgels can improve the solubility of poorly water-soluble drugs, facilitating their absorption in the gastrointestinal tract. This can lead to higher bioavailability and more consistent therapeutic effects.

Additionally, the encapsulation of the API within the softgel shell can protect it from degradation from factors like light, oxygen and moisture. This can enhance the stability and shelf-life of the drug product.

From a patient compliance perspective, softgels are generally easier to swallow than tablets and capsules, particularly for patients who have difficulty swallowing solid dosage forms. The smooth, gelatin-based shell can also mask the taste and odor of the API, improving medication adherence.

Softgels have long been depicted as a product most applicable for vitamins, fish oils and herbal supplements, or over-the-counter (OTC) medications, such as nonsteroidal anti-inflammatory drug (NSAID) ibuprofen (IBU). Indeed, softgels are widely accepted by consumers, and features such as improved bioavailability

(e.g., diclofenac softgels) and quicker onset of action (eg, IBU softgels) that are achieved for these OTC drugs are, of course, equally applicable for prescription drugs. Greater familiarity and adaptation of soft gelatin capsules for prescription drugs could help address bioavailability challenges that are currently unmet.

However, despite their slower rate of adoption, softgels are technically excellent for most molecules and offer improved bioavailability, especially when applied to the delivery of lipid-based formulations.

LIPID FORMULATION: A STAGED DEVELOPMENT APPROACH

An early phase lipid-based fill formulation development program consists of several stages that ultimately result in identification of lead candidates for pharmacokinetic study. One of the key criteria to determine is the drug loading feasibility in lipid formulations for the drug candidate. Therefore, drug developers typically start with a solubility assessment in single vehicles, followed by prototype selection and emulsion characterization in water.

Then, a formulator assesses characteristics such as the speed and quality of emulsion formed, droplet size, dispersion behavior and recovery from the biorelevant fluids over time. They study *in-vitro* digestion models in biomimicking fluids like simulated gastric fluid (SGF) or simulated intestinal fluid (SIF), to generate the drug recovery profile in the aqueous phase of the digested component. Next to all *in-vitro* data, short-term chemical stability data on the fill formulation is collected under accelerated conditions.

Based on the *in-vitro* characterization outcome coupled with chemical stability data from previous stages in the process, final selection of lead formulation candidates is made for pharmacokinetic study. This general approach requires limited quantities of API and generates a comprehensive formulation package in just a few

FIGURE 1

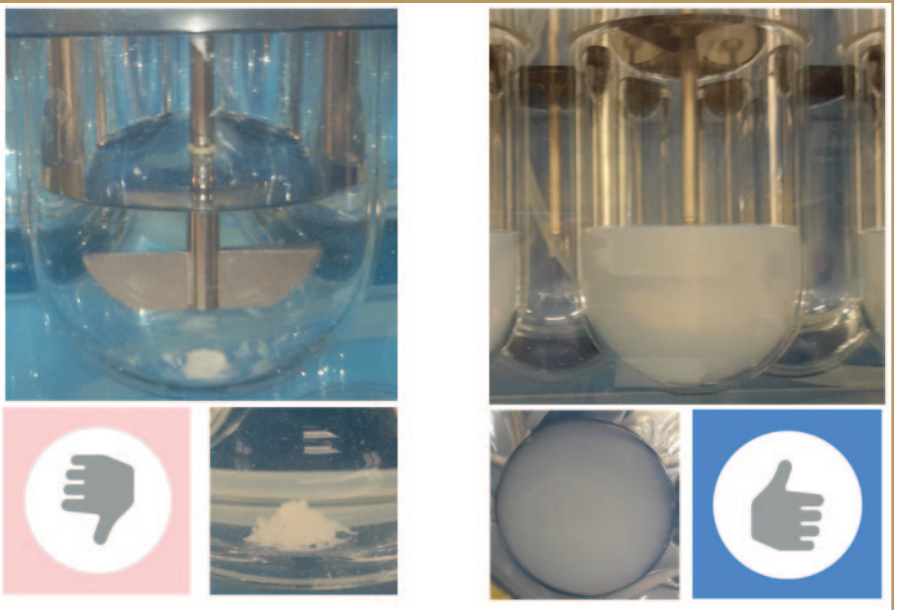
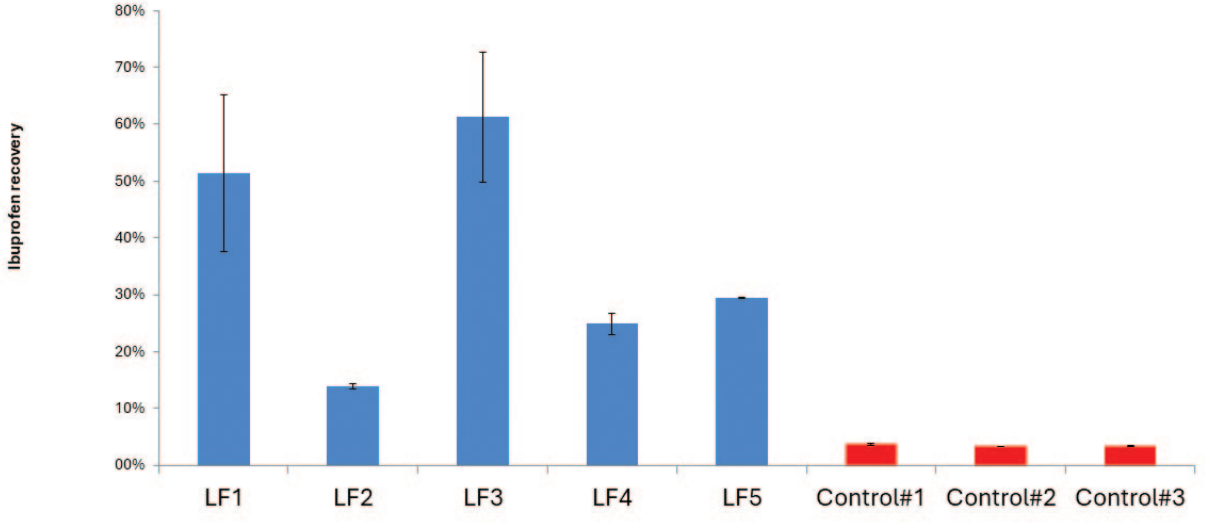


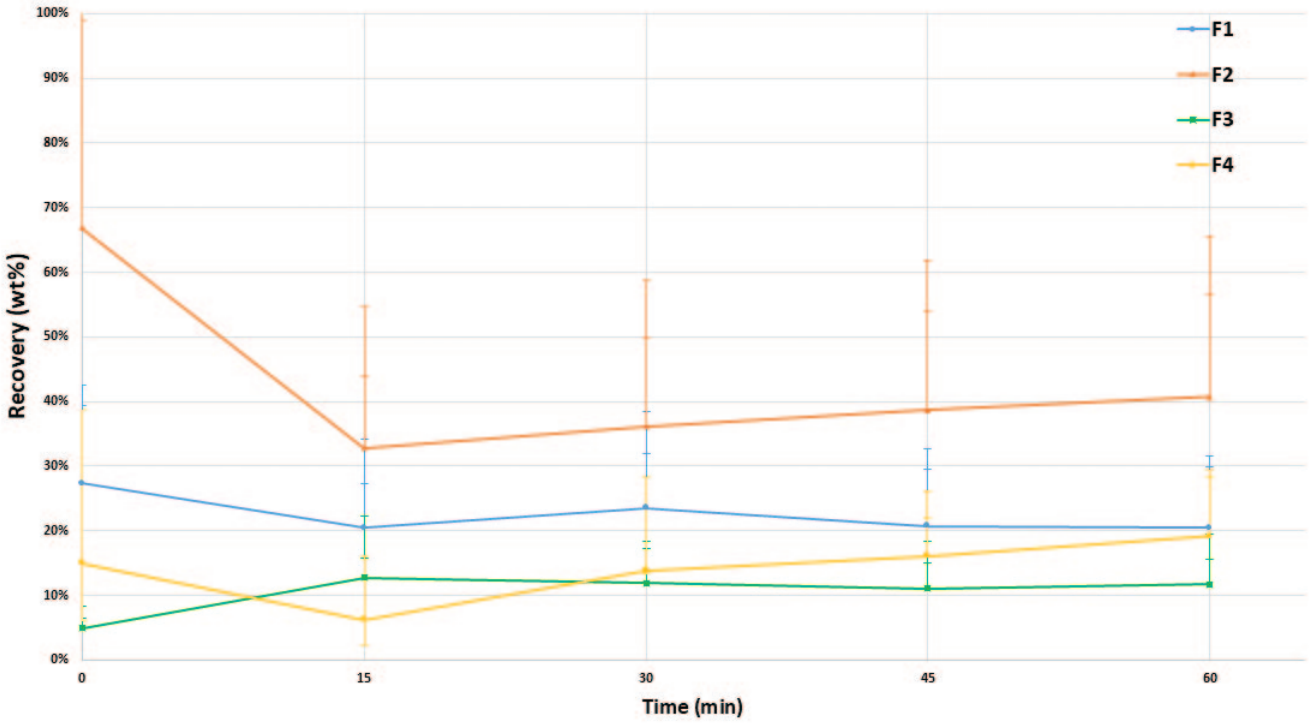
Figure 1 A. In PEG-based formulation (control), API crashes out in SGF
Figure 1B. LFs can form S(M)EDDs, keeping the API solubilized in SGF

FIGURE 2



Recovery of IBU after aqueous dispersion in SGF

FIGURE 3



***In-vitro* lipolysis: Drug recovered over time in aqueous phase**

months. To provide more context on the described approach, some case studies where these screening tools and techniques were used to design lipid formulations targeting bioavailability enhancement are outlined in the next section.

CASE STUDIES & EXAMPLES

Lipid-Based Self-Microemulsifying Drug Delivery System (SMEDDS) Formulation of Ibuprofen (IBU) and Phenylephrine (PE) for Softgels[7]

A lipid-based formulation for a cough and cold medication containing 200mg of IBU and 5mg of PE was developed. Using a streamlined approach, the solubility of IBU in various excipients was assessed. Due to the differing properties of IBU and PE, their solubility profiles varied significantly.

Propylene glycol monocaprylate (type II) and Caprylocaproyl macrogol-8 glycerides were selected after initial testing, with Vitamin E TPGS added as a co-surfactant and antioxidant, and Propylene Glycol for PE. Five lipid formulations with different ratios of these ingredients were created and tested against three PEG-based control formulations. These samples were dispersed in water and SGF to observe their behavior.

The lipid formulations successfully formed nano-sized emulsions, keeping the active ingredients dissolved in SGF, unlike the PEG-based controls where the API precipitated (Figure 1). Further testing showed that lipid formulations (LF) LF1-LF4 formed nano-sized droplets, while LF5 and the PEG-based control did not.

Hence, the streamlined solubility screening led to effective lipid-based formulations that maintained the active ingredients in a dissolved state, showing promising results for IBU recovery in acidic SGF (Figure 2).

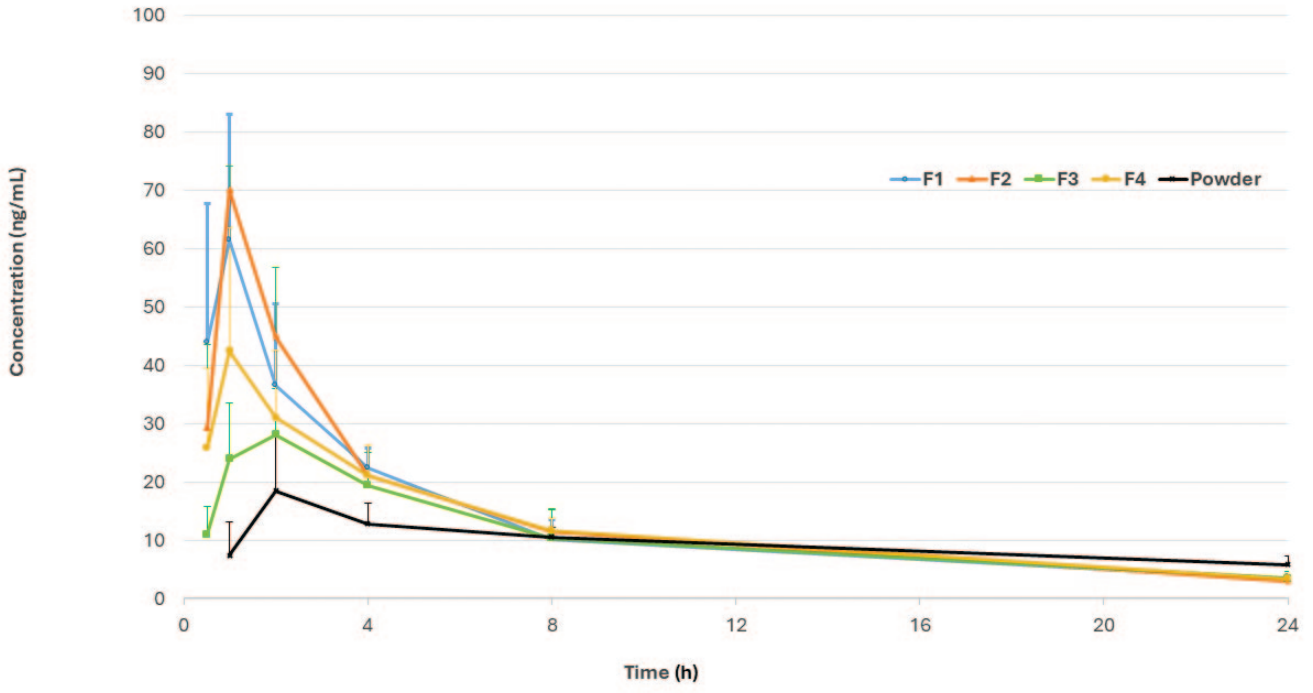
Relationship Between *In-Vitro* Lipolysis Release and *In-Vivo* Performance of Lipid-Based Drug Delivery Systems (LBDDS) for a Biopharmaceutics Classification System (BCS) Class II Compound[8]

A study was conducted to link the *in-vitro* release of a BCS class II compound from LBDDS to its *in-vivo* bioavailability. The compound was formulated into four different LBDDS, each with varying combinations of excipients.

Using a methodology described in literature , the drug's release during *in-vitro* lipolysis was analyzed. Formulation (F) F2 showed the highest drug recovery, suggesting a potential for supersaturation that could lead to better absorption *in vivo*.

In vivo animal testing of these formulations these formulations revealed that lipid formulations significantly improved drug exposure compared to the drug in powder form. Formulations F1 and F2 showed the highest peak concentrations

FIGURE 4



***In-vivo* drug exposure of LBDDS measured against drug powder**

and faster absorption rates (Figure 4).

Therefore, a strong correlation between *in-vitro* lipolysis data and *in-vivo* performance was demonstrated, highlighting the value of the lipolysis model in selecting effective lipid-based drug delivery systems.

SUMMARY

Solubility and bioavailability in OSD formulations remain major challenges within the early stages of drug development. While technological innovations have allowed the pharmaceutical industry to make progress in solving this hurdle, choosing formulations that help achieve desirable solubility and bioavailability can help speed up development of the most promising molecules. Ultimately, lipid formulations, particularly softgels, offer a compelling solution.

The advantages of improved bioavailability, efficient use of API, ease of scale-up, versatility across development stages and consumer preference make softgels a technology of choice. By addressing bioavailability issues early in the development process, companies can increase the likelihood of success for their drug candidates, bringing more effective therapies to market. As the pharmaceutical industry continues to evolve, embracing these innovative formulation technologies will be crucial in overcoming the challenges of drug development and improving patient outcomes. ◆

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BIOGRAPHIES

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Dr. Kaspar van den Dries is Senior Director Science & Innovation, Softgels Pharma Services at Thermo Fisher Scientific. In his current role, he provides strategic direction to the research and development team, focusing on the creation of innovative softgel formulations, processes, and technologies to better serve pharmaceutical companies and patients. He earned a Master's degree in Pharmaceutical Sciences, with a thesis on the Formulation of poorly soluble drugs with self-emulsifying drug delivery systems, and a doctoral degree from the University of Utrecht, where he explored The paradox of high shear granulation; the formation of non-homogenous granules. He has an extensive publication record on pharmaceutical manufacturing processes, has presented at numerous scientific conferences, and has supported multiple patent applications.

CONTAINER SELECTION

Why Container Selection is Key to Overcoming Sterile Fill & Finish Challenges for Next-Gen Biologics

By: Vincenza Pironti

INTRODUCTION

The biological drug market continues to grow due to a robust and steady pipeline of product innovation. Eighteen biologics were approved by the US Food and Drug Administration (FDA) in 2024 compared with just 12 in 2021.[1,2]

Biologics are typically administered via injection due to two key factors: their large molecular size, which can hinder bioavailability and make oral or inhalation formulation difficult, and their sensitivity to degradation in the gastrointestinal (GI) tract if taken orally. Consequently, these biologics must be manufactured, filled, and finished in a sterile environment adhering to Annex 1 of the EU Good Manufacturing Practice (GMP).

The growth of the biologics sector has led to the diversification of alternative container formats for injectable products beyond the standard vial. It is vital that pharmaceutical companies select the most appropriate format to achieve the target product profile (TPP), as each format has features and benefits that make it suitable for different therapies and use cases. Careful consideration of drug product and end-patient needs, as well as sterile integrity requirements, is needed in this selection process.

The following explores the importance of container selection for sterile injectable drug products and outlines key factors to consider to optimize the performance, quality, and efficacy of biologics.

THE IMPORTANCE & CHALLENGES OF CONTAINER SELECTION

The complexity of the protein structures within biological actives means meticulous consideration of fill form is particularly vital. Unlike small-molecule pharmaceuticals, biologics are highly susceptible to degradation from external factors, making container selection a critical determinant of product safety and efficacy. The primary container is a protective shield, doing more than just ensuring patient safety by preventing microbial and foreign body contamination. It also helps maintain the drug's integrity throughout its shelf- life.

However, the interactions between these complex drug formulations and their containers present unique challenges during sterile fill and finish. Key considerations include:

Material compatibility: Biologics can interact with container materials, leading to leaching of chemicals, which can compromise drug stability or induce adverse patient reactions. Oxidative stress can also occur during storage, which can lead to premature degradation of the formulation within. To maximize shelf-life and ensure the packaging is compatible with the formulation, it is essential to conduct sufficient extractables and leachables testing of both the container and closure in the early stages of development.

Viscosity and delivery: High-concentration biologics often exhibit high viscosity, demanding precise fill volumes and consistent de-

livery forces. Container design must accommodate these properties to ensure accurate dosing. This is especially important in self-administration devices, where patients must be able to reliably inject the medication.

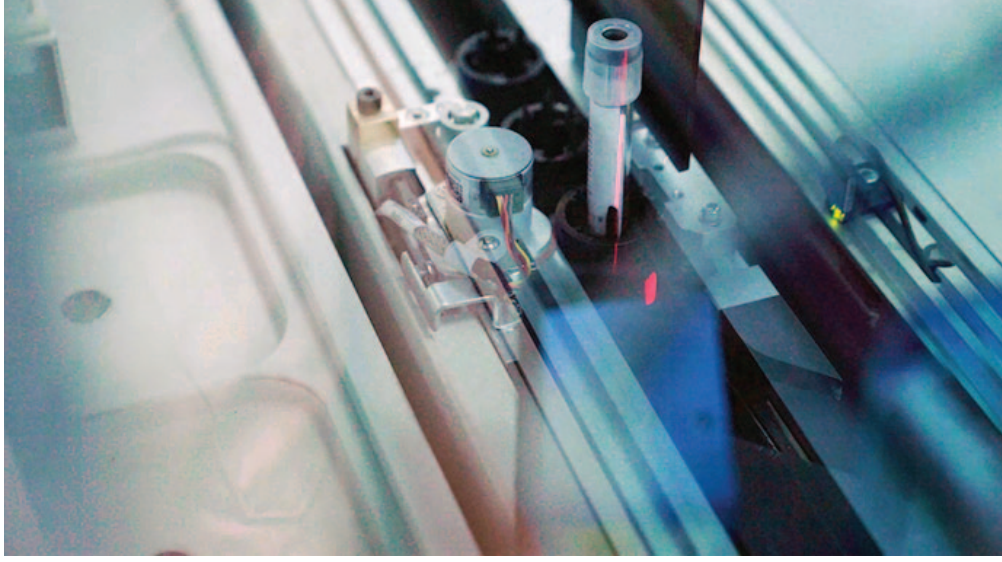
Meeting sterile fill & finish needs: The container must be able to support sterile integrity during and after the filling process. Flawless container closure integrity is needed to prevent microbial contamination. The containers must also be capable of withstanding terminal sterilization processes, if such a step is needed, without degrading.

Container closure integrity: Maintaining container closure integrity is especially difficult when considering the extreme temperature ranges that some biologics must be stored within.

In addition to these challenges, biopharmaceutical companies must consider other issues. Human factors, such as patient experience and convenience, play an important role in container selection. If a product is to be self-administered, for example, then the container should be able to support easy administration by the patient, without the need for professional training. Logistics considerations, such as transport and storage, should also be taken into account during container selection, to ensure the final choice meets the needs of the drug product.

CHOICE OF FILL FORM

A number of presentations are now available for biologics, including:



Vials: Well-established, these are simple, small vessels made of glass or plastic with a metal or plastic closure to seal the product inside.

Pre-filled syringes (PFS): Containing a single dose of medication, PFS streamline the administration process, minimizing the risk of dosage errors and reducing medication waste. This method also has the potential to enable self-administration of a wider range of treatments, leading to increased accessibility and convenience for patients.

Blow-fill-seal (BFS): This is a sterile manufacturing process that forms, fills, and seals lightweight plastic containers in a single, continuous operation. This process is ideal for single-dose applications, as it enhances self-administration, reduces product waste, and streamlines production and transportation costs.

Alternative administration routes: Alternative delivery routes to injectables are also available for a range of biologics therapeutics due to innovation in formulation technology and administration devices. Inhalation in particular offers advantages in terms of ease of administration and enhanced patient comfort, which makes it highly attractive for the localized treatment of chronic pulmonary diseases, where patient compliance is crucial to the successful management of the condition.

When selecting the most appropriate fill form for biologic drug development projects in which injection is the chosen format, several priorities must be considered. These priorities will vary depending on the stage of drug development, as the requirements for a Phase 1 clinical trial therapy differ significantly from those for a commercialized treatment.

The decision on fill form should not be delayed until Phase 3. Instead, it should be made and agreed upon early in the development process. This proactive approach ensures that measures are in place to facilitate the smooth transition of the therapy into clinical trials and commercialisation.

FACTORS TO CONSIDER DURING SELECTION

The unique features and benefits of each container format (whether it is new to the market or has been around for a long time) will influence the selection process. The specific biological therapy, desired product profile, and patient needs will de-

termine the best format.

The benefits and key considerations of the most important formats impacting on the injectable market include:

Vials: These are readily available and have well-established production infrastructure, making them a cost-effective and easy option with quick speed-to-market. Suitable for various biologic formulations, they are ideal for Phase 1-3 clinical trials. Additionally, they can hold multiple doses, which decreases filling and transportation costs. When choosing a vial for a project, consider the development stage and whether a multi-dose container would be better than a single-dose container. If so, vials may be the ideal choice.

PFS: Offer significant advantages, improved dosing accuracy, and minimized waste. These benefits are achieved by providing a single, pre-measured dose, thereby reducing microbial contamination risk because reconstitution is needed and ensuring patients receive the correct amount of medication. The ease of self-administration also improves patient convenience. As a result, PFS are particularly valuable for high-value products in which waste reduction is essential and for commercialized products treating chronic conditions, as they enhance usability.

BFS: These provide numerous advantages, including reduced risk of breakage and contamination, elimination of preservatives, improved dosing accuracy, and minimized drug waste. These benefits are due to the plastic composition, single-dose feature, and immediate sealing after filling. BFS is suitable for ophthalmic and injectable biologic projects, high-value drug formulations, and high-volume commercial filling, due to innovations in the process and efficiency advantages.

OTHER CONSIDERATIONS TO BEAR IN MIND FOR BIOLOGICS

Temperature control is frequently a key requirement to guarantee biologics reach the patient in good condition and remain stable when stored for long periods. This means the formulations must be kept at fresh, frozen, or even ultra-frozen temperatures during both transit and storage. Due to the need for specialist storage and transport infrastructure, temperature control creates logistical challenges. This can be a problem for products that are shipped across international borders, to emerging markets, and to remote locations where cold-chain resources are not readily available.

When suitable, this issue can be addressed by incorporating lyophilization into the formulation's manufacturing process. Lyophilization freeze-dries a solution under a vacuum and dries the resulting product into a powder that is more stable at more moderate, non-cryogenic temperatures. As lyophilization impacts other choices like container selection, it has to be built into the manufacturing process to maintain optimum manufacturing output and efficiency.

EXPERT GUIDANCE NEEDED

Getting container selection right at the earliest phase of drug development is vital to ensuring the overall success and profitability of the project, and to delivering a truly life-transforming treatment for patients.

A contract development and manufacturing organization (CDMO) partner with specialist experience in sterile fill and finish of an array of injectable container formats can support biopharmaceutical companies in understanding the fill form needs of their biologics. They can help select the most effective presentation to fit their product's TPP, addressing human factors, transport and storage needs.

With such support, biopharmaceutical companies can have peace of mind that they have the information they need to make an informed decision to optimise the performance of their therapy.

FUTURE CHALLENGES FOR BIOLOGICS FILLING

The steady introduction of new drugs by the CDER over the past 2 decades has created a marketplace with increased competition and a need for product differentiation.3 This creates both opportunities

and challenges for biopharmaceutical companies, which will need to develop less invasive and more convenient methods of drug administration to improve patient access and compliance.

The biopharmaceutical industry has seen a shift towardd subcutaneous (SC) injection, particularly for monoclonal antibodies (mAbs), as opposed to intravenous (IV) administration. SC offers differentiation opportunities and improved patient access and compliance, responding effectively to challenges associated with biotherapeutics. SC drug delivery, using existing formulation and device technologies, allows patients to self-administer therapies at home, rather than going to a clinic for professional administration. Convenience for patients is enhanced, reducing the burden on healthcare systems.

Further formulation advancements, such as the development of fluid suspension in non-aqueous vehicles and new buffering agents to improve protein stability in aqueous solutions, will enable SC delivery for more biological treatments over the coming years.

READY TO FACE THE FUTURE

For the biopharmaceutical sector, the choice of primary container will continue to have enormous importance for the success of a new therapy. The ideal container will improve the efficiency of the sterile fill and finish process by minimising waste and energy consumption while optimizing sterile integrity. It will also support ease of use and convenience for patients, with additional implications for logistics and storage of finished products.

Therefore, it is crucial to work with expert sterile fill and finish partners to identify the appropriate container for the finished biologic and ensure commercial success. Biopharmaceutical companies can be confident that specialist CDMOs will provide the guidance they need to make the right container selection.◆

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BIOGRAPHY

Vincenza Pironti is the current Head of Business Development at Recipharm, having joined the company in 2023 as Strategic Marketing Director for Sterile Fill and Finish. She supports the design of strategies for the global sales and business development teams, and the analysis of new business opportunities for Recipharm's commercial business. With almost 20 years in the pharmaceutical industry and consolidated experience in business development, product development, aseptic manufacturing, and filling, she brings valuable expertise to Recipharm. She comes to the business with extensive knowledge of all phases of product development, from formulation screenings to sterile product commercial manufacturing, with expertise in small molecules and biologics in sterile formulation. Previously, she worked as Business Development Manager in Pharmatex and CordenPharma, managing multiple projects in sterile fields.

EXCIPIENT TECHNOLOGY

Driving Oral Drug Delivery Innovation With Safe, Reliable Lipid Excipients

By: Nick DiFranco, MEM

INTRODUCTION

As drug discovery continues to advance into new therapeutic frontiers, pharmaceutical formulators are increasingly challenged by the poor solubility, permeability, and absorption of modern APIs. From complex small molecules to the promise of oral biologics, the demand for safe, effective formulation strategies has never been greater.

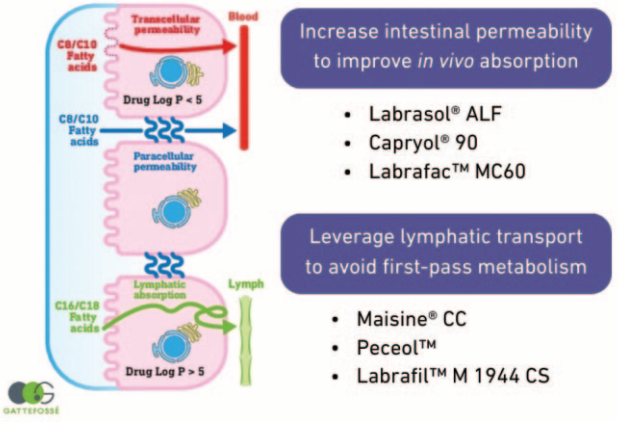
Amidst the uncertainty of novel ingredients and formulation techniques, lipid excipients provide a safe, proven platform for enhancing *in vivo* formulation performance, enabling innovation without sacrificing scalability or regulatory confidence.

This whitepaper explores three areas where lipid-based systems are transforming oral drug development: synergistic lipid–polymer combinations, lifecycle management through reformulation and food effect mitigation, and oral delivery of peptides and biologics.

LIPID EXCIPIENTS ENHANCE *IN VIVO* PERFORMANCE

Lipid excipients leverage the body's natural digestive processes to enhance the solubility, permeation, and absorption of many active pharmaceutical ingredients (APIs).

FIGURE 1



Enhanced Absorption Mechanisms Enabled by Lipid Excipients

SOLUBILITY & SUPERSATURATION MAINTENANCE

The lipid digestion process, involving gastric lipase, bile salts, and pancreatic enzymes, creates colloidal carriers and mixed micelles that maintain API solubility and prevent drug precipitation. Lipid excipients also maintain drug supersaturation *in vivo*, allowing for greater absorption across the intestinal epithelium.

Formulations leveraging self-emulsifying drug delivery systems (SEDDS) are especially effective at promoting solubilization. These systems utilize combinations of lipid excipients (oily vehicles, surfactants, or cosurfactants) to form emulsions in GI fluids that enhance solubility and bioavailability.

PERMEABILITY ENHANCEMENT VIA TIGHT JUNCTION MODULATION

Excipients with high medium-chain fatty acid ester content (C8, C10) are known for their ability to modulate tight junctions, enhancing both transcellular and paracellular permeation for challenging APIs (Figure 1).[1-3]

Medium-chain fatty acid esters found in excipients like Capryol® 90, Labrasol® ALF, and Labrafac™ MC60 can:

- Enhance transcellular absorption through the lipid digestion and supersaturation process (BCS Class II and IV)
- Enable paracellular permeation by safely and reversibly modulating tight junctions (BCS Class III and IV)
- Improve absorption of drugs subject to P-gp inhibition through the combination of supersaturation and tight junction modulation

These interactions make lipid excipients effective tools for delivering both poorly soluble and poorly permeable compounds while offering consistent, scalable performance *in vivo*.

INCREASED ABSORPTION VIA LYMPHATIC UPTAKE

For highly lipophilic compounds, lipid excipients can further enhance absorption by leveraging lymphatic uptake. This effect is observed in formulations containing unsaturated, long-chain fatty acids (C16, C18) such as those found in Maisine® CC, Peceol™, and Labrafil™ M 1944 CS.

Following digestion, long-chain fatty acids are re-esterified into triglycerides within enterocytes and packaged into chylomicrons, which carry lipophilic drug molecules into the lymphatic system (Figure 1).

The lymphatic route not only enhances systemic exposure but also allows drugs to bypass first-pass hepatic metabolism, a major barrier for many APIs with low oral bioavailability.

TABLE 1

Drug	Formulation	AUC (Fed)/ AUC (Fasted)	Model	BCS class
Seocalcitol[6] (vitamin D analog)	SMEDDS	1.08	Mini-Pigs	II
	PG Solution	1.57		
Dronedarone[7] (antiarrhythmic)	SMEDDS	2.9	Dogs	II or IV
	Tablet (Multaq®)	10.4		
Cinnarizine[8] (antihistamine)	SNEDDS Capsule	1.4	Dogs	II
	Conventional Tablet	2.2		
Nelfinavir mesylate[9] (antiviral)	SMEDDS	1.04	Rabbit	IV
	Suspension	1.5		
Ziprasidone[10] (antipsychotic)	SNEDDS Pellets	1.05	Dogs	II
	Capsule (Powder Filled)	1.86		
Itraconazole[11] (antifungal)	SEDDS	1.6	Human Volunteers	II
	Capsule (Powder Filled)	2		

Examples of Drugs in SEDDS Formulations With Reduced Food Effect

IMPROVED DOSING VIA FOOD EFFECT MITIGATION

Food is a well-known source of variability in oral drug absorption, leading to reduced drug absorption (negative food effect), delayed absorption rate, or increased absorption (positive food effect).[4] This "food effect" can lead to inconsistent dosing, reduced patient adherence, and additional regulatory hurdles. Lipid-based formulations offer a proactive solution by building the physiological benefits of dietary lipids into the dosage form itself.

In lipid-based formulations, oily vehicles, surfactants, and/or cosurfactants are combined to create SEDDS that mimic the fed state, stimulating lipolysis and triggering the release of lipase, bile salts, and pancreatic enzymes. As a result, orally administered drugs formulated with lipid excipients show more consistent exposure in both fed and fasted states (Table 1).[5]

LIPID-POLYMER SYNERGIES: PRACTICAL INNOVATION FOR CHALLENGING SMALL MOLECULES

Modern APIs, including bRo5 compounds like molecular glues and PROTACs, often exhibit poor solubility and limited absorption. To formulate these molecules, scientists must balance solubilization and drug loading with *in vivo* performance and stability.

Traditionally, binary amorphous solid dispersions (ASDs) consisting of API in a polymer carrier have been the go-to strategy for solubility enhancement. While scalable, they may fall short *in vivo*, as high drug loading can trigger recrystallization, and polymers alone may not overcome poor permeability.

To address these limitations, ternary ASDs incorporate a third functional excipient — often a surfactant — into the polymer–drug system.[12-14] These surfactants may act as precipitation inhibitors, dissolution enhancers, and/or processing aids.

When lipid excipients are incorporated into ternary ASDs, they not only maintain drug solubility, but they bring added *in vivo* performance and processing benefits.[15-18] This allows formulators to combine the advantages of lipid excipients with existing polymer-focused manufacturing infrastructure.

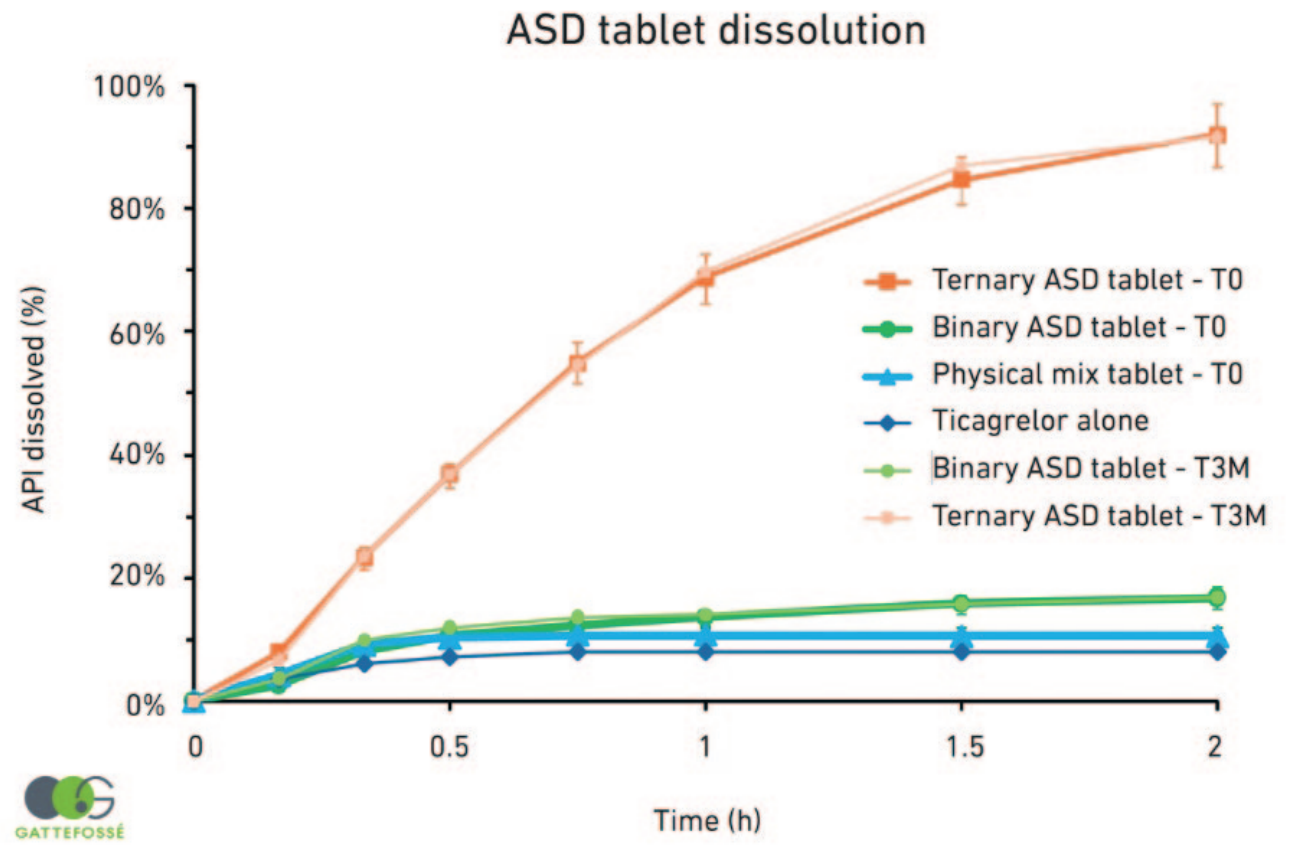
CASE STUDY: AN ENHANCED ORAL TABLET FORMULATION OF TICAGRELOR USING PVPVA & GELUCIRE® 48/16

Recent Gattefossé research has demonstrated the impact of incorporating Gelucire lipid excipients into amorphous solid dispersions (ASDs) using ticagrelor (BCS Class IV) as a model compound.

In a 2024 study, Gelucire 48/16 (Polyoxyl-32 stearate (Type I) NF) and Gelucire 50/13 (Stearoyl polyoxyl-32 glycerides) were incorporated into ticagrelor–PVPVA dispersions via hot melt extrusion. This study demonstrated that both Gelucire excipients acted as plasticizers, reducing the required extrusion temperature by as much as 70°C. The addition of Gelucire 48/16 also significantly improved in vitro drug release over a binary ASD.

Building on this work, a 2025 study incorporated the most promising formulation into an oral tablet. A ternary ASD containing 14.3% ticagrelor, 21.4% Gelucire 48/16, and 64.3% PVPVA was successfully incorporated into a tablet formulation (Table 2).

FIGURE 2



ASD Tablet Dissolution at T0 and 3 months (USP II, Phosphate Buffer pH 6.8, 900 mL)

Three key findings were observed:

1. The addition of Gelucire 48/16 reduced processing temperatures by nearly 40°C relative to the binary ASD (115°C vs. 153°C).
2. The ternary system containing Gelucire 48/16 showed a significant increase in dissolution, with API release reaching 92% compared to only 18% for the binary ASD (Figure 2).
3. Dissolution performance was maintained after three months of storage at 25°C/60% RH (Figure 2).

These studies highlight the value of combining polymer carriers and lipid excipients to improve both ASD manufacturability and performance.

REFORMULATION & LIFECYCLE MANAGEMENT: MITIGATING THE FOOD EFFECT

Food effect is a well-documented obstacle in oral drug delivery.4 Drugs that depend on dietary fat for solubilization often exhibit variable absorption and bioavailability, complicating dosing schedules and patient adherence.

From a regulatory standpoint, the food effect also adds uncertainty. In June 2022, the FDA published an updated guidance document that recommended "conducting food effect studies early in development" to identify and mitigate risk associated with variable absorption.[19,20] And this is not a niche issue — an analysis of FDA and EMA approvals from 2010 to 2017 showed that >40% of orally administered drugs exhibited a positive food effect, and a similar analysis of oncology drug approvals from 2003-2016 showed that anywhere from 55% to 69% of compounds exhibited fed and fasted differences in AUC or C_{max}.[21,22]

The food effect is often viewed as a barrier in oral drug development, complicating clinical translation and patient use. However, it also presents an innovation opportunity. Reformulating an existing molecule to reduce or eliminate its food effect can unlock significant value as part of a broader lifecycle management strategy or 505(b)(2) program. Lipid-based systems offer a proactive approach by replicating the physiological benefits of dietary lipids without relying on the patient's meal timing or content.

TABLE 2

	Component	Ternary ASD tablet	Binary ASD tablet	Physical mix tablet
Internal phase	Extrudate	70%	40%	/
	Silicified MCC	14%	44%	44%
	Mannitol	10%	10%	10%
	Crospovidone	5%	5%	5%
	PVP-VA	/	/	30%
	Ticagrelor	/	/	10%
External phase	Mg stearate	1%	1%	1%

Composition of Tablets

CASE STUDY: MITIGATING FOOD EFFECT FOR VENETOCLAX WITH SEDDS

Venetoclax (Venclexta®/ Venclyxto®) is a BCL-2 inhibitor, indicated for the treatment of adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma. It has a MW of 868.44, low aqueous solubility with LogP 5.5, and it is classified as BCS IV. According to the FDA approved product label (Venclexta tablet), there is a 5-fold C_{max} and AUC increase with a high fat meal.

A 2022 study showcased a self-emulsifying drug delivery system (SEDDS) containing a lipophilic salt of the API (venetoclax docusate) to mitigate the food effect.[23] The formulations are shown further:

1. Long Chain SEDDS

-30 % Peceol® (Glyceryl monooleate, Type 40)

-70% surfactant mix (Kolliphor® RH40: Tween® 85, 1:1)

2. Medium Chain SEDDS

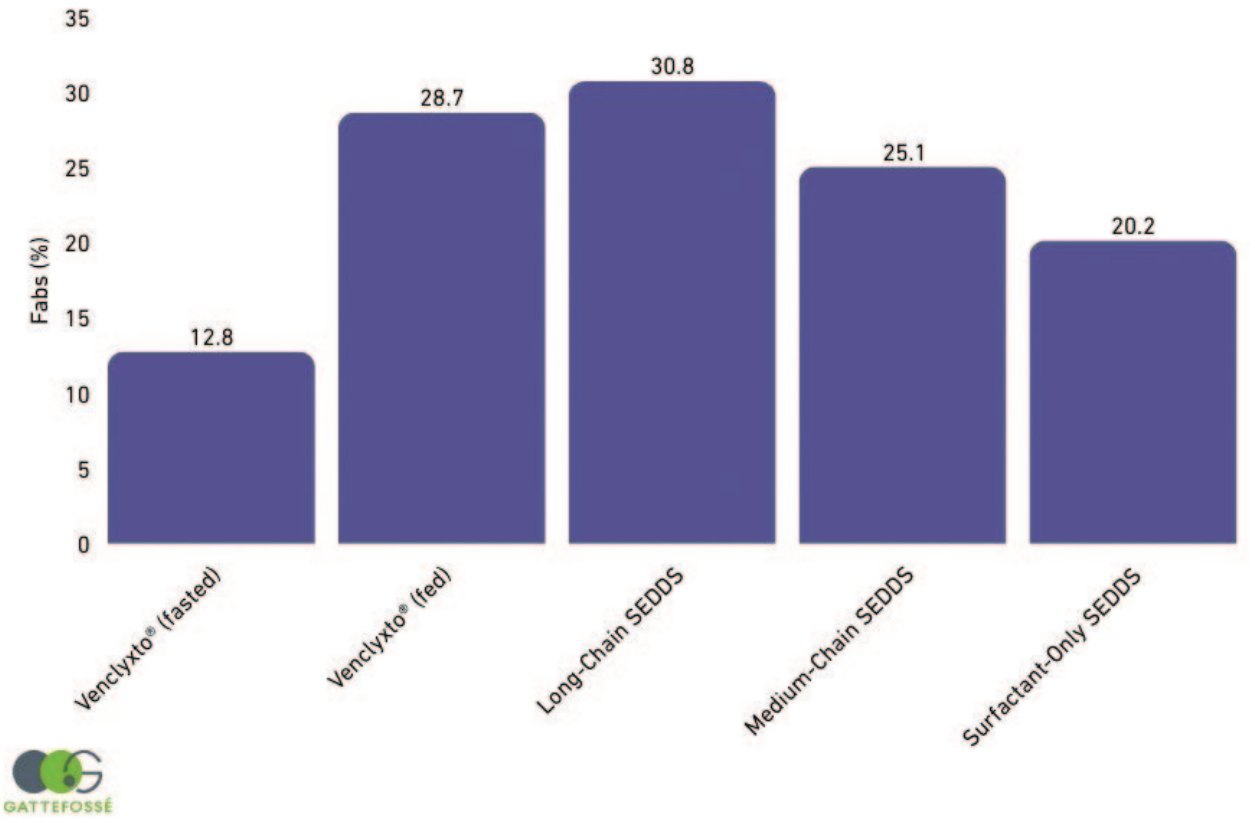
-30% Capmul® MCM (Glyceryl monocaprylate)

-70% surfactant mix (Kolliphor RH40: Tween 85, 1:1)

3. Surfactant-Only SEDDS

-100% of surfactant mix (Kolliphor RH40: Tween 85, 1:1)

FIGURE 3



Bioavailability of 100 mg Venetoclax SEDDS Formulations Versus Marketed Product in Fed & Fasted States

The bioavailability of these formulations in the fasted state were compared with the bioavailability of the commercial product (Venclyxto tablet) in fed and fasted states in male landrace pigs (Figure 3).

The SEDDS formulations showed an increase in oral bioavailability of venetoclax docusate up to 2.4-fold compared to the commercial amorphous solid dispersion in the fasted state. All SEDDS formulations in the fasted state showed a similar bioavailability compared to Venclyxto in the fed state.

This study highlights the feasibility of SEDDS not only for enhancing the bioavailability of highly lipophilic and BCS class IV compounds but also for mitigating the food effect.

ORAL DELIVERY OF BIOLOGICS: REACHING THE NEXT FRONTIER

Biologics, such as peptides and proteins, face formidable barriers in oral delivery due to their size, hydrophilicity, and enzymatic instability. Consequently, most peptide therapies are currently administered via parenteral injection, which ensures bioavailability but sacrifices patient convenience and adherence. The pharmaceutical industry has long recognized the need for effective oral peptide delivery systems, yet few have reached the market.

This landscape presents an opportunity for innovation. Leveraging excipients that enhance permeability, protect against enzymatic degradation, and exploit alternative absorption pathways can help overcome these barriers, enabling patient-friendly oral peptide medicines. Lipid excipients, particularly those with medium-chain fatty acid ester content, provide a physiologically compatible strategy to enhance permeability and protect peptides in the GI tract.[1,2]

CASE STUDY: ORAL DELIVERY OF A MACROCYCLIC PEPTIDE WITH LABRASOL® ALF

In a recent human clinical study, Merck & Co. explored formulation approaches for an orally administered form of enlicitide chloride (MK-0616), a novel macrocyclic peptide designed to treat elevated levels of LDL cholesterol. Macrocyclic peptides sit at the intersection between small molecules and biologics, offering a unique combination of properties that make them attractive as next-gen-

TABLE 3

Parameter	200 mg enlicitide chloride without Labrasol® ALF (n=8)	200 mg enlicitide chloride with Labrasol® ALF (n=8)	Parameter With Labrasol®/ Without Labrasol®
$AUC_{0-\infty}$[a] (h•nmol/L)	556 (448, 690)	1250 (946, 1650)	2.25
AUC_{last}[a] (h•nmol/L)	481 (394, 588)	1160 (880, 1520)	2.41
C_{max}[a] (nmol/L)	7.84 (6.32, 9.72)	45.3 (24.6, 83.2)	5.78
T_{max}[b] (h)	14.53 (0.50, 36.00)	2.02 (1.07, 5.00)	0.14
$t_{1/2}$[c] (h)	56.41 (12.0)	95.47 (27.7)	1.69

Comparison of Plasma Pharmacokinetics Following Administration of Enlicitide Chloride With or Without 1800 mg Labrasol® ALF to Healthy Male Participants

eration therapeutics, especially in an oral dosage form.

In the study, Labrasol ALF (Caprylocaproyl Polyoxyl-8 glycerides) was evaluated as a permeation enhancer. A simple mixture of 1800 mg of Labrasol ALF with 200 mg of enlicitide chloride enabled a 2- to 3-fold increase in plasma concentration, showcasing the translational relevance of lipid-based approaches for oral delivery of biologics (Table 3).[24]

LIPID-ENABLED INNOVATION OFFERS SAFETY & REGULATORY CONFIDENCE

Across all these categories, lipid excipients offer more than performance — they offer reliability. In a world where novel excipients continue to face significant regulatory hurdles, the robust safety data and global precedence of use (Figure 4) that accompany lipid excipients make them a low-risk, high-reward option for pharmaceutical innovation.

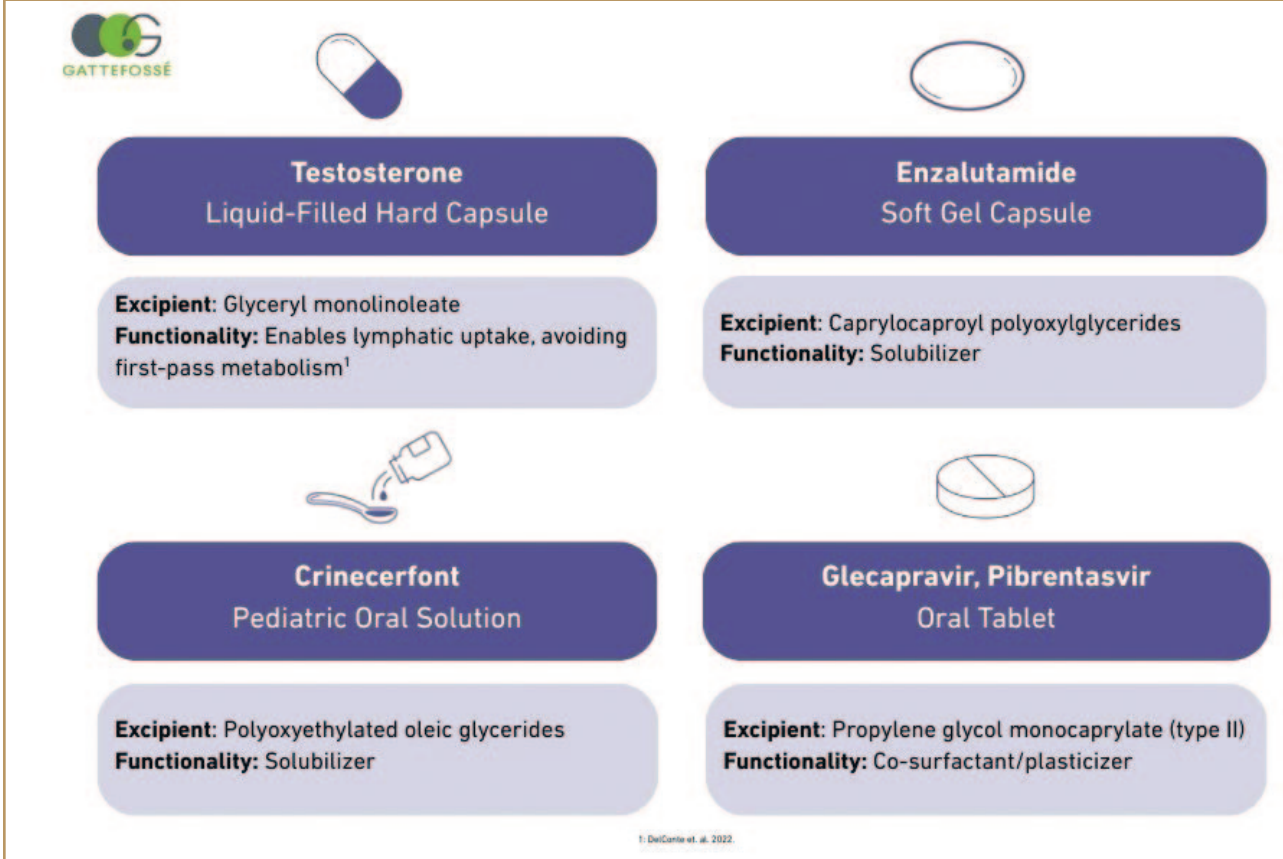
Whether driving new product development or revitalizing existing assets, lipids remain a valuable option in the formulation toolkit, and Gattefossé Pharmaceuticals is committed to the scientific advancement of lipid-enabled drug delivery. Through innovative research, hands-on formulation support at our global technical centers of excellence, and collaborations across industry and academia, Gattefossé continues to uncover the unique benefits of lipids in drug delivery. When coupled with industry-leading safety and regulatory support, lipid excipients offer a truly streamlined path to innovation.

SUMMARY

Delivering the next generation of poorly soluble and permeable APIs requires innovative, reliable formulation strategies. Lipid excipients are a uniquely effective solution, leveraging the body's digestive mechanisms to overcome critical bioavailability barriers. By enhancing solubility through supersaturation, increasing permeability via tight junction modulation, and enabling lymphatic uptake, these excipients provide a multi-faceted approach to improving drug performance.

From creating ternary ASDs that improve manufacturability and drug release to reformulating existing drugs to mitigate food effect, lipid-based systems offer tangible solutions to today's formulation challenges. Furthermore, they represent a critical enabling technology in the quest for oral biologics.

FIGURE 4



Global Precedence-of-Use Examples for Lipid Excipients

Ultimately, the value of lipid excipients lies in their combination of performance and precedent. With a long history of use in globally approved medicines and an established safety profile, they offer a low-risk, high-reward pathway for innovation. For formulators tasked with developing the next generation of oral therapies, lipid-based systems provide a flexible, scalable, and proven platform to transform challenging molecules into effective, patient-centric treatments.

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BIOGRAPHY

Nick DiFranco, MEM, is the Senior Marketing Manager for the Pharmaceutical Division at Gattefossé USA, a well-established supplier of pharmaceutical excipients and drug delivery solutions. In this role, he leads the strategy and marketing efforts for the North American excipients business — seeking opportunities to expand the use of lipid excipients at innovative pharmaceutical companies. Mr. DiFranco has many years of experience coordinating multi-disciplinary teams in the pharmaceutical excipient and contract development and manufacturing (CDMO) industries. He previously led global marketing efforts for solubility/bioavailability enhancement technologies, oral drug delivery portfolios, and long-acting implantable and injectable offerings. Mr. DiFranco holds a B.S. in Biomedical Engineering (Biomaterials focus) and a Master of Engineering and Management degree from Case Western Reserve University.

Drug Development
EXECUTIVE

Lew Bender

Founder & CEO

Intensity Therapeutics

Intensity Therapeutics: Providing Cancer Patients With Treatments That Work

Current cancer treatments can be awful for the patients who are forced to undergo them. Sometimes treatment itself can be almost as bad as the cancer, but doctors are left with little choice but to provide their patients the best chance to keep the cancer from returning. Cancer patients want treatments that work, helping them live longer without the fear of serious harm to their bodies or other side effects from their treatment.

Intensity Therapeutics is on a mission to do just that. Intensity's products focus on injecting drugs directly into tumors to kill them, instead of traditional cancer therapies that are typically delivered intravenously through the whole body, making it a struggle to target cancers directly. The company's lead product candidate, INT230-6, is currently in human clinical studies to treat refractory solid tumors like localized triple-negative breast cancer and metastatic soft tissue sarcoma.

Drug Development & Delivery recently interviewed Lew Bender, Founder and CEO of Intensity Therapeutics, to discuss the company's science, clinical program, the drug development process, and more.

Q: Can you tell us about Intensity Therapeutics and how your intratumoral therapies work?

A: Intensity Therapeutics is a late-stage clinical biotechnology company with a mission to help patients live longer, higher-quality lives by discovering, developing, and commercializing first-in-class cancer drugs that attenuate tumors with minimal side effects while training the patient's immune system to fight the cancer. Treatments, such as chemotherapy and immunotherapy, impact patients' entire bodies, administering toxic side-effects throughout the system. Our technology is different, with our drug

being injected directly into patients' tumors, sparing healthy cells throughout the body. As the cancer cells die, the immune system begins to recognize the cancer. We debulk the live cancer and essentially convert a person's tumor into their own personal anti-cancer vaccine, inducing a systemic adaptive immune response. Our lead product candidate, INT230-6, is currently in human clinical studies to treat refractory solid tumors like localized triple-negative breast cancer and metastatic soft tissue sarcoma. INT230-6 is a product comprising two potent commercial cytotoxic agents (cisplatin and vinblastine), which are typically given intravenously, along with a dispersion and diffusion enhancer. The new drug is designed explicitly for intratumoral delivery. After the direct injection, the drug saturates the cancer cells with the potent agents and causes tumors to die. Cisplatin and vinblastine each have dual killing and immune-activating mechanisms-of-action. With the proper amount of drug dosed into the tumor, our drug can cause the majority of cancer cells to die in an immunologically activating manner. Our drug creates a personal vaccine from a patient's tumors that leads to a T-cell attack on the injected and uninjected tumors.

Q: Why did you decide to use intratumoral injection as your delivery method? How did you come up with this idea?

A: When immunotherapies began to gain traction, I learned that their immune-stimulating mechanisms are analogous to releasing the brakes (PD-1 antibodies) or stepping on the gas (CTLA-4 antibodies) in the immune system. I thought there needed to be a steering wheel to guide the immune cells to target the tumor more precisely. I'm a chemical engineer by trade and have worked for more than 20 years in drug delivery, focusing on delivering the precise amount of drug to the right place at the right time.

Intratumoral delivery has been a concept that others had previously explored, but unfortunately, they were unsuccessful in creating a viable product. Due to the high fat content found in tumors, water-soluble drugs are unlikely to be absorbed. We published data on this effect in 2020. To combat this water-fat incompatibility, I leveraged my previous training in drug delivery to develop INT230-6, which utilizes a dispersion and cell penetration enhancer molecule to facilitate the diffusion of therapeutic agents throughout the fatty, dense tumor and into cancer cells. Our proprietary chemistry enables the active agents to be soluble in both fat and water simultaneously. Almost all drugs are given intravenously or orally to fight metastatic disease systemically. Our local therapy kills tumors and stimulates the immune system to attack the tumors that we do not inject. After intratumoral injection, the cytotoxic agents disperse throughout the tumor and diffuse into the cancer cells. The agents remain in the tumor, and side effects are minimal; the tumor dies, and the immune system recognizes the cancer and attacks the injected and uninjected tumors. Our approach is a new way to kill cancer, unlike any current therapy.

Q: What indications have you targeted for this type of treatment to date, and do you expect this to be applicable to more indications in the future?

A: So far, we have targeted advanced soft tissue sarcoma, as well as neoadjuvant and metastatic triple-negative breast cancer. We hope this delivery technology will be a valuable tool across various cancer indications. This is not a cure for every type of cancer, there will be some tumors you can't get a needle to for the intratumoral injection and there will be some instances in which it just won't be a feasible treatment, such as the tumors are too diffuse or blood cancers, which are not amenable to injection, etc. But there are enough cancers I believe can be injected in which this new drug may have a real impact and make a difference for patients.

The other thing to consider is cancers can develop resistance. Even if an initial drug is effective, the cancer could come back and then be resistant to the treatment. The idea is to use diffusion-based technologies like ours to overwhelm the tumor and delay or eliminate the onset of resistance. Also, there could be other active drugs that might be better than the cisplatin and vinblastine. There could be a whole host of other payloads that we could load into this intratumoral delivery technology that could be effective. We're committed to seeing this drug delivery product through to the end and then sharing it with doctors who can determine the best path forward for their patients.

Q: Can you tell us about the progress of Intensity's current clinical programs?

A: Currently, we have in-progress trials in both operable triple-negative breast cancer and advanced soft tissue sarcoma. The INVINCIBLE-4 study is a Phase 2 randomized, open-label, multicenter study to analyze the clinical activity, safety, and tolerability of INT230-6 administered before the standard-of-care treatment in patients with early stage, operable triple-negative breast cancer, compared to SOC alone. The primary endpoint is to determine the change in the pathological complete response rate for the combination and the SOC alone.

The study is recruiting patients in Switzerland and France and is expected to enroll 54 patients. The INVINCIBLE-3 study is a Phase 3, open-label, randomized study testing INT230-6 as monotherapy compared to standard of care (SOC) drugs in second- and third-line treatment for three specific soft tissue sarcoma subtypes. The study is expected to enroll 333 patients and initiate sites in eight countries. This study has been authorized by the US FDA, Health Canada, the European Medicines Authority (for France, Germany, Italy, Poland and Spain), and Australia's Therapeutics Goods Administration. The primary endpoint in the INVINCIBLE-3 study is overall survival. We've had to pause new site activations and patient enrollments in the INVINCIBLE-3 study due to funding constraints, but we continue to treat all patients already enrolled, and the treatment has been effective and well-tolerated to date.

Q: Can you tell us more about triple-negative breast cancer, a target of your INVINCIBLE-4 Study, and why it's important to find improved treatment options?

A: Triple negative is a very aggressive form of breast cancer. The negative refers to the absence of target protein receptors (estrogen, progesterone, and Herceptin) on the cancer cell. This status limits the amount of drugs available to treat the cancer. When women undergo chemotherapy prior to a lumpectomy or mastectomy, they are trying to eliminate all live cancer in the tumor and lymph nodes by the time of surgery. The absence of live cancer is referred to as a pathological complete response (pCR), which strongly correlates with a more prolonged event-free survival (ie, a delay in the return of the cancer). Unfortunately, only a fraction of women achieve a pCR, and up to 0.5% of women can die from the chemotherapy itself. By adding our drug upfront, before initiating the current standard treatment regimen, we hope to increase the percentage of women having a pCR without increasing toxicity and possibly even decreasing the toxicity.

One of the biggest trends we're seeing is using drugs before surgery. Dosing before surgery is referred to as the neoadjuvant setting. The goal is to increase the chances of a patient delaying disease recurrence. Another trend is the earlier and earlier diagnosis of breast cancer using mammograms. Only a few years ago, women over 50 were the only ones recommended to get tested. Now, according to the United States Preventive Services Task Force (USPSTF), women should get their first mammogram at age 40 and continue to get screened every other year until they are 74. ◆

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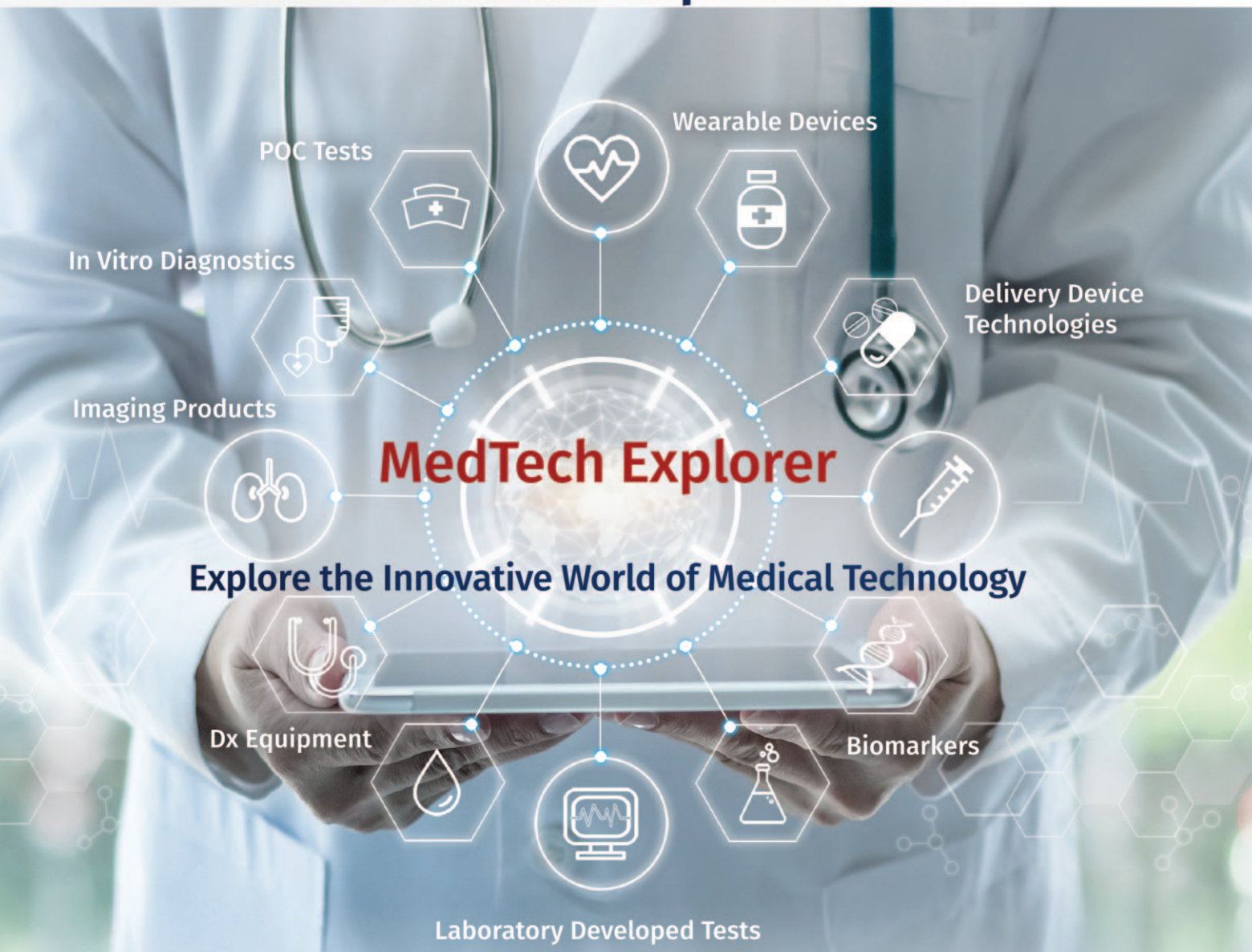

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CLINICAL TRIALS

Keeping Pace With Shifting Drug Development Paradigms for Multi-Indication Therapies

By: Simon Bruce, MD, and Jack L. Martin, MD, FACC

INTRODUCTION

Adoption of multi-indication pipelines has extended to the cardiometabolic landscape and beyond. The successful label expansion of GLP-1 receptor agonists (GLP-1 RAs), which mimic a metabolic hormone, established compelling evidence for the commercial value of multi-indication drug development beyond obesity.[1] The growing appetite for multi-indication drug development was reflected in a 2025 survey from ICON, questioning 155 biotech and pharmaceutical professionals across the US and Europe whose research included cardiometabolic indications.[2] A strong majority of sponsors (92%) reported that at least one therapy in their pipeline had potential efficacy in more than one indication, and 83% reported actively developing a therapy in their pipeline for multiple indications.

To compete in today's increasingly competitive cardiometabolic market, developers of therapies with multi-indication potential must take a strategic approach that will accelerate cross-indication approvals and improve resource efficiency during development. This requires a proactive, strategic multi-indication development and commercialization strategy, which represents a paradigm shift from a historically reactive, serendipitous process.

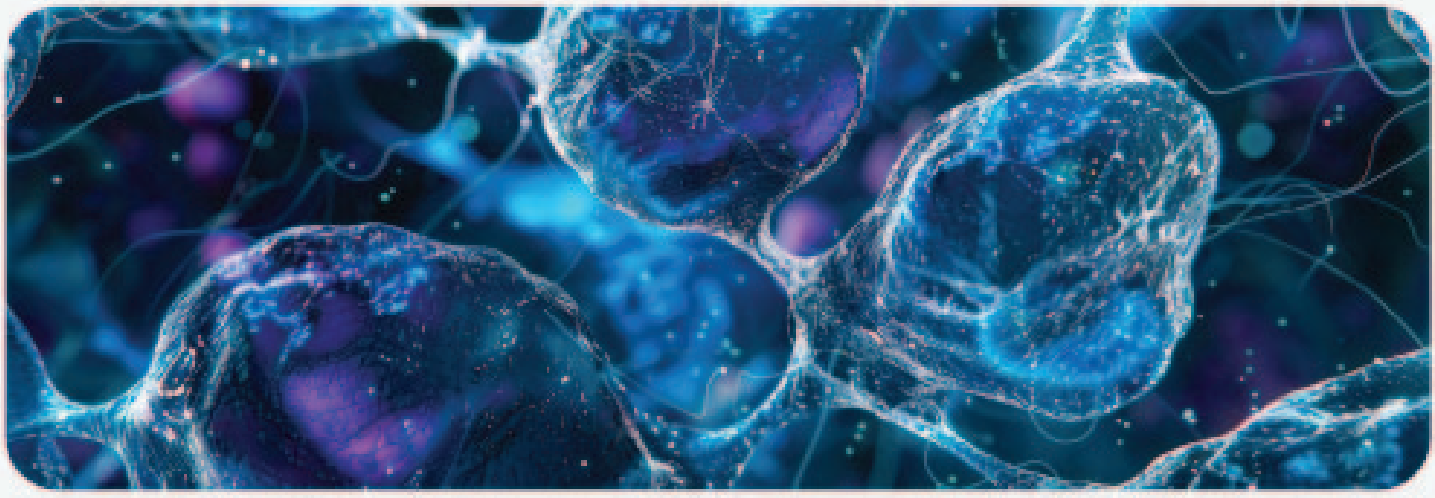
Eli Lilly's tirzepatide exemplifies a proactive multi-indication strategy. Initially approved for type two diabetes (Mounjaro) in May 2022, based on the Phase 3 SURPASS study, it was then approved for chronic weight management as Zepbound 1.5 years later, in November 2023.[3,4] The rapid succession of approvals was enabled by early stage trials designed to support multiple indications, followed by parallel pivotal trials supporting individual indications.[5] By contrast, Novo Nordisk's GLP-1 RA received weight loss approval in June 2021 3.5 years after initial type two diabetes approval in December 2017, using a more sequential and less integrated development approach.[6,7]

Unconventional clinical development strategies may be better adapted to multi-indication approaches than conventional approaches developed with single-indication therapies in mind. However, the 2025 survey suggests that many sponsors are hesitant to adopt these strategies, even as they recognize the value of multi-indication development. For instance, 1 in 10 developers said they used master protocols or other nontraditional study arms that enable multi-indication trials.[2]

Early consideration of unconventional trial formats, patient screening approaches, and endpoint selection in clinical trials may introduce efficiencies into the development of a single therapeutic for multiple indications. Similarly, cross-indication approvals can be supported by the implementation of more intentional long-term follow-up and real-world evidence (RWE) generation. In turn, more strategic multi-indication development strategies will accelerate cross-indication approvals for emerging cardiometabolic drugs going forward.

ADAPTIVE DESIGNS & MASTER PROTOCOLS

The survey reflected the persistent use of conventional trial formats, which were initially designed for single-indication therapies.[8] However, nontraditional trial formats can be better suited to multi-indication development. For instance, master protocols can allow researchers to test a drug across several conditions in one study, saving resources needed to run separate studies in parallel. Adaptive trial designs are another useful trial framework, which allow for data-based decision-making earlier in the clinical trial process, and can aid dose selection and early signal detection across related pathways. Especially when trial populations overlap, implementing adaptive designs or master protocol trial



formats can reduce timelines and costs during multi-indication development.

Frequently, hesitation to adopt adaptive and master protocols stems from uncertainty around regulatory expectations and operational feasibility, rather than resistance. Scenario-based planning and early strategic consultation can help clarify the value and mitigate risks of adopting new or unfamiliar clinical trial models. For instance, partners can help sponsors select fit-for-purpose adaptive elements tailored to their therapeutic profile and pipeline, such as interim dose selection based on short-term weight loss, related biomarkers or tolerability signals. Rather than pushing a fixed model, experts in multi-indication development can help sponsors tailor innovative trial designs to their specific risk profile, resource limits, and regulatory path — ensuring the design serves the program, not vice versa.

PATIENT SCREENING

In the ICON survey, four in five respondents reported using traditional patient screening methods that often rely on broad inclusion criteria based on simple metrics such as body mass index (BMI) or waist circumference measurements.[2] However, this approach often fails to recognize that individuals may have different underlying causes for disease, varying risk profiles, and diverse treatment responses.

Sponsors can benefit from taking a precision approach to patient screening that enables stratification by relevant comorbidities and related factors, such as insulin resistance, inflammatory markers, or psychological indicators. Stratified recruitment can enhance the clinical and commercial success of therapies with multi-indication potential by identifying subpopulations most likely to benefit from treatment, strengthening the evidence base for label expansions, and potentially improving payer and physician acceptance of multi-indication approvals.[9]

ENDPOINT SELECTION

Effective patient recruitment, guided by precise inclusion criteria, must be complemented by a thoughtful selection of endpoints to ensure trial success. Endpoint choices directly influence regulatory approval and the commercial viability of a drug. However, sponsors of multi-indication therapies often face the challenge of reconciling regulatory mandates with clinically meaningful outcomes.

For instance, while regulatory bodies typically prioritize BMI change as a primary endpoint for obesity trials, this metric may not fully encompass the broader health benefits relevant to physicians and payers. A singular focus on primary, regulatory-accepted endpoints can, therefore, limit the commercial potential of obesity treatments that offer other significant improvements in how patients feel, function and survive.

To address this, incorporating secondary, surrogate and exploratory biomarkers, alongside primary endpoints, can provide a more comprehensive understanding of treatment effects. Exploratory endpoints, for instance, are invaluable for evaluating a therapy's mechanism of action and identifying differential benefits across patient subgroups. Although not typically used for regulatory submissions, they can justify the investigation of a wider range of outcomes and generate new hypotheses about a drug's effects or mechanisms.

Despite their importance, nontraditional endpoints — such as exploratory measures — remain underutilized, with fewer than one in six sponsors reporting their use. Nevertheless, the significance of endpoint selection is widely recognized, with 43% of survey respondents identifying it as the most critical factor in successful multi-indication drug development.[8]

REAL-WORLD EVIDENCE

Real-world evidence (RWE) — clinical evidence derived from real-world data (RWD) on a patient's health status and routine healthcare — is increasingly vital for clinical developers. This is especially true for medicines with broad indications, diverse patient populations and uncharacterized long-term impacts. RWE studies can guide multi-indication expansion strategies by quantifying a therapy's real-world impact on various conditions and comorbidities. In certain cases, RWE can even support regulatory decisions for new indications or post-market requirements. Furthermore, RWE bridges knowledge gaps from clinical trials, demonstrating a therapy's value to payers and healthcare providers.

Despite its importance, generating high-quality RWE presents challenges due to limitations in RWD generation and the complexities of RWE study design. A 2025 ICON survey revealed that fewer than one in six respondents used RWE to inform multi-indication development, and only one in five integrated long-term follow-up strategies beyond 3 years into clinical development.[8] Early guidance from experienced partners can help developers more effectively leverage RWE to demonstrate a therapy's value, safety and effectiveness across multiple indications in diverse real-world settings.

EMBRACING MULTI-INDICATION DESIGNS

As developers increasingly embrace multi-indication development, the success of multi-indication therapies will stem not merely from pipeline adjustments, but also from development strategies designed with multi-indication objectives at their core. Companies that prioritize early cross-functional planning, innovative trial architecture and a dedication to evidence generation will be best positioned to unlock the full value of their therapies. ◆

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BIOGRAPHIES

Dr. Simon Bruce is Vice President, Internal Medicine at ICON. He was trained in Internal Medicine with sub-specialization in Endocrinology at the National Institutes of Health. At NIH, he received training and conducted human patient-oriented clinical research. For the past 19 years, he has held positions of increasing responsibility in both large pharmaceutical and small to medium sized biotech companies. He has broad experience across all phases of clinical development and has been responsible for clinical development strategy and execution from pre-IND to first-in-human and phase 1/2 proof-of-concept trials through Phase 3 planning, execution and filing. Before joining ICON in 2021, he was a biopharma consultant leading clinical development of multiple compounds at Kinexum in the Metabolic and Diabetes therapeutic areas, including DPP4 and SGLT2 inhibitors, GLP-1 agonists, leptin and prandial insulins among others. Prior to Kinexum, he served as Chief Medical Officer with Adocia Inc (2014-2017), working on an ultra-rapid insulin in collaboration with Eli Lilly. His position at Kinexum was preceded by the role of Executive Medical Director, Endorcrinology at Halozyme Therapeutics (2012-2014) and Executive Director, Global Program Medical Director at Novartis (2010-2012).

Dr. Jack L. Martin is Senior Director, Cardiovascular Therapeutics, Drug Development Solutions at ICON. He is board certified in Cardiovascular Diseases and Interventional Cardiology. He has over 35 years of clinical practice and investigational experience. He is an experienced consultant for pharmaceutical and medical device companies. This includes all phases of product development including device design, trial design, FDA pre-sub and panel meetings. He has served as study chairman or the coordinating investigator for multiple multicenter international pharmaceutical and device trials. His previous roles included Assistant Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Chief, Division of Cardiovascular Diseases and Chief of Interventional Cardiology, Health System.

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Credence MedSystems is an innovator in drug delivery devices. Credence's philosophy of *Innovation Without Change* results in products that impress and protect end-users while preserving pharma's existing processes, sourcing strategies and preferred primary package components. The Companion® family of syringe systems includes proprietary integrated needle-retraction technology, reuse prevention, critical safety & usability features as well as sustainability advantages. The Dual Chamber platform offers simplified delivery for drugs requiring reconstitution or sequential injection at the time of delivery. The Credence Connect™ Auto-Sensing Injection System incorporates automatic real-time monitoring of critical injection data into a reusable ergonomic finger grip. Credence's Metered Dosing product line allows precise delivery of small volumes and a force advantage when viscosities are high. For more information, call +1 844-263-3797 (+1-844-CMEDSYS), email info@credencemed.com, or visit **www.CredenceMed.com.**

Hands-On Formulation Support

GATTEFOSSÉ

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

On-Body Drug Delivery

SensAIR is a platform for on-body drug delivery that can deliver drugs of higher viscosity, such as monoclonal antibodies. The aim is to provide patients with the best possible support in the subcutaneous delivery of large-volume biologics. The ready-to-use SensAIR On-Body Delivery Device is easy to use and enables patients to start medication in a self-determined manner in familiar surroundings. The SensAIR On-Body Delivery Device can be adapted to medications of different viscosities and with different requirements. This applies to the size of the medical device as well as to the needle used, variable cartridge sizes and possible connectivity, for example to the patient's smartphone. Together with **Gerresheimer's** One-Stop-Shop quality promise, which includes a solution from the cartridge to the drug delivery device from a single source, SensAIR enables optimized delivery of biologics. For more information, visit Gerresheimer at **www.gerresheimer.com.**

Research Chemical Supplier

Oakwood Chemical
Enabling Discovery

Oakwood Chemical wants to be your research chemical supplier of choice. Since our founding 30+ years ago as a research chemical supplier specializing in fluorine and sulfur chemistry, we have remained focused on providing our customers the chemicals needed to advance science. Our catalog of over 45,000 chemicals includes a comprehensive collection of the essential chemicals needed to perform the broad range of reactions that enable discovery research. In addition, we have increased our in-house production capacity to provide support for both catalog products and custom synthesis projects, while also increasing our overall scale to support development efforts. Our experience in manufacturing, sourcing, and handling a wide range of chemicals enables us to respond quickly and efficiently to your research chemical needs. For more information, visit Oakwood Chemical at **www.oakwoodchemical.com.**

Technology & Services Showcase

Excipients & Ingredients

Roquette Health & Pharma Solutions offers a broad and versatile portfolio of reliable excipients designed to enhance productivity, cost efficiency, and supply stability across the pharmaceutical and nutraceutical value chain. Our plant-based, high-quality, and multi-compendial excipients support a wide range of applications, from prescription and OTC drugs to generics, nutraceuticals, and biopharmaceuticals. With a strong focus on innovation, Roquette also delivers specialty ingredients that help customers optimize formulations and maintain consistent performance while meeting stringent global standards. By combining robust sourcing capabilities with scientific expertise, we help our partners improve development speed, strengthen supply security, and advance patient outcomes. For more information, visit Roquette Health & Pharma Solutions at **www.roquette.com/pharma.**

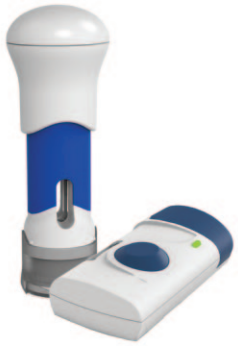
CDMO Services

UPM Pharmaceuticals is CDMO with 30+ years of US based experience in development to later-stage clinical and commercial manufacturing of oral solid and semi-solid dosage forms. Beyond our expertise and technology, UPM is a contract manufacturing organization that has a passion for propelling our customers' journeys from early-stage development to the market, even when the journey doesn't begin with us. As a large-scale CDMO, technology transfer and scale-up are our specialties; we welcome the opportunity to sit down with you to create a pharma solution by understanding the evolution of your project, your clinical and commercial goals, and how we can work together to get your product across the finish line. For more information, visit UPM Pharmaceuticals at **www.upm-inc.com.**

Full-Service CDMO

Vetter is a leading independent contract development and manufacturing organization (CDMO) specializing in clinical and commercial aseptic filling and packaging as well as the assembly of syringes, cartridges, and vials. With extensive expertise in biologics and other complex compounds, Vetter collaborates with pharma and biotech companies worldwide to support their unique products from preclinical development through to global market supply. With state-of-the-art facilities in the US and Europe, the CDMO provides comprehensive support for early stage products, transfer to Phase 3, and commercial supply for large-scale production. Vetter's commitment to quality and innovation results in reliable and efficient solutions tailored to meet the needs of each customer. For more information, visit **www.vetter-pharma.com.**

Integrated Delivery Systems



West is a leader in developing and manufacturing pharmaceutical delivery systems. The company has unique technologies in self-injection systems, including the SmartDose® drug delivery platform and the award-winning SelfDose® patient-controlled injector, that enable patients to self-administer injectable medicines at home. West is also collaborating with HealthPrize Technologies on a connected health offering that is designed to improve and reward medication adherence with unique technologies. The offering integrates HealthPrize's Software-as-a-Service medication adherence and patient engagement platform into injectable drug delivery systems, providing biopharmaceutical companies and their patients with an end-to-end connected health solution. For more information, contact West at (800) 345-9800 or visit **www.westpharma.com.**

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