# Drug Development & Delivery

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The Science & Business of Pharmaceutical and Biological Drug Development

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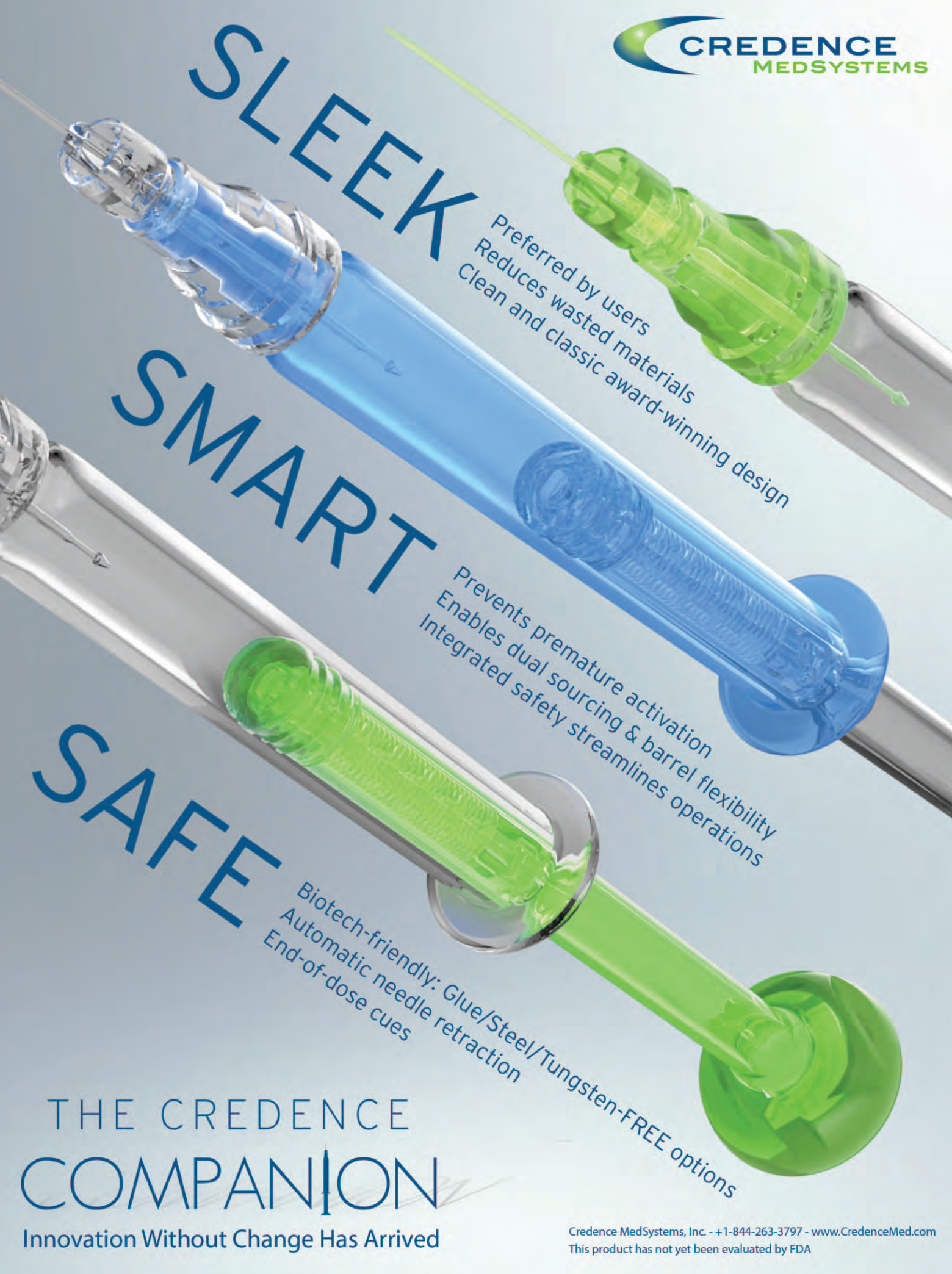
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# Transforming Analytical Labs

"Stringent regulatory guidelines and specialized capabilities are also contributing to bio/pharma companies seeking to outsource analytical testing providers. Some of these specialized capabilities include artificial intelligence (AI), which requires a depth of expertise and provides access to large quantities of high quality data. Industry insiders say the potential of AI to increase reproducibility and accuracy has the potential to transform analytical labs in the future."


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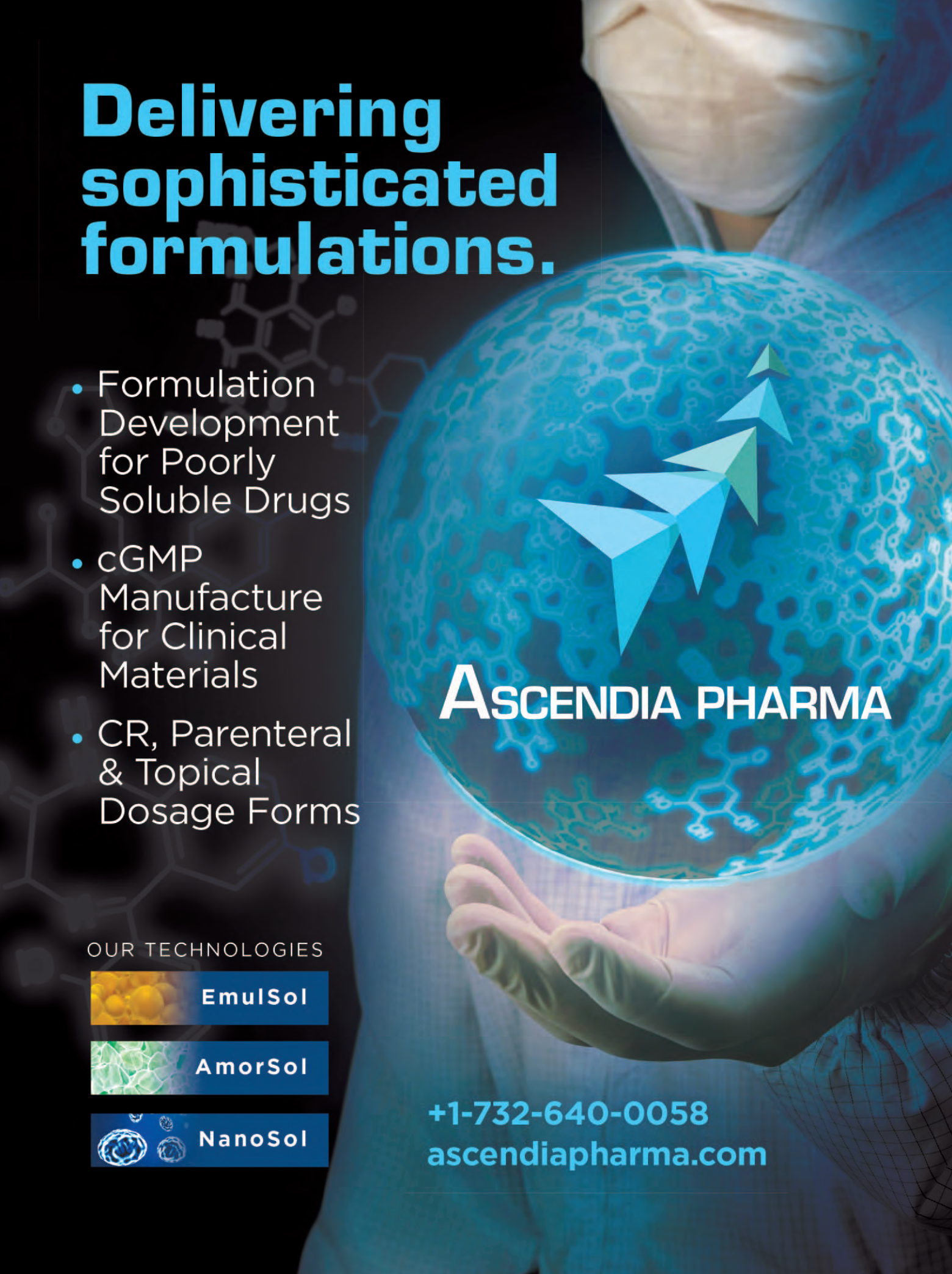
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"Drug shortages in the US are at an all-time high, with no relief in sight. Solutions are urgently needed to improve supply chain visibility – the ability to "see" where products are located at any point in time during their life cycle – to infuse product stability and help ensure necessary supplies are available when and where they are needed."


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## Recipharm, Medspray & Resyca Enter Exclusive License Agreement to Develop Nasally Delivered Drug Products Using Proprietary Soft Mist Technology

Recipharm recently announced an exclusive license and collaboration agreement with Medspray and Resyca to develop soft mist nasal delivery devices for single and combination drug products. This collaboration extends the successful partnership between Recipharm and Medspray, which resulted in the joint venture, Resyca; a company which is developing soft mist inhalers utilizing Medspray's nozzle technology to achieve high lung doses and less degradation of biological active pharmaceutical ingredients.

Under the terms of the agreement, Resyca gains exclusive rights to Medspray's proprietary spray nozzle technology for use in nasal devices and combination drug products. This collaboration enables Resyca to provide all aspects of turnkey solutions for both oral and nasal inhalation, leveraging soft mist technology.

Han van Egmond, CEO at Medspray, said "Extending this agreement involves combining our cutting-edge nasal technology with Resyca's product development capabilities. This collaboration with Resyca will enable us to bring innovative solutions to the market that will redefine the landscape of nasal drug delivery."

It is anticipated that the enhanced collaboration will result in breakthroughs in the nasal delivery of fragile biological formulations, such as mRNA vaccines for pandemic applications.

"We are thrilled to enter into this extended strategic partnership with Medspray," said Remko Beimers, CEO at Resyca. "This move aligns perfectly with our mission to pioneer advancements in aerosol drug delivery systems. The exclusive licence from Medspray will significantly strengthen our position in the market, allowing us to bring innovative and effective soft mist nasal delivery devices to patients worldwide together with our pharma customers."

Recipharm, as a key player in the pharmaceutical CDMO industry, recognizes the potential impact of this collaboration on the advancement of nasal drug delivery. "We are proud to be associated with Medspray and Resyca in this landmark licensing agreement," said Chris Hirst, President, Advanced Delivery Systems at Recipharm. "As a CDMO committed to driving innovation, we look forward to supporting both companies in bringing their pioneering soft mist nasal delivery devices to the market to improve patient experience and expand what is possible via the nasal delivery route."

Recipharm is a leading Contract Development and Manufacturing Organization (CDMO) in the pharmaceutical industry employing almost 9,000 employees. Recipharm offers manufacturing services of pharmaceuticals and biologics in various dosage forms, production of clinical trial material and APIs, pharmaceutical product development and development and manufacturing of medical devices. Recipharm manufactures several hundred different products for customers ranging from big pharma to smaller research and development companies. The company operates development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US and is headquartered in Stockholm, Sweden.

## Artelo Biosciences Announces Publication of New Peer-Reviewed Preclinical Research Demonstrating Effectiveness in Treating & Preventing Oxaliplatin-Induced Peripheral Neuropathy

Artelo Biosciences, Inc. recently announced new research published in the peer-reviewed Journal of Pain. The research article, titled Discovery and preclinical evaluation of a novel inhibitor of FABP5, ART26.12, effective in Oxaliplatin-induced Peripheral Neuropathy, highlights Artelo's preclinical asset, ART26.12, and its potential ability to treat and prevent Oxaliplatin-Induced Peripheral Neuropathy (OIPN) in a series of separate studies.

ART26.12 is a Fatty Acid Binding Protein 5 (FABP5) inhibitor in development for the treatment of chemotherapy-induced peripheral neuropathy (CIPN), a type of neuropathic pain caused by chemotherapy as well as non-chemotherapy cancer treatments such as immunomodulating drugs. Oxaliplatin (OXA) is a commonly used platinum-based antineoplastic agent that causes oxaliplatin-induced peripheral neuropathy (OIPN) in up to 98% of patients treated with OXA, oftentimes resulting in treatment dose reduction, cessation of anti-cancer treatment prematurely, or can result in a painful persistent peripheral neuropathy even after chemotherapy is stopped.

"In preclinical safety studies, ART26.12 has shown minimal off target effects, high oral bioavailability, and a NOAEL (no-observed-adverse-effect-level) of 1000 mg/kg/day administration," said Andy Yates, PhD, Senior Vice President and Chief Scientific Officer at Artelo. "We are highly encouraged by the four research studies presented in this paper demonstrating ART26.12, our patented and novel treatment approach to inhibiting FABP5, was effective in treating and preventing the painful condition of OIPN."

According to Coherent Market Insights, the global neuropathic pain market is estimated to be valued at $7.6 billion, demonstrating the need for an innovative therapy that has the potential to provide non-opioid pain relief. Artelo has conducted multiple pre-clinical studies in painful neuropathies, including diabetic neuropathy, paclitaxel-induced peripheral neuropathy, and OIPN, the latter two of which has no FDA-approved treatment. The company previously reported a positive pre-IND (investigational new drug) meeting with the Food and Drug Administration (FDA) and anticipates filing the IND for ART26.12 in the first half of 2024.

Fatty Acid Binding Proteins (FABPs) are a family of intracellular proteins that chaperone lipids including endocannabinoids and fatty acids. FABP is overexpressed and associated with abnormal lipid signaling in a number of pathologies. ART26.12, Artelo's lead FABP inhibitor, is a potent and selective inhibitor of FABP5 being developed as a novel, peripherally acting, non-opioid, non-steroidal analgesic, with an initial clinical study planned for chemotherapy-induced peripheral neuropathy (CIPN). Beyond ART26.12, Artelo's extensive library of small molecule inhibitors of FABPs have shown therapeutic promise for the treatment of certain cancers, neuropathic and nociceptive pain, and anxiety disorders.

Artelo Biosciences, Inc. is a clinical-stage pharmaceutical company dedicated to the development and commercialization of proprietary therapeutics that modulate lipid-signaling pathways, including the endocannabinoid system. Artelo is advancing a portfolio of broadly applicable product candidates designed to address significant unmet needs in multiple diseases and conditions, including anorexia, cancer, anxiety, pain, and inflammation. Led by proven biopharmaceutical executives collaborating with highly respected researchers and technology experts, the company applies leading edge scientific, regulatory, and commercial discipline to develop high-impact therapies.

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## Alcami Announces Acquisition of West-Coast Based Pacific Pharmaceutical Services

Alcami Corporation recently announced it has completed the acquisition of Pacific Pharmaceutical Services, Inc. (PPS), a preferred provider of cGMP pharma storage and services.

"The Pacific Pharmaceutical Services acquisition is part of our highly intentional strategy to supercharge the capabilities of our pharma storage and services business with locations that best serve biotech and pharma clients across the country," said Bill Humphries, CEO of Alcami. "With its strategic West Coast location, we can better address bicoastal market needs, improve material safe-guarding from natural disasters with multi-location facilities and support multi-center clinical trials. Adding PPS to the Alcami family cements our status as the US CDMO for West Coast projects as we continue to focus on the stability and security that matters most in storage of preclinical and clinical materials."

In addition to the acquisition of PPS, Alcami is strategically expanding its central North Carolina pharma storage and service footprint with the opening of a new 65,000-sq-ft facility co-located near the Research Triangle Park's biotech and pharma hub. Combined with the acquisition, this additional expansion underscores Alcami's focus on its comprehensive pharma storage and services business.

With its hallmark of personalized, responsive customer care, PPS offers key controlled storage and material management solutions (controlled temperature storage from room temperature down to cryo temperatures and material aliquoting) as well as clinical labeling and support for most development lifecycle stages spanning from pre-clinical to early clinical trials. PPS also provides clinical distribution and material management across various conditions. PPS founder Scott Chadwick will continue with the company in the role of General Manager and Site Head.

"I'm proud of the business we built, and look forward to partnering with Alcami. Combining forces enables us to offer clients even more solutions with the same agile, flexible approach that continues to make us successful," Chadwick shared.

PPS' clients will benefit from immediate access to Alcami's comprehensive service offerings ranging from analytical development and testing to full drug product development and manufacturing of both sterile fill-finish and oral solid dose. Similarly, Alcami's extensive client base will have access to PPS' West Coast cGMP pharma storage capacity and support services, ensuring a seamless experience across the Alcami network of laboratory, pharma storage and manufacturing services.

Alcami is a contract development and manufacturing organization headquartered in North Carolina with over 40 years of experience advancing products through every stage of the development lifecycle. Alcami serves pharmaceutical and biotech companies of all sizes for small molecules and biologics, providing customizable and innovative solutions for analytical development, clinical to commercial sterile and oral solid dose drug product manufacturing, packaging, microbiology, cGMP biostorage, environmental monitoring, and pharmaceutical support services. Alcami's private equity ownership includes GHO Capital, The Vistria Group, and Ampersand Capital Partners.

Founded in 2010, Pacific Pharmaceutical Services, Inc. is a GMP-certified warehousing provider for pharmaceutical and biotech companies with operations in Reno, Nevada. Key services include cGMP storage (controlled room temperature to cryo storage) and material management. In addition, it offers clinical labeling and distribution for early phase clinical trials.

## Kindeva Drug Delivery Acquires Summit Biosciences, a Specialized Nasal Drug Development & Manufacturing Organization

Kindeva Drug Delivery recently announced it has acquired Summit Biosciences Inc., an intranasal drug delivery contract development and manufacturing organization (CDMO), from its founding family shareholders. Established in 2009, Summit has an extensive track record of innovation in the unit dose nasal spray market. The acquisition of Summit enhances Kindeva's existing drug delivery capabilities by adding a new drug delivery platform, further expanding Kindeva's ability to serve biopharma customers across a wider range of complex drug-device combination products (pulmonary, injectable, transdermal, and nasal).

"Nasal drug delivery is becoming a preferred dosage format for a growing number of indications, as it allows users to non-invasively administer medications in an acute or emergency setting," said Kindeva CEO Milton Boyer. "Summit brings a differentiated understanding of how to effectively formulate drugs for nasal delivery and the capability to manufacture them at commercial scale. This addition not only fits Kindeva's ambition to be a global leader in the drug-device combination products CDMO market, but also expands the toolbox we can offer our customers to help improve patient outcomes and experience of care globally."

Departing Summit Chairman and CEO Richard D. Cohen added "Joining Kindeva strengthens our ability to deliver best-in-class nasal product development and manufacturing. Under Kindeva's leadership, our dedicated and talented workforce will further drive our founder's vision of increasing the availability of nasal drug-delivery options."

Summit's 55,000-sq-ft cGMP facility in Lexington, KY, adds to Kindeva's global manufacturing footprint of nine development and manufacturing facilities across the US and UK. The facility is approved by the US FDA and European Medicines Agency (EMA) and features specialized laboratories and integrated manufacturing operations with a long track record in bringing intranasal medicines to market.

Kirkland & Ellis acted as legal counsel to Kindeva. Frost Brown Todd acted as legal counsel, and Bourne Partners served as the exclusive financial advisor, to Summit.

Kindeva is a global contract development manufacturing organization (CDMO) focused on drug-device combination products. The company develops and manufactures products across a broad range of drug delivery formats, including pulmonary and nasal, injectable, and transdermal. Kindeva's service offerings span early stage feasibility through commercial scale drug product fill-finish, container closure system manufacturing, and drug-device product assembly. Kindeva serves a global client base from our nine manufacturing, research, and development facilities located in the US and UK.

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## Evaxion to Develop Tailored Novel Cancer Vaccines Based Upon a New Untapped Source of AI-Discovered Targets

Evaxion Biotech A/S recently announced an expanded commitment to developing tailored cancer vaccines by targeting a novel category of AI-identified tumor antigens, named Endogenous Retroviruses (ERVs).

The new treatment opportunity may broaden the applicability of cancer vaccines. Through the new vaccine targets, ERVs, treating patients unresponsive to conventional cancer immunotherapy may become possible. With the elevated focus on this groundbreaking therapeutic concept, Evaxion has initiated preclinical activities with a goal of generating Proof-of-Concept data by the second half of 2024.

Evaxion's Chief Scientific Officer, Birgitte Rønø, said "With our intensified focus on ERV cancer vaccines, we aim to expedite the development process to deliver treatment solutions to cancer patients who, until now, have been deemed unresponsive to immunotherapy. The ERV cancer vaccine targets represent a promising breakthrough that could significantly broaden the horizons of cancer vaccine applicability and marks a significant step forward in our commitment to improving healthcare through innovative and AI-powered approaches. We are already seeing significant interest in ERV-based vaccines and look forward to further underpinning the significant potential by these Proof-of-Concept data."

Recent insights into these exciting opportunities were presented by Evaxion at the last American Society of Hematology (ASH) Annual Meeting.

ERVs are remnants of ancient viruses lying dormant in our genome. ERVs are often overexpressed in cancer but not in healthy tissue, making them visible to the immune system and hence promising targets for cancer vaccines. AI-Immunology is crucial in allowing the identification of therapeutically relevant ERV tumor antigens from genomic patient tumor data.

AI-Immunology is a scalable and adaptable artificial intelligence technology platform at the forefront of vaccine discovery for infectious diseases and cancers. By integrating the collective power of proprietary AI models PIONEER, EDEN, RAVEN, and ObsERV, the platform can model the complexity of the patient's immune system. AI-Immunology advanced computational modeling swiftly and uniquely identifies, predicts, and designs vaccine candidates, revolutionizing the landscape of immunotherapy by offering a holistic and personalized approach to combat fast-evolving pathogens and malignant cells.

Evaxion Biotech A/S is a pioneering TechBio company based upon its AI platform, AI-Immunology. Evaxion's proprietary and scalable AI prediction models harness the power of artificial intelligence to decode the human immune system and develop novel immunotherapies for cancer, bacterial diseases, and viral infections. Based upon AI-Immunology, Evaxion has developed a clinical-stage oncology pipeline of novel personalized vaccines and a preclinical infectious disease pipeline in bacterial and viral diseases with high unmet medical needs. Evaxion is committed to transforming patients' lives by providing innovative and targeted treatment options.

## Ensysce Biosciences Announces FDA Breakthrough Therapy Designation Granted for PF614-MPAR

Ensysce Biosciences, Inc. recently announced receipt of notice from the US FDA that it has granted Breakthrough Therapy Designation (BTD) for PF614-MPAR. A next-generation opioid, PF614-MPAR represents a major scientific innovation, as it is what we believe to be the first product with oral overdose protection in any drug class.

BTD is a rarely used designation, having been granted to fewer than 300 drugs. It is designed to expedite the development and review of drugs that are intended to treat a serious condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies.

Prescription overdose deaths in the US remain at a crisis point and the latest figures from the Centers for Disease Control indicate almost two overdose deaths per hour. Safer opioids to treat severe pain while providing protection against abuse and oral overdose are vital to reverse this tragic trend and Ensysce is forging the way with two new opioids in clinical development.

PF614-MPAR is designed to provide optimal pain relief at prescribed doses yet limit accidental or intentional overdose by "shutting down" opioid release if too much active drug is consumed. PF614-MPAR could herald a new class of treatment for the most severe forms of pain and could save lives if approved, as each capsule contains built-in protection against both abuse and overdose which plague traditional opioids.

Dr. Lynn Kirkpatrick, Chief Executive Officer of Ensysce Biosciences, said "We are highly encouraged with the receipt of Breakthrough Therapy Designation by the FDA based on the data we generated in our Phase 1 study, PF614-MPAR-101, that demonstrated our approach can provide protection from taking too many opioids orally. This is unique for the opioids class. We previously received Fast-Track Status for PF614, and this recognition of BTD for PF614-MPAR highlights the advancement we have made with our approach to treating severe pain. BTD facilitates our ability to expedite our programs through the approval processes in an efficient manner, with rolling review of both programs. We believe our goal of bringing the "next generation" of analgesics for severe pain to those in need is becoming a reality."

The primary intent of BTD is to develop evidence needed to support approval as efficiently as possible. The designation provides all the features of Fast Track designation including accelerated approval and priority review along with intensive guidance involving senior managers on an efficient drug development program.

Ensysce Biosciences is a clinical-stage company using its proprietary technology platforms to develop safer prescription drugs. Leveraging its Trypsin-Activated Abuse Protection (TAAP) and Multi-Pill Abuse Resistance (MPAR) platforms, the company is developing unique, tamper-proof treatment options for pain that minimize the risk of both drug abuse and overdose.

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## Vaxxinity Announces Collaboration on Space Medicine Research With University of Central Florida

Vaxxinity, Inc. recently announced a collaboration with the University of Central Florida (UCF) to advance space medicine research. The research, funded by a grant from the State of Florida, aims to further the development of Vaxxinity's active immunotherapies to prevent and mitigate muscle and bone wasting, which are well known health challenges related to long-term spaceflight, and which share biological mechanisms implicated in highly prevalent age-related diseases.

"If humanity is to become a spacefaring species, solving fundamental problems related to space travel and living are table-stakes. Vaxxinity is all-in on developing and commercializing these solutions, and working with the State of Florida and UCF, collectively, we strive to promote both healthy aging and ensure humanity can become multi-planetary, brave low gravity exposure, and be of the stars," said Lou Reese, Executive Chairman of Vaxxinity. "The support for this research from the State of Florida exemplifies a commitment to pioneering solutions in the fields of space travel, as well as longevity and age-related diseases."

Research will include studies to assess the effects of Vaxxinity's active immunotherapies on undisclosed proteins implicated with bone and muscle growth through in vitro and in vivo experiments, and animal models established by UCF.

Vaxxinity's platform is designed to harness and selectively activate the immune system by overcoming immune tolerance, stimulating the production of antibodies against endogenous targets. The company will provide materials including candidates derived from its platform to support the collaborative research at UCF.

"UCF was born as a university to support the space program, and the College of Medicine is continuing that mission, working to bring back to Earth the secrets that space medicine research can reveal," said Dr. Deborah German, Vice President for Health Affairs and Dean of UCF's College of Medicine. "We look forward to collaborating with Vaxxinity on this research and applying their unique technology to benefit the aging population on our planet and future space travelers. The research we are doing targeted towards space-based physical challenges is directly translatable to issues faced by humanity here on Earth. We know what we do for tomorrow will yield results for today."

Vaxxinity, Inc. is a purpose-driven biotechnology company committed to democratizing healthcare across the globe. The company is pioneering a new class of medicines aimed at disrupting the existing treatment paradigm for chronic disease, increasingly dominated by monoclonal antibodies, which suffer from prohibitive costs and cumbersome administration. The company's proprietary technology platform has enabled the innovation of novel synthetic peptide immunotherapy candidates designed to bring the efficiency of vaccines to the treatment of chronic diseases, including Alzheimer's disease, Parkinson's disease, migraine, and hypercholesterolemia. The technology is also implemented as part of a COVID-19 vaccine program. Vaxxinity has optimized its pipeline to achieve a potentially historic, global impact on human health.

## Akoya Biosciences' Technology Enables Queensland Spatial Biology Centre to Revolutionize the Diagnosis & Treatment of Cancer & Other Diseases

Akoya Biosciences, Inc. recently announced the newly established Queensland Spatial Biology Centre (QSBC), located in Brisbane, Australia, is using the PhenoCycler-Fusion spatial biology platform as the core technology to revolutionize the way cancer and other debilitating diseases are diagnosed and treated.

The PhenoCycler-Fusion platform facilitates the understanding of the cellular compositions, neighborhoods, and functional states that are present in complex diseases, and that next-generation therapeutics may be able to target. Bringing a new level of clarity to this complex biology will help explain why individual patients have varying degrees of success in terms of their response to treatment.

"Akoya's industry-leading spatial biology platform is enabling our experts to rapidly map the presence, location, phenotype, and interaction of millions of cells," said Professor John Fraser, Clinical Director and co-lead of the QSBC. "This ability represents a significant leap forward in the effort to more accurately diagnose a wide range of diseases, map pathways for highly personalized treatment, and ultimately improve patient outcomes."

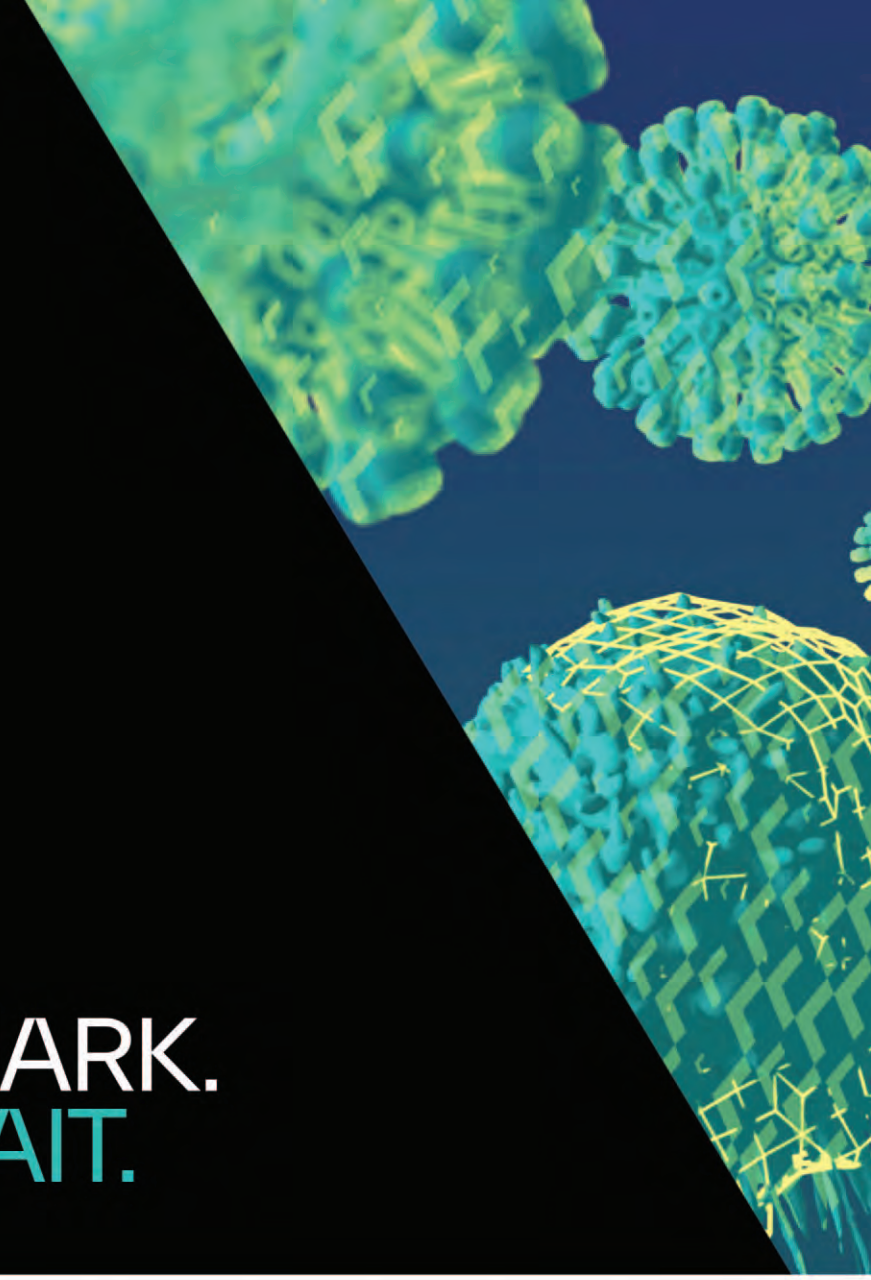
With multi-slide automation, the PhenoCycler-Fusion system enables researchers to generate ultrahigh-plex spatial phenotyping data for larger and more complex samples at unprecedented speed and scale. Studies conducted using the platform reinforce the value of single-cell ultrahigh-plex spatial phenotyping as a powerful tool for defining spatial tissue signatures associated with therapy response and resistance.

"We are extremely excited to be an integral part of this important initiative," said Brian McKelligon, Chief Executive Officer of Akoya Biosciences. "The QSBC has brought together a remarkable group of researchers, clinicians, pathologists, and computational biologists who are unrelenting in their commitment to leverage the enormous power of spatial biology. Their passion is inspiring and we look forward to supporting them with the most advanced spatial biology solutions."

The hospital-based QSBC initiative is led by the Wesley Research Institute in conjunction with other medical and research organizations. Among the benefits of this network of organizations is access to an extensive biobank of curated patient tissue samples that are amenable to deeper tissue and cellular annotation through the QSBC. The Centre also collaborates with laboratories at Harvard Medical School, Yale University, and St. Jude's Children's Research Hospital in the areas of protocol development, assay optimization, and data analysis.

"Spatial biology is revolutionizing the pathology field by enabling deeper biology and clinical markers to be measured from a single tissue section," said Dr. Arutha Kulasinghe, QSBC Scientific Director and co-lead. "Digitizing tissues is likely to lead to new fields in spatial informatics and data analysis where machine learning and predictive biomarkers can be rapidly developed and deployed to personalize therapies."

RESILIENCE



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# Formulation Forum

## Lipid Nanoparticles – Carriers for Nucleic Acids Delivery

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

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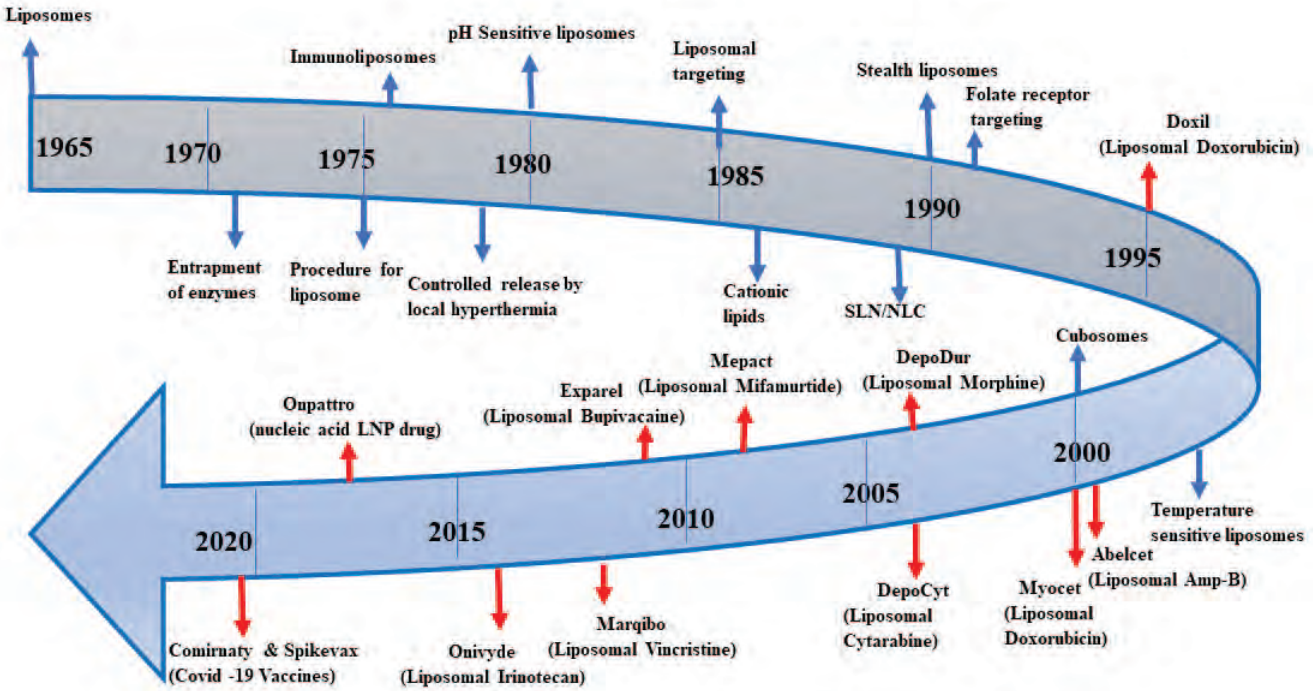
### INTRODUCTION

Nucleic acid therapeutics has emerged as a new class of potential drugs for targeting and treatment of various diseases. In recent years, there has been a considerable interest in finding the appropriate technologies to formulate nucleic acids into an appropriate and bioavailable dosage form, especially mRNA.[1] This continued interest in nucleic acid encapsulation for vaccines stems from their ability to induce antigen expression and adaptive immune responses from encoded antigen safely and effectively. As a result of the introduction of life-saving Covid 19 vaccines for severe acute respiratory syndrome coronavirus (SARS-CoV-2), Spikevax (Moderna) and Comirnaty (Pfizer/BioNTech), and the launch of small interfering RNA (siRNA) as a polyneuropathy drug by Alnylam, the industry is renewing interest in the next generation of lipid nanoparticle technology for the delivery of mRNA therapeutics for cancers, anti-inflammatories, and rare diseases, among others.[2] With modern synthetic technologies, mRNA can be produced at a large scale by an enzymatic manufacturing process, making nucleic acids more affordable for larger populations with unmet medical needs.[2] As shown in Figure 1, the innovation in LNP technologies has made it possible for the commercial launch of several small molecules, peptides, nucleic acids, and biologics to the market.[3]

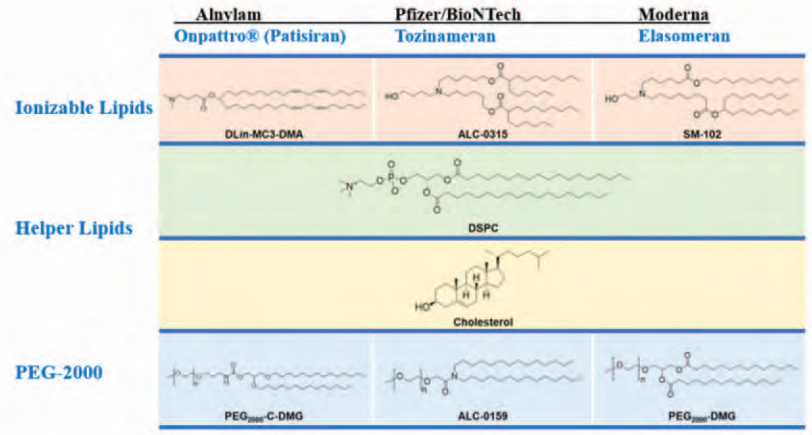
Due to their complex structure, encapsulation and delivery of nucleic acids by LNPs in an efficient and effective manner creates challenges and

**FIGURE 1**




**Evolution of LNP Enabling Technologies (Blue Arrows) & New Drugs & Vaccines (Red Arrows)**

## FIGURE 2




**Lipids Used for Encapsulation of Nucleic Acids in LNP Carriers**

opportunities for the pharma industry. For instance, these lipid assemblies have been proven to be ideal vehicles for intracellular delivery of mRNA due to their inherent abilities to protect the delicate nucleic acids from degradation under aqueous and nuclease environment.[4-7] However, the encapsulation of mRNA into LNPs warrants a closer scrutiny because every component of LNPs, especially cationic lipids, plays a crucial role in protecting, delivering, and stabilizing these large macromolecules.[8]

This following describes the role of individual components in aggregation, packing, stability, efficacy, and potency of nucleic acids, the understanding of which is important to achieve better designed and smarter formulations, and robust scale up and manufacturing of LNPs.

## STRUCTURE OF LNPS WITH NUCLEIC ACIDS

To design a robust lipid nanoparticle, a comprehensive understanding of lipid components is required. LNPs used in encapsulation of negatively charged nucleic acids are typically composed of four components, all of which are synthetic in nature as shown in Figure 2.

The formulation compositions of mRNA LNPs are composed of four lipids.[9] For example, the SPIKEVAX® formulation by Moderna for each 0.5-mL dose contains: 50 mcg of nucleoside modified messenger RNA: mRNA and total lipid content of 1.01 mg (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-*sn*-glycero-3-phosphocholine [DSPC]).

While, COMIRNATY® by Pfizer for each 0.3-mL dose contains: lipids (0.43 mg [(4-hydroxybutyl)azanediyl) bis(hexane-6,1-diyl)bis (2-hexyldecanoate), 0.05 mg (polyethylene glycol 2000)-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.19 mg cholesterol].

For ONPATTRO® (Patisiran), each 1-mL dose contains 6.2 mg cholesterol USP, 13.0 mg [6Z,9Z,28Z,31Z)-heptatriaconta6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate (DLin-MC3-DMA), 3.3 mg 1,2- distearoyl-*sn*-glycero-3-phosphocholine (DSPC), 1.6 mg α-(3'-{[1,2- 2 di(myristyloxy)propanoxy] carbonylamino}propyl)-ω-methoxy, polyoxyethylene (PEG -C-DMG)]. The details of formulation compositions of these products are outlined in Table 1 and are published elsewhere.[10]

Most of the ingredients used in the marketed drugs are also listed in the FDA inactive ingredient database. However, how these lipids are distributed within the complex nanostructured LNPs has been debated.[11,12] It is obvious the negatively charged nucleic acid is complexed with positively charged ionizable lipids (as a lipoplex) and is entrapped within the LNPs. For LNPs designed with helper phospholipids, such as di-stearoyl phosphocholine and cholesterol, these lipids are distributed asymmetrically to create an outer stable monolayer boundary, whereas the pegylated lipids are situated outside for providing steric stability of the core surface. Efforts are still being made by researchers to design better and smarter ionizable lipids to yield greater nucleic acid stability and fusogenicity.[13,14] Likewise, several of the PEGylated lipids are discovered aiming at sterically stabilized LNPs with longer circulation time in the blood without being opsonized.

## TABLE 1

| Formulation | Patisiran (Onpattro®) (Alnylam) | Tozinameran (Pfizer/BioNTech) | Elasomeran (Moderna) |
|---|---|---|---|
| Single dosage | 0.3 mg/kg siRNA | 0.030 mg mRNA | 0.10 mg mRNA |
| Unit | 5 mL | 0.45 mL | 0.5 mL |
| Drug substance | 10 mg | 0.225 mg | 0.10 mg |
| Ionizable lipid | 65.0 mg | 3.23 mg | 1.075 mg |
| Phospholipid | 16.5 mg | 0.7 mg | 0.275 mg |
| Cholesterol | 31.0 mg | 1.4 mg | 0.47 mg |
| PEG-lipid | 8.0 mg | 0.4 mg | 0.115 mg |
| Total lipid | 120.5 mg | 5.7 mg | 1.94 mg |
| Total lipid/RNA (wt/wt) | 12.1 | 25.5 | 19.4 |
| Drug concentration | 2.0 mg/mL | 0.5 mg/mL | 0.2 mg/mL |
| Sucrose in formulation | - | 46 mg | 43.5 mg |
| Sucrose concentration | - | 102 g/L | 87 g/L |
| pH | 6.4-7.5 | 6.9-7.9 | 7.0-8.0 |
| State of drug product | liquid | frozen suspension | frozen suspension |
| Shelf life of drug product | 27 months (2-8 oC) | 6 months (-90 to -60 oC) | 6 months (-25 to -15 oC) |

**Formulation Compositions in FDA-Approved siRNA & Vaccines**

**FIGURE 3**

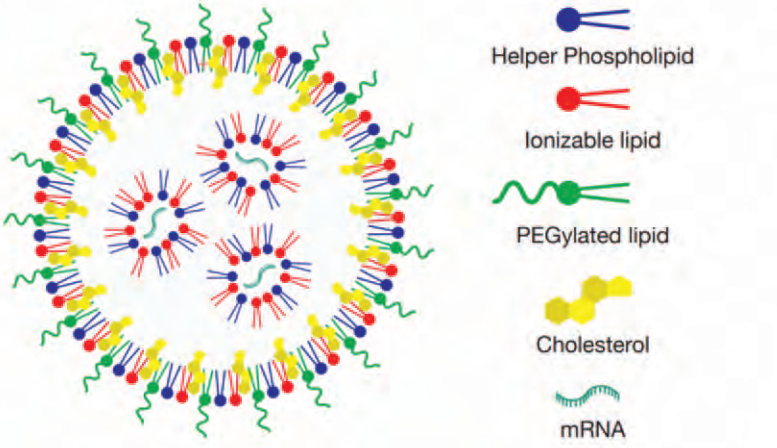



**Illustration of an mRNA-Encapsulated LNP**

Unlike larger mRNA, it is believed siRNA nucleic acid is encapsulated within a spherical multilamellar structure in which the nucleic acid is sandwiched between bilayer assemblies.[15] Cryo-EM and small angle X-ray scattering could shed some light on the packing of nucleic acids within the LNPs; however, because the mass density contrast is not appreciably distinctive enough to resolve RNA from the lipid components, attempts are still continuously made to identify the RNA within the lipid nanoparticles. Brader, et al (2021) used a cationic dye (thionine) as a contrast agent in cryogenic electron microscopy (Cryo-EM); they found the chemical microenvironment of mRNA appears to be located within solvent-filled cavities and fully associated with lipids (Figure 3).[16] According to a recent study, it appears the LNP interior is composed of electrostatically neutral inverted micelles in which nucleic acid is surrounded by the ionizable cationic lipid and other lipid components, whereas the surface of the LNP is composed of a hydrophilic shell containing the PEG–lipid.[17]

McKenzie et al (2023) used ionizable lipids, for example, Dlin-MC3-DMA (MC3), to design mRNA-encapsulated LNPs.[18] In this method, the authors used a microfluidic mixer to control the nanoprecipitation of lipid and mRNA in acidic buffer followed by the pH adjustment step with phosphate buffer that yielded stable LNPs with 80-250-nm diameters in size and encapsulation efficiency of > 80%. Different ionizable lipids have been used to design LNPs for encapsulation of mRNA.[14] Jayaraman, et al (2012) prepared stable LNPs from a composition composed of ionizable lipid/DSCP/Cholesterol/DMG-PEG-2000 (50:10:38.5:1.5), with an N/P ratio of 4 (N being the ionizable amine and P being the phosphate associated with mRNA).[19] The PEGylated lipids and helper phospholipids are in the range of 1%-2% and 8%-12%, respectively. The typical Helper phospholipid used is DSPC (1,2-distearoyl-*sn*-glycero-3-phosphocholine) that can help to yield highly stable LNPs. DOPE (dioleoyl-*sn*-glyecro-3-phosphatidyl ethanolamine) is also used to form a cone fluidic structure as opposed to a cylindrical stable structure of DSPC. The percentage of ionizable lipid could range from 40%-50% to create stable LNPs and promote fusogenicity for transfection efficacy. There are a few case studies to identify novel ionizable lipids to stabilize mRNA-encapsulated LNPs at subzero and nonfrozen conditions.[20] COVID-19 mRNA vaccines are stored in freezing conditions with added sucrose to provide additional stability. Other studies tried to optimize the mRNA nucleotide composition to help stabilize the LNPs by using lyophilization technology.[21]

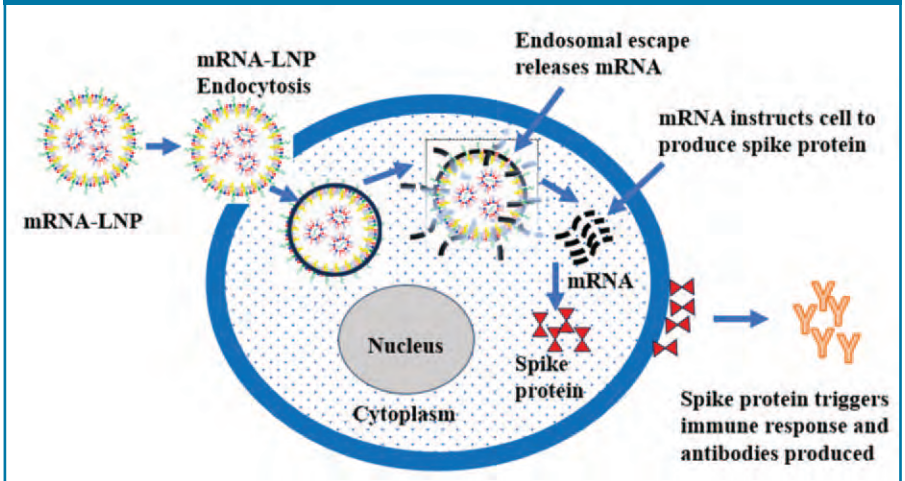
## MECHANISM OF RNA RELEASE AND IMMUNE RESPONSE

Ionizable lipid nanoparticles (iLNPs) are composed of cationic lipids with amino moiety as the head group, PEGylated lipid, and the helper lipids, including phospholipid and cholesterol, which provide the stability of the outer layer core. The amino head group of the ionizable lipids are typically tertiary amine with a pKa of 6.2-6.9. The ionizable lipids available commercially are MC3 and ALC-0315 in the Comirnaty vaccine (Pfizer/BioNTech), and SM-102 in the Spikevax vaccine (Moderna). All these lipids are protonated at an acidic pH but are neutral at physiological pH. Their structures are such that they help LNPs to fuse with endosomal membranes while being recognized at the cell surface due to their positive charge. As shown in Figure 4, once LNPs are endocytosed into the cell, they release mRNA into cytosol via endosomal scape, which instructs the cell to produce spike proteins that in turn triggers the immune response and produces the antibodies to fight the viruses.[3]

## MANUFACTURING LNPS

Because these amphiphilic lipids can spontaneously aggregate into LNPs in aqueous solution, the process to make LNPs only requires direct mixing of lipid (organic) and nucleic acids (aqueous solution) by agitation that results in encapsulation of negatively charged mRNA. Hydrophobic fatty acid chains and polar headgroups help create the lipid assemblies that can further be sized into desired particle sizes. Top down and bottom-up approaches are commonly used for generating these particles. Top-down approach requires high shear and high energy in which the lipid (dried film) is hydrated and homogenized in aqueous buffer to yield a desired particle size. The bottom-up approach, such as nanoprecipitation, requires the ethanol injection that results in the formation

## FIGURE 4




**Mechanism of Producing Antibodies Through Endosomal Uptake of LNP-mRNA by Cell**

of nanoparticles, but this method suffers from uncontrolled particle size due to inhomogeneous mixing.[22] To alleviate such challenges, microfluidic mixing is highly sought after for generating desired particle sizes with uniform size distribution under the laminar flow conditions. This technique is fast and easy to scale up for manufacturing of large batches of LNPs. Precise control of mixing through T-junction or staggard herringbone mixer or ring mixer prevents premature premixing and results in uniform particle size distribution with low polydispersity under precisely controlled temperature and flow rate.[23] Shepherd, et al (2023) developed a microfluid chip method (so-called SCALAR) for producing the LNPs with throughput of >17 L /h at commercial manufacturing scale compared to >10 L/h device available commercially by Precision Nanoassemblr.[24] Based on silicon and glass substrates, these chips (each 100 mm in length) are solvent compatible, stable at higher temperature (>500°C) and pressure (100 pounds per square). Designed and fabricated with arrays of 256 parallel mixing units, this microfluidic device yields precisely well-defined potent and robust mRNA-LNPs. Using SCALAR 256x chip and PolyA as substrate (a mRNA substitute), Shepherd, et al demonstrated the formation of LNPs (composed of ionic lipid D-Lin-MC3-DMA:DSPC:Cholesterol:DMG-PEG 2000; 50:10:38.5:1.5) in high throughout production with uniform particle size (ca. 70 nm by intensity-weighted average), low polydispersity index (PDI), high encapsulation efficiency, and comparable *in vivo* data in mice.[24]

Hengelbrock, et al (2023) used the continuous manufacturing process for LNPs encapsulated with mRNA through microfluidic mixing (using a T-mixer) that meet the specifications and critical quality attributes of the products with a high encapsulation efficiency (ca. 88% EE),consistent particle size (ca. 71 nm), and low polydispersity index of 0.004.[25] These attributes are aligned with the target profile (ca. 66-93 nm and 88% EE) of Pfizer's Comirnaty mRNA vaccine. The scale up manufacturing requires a T- or Y-mixer that allows for rapid mixing of lamellar flow liquids into a turbulent flow at the mixing point with a Reynolds number of 11,000.[26] By changing the lipid composition and the flow rate ratio between the two phases (organic/aqueous), the size of LNPs can be controlled. For typical mRNA encapsulation, one part of lipid solution is mixed with three parts of aqueous phase. Downstream tangential flow filtration (TFF) is used to concentrate the LNPs to remove ethanol, any residual lipids and non-encapsulated nucleic acids, and to neutralize the formulation to the target pH of 7.4. The authors demonstrated that for LNPs generated by the continuous T- or Y- mixing modes, those formulations meet the quality critical attributes of mRNA vaccines with particle size of 71 nm and EE of 88%. This continuous process can significantly save time and costs.

Other manufacturing devices applied for large-scale production of LNPs include the impingement jet mixer (IJM), which involves mixing of two fluids at a high-velocity stream, resulting in effectively homogenization at intense shearing forces. This process has now been used in manufacturing COVID-19 vaccines. For instance, Knauer utilizes IJM system, which allows the mixing of lipid solvent solutions with an mRNA aqueous solution at 400 pounds pressure with a controlled flow to effectively force the two fluids to mix. Pfizer has also used this method successfully to significantly increase the vaccine productivity to 100 million doses per month.[27] Thus, IJM is a unique manufacturing process for producing uniform, robust, and stable LNPs for drug delivery applications. Maeki et al (2023) used a microfluidic design comprising five layered microchannels created in parallel stacking glass-iLiNP (invasive lipid nanoparticle) devices to achieve mass production.[28] This iLiNP device efficiently produces lipid nanoparticles with 20 to 60 nm sizes at a flow rate of 20-50 ml/min in a continuous mode as the NanoAssemblr's microfluidic commercial device.

LipidSol® by Ascendia Pharma is an LNP platform technology that provides different process methods, such as microfluidics, thin film hydrating, extrusion, high pression homogenization, nanoprecipitation, and emulsification/double emulsification to make LNPs for various therapeutic modalities with both hydrophilic and lipophilic properties.[4] Coupled with lab-scale screening and cGMP sterile manufacturing capabilities, Ascendia is leading the way in design, development, and

manufacturing of LNPs for novel therapeutics for treatment of cancers and infectious and many other rare diseases.

## SUMMARY

LNPs offer an innovative drug delivery method for targeting certain tissues with mRNA lipoplexes composed of ionizable lipids varied in their structures and properties. This will open the doors for numerous opportunities in drug delivery of biologics due to efficient encapsulation and greater protection of the nucleic acid within LNP cargo.[29] As a result of such technologies, many new and innovative drugs are undergoing clinical studies for delivery of mRNA for cancer vaccines and immunogenic therapeutics.[30] For example, mRNA-4150 and mRNA-5671 vaccines are undergoing the clinical phases for treatment of specific melanoma cancer and non-small cell lung cancer, respectively.[31] Likewise, there are many other clinical studies with mRNA ongoing for development of several therapeutics in LNPs for cancer vaccines and for treatment of infectious diseases.[3] As we continue to search for targets, it is our understanding that LNP-mRNA technologies hold a greater promise for future drug development in finding the cures of life-threatening diseases.

Supporting the development of mRNA technologies for innovative medicines for unmet medical needs, CDMOs with the right expertise and in-house capabilities will play a key role in providing the greater flexibility in manufacturing of modern medicines.[32] More specifically, CDMOs offering a one- stop solution with end-to-end services from formulation, process development to cGMP manufacturing with fill-finish capabilities will accelerate the drug development process to market. ◆

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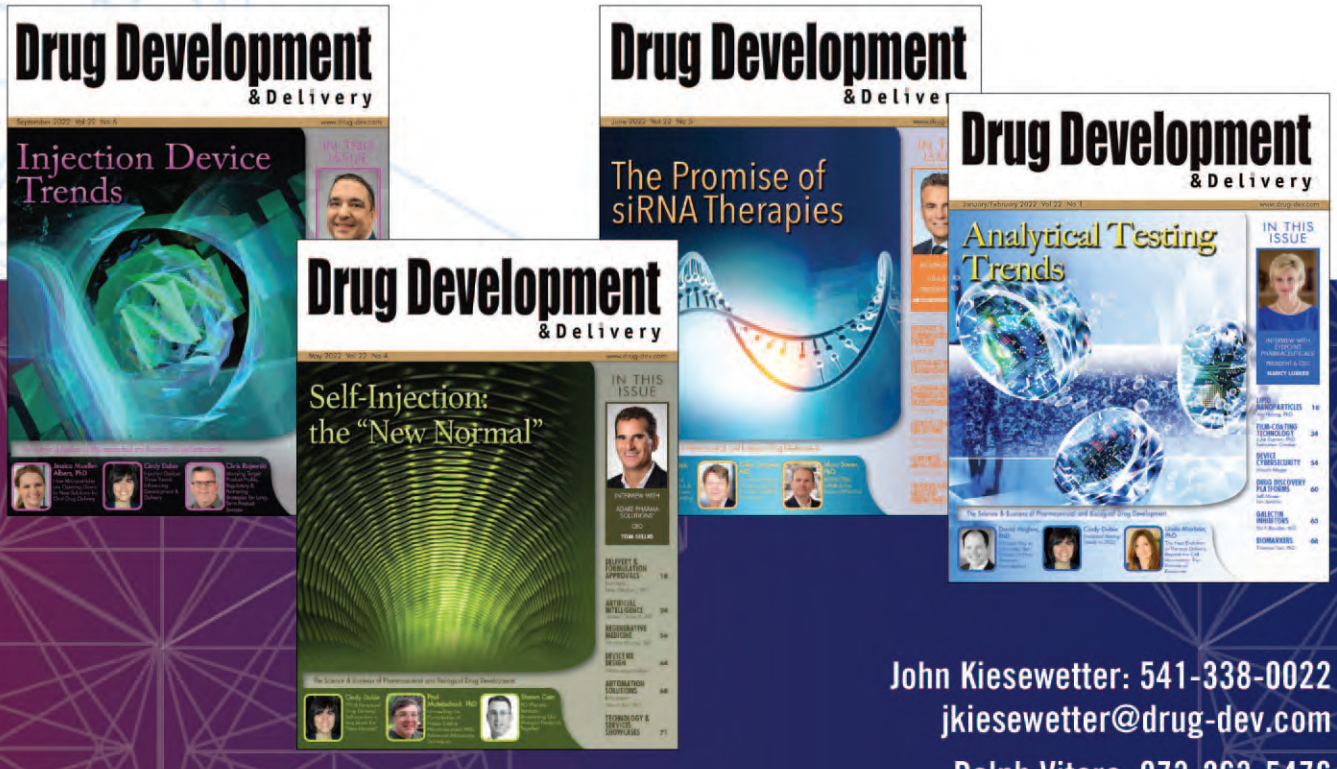


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# Leadership Panel

## 4 Trends That Will Have the Most Impact on Drug Development in 2024

By: Cindy H. Dubin, Contributor

Next-generation biomanufacturing, partnering for success, formulating the future, innovative therapies, manufacturing 4.0, patien-centric development, and quality management fundamentals were the hot topics of discussion at CPhI Barcelona 2023. These topics are the framework for what we anticipate seeing more of in 2024. *Drug Development & Delivery* asked some of today's life science leaders what they expect will have the greatest impact on drug development this year and beyond. So, back by popular demand, below is the third annual exclusive Leadership Panel discussion.

## 1. DEMAND FOR COMPLEX INGREDIENTS

**Dr. Paul Quigley,** Principal Research Fellow, Drug Substance, Quotient Sciences

As promising treatments for oncological, chronic, and rare disease indications, the demand for more complex and potent active pharmaceutical ingredients is on the rise. This is reflected in the global HPAPI market, forecast to be worth $81.8 billion by 2028 with a compound annual growth rate of 9.27%, up from $26.9 billion in 2023.[1] These complex potent materials provide enhanced therapeutic efficacy at low concentrations. Consequently, when harnessing compounds with increasing potency and complexity, only low quantities are required in final formulations. As the chronic and rare disease patient populations tend to be small, contract development and manufacturing organizations (CDMOs) — traditionally built for large-volume manufacturing — must adapt their capacity to cater to smaller-volume needs. This flexibility is key to maintaining a competitive market advantage and meeting the ever-evolving needs of the industry. As the pharmaceutical industry moves toward new molecular entities (NMEs) such as HPAPIs and new modalities, the need for these products to be made at accelerated rates to meet industry demand has been growing. In addition, the current financial constraints impacting the biotech industry mean production processes need to be particularly cost-efficient.

## 2. A SAFER & RESILIENT SUPPLY CHAIN FOR GREENER MANUFACTURING

**Felix Solamo,** Senior Global Director, Field Applications Scientist from Purolite, an Ecolab Company

At CPhI Barcelona 2023, industry demonstrated continued commitment to addressing the myriad of challenges within the biopharmaceutical industry, including the need to ensure security of supply and hurdles in meeting growing market demand for bioprocessing materials. Ensuring uninterrupted access to critical bioprocessing materials is essential. Innovative technology in this area promises to revolutionize bioprocessing purification by widening the window of operation for the elution of antibodies at a higher pH. Market demand for bioprocessing materials remains strong, driven by the growing pharmaceutical sector's demand for high-quality resins. A focus on security of supply, strategic partnerships, cutting-edge technologies, and a keen understanding of market dynamics will continue making a significant impact in the industry.

**Dr. Michael Quirmbach,** CEO & President of CordenPharma

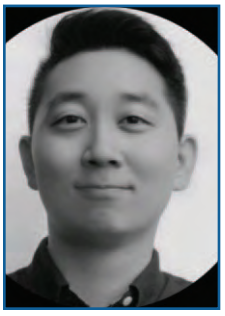
As we look ahead to 2024, there will be industry commitment to innovation, sustainability, and customer-centric solutions. This was evident at CPhI in Barcelona where key takeaways on the agenda included supply chain resilience and diversification, which are critically important topics. Industry's ability to support a resilient supply chain and drive innovation with greener manufacturing processes will be highly valued, as the whole world continues to face geopolitical challenges and sustainability concerns. To that end, there will be increased participation in the Science-Based Targets initiative (SBTi), which is committed to reducing global emissions by evaluating and setting science-based reduction targets that reflect an ongoing, proactive approach to environmental responsibility. In addition, utilizing green technologies, such as innovative methods for recycling solvents, Supercritical Fluid Chromatography (SFC), and continuous manufacturing demonstrates a commitment to environmental, social, and governance (ESG) manufacturing processes, which is increasingly essential in the life sciences.

## 3. ADVANCED TECHNOLOGY

**Ramesh Jagadeesan, PhD,**
Vice President, Analytical Development, Recipharm

The ever-evolving drug development landscape, which is enhanced by investments, novel technologies, patent expiries, collaborations, and a supportive regulatory environment, presents several key considerations as we move into 2024. As technology continues to advance and analytical capabilities progress, there is a need for more specialized and innovative testing.

Providing insight into specific characteristics, part of harnessing customized analytical testing is identifying the right techniques to use at the right time to get the most insight. The adoption of automated robotic systems in laboratories boosts efficiency, reduces errors, and increases productivity, and barcode-based management systems streamline inventory management and improve drug safety.



**Joon Yoon,**
Senior Data Scientist, Samsung Biologics

Bringing in unprecedented efficiency may be to my knowledge one of greatest impacts Artificial Intelligence has had on drug development. Any *in silico* automation, from an academia perspective, can be considered a work assisted by AI technology. Drug developers had wanted to find a way to reduce the so-called "searching space," a pre-filtered range of drug combination to be considered in a wet-lab, in the pre-AI era in order to minimize and get a practical iteration number of experimental trials to find a compound with drug-like properties. The advent of AI in the early 2000s then enabled developers to reduce the searching space thanks to the advances in computational power, which made the calculations/computations possible for reliable multimodal prediction models. The reduced searching space from testing a near-infinite number of drug-combinations to tens of thousands not only has empowered drug screening with the cost of reasonable time and budget, but also has made it easier to optimize the drug development process. Furthermore, with AI in hand, drug developers have become capable of predicting drug responses, helping them save a significant amount of development time. The biopharmaceutical industry now has enough drug development data incorporated into an AI system that predicts chemical reactions and alerts which genetic modification could alter drug response. The AI-based drugs, or at least the drugs that were screened using AI, will soon become the norm in the near future.

## 4. SUSTAINABLE PACKAGING & ENVIRONMENTALLY FRIENDLY PRODUCTS

**Chris Hirst,**
President, Advanced Delivery Systems Business Unit, Recipharm

Innovation is essential as the industry considers pressurized metered dose inhalers (pMDIs) and their release of hydrofluorocarbons (HFCs) into the atmosphere upon actuation. Given that existing HFC propellants have carbon footprints that are no longer acceptable to any of us, the transition to propellants with a lower global warming potential (GWP) is a priority for the pharmaceutical industry.[2] As a result of the Kigali Amendment to the Montreal Protocol, the introduction of legislation aims to phase down HFC use and promote the move towards low-GWP alternatives.[3] In fact, the phase down of HFC use is accelerating in certain regions such that the availability of HFC-134a and -227ea in inhalers is likely to be impacted. As a result, pMDI developers must navigate existing regulations and changing legislation, to effectively transition to low-GWP propellants in order to maintain patient access to this familiar and life-saving method of drug delivery.

**Marcelo Cruz**, Vice President Business Development & Marketing, Tjoapack

The pharmaceutical packaging sector played a significant role in addressing issues experienced by the wider industry, such as supply chain disruptions and regulatory hurdles during CPhI this year. The industry's resilience and commitment to innovation were evident in the face of these challenges, along with the desire to enhance drug packaging solutions for safety, sustainability, and security. We discussed innovations in packaging materials, labeling, and serialization to combat counterfeiting and improve patient adherence. Reflecting on the learnings of CPhI, the outlook for the global pharmaceutical sector remains promising as we move into 2024. Advances in smart packaging technologies such as Radio Frequency Identification (RFID) and QR code integration will enhance traceability and ensure the authenticity of pharmaceutical products. RFID is being used increasingly to streamline the packaging process via a unique chip that processes information, such as the number of units or location. Overcoming challenges to ensure sustainability will continue to be a focus, with eco-friendly packaging materials and reduced waste solutions gaining traction. Personalized medicine and collaboration between pharmaceutical developers and their packaging partners will be key to harnessing these trends to drive growth over the next 12 months." ◆

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Drug Development
EXECUTIVE

Kevin Sharp

Senior VP & Head of Sales

Samsung Biologics

SAMSUNG BIOLOGICS

# Samsung Biologics: Exploring The Evolving Biopharma Landscape

Biologic development and manufacturing is a rapidly growing sector requiring ample investment and attention to meet rising demands. Advancements in technology, growing understanding, and strategic approaches have shifted the biopharmaceutical industry to better position itself to meet growing demands with innovative thinking.

*Drug Development & Delivery* recently interviewed Kevin Sharp, Senior Vice President and Head of Sales for Samsung Biologics, to discuss the evolving biopharma space, exploring current challenges, and the demand for sustainable solutions.

**Q: The biologics market is rapidly evolving, what are some of the current trends shaping the biologic landscape?**

**A:** The biggest shift in biologics is the modalities currently in development. As antibody-based therapies have risen to be the most important therapies in the biologics space, our understanding of biologics, how to manipulate and tailor their production through strategies such as cell line development, and the impact they have on the body have been extensively studied, paving the way for new drug products.

Innovative thinking has already led to the design of powerful advanced therapeutics, such as bispecific antibodies (BsAbs), fusion proteins, and antibody-drug conjugates (ADCs). We are seeing a drive toward developing these novel materials, which often provide enhanced performance, with improved efficacy and binding specificity compared with monoclonal antibody counterparts. As a result, BsAbs and ADCs can offer improved safety and lower dosage requirements.

BsAbs are engineered to bind two different epitopes or antigens, improving

specificity by simultaneously binding two targets. BsAbs have shown promise for treating severe cancers, such as multiple myeloma, non-small cell lung cancer, and cervical cancer, and the number of novel DPs like BsAbs entering clinical trials is expected to increase further. In addition to BsAbs, ADCs, which are formed when an antibody is attached to a cytotoxic payload, are commonly used as cancer treatments.

Utilizing these complex biologic products for treating complicated diseases, such as chronic and rare disorders, is on the rise. As a result, we will see more of these novel treatments entering the drug market. However, the complexity of these materials means the processes used in their production are complex, necessitating experience and expertise to overcome any issues that may arise and successfully produce biologic therapeutics.

**Q: How are technological advancements shaping biologic manufacture, and how can CDMOs offer support to help overcome potential challenges?**

**A:** Digital technologies are advancing quickly, and industries must be quick to keep up with it or risk falling behind. This is no different when it comes to the development and manufacture of biologic drug products. The advancements in manufacturing efficiency and productivity as a result of technological advances can lead to a significant competitive market advantage. In a highly regulated industry, these technological advancements also provide regulatory compliance benefits, helping to ensure product quality through cutting-edge sensors and efficient data management.

Using data management systems such as cloud-computing platforms can ensure accurate, complete, and reliable data throughout drug product manufacture and life cycle, allowing for informed decision-making at every stage and easing collaborative efforts. Although helping to streamline development and manufacturing, the data hosted on digitized systems is at risk of cyber attacks. Effective cybersecurity must be in place to safeguard all sensitive data from cyber threats, in line with regulations. Encryption, multi-factor authentication, access controls, and continuous monitoring can all be leveraged for data protection. Deciding upon a trusted cloud-computing provider reduces the burden, and with built-in security, data safety is assured.

Contract development and manufacturing organizations (CDMOs) that have many of these data management systems already in place can support biotechs in optimizing data management and information flow during their outsourced projects. This can help significantly streamline overall development, saving time and cost.

**Q: Why do you believe the biologic industry is currently experiencing capacity shortages, and what steps can be taken to overcome them?**

**A:** There are many factors currently contributing to capacity issues in biologic manufacturing; the primary reason being shifts in demand for drug products. Expansion of a commercialized drug products, repurposing pre-approved drugs for alternative treatment uses, or the approval of a new drug to market can all lead to significant changes in demand.

Meeting the growing demand for biologics isn't as simple as providing more space for manufacturing. Producing a biologic can be complex and requires dedicated capacity featuring specialized equipment and facilities, including the use of sterile processing lines for parenteral therapeutics.

The industry is adapting to try and address this capacity shortage by:

- Harnessing technological advancements like automation and cloud computing to increase productivity.
- Utilizing innovative technologies like single-use systems or continuous manufacturing to enhance scalability and efficiency.
- Prioritizing efficiency to increase drug product output without significant changes to bioprocessing infrastructure.
- Designing manufacturing sites with consideration for the future, such as flexible and modular solutions for easy scaling and reconfiguration to continuously adapt to the market demands, seamlessly expanding as demand increases.

Introducing these changes in-house or partnering with a CDMO that has both capability and flexibility can help to meet evolving demands in capacity.

**Q: Why is it important to carefully consider the location of a CDMO facility?**

**A:** Partnerships and outsourcing are integral to biologics production. Being strategically placed geographically for these partnerships can help increase supply chain efficiency and ease collaborative efforts. Biopharma hubs have well-established supply chain networks, helping participants to navigate the

procurement of essential materials and equipment cost-effectively, and with ease, for the efficient manufacture of drug products. Established transport links allow for efficient movement of raw materials, intermediates, and final drug products to and from a site, easing transfer logistics.

**Q: Why is there such a demand for speed in the industry at the moment, and what changes are being made to meet these demands?**

**A:** To deliver life-altering treatments to patients faster, there is a need for developers to deliver essential therapeutics to market at speed. Demand for shortened timelines to market is also driven by investors who require demonstrations of a return on investment (ROI).

An integrated development strategy provides a holistic understanding of the developability of a complex biologic. Implementing the right development strategy will allow the drug products most likely to reach Investigational New Drug (IND) filing and Biological License Application (BLA) to be quickly identified. The following features must be included in a successful development strategy to enable streamlined drug production:

- Taking into account the impact early decisions will have on stages further down the processing line.
- Relying heavily on free-flowing information for all aspects of development - from data on drug candidate performance to information on operations - among all teams and sites involved in the project.
- Understanding the developability risks of complex projects to identify potential risks early, allowing for rapid implementation of solutions.
- Using a developability platform, to score candidates based on their developability criteria and provide quantitative data to highlight the candidates with the highest likelihood of progressing through development and manufacture successfully.
- With a comprehensive understanding of the molecule early in development, biologics developers can mitigate risk and gather essential information needed to initiate processes further down the development and manufacturing pipeline.

**Q: Why is sustainability such an important goal in the industry, and what are the biggest challenges preventing companies from reaching their sustainability targets?**

**A:** Following the Paris Agreement in 2015, businesses throughout the healthcare industry have made commitments to limiting global warming to 1.5°C above pre-industrial levels. Sustainability is a focus across the globe, and to reach the Paris Agreement target, the biopharma industry must look at its operations and establish goals to minimize its greenhouse gas (GHG) emissions.

There are many hurdles hindering progress toward sustainable solutions. The biopharma industry is highly regulated, and any changes to a manufacturing process to reduce emissions will result in process re-validation.

The supply chain is the largest contributor to carbon emissions in the industry, accounting for more than 50%. The complexity of a supply network makes it hard to successfully navigate and decarbonize, with every part of the supply chain contributing to a company's overall carbon emissions. Reaching sustainability goals relies heavily on communicative collaboration between supply partners, aiming to introduce sustainable systems, such as renewable energy and clean transport, across the entire supply chain.

Making use of the resources available can help guide companies to reach their sustainability goals. The Sustainable Markets Initiative (SMI) task force has outlined a number of actions that healthcare stakeholders can enforce as part of their decarbonization initiatives. Establishing and disclosing these sustainability goals and progress year after year can provide confidence the industry is doing its part in the sustainability initiative. ◆

# DRUG DISCOVERY

# Overcoming Traditional Challenges: Innovative Chemoproteomics Strategies to Revolutionize Drug Discovery

By: Ping Cao, PhD, and Irene Yuan, MSc

## ADVANCING DRUG DISCOVERY: NEW STRATEGIES FOR ENHANCED EFFICACY AND SUCCESS

In the realm of drug discovery, two primary approaches take center stage: Phenotypic Drug Discovery (PDD) and Target-Based Drug Discovery (TDD). Each approach offers unique advantages and has contributed significantly to the development of novel therapeutic agents.

PDD involves the identification of compounds that can modify the disease phenotype without prior knowledge of the specific molecular target. Instead of focusing on a predetermined target, PDD screens potential drug candidates based on their ability to elicit a desired therapeutic effect in cellular or animal models. This approach allows for the discovery of drugs that may act through previously unknown mechanisms, opening up opportunities for uncovering new pathways and molecular interactions.

TDD aims to find drugs that can interact with a specific target molecule that is believed to play a crucial role in the disease process. TDD relies on a profound understanding of the underlying biological pathways and molecular targets associated with the disease. By precisely targeting a known molecular player, TDD offers the advantage of increased specificity and reduced off-target effects, potentially enhancing the drug's safety and efficacy profile.

Both PDD and TDD offer distinct advantages, and in recent years, researchers have increasingly recognized the value of integrating these approaches in a complementary manner. This innovative hybrid strategy combines the strengths of both PDD and TDD, leading to more effective drug development processes. It allows for the identification of novel compounds through phenotypic screening while simultaneously gaining insights into their underlying targets through subsequent investigations.

In this context, BridGene's Chemoproteomic platform IMTAC™ (Isobaric Mass-Tagged Affinity Characterization) has emerged as one of the most powerful technologies to seamlessly merge the benefits of PDD and TDD. By utilizing IMTAC, researchers can efficiently analyze the interactions between potential drug compounds and cellular proteins, allowing for the identification and validation of target molecules associated with specific phenotypic responses. This technology empowers scientists to explore new avenues in drug discovery by bridging the gap between phenotypic screening and target identification.

The IMTAC platform consists of three key components:

1. Designing and synthesizing a high-quality library of covalent small molecules.

2. Screening against the entire proteome of live cells: The heart of the IMTAC platform lies in its unique capability to screen the designed small molecules against the entire proteome of live cells. The small molecules will selectively bind to structurally matching protein pockets and form covalent bonds.

3. Qualitative and quantitative mass spectrometry analysis: This analytical prowess enables the identification and characterization of the interacting proteins. Moreover, it quantifies the binding strengths of these interactions, offering valuable insights into affinity and selectivity, critical factors in successful drug discovery.

Through the integration of these three key components, the IMTAC platform revolutionizes drug discovery by providing re-

searchers with a comprehensive understanding of the proteome's interactions and responses to covalent small molecules. This information opens new doors for the development of highly targeted and effective therapeutics, offering a promising path toward addressing unmet medical needs and improving patient outcomes.

In a remarkable step toward advancing drug discovery, BridGene and Takeda Pharmaceuticals have joined forces in a substantial collaboration aimed at implementing a cutting-edge drug development approach that combines PDD and TDD. This strategic partnership is particularly focused on tackling the complexities of neurodegenerative diseases, signaling a shared commitment to revolutionizing therapeutic interventions in this critical area of medicine.

This forward-thinking partnership between BridGene and Takeda Pharmaceuticals not only represents a significant advancement in drug discovery, but also showcases the commitment of both organizations to addressing the challenges posed by neurodegenerative diseases. By harnessing the potential of PDD+TDD strategies, the collaboration endeavors to pave the way for novel and more effective therapeutic solutions, bringing hope to patients and their families.

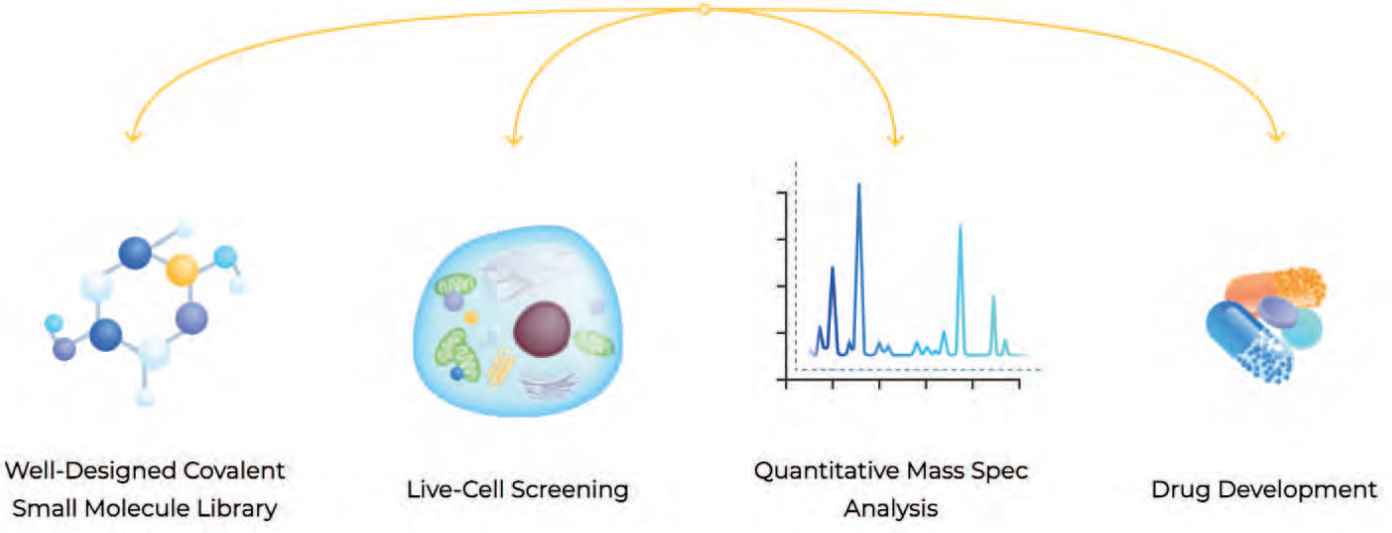
## UNLOCKING NEW FRONTIERS IN DRUG DISCOVERY: TARGETING "UNDRUGGABLE" PROTEINS WITH IMTAC™

The human proteome comprises more than 20,000 proteins, with approximately 12,000 proteins having been identified as playing a role in human diseases and are therefore considered potential targets for precision treatment. Despite this large number, approximately 10% of the protein targets have been targeted by drugs approved by the FDA in the past few decades. In essence, a substantial majority of potential drug targets within the human proteome still lack corresponding therapeutic interventions. Many of these targets are often deemed "undruggable" due to their structural or functional characteristics, presenting significant challenges in designing small molecule drugs that can selectively bind and modulate their activities. Several common reasons contribute to the classification of certain targets as "undruggable," including:

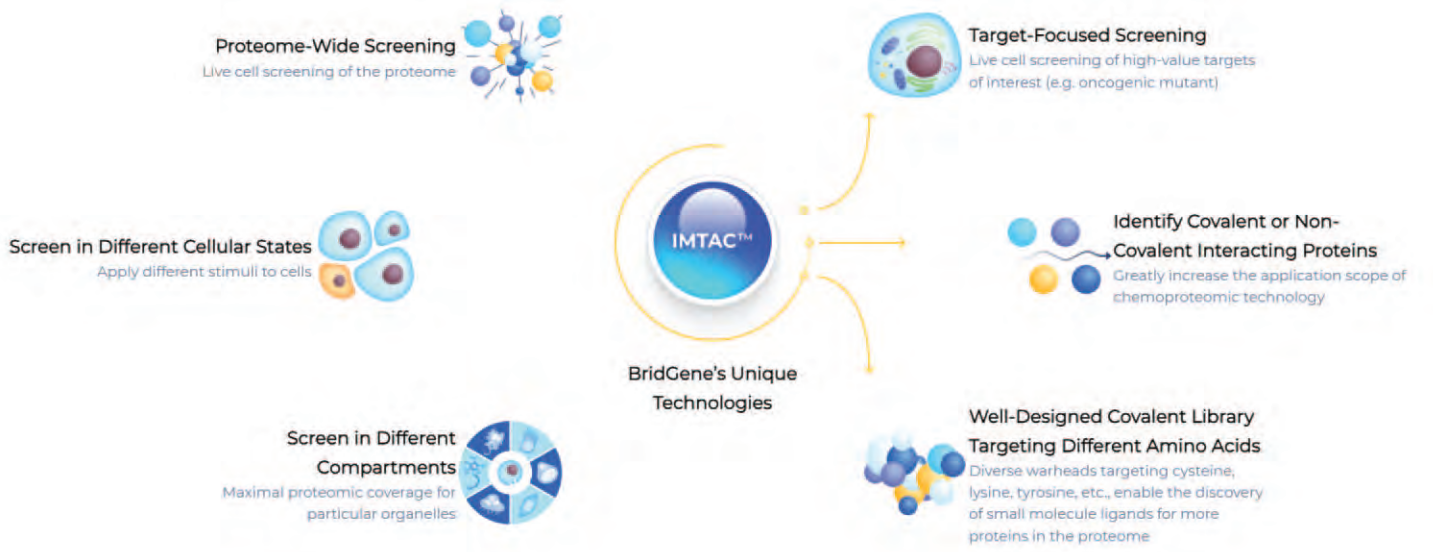
**Lack of Binding Sites:** Some targets lack well-defined binding pockets that can accommodate small molecule ligands, thereby restricting the feasibility of traditional drug binding approaches.

**Protein-Protein Interactions or Transient Nature:** The pockets of certain targets may exhibit transient or dynamic properties, complicating efforts to capture and stabilize them using small molecule drugs.

Traditional drug discovery techniques typically rely on screening small molecule libraries against a purified protein in a non-cellular environment. However, these methods may prove ineffective in targeting proteins with shallow or transient pockets. Moreover, purified proteins may not fully represent the dynamic protein interactions




**Key components to the IMTAC™ platform include a well-designed covalent small molecule library along with live-cell screening, which allows for quantitative mass spec analysis leading to new drug development.**




**The IMTAC platform combines cutting-edge technologies, including covalent chemistry, chemical proteomics, and quantitative mass spectrometry.**

and structural complexity of the target within living cells. Consequently, traditional approaches often fall short when it comes to discovering drugs capable of effectively engaging "undruggable" targets.

BridGene's revolutionary Chemoproteomic platform, IMTAC, stands at the forefront of drug discovery, offering a transformative solution to the long-standing challenge of targeting "undruggable" proteins. Through IMTAC, researchers can unlock unprecedented opportunities for developing therapeutic agents against a wide array of elusive targets. The platform boasts significant advantages that pave the way for groundbreaking advancements in drug development:

**Efficient Discovery of Small Molecule Ligands for "Undruggable" Targets:** IMTAC employs a dual strategy to tackle two main types of "undruggable" targets. For targets with shallow protein pockets, the platform utilizes covalent small molecules, expertly designed to form robust bonds with these challenging sites. For targets with temporary or transient pockets formed within live-cell environments, IMTAC leverages live-cell screening to identify ligands capable of engaging and modulating these dynamic targets. By skillfully combining these unique approaches, IMTAC opens a gateway to discovering small molecule ligands with remarkable potential for modulating the activity of "undruggable' targets."

**Exploration of Targets With Unknown Structures in Living Cells:** IMTAC empowers researchers to venture into uncharted territory, enabling the pursuit of targets with unknown structures. By probing the entire proteome within living cells, the platform provides an exceptional opportunity to unravel the intricacies of protein interactions and cellular responses. Simultaneously, IMTAC offers critical insights into the properties of molecules, such as their cellular permeability, activity, and selectivity. This multifaceted information equips researchers with a comprehensive understanding of the drug candidates' behaviors in living systems, accelerating the path to identifying potential therapeutic leads.

Through BridGene's IMTAC platform, the pursuit of "undruggable" targets transcends previous limitations, ushering in a new era of therapeutic interventions. By harnessing the platform's unparalleled capabilities, researchers gain the means to confront diseases associated with challenging targets, instilling hope for patients and their families. With each successful discovery, the boundaries of drug development are pushed further, heralding a transformative future in medicine.

## REVOLUTIONARY POTENTIAL OF COVALENT DRUGS: ADDRESSING THE LIMITATIONS OF NON-COVALENT THERAPIES

Covalent drugs have emerged as a highly promising therapeutic strategy, addressing the limitations faced by traditional non-covalent drugs, particularly when targeting challenging "undruggable' proteins."

To better understand their distinct mechanisms, envision non-covalent drugs as ships, gracefully docking into a harbor (protein pocket) that perfectly accommodates their shape. This docking disrupts the harbor's traffic, modulating its signal-

ing and controlling the associated disease. However, like ships that can sail in and out of the harbor freely, non-covalent drugs interact transiently with target proteins, limiting their sustained effects. In contrast, covalent drugs present a game-changing paradigm. When their ship docks into the protein pocket harbor, their covalent warhead forms an enduring covalent bond with a specific amino acid adjacent to the pocket. This bond acts like a steadfast anchor, preventing the ship from leaving the harbor and ensuring prolonged target engagement.

This unique mechanism confers several transformative advantages:

**Higher Biochemical Efficiency:** Covalent drugs' irreversibility translates into higher biochemical efficiency, leading to potent and sustained effects on target proteins.

**Stronger & More Persistent Effects:** The stable covalent bond enables prolonged target modulation, resulting in stronger and more persistent therapeutic outcomes.

**Reduced Dosage & Frequency of Administration:** Covalent drugs often require lower doses and less-frequent administration due to their enduring impact, potentially minimizing side effects.

**Separation of Pharmacokinetics and Pharmacodynamics:** Covalent bonding allows for a clearer separation between drug clearance from the body and its pharmacological action, optimizing therapeutic potential.

**Potential to Prevent Drug Resistance**: By irreversibly modifying target proteins, covalent drugs can thwart the development of drug resistance, a formidable challenge in traditional non-covalent therapies.

Additionally, many target protein pockets are relatively shallow and lack the necessary features to effectively accommodate non-covalent drugs. These targets are often referred to as "undruggable" for non-covalent drugs. However, covalent drugs offer a groundbreaking solution by forming enduring covalent bonds with these elusive pockets, acting as steadfast anchors to regulate target signaling. A notable example is KRAS G12C, a historically "undruggable" target due to its shallow pocket. However, in 2013, Professor Shokat's publication in Nature demonstrated the successful targeting of KRAS G12C with a covalent drug, subsequently leading to the industry's development of covalent drugs against KRAS G12C.

Covalent drugs also possess unique advantages for targeting other types of "undruggable" targets, including:

**Protein-Protein Interactions:** covalent drugs can disrupt protein-protein interactions by covalently modifying one of the interacting proteins, thereby interrupting the interaction and modulating cellular signaling.

**Disease-Driving Mutant Proteins:** covalent drugs can exploit unique binding pockets or altered conformations present in disease-driving mutant proteins, allowing for the development of covalent inhibitors with specific activity against these mutants.

**Redox-Regulatory Proteins**: covalent drugs can specifically target and modify the cysteine residues within redox-regulatory proteins, thereby influencing the redox state of the protein and modulating its activity.

**Enzyme Activation or Alteration:** covalent compounds are well-suited for activating or altering the activity of enzymes in emerging therapeutic modalities that involve intervention in gain-of-function scenarios.

BridGene stands at the forefront of covalent drug discovery and development, leveraging proprietary covalent libraries for IMTAC screening and covalent PROTACs. Our expertise empowers us to unlock new therapeutic possibilities and revolutionize drug development with covalent drugs and covalent PROTACs, pushing the boundaries of medical advancements.

## IMTAC™: A PIONEERING APPROACH TO BROAD PROTEOME EXPLORATION

IMTAC offers a distinct advantage by enabling the simultaneous exploration of the entire proteome, setting it apart from other drug discovery technologies that typically focus on individual targets. This unique capability allows IMTAC to rapidly discover a large number of small molecule ligands for diverse targets.

To date, IMTAC has successfully identified small molecule ligands for over 4,000 proteins, with approximately 75% of these targets lacking known ligands prior to the discovery.

This extensive coverage includes traditionally "undruggable" proteins, such as transcription factors, epigenetic regulators, splicing factors, and E3 ligases. These 4,000 proteins represent a valuable resource for the development of small molecule inhibitors, allosteric modulators, and the application of protein-degradation technologies to create degraders that im-

pact protein activities.

Moreover, the broad spectrum of disease areas impacted by these 4,000 proteins spans oncology, immunology, CNS disorders, and more. This vast potential offers an exciting opportunity for collaborative efforts with other pharmaceutical companies to co-develop potential therapeutics. Leveraging IMTAC's small molecule ligands, our partners benefit from streamlined lead optimization, allowing focused efforts on enhancing clinical efficacy, safety, and other critical parameters. This collaborative approach significantly expedites the drug development process, ultimately accelerating the delivery of new and effective treatments to patients in a shorter timeframe. ◆

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## BIOGRAPHY

**Dr. Ping Cao** is the Co-founder and CEO of BridGene Biosciences, Inc. and has more than 18 years of biopharma industry experience in both large and small-molecule drug discovery research. An expert in biophysical/biochemical characterization of proteins/peptides focusing on leveraging mass spectrometry to support the biopharmaceutical pipeline, he has led teams that have helped advance multiple programs into the clinic in a variety of disease indications, including diabetes, obesity, dyslipidemia, and cardiovascular disease. He was responsible for establishing a state-of-the-art mass spectrometry and analytical group at Tularik, Inc. (acquired by Amgen in 2004). Most recently, he was the Head of the Protein Characterization Group in the Discovery Analytical Attributes Group at Amgen, Inc. He earned his PhD from the University of Texas at Austin in Analytical Chemistry and did his Post-doctoral fellowship at Genentech, Inc. He earned his MS in Chemical Engineering from SINOPEC Research Institute of Petroleum Processing in China and his BS in Physical Chemistry from Shandong University in Jinan, China.

**Irene Yuan** is the Co-Founder and Executive Vice President of BridGene Biosciences. She has more than 15 years of operation management experience. Prior to her role at BridGene, she served as Vice President at MUFG Union Bank and Chief Operation Officer at Redstar Global. She earned her BS in Economics and her BA in Business Administration and Law from Nankai University, and her Master of Sciences in Applied Economics and Finance from the University of California, Santa Cruz.


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Drug Development
EXECUTIVE

Syed T. Husain

Chief Commercial Officer

Resilience

RESILIENCE

# How Resilience Is Bringing Forward Thinking to Disrupt the Biomanufacturing Landscape to Increase Access to Medicines

While many biopharmaceutical companies are built to fulfil a need, Resilience was built to serve innovation. Founded during the COVID-19 pandemic in 2020, it was clear that there was a need to revolutionize the CDMO space with a refocus on the foundations of biomanufacturing, a reprioritization on manufacturing technology development, and a redefinition of partnership. This defined the mission of Resilience today – increasing access to complex medicines across the world.

With a sustainable network of high-tech, end-to-end manufacturing facilities supported by a team with decades of experience, Resilience is a technology-focused biomanufacturing company dedicated to providing solutions to ensure the treatments of today and tomorrow can be made quickly, safely, and at scale. *Drug Development & Delivery* recently interviewed Syed T. Husain, Chief Commercial Officer of Resilience, to discuss how the company became an industry-leading service provider in less than four years.

**Q: Resilience was founded in 2020; tell us a little about the company's history - where did you come from?**

**A:** Resilience was formed during the COVID-19 pandemic in 2020. During that time, it was clear that there was a need for a new type of biomanufacturing partner. Biomanufacturing had generally not kept up with the ability to develop the new, complex medicines of the future. Our world faced the challenge of rapidly developing new treatments for emerging threats and scaling up biomanufacturing during the pandemic. These factors were, and still are, crucial for our country's health, economy, and national security. And that's the reason why Resilience was founded.

We responded to two major problems – serving as a biomanufacturing powerhouse for process and analytical development, drug substance, and drug product across established (Biologics, Vaccines) to emerging (Nucleic Acids, Cell and Gene Therapy) modalities, as well as focusing on the development of next-generation manufacturing technology platforms to keep up with essential product developments and increase access to complex medicines. We

also focused on how a partnership in Pharma and Biotech, and with Governments/NGOs, is actually constructed. We considered the attitudes, behaviors, and mindset of a true partner with aligned incentives versus a transactional relationship.

Our mission was not only to develop cutting-edge next-generation manufacturing technologies but also to develop business models that redefine the partnership that could be formed between the service provider and an innovator. Throughout the process, we were fortunate to receive funding and become backed by prominent VC firms ARCH Venture Partners and 8VC, along with industry veterans as our founding executive team, which have made it all possible.

**Q: You're a young company; how do you infuse operational experience and excellence in an organization that's only existed for 3 years?**

**A:** The founders of Resilience took a methodological and deliberate approach to building the company, with exceptional underlying fundamentals. The infrastructure featured a mix of existing CDMOs, pharma carve-outs, and green/ brownfield builds. There was a focus on ensuring that the company originated from a multitude of talents and experiences because, typically, when companies are formed, they're kind of starting from scratch, whereas we were able to provide embedded experience from day one.

The talent brought on board purposefully comes from diverse backgrounds – pharma and biotech, CDMO, product development, manufacturing, and established and emerging modalities. Resilience took this purposeful approach with its people because our founders knew that they would be at the heart of what makes biomanufacturing possible.

The other key element the company decided upon was to invest upfront in digital, quality, and operational systems. Our leaders recognized the importance of offering platforms that serve as a foundation for an integrated operational and quality network. We ensured the rapid stand-up of our manufacturing capacity was supported by interconnected modular platform technologies. When you look at the company's early years, it began by ensuring we had a solid foundation before we rapidly grew with customer projects.

**Q: What sets Resilience apart from traditional CDMOs?**

**A:** The acquisition of each of our manufacturing and development facilities that created what Resilience is today enabled our client's instantaneous access to high in-demand capabilities in established and emerging modalities. With our initial mission in mind, we have upgraded digital, quality, and capacity at our sites across North America. This approach has begun to expand internationally as well.

We chose to make investing in digital a priority to maximize operational performance and customer delight. Meaning that the enhancements we've carefully considered for each of our biomanufacturing facilities were done with a purpose in mind – to serve our client's needs. These three pillars point to what differentiates us in the pharma and biotech community: our end-to-end capabilities that support diverse development and manufacturing needs, innovative technologies, and a distinguished business and partnership model.

**Q: How does Resilience fit into the CDMO space?**

**A:** Resilience has built a strong reputation as a development and manufacturing service provider, which allows us to serve customers efficiently and enhance access to complex medicines. In addition, our differentiation is directly linked to the next-generation technologies we currently have in development and business models that genuinely form an aligned incentive partnership that befits our partners and, most importantly, the patients they serve. While we're a CDMO in practice, we consider ourselves a standout partner in the industry based on our innovation, cutting-edge technologies, non-standard offerings, and unique viewpoint on how contract partnerships should function.

**Q: How is Resilience revolutionizing the way medicines are made?**

**A:** Our mission is to create a healthier world by increasing access and affordability to medicines and therapies. Our vision is to become the most trusted biomanufacturing partner through operational and quality excellence. Our strategy is to serve customers with reliable, technology-enabled, end-to-end biomanufacturing solutions for complex medicines using flexible business models unique to Resilience.

We're changing the status quo of contract development and biomanufacturing by creating processes and platforms that allow our team to make novel therapies quickly, safely, and at scale. Collaboration is also at the heart of what we do – with leaders across different industries working together to improve the way complex medicines are made, making it possible for more patients worldwide to get the medicines they need. ◆


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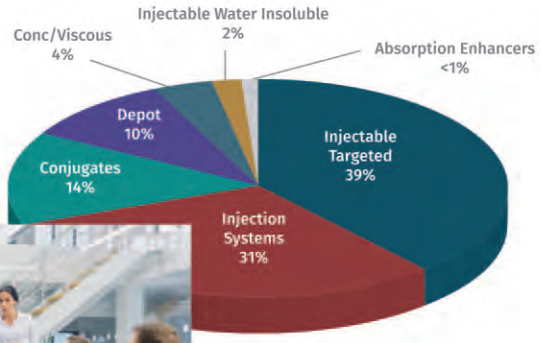
| Excipient vs Strength | 375 mg telaprevir |
|---|---|
| HYPROMELLOSE ACETATE SUCCINATE 12070923 (3 MM2/S) **(Core/Content)** | 375 mg |
| SODIUM LAURYL SULPHATE (Core/Content) | 7.58 mg |
| DIBASIC CALCIUM PHOSPHATE ANHYDROUS **(Core/Content)** | 75.76 mg |
| CROSCARMELLOSE SODIUM **(Core/Content)**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

## Evaluate New and Promising Technologies

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# Special Feature

## Outsourcing Analytical Testing: AI Could Transform Analytical Labs

By: Cindy H. Dubin, Contributor

Largely driven by the complexity of biologics, biosimilars and personalized medicine development, the global pharmaceutical analytical testing outsourcing market is expected to reach $15 billion by 2030, almost doubling in growth from $8 billion in 2022.[1] Stringent regulatory guidelines and specialized capabilities are also contributing to bio/pharma companies seeking to outsource analytical testing providers.

Some of these specialized capabilities include artificial intelligence (AI), which requires a depth of expertise and provides access to large quantities of high quality data. Industry insiders say the potential of AI to increase reproducibility and accuracy has the potential to transform analytical labs in the future. For example, AI can automate and streamline chromatography analysis by enabling property predictions of unknown samples based on previous data.[2] The result is a reduction in time and labor required to analyze chromatography data and improve accuracy and reliability. The promise that AI holds in the pharma sector has experts valuing the

**Scientists working in MilliporeSigma's contract testing analytical development lab in Rockville, MD.**

market at $6.7 billion in 2030, up from $1.56 billion in 2022.[3]

This exclusive annual report from *Drug Development & Delivery* presents how today's leading analytical testing service providers are taking advantage of AI and other types of automation and innovative technologies.

## Adare: Robust Technologies for More Efficient Drug Development

Personalized and tailored drug treatments escalate the complexity of drug development significantly, often demanding a departure from traditional methods used in conventional development. Analytical testing, therefore, plays a pivotal role in ensuring that these novel treatments meet the diverse and specific requirements of the medication. An example of this is a specialized device that Adare is currently working on with a customer. This device enables precise and adjustable dosing, even outside standard dose ranges, such as administering a 35mg dose when only 25mg and 50mg tablets are available, explains Mike Markham, Associate Director, Analytical Sciences, Adare. This flexibility also allows doctors to modify dosages without issuing new prescriptions.

"Achieving such precision demands robust analytical testing, focusing on the exact particle size and shape that is crucial for the device's functionality," he says. "Our formulation scientists are employing highly controlled methods, particularly in analyzing particle size with greater accuracy than usual."

This need for robust analytical testing is amplified by the multiple active ingredients contained in the formulation, with half used for immediate release and the other for extended release. This necessitated enhanced testing procedures in both material characterization and chemistry, as each API needed precise control. "This exemplifies the increased robustness and specificity often required in analytical testing during the development of personalized and tailored drug treatments," says Mr. Markham. "The demands of pharmaceutical development are ever-growing, and analytical testing is evolving to meet those demands."

One of Adare's strengths is mastering available technologies, then thoughtfully applying them to overcome customers' challenges, says Jason Brown, Analytical Science Manager, Adare. For example, the company recently utilized a unique microdissolution apparatus for a kinetic solubility study. "This specialized tool, not commonly found at CDMOs, enabled us to swiftly assist the customer in selecting the optimal salt form for their drug development."

Mr. Brown says that this not only highlights Adare's technological capabilities, but also underscores the importance to the industry of understanding and innovatively utilizing existing technologies. "As important as new technologies like AI are, just as important – if not more so – is gaining a deep understanding of technologies that already exist and applying them in unique and novel ways that benefit sponsors and their patients," Mr. Brown says.

As a result, he says, in the future, analytical labs in the bio/pharma industry are expected to increasingly integrate robotics and artificial intelligence. AI in particular will be instrumental in data workup, especially for tasks like chromatographic data interpretation and data summarization. "We have been exploring these innovations and will continue to do so, but we also greatly anticipate ongoing advancements in automation, online collaboration, remote operations, and paperless workflows. These developments, though less headline-grabbing than AI or robotics, have already significantly streamlined daily operations in analytical labs. We foresee these advancements continuing to evolve, further reducing operational friction and shaping the future of analytical lab environments in a meaningful way."

## Catalent: Digitization & People Create High Quality Data

Catalent has supported the pharmaceutical and biotech industry with integrated and stand-alone large-molecule analytical services. One example is a customer that recently came to our Research Triangle Park, NC, site because a CRO had been working with a validated cIEF method on the Maurice to look at charge heterogeneity. Over the course of 18 months of developing and validating the method and testing stability samples, it was found that the method was not reproducible.

"The CRO could not find a solution to make the method more reproducible, so the customer brought the method to Catalent to troubleshoot it and make it more robust," explains Joe Nawrocki, Associate Director, Catalent Biologics. "We accepted the challenge and purchased a Maurice instrument capable of CE-SDS and cIEF. With the instrument currently being onboarded, we were able to take the method and accomplish the customer's need in just one month. Once we complete the onboarding of the Maurice instrument, we will perform method validation and stability testing."

Luke Mercer, Bioassay Manager, Catalent Biologics, says that while plat-

form analytical methods continue to have their place, there is increasing need for molecule-specific analytical development to support treatment advances. This focused evaluation and optimization, when done properly, results in well-designed methods that provide robust data to progress these innovative treatments to patients. The use of robotics allows the standardization of these setups to minimize some of the human variables that are always present. This can result in less variability across test occasions.

"Digitization of all processes has been underway for years and continues to advance," says Mr. Mercer. "We will continue to see advancements in this area to allow more instruments interfaced. People will always have a key role in analytical labs, but with a goal to simplify their workday. Through more efficient digital and instrumentation design, we will allow analysts flexibility to have more time outside the lab while still generating high quality data."

## Cyclolab Ltd.: Facilitating the Separation & Analysis of Challenging Contaminant Pairs

Cyclolab is an all-around cyclodextrin research and development company, operating as a CRO for cyclodextrin-related services including:

- development of products (pharma, cosmetic, food, agricultural industries);
- offering custom synthesis of cyclodextrins, fine-tailored for certain guest molecules (like Sugammadex) or purposes;
- performing pilot-scale cGMP-compliant manufacturing of cyclodextrins to be used as APIs or excipients in clinical studies or cyclodextrin-enabled formulations for the same purpose; and
- all analytical tasks related to the above, under GMP (method development, validation, stability studies for formulation ingredients (APIs, cyclodextrins) and final products as well).

One of Cyclolab's main activities involves the synthesis of Sugammadex (SGM) impurities. SGM is a gamma-cyclodextrin derivative, indicated for the reversal of neuromuscular blockade initiated by the administration of rocuronium or vecuronium. "The intellectual property rights for this molecular entity have either recently lapsed or are approaching expiration," says Dr. Erzsébet Varga, Head of HPLC Laboratory, Cyclolab Ltd. "Consequently, multiple manufacturers have approached us seeking assistance in their respective developmental endeavors."

Given the extensive array of potential reaction pathways, a multitude of impurities can arise during the process. In the absence of precise information regarding these impurities, it becomes challenging to determine the optimal reaction pathway.

Cyclolab's analytical department successfully assisted its partners in the following areas:

- Identification of unknown impurities through a comprehensive approach involving High-Performance Liquid Chromatography-Mass Spectrometry (HPLC-MS) and Nuclear Magnetic Resonance (NMR): Initial analysis includes HPLC-MS examination of the sample with unidentified impurity followed by the assessment of the mass spectrum. "Subsequent to spectrum analysis, our validation process extends to NMR studies to corroborate structural details," she explains. "It is crucial to emphasize that NMR measurements demand a sample of adequate quantity and quality for accurate analysis. To meet this prerequisite, we employed one of our HPLC equipped with an automated fraction collector, ensuring the precise and efficient collection of samples for subsequent NMR investigations."
- Development of an HPLC method designed for the effective separation of critical pairs: The structural characteristics of SGM may lead to the formation of isomers and racemic compounds during the production process. Dr. Varga says: "Utilizing our extensive inventory of over 100 HPLC columns, we are well-equipped to facilitate the separation and analysis of challenging contaminant pairs."
- Analysis of products from alternative manufacturers: Given the uniqueness of these impurities, their presence enables the identification of possible starting materials and reaction pathways. This information can also assist manufacturers in making informed decisions.

"Presently, Cyclolab offers more than 30 Sugammadex-related impurities, actively aiding manufacturers in navigating the challenges encountered during the formulation/development process.

## Daicel: Partnering Approach with Generic Peptide Manufacturers

Successful development of a generic peptide drug product requires a high level of technical expertise, a deep understanding on regulatory requirements, and excellent planning. Similar to small-molecule generic medicine, peptide generic medicine has to be bioequivalent to the innovator drug and ensure the same biological effect with proper safety and efficacy. However, it can be challenging to prove the sameness for synthetic peptide drugs

A Daicel chemist is performing analytical testing at the FDA-audited lab.

against the reference listed peptide drugs of rDNA origin. Several governing guidances are now available such as: FDA Guidance for Industry: ANDAs for Certain Highly Purified Synthetic Peptide Drug Products that refers to listed drugs of rDNA origin, May 2021; USP general chapter 1503: Quality Attributes of Synthetic Peptide Drug Substances; EMA guidelines on the Development and Manufacture of Synthetic Peptides, October 2023.

"It is very difficult for mid-size generic peptide drug manufacturers to equip themselves with advanced analytical infrastructure and expertise to fulfil the criteria for successful regulatory filings, and partnering with a specialized analytical CRO is more efficient in many aspects," says Dr. Ch. Lakshmi Narayana, FRSC, Managing Director, Daicel Chiral Technologies India.

Japan-based Daicel Corporation established an Indian subsidiary in 2008 and, in turn, developed an analytical testing facility in Hyderabad, India, which has a track record of successful inspections by the US FDA in 2016, 2019, and 2023.

"Daicel has rich experience, expertise and knowledge in designing analytical studies for DMF and ANDA filings of both small-molecule drugs and peptide drugs," explains Dr. Narayana. Daicel analytical packages for peptide drugs include method development, method validation, aggregation studies, orthogonal methods for related substances by HRMS, primary and higher order structure characterization, bio-identity tests by cell-based bio assays, and E&L studies. Further, Anand Khatavkar, Senior Director, Sales & Marketing, adds Daicel's expertise in synthesizing well-characterized, high-quality peptide impurity standards is an advantage for generic peptide drug manufacturers partnering with Daicel.

Both Dr. Narayana and Mr. Khatavkar say that generic peptide drug manufacturers partnering with Daicel are privy to a range of analytical testing with faster turnaround and quick synthesis of peptide impurity standards, together with timely updates and transparent communication.

## ICON plc: Faster Data Turnaround is a Differentiator

ICON offers true one-stop-shopping experience that includes on-site manufacturing and release of dosing drug product, a co-located clinical unit, and analytical testing facilities that cover all types of samples, including chromatographic and ligand-binding assays.

At ICON, multiple test facilities around the globe conduct clinical studies across all phases of development. This is currently demonstrated by analysts operating analytical equipment from remote offices via secure networks, mainly for data processing. "Quality Control laboratories responsible for the analysis and ultimately safety of our manufactured medications are equipped with identical UPLC systems at several locations in both Europe and the United States to enable flawless communication across our operations," explains Suzanne Jansen, Head of QC Laboratory, ICON plc.

When it comes to focusing on technically challenging aspects, various automated sample pipetting robotics are employed globally that allow high-volume consistent workflows. "Pipetting robots are taking over the performance of repetitive lab activities and this approach indeed works very well for standard work with large numbers of samples," she says. "ICON does, however, value the importance of hands-on lab activities, especially when it comes to the highly specific needs of our clients who require a flexible approach from our analysts, with the ability to rapidly change strategies when needed."

Pharma/biopharma companies are always looking for faster proof-of-concept data, which enables them to invest in the successful compounds and kill those that are not effective or safe. However, clinical trial designs of early-phase studies have become more complicated over the last couple of years to include multi-purpose protocols. Ms. Jansen explains that both PK and PD parameters are monitored throughout the clinical trial and serve as input for the intended dose for the remaining cohorts of the clinical trial. Tailoring the dose of the IMP is, therefore, essential for meeting the endpoints of the clinical trial.

"Adaptive doses can be realized by on-demand manufacturing and pharmaceutical analysis," she says. To allow the dose to be adapted, a dose range and/or concentration needs to be manufactured and analyzed. The analytical method requires validation (or bracketing) of all possible doses in advance of the trial. PK/PD data may show that the formulation is not suitable for the drug substance used and lead to a non-linear bioavailability or an unexpectedly low or high bioavailability. A new formulation may then be needed, which calls for a rapid turnaround of the manufacturing method and analysis.

"The future analytical laboratory must be specialized in this quick turnaround," she says. "The ability to serve the client with high quality analysis within a short timeframe will become the differentiator between pharmaceutical laboratories."

## Lifecore Biomedical, LLC: Pivoting Toward Technologies That Reduce Turnaround Time

Lifecore predicts there will be a need for higher throughput, which is leading the company to pivot toward more plate-based assays, automation options, and rapid microbiological testing technologies to reduce turnaround time. "Growth in the biologics market will result in greater need for cell-based assay capabilities and the development of platform methods," says Jessica Raddatz Hensley, Quality Control Director at Lifecore. "In addition, the development of alternative technologies for pyrogen detection is a new area of focus for the industry."

Lifecore's analytical testing team recently identified unexpected degradation of a client's development-stage product through our comprehensive stability services program. The assay and impurity data the analytical team provided allowed Lifecore to assist the client in optimizing their formulation to extend the shelf life of their product.

"We used our experience in handling viscous formulations to develop a bioburden test method for a client whose previous contract lab was not able to work with their material successfully," she describes. "Lifecore's microbiologists also overcame challenges posed by the viscosity and turbidity of the sample to develop a kinetic chromogenic endotoxin assay that has greater sensitivity than the gel clot methodology used previously."

Anticipating that the regulatory focus on data integrity controls will continue to increase, Lifecore Biomedical is prioritizing investment in electronic laboratory information management systems and automated data transfer from analytical equipment. "The investment in paperless technology will also provide the enhanced transparency clients are seeking, allowing us to have more data and metadata readily available for custom reporting," says Ms. Raddatz Hensley.

## Lonza: Systems to Enable Remote Access for Data Analysis

Lonza recently deployed Native Ionization MS (mass spectrometry) linked to Protein A affinity chromatography. Titer by protein A is a well-established and robust method, deployed for many programs. This method was developed to generate structural information on bispecific assembly alongside titer. The combination allowed high throughput screening of clones for both assembly and titer simultaneously, directly from the culture supernatant.

"The outcome of this innovation is that we can deliver additional key information to support decision making without extending timelines," says James Graham, Director, R&D, Protein and Process Analytics, Lonza.

Historically, MS data processing has limited productivity, often taking longer than sample preparation and data acquisition combined. To that end, he envisions a future where systems will enable remote access for data analysis and effectively debottleneck a task that previously relied on the availability of a limited number of physical workstations. Remote analytical technologies are predominantly based around instrument control and, critically, data processing. This includes chromatography data systems, and more recently has become very important for processing of high-resolution mass spectrometry.

Robotics are currently in use for several analytical platforms. Predominantly, they are used for sample preparations, but in some cases also for end-to-end execution of analytical procedures, resulting in higher standardization and cost savings. This also allows scientists to focus on the development of new methods that are required for new molecular formats, rather than rote execution of platform methods. Machine Learning models are now being developed and used to improve cell lines and processes.

"We at Lonza believe analytics will become far more integrated into the overall process," he says. "Scientists should be able to generate robust analytical results quickly and easily by themselves, at the point of need, rather than having to hand off samples and information to a different department. This change requires both method simplification and substantial levels of automation."

This is already the case within the

R&D organization, he adds, where analytical instruments are sitting alongside bioreactors for at-line testing. "In the future, the role of analytical scientists will be much more focused on method development/transfer and oversight of the analytical platforms. Therefore, analytical labs will focus on more advanced applications and instruments, rather than containing banks of HPLCs for routine testing."

## MedPharm: Increasing the Robustness of IVPT Experiments

*In vitro* penetration/permeation test (IVPT) is a well-validated tool for the study of the pharmacokinetics of topically-applied drugs. The model uses excised human skin mounted in specially designed diffusion cells that allow the skin to be maintained at a temperature and humidity that match real-use conditions. The product/formulation is applied to the skin's surface, and the compound is measured by monitoring its rate of appearance in the receptor solution underneath the excised skin. This model also allows the amount of the drug and metabolites within the different layers of the skin to be measured (i.e., epidermis or dermis). Additionally, this model has the potential for carefully controlling many of the variables involved in topical application, like dosing volumes, humidity, temperature, drug stability, skin thickness, etc.

According to Dr. Jon Lenn, Chief Scientific Officer at MedPharm, the most common commercially available diffusion cell systems are tedious and manual, which take hours to set up, require scientists to manually sample at designated time intervals (sometimes in the middle of the night), and require constant monitoring to ensure air bubbles are not introduced.

"To combat these challenges, we developed a fully automated diffusion cell system (MedFlux-HT®) that uses peristaltic pumps, robotic sampling rails, optimized fluidics, and computer-controlled sample collection," he explains. "The modification in the fluidics and automation of the sampling has allowed sample collection to occur simultaneously across 96 diffusion cells at 15-minute increments, which is not technically feasible with the commercial systems. The system has transformed the analytical testing to ensure accuracy of highly lipophilic drugs at sub-nanogram levels and a better characterization of the pharmacokinetics of topically-applied products."

In addition, the system has a fully integrated transepidermal water loss (TEWL) instrument that measures the integrity of the skin's barrier across 32 diffusion cells simultaneously taking multiple readings each minute. The TEWL ensures the accuracy of the data by allowing for skin that is damaged or has a defective barrier to be removed prior to experimentation.

Dr. Lenn says that MedFlux-HT is routinely used for R&D and regulated IVPT experiments during formulation development and optimization, and generic product approval in lieu of clinical trials. He says: "This system has decreased the workload by about 80%, increased efficiency by several hundred percent, and increased the robustness of IVPT experiments."

## MilliporeSigma: Evolving Workflows for More Vigorous Personalized Drug Testing

Robotic technologies represent a growing industry trend because they enable faster initiation of analytical testing and deliver consistent performance with low error rates. MilliporeSigma is integrating these technologies into its contract testing services and currently employs robotic technologies across laboratories for virology, immunology, molecular, and more.

According to Brian Woodrow, Global Head of Operations for Product Characterization at MilliporeSigma, analytical testing teams: employ robotic pipetting instruments in cell culture activities to increase accuracy and volume consistency from well to well; apply Machine Learning (ML) technology for automated cell counting and cell confluency determination; and utilize Artificial Intelligence (AI) for automated cell monitoring, aiming to eliminate variability with manual cell confluency determination, reduce lab time, and increase cell count accuracy.

He says: "This all contributes to enhanced data reproducibility and increased efficiency for cell-based assays."

Looking ahead, analytical testing in the future will need to re-work workflows and become more robust to drive high throughput, one-off testing for personalized medicine. Fundamentally, personalized medicine involves developing a single drug tailored to a patient's needs.

"This demands rapid turnaround and, often, specialized testing," he says. "Our teams are determined to help realize the promise of personalized medicine by driving adaptation of testing approaches. We continuously apply operational excellence principles to conduct step-by-step deep dives into workflows across our laboratories that offer analytical testing for personalized therapies. From lab operations to report writing, quality assurance and more, we seek opportunities to optimize processes, improve turnaround time, and further specialize offerings."

Based on current industry needs, Mr.

Woodrow is certain that small molecules will continue to be relevant, while medicine based on biologics will thrive. Many biologic-based therapies demand faster turnaround time – within weeks or days – before administration to patients.

"Time does not allow for retests, as patients are scheduled for injections of engineered therapies within a pre-set timeframe," he says. "Therefore, analytic testing providers must achieve two key performance indicators: on-time delivery (OTD) and right first time (RFT). These measures will become more decisive in the move from bulk-based to personalized medicine."

## PCI: New Technologies Will Enable ESG Manufacturing

New technologies, artificial intelligence, robotics, and automation will play a significant role in the future state of analytical laboratories. The focus will be on less lab-to-lab, scientist-to-scientist, system-to-system variability ensuring accuracy and consistency from one test to another, as well as faster data analysis to support formulation development and process optimization studies.

"Currently, Artificial Intelligence technology in analytical laboratories is not well established," says Lauren Parry, Director of Analytical Services at PCI's high potent manufacturing facility in Wales, UK. "Automation is certainly on the increase from automatic pipettes through to dissolution and HPLC autosamplers as standard."

She says this means the equipment can perform the analysis without the scientist around, which provides more consistency in the test execution and less scientist-to-scientist variability as well as allowing the scientist to work on a separate task in parallel. However, in the development phase of a product, observing how a finished product behaves in a dissolution vessel, can be value adding.

**Analyst meticulously examining a sample in Recipharm's state-of-art sample preparation lab.**

While solutions, samples, and system set-up do need to be performed on site within the laboratory, it is possible to control HPLC instrumental analysis remotely through software. This includes system purging, column equilibration, system suitability execution, and launching of data analysis. The analysis can be monitored remotely and data processing of the acquired data can also be performed once the analysis is complete.

"The future analytical laboratory will be fully digital with end-to-end connected instrumentation capable of measuring, trending, and reporting of data with AI solutions to detect errors and resolve real-time without user intervention," says Ms. Parry. "New technologies will form part of the Environmental, Social, and Corporate Governance utilizing alternatives to plastics and single-use consumables and renewable solvents."

## Recipharm: The Future Lab Combines Automation & Technological Innovation

Recipharm embraces innovation and incorporates cutting-edge technologies into its laboratory practices, with an initial focus on incorporating robotics into its workflows. All analytical tools have been upgraded, swapping out manual work for automated processes.

The company's analytical processes predominantly rely on chromatography, such as high-performance liquid chromatography (HPLC), ultra-performance liquid chromatography, and gas chromatography, supported by suitable software. Automated sample preparation techniques help to accelerate the analysis of samples compared with manual sampling and dramatically improving productivity.

"Automating these analyses enabled remote monitoring during the pandemic, allowing us to summon a limited number of analysts to the lab in a staggered manner to perform essential wet lab tasks like sample and standard preparations," explains Ramesh Jagadeesan, PhD, Vice President, Analytical Development, Reci-

pharm. "The valuable experience gained from navigating these unforeseen challenges continues to inform our approach in the current scenario."

Another example of how robotics has influenced Recipharm's analytical technology is its automated robotic diffusion system for *in vitro* release testing (IVRT) of semisolid dosage forms. The system automates sampling, improves time efficiency, increases consistency, and prevents accidental contamination, ultimately making analytical testing more efficient.

Combined automation techniques, such as robotics and AI solutions, will allow analytical systems to perceive mistakes or non-ideal conditions and make real-time corrections. As exemplified in a client project, Recipharm adopted innovative approaches in equipment design and integration. Dr. Jagadeesan explains: "We were approached by a sponsor to produce a method for low-dose dissolution testing of an active corticosteroid component in a topical solution. As this was not compatible with traditional dissolution methods, we had to devise a new approach. Challenges stemmed from first adapting the traditional United States Pharmacopeia 2 dissolution apparatus for small volumes and developing an HPLC method with the capability to detect very low concentrations. In making these customizations, we could test with smaller sample volumes and reduce receptor fluid volume, leading to a higher concentration for quantification via analytics."

The future analytical lab envisages advanced instruments for intricate projects, necessitating the integration of multiple instruments with diverse working principles for immediate results. Analytical labs need to adopt more automation techniques and utilize technological innovations to speed up projects. Recently, Recipharm has provided analytical services related to the reverse engineering of a reference-listed drug (RLD) with an aerosol formulation. The client wanted to develop a generic formulation and wished to submit the Q1 and Q2 details to the FDA for approval. Dr. Jagadeesan says Recipharm sourced three different lots of RLD samples from the US market and analyzed them using a method developed in-house. The excipient content was quantified (±5%) and the client submitted a complete report within a very short time.

**Characterizing primary packaging is the first step to de-risk drug product development at Stevanato Group.**

"Fast-tracking therapeutics is a common goal that helps expedite time-to-market and allow patients to receive vital medicines sooner," he says.

## Stevanato Group: Mechanical and Closure Integrity Testing for Optimal Packaging

Pharma companies often choose a readily available drug container in a bid to accelerate the time to market for their drug product. But they risk encountering problems at the last minute if they have not thoroughly vetted the container right at the start.

"One of our US customers used a Stevanato Group's Technology Excellence Center (TEC) to evaluate a range of glass and polymer syringes and elastomer stoppers to identify which container combination was optimal for their unique drug product," says Alan Xu, Product Manager, Analytical Services, Stevanato Group. "The TEC was able to perform a range of mechanical and closure integrity testing to identify which syringe combinations were strong candidates – and which ones should be dropped from the evaluation."

Root-cause analysis is also a key service offered by Stevanato Group's TECs – for example, identifying unknown fibers or components. Breakages and other quality issues are a constant challenge for pharma companies, so evaluating potential root causes with TEC's glass fractography or forensic service has been crucial, Mr. Xu says.

Preparing for FDA submissions is another critical service offered by the TECs – evaluating whether glass container performance has changed over time, for example. "Several of our customers have requested validated testing in anticipation of follow-up questions from the FDA, so having the data early brings peace of mind – both in terms of characterizing the

product and also being able to respond to the FDA in a timely manner."

Concentrating a variety of different services under one roof – as Stevanato Group does – is a trend that is likely to continue in the future. "Offering multiple services as a one-stop-shop provider reduces logistical overheads and the time between tests, as well as the risk of confounding variables," says Mr. Xu. "The drug product, drug container, and drug delivery system can all be analyzed in the same place and benefit from economies of scale, particularly when it comes to automated testing."

Automating services such as data collection, tracking samples, environment monitoring, equipment maintenance, and calibration schedules allow laboratories to minimize scheduling issues and keep projects running smoothly. Laboratory Information Management Systems (LIMS) and electronic lab notebooks are becoming increasingly popular to centralize traceability.

Combining multiple tests to be run by the same machine is also starting to happen – to minimize the human element of shifting samples from machine to machine and reducing total samples needed, he says. There are already automated drug delivery device testing machines, for example, that simultaneously test and record multiple performance features, ranging from activation force to sound to dose accuracy. "This is set to become commonplace in the future, as it delivers faster throughput and more consistent results."

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# DRUG DEVELOPMENT

# Using a Novel Deep Cyclic Inhibition Mechanism to Treat Broad Range of RAS-Mutant Cancers

By: Ben Zeskind, PhD, MBA

## INTRODUCTION

In recent decades, there has been significant progress in the treatment of a wide range of cancers, with new immune-oncology therapies including programmed cell death protein 1 (PD-1) inhibitors reaching the market and several key regulatory approvals of new targeted therapies including both mitogen-activated protein kinase kinase (MEK) inhibitors and KRAS G12C inhibitors.[1-4] Targeted therapies have rapidly advanced to standard-of-care for treatment of many solid tumors, demonstrating clinical efficacy as monotherapies or in combination with other agents.[1,3,4] While representing significant advances in care for millions of patients, they also are associated with tolerability issues and drug resistance and are limited to use in specific or small subsets of patients.[2,5] Most importantly, they do not address a primary challenge in the treatment of cancer that continues to elude drug developers – the ability to safely target and kill tumor cells while sparing healthy cells.

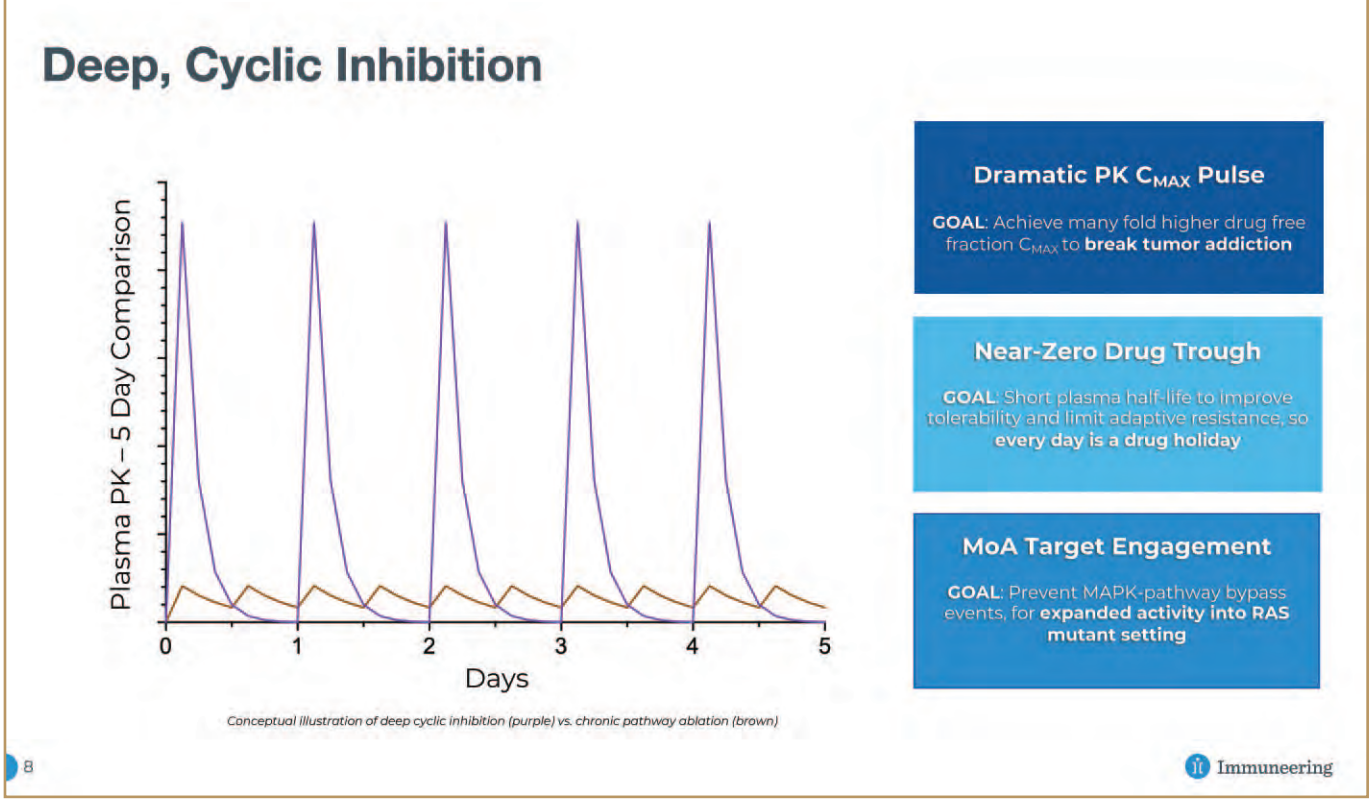
There remains a substantial need to enhance and improve upon current treatment approaches and to broaden the therapeutic activity of cancer therapies to make them appropriate and effective options for more patients. Next-generation therapies will require novel approaches in drug delivery and targeting, some of which may be counterintuitive to conventional treatment protocols, to be able to safely and effectively address underlying cancer-causing mutations and create better outcomes for more patients.

## TARGETING RAS MUTATIONS

In several types of cancer, including pancreatic, melanoma, colorectal, and non-small cell lung cancer, tumors can be driven by mutations of RAS or RAF genes in the mitogen-activated protein kinase (MAPK) pathway.[3] Activating mutations of RAS or RAF genes in the MAPK pathway are observed in approximately 30% of all cancer patients, and inappropriate or abnormal activation of this pathway is observed in up to 50% of all tumors and represents one of the most highly used signaling pathways in oncology.[6,7] In aggressive solid tumors of the pancreas, skin, lungs, and colon, mutations in RAS or RAF genes are even more common.[8] For example, approximately 40% of lung cancers and approximately 90% of pancreatic cancers are due to RAS or RAF genetic mutations.[6,8]

The most common types of RAS genes – KRAS, HRAS, and NRAS – encode proteins that play an important role in cell signaling.[3,6] When RAS genes are mutated, cells grow uncontrollably and evade death signals. RAS mutations also make cells resistant to many available cancer therapies.[5] Currently, RAS-selective inhibitors each target single specific RAS mutations that drive different cancer tumors, including the most common KRAS G12C mutation.[6] They are also typically designed to sustain target engagement 24/7 to shut down the MAPK pathway chronically.[3,5] But treatment based on this chronic inhibition strategy can yield undesirable side effects given that healthy cells also rely on the MAPK pathway, and patients can become resistant to drugs that are specific to a single mutation, as the constant selective pressure against, say, KRAS G12C can cause tumors to mutate again and become reliant on a different mutation in KRAS. Researchers at Immuneering are working to address the question: rather than targeting individual RAS mutations and treating chronically, is it

FIGURE 1




possible to achieve broad therapeutic activity in a way that focuses on malignant cells while minimizing damage to healthy cells?

## A NEW APPROACH BASED ON DEEP CYCLIC INHIBITION OF THE MAPK PATHWAY

Immuneering's journey began with a counterintuitive observation from the company's proprietary informatics platform. First-generation inhibitors of the MAPK pathway were effective in reversing disease-associated gene expression changes at early time points, such as 3 hours and 6 hours post-administration, but by 24 hours were amplifying disease-associated transcriptomic changes. These observations led the company to conduct extensive research, the results of which support the notion that tumor cells and healthy cells need the MAPK pathway, but in different ways.[9] Tumor cells need continuous MAPK pathway signaling to grow and divide, whereas healthy cells can tolerate more moderate or sporadic levels of MAPK signaling. In other words, tumor cells need the MAPK pathway like we need air (a constant supply), and healthy cells need the pathway like we need water (on a more intermittent basis). Thus, healthy cells likely can go several hours without "water," or MAPK signaling. The company's observations strongly support further assessment of a unique and counterintuitive approach to patient dosing known as deep cyclic inhibition (DCI).

The concept of DCI is to focus therapeutic intervention more against tumor cells than healthy normal cells by deeply cycling and disrupting the MAPK pathway in a rapid series of on and off cycles instead of aiming for 24/7 chronic disruption. This novel approach has two essential goals:

1. Hit the tumor hard with pulses of inhibition to break tumor addiction to the MAPK pathway – reaching levels of pharmacokinetic (PK) $C_{max}$ many fold higher than traditional "chronic" therapeutic approaches.

2. Quickly drop off to a near-zero drug trough or drug level (before the 24-hour mark) to give healthy cells an opportunity to reset and restore homeostatic MAPK pathway signaling – enabled by features including a short therapeutic half-life of approximately two hours.

This two-step process is repeated at least once daily in an ongoing cycle. All the action happens behind the scenes based on the drug's chemical structure, so for patients, it is a very simple matter of taking the drug orally once or twice a day.

Earlier generation cancer therapies are designed to have a long half-life to en-

sure 24/7 suppression of the MAPK pathway. Designing therapies to have a shorter half-life is essential to support the DCI process – it enables high peak drug exposures (or $C_{max}$) that can then swiftly drop to near-zero drug troughs. Patients essentially experience a daily "drug holiday." While this may seem counterintuitive compared to currently available treatment approaches, DCI has the potential to target and kill cancer cells more effectively by limiting adaptive resistance, a process where cells upregulate compensatory pathways in response to drug-related activities, while improving drug tolerability.

A very important consideration related to DCI is the potential to broadly target a range of RAS mutations including KRAS, HRAS, and NRAS. This contrasts sharply with most current therapies that target only one specific RAS mutation.[3,5,6] The DCI approach targets MEK (a key protein kinase in the MAPK signaling pathway) downstream of RAS and thus could have broader potential applications in treatment of some of the most challenging tumor types.

## FIRST-EVER DEMONSTRATION OF DCI IN HUMANS

The DCI approach has been modeled extensively in preclinical research using animal models, proprietary humanized 3D tumor growth assays (3D-TGAs), pharmacogenomics modeling, and *in vitro* and *in vivo* models to assess safety and efficacy along with optimal patient populations for treating different RAS-mutant cancers. Researchers at Immuneering leveraged more than 100 tumor models, including 75 different models displaying various RAS mutations.[10] Immuneering assessed whether DCI was an optimal therapeutic approach for a range of cancers, including pancreatic, lung, colorectal, melanoma, thyroid, sarcoma, breast, ovary, liver, and neuroblastoma, among others. Targeting this range of tumor models was essential to determine which types of cancer may be addicted to the MAPK pathway and responsive to the DCI mechanism of action. Data from preclinical studies showed the company's lead product candidate, called IMM-1-104, resulted in comparable to greater tumor growth inhibition versus standards of care and was well tolerated.

Building on this research, Immuneering recently announced the first-ever use of DCI in humans. Positive initial PK, pharmacodynamic (PD), and safety data from a Phase 1/2a clinical trial of IMM-1-104 were presented at the American Association for Cancer Research (AACR) Annual Meeting in April 2023 showing that DCI has potential applications across a number of RAS-mutant solid tumors.[11] The Phase 1/2a clinical trial was designed to evaluate the safety, tolerability, PK, PD, and preliminary efficacy of IMM-1-104 in patients with RAS-mutant advanced or metastatic solid tumors, including pancreatic, colorectal, lung, and melanoma. Results from the trial presented at the AACR meeting included the following:

- Significant PK $C_{max}$ levels (the plasma concentration of therapy) observed with IMM-1-104 of >2,000 ng/mL (or approximately 1-μM drug free-fraction at 160 mg once daily oral dose).
- >90% PD inhibition of phosphorylated extracellular signal-regulated kinase (pERK) with IMM-1-104 compared to pre-treatment baseline for patients at the third dose level (160 mg once daily oral).
- A median plasma half-life of 1.94 hours observed with IMM-1-104 across the first three dose levels evaluated (40 mg, 80 mg, and 160 mg once daily oral), in patients with pancreatic and colorectal cancer with different RAS mutations, including KRAS-G12D, the most common mutation present in pancreatic cancer.
- IMM-1-104 was well tolerated with no dose limiting toxicities.

Immuneering announced completion of the dose escalation portion of the Phase 1/2a trial of IMM-1-104 in June 2023, achieving this important milestone ahead of the company's original timeline.[12] Additional safety data are now expected in early 2024.

## ACCELERATING THE DCI MECHANISM

The company's second development program IMM-6-415 has also demonstrated preclinically the potential to broadly target MAPK-dependent cancers regardless of the underlying mutation in RAS or RAF. IMM-6-415 is designed to target RAS- and RAF-mutant tumors through DCI of the MAPK pathway, with an accelerated cadence enabled by an exceptionally short therapeutic half-life. While IMM-6-415 has a shorter half-life (about 20 minutes in mice) than IMM-1-104 (about 2 hours in humans) it is still shown to inhibit RAS- and RAF-mutant tumor models. Despite their design differences, the goal of IMM-6-415 and IMM-1-104 is the same – to deprive cancer cells of the continuous pathway signaling they need to rapidly grow and divide while providing

healthy cells with the intermittent signaling they need to function.

Promising preclinical data highlighting the therapeutic activity of IMM-6-415 were presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics in October 2023.[13] Researchers at Immuneering assessed IMM-6-415 alone and in combination with encorafenib, a BRAF inhibitor approved for the treatment of melanoma and certain types of colorectal cancer, in a series of preclinical models of RAS- and RAF-mutant disease. Results showed the following:

- >60 humanized 3D-TGA models, including 30 BRAF class I-mutant tumor models, showed a high sensitivity profile for IMM-6-415 in a wide range of MAPK-driven tumor types, including models of RAS- and RAF-mutant disease.
- As monotherapy, IMM-6-415 demonstrated anti-tumor activity in over 50% (34 of 66) of the 3D-TGA models tested, including 30 BRAF mutant preclinical models in which 19 (63%) showed activity.
- Monotherapy treatment with encorafenib or IMM-6-415 displayed superior tumor growth inhibition (TGI) compared to binimetinib in melanoma and colorectal $BRAF^{V600E}$ tumor models.
- IMM-6-415 in combination with encorafenib achieved greater TGI in vivo than encorafenib plus binimetinib in $BRAF^{V600E}$ colorectal cancer and melanoma tumor models. For reference, the combination of encorafenib plus binimetinib was recently approved by the US FDA for the treatment of adults with $BRAF^{V600E}$ metastatic non-small cell lung cancer.[14]

These data suggest that DCI of the MAPK pathway with an accelerated cadence is active in tumors caused by RAS and RAF mutations and further support the potential of IMM-6-415 as monotherapy or in combination regimens to treat solid tumors. Immuneering anticipates filing an investigational new drug (IND) application for IMM-6-415 in the fourth quarter of 2023.

## THE FUTURE OF CANCER TREATMENT

By challenging the conventional 24/7 inhibition paradigm, DCI has the potential to redefine the treatment landscape for RAS- and RAF-mutant cancers. It offers a novel and potentially more effective therapeutic strategy with improved tolerability. As with all new approaches in the treatment of cancer, support must be deeply rooted in data. The DCI mechanism is supported by extensive preclinical and now clinical data demonstrating its potential to be translated on a larger scale.

Immuneering's progress in understanding the DCI mechanism can also present opportunities to rethink treatment methods in other areas. The approach is not limited to MEK inhibition. It could potentially be applied to additional targets or pathways that: 1) are inappropriately activated in a disease state; 2) demonstrate a biologic addiction to sustained signaling; and 3) allow the DCI cycle to align with underlying disease biology. Immuneering will continue to follow the data to expand and optimize the potential of DCI to play a role in treatment of a broad range of cancers in the years ahead. ◆

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**Dr. Ben Zeskind** is Co-founder and Chief Executive Officer of Immuneering Corporation, a public, clinical-stage oncology company dedicated to developing medicines for broad populations of cancer patients, and has served in these roles at the company since February 2008. He earned his SB in Electrical Engineering and Computer Science, his PhD in Bioengineering from Massachusetts Institute of Technology (MIT), and his MBA from Harvard Business School, where he was recognized as a Baker Scholar, the highest award for distinction.

# CLINICAL TRIALS

## The Power of AI in Overcoming Patient Diversity Challenges

By: Isaac Bentwich, MD

### INTRODUCTION

Clinical trials continue to be a major stumbling block in the drug discovery and development life cycle. A stumbling block so overwhelming, current pharmaceutical practices do not even provide a 50% shot of success. In fact, clinical trial success rates do not even top 10%; there is an abysmal 90% failure rate for novel drugs in clinical trials, meaning only 1 out of every 10 drug candidates. There is no question the novel drugs that manage to work their way through to market make a critical impact, but those life-changing – and often life-saving – drugs are too few and far between.

The following explores why patient diversity is such a challenge for clinical trials, where that pain is often felt the most, some of the regulatory, technological, and industry changes already underway to solve the clinical trial gap, and where artificial intelligence (AI) changes the future of patient diversity.

### THE ROOT ISSUE

Clinical trials serve as the primary pre-market evaluation step for novel drugs that have made it through the time- and cost-intensive preclinical phase. Unfortunately, the traditional drug development process puts novel drug candidates at a significant disadvantage before they even make it to clinical trials. Still overwhelmingly tied to the faulty animal/mouse model, the data used to advance novel drug candidates into the clinical trial phase relies on animal studies.

In the words of Nobel Laureate Aaron Ciechanover, MD, DSc, "One of the main problems in drug development is the model that we are using – the mouse. We are not mice, so what works in animal-based trials is not a proper indicator of what will work for people."

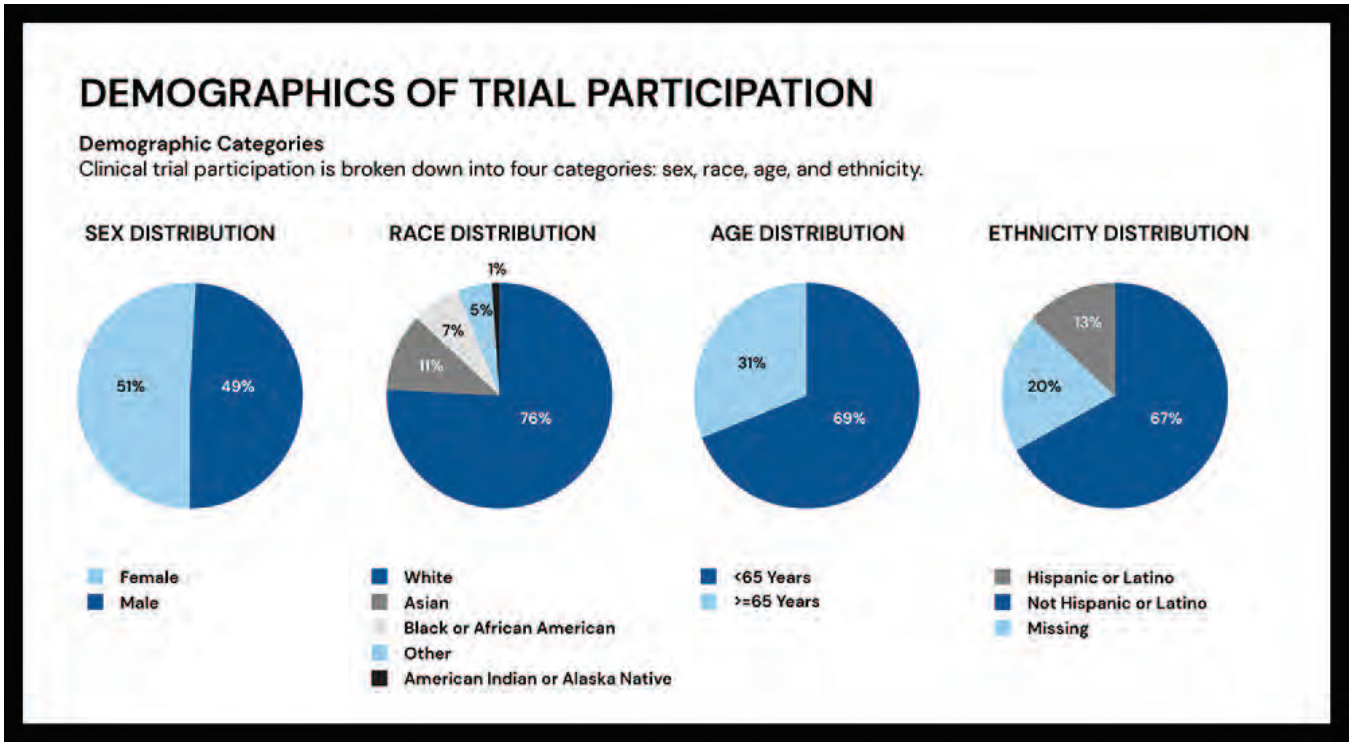
Yet despite the incredible failure rate consistently demonstrating its limitations, animal models have reigned as the preclinical kings for 80+ years due to animal testing requirements mandated by outdated regulations. Even predictive models based on mice that show promise at predicting lethal doses of drugs struggle to effectively screen for likely side effects. Some studies have even compared the variations by animal species for predicting compounds' metabolic behavior in humans. There are simply too many critical differences in the organ systems as well as the composition, expression, and catalytic activities of drug-metabolizing enzymes to effectively extrapolate data from animal models to humans.

### THE PRIMARY PATIENT DIVERSITY PAIN POINT

For the drug candidates that make their way to trial, patient diversity is the primary pain point. And much like the limitations of relying on animal models in the preclinical phase, the diversity dilemma has been a decades-long issue. Early clinical trials often relied solely on white male participants, and the problem is not going away. Worse yet, this is a global issue; an in-depth study of trials across 29 countries between 1997 and 2014 found that participants were almost 90% white. Yet, racial/ethnic minorities are 1.5 to 2 times more likely than whites to suffer from major chronic diseases.

The dearth of diversity creates major gaps in the resulting clinical trial data as those trials typically fail to properly represent the individuals most affected by the specific disease or condition the drug was intended to treat. The groups who likely stood the

FIGURE 1




best chance to benefit from the drug, whether by a combination of age, biological sex, race, sexual orientation, or other risk factors like medical history or environmental conditions, were woefully underrepresented in many trials. If a trial underrepresents certain groups by design or mere oversight, the resulting knowledge gap severely limits the ability to pinpoint optimal treatments, fully understand potential risks, and properly determine safe use cases.

Disappointingly, the disconnect between trial participants and future patient demographics still runs rampant today. Recent studies continue to confirm that white participants are overrepresented in all types of clinical trials, and the lack of diversity extends to sex, age, etc. as well (Figure 1). Despite decades of advancements in our understanding of the need for patient diversity in trials, advocacy efforts, and regulatory changes to try to make trial data more representative of the long-term treatment demographic, most clinical trials still fail to meet patient diversity demands.

According to Raeka Aiyar, PhD, of The NYSCF Research Institute, "Many minoritized populations have been excluded from research. And as a result, we have a biased understanding of disease and treatments that do not work for everyone who needs them. A black woman is 22% more likely to die from heart disease than a white woman, and 71% more likely to die from cervical cancer," she continued. "Before COVID, less than 5% of NIH funded respiratory research reported inclusion of racial or ethnic minorities."

When researchers actively try to recruit a more diverse trial set, they still often find members of minority groups – be it by age, race, ethnicity, or gender – are more reluctant to participate. Often it is driven by a lack of awareness in underinsured populations. Access, resource, and visibility limitations aside, fears of discrimination, unethical treatment, exploitation, job loss, or financial ramifications also contribute to inadequate participation. Regardless of the cause(s) of the continued lack of diversity in clinical trials, the ramifications are far-reaching and life-threatening as some treatments can be rendered ineffective or deadly when that demographic group is not included in trial data. Biological differences can change how patients will respond to certain drugs or therapies – making a treatment more or less effective, or even more or less toxic, for one group than another.

The absence of diverse research impacts patients and treatments in many ways; asthma is one easy-to-understand example. "In the Bronx, we talk about 'ABCD' being the priorities in terms of healthcare: asthma, blood pressure, cancer, and diabetes," noted John Greally, PhD, DMed, Montefiore Hospital, Albert Einstein College of Medicine, in the same NYSCF webcast. "The treatment of asthma using the standard bronchodilators that relax the muscles of the airway and prevent spasm work much better in some ancestry than others. The non-responsiveness

to albuterol, which is our first line treatment, is about 47% of people who identify as African American and 67% of Puerto Rican kids. It's about 20% for people who are Northern European white. Unless we study [diverse groups], we're not going to understand where we could be doing harm with these sorts of medications."

Perhaps a silver lining for the future of drug research and development, the pandemic confirmed the need for clinical trial diversity and health equity, making it a medical and media priority. In response to the continued lack of diversity, the FDA issued draft guidance for the industry, focused on developing plans to enroll more participants from underrepresented racial and ethnic populations into US clinical trials. Adding to the regulatory push, the omnibus spending bill was enacted (Public Law 117-328) requiring diversity action plans for the clinical trials used by the FDA to decide whether drugs are safe and effective. The National Institutes of Health even recently released its Minority Health and Health Disparities Strategic Plan 2021-2025, which focuses on improving diversity and inclusion in NIH-funded research through updated clinical trial policies and guidelines. Trial diversity has come to the forefront of the clinical approval process.

While the pandemic disproportionately affected racial and ethnic minority groups, Black or African American, American Indian or Alaska Native, Hispanic or Latino, and older adults were underrepresented in early U.S.-based vaccine clinical trials. However, due to the intense public scrutiny and shockwaves of change the pandemic created throughout the medical research community, clinical trial sponsors eventually saw an increase in diversity among participants as a result of the pandemic. As researchers adopted a decentralized model that allowed for remote assessments and community-based recruitment, it eliminated the need for trial participants to be within close proximity to the testing center, which is a primary barrier for many minority groups.

As evident during the height of the pandemic, fully embracing recent advances in the pharmaceutical arena can push life-saving treatments into circulation faster. However, patients should not need to wait for the next global health crisis. Plagued by low patient access pools for trials and regulatory roadblocks, rare diseases certainly don't elicit the same urgency for review and approvals as pandemic treatments and vaccines.

When considering the patient diversity challenge in clinical trials, rare disease trials top the list. If finding strong, diverse trial patient pools for common health conditions like asthma, diabetes, or cholesterol concerns is tough, imagine the hardship of a diverse trial set that properly accounts for child/minority group representation for rare diseases.

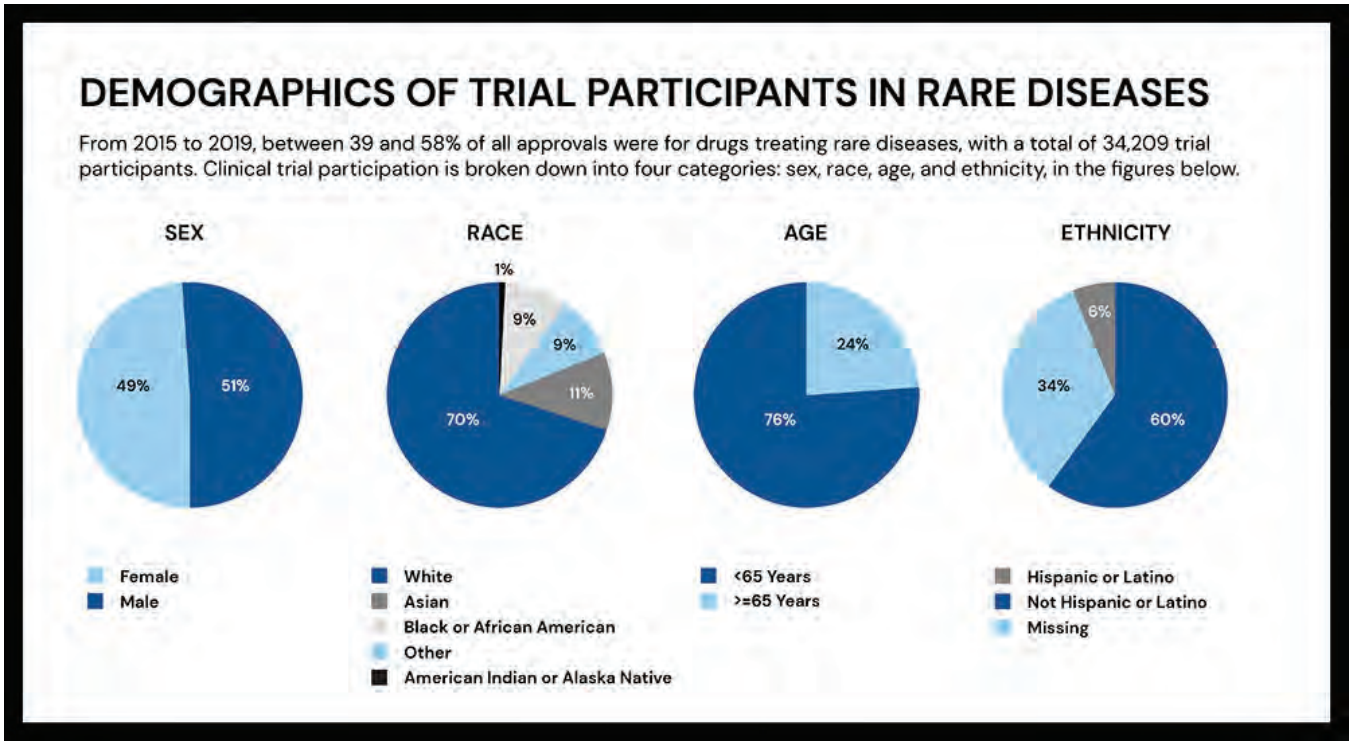
According to the National Organization for Rare Disorders (NORD), an estimated 350 million people worldwide have a rare disease. That includes 25-30 million Americans – half of whom are children. Taking an average of 5 years to reach an accurate diagnosis, many patients are then left with no options or hope as only 10% of rare diseases even have an FDA-approved treatment. Rare diseases generally receive inadequate funding and have even longer development and approval timelines, so life-saving treatments are either seriously delayed or never reach the market due to the extremely high cost and trial constraints. NORD's Rare Disease Video provides additional information, including the often overlooked fact that ALL pediatric cancers are considered rare diseases.

At the start of 2023, we marked the 40th anniversary of the Orphan Drug Act, which drove a push to develop and approve more than 550 drugs and biological treatments for 1,100+ rare disease indications since its inception, and the fifth anniversary of the Memorandum of Understanding Between the US Department of Health and Human Services, FDA, and NORD. However, much like how outdated regulations drove the continued reliance on animal-testing models, rare diseases cannot be left behind in the next era of drug development innovation. As our scientific knowledge evolves, so must our laws and our practices.

Unfortunately, federal mandates continue to threaten rare-disease breakthroughs, and minority groups face added treatment access barriers, according to Jenifer Ngo Waldrop, Executive Director of the Rare Disease Diversity Coalition. "What little federal funding goes toward rare-disease research often flows to conditions that primarily affect white Americans. For example, compare cystic fibrosis (CF), a lung disease with an outsized impact on white Americans, with sickle cell disease (SCD), which disproportionately affects Black Americans. The overall number of Americans with SCD is three times higher than the number with CF. Yet, a study found that government funding between 2008 and 2017 was nearly $2,000 higher per person for CF," Waldrop stated.

Looking at Figure 2, the lack of patient diversity in rare disease trials is stark – compounding the challenge for minority groups suffering from rare diseases. It is time to reshape rare disease drug discovery and development by embracing new

FIGURE 2




technologies and answering the call of patient-driven advocacy to accelerate future drug development.

## WAYS AI CAN FILL THE DIVERSITY GAPS

Since the FDA Modernization Act 2.0 was signed into law, a shift in the drug discovery and development model has begun. As the FDA no longer requires animal testing on drugs in development, the pharma industry is beginning to embrace valid non-animal drug testing methods and technologies. Furthermore, the House and Senate recently pushed for broader FDA integration of non-animal approaches and requested periodic reports on the progress of the removal of any remaining barriers to integrating non-animal methods.

The current technology transition will correct the root issue of the faulty animal-testing model and extend well beyond, into all aspects of trial data. Advances in artificial intelligence (AI) are primed to rapidly disrupt the entire drug development process by ensuring more expansive, diverse, and accurate trial data earlier in the process – helping to get new, safe drugs to patients sooner.

So how exactly can AI help overcome patient diversity challenges and speed up the introduction of safe drugs? Let's focus on four primary elements – trial site selection, patient recruitment and retention, stem cell diversity, and patient-on-chip platforms.

### Site Selection

Clinical trial site selection has always been challenging, but global crises like the pandemic and war in Ukraine created new obstacles. The need to still ensure trial participants accurately represent a diverse global population despite unpredictable setbacks infinitely complicates the process.

As manual search and curation of sources are painfully slow and inefficient, Natural Language Processing (NLP) can quickly integrate advanced searches, systematically analyze potential sites, and condense the selection timeline. To remove discriminatory biases, AI can help identify sites that will provide access to diverse, relevant patient populations if properly trained using a mix of clinical trial metadata, medical and pharmacy claims data, and patient group membership data. Creating the proper cohort composition often depends on the site selected; cognitive computing has been effectively used to match trial cohort sites at the Mayo Clinic. To remove discriminatory biases, AI can also be taught to consider which sites minimize enrollment and participation barriers.

Another option when site selection challenges seem insurmountable, especially with rare diseases, is to consider decentralized clinical trials (DCTs). DCTs often invite more diversity as they allow more flexibility and reduce transportation barriers as some components of the trial –

be it drug delivery, imaging, electronic surveys, and remote patient monitoring (RPM) – take place remotely rather than at a primary trial site. AI could improve the patient experience in DCTs through reinforcement learning, computer vision, and AI models designed for temporal data to improve user interfaces and engagement as, despite the added flexibility, DCTs place more responsibility on participants and shortcomings in digital health user interfaces can put retention at risk.

### Patient Recruitment and Retention

Once a site is selected, AI can ease core clinical trial design headaches – from patient recruitment to patient monitoring and retention. Recruitment is a costly, time-intensive exercise, but doing it correctly is well worth the investment, as under-enrolled or unfinished trials create a ripple effect of additional costs and lost opportunity.

Unfortunately, 86% of trials do not meet enrollment timelines, almost one-third of Phase 3 trials fail because of slow enrollment and 40% of patients become non-adherent 150 days into a clinical trial. AI, in combination with wearables, sensors, and/or video monitoring solutions, can alleviate some of the tedious, patient-driven self-monitoring tasks like disease diaries and logging while also collecting more reliable data. In the years ahead, generative AI tools will become part of the clinical trial toolkit to automate the patient identification/eligibility process, personalize recruitment messaging, and track patient care and progress – ensuring diversity along the way.

### Stem Cell Diversity

The science behind stem cell development and usage has significantly evolved. The ability to create miniaturized organs called organoids, representing a specific patient profile, is rapidly becoming more common, reliable, and affordable. Due to the massive cost reduction in developing human-induced pluripotent stem cells (iPSC), thousands of patient-specific stem cells and organoids can be created with ease, while disease models based on human iPSCs have also advanced.

But what does this mean for patient diversity and where does AI fit in? Stem cells, or more specifically the organoids or full patient-on-a-chip organ systems developed from the stem cells, hold the key to unlocking clinical trial diversity.

"Increasing the diversity of stem cell biobanks presents a key opportunity to ensure disease research captures the full diversity of humanity and benefits all communities in need," Dr. Greally told the NYSCF. "What we can and should do in terms of research is to try to bring the same amount of genomic insights to all populations so that we can provide the same care to everybody, no matter their ancestry."

### Patient-on-a-Chip Platforms

Patient-on-a-Chip platforms combine the power of AI and stem cell science. Integrating machine learning with patient-on-a-chip technology, interconnected miniaturized versions of human organs created from stem cells, provides a more accurate model of how a specific drug will react in the human body. An advanced patient-on-a-chip platform can test known drugs on thousands of genomically diverse patients-on-a-chip. To optimally train the machine learning, the known drugs (clinically safe ones and unsafe ones) must be tested on hundreds or thousands of different individual patients-on-a-chip.

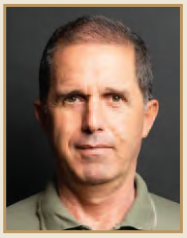
Advanced Bio-AI platforms can solve the core clinical prediction challenge – predicting, before expensive clinical trials, which drug candidates will work safely in the human body. Whether to determine drug toxicity or treatment viability for a specific patient in a personalized medicine approach or to build an entire clinical prediction platform on specific, yet diverse, patient profiles, this is arguably the most powerful application of AI in terms of clinical trial viability and patient diversity. These clinical trials-on-a-chip capture the full spectrum of drug responses, so the data generated can be used to train an AI model to not only accurately predict if a drug is safe, but also for whom. AI-powered patient-on-a-chip platforms create access to a diverse trial participant pool without the geographic or social constraints that may limit conventional clinical trial models. To start, this is most helpful in the preclinical trial phase as it weeds out the drug candidates that won't work while providing a more diverse data set to confidently move certain candidates forward into the clinical phase.

## THE FUTURE OF AI & PATIENT DIVERSITY

AI has the ability to support patient diversity efforts. Its application at various stages of the drug discovery and development life cycle will provide tremendous ongoing benefits to stakeholders throughout the drug ecosystem. However, the most important benefit is to potential patients. While applicable to all ailments, rare disease patients will benefit most from AI's

ability to better predict clinical safety and efficacy without animal trials from a diverse data set, significantly accelerating new drugs' path to market. ◆

## BIOGRAPHY



**Dr. Isaac Bentwitch** is the Founder and CEO of Quris-AI. Prior to Quris-AI, he founded and led three bio-AI technology companies, each of which led revolutions in medicine, genomics, agriculture, and conservation. He is a physician and entrepreneur with a passion for leading interdisciplinary teams of scientists and technologists to tackle impactful challenges in the intersection between machine-learning and life-sciences; and to leverage and commercialize the resulting solutions. One of the companies he founded was Rosetta Genomics, which analyzed the human genome. He led the team at Rosetta Genomics in the discovery of hundreds of novel genes, more so than all the universities in the world combined, and delivered novel cancer diagnostics based on these genes. Its subsidiary, Rosetta Green, was acquired by Monsanto for $35M. Under his leadership, team members at Rosetta went on to lead artificial intelligence at IBM, Google, and Microsoft. Now, at Quris-AI, he and his team are using a similar bio-AI approach to disrupt the drug development process.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# SUPPLY CHAIN VISIBILITY

## New Tracking Technologies Driving Improvements to Reduce Drug Shortages, Expedite Recalls, Protect & Inform Patients

By: Tracy Nasarenko, MBA

### INTRODUCTION

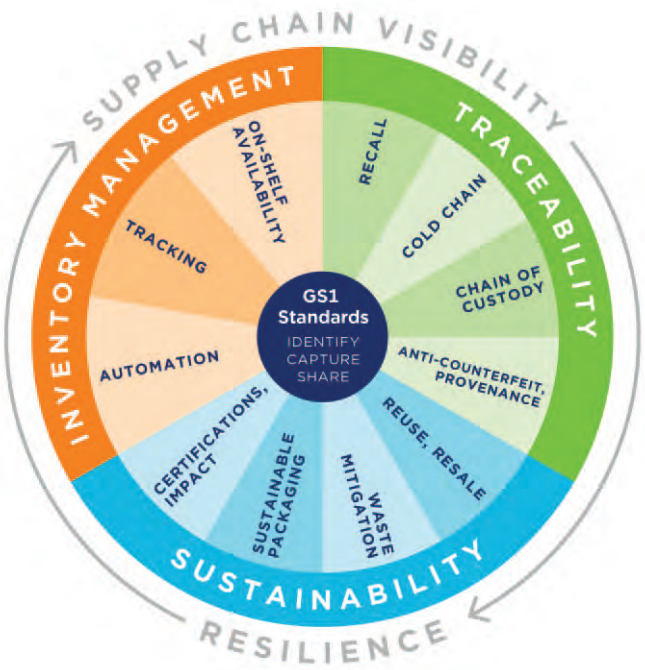
Supply chain issues continue to plague the healthcare industry, creating delivery delays and product shortages that can interrupt and seriously compromise patient care. Imagine cancer patients, for example, having to stop chemotherapy before the prescribed course of treatment is finished because the necessary drugs are unavailable. If you know someone in this predicament, you're not alone.

Drug shortages in the US are at an all-time high, with no relief in sight. Solutions are urgently needed to improve supply chain visibility – the ability to "see" where products are located at any point in time during their life cycle – to infuse product stability and help ensure necessary supplies are available when and where they are needed.

To that end, healthcare industry leaders have been working together to upgrade existing supply chains with long-term, sustainable solutions. New technologies are being leveraged along with industry standards to enable full visibility across the entire supply chain, tracking products all the way from manufacturer to end user. Among them are new, advanced data carriers – capable of holding vast amounts of product information within a tiny footprint on a product label – including two-dimensional (2D) barcodes and improved radio-frequency identification (RFID) tags.

### DIGITAL IDENTIFICATION IS THE CORNERSTONE OF TRACEABILITY

Unique product identification is the first building block for track-and-traceability. Encoding a standardized, digital identifier on the product label marks that item and differentiates it from all others. For pharmaceuticals, the identifier is a National Drug Code, embedded in a standardized GS1 Global Trade Item Number® (GTIN®). The US FDA's Drug Supply Chain Security Act (DSCSA) requires the product identifier plus serial number, lot number, and expiration date to be included in a 2D barcode (eg, GS1 DataMatrix) on unit-level pharmaceutical product packaging. Homogeneous cases must include either a 2D or linear (eg,



GS1-128) barcode.

GS1 US, a not-for-profit information standards organization, supports these efforts by providing a system of standards for identifying products, locations, and logistic units, thus enabling supply chain stakeholders like manufacturers, wholesale distributors, and dispensers to meet the DSCSA requirements. The standards-based data enables interoperable, electronic exchange between trading partners, required by the FDA to meet the final DSCSA deadline of November 27, 2023. (The FDA recently announced an enforcement delay until November 27, 2024).

DSCSA is aimed at improving drug traceability and is primarily focused on trace-back to swiftly address issues that could potentially affect patient safety. If a product is suspected to be or deemed illegitimate, understanding the journey of a product at the serialized unit-level enables the identification of vulnerable points within a supply chain where counterfeit drugs can be inserted. Additionally, enabling fast identification and pinpointing the location of products that are recalled, withdrawn, or expired facilitates quick, precise removal from the supply chain to prevent those drugs from being used or sold.

## COLLABORATION ACROSS THE SUPPLY CHAIN IS KEY

The supply chain benefits of using 2D barcodes for tracking and tracing can only be realized when all trading partners are aligned on standards and capabilities. Manufacturers are advised to discuss their 2D transition plans with key trading partners, including distributors, wholesalers, third-party logistics providers, healthcare providers, and pharmacies. Potential impact, cost, and benefits of implementing 2D barcodes should be understood for every point where the product is touched – from manufacturing through distribution, storage, and end use.

Optical scanners are needed to automate data capture from the barcode so that all stakeholders can access, ingest, utilize, and share information about the products' movement all the way through the supply chain. This enables all parties to confirm transactional events (shipping, receiving) and locations to enable real-time visibility – the products can be tracked down to an exact location and status at any point in time by any of the connected trading partners. Locations are identified with Global Location Numbers (GLNs). The record of transactional data detailing the movement of products through the supply chain can be created and shared with the use of GS1's Electronic Product Code Information Services (EPCIS) standard, as recommended by the FDA for DSCSA.

With such alignment, benefits are also spread across the whole network. From inventory visibility to shipping/receiving awareness, to operational efficiencies and cost savings, and most importantly patient safety – all can be positively impacted by a smoothly run supply chain supported by digitally interoperable, complete records of product manufacture, distribution, and use.

## 2D BARCODES OFFER PRODUCT TRANSPARENCY ALL THE WAY TO THE PATIENT

Medications are dispensed in healthcare facilities as well as in retail pharmacies and, in the case of OTC drugs, other retail outlets. It makes sense for the traceability mechanisms to also cross channels, and using 2D barcodes makes that possible. Product identification and verification is necessary throughout the entire supply chain for DSCSA even at small, independent pharmacies or individual practitioners who are acting like dispensers, which can be challenging. Industry leaders have provided assistance in the form of assigned GLNs to bring these locations into the traceability information loop.

The benefits do not stop at the hospital or store, however. The utilization of 2D barcodes is further driven by consumers' growing demand for detailed product data. The expanded capacity of these barcodes enables brands to encode critical product information and to additionally embed a wealth of information, such as ingredients, interactions, contra-indications and side effects, dosing recommendations, and even research results documenting efficacy and outcomes. Links to all that data can be embedded in a 2D barcode and scanned by the consumer with a smartphone. This may be especially useful in pharmaceutical products that are sold at retail. Products could someday even proactively notify users, such as a pill bottle reminding a person to take their daily dose.

Furthermore, the adoption of automatic data capture at the point of care through 2D barcodes streamlines clinical workflows, saving time for clinicians and allowing them to focus on patient care rather than manual data entry into inventory sheets and electronic health records. This technology offers increased accuracy and clinical efficiencies, serving as a valuable cost containment measure for healthcare providers.

## NEW & IMPROVED RFID TECHNOLOGY IS GAINING TRACTION

Until recently, RFID has not been considered useful for the healthcare supply chain due to prohibitive costs and technological limitations. But today, new and improved RAIN RFID technology, which uses the UHF band, is generating new attention and a fresh look.

Fast, automated scanning of multiple units, even without a line of sight, can be achieved with RAIN RFID, offering improved efficiency for scanning bulk products in distribution. An RFID reader can scan entire shipments automatically and remotely in a fraction of the time it takes to manually scan individual cases or packages.

Fresenius Kabi, a healthcare company that specializes in life-saving medicines and technologies for infusion, transfusion, and clinical nutrition, became the first pharmaceutical manufacturer to embed medication identification data into an RFID tag in 2020, relying on GS1 Standards to permit full interoperability and compatibility. The company has been using these tags on specified products, including glass and plastic vials and syringes. They reported that using RAIN RFID tracking on medication inventory allows them to scan many drugs at once, more easily track expiry dates, and better maintain tighter inventory levels.

RAIN RFID cannot serve DSCSA requirements on its own; instead, it is considered useful in conjunction with 2D data matrix barcodes. The RAIN RFID tags provide an added layer of protection for pharmaceutical integrity in patient care, while saving healthcare providers time and providing precise inventory control throughout the product's life cycle.

Using GS1 Standards makes the RFID tags readable anywhere, allowing the industry consistency and delivering on interoperability. To ensure all recipients of RFID-tagged products can decode and understand the product information, healthcare industry stakeholders worked together to identify how manufacturers should encode and provide a "roadmap" to assist the industry in adoption. *The Implementation Guideline for RFID in Healthcare Manufacturing: Using GS1 Standards to Enable Visibility and Efficiency* document defines the application of GS1 Standards to support adoption of RFID by healthcare supply chain stakeholders. It informs pharmaceutical and medical device manufacturers about how to encode RAIN RFID tags using GS1's Electronic Product Code (EPC) schemes outlined in the EPC Tag Data Standard (TDS) for automatic data capture to be utilized across the healthcare supply chain.

## SUMMARY

Supply chain visibility is crucial in the healthcare industry, perhaps more than in any other marketplace. The ability to know where products are located at any moment in time across the entire supply chain helps all stakeholders improve inventory management, reduce stockouts, and streamline logistics operations. It gives providers and dispensers a chance to make adjustments when necessary, such as finding new alternative sources or substitute products as efficiently as possible. And it enables full traceability for product authentication, provenance, and removal in the case of a recall or product expiration.

The challenges of today's evolving markets and healthcare infrastructure demand new, digitally interconnected solutions that can be shared across increasingly complex supply chains. Two-dimensional barcodes offer wide-ranging benefits and are needed to satisfy the traceability requirements of DSCSA, while new and improved RAIN RFID technology holds promise for operational efficiencies that can help pave the way to faster, more reliable delivery of drugs, helping maintain the integrity of our healthcare systems. ◆

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### BIOGRAPHY

**Tracy Nasarenko,** Senior Director of Community Engagement at GS1 US, is an accomplished leader with more than 20 years of experience in healthcare and pharmaceutical supply chain, finance, product management, marketing, and operations. In her current role, she leads a collaborative pharmaceutical industry group focused on addressing supply chain challenges and meeting the requirement of the Drug Supply Chain Security Act (DSCSA). Using GS1 Standards, the most widely used supply chain standards in the world, she guides the implementation of these standards to help the pharmaceutical industry deliver safe products to patients. Prior to joining GS1 US, she held several leadership positions with SPI Pharma Inc. Most recently, she served as a site general manager, overseeing end-to-end operations and performance of the entire team, where she built a culture of engagement, innovation, and collaboration. She earned her Bachelor's degree from Villanova University and her MBA from West Chester University.

# PHARMACOVIGILANCE AUTOMATION

## Improving CRO Efficiency Through Automation

By: Emmanuel Belabe

### INTRODUCTION

Big Pharma drives demand for contract resource organizations (CROs) by outsourcing up to 45% of research and development (R&D) activities. The global biotechnology and pharmaceutical services outsourcing market is set to grow to $108 billion by 2030 to meet these rising demands, putting pressure on CROs.

Many CROs believe they've reached a breaking point as they work to keep up with rising case volumes, data complexities, and changing regulations. To combat these pressures, CROs need access to modern pharmacovigilance (PV) automation that promotes flexibility, scalability, efficiency, and cost-effectiveness.

### TRADITIONAL SAFETY PROCESSES AREN'T ENOUGH

Many CROs rely on tedious, outdated manual methods to handle the influx of safety data and process cases. Those traditional workflows make it more challenging for CROs to accomplish the following essential tasks:

**Efficiently Process Data** - The first steps in safety case processing involve extracting safety case attributes from source documents and populating that data into a database. Traditional, manual approaches typically require PV teams to carefully read incoming documents and forms before re-keying the data into a case-intake system. This process involves expending manual efforts on redundant data entry and requires multiple stages of manual reviews and quality checks, resulting in an error-prone and monotonous data entry flow.

**Scale Cost-Effectively** - Traditional workflows impair a CRO's ability to process hierarchies, adjust to changes in volume, and introduce new services. In turn, this drawback makes it harder to scale operations and become a one-stop-shop vendor. While using legacy systems, CROs have to throw more human resources at increased case volumes, which isn't sustainable long-term.

**Identify Safety Signals** - Discovering safety signals is a critical aspect of pharmacovigilance. A manual review of individual cases or data may make it challenging for PV teams to efficiently identify patterns, trends, or potential safety concerns. Organizations may miss essential signals or face delays in detecting and acting upon emerging safety issues.

**Meet Complex Global Operations** - PV operations are subject to strict regulatory requirements and reporting obligations. Traditional workflows may lack built-in compliance checks and automated reporting mechanisms, making it harder for CROs to ensure compliance with evolving standards and regulations. Reliance on manual processes can introduce errors, data inconsistencies, and delays in meeting regulatory deadlines.

By embracing modern tools and technologies, CROs can overcome these limitations and optimize their PV activities, leading to the delivery of more value to their clients.

### AN INDUSTRY NEED FOR AUTOMATION

Recent trends across the life sciences industry also create a need for faster and more accurate adverse events (AEs) reporting. Safety caseloads are increasing 15% year over year (YOY), on average. This increase can be attributed to a number of factors, including the following:

**Changing Regulations** - The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) continually update their safety data reporting requirements. Increased regulatory scrutiny to ensure patient safety will continue driving the need for more PV capabilities and for organizations to review and revise their safety cases.

**Rising Clinical Trial Complexities** - More clinical trials require larger patient populations due to the increasing prevalence of chronic diseases and the need for additional data to support the approval of new treatments and drugs. Larger patient populations make clinical trials more complex as PV teams manage and track a large number of patients. Clinical trials are also becoming more globalized, with CROs conducting trials across study sites in multiple countries. This reach requires coordination between different teams and compliance with varied regulations. Additionally, CROs are conducting clinical trials in numerous diverse therapeutic areas, which require a broader range of expertise.

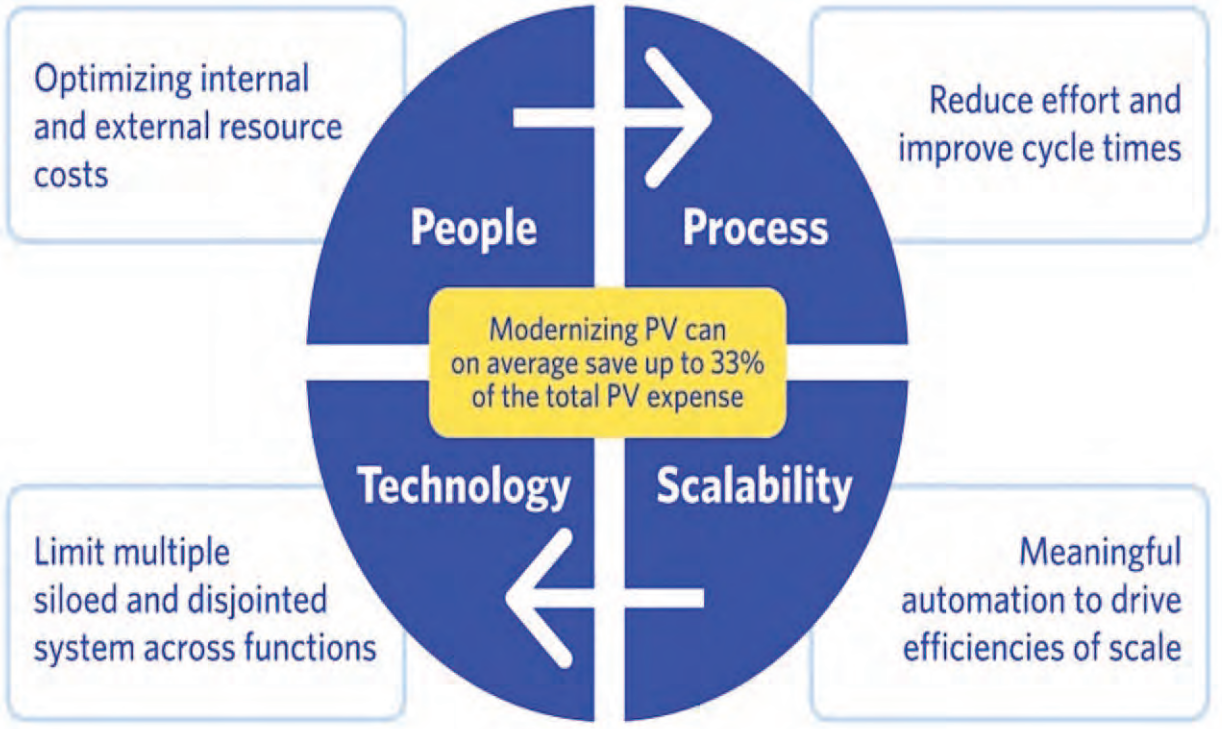
**Increasing Adverse Event Data** - More cases – or patients experiencing "an AE of interest" – are emerging during post-approval drug safety surveillance. During the monitoring of the safety and effectiveness of drugs currently available to the public, PV teams identify a need for preventive actions, like changes in product labeling information and, rarely, the re-evaluation of an approval decision.

Advanced technology in the life sciences industry also contributes to increased AE data. More organizations use electronic data capture (EDC) systems, allowing for the efficient collection of more data. Patients are also using social media platforms to report AEs. Social media empowers patients to take an active role in their health by providing an outlet to share their experiences with treatments. This unsolicited RWD systematically adds valuable context to signals found in reported AE data sets. However, because technology makes reporting easier, there's also a rise in the number of false or incomplete reports that need to be logged and processed.

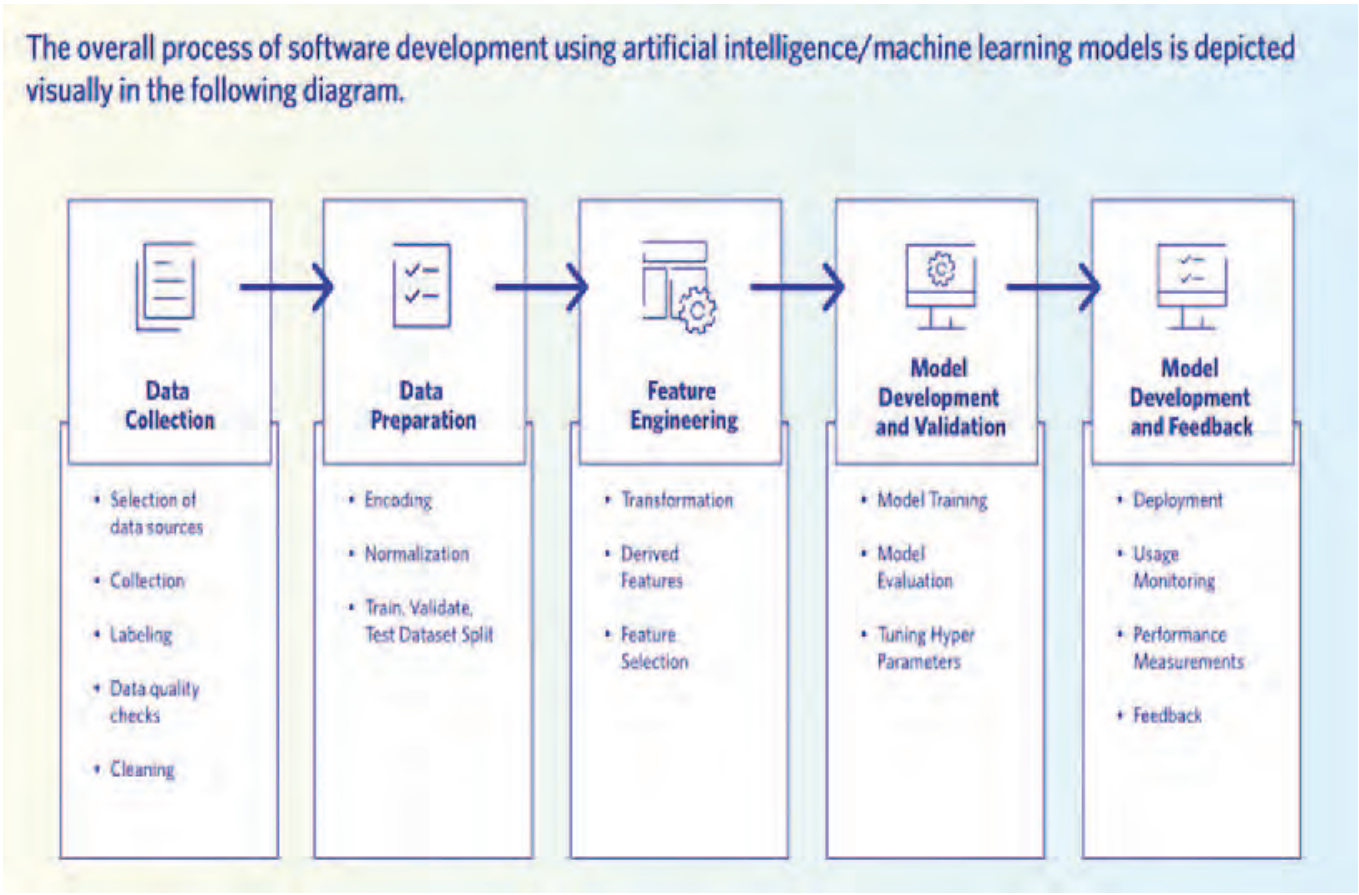
Given these challenges, CROs need intelligent and innovative technology to help with growing case volumes.

## DIFFERENT TYPES OF AUTOMATION

When considering which technology capabilities best align with their PV efforts, CROs should look at the following three types of automation:




**Modernizing Pharmacovigilance**




**Software Development Using Artificial Intelligence/Machine Learning Models**

**Rule-Based Automation** - Applies man-made rules to store, sort, and manipulate data. Rule-based automation best handles repetitive tasks, like duplicate checks.

**Knowledge-Based Automation, ie, Artificial Intelligence (AI), Natural Language Generation, or Machine Learning (ML)** - Unlocks insights into large data sets related to compliance and patient safety. Knowledge-based automation contains sophisticated algorithms that perform tasks requiring cognitive reasoning, visual perception, speech recognition, and decision-making.

**Knowledge-Assisted Automation, ie, Natural Language Processing (NLP) or Machine Translation** – Combines the power of automation with human insights and expertise to achieve more efficient and effective outcomes. Knowledge-assisted automation addresses increased case volumes and can better handle structured or unstructured case sources. Examples of knowledge-assisted tasks include causality assessments or literature database screenings.

Automation increases efficiency and provides benefits like greater process consistency, improved data quality, and the opportunity to shift resources to higher-value initiatives like PV analytics and benefit-risk assessment. However, technology shouldn't replace all the work humans do. Instead, it should act as a means to help humans do their jobs better and transform safety from a cost center to a strategic pillar of innovation.

## HOW AUTOMATION BENEFITS CROS

Before taking steps to implement automation, CROs should consider the advantages specific to their operations, which could include the following:

- Reducing manual efforts and repetitive tasks.
- Helping CROs comply with changing regulations while reducing the risk of inconsistencies and errors.
- Ensuring distribution protocols adhere to each region's regulatory requirements.
- Streamlining PV operations and reducing the expenses and time associated with linear data processing.
- Dissolving data silos that keep CROs from gleaning insights.

- Allowing data streams from other sources or systems to connect, leading to better risk assessment and decision-making.

In practice, CROs use automation to extract information from inbound data forms, discover relevant safety data points, and annotate those data points from literature articles. Leveraging automation to take care of those manual tasks frees PV teams to redirect their attention toward more valuable activities like understanding what those data points mean. Resources with high levels of specialization can be alerted when cases fall outside of predetermined thresholds, which require humans to make a decision using their judgment.

## CHALLENGES OF ADOPTING AUTOMATION

Automation can be a valuable tool for CROs, but automating PV workflows isn't always simple. CROs may have to navigate the following obstacles:

**Training** - PV teams must go through training to strengthen their knowledge of automated systems. This education can be a challenge if employees are under time constraints due to heavy caseloads or resist change due to a "we've always done it that way" mentality.

**Integration** - CROs must integrate automated systems with existing PV systems and processes that often involve multiple teams, which can be complex and time-consuming.

**Maintaining Data Quality** - CROs need clean, accurate, and complete data to ensure automated processes produce reliable results. The best safety solutions include intelligent automation pre-trained with an incredibly extensive data set.

**Ensuring Compliance** - CROs must ensure their automated systems comply with regulatory requirements, including those related to safety reporting and data privacy.

Despite these challenges, CROs can successfully adopt automation with careful planning and the right automated safety solution.

## SAFETY PRIORITIES FOR CROS

When replacing traditional workflows with a modern safety solution, CROs should seek a versatile cloud-based solution that enables a single source of truth for improved data quality. An automated end-to-end solution should include the following qualities:

**Flexibility** - Adapts to an organization's unique requirements with flexible configuration of workflows, dashboards, and reports.

**Speed** - Increases the rate at which specialized treatments effectively make it to market. With automation, CROs can see a 30% reduction in time to complete clinical site monitoring reports.

**Scalability** - Strengthens a full-service model with seamlessly scalable post-market safety operations.

**Efficiency** - Delivers more with the same resources with end-to-end production-ready automation. CROs can achieve up to 30% efficiency gains using automation solutions.

**Always Up-to-Date Global Compliance** – Expands a CRO's serviceable market with support for all current and upcoming regulatory standards.

Additionally, the fact that clinical trials are increasingly global can add to data challenges. A complete cloud-based clinical trial management system makes it easy for CROs to manage data centrally and thereby achieve cost savings.

## TIPS FOR ADOPTING AUTOMATION

After choosing the right safety solution for their needs, CROs can follow these tips for adopting automation:

**Assess Current Processes** - CROs should assess the specific needs and pain points within their PV operations. By understanding current processes, CROs can start to pinpoint areas where automation can bring the most significant benefits, such as data entry, case processing, or reporting.

**Start Small** - CROs shouldn't try to automate everything at once. Instead, PV teams can start with a few key processes and scale up as they gain experience. A slower pace keeps employees from feeling overwhelmed and facilitates successful automation adoption.

**Provide Training & Support** - CROs must provide comprehensive training to em-

ployees who will work with automation tools. Education is crucial to ensure staff members understand automation's benefits, know how it works, and can effectively leverage its capabilities. Ongoing engagement and communication throughout the implementation process will address concerns and promote buy-in from all stakeholders.

**Monitor & Evaluate** - PV teams have to continuously monitor and evaluate the performance of their automation solutions. Key metrics like processing times, error rates, compliance adherence, and resource utilization will help identify areas for optimization and improvement. Regularly assessing automation's effectiveness in achieving defined objectives will facilitate necessary adjustments.

**Embrace Continuous Improvement** - CROs should also continuously seek opportunities for improvement by leveraging feedback from users and stakeholders. Regular assessment of automation's impact on operations will identify areas for refinement or expansion. Embracing a culture of continuous improvement will maximize the benefits of automation in CROs' operations.

## SUMMARY

More CROs realize the powerful impact PV automation can have on their operations. In fact, nearly 75% of life sciences organizations say that the opportunity to have automated risk management and safety signal detection would be beneficial or even game-changing.

With automation, organizations can designate fewer resources to process and sift through the majority of cases and data. CROs realize better outcomes because PV teams can work faster and smarter with reliable data at their fingertips. ◆

## BIOGRAPHY

**Emmanuel Belabe,** better known as "Manny," has worked within ArisGlobal in a number of different roles throughout his 18 years with the company. During this time, he developed an approach that sought to educate clients on best practices for leveraging ArisGlobal products while advocating the best way to deliver additional value through the implementation of additional ArisGlobal solutions. This led to his current role of Product Owner for Safety Solutions, where he is responsible for implementing tightly integrated tools that fit within the company's vision of providing a unified platform across all R&D domains.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# ARTIFICIAL INTELLIGENCE PLATFORM

## Advancing Precision Medicine With bfLEAP™: Next Generation AI for Drug Development

By: Thomas Hazel, PhD, and JT Koffenberger

### INTRODUCTION

In the ever-evolving landscape of drug development, the pursuit of precision medicine has gained tremendous momentum. This approach aims to revolutionize healthcare by tailoring treatments to individuals based on their unique genetic makeup, lifestyle, and environmental factors.

BullFrog AI (NASDAQ: BFRG) is a digital technology company that is leveraging the potential of artificial intelligence (AI) and machine learning (ML) to advance this field and improve success rates in drug development. AI and ML have emerged as game-changers in the drug discovery and development industry, enabling computers to analyze vast amounts of complex data, identify patterns, and extract valuable insights for drug developers and clinicians. These technologies hold promise for revolutionizing patient care and advancing more effective therapies to market faster. Why is this so important?

- Getting a drug to market can take close to a decade, with a cost of $0.8 to $2.8 billion, while patients are desperately waiting for treatments that often don't come.[1]
- Almost 90% of drugs fail at some point along the way.[2]

BullFrog AI is focused on changing this narrative using bfLEAP™, an AI platform exclusively licensed from the prestigious Johns Hopkins Applied Physics Laboratory (APL) for biological and chemical pharmaceutical therapeutics applications. bfLEAP is a robust platform that can help to rapidly detect anomalies and uncover hidden associations within patient data, making it a powerful tool with the potential to help researchers predict drug responses and identify patient subgroups.

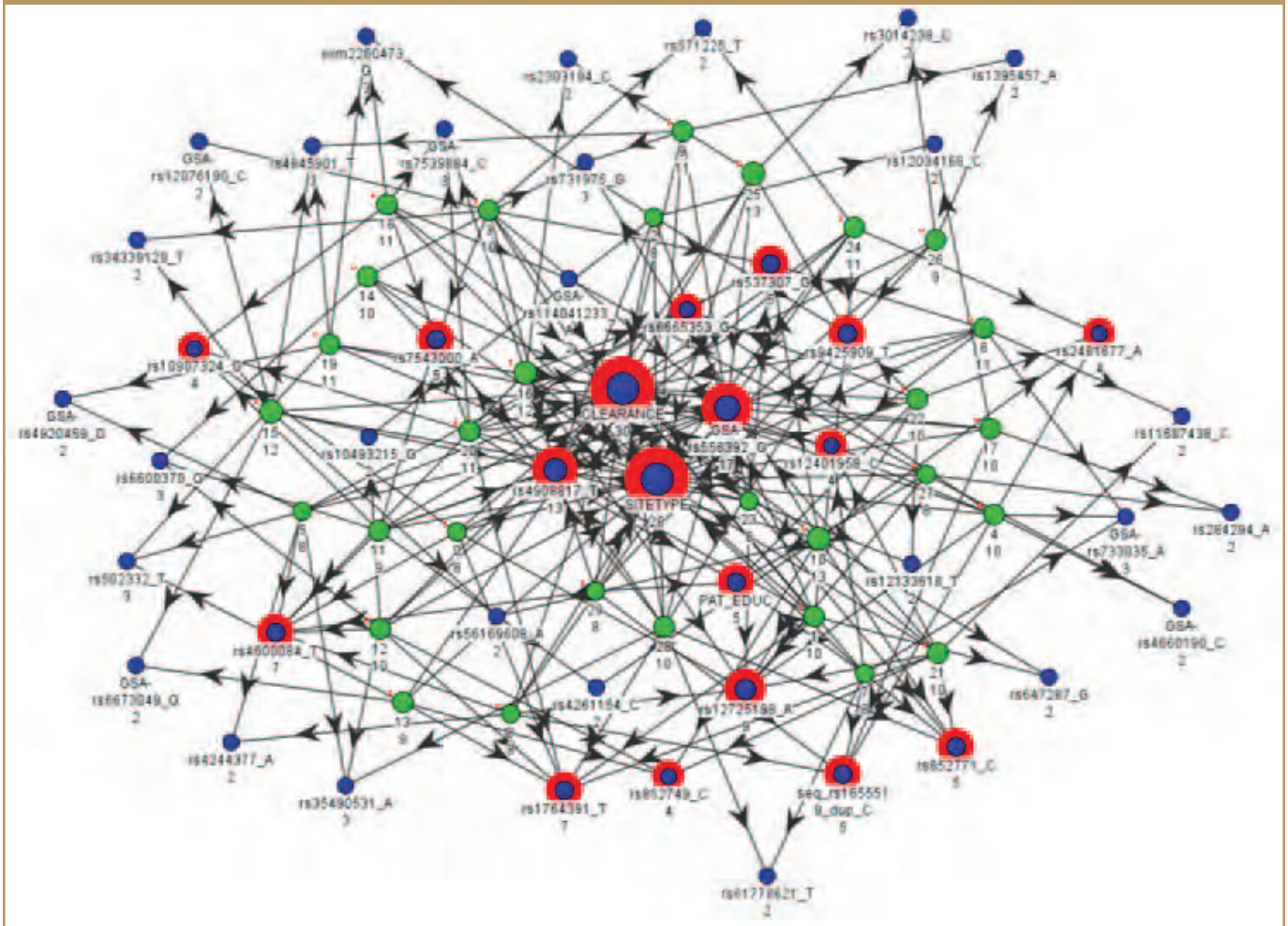
With an advanced technical architecture, bfLEAP solves numerous scalability and flexibility challenges, facilitating the comprehensive analysis of diverse and complex data sets. Using unsupervised ML algorithms and proprietary clustering techniques, the platform identifies potentially meaningful and understandable information, paving the way for the creation of personalized treatments, optimized clinical trials, disease progression predictions, and drug target identification.

The following explores the technical architecture and capabilities of bfLEAP, delving into its ML algorithms, proprietary clustering techniques, and visually understandable outputs. Additionally, some of the potential use cases for the platform in drug development and discuss future developments that hold tremendous promise are examined.

### TECHNICAL ARCHITECTURE - HIGH-THROUGHPUT, DATA-AGNOSTIC PROCESSING POWER

The true strength of bfLEAP lies in its highly efficient architecture. The platform is capable of handling either small, homogeneous data sets or large, complex data sets with equal ease. By overcoming the scalability and flexibility challenges that are commonly faced by researchers and clinicians, bfLEAP can provide a path to more efficient and comprehensive data analysis.

## FIGURE 1




**Through the display of nodes and edges that users can explore and interact with, weighted relationships between various factors are visually illustrated, facilitating an intuitive understanding of the data.**

One of the standout features of bfLEAP is its ability to handle incomplete data sets, an all-too-common occurrence in real-world clinical settings. Whether it comes from patient dropouts, missed appointments, technical glitches, human error, or other causes, researchers are frequently faced with data gaps upon study completion. By effectively incorporating and interpreting incomplete information, this platform ensures that valuable insights are preserved.

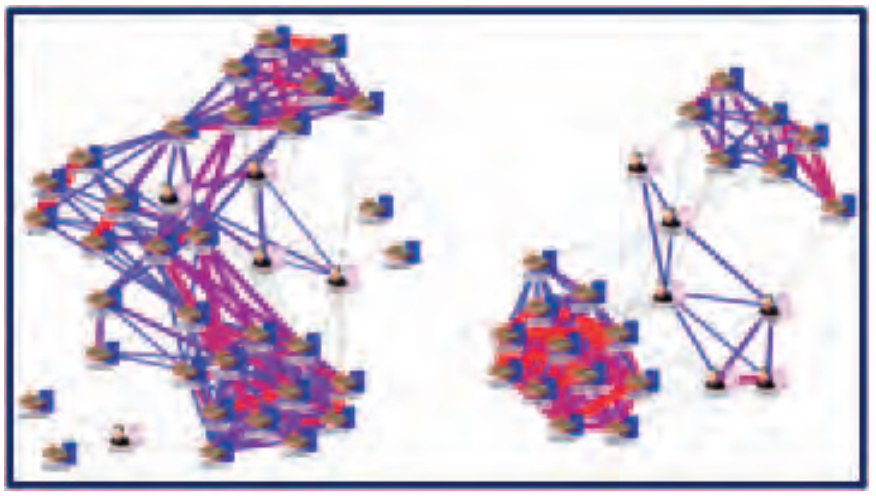
Data agnosticism is another key attribute of bfLEAP, allowing it to integrate, analyze, and interpret heterogeneous data sources. Whether inputs consist of medical records, demographics, genomic data, or real-world evidence, the platform's ability to integrate and process disparate data sets is a valuable benefit to users. This versatility enables a more comprehensive analysis, unlocking new possibilities for understanding even the subtlest relationships.

bfLEAP excels through its powerful high-throughput processing capabilities, fueled by the TinkerPop™ API for parallel computing. This enables the rapid analysis and interpretation of data, facilitating the accelerated identification of meaningful information and potentially enabling a more efficient drug development process. This will provide researchers and clinicians actionable insights on an optimized timescale, allowing them to make data-driven decisions quickly.

## UNSUPERVISED ML & PROPRIETARY CLUSTERING ALGORITHMS

The bfLEAP platform takes full advantage of the power of unsupervised ML algorithms to discover hidden patterns and relationships. Unlike supervised learning methods that rely on labeled data and predefined assumptions, its unsupervised ML approach allows bfLEAP to uncover patterns organically - without human intervention. This approach ensures important insights are not overlooked due to false or limiting assumptions.

## FIGURE 2



**Using unsupervised ML algorithms and proprietary clustering techniques, the platform identifies potentially meaningful and understandable information.**

One of the significant advantages of bfLEAP is its proprietary suite of clustering algorithms, all of which are designed to uncover unknown associations between key entities, regardless of data type or use case. This versatility and flexibility allow bfLEAP to open doors in drug development that may not have previously been known to exist.

With a total of over 200 analytic utilities and algorithms at its disposal, the bfLEAP platform provides a comprehensive toolkit for data analysis and clustering. These algorithms have been carefully selected and fine-tuned over time to deliver optimal performance with maximum efficiency.

Another important feature of the platform is its anomaly detection algorithm, a random subspace mixture model (RSMM). In a rigorous benchmarking study that analyzed 12 open-source data sets, this algorithm outperformed the top 10 currently used algorithms for anomaly detection.[3]

## EXPLAINABLE AI

Transparency and interpretability are essential qualities in AI platforms, though they are often lacking. This is particularly critical in domains such as drug development, in which the details of complex relationships - like drug interactions - are essential to comprehend.

bfLEAP addresses this issue through its layered processes and explainable AI approach. The platform provides critical context to the data outputs, allowing researchers and clinicians to understand the steps involved in generating insights. This purposeful transparency is designed to not only facilitate comprehension, but to also enable sponsors to validate and trust their results.

A key component of bfLEAP's "explainable AI" approach is its graph analytics output. This visual representation of relationships and correlations within the data greatly simplifies interpretation. Through the display of nodes and edges that users can explore and interact with, weighted relationships between various factors are visually illustrated, facilitating an intuitive understanding of the data. This important software feature enhances sponsor engagement, as it presents complex information in an easily digestible format.

Yet another advantage of bfLEAP's explainable AI approach lies in its minimal custom coding requirements. Apart from the initial data cleaning and ingestion process, the platform requires few adjustments, ensuring shorter lead times and consistent output interpretation. This ease of use and interpretability maximizes efficiency and allows the platform's full capabilities to be leveraged without the need for extensive programming expertise.

## POTENTIAL USE CASES IN DRUG DEVELOPMENT

The versatility of the bfLEAP platform offers numerous potentially impactful use cases within the field of drug discovery and development. The following lists some specific ways in which this platform can help provide meaningful impact in the clinical research field:

**Identifying Patient Subgroups to Better Predict Drug Response:** By analyzing patient data, bfLEAP can assist in the identification of distinct subgroups based on factors such as genetic information, biomarkers, demographic information, or a variety of other patient factors and characteristics. This can help researchers and clinicians predict drug response within specific patient subgroups, potentially facilitating personalized treatment approaches and improved patient outcomes.

**Informing Better Inclusion & Exclusion Criteria for Clinical Trials:** Designing effective clinical trials requires the inclusion of relevant patient populations while excluding confounding factors. bfLEAP can aid researchers in identifying significant patient characteristics, helping them to optimize inclusion and exclusion criteria. This helps ensure clinical trials are highly targeted, efficient, and yield robust results.

**Predicting Disease Progression:** By thoroughly analyzing longitudinal patient data, the bfLEAP platform can help researchers predict disease progression patterns. With this knowledge in hand, clinicians may be able to intervene at appropriate stages more effectively, facilitating early detection, proactive treatment, and improved disease management for patients. Further, they may be able to use this knowledge to better design the subsequent phases of their program.

**Identifying Pathways for Drug Application:** bfLEAP analyzes genomic data and gene expression data to uncover associations between networks of genes and proteins. By identifying these novel connections, the platform may help researchers discover important new targets and disease biomarkers. This enables the development of transformative therapies for unmet areas of patient need.

**Drug Target Identification:** By leveraging its comprehensive data analytics capabilities, the bfLEAP platform can assist researchers in identifying potential drug targets. By exploring intricate relationships and patterns within the data, the platform may help to expedite the drug discovery process and facilitate the development of highly targeted precision medicines.

**Drug Repurposing and Rescue:** The ability to recognize previously undetected patterns also creates the potential to revisit the efficacy of failed drug candidates or repurpose existing drugs for new indications.

## FUTURE DEVELOPMENTS FOR bfLEAP

As the landscape of drug development evolves, BullFrog AI remains committed to advancing bfLEAP and addressing this industry's growing needs. The platform's architecture is also designed to accommodate future developments, allowing for the seamless addition of bolt-ons to enhance its already impressive capabilities. One key example is the implementation of natural language processing (NLP) and GraphQL integration, which can be leveraged to mine the existing literature and further expand scientific knowledge.

This platform is continuously being refined and enhanced. Recent updates have streamlined the data input process, making this process faster and more efficient. This enhancement benefits sponsors who often operate on tight timelines.

Overall, by prioritizing collaboration and innovation with leading organizations and eminent scientists, BullFrog AI strives to ensure bfLEAP will remain at the forefront of AI-driven drug development for years to come. Continued technological advancements will mean even greater sophistication and more powerful capabilities that will enable researchers and clinicians to unlock new frontiers in the pursuit of advanced therapies.

With an unwavering commitment to innovation and collaboration, BullFrog AI is well positioned to help shape the future of drug development, revolutionize patient care, and transform the landscape of precision medicine. ◆

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## BIOGRAPHIES

**Dr. Thomas Hazel,** BullFrog AI VP of Drug Development, has over 20 years of industry experience in R&D and business development. He most recently served as senior VP of R&D at Seneca Biopharma, overseeing the development of the company's stem cell-based therapeutics platform. He has been granted 9 US patents and multiple foreign patents in stem cells and regenerative medicine. He earned his PhD in Genetics at the University of Illinois College of Medicine.

**JT Koffenberger,** BullFrog AI Chief Information Officer, has over 30 years of experience leveraging IT services for business. His range of expertise includes providing better security through custom application development and automating cumbersome business practices. He is Founder of Delmarva Group, LLC and Director of IT Architecture for Day and Zimmerman.

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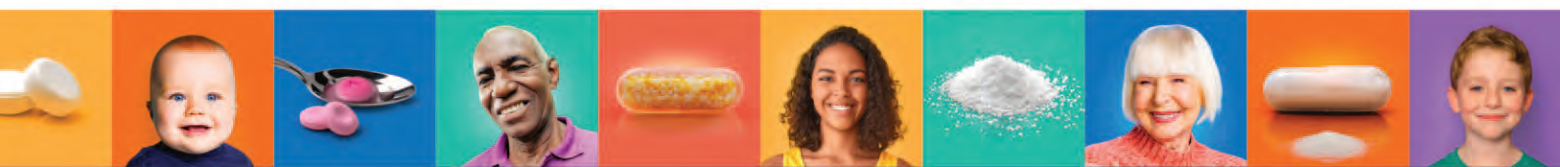

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